A Comparative Evaluation of the Clinical Course, Laboratory Data and Chest CT scan Findings in Pediatric Patients with Covid-19 and Their Prognostic Value in Disease Outcome Estimation

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Abstract

Background: Most research on children and adolescents with COVID-19, had limited sample sizes and little clinical, laboratory, and radiological findings. The purpose of this research was to examine the features of children and adolescents with COVID-19 infection.

Methods: This analytical retrospective study was conducted on children (1 to 12 years old) and adolescents (13 to 19 years old) with COVID-19 in Shahid Beheshti Hospital, Kashan, Iran. The data were then collected, entered into SPSS and analyzed.

Results: In the adolescent group, the frequency of dyspnea (47.1 % vs. 11.9%), cough (67.1 % vs. 39.2%), lethargy (42.9 % vs. 25.9%), headache (35.7 % vs. 10.5%), myalgia (38.6 % vs. 14%), and chest pain (12.9 % vs. 0.7%) were significantly higher than those in children (p<0.05). Furthermore, in terms of laboratory findings, the normal range of neutrophils (13.8% vs. 1.4%), Cr (95% vs. 75.7%), and CRP (77.9% vs. 58%) were higher in children. Moreover, we found that the CT severity score among adolescent patients was significantly higher than that in children (4.84 ± 5.21 vs. 1.76 ± 3.25, p=0.006). Also, the frequency of consolidation (61.3 % vs. 19%), and ground-glass opacity (58.1 % vs. 28.6%) among adolescents were significantly higher compared to child cases (p<0.05) while only the frequency of mosaic pattern of pulmonary parenchymal attenuation was significantly higher among children (p=0.035).

Conclusion: This research found milder clinical, biochemical, and radiological symptoms in children with COVID-19 than adolescents. However, radiological examinations showed greater rates of pulmonary parenchymal mosaic attenuation, which might help early diagnosis of COVID-19.

Key Words: Adolescents, Chest Ct Scan, Coronavirus Disease 2019 (Covid-19), Pediatrics.

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1- INTRODUCTION

An outbreak of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection which causes coronavirus disease 2019 (COVID-19) was spreading rapidly around the world and became a global pandemic on 11 March 2020 after it was declared by World Health Organization (WHO) and brought unprecedented economic, social and health disruption worldwide (1, 2). In the early stages of the epidemic, most patients were especially middle-aged and elderly and it soon became surprisingly clear that pediatric patients were infected far less frequently than adult individuals and with less severe symptoms which may be attributed to higher prevalence of underlying disease in adults, lower social distancing and higher expression of the SARS-CoV-2 host cell receptor angiotensin-converting enzyme 2 (ACE2) in adults (3, 4). While, in the current situation of the pandemic, children and adolescent cases show an increasing trend in many countries of the world (5, 6), asymptomatic or mildly symptomatic children and adolescents with COVID-19 can be managed safely without hospitalization (7). However, few studies worldwide have reported severe forms of SARS-CoV-2 infection in children and adolescents (8–10), which are assumed to be rare and only account for 1.7–2% of the diagnosed patients (11).

Risk factors for the severe form of SARS-CoV-2 infection in children and adolescents include young age (12) and comorbidities such as asthma, obesity, diabetes mellitus and cancer (13). Children and adolescents with this severe form of SARS-CoV-2 infection require intensive care level management and support; and it's necessary to understand the exact clinical and paraclinical features of COVID-19 in these cases (13). Besides clinical and laboratory findings, radiological investigations in pediatrics and adolescents experiencing the severe form of COVID-19 infection and its association with higher mortality rates and poor outcomes may help us to perform better management for these patients (7). Unfortunately, the published articles in the field of pediatrics are limited. The studies have confirmed the difference in clinical, laboratory and radiological findings between adults and children, but literature lacked a study comparing clinical and paraclinical features in the population of children and adolescents, who are known to have different immunity statuses. On the other hand, the non-specificity of the clinical findings and the necessity of early treatment in children with the severe form of COVID-19 infection, especially in cases with immunodeficiency/underlying disease and the challenge for radiation dose in children after radiological investigations (14-28), highlights the importance of the study on this issue; thus, in our research, we reviewed and analyzed children and adolescents with COVID-19 infection to provide evidence-based data involving clinical, laboratory and radiological manifestations in these age groups. It will help to formulate policies on controlling COVID-19 infection among children and adolescents for pediatricians and public health specialists.

2- MATERIALS AND METHODS

2-1. Design and participants

This analytical retrospective study was conducted in the Pediatric and Radiology Departments of Kashan Shahid Beheshti Hospital of Iran, from January 2019 to March 2021. The clinical laboratory and radiological manifestations in children (1 to 12 years old) with COVID-19 infection were compared to those in adolescent patients (13 to 19 years old).

2-1.1. Inclusion and exclusion criteria

Inclusion criteria encompassed the patients with COVID-19 infection confirmed by

nucleic acid positivity in nasal, and pharyngeal swabs or blood samples via reverse transcription polymerase chain reaction (RT-PCR) who have undergone chest computed tomography (CT) scan on the first day of referral and have the clinical and laboratory factors required for the study. Exclusion criteria included patients with other pulmonary disorders that lead to similar manifestations in CT scans (such as previous pulmonary edema or lung contusion), positive blood culture for any of the causative factors of community-acquired pneumonia, and inappropriate quality of CT scan images due to artifacts. We also excluded patients with incomplete data.

2-2. Procedure

The study flowchart is shown in **Fig. 1**. Two hundred thirteen children and adolescents were included based on clinical and paraclinical results as well as the inclusion and exclusion criteria. (143 cases in the child group and 70 in the adolescent group).
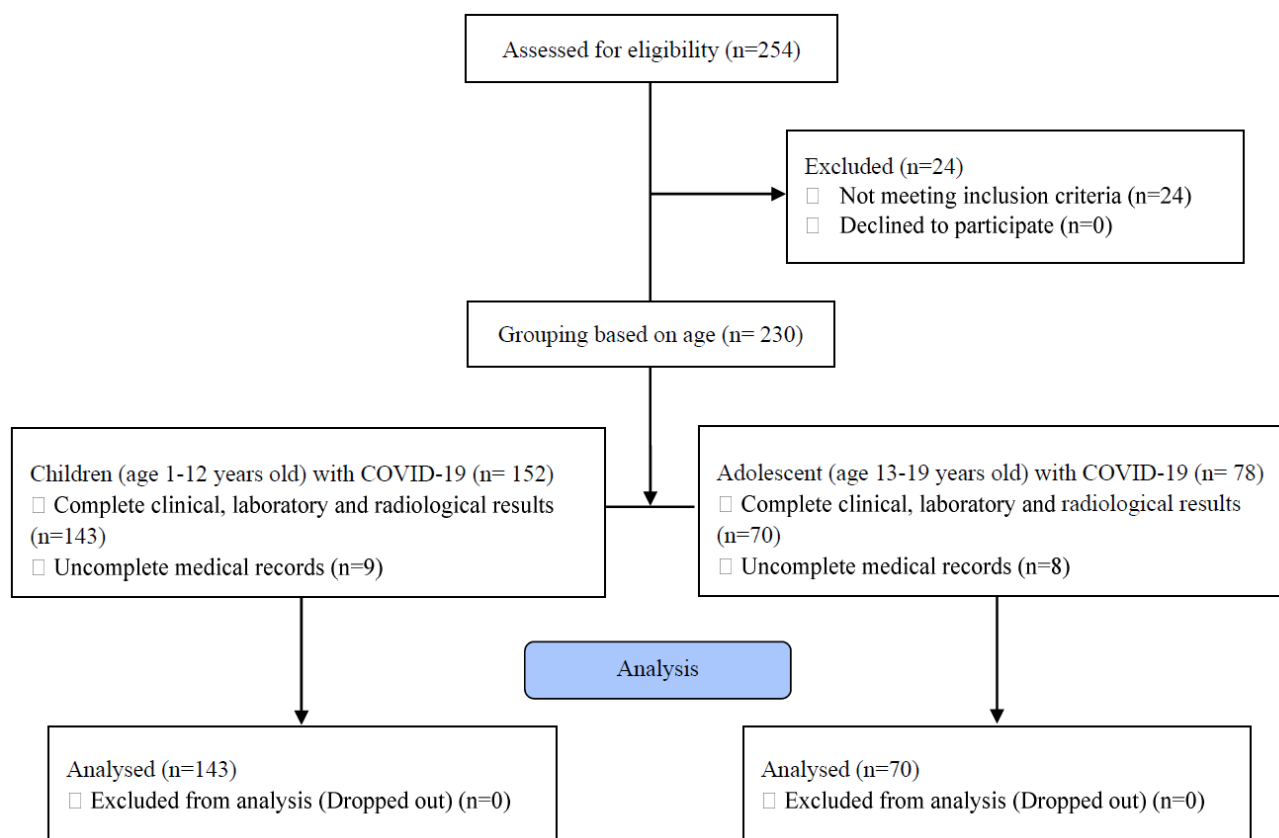

Fig. 1: Study flowchart

Clinical findings based on the patient's file, laboratory findings (complete blood count (CBC), blood urea nitrogen (BUN), Creatinine (Cr), erythrocyte sedimentation rate (ESR), C - reactive protein (CRP), liver enzymes, electrolytes, and inflammatory biomarkers) were recorded through the hospital's HIS (Hospital Information System) software.

In this study, the CT scanner (Toshiba, Canon, Alexia, Japan) with sixteen slices and reconstructed images in the axial section (1-3 mm), mAs at 100 milliamperes per second and kvp at 100-120 was used. To view the images,

Marcopacs version 8.6.6.7 was used. The CT scan images of each group were evaluated and reported by two radiologists, who were completely unaware of the clinical and laboratory findings, a soft tissue window and lung parenchyma were assessed, and the CT severity score was measured. Visual CT severity score for each pulmonary lobe was classified as Score-1 (< 5% area involved), Score-2 (5–25% area involved), Score-3 (25–50% area involved), Score-4 (50–75% area involved), and Score-5 (more than 75% area involved). Then, the scores obtained from the 5 pulmonary lobes were added together to the CT severity score. Also, the CT scan findings were defined based on Fleischner's standard definitions. Radiologists divided CT scan results into the ground glass opacity and consolidation findings. Also, the morphology of lesions was divided into linear/reticular, round/nodular, and patchy/segmental. The distribution of lesions was classified as peripheral-central, upper-middle-lower, and anterior-posterior. The involvement of each lobe of the lung was also mentioned separately. Moreover, the presence of air-bronchogram radiological views, cavitation, subpleural sparing, tree-in-bud nodules, and crazy paving view, reverse halo, mediastinal and hilar lymphadenopathy, pleural effusion and splenomegaly were reported. According to the report of many cases of halo sign in children, which was explained earlier in the literature review, this radiological pattern was recorded separately. Then the interpretation results of the two radiologists of each group were compared with each other and if there was any difference, an agreement was reached between them during a meeting.

It should be noted that infection control and supportive care were used for the management of children and adolescents admitted to hospital because of COVID-19. These treatments included corticosteroid drugs or inhaled corticosteroids, remdesivir, favipiravir, pantoprazole, etc. Since the study was retrospective in design, the patients' information was gained through their medical file records; and thus, the follow ups were until the end of hospitalization.

2-3. Data analysis

Only patients with complete information had their data analyzed and reported on. The data was statistically analyzed using SPSS version 22 software (SPSS Inc., Chicago, IL, USA). To compare the qualitative characteristics between the groups, Chi-square test was performed. Kolmogorov-Smirnov test was also performed to assess the normal distribution of all quantitative parameters evaluated. For variables with normal distribution, Student t-test was used; for variables with non-normal distribution, Mann-Whitney test was used. The two-tailed p-values less than 0.05 were considered significant.

3- RESULTS

In this study, medical records of 143 children (89 boys; age 5.72 ± 3.74 years old) and 70 adolescents (33 boys; age 16.95 ± 1.91 years old) were evaluated. The groups had significant differences in age and sex (P<0.05). The most common clinical symptoms in both groups were fever and cough. Also, in the adolescent group, the frequencies of dyspnea (47.1 % vs. 11.9%), cough (67.1 % vs. 39.2%), lethargy (42.9 % vs. 25.9%), headache (35.7 % vs. 10.5%), myalgia (38.6 % vs. 14%), and chest pain (12.9 % vs. 0.7%) were significantly higher than in the child group (p<0.05). In addition, in the child group, the frequency of abdominal pain (15.4 % vs. 4.3%) and diarrhea (21.7 % vs. 8.6%) were significantly higher compared to adolescent cases (p<0.05). (**Table 1**). In addition, we did not observe significant differences in the term of SPO2 (P=0.849) (**Table 1**).

Table-1: Sample clinical and laboratory findings in children and adolescents

Group Variables		Children (n=143)	Adolescents (n=70)	p-value
Age (years)		5.72±3.74	16.95±1.91	P<0.001
Gender (male)		89 (62.23)	33 (47.1)	0.036
Symptoms (%)	Fever	112 (78.3)	47 (67.1)	0.078
	Dyspnea	17 (11.9)	33 (47.1)	<0.001
	Cough	56 (39.2)	47 (67.1)	<0.001
	Runny nose	4 (2.8)	3 (4.3)	0.686
	Lethargy	37 (25.9)	30 (42.9)	0.012
	Headache	15 (10.5)	25 (35.7)	<0.001
	Dizziness	3 (2.1)	3 (4.3)	0.397
	Convulsions	6 (4.2)	0	0.181
	Myalgia	20 (14)	27 (38.6)	<0.001
	Sore throat	15 (10.5)	6 (8.6)	0.659
	Chest pain	1 (0.7)	9 (12.9)	<0.001
	Abdominal pain	22 (15.4)	3 (4.3)	0.018
	Nausea	16 (11.2)	14 (20)	0.082
	Vomit	34 (23.8)	11 (15.7)	0.176
	Diarrhea	31 (21.7)	6 (8.6)	0.018
	Loss of appetite	38 (26.6)	11 (15.7)	0.077
	Skin-mucous	0	0	-
Laboratory results (%) (normal serum levels)	WBC	99 (70.7)	48 (68.6)	0.749
	Neutrophil	18 (13.8)	1 (1.4)	0.004
	Hb	105 (75.5)	48 (68.6)	0.283
	LDH	29 (28.7)	12 (20.7)	0.266
	ALT	104 (89.7)	56 (82.4)	0.156
	AST	87 (77.7)	53 (77.9)	0.967
	ALP	53 (49.1)	43 (63.2)	0.066
	BUN	44 (31.7)	24 (34.3)	0.702
	Cr	133 (95)	53 (75.7)	<0.001
	CRP	106 (77.9)	40 (58)	0.003
	ESR	73 (53.7)	38 (55.9)	0.766
	K	120 (88.2)	66 (94.3)	0.165
	Na	118 (86.1)	61 (88.4)	0.648
	Mg	72 (62.1)	39 (57.4)	0.528
	D-dimer	62 (72.9)	25 (73.5)	0.948
SPO2 (%)		93.6 (13.2)	94.3 (6.6)	0.849
Length of hospitalization (days)		4.88 ± 4.05	5.07 ± 5.23	0.771
Mortality (%)		0	1 (1.4)	1

WBC: white blood cells, Hb: hemoglobin, LDH: lactate dehydrogenase, ALT: alanine transaminase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, BUN: blood urea nitrogen, Cr: creatinine, CRP: C - reactive protein, ESR: erythrocyte sedimentation rate, K: potassium, Na: sodium, Mg: magnesium, Spo2: oxygen saturation

Furthermore, in terms of laboratory findings, the normal range of neutrophils (13.8% vs. 1.4%, P=0.004), Cr (95% vs. 75.7%, P<0.001) and CRP (77.9% vs. 58%, P=0.003), were higher in the pediatric group as compared to adolescents (**Table 1**).

Moreover, we found that the CT severity scores among adolescent patients were significantly higher than those in the pediatric group (4.84 ± 5.21 vs. 1.76 ± 3.25, p=0.006). Also, the frequency of consolidation (61.3 % vs. 19%) and ground-glass opacity (58.1 % vs. 28.6%), mid-zone (51.6 % vs. 21.4%), lower zone (64.5 % vs. 23.8%), central (25.8 % vs. 7.1%), peripheral (58.1 % vs. 31%) and bilateral (48.4 % vs. 16.7%) involvement were significantly higher among the adolescents than pediatric cases (p<0.05); only the frequency of mosaic pattern of pulmonary parenchymal attenuation was significantly higher (p=0.035) among the child group. Furthermore, Peripheral halo signs did not show significant differences between the two age groups (P>0.05) (**Table 2**). Finally, there was no significant difference in outcomes such as the duration of hospitalization and mortality rate between the two groups of children and adolescents (p>0.05) (**Table 1**).

4- DISCUSSION

Our results showed that COVID-19 infection symptoms were significantly higher in adolescents, while gastrointestinal symptoms were higher in children. Furthermore, abnormality in the laboratory and radiological findings were significantly higher in adolescent patients except for the mosaic feature in radiological assessment, which was observed only in the child group. Therefore, COVID-19 infection was milder with non-specific symptoms in pediatrics as compared to adolescents. However, we did not include adult cases, but the results showed that COVID-19 features in adolescents were more like adult patients based on other studies (29) and children experience milder signs and symptoms.

Previous studies have reported that COVID-19 infection can be completely asymptomatic in some children (varying from 10% to 90% of infected children) (30, 31), while the majority of symptomatic cases have had mild degrees of the disease, which was similar to our results.
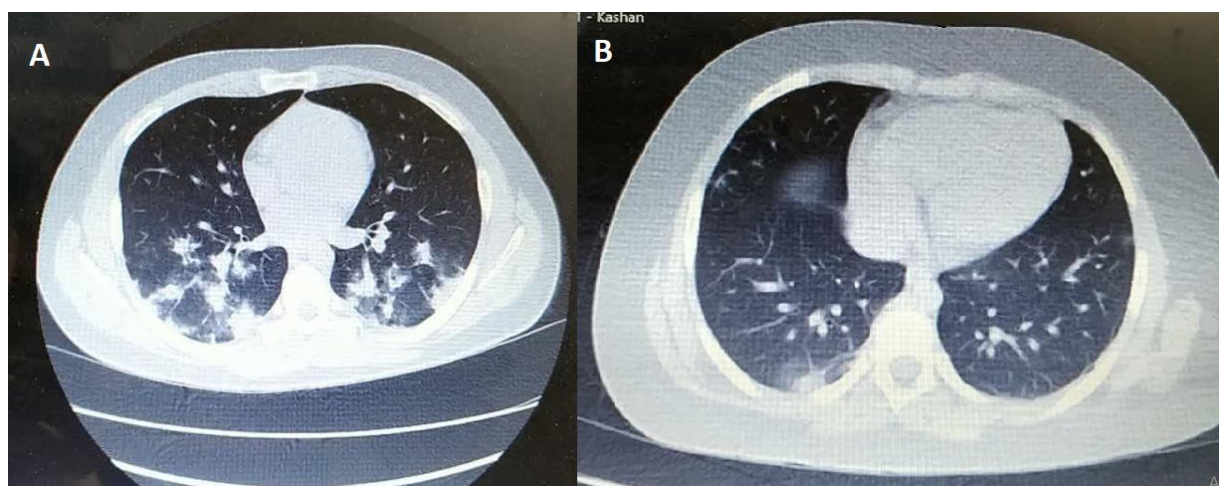

Fig. 2: Computed Tomography (CT) scan of lung showing halo sign in the axial section

Table-2: Sample radiological findings in children and adolescents

Group Variables		Children (n=143)	Adolescents (n=70)	p-value
Radiological findings (%)	CT severity score (CT-SS)	1.76 ± 3.25	4.84 ± 5.21	0.006
	Consolidation	8 (19)	19 (61.3)	<0.001
	Air bronchogram	6 (14.3)	8 (25.8)	0.217
	Ground-glass opacity	12 (28.6)	18 (58.1)	0.011
	Round opacity	0	0	-
	Mosaic	6 (14.3)	0	0.035
	Nodular	4 (9.5)	2 (6.5)	1
	Centrilobular	2 (4.8)	3 (9.7)	0.645
	Random	0	0	-
	Peribronchovascular	0	0	-
	Tree-in-Bud (TIB)	1 (2.4)	1 (3.2)	1
	Linear opacity	4 (9.5)	1 (3.2)	0.387
	Crazy-Paving	0	0	-
	Reverse halo sign (RHS)	1 (2.4)	4 (12.9)	0.156
	Peripheral halo	7 (16.7)	11 (35.5)	0.065
	Upper zone	11 (26.2)	13 (41.9)	0.157
	Mid zone	9 (21.4)	16 (51.6)	0.007
	Lower zone	10 (23.8)	20 (64.5)	<0.001
	Central	3 (7.1)	8 (25.8)	0.045
	Peripheral	13 (31)	18 (58.1)	0.021
	Unilateral	7 (16.7)	3 (9.7)	0.502
	Bilateral	7 (16.7)	15 (48.4)	0.004
	Single lesion	0	0	-
	Pleural effusion	2 (4.8)	2 (6.5)	1
	Pericardial effusion	0	1 (3.2)	0.425
	Lymphadenopathy H	5 (11.9)	3 (9.7)	1
	Lymphadenopathy M	1 (2.4)	0	1
	Lymphadenopathy A	0	0	-
	Cardiomegaly	17 (40.5)	11 (35.5)	0.665
	Cavitation	0	0	-
	Subpleural sparing	1 (2.4)	0	1
	Splenomegaly	0	0	-
	Pneumothorax	0	0	-
	Pneumomediastinum	0	0	-

Moreover, similar to our study, a meta-analysis found that cough (49%) and fever (47%) are the most frequent symptoms in both children and adolescent cases (32).

A review concluded that the clinical symptoms of COVID-19 infection in adolescents differed from children. They reported that adolescents were more likely to suffer from specific symptoms such as myalgia, dizziness and chills, while these symptoms were uncommon in children and gastrointestinal symptoms were more frequent among them instead (33).

Gastrointestinal symptoms can be correlated with severe SARS-CoV-2 infection in children. A multicenter study on pediatric cases with COVID-19 infection described that patients presenting

with gastrointestinal symptoms had higher ferritin, procalcitonin, and CRP values at their admission to the hospital (34).

Another study reported that gastrointestinal symptoms of COVID-19 in children include: vomiting (4%–67%), anorexia (40%–50%), diarrhea (2%–50%), nausea (1%–30%) and abdominal pain (2%–6%). Diarrhea and vomiting were the most common gastrointestinal manifestations described (35). We observed that diarrhea and abdominal pain were more frequent in child cases as compared to adolescents. Therefore, during the COVID-19 pandemic, we should pay more attention to non-specific symptoms such as gastrointestinal manifestations in children and based on the results of other studies, gastrointestinal symptoms may be correlated to the severe form of SARS-CoV-2 infection (36).

In this study, a high percentage of adolescents had abnormalities in their neutrophil and Cr (95%) as well as CRP serum levels, while in most of the children, those laboratory results were within the normal limits. According to similar studies, the majority of children with SARS-CoV-2 infection have normal WBC, with normal inflammatory results (37, 38). Henry et al. showed that in most children, the number of leukocytes was in the normal range (39). In addition, dominant neutrophil serum levels were found more frequently in adults and adolescents than in children in the study by Du et al. (40). According to Kosmeri et al., the most prevalent finding in lower-age patients with COVID-19 infection was lymphocytosis (41).

In our study, an imbalance in the number of neutrophils was recognized as one of the most prevalent laboratory disorders among adolescents; based on data, more than 24 % of adolescent patients had elevated Cr levels, and 42 % had high levels of CRP which were significantly lower than those in children. According to

the study by Du et al., in most cases, CRP levels were in the normal range but 50% of children with COVID-19 had abnormal LDH levels, which were much greater than in adolescents and adults (40). But we found that LDH levels did not differ between the two age groups. These differences may be due to the sample size, the time for laboratory measurements, and differences in underlying diseases.

Studies have demonstrated that chest imaging, e.g., CT scan, in children is comparable to adolescents in principal features; however, most of CT findings are mild in childcases. (42, 43) The most common manifestations have been ground-glass opacities and consolidations in both age groups; but in adolescents, we found a higher frequency of positive CT findings. As consolidations account for up to 61% of adolescent cases, they should be regarded as usual symptoms in patients in this age group, while ground-glass opacities were detected in more than 28% of the pediatrics as the main radiological manifestation of this age group and consolidation was in the second place. In pediatrics, SARS-CoV-2 infection should be distinguished from other viral pneumonia, such as respiratory syncytial virus, influenza virus, adenovirus, and parainfluenza virus by the use of CT imaging. (44) Parainfluenza virus and respiratory syncytial virus are more spread along the bronchial tree with a thick bronchial wall.

Lesions caused by Adenovirus pneumonia showed more consolidations, a greater density, and less subpleural lesions. Influenza viruses have the potential to create gridlike alterations in the lungs. Furthermore, bacterial pneumonia, chlamydia pneumonia, and mycoplasma pneumonia should be distinguished, since the latter infections create a higher density of pneumonia lesions. However, because various bacteria induce overlapping chest CT presentations, and COVID-19

pneumonia can be coupled with pneumonia caused by other types of pathogens and display more complicated and dangerous imaging characteristics, epidemiological and etiologic studies should be integrated. (45)

4-1. Limitations of the Study

Our study had some limitations. First, we did not evaluate heart disease factors including laboratory results and imaging findings, such as troponin, echocardiography, etc.

This needs more attention in future studies. Second, we used CT severity score (CT-SS) for comparing severity between the two groups of patients and we did not record clinical severity of COVID-19 disease or grading of patients based on signs and symptoms at the admission, which should be considered in further studies in this field. Furthermore, we did not include the types of treatment to compare them between the groups, because it was not among our study targets. But further studies should focus more on types of treatment in children and adolescents and their efficacy on patient outcomes.

5- CONCLUSIONS

The results of this study revealed that the available evidence confirms milder clinical, laboratory, and radiological manifestations in children with COVID-19, compared to adolescent cases. However, in clinical practice, gastrointestinal symptoms, and radiological assessments, Mosaic features were significantly higher in children which could be used as an indicator for the early diagnosis of COVID-19 infection.

6- ETHICAL CONSIDERATIONS

The Ethics Committee of Kashan University of Medical Sciences approved the study's ethics under the code of IR.KAUMS.MEDNT.REC.1400.055.

7- CONFLICTS OF INTEREST

None.

8- ACKNOWLEDGMENTS

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