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Clinical Manifestations and CT Scan Features in Children with COVID-19

Hosseinali Ghaffaripour [1], * Sedigheh Hasani Ranjbar [1], Maryam Hassanzad [1], Mahsa Mirzendedel [1], Elham Sadati [1]

[1] Pediatric Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Background: There is a paucity of quantitative studies on COVID-19 in children, and with the rising trend of infection in children, there is a need for more information in the clinical and paraclinical domains to be shared.

Objectives: The present research was designed to investigate the clinical and paraclinical manifestations of children with COVID-19 referred to Dr. Masih Daneshvari Hospital from September 2021 to September 2022 to maintain intuition into assessment and effective management of COVID-19 infection in children.

Methods: In this cross-sectional study, 70 children (under 18 years old) with COVID-19 who met the study entry criteria were included. Demographic characteristics, including the age and gender of the patients, as well as the family history of COVID-19 exposure, were recorded for the patients. CT scan findings of the patients were documented according to a standard questionnaire. The study results were analyzed and examined using SPSS software to enhance the diagnosis.

Results: Among the 70 study subjects, 66 individuals (94.3%) tested positive for PCR-COVID, and four individuals tested negative for PCR-COVID. Only 38 cases (54.3%) reported common findings on CT scans. Fever, cough, and lethargy were the most common clinical findings in the study population.

Conclusions: The presence of GGO on CT scans in children with COVID-19 should be regarded as an important indicator of the disease worsening. Among the clinical symptoms of chills, dyspnea, and myalgia had significant correlations with CT findings—particularly when two or all three symptoms were present. This allows clinicians to predict pulmonary involvement with reasonable accuracy and may help in deciding when to avoid unnecessary CT scans.

Key Words: COVID-19, Computed tomography (CT), Chills, Dyspnea, Fever, Ground-Glass Opacity (GGO), Myalgia.

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****Corresponding Author:***

Sedigheh Hasani Ranjbar. Pediatric Respiratory Disease Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: se.hasaniranjbar@gmail.com

1- INTRODUCTION

The novel coronavirus, temporarily named "2019 Novel Coronavirus (2019-nCoV)," emerged in Wuhan, China, and is now commonly known as COVID-19. Reports of its occurrence in individuals aged 18 and below have been relatively low (4.2% of reported cases) (1). The incubation period of COVID-19 is approximately 2 to 14 days, and it is transmitted through respiratory droplets and close contact. Reported cases have exhibited a wide range of symptoms, from mild to severe, with variable outcomes, including fatalities (2). Initially, the epidemiological pattern of the disease indicated that it primarily affected adults (3). However, later, especially after March 2020, some children infected with COVID-19 have severe manifestations similar to those of Kawasaki Disease (KD) (3). This condition is called Multisystem Inflammatory Syndrome (MIS-C). Further research has shown that unlike adults, clinical manifestations of COVID-19 among children are not uniform and may encompass a diverse spectrum (4).

Assessing quantitative innate immune deficiency is more challenging, although similar results apply to children with a healthy immune system (5). Children with malignancy have a similar disease severity, although mortality in this group seems to be higher than that in the public population (6).

Children constitute a small percentage of SARS-CoV-2 infections at the population level (7) and typically acquire the disease from an infected adult. Transmission of the disease occasionally occurs from children with clinical signs to ancestral strains (19A/19B) of SARS-CoV-2 (8). However, children's contribution to the epidemic has been partial (9). Understanding these data is evolving for emerging and established COVID types like Delta (B.1.617.2) (10). Initial studies on the Delta type indicate that the transmission rate, especially within families, is higher, but transmission from adults is more than that from children. The emergence of new variants may pose unique challenges, and continued critical evaluation of existing paradigms in relation to new data on different types will be essential. Although children represent a minority of SARS-CoV-2 cases in most regions, the high rate of household transmission of the Delta variant, coupled with increased vaccination in adults, is shifting the infection frequency toward younger age groups (11).

The immune reply to SARS-CoV-2 in children is particularly important for two reasons: Firstly, the spectrum of mild acute manifestations may pave the way for managing severe forms of the disease; and secondly, the phenomenon of systemic inflammation following infection, known as Multisystem Inflammatory Syndrome in Children (MIS-C), which is temporarily associated with SARS-CoV-2 (PIMS-TS), may provide new insights into immune responses (which predominantly occur in children) (12).

It is interesting to note differences in children's innate immune cell dynamics compared to adults during SARS-CoV-2 infection (13).

Overall, it seems that innate immune response in the upper respiratory tract is better in children, and prior common coronavirus infections in adults may lead to immunological memory that hinders the immune response's specificity against neoantigens like SARS-CoV-2 rather than enhancing them. Additionally, aging of the immune system with thymus involution and alterations in T cell receptor repertoire in older individuals, along with potential effects of overweight and metabolic syndrome, may disrupt innate immune function and hinder immune response to SARS-CoV-2 (14).

Studies on the relationship between human leukocyte antigen genotype and disease

intensity are limited (15). Limited evidence suggests that specific HLA genotypes may predispose (or protect against) severe diseases; and differences may underlie variability in the disease spectrum between ethnic groups (16). However, more information is needed in larger patient groups.

Radiological examinations in hospitalized children have shown patchy opacities in plain chest radiographs and ground-glass opacities in chest computed tomography (CT) scans (17). Given the radiation burden of CT imaging, this method is not performed in mildly symptomatic children. Earlier research has demonstrated the importance of HRCT examinations in COVID-19 patients. While recent recommendations from the American College of Radiology emphasize that CT should not be used as a screening or diagnostic tool for patients suspected of COVID-19, radiologists should be familiar with the imaging appearance of this disease to identify it in patients undergoing CT for other reasons. Steinberger et al. described CT findings in children with COVID-19, reporting that 10 cases (91%) showed no changes on follow-up CT scans of the lungs, raising questions about the utility of CT in the diagnosis and management of pediatric patients. Mehrabi et al. concluded from their review of current articles that in comparison to adults infected with SARS-CoV-2, children exhibit milder symptoms and less lung involvement on CT imaging. However, patterns of imaging changes are nearly similar (18).

In disease management, physicians rely more on supportive care for children with mild disease. There is very limited and insufficient Evidence for treating children with the common treatments, such as corticosteroids, redes vir, and Tocilizumab, used for adults. Multiple guidelines for treating children with acute COVID-19 recommend a tailored approach adduced of safety data from research in adults, with considerations given to antiviral treatment with remdesivir and/or immunomodulatory treatment with steroids or biologics (tocilizumab) (19). Steroids have constant profiles in children, while less information is available for remdesivir and tocilizumab. Other newfound treatments have no safety in children.

Iran was one of the first countries significantly impacted by COVID-19. Until July 2020, Qatar reported the highest prevalence of COVID-19 in the Middle East, with 38,939 cases per million population. According to the Ministry of Health, COVID-19 was present in Iran since February 2020, and Iran had the highest mortality rate in the region, at 212.5 deaths per million population (20). Epidemiological studies on COVID-19 in the Iranian population have been conducted, but quantitative studies on this disease in children are lacking, and further information is needed on clinical and paraclinical aspects to be shared. Thus, this exploration attempted to investigate the paraclinical features of children with COVID-19 referred to Dr. Masih Daneshvari Hospital (from September 2021 to September 2022) to maintain insight into the assessment of COVID-19 infection in children.

2- METHODS

2-1. Design and population

This study employed a cross-sectional research design. Since data on the prevalence of COVID-19 in Iranian children were not readily available, the study population was determined based on previous studies (21-24). 70 children (aged less than 18 years) with confirmed COVID-19 were included in the study.

2-1-1. Inclusion and exclusion Criteria

Participants had confirmed COVID-19, determined through laboratory viral

nucleic acid testing (RT-PCR) using throat swab samples or compatible chest CT manifestations of COVID-19. Additionally, a history of close contact with suspected or confirmed SARS-CoV2 individuals within the family was considered. If both radiological and RT-PCR assessments were not conducted for a patient, they were excluded from the study.

2-2. Procedure

Demographic characteristics, including age, sex, and family history, were recorded for the registration of COVID-19 patients. Clinical manifestations like fever, sore throat, cough, myalgia, headache, dyspnea, diarrhea, vomiting, abdominal pain, and runny nose were also documented. CT findings of patients were recorded. Correlations between the variables were investigated using IBM SPSS Statistics v.23 software. The level of significance was considered as $p < 0.05$.

3- RESULTS

3-1. Clinical Manifestations

The most common clinical findings among the studied individuals were fever (41 cases), cough (38 cases), lethargy (13 cases), myalgia (9 cases), dyspnea (9 cases), chills (6 cases), runny nose (3 cases), headache (3 cases), vomiting (3 cases), diarrhea (3 cases), anorexia (3 cases), sore throat (2 cases), abdominal pain (2 cases), poor feeding (2 cases), chest pain (1 case), unconsciousness (1 case), and tachycardia (1 case).

3-2. Demographic information

Among the 70 study participants, 66 (94.3%) tested positive for PCR-COVID, while 4 had negative PCR-COVID results. Moreover, common CT scan findings were reported in only 38 cases (54.3%). Additionally, a positive family history was reported in only three patients, of which 2 had positive PCR-COVID tests (Fig. 1).

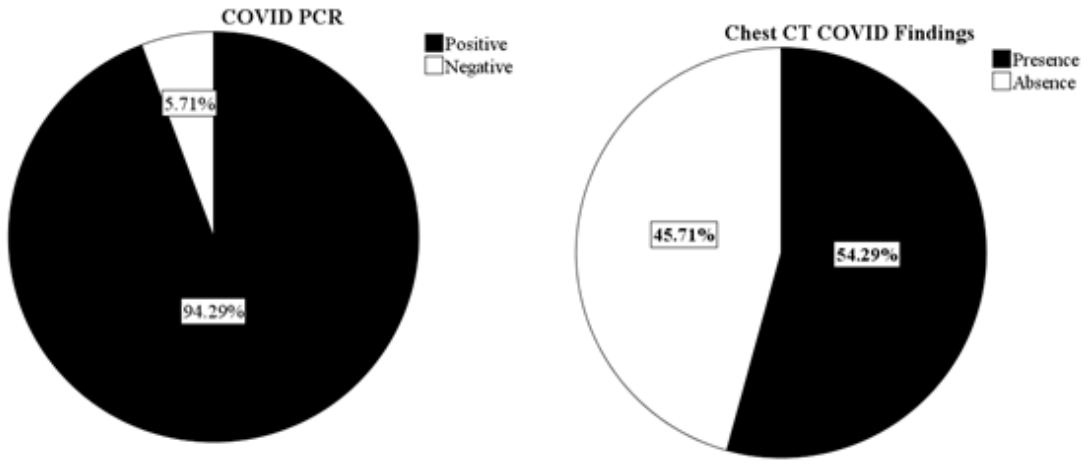

Fig. 1: Frequency distributions of PCR test and CT scan

Eight patients had underlying diseases, including cystic fibrosis (n=3), immunodeficiency (n=2), sarcoma (n=1), and Hodgkin's lymphoma (n=1).

3-3. CT scan Findings

Among 38 patients who underwent CT scans, 19 cases showed evidence of consolidation (6 cases), cystic lesion (2

cases), GGO (1 case diffuse, 1 case RLL, 1 case LLL and 1 case RML), hilar adenopathy (2 cases), bronchiectasis (2 cases), peribronchial thickening (1 case), atelectasis (1 case), pleural effusion (1 case), paratracheal adenopathy (2 cases), and mediastinal mass (2 cases) (Fig. 2).

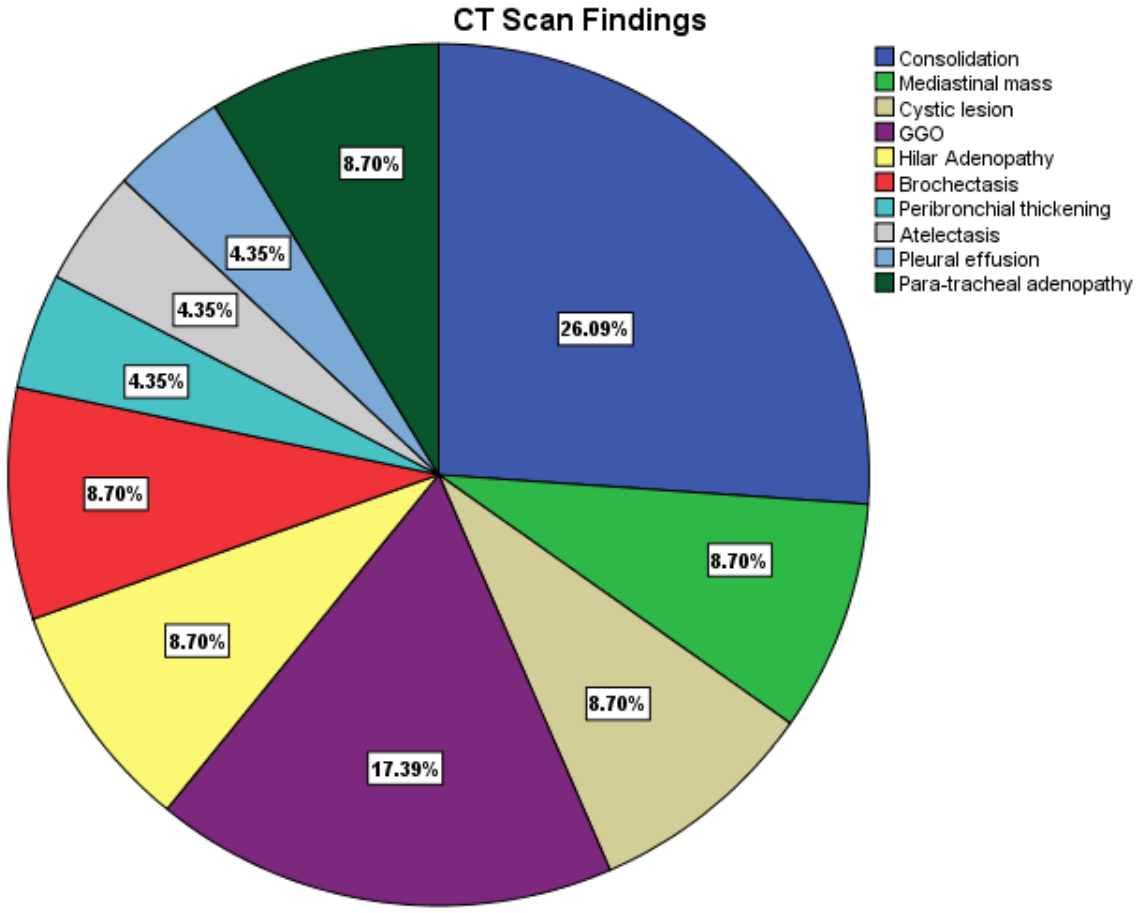

Fig. 2: Frequency of CT scan findings

3-4. Evaluation of the correlation between CT Features and Clinical Manifestations in Children with COVID-19

A significant direct correlation was reported between myalgia, GGO RLL, and GGO LLL (r=0.380, p=0.017) (Table 1). Rhinorrhea showed a significant direct correlation with diffuse findings on CT (r=1.000, p<0.0001). Significat direct correlations were reported between dyspnea, GGO RML, and mediastinal mass (r=0.480, p=0.002 and r=0.305, p=0.059, respectively). Malaise showed an obvious direct correlation with diffuse findings on CT (r=0.319, p=0.048). Significant direct correlations were reported between chills, GGO RLL, and GGO LLL (both r=0.480, p=0.002) (Table 1).

4- DISCUSSION

Iran was one of the first countries affected by COVID-19. Previous studies on children have been largely case-based. This exploration was conducted on hospitalized patients at Masih Daneshvari Hospital to maintain intuition into assessment and effective management of COVID-19 infection in children.

Table-1: Evaluation of the correlation between CT features and clinical manifestations

Variable			CT Evidence	Consolidation	Cystic Lesion	GGO RLL	Hilar Adenopathy	GGO LLL	Bronchiectasis	Peribronchial Thickening	Atelectasis	Pleural Effusion	GGO RML	Diffuse	Unifocal GGO	Para tracheal adenopathy	Mediastinal mass
Spearman's rho	Fever	Corr	-0.037	-0.279	-0.082	0.115	-0.329*	0.115	-0.082	0.115	0.115	0.115	-0.229	0.115	-0.229	-0.329*	-0.329*
		Sig.	0.822	0.081	0.619	0.487	0.041	0.487	0.619	0.487	0.487	0.487	0.160	0.487	0.160	0.041	0.041
	Vomiting	Corr	-0.152	-0.067	-0.038	-0.026	-0.038	-0.026	-0.038	-0.026	-0.026	-0.026	-0.026	-0.026	-0.026	-0.038	-0.038
		Sig.	0.348	0.680	0.820	0.874	0.820	0.874	0.820	0.874	0.874	0.874	0.874	0.874	0.874	0.820	0.820
	Sore Throat	Corr	0.168	-0.067	-0.038	-0.026	-0.038	-0.026	-0.038	-0.026	-0.026	-0.026	-0.026	-0.026	-0.026	-0.038	-0.038
		Sig.	0.299	0.680	0.820	0.874	0.820	0.874	0.820	0.874	0.874	0.874	0.874	0.874	0.874	0.820	0.820
	Cough	Corr	-0.302	-0.157	0.164	0.115	-0.329*	0.115	-0.082	0.115	0.115	0.115	0.115	-0.229	-0.229	-0.329*	-0.082
		Sig.	0.058	0.333	0.317	0.487	0.041	0.487	0.619	0.487	0.487	0.487	0.487	0.160	0.160	0.041	0.619
	Myalgia	Corr	-0.259	0.020	-0.099	0.380*	-0.099	0.380*	-0.099	-0.069	-0.069	-0.069	-0.069	-0.069	-0.069	-0.099	-0.099
		Sig.	0.106	0.904	0.548	0.017	0.548	0.017	0.548	0.676	0.676	0.676	0.676	0.676	0.676	0.548	0.548
	Runny Nose	Corr	0.168	-0.067	-0.038	-0.026	-0.038	-0.026	-0.038	-0.026	-0.026	-0.026	-0.026	1.000**	-0.026	-0.038	-0.038
		Sig.	0.299	0.680	0.820	0.874	0.820	0.874	0.820	0.874	0.874	0.874	0.874	<0.001	0.874	0.820	0.820
	Headache	Corr	-0.152	-0.067	-0.038	-0.026	-0.038	-0.026	-0.038	-0.026	-0.026	-0.026	-0.026	-0.026	-0.026	-0.038	-0.038
		Sig.	0.348	0.680	0.820	0.874	0.820	0.874	0.820	0.874	0.874	0.874	0.874	0.874	0.874	0.820	0.820

Variable			CT Evidence	Consolidation	Cystic Lesion	GGO RLL	Hilar Adenopathy	GGO LLL	Bronchiectasis	Peribronchial Thickening	Atelectasis	Pleural Effusion	GGO RML	Diffuse	Unifocal GGO	Para tracheal adenopathy	Mediastinal mass
	Dyspnea	Corr	-0.208	0.053	0.305	-0.055	-0.079	-0.055	-0.079	-0.055	-0.055	-0.055	0.480**	-0.055	-0.055	-0.079	0.305
		Sig.	0.197	0.746	0.059	0.740	0.634	0.740	0.634	0.740	0.740	0.740	0.002	0.740	0.740	0.634	0.059
	Diarrhea	Corr	0.011	-0.096	-0.054	-0.038	-0.054	-0.038	-0.054	-0.038	-0.038	-0.038	-0.038	-0.038	-0.038	-0.054	-0.054
		Sig.	0.944	0.554	0.744	0.820	0.744	0.820	0.744	0.820	0.820	0.820	0.820	0.820	0.820	0.744	0.744
	Abdominal Pain	Corr	0.011	-0.096	-0.054	-0.038	-0.054	-0.038	-0.054	-0.038	-0.038	-0.038	-0.038	-0.038	-0.038	-0.054	-0.054
		Sig.	0.944	0.554	0.744	0.820	0.744	0.820	0.744	0.820	0.820	0.820	0.820	0.820	0.820	0.744	0.744
	Lethargy	Corr	-0.225	-0.210	-0.118	-0.082	-0.118	-0.082	-0.118	-0.082	-0.082	-0.082	-0.082	0.319*	-0.082	-0.118	-0.118
		Sig.	0.162	0.193	0.474	0.618	0.474	0.618	0.474	0.618	0.618	0.618	0.618	0.048	0.618	0.474	0.474
	Ague	Corr	0.184	0.093	-0.079	0.480**	-0.079	0.480**	-0.079	-0.055	-0.055	-0.055	-0.055	-0.055	-0.055	-0.079	-0.079
		Sig.	0.257	0.567	0.634	0.002	0.634	0.002	0.634	0.740	0.740	0.740	0.740	0.740	0.740	0.634	0.634
	Anorexia	Corr	0.168	-0.067	-0.038	-0.026	-0.038	-0.026	-0.038	-0.026	-0.026	-0.026	-0.026	-0.026	-0.026	-0.038	-0.038
		Sig.	0.299	0.680	0.820	0.874	0.820	0.874	0.820	0.874	0.874	0.874	0.874	0.874	0.874	0.820	0.820

The underlying mechanisms of milder disease manifestation in children in comparison to adults have been the subject of numerous studies. One likely comment is a reduced inflammatory answer due to children's less developed immune system compared to adults.

This study reported only 54.3% of the common CT scan findings. This contrasts with the much higher prevalence of CT features in adults with COVID-19. In a study by Kim et al. in 2022, individuals with a higher age had positive CT scans (25). This can be justified by the direct relationship between the disease's severity, the patient's age, and CT scan findings in chest imaging. Among 40 patients with consolidation on CT scan, cystic lesions and GGO were the most common findings. It appears that the patterns of imaging changes may differ even in a single geographical location. Therefore, the root causes of these differences in reports should be investigated in other cases. One possible factor is inflammation's role in forming lung lesions, and differences in inflammatory factors may account for these differences (26). Another reason is the different viral load in individuals, which depends on each individual's immune system's ability to prevent the spread of the virus in their body (27). Finally, the exposure status may also contribute to the differences in children between the current and previous studies. To identify the main reason for these differences, more studies are needed to elucidate the correlation between SARS-CoV-2 viral load and exposure status. Ultimately, the time course of lung changes in adult patients has been determined, but the progression period in children remains unclear.

There are specific clinical and epidemiological criteria for patients suspected of having COVID-19. These clinical criteria include fever, cough, and three other cases: lethargy, headache, myalgia, sore throat, and dyspnea. The presence of these symptoms in patients acutely and severely necessitates a chest CT scan to identify main findings of the infection. GGO is one of the leading CT features in COVID-19, although its presence is not dedicated to this particular viral pneumonia. Similar to the present study, a previous systematic review by Ghodsi et al., in Mashhad, based on the results of research on children with COVID-19, showed that GGO is the most common CT finding in these children (28). They stated that this disease is mainly presented as an atypical pneumonia (thickening of peribronchial and linear or ribbon-like opacities) in this age group.

In the present study, a significant positive correlation was reported between myalgia and ground-glass opacities (GGO) in the right lower lobe (RLL) and left lower lobe (LLL) (both $r=0.380$, $p=0.017$). A significant positive relationship was found between dyspnea and GGO in the right middle lobe (RML) and mediastinal mass ($r=0.480$, $p=0.002$, and $r=0.305$, $p=0.059$, respectively). Furthermore, a significant positive relationship was reported between shivering and GGO in the right lower lobe (RLL) and left lower lobe (LLL) (both $r=0.480$, $p=0.002$). In addition to GGO in the form of RLL, LLL, and RML in children in the present study, diffuse GGO on CT with nasal discharge and lethargy also showed a significant positive correlation ($r=1.000$, $p<0.0001$ and $r=0.319$, $p=0.048$, respectively). Therefore, the presence of GGO on CT in children with COVID-19 should be considered a valuable finding associated with the severity of the disease.

Disease induced by SARS-CoV-2 occurs with lower prevalence and intensity in children in comparison to adults, and a very low mortality rate is estimated. However, growing evidence shows that children are just as susceptible to infection as adults. This may be due to the fact that

children are less exposed to the primary transmission sources (especially in healthcare settings) and exhibit milder symptoms, which may result in fewer diagnostic tests. In symptomatic patients, radiological findings are mainly available and can help identify individuals who are intensity ill. More research is needed to better understand the potential outcomes of COVID-19 infection in children.

4-1. Limitations of the study

The main limitation of the present study is the inability to examine viral load and other factors involved in the inflammatory pathway (such as IL-6).

5- CONCLUSION

Based on the research findings in symptomatic patients, there are predominantly radiological findings that can assist in identifying severely ill individuals.

GGO is an important detector of the CT findings in COVID-19, but it's not exclusive to it. In the present study, a significant direct correlation was reported between myalgia and GGO. Also, a significant direct correlation was reported between dyspnea and GGO in the right middle lobe (RML) and mediastinal mass. In addition, a significant direct correlation was reported between shivering and GGO in the RLL and LLL. Besides localized GGO in the RLL, LLL and RML in children in the present study, the finding of diffuse GGO on CT showed a significant direct correlation with runny nose and lethargy. Therefore, it seems that the presence of GGO on CT scans of children with COVID-19 should be considered a valuable finding related to the disease worsening.

CT scans are frequently performed on COVID-19 patients, but the danger of radiation, particularly in children, is a concern. In the current study, 54.3% of the reports showed common findings on CT scans. Based on these findings, it may be possible to rely on alternative methods to avoid unnecessary CT scans in certain cases.

Among clinical symptoms, chills, dyspnea, and myalgia were found to be directly correlated with CT findings, especially when two or more symptoms were present. Therefore, in patients with a positive prediction of pulmonary involvement, treatment can proceed without always resorting to CT imaging**.**

More extensive studies must be conducted to understand the potential outcomes of COVID-19 infection in children.

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