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Efficacy of Clinical and Chest Radiography Features in Predicting Patient Prognosis in Children with COVID-19

COVID-19'lu Çocuklarda Klinik ve Göğüs Radyografisi Özelliklerinin Hasta Prognozunu Öngörmedeki Etkinliği

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Abstract

The findings of chest radiography (*chest-X ray*, CXR) have not been confirmed in evaluating the prognosis of pediatric patients with coronavirus disease 2019 (COVID-19). In this study, we aimed to analyze the prognostic value of the CXR infiltration severity scoring system at the initial presentation of pediatric patients with COVID-19. Hospitalization and long-term data were recorded. The admission CXR data of 310 patients aged 1 month to 18 years who presented to our hospital between March 2020 and January 2021 with the diagnosis of COVID-19 confirmed by the real-time reverse transcription-polymerase chain reaction (RT-PCR) test were included in the study. The CXR images of each patient were evaluated in terms of the presence, type and localization of lesions by a radiologist, and the lung severity scores were calculated. Clinical and laboratory variables were also noted. The relationship between clinical parameters, imaging findings and patient outcomes was statistically evaluated. The median age was 9.1±5.2 years, and 59.7% of the patients (185/310) were male. Abnormal CXR findings were found in 6.5% (20/310) of the patients. CT was performed in 25 patients (8.1%), of whom 20 had normal CT findings. The time between the onset of complaints and admission to the hospital was 2.8±1.1 days in patients with abnormal CXR findings 3.0±1.4 days in those with normal findings, indicating no statistically significant difference (p=0.58). The duration of hospital stay of the patients with abnormal and normal CXR findings was 9.75±2.6 vs 9.47±2.0 days, respectively, and the difference was not statistically significant (p=0.78). None of the patients required intubation, and all had a good prognosis. For patients aged 1 month-18 years presenting to the emergency department with COVID-19, CXR presents as a useful modality in the diagnosis of associated pneumonia and it has similar results compared with CT. Our results revealed that CXR could be used in symptomatic children to assess COVID-19 pneumonia. We suggest that CT should be used for the further analysis of possible pathologic findings or complications on CXR, if clinically indicated.

Keywords: Chest X-ray, COVID-19, Children, Computed tomography.

Özet

Pediatrik COVID-19 (*coronavirus disease 2019*) hastalarında prognozun değerlendirilmesinde göğüs radyografisi (*chest-X ray*, CXR) bulguları doğrulanmamıştır. Bu çalışmada COVID-19'lu çocuk hastaların ilk

başvurularında CXR infiltrasyon şiddeti skorlama sisteminin prognostik değerini analiz etmeyi amaçladık. Hastaneye yatış ve uzun dönem verileri kaydedildi. Çalışmaya Mart 2020 - Ocak 2021 tarihleri arasında gerçek zamanlı ters transkriptaz polimeraz zincir reaksiyonu (RT-PCR) testi ile doğrulanmış COVID-19 tanısı ile hastanemize başvuran 1 ay ile 18 yaş arası 310 hastanın kabul CXR verileri dahil edildi. Her hastanın CXR görüntüsü lezyonların varlığı, lezyon tipi ve lokalizasyonu açısından bir radyolog tarafından değerlendirildi ve akciğer şiddet skorları hesaplandı. Klinik ve laboratuvar değişkenleri kaydedildi. Klinik parametreler, görüntüleme bulguları ve hasta sonuçları arasındaki ilişki istatistiksel olarak değerlendirildi. Medyan yaş 9.1±5.2 yıl idi ve hastaların %59.7'si (185/310) erkekti. Hastaların %6.5'inde (20/310) anormal CXR bulguları saptandı. Yirmi beş hastaya (8.1%) BT çekildi ve bunların 20'sinin BT görüntüleri normaldi. Şikayetlerin başlaması ile hastaneye başvuru arasındaki süre anormal ve normal CXR bulguları olan hastalarda sırasıyla 2.8±1.1 gün ve 3.0±1.4 gündü ve gruplar arasındaki fark istatistiksel olarak anlamlı değildi (p=0.58). Anormal ve normal CXR bulguları olan hastaların hastanede kalış süreleri sırasıyla 9.75±2.6'ya karşı 9.47±2.0 gündü ve fark istatistiksel olarak anlamlı değildi (p=0.78). Hastaların hiçbiri entübasyona ihtiyaç duymadı ve tümünün prognozu iyi idi. COVID-19 ile acil servise başvuran 1 ay-18 yaş arası hastalarda, COVID-19 pnömonisi tanısında CXR yararlı bir modalite olup BT ile karşılaştırıldığında benzer sonuçlar sunmaktadır. Çalışma verilerimiz semptomatik çocuklarda COVID-19 pnömonisini değerlendirmede CXR'nin kullanılabilir olduğunu göstermekte olup, BT'nin CXR'deki olası patolojik bulguların veya komplikasyonların ileri değerlendirmesi için ve klinik olarak endike olduğunda kullanılmasını öneriyoruz.

Anahtar Kelimeler: Göğüs röntgeni, COVID-19, Çocuk, Bilgisayarlı tomografi.

An abstract of this study was presented as an oral presentation at the 5th International Hippocrates Congress on Medical and Health Sciences (18-19 December 2020).

Introduction

Coronavirus disease 2019 (COVID-19), caused by a novel coronavirus species [Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2], emerged at the end of December 2019 in Wuhan, China [1,2]. Due to its spread rate and destructive effects, this important public health crisis that threatens humanity was declared as a pandemic by World Health Organization (WHO) on March 11, 2020 [3]. As of December 19, 2021 the disease remains a global threat with over 275 million cases and 5 million deaths being reported in a period of nearly two years [4]. In the adult population, the clinical course of SARS-CoV-2 infections ranges from mild to severe respiratory tract disease (with pneumonia usually being a prominent clinical finding) and death, whereas in children, the infection is mostly asymptomatic or milder forms of the disease are reported with a wider clinical manifestation range and low hospitalization and mortality rates [5,6]. During the early period of the pandemic, chest radiography (*chest-X ray*, CXR) was preferred as the primary imaging modality for clinical monitoring and treatment adjustment in adult patients with COVID-19 [7]. Chest CT is another important diagnostic method when evaluated together with clinical findings in the diagnosis of COVID-19 pneumonia and management of adult patients, and it was extensively used in the early period of the pandemic [7–9].

CDC recommends performing virological tests primarily from the upper respiratory tract or, where appropriate, lower respiratory tract specimens as the initial diagnostic test for suspected COVID-19 infection and does not currently indicate CXR or CT for the diagnosis of COVID-19 [10]. Similarly, the American College of Radiology (ACR) and Society of Thoracic Radiology (STR) do not recommend the use of CT or CXR for large-scale scans and first-line diagnosis [11,12]. However, in the United States, chest radiography is routinely performed in emergency departments for all patients presenting with dyspnea regardless of the COVID-19 diagnostic approach [10]. Early studies on radiological findings in COVID-19 patients focused heavily on CT data, and therefore there is only limited research on the distribution and variety of CXR findings, their relevance for the patient's clinical status, and their value in predicting prognosis [10,13]. In a study including a small number of cases (64 patients), only 44 (68.9%) had abnormal findings in their initial CXR among

the real-time reverse transcription- polymerase chain reaction (RT-PCR)-confirmed COVID-19 cases [13]. Although the initial CXR sensitivity was lower compared to RT-PCR (68.9% vs 90.6%), there was no significant difference between radiological recovery and viral recovery [13]. Bilateral disease and involvement of more than two sites (*lung zones*) in CXR were found to be associated with poorer outcomes in various pneumonia cases [14,15]. However, to avoid radiation, imaging is not usually considered necessary in pediatric cases with no clinical signs. Due to the good clinical course of COVID-19 in pediatric patients, there are a limited number of studies in the literature presenting comparative analyses of radiological imaging findings in the pediatric population compared to adults [16]. The aim of this study was to examine the relationship between the initial CXR findings and clinical manifestation, hospitalization, and results obtained during patient follow-up in pediatric patients with COVID-19.

Material and Method

This retrospective study was approved by the Ethics Committee of University of Health Sciences Gulhane Training and Research Hospital with the decision number 2020/294 on June 30, 2020. Informed consent was obtained from all parents of the individual participants included in the study.

Patients

The records of a total of 310 patients aged 1 month to 18 years, who presented to Ankara Gulhane Training and Research Hospital between March 2020 and January 2021 and were diagnosed with COVID-19 confirmed by the RT-PCR test and underwent a CXR or CT scan within 24 hours of admission were examined (Figure 1). The entire study population consisted of patients who were given treatment according to the national guidelines. The patients' initial CXR and CT scan images at the time of admission were evaluated. In addition, the CXR and/or CT images taken during the hospital stay were assessed to compare the clinical features of the patients in terms of radiological progression or regression. Using these images, the presence, type [ground-glass opacity (GGO) or consolidation], and localization (zone and central-peripheral distribution) of the lesions were evaluated. The differences between two imaging modalities were evaluated. Patients with normal and abnormal CXR findings were statistically compared according to the time from the onset of symptoms to hospital admission, length of hospital stay, and clinical-radiological course of the disease

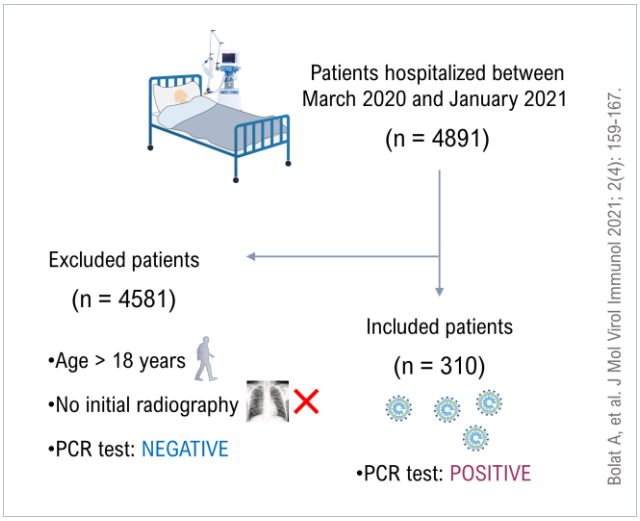

Figure 1. Flow diagram of the study group.

X-ray and CT imaging

All the patients were imaged using a computerized radiography technique with a mobile X-ray device (GE Healthcare Mobile X-ray: Ukiah Valley AMX 240, USA) during hospitalization and follow-up. CXR images were obtained in the posterior-anterior projection.

Thorax CT images were obtained without contrast media injection, using a 64- scanner multi-detector computed tomography, *MDCT* (Aquilion ONE, Toshiba Medical System, Tokyo, Japan). All the patients were scanned in the supine position, when holding their breath at the end of inspiration, and covering the entire rib cage from apex to basal. Automatic tube current modulation (100-400 mA) with 100 kV or 120 kV tube voltage was used. The section thickness was 1.0-3.0 mm, and the reconstruction matrix size was 512 × 512.

Radiographic evaluation

All the CXR images were examined by an experienced radiologist based on general consensus. Findings were reported with a description of the glossary of Fleischner Society [17–19].

Concerning the distribution of lesions:

1. Peripheral and/or central involvement was noted (the border was set at the mid-distance between the outer edge of the lung and the hilum).

2. The lungs were divided into three zones, (lower, middle, and upper): the first from the costophrenic sulcus to the lower hilar marks; the second defines the region from the lower hilar marks to the upper hilar marks, and the last defines the region from the upper hilar mark to the apex [10].

CT Evaluation

All the CT images were examined by a radiologist experienced in thoracic imaging. Lesion descriptions for pneumonic infiltration were made with the nomenclature specified by the Fleischner Society [17,18]. Only the presence of GGOs and consolidation, the two most frequently reported lesions in the CT scans, was assessed [20]. A lesion was categorized as consolidation if there was an onset of consolidation of any size within the GGO density. Concerning the distribution of lesions, both lungs were divided into three zones (upper, middle, and lower) as previously determined, and the lesions were recorded as centrally and/or peripherally located [20]. One-third of the parenchyma close to the pleura was considered as peripheral, while two-thirds of the perihilar parenchyma was regarded as central.

Statistical analysis

Mean and ± standard deviation, frequency and other basic statistical calculations were performed for study variables. SPSS for Mac, v. 20.0 (SPSS Inc, Chicago, IL, USA) was used to analyze the obtained data. The Kolmogorov-Smirnov test, chi-square test, Student's t-test, and Mann-Whitney U test were applied for statistical analyses. P values of less than 0.05 were considered statistically significant, with a 95% confidence interval.

Results

A total of 310 pediatric patients with COVID-19 confirmed by the RT-PCR test were included in the study. The median age was 9.1±5.2 years. There were 185 male (59.7%) and 125 female (40.3%) patients. Twenty-five patients (8.1%) had CT imaging results in addition to CXR. The average age of these patients (20 boys, five girls) was 10.8 (2-17) years. All the patients had either a CXR or CT scan at the time of admission.

Abnormal pulmonary findings were found in initial CXR imaging in 20 (6.5%) patients. Concerning the lesion distribution characteristics in the lungs, CXR revealed an increase in the number of lesions from the upper zone to the lower zone, with most lesions being detected in the lower lobes (Table 1). The lesions were unilateral and solitary in all the patients. No statistically significant difference was observed between the lungs (right and left) in terms of lung involvement patterns. In patients with abnormal findings, lower-zone involvement was most common (Table 1). One patient (16-year-old female) had pneumothorax (Figure 2). Pleural effusion was not identified in any of the patients.

CT was performed in 25 patients, of whom 20 (80%) had normal findings, five had abnormal findings, with one presenting with pneumothorax (Figure 2). Only 20 of the 310 patients (6.5%) had abnormal CXR findings, but the CT findings of 15 of these patients were normal. The properties and distribution of the CT lesions (25/310, 8.1%) are summarized in Table 1. Unilateral single lobe involvement was detected in five patients (20%), of whom all had a solitary lesion and one had pneumothorax.

The mean time from the onset of complaints to hospital admission was 2.95±1.3 days. The time from the beginning of complaints to hospital admission was 2.8±1.1 days for the patients with normal CXR findings and 3.0±1.4 days for those with abnormal CXR findings, indicating no statistically significant difference (p=0.58). All the 310 patients in our study group were evaluated to have "mild disease" according to the clinical classification. None of the patients required intensive care or intubation.

The mean duration of hospitalization was 9.48±2.0 (range, 4-13) days. The subgroup analysis showed that 48 of the 310 patients (15.4%) had a hospitalization period of more than nine days. The hospitalization duration of the patients with normal and abnormal CXR findings

were 9.75±2.6 and 9.47±2.0 days, respectively, and did not statistically significantly differ between the two groups (p = 0.78). Moreover, of the 48 patients who were hospitalized for more than nine days, five had abnormal and 20 had normal CT findings. The length of hospital stay of the patients with abnormal and normal CT findings were 10±0.70 and 8.75±2.75 days, respectively, and the difference was not statistically significant (p=0.21).

Control imaging was not required in any of the cases. Radiological or clinical progression was not observed in any of the patients.

Table 1. CXR and CT findings in the pulmonary radiological imaging of pediatric patients with COVID-19.

CXR findings	n (%)		CT findings	n (%)
Normal	290 (93.5%)		Normal	20 (6.5%)
Pathological	20 (6.5%)		Pathological	5 (1.6%)
Affected side			**Affected side**	
Unilateral	20 (6.5%)		Unilateral	5 (1.6%)
Bilateral	0 (0%)		Bilateral	0 (0 %)
Number of lesions			**Number of lesions**	
Single	20 (6.5%)		Single	5 (1.6%)
Multiple	0 (0%)		Multiple	0 (0%)
Affected zone			**Affected zone**	
Left middle zone	5 (1.6%)		Right lower zone	5 (1.6%)
Right lower zone	10 (3.2%)			
Left lower zone	5 (1.6%)			

CXR: Chest-X Ray. CT: Computed Tomography.

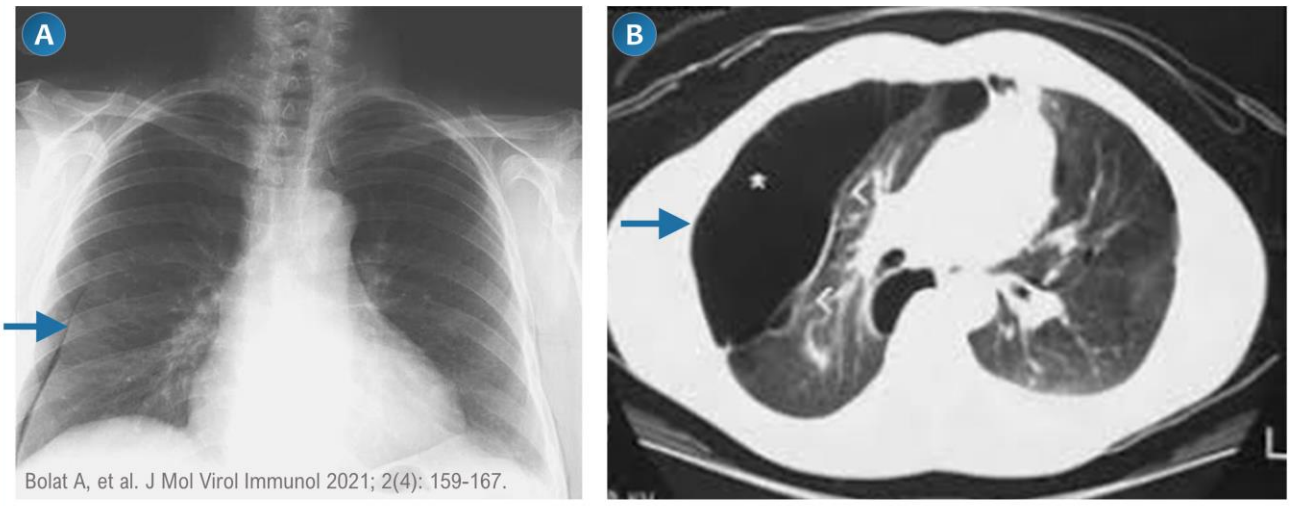

Figure 2. A 16-year-old female patient with COVID-19 presentied with the complaint of mild dyspnea. CXR image showing pneumothorax in the lower-right zone in (**A**). Axial thorax CT image showing the atelectatic parenchyma and pneumothorax in the lower-right zone (**B**).

Discussion

Typical initial or follow-up chest CT imaging findings in adults with COVID-19 pneumonia have recently been reported [8,9,21]. The most common typical findings in COVID-19 pneumonia are described as multifocal peripherally located GGO appearance accompanied by thickening of the interlobular septa, prominent vascular structures, and halo and reverse halo signs [5,19,21–23]. In a study including a small number

of patients (47 adults and 14 pediatric patients), CT positivity and degree of involvement were lower in the pediatric patients with COVID-19, while bronchial wall thickening was found to be relatively more frequent compared to the adults [24]. However, a systematic review on this subject suggested that chest CT findings were very similar between pediatric and adult patients [25]. In terms of distribution, lesions are more common in the lower lobes and spread to other regions within days the progression of the disease [9,26,27]. In an early study that included 866 respiratory samples from 213 patients, the sensitivity of RT-PCR was found to vary between 42.9% and 88.9%, depending on the stage of the disease and the type of clinical sample examined [28]. In the same study, it was noted that the rate of RT-PCR positivity was low, especially in throat swabs taken from mild cases. In addition, viral RNA could not be detected in some cases with typical viral pneumonia findings with GGO on CT [28]. In another presenting the data of 1,014 patients, Ai et al. reported the RT-PCR positivity as 59% and the CT scan positivity as 88% in adult patients with COVID-19 [29]. The authors stated that CT findings were correlated with clinical findings in the early stage of the disease where the first RT-PCR positivity had not yet been detected, and therefore CT could be useful in the early detection of suspicious cases [29].

Although adult studies have shown the importance of imaging in the diagnosis of COVID-19 pneumonia, our results suggest that CXR is sufficient and can be used instead of CT in the diagnosis and follow-up of children with mild dyspnea caused by COVID-19. We explored the value of initial CXR in the evaluation of children with COVID-19 in the hospital setting. Although it is emphasized in the literature that the sensitivity of CXR is low in the diagnosis of COVID-19, it is stated that early treatment can positively affect the healing process as in early diagnosis [30]. In support of this view, we observed no radiological deterioration in any of our patients.

Since COVID-19 disease predominantly affects adults, there are only a limited number of studies examining pulmonary imaging findings and the contribution of these findings to the diagnosis in pediatric population, and investigating their correlation with RT-PCR or comparing them to adults [24,25,31,32]. Due to the mild course of COVID-19 and avoidance of high-dose radiation load, CXR is primarily preferred instead of CT for the radiological evaluation of pediatric cases in the presence of clinical indications, but it cannot be used as a screening tool or routine supplementary test [5,33]. Indications for chest radiological imaging in pediatric patients with COVID-19 remain unclear, as their radiological findings are milder and less specific [5]. However, multisystem inflammatory syndrome related to coronavirus can develop in children, and since the clinical presentation of this disease is usually non-specific, radiological imaging may be important as an alternative diagnostic approach for early diagnosis [5,34]. In our study, CXR showed abnormal findings only 6.5% (20/310) of the cases. In a study conducted in Spain, CXR findings were found to be normal in 53% of the 35 symptomatic (respiratory distress and fever) pediatric patients with COVID-19, while the classic bilateral diffuse interstitial pattern was found in only 22% of the cases [5]. None of our patients required intensive care or intubation. We also did not find a statistically significant difference between the patients with normal and abnormal CXR findings in relation to the time from the onset of complaints to hospital admission or the length of hospital stay. This may be related to the early admission of patients to the hospital as a result of the active surveillance program implemented throughout Turkey. In a study of 95 pediatric patients with COVID-19 with a 20% intensive care unit admission rate, the most common CXR abnormalities identified were reported as GGOs/consolidations (35%) and increased peribronchial marking/cuffing (33%) [35].

As a general rule, also for COVID-19, the CXR sign of pneumonia is GGO due to consolidation [27,33]. The most common abnormal CXR finding in the patients included in our study was unilateral increase in intensity, and we observed that the lower lung zones were mostly affected, which is in line with the literature. In general, CXR is not recommended as a screening method for COVID-19 pneumonia due to its low sensitivity in the early stages of mild infection, as some variables

may affect CXR sensitivity [36]. Lesion detection with CXR increases in parallel with the worsening clinical prognosis in cases where hospitalization is delayed considering the onset of symptoms [10]. On the other hand, the chance of early admission to the hospital is a factor that can reduce the sensitivity of CXR. In the current study, the length of hospital stay was not statistically significantly differ between the patients with abnormal and normal CXR findings. In the literature, it has been suggested that CXR can be used in the diagnosis and follow-up of patients with lower respiratory tract infections [37]. However, according to our study data, the CXR findings did not predict long-term hospitalization.

Since the sensitivity of CXR (33-69%) is lower than CT in the diagnosis of COVID-19 [38], chest CT was also performed in all our patients with pathological CXR findings. In the pediatric population, diffuse GGO appearance was the most common finding in the chest CT studies similar to that in adults, followed by patchy consolidation [33,39]. In some studies, the most frequent involvement of COVID-19 pneumonia was reported as the bilateral diffuse interstitial pattern and multifocal involvement in children [5]. In our study group, single lobe involvement was observed in all cases while multifocal involvement was not detected in any of our cases. In a study including 130 young adults and 36 children, bilateral multiple distributions, subpleural involvement and pleural thickening, and GGOs with internal consolidation were reported to be more common in adults [32]. Lower lobar involvement and prevalence have been reported in children due to their lower immune response and milder inflammatory response [40]. Consolidation accompanying the GGO appearance may be a result of the progression of pneumonia due to the low immune response rate or the insufficient development of lung structures due to immaturity [40,41]. We did not detect multiple round GGOs or GGO with consolidation in our cases. Imaging may be normal at the beginning of the disease in adult cases and clinical and radiological deterioration can be seen later in the process. Radiological or clinical progression was not observed in any of our patients.

Institutions such as the Fleischner Society, ACR, and STR do not recommend CT for COVID-19 screening and diagnostic tests for infection control or diagnostic purposes in children [10–12]. However, it is emphasized that CXR can be preferred, especially in children with mild symptoms [11]. These professional radiology societies recommend that CT imaging be undertaken in symptomatic patients hospitalized with specific clinical indications or for the evaluation of complications such as abscess and empyema [11,12].

The main limitation of this study is its retrospective design and the possible observer bias in the interpretation of the results. Another limitation is the low number of cases in both the CXR and chest CT series.

Conclusion

The findings of this study suggest that the preference of CXR as the first imaging modality in pediatric patients with COVID-19 presenting with mild symptoms did not result in significant differences compared with CT. CXR can be used in symptomatic children to assess pneumonia and should be preferred in the diagnosis and treatment process when there is no clinical deterioration. CT should be used in the presence of pathological findings or complications on plain radiography and if clinically indicated.

Conflict of interest: The authors declare that there is no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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