









# Can laboratory findings predict pulmonary involvement in children with COVID-19 infection?

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## Abstract

**Background:** Studies investigating clinical and imaging findings of coronavirus disease 2019 (COVID-19) pneumonia and predictors for lung injury mostly focus on adults. In this study, we aimed to evaluate the role of laboratory findings in predicting lung involvement in children with COVID-19.

**Methods:** Children with COVID-19 confirmed by reverse-transcription polymerase chain reaction or COVID-19 IgM and who underwent chest computed tomography (CT) scans were reviewed retrospectively. Admission absolute neutrophil count (ANC), absolute lymphocyte count (ALC), ANC/ALC ratio, platelet count, D-dimer, fibrinogen, ferritin, procalcitonin, C-reactive protein (CRP), and lactate dehydrogenase levels were compared in patients with normal and abnormal CT scans.

**Results:** A total of 101 children were included. Among the patients, 68 (67.3%) had normal CT scans, and 33 (32.7%) had pulmonary involvement. The median CRP, ferritin, and fibrinogen levels were significantly higher in children with abnormal CT findings. The model of binary logistic regression based on the presence of cough, shortness of breath, fibrinogen, ferritin, and CRP levels showed that the possibility of having abnormal CT was 1.021 times more likely for every one unit increase in fibrinogen levels.

**Conclusion:** Fibrinogen might be useful to predict pulmonary involvement of COVID-19 in children. Restricting radiological imaging to patients with significant symptoms and high fibrinogen levels might be helpful in children with COVID-19 infections.

## KEYWORDS

children, COVID-19, CT scan, fibrinogen

## 1 | INTRODUCTION

Children have been reported to have a different disease course than adults with coronavirus disease 2019 (COVID-19) worldwide. Studies investigating clinical and imaging findings

of COVID-19 pneumonia and predictors for lung injury mostly focus on adults, and limited data are available for children. In this study, we aimed to evaluate the role of laboratory findings in predicting lung involvement in children with COVID-19.

## 2 | METHODS

This cross-sectional study was conducted in Dr. Behçet Uz Child Disease and Pediatric Surgery Training and Research Hospital which is a referral center for pediatric patients in the Aegean Region of Turkey. Between March 11, 2020, and December 25, 2020, a total of 101 pediatric COVID-19 patients, confirmed by real-time reverse-transcription polymerase chain reaction (RT-PCR) or antibody test (COVID-19 IgM), and who underwent chest computerized tomography (CT) scans were reviewed retrospectively. Demographic data and symptoms of the patients and admission C-reactive protein (CRP) levels, absolute neutrophil count (ANC), absolute lymphocyte count (ALC), ANC/ALC ratio, platelet (PLT) count, D-dimer, fibrinogen, ferritin, procalcitonin, and lactate dehydrogenase (LDH) levels were obtained from the electronic medical record system. Chest CT scans of the patients were reviewed by two radiology specialists. The extent of lung involvement was scored as a percentage of the total lung area: score 1, 1%–5% involvement; score 2, 6%–25% involvement; score 3, 26%–50% involvement; score 4, 51%–75% involvement; and score 5, greater than 75% involvement.

### 2.1 | Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 22; SPSS). Measurement data with normal distribution are expressed as mean  $\pm$  standard deviation (mean  $\pm$  SD). The Student's *t*-test was used to compare continuous parametric variables, the Mann-Whitney U test was used to compare continuous nonparametric variables, and  $\chi^2$  was used for categorical variables. A two-tailed *p* value of less than .05 was considered to be statistically significant. The odds ratio (95% CI) was calculated for risk factors for positive CT findings and dependent variables with *p* < .05 were included in the univariate analysis. Adjusted odds ratios for risk factors were determined by using these variables in a stepwise forward logistic regression model. Ethics approval for this study was obtained from the Institutional Review Board of Dr. Behçet Uz Children's Hospital.

## 3 | RESULTS

One hundred and one children with confirmed COVID-19 infection and pulmonary CT scans were included in the study. Of the patients, 47 (46.5%) were male and 54 (53.5%) were female. The mean age of the patients was 14.1  $\pm$  2.4 years (range 6–18 years). Regarding the age distribution, 22.8% of the patients were between 6 and 12 years, 77.2% were 13 years and over. The most common presenting symptoms were fever (43.6%) and cough (33.7%) (Table 1). In the group with pulmonary involvement based on CT findings, the mean age was 13.7  $\pm$  2.8 years (ages 6–18) and there were 17 males (51.5%) and 16 females (48.5%); while in the group without pulmonary involvement, the mean age was 14.3  $\pm$  2.1 years (ages 9–18)

**TABLE 1** Demographic features and symptoms of the patients

	Patients with CT findings (n = 33)	Patients without CT findings (n = 68)	<i>p</i> value
Age (years)	13.7 $\pm$ 2.8 (6–18)	14.3 $\pm$ 2.1 (9–18)	>.05
Gender	<i>n</i> (%)	<i>n</i> (%)	
Male	17 (51.5)	30 (44.1)	>.05
Female	16 (48.5)	38 (55.9)	
Symptoms	<i>n</i> (%)	<i>n</i> (%)	
Fever	15 (45.5)	29 (42.6)	>.05
Cough	17 (51.5)	17 (25)	.008
Shortness of breath	8 (24.2)	4 (5.9)	.017
Headache	6 (18.2)	17 (25)	>.05
Chest pain	5 (15.2)	8 (11.8)	>.05
Fatigue	7 (21.2)	7 (10.3)	>.05
Anosmia	5 (15.2)	7 (10.3)	>.05
Diarrhea	6 (18.2)	8 (11.8)	>.05
Sore throat	6 (18.2)	9 (13.2)	>.05
Myalgia	3 (9.1)	8 (11.8)	>.05

Abbreviation: CT, computed tomography.

there were 30 males (44.1%) and 38 females (55.9%). There was no significant statistical difference of gender and mean age between the two groups (*p* > .05). The most common presenting symptom was fever (45.5% vs. 42.6%) in both groups. The mean duration of fever was 2.85  $\pm$  2.04 days (range 1–6 days) in the group with pulmonary involvement and 1.83  $\pm$  1.34 days (range 1–7 days) in the group without pulmonary involvement. There was no statistical significance in fever duration between the two groups (*p* > .05). Cough was two times (51.5% vs. 25%) and shortness of breath was four times more common (24.2% vs. 5.9%) in the group with pulmonary involvement versus no pulmonary involvement and the difference was statistically significant (*p* = .008 vs. *p* = .017, respectively). There was no statistical significance in headache, chest pain, fatigue, anosmia, diarrhea, sore throat, and myalgia between the two groups.

Among the patients, 68 (67.3%) had normal CT scans, and 33 (32.7%) had pulmonary involvement. Unilateral involvement was present in 19 (57.6%) children and bilateral involvement was present in 14 (42.4%) children. The most common infiltrated lobe was the right lower lobe in 18 cases (54.5%) and left lower lobe in 21 (63.6%), followed by the right upper lobe in 11 (33.3%), left upper lobe in 6 (18.2%), and right middle lobe in 8 (24.2%) children. The presence of pure ground-glass opacity was observed in 72.7% of the CT scans. Chest CT findings of children were summarized in Table 2. Regarding lung involvement scores, 12 (36.4%) patients had a score of 1, 14 (42.4%) had a score of 2, 4 (12.1%) had a score of 3, 2 (6%) had a score of 4, and only 1 patient had a score of 5. (Table 2)

**TABLE 2** CT findings of the patients

	Number of patients (%)
Affected lung side	
Unilateral	19 (57.6%)
Bilateral	14 (42.4%)
Affected lung field	
Central location	4 (12.1%)
Peripheral location	21 (63.6%)
Both central and peripheral location	8 (24.2%)
CT features	
Ground glass opacity	24 (72.7%)
Consolidation	3 (9.09%)
Ground glass opacity and consolidation	3 (9.09%)
Other (semisolid nodular infiltration or reticulonodular infiltration)	3 (9.09%)
Affected lung lobe	
Right upper lobe	11 (33.3%)
Right middle lobe	8 (24.2%)
Right lower lobe	18 (54.5%)
Left upper lobe	6 (18.2%)
Left lower lobe	21 (63.6%)
Lung involvement score <sup>a</sup>	
Score 1	12 (36.4%)
Score 2	14 (42.4%)
Score 3	4 (12.1%)
Score 4	2 (6%)
Score 5	1 (3%)

Abbreviation: CT, computed tomography.

<sup>a</sup>Extent of lung involvement was scored as a percentage of the total lung area: score 1, 1%–5% involvement; score 2, 6%–25% involvement; score 3, 26%–50% involvement; score 4, 51%–75% involvement; and score 5, greater than 75% involvement.

### 3.1 | Comparing the patients with abnormal and normal CT results

As mentioned in Section 3, cough was two times (51.5% vs. 25%) and shortness of breath was four times more common (24.2% vs. 5.9%) in the group with pulmonary involvement vs no pulmonary involvement and the difference was statistically significant ( $p = .008$  vs.  $p = .017$ , respectively) (Table 1).

The median CRP value was 1.2 mg/dL (range 0.2–19.9 mg/dL) in the subjects with abnormal chest CT and 0.2 mg/dL (range 0.1–8.5 mg/dL) in the subjects with normal CT findings and the difference between the two groups are statistically significant ( $p = .036$ ). The median ferritin and fibrinogen values in the subjects

with abnormal CT findings were also higher compared with the subjects with normal CT findings ( $p < .001$  vs.  $p = .012$ ). The ALC, ANC, ANC/ALC ratio, PLT count, LDH, procalcitonin, and D-dimer levels were not significantly different in these two groups (Table 3).

### 3.2 | Logistic regression analysis of factors affecting the pulmonary involvement on CT scans

The model of binary logistic regression was calculated to predict pulmonary involvement of COVID-19 on CT scans based on the presence of cough, shortness of breath, fibrinogen, ferritin, and CRP levels. The full model containing all predictors was statistically significant  $\chi^2$  ((5,  $N = 101$ ) = 69.6,  $p < .001$ ) suggesting that the model was able to distinguish between the patients with abnormal CT and normal CT. As shown in Table 4, only the independent variables of fibrinogen levels made a unique statistically significant contribution to the model.

The odds ratio of 1.021 for fibrinogen level indicated that for every one unit increase in fibrinogen, there was a 1.021 times greater risk of having abnormal CT, controlling for other factors in the model.

## 4 | DISCUSSION

In this study, consistent with the literature, fever, and cough were the most common presenting symptoms, and CT findings were generally mild (Score 1 and Score 2).<sup>1</sup> While CRP, fibrinogen and ferritin levels differ significantly in patients with pulmonary involvement, ALC, ANC, LDH, D-dimer, PLT, procalcitonin, and ANC/ALC ratio were similar compared with the patients with no pulmonary findings. In our study, only fibrinogen level was found to be an independent risk factor for pulmonary involvement on CT scans.

Studies regarding the immune response to COVID-19 in children are limited compared to adults.<sup>2</sup> As a result, the reason for the mild clinical picture in children is based on hypotheses only. One of the theories is children trigger a milder inflammatory response because they produce a more controlled immune response, have fewer comorbidities that predispose to a pre-existing pro-inflammatory state, and they have relatively lower viral loads.<sup>2</sup> Another theory is the age-related differences in ACE2, which is defined as a key factor of the inflammatory processes established in conditions such as lung injury and sepsis.<sup>3</sup> It was reported that a higher concentration of ACE2 in pneumocytes provides protection for the pediatric age group against the severe clinical manifestations of COVID-19.<sup>4,5</sup> All these assumptions suggest that laboratory findings may not change significantly in children.

Previous studies in adults have identified hematologic, biochemical, and inflammatory biomarker abnormalities in patients with severe disease compared to mild systemic disease. In our study, the logistic regression model suggested only one parameter among the studied ones could estimate the presence of pulmonary involvement on CT.

**TABLE 3** Laboratory test results of the patients

Laboratory parameters	Patients with abnormal CT		Patients with normal CT		p value
	N	Median/mean ± SD (min.-max.)	N	Median/mean ± SD (min.-max.)	
CRP (mg/dL)	33	1.2/1.93 ± 4.36 (0.2–19.98)	67	0.2/0.63 ± 1.53 (0.1–8.5)	.036
ALC (/μl)	33	1770/2037 ± 1048 (590–4550)	68	1680/1777 ± 858 (360–4820)	>.05
ANC (/μl)	33	3780/4167 ± 2907 (1260–14860)	68	2870/3441 ± 2572 (850–20520)	>.05
ANC/ALC	33	1.84/2.46 ± 1.78 (0.49–6.83)	68	1.57/3.21 ± 7.06 (0.47–57)	>.05
PLT (/μl)	33	253000/270788 ± 68619 (130,000–462,000)	68	244500/244412 ± 61810 (114,000–391,000)	>.05
Procalcitonin (ng/ml)	24	0.01/3.96 ± 15.61 (0.01–75)	51	0.01/0.67 ± 0.34 (0.01–0.48)	>.05
Ferritin (μg/L)	18	72.62/107.8 ± 169.19 (16.61–774.61)	46	40.46/49.94 ± 33.86 (7.4–157.1)	.012
LDH (IU//L)	23	185/259.57 ± 312.166 (133–1678)	52	176.50/188.06 ± 133.4(11–1094)	>.05
D-dimer (ng/ml)	18	216.5/463.78 ± 712.051(150–3037)	15	211/297.53 ± 249.52 (70–1045)	>.05
Fibrinogen (mg/dL)	30	341.5/357.50 ± 113.48 (210–735)	55	259/275.56 ± 77.237(169–536)	.000

Abbreviations: ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CRP, C-reactive protein; CT, computed tomography; LDH, lactate dehydrogenase; PLT, platelet; SD, standard deviation.

**TABLE 4** Logistic regression analysis of factors affecting the pulmonary involvement

	B	Odds ratio	p value	95% CI
Fibrinogen	0.021	1.021	.004	1.007–1.036
Ferritin	–0.007	0.993	.382	0.977–1.009
CRP	0.329	1.389	.702	0.258–7.486
Cough	1.034	2.813	.197	0.584–13.557
Shortness of breath	1.102	3.011	.206	0.206–43.980

Abbreviations: CI, confidence interval; CRP, C-reactive protein.

While severe cases in previously published studies were shown to have lower lymphocyte-, higher leukocyte-counts, and higher ANC/ALC ratio,<sup>6–10</sup> in our study these parameters were not significantly different which supports the course of the disease is somehow different from the adults. A meta-analysis reviewing the prognostic value of 36 laboratory parameters concluded that cohorts with high levels of white blood cell count, neutrophil count, D-dimer, fibrinogen, and procalcitonin were more likely to progress to severe disease.<sup>11</sup> Also, increased levels of serum ferritin were observed among nonsurvived patients compared with survived patients.<sup>11,12</sup> Decreased lymphocyte count and LDH, which is released from cells upon damage of their cytoplasmic membrane, was shown to have a strong relationship with lung involvement and to be positively associated with CRP while negatively associated with lymphocyte count.<sup>13,14</sup> In another study that included 11 COVID-19 infected adults and one adolescent, the relationship between lung injury (according to Murray score of ARDS<sup>15</sup>) and laboratory findings were evaluated. Albumin, lymphocyte count and ratio, LDH, neutrophile ratio, and CRP were found to be highly correlated with acute lung injury.<sup>16</sup>

A systematic review including 551 pediatric patients with laboratory-confirmed COVID-19 infection reported that only a small proportion of pediatric cases had abnormal laboratory

results. While lymphocytosis (35%) and increased LDH (29%) were the most prevalent laboratory abnormalities, increased CRP (17%), procalcitonin (10%), and D-dimer (12%) levels were less frequent.<sup>1</sup> Sun et al.<sup>17</sup> reported normal CRP levels in 37.5% of children requiring intensive care. In a review of 92 pediatric studies, while lymphocytosis was present in 44% of the children, the lymphocytopenia rate was only 17.5%. The low prevalence was explained by the high frequency of mild cases.<sup>18</sup>

Whereas the laboratory changes are well-defined, little is known about their correlation with CT findings. Tan et al.<sup>19</sup> reported that CRP ( $R = .62$ ;  $p < .01$ ), and granulocyte/lymphocyte ratio ( $R = .49$ ;  $p < .01$ ) were positively associated with the CT severity scores while the number of lymphocytes ( $R = -.37$ ;  $p < .01$ ) was negatively correlated. The reason why the ANC/ALC ratio is not an indicator for lung involvement might be that the mean ALC values in both groups were in the normal ranges, possibly due to the mild course of disease in both groups consistent with the pediatric studies in the literature. In another study, CRP levels were found to be highly correlated with the diameter of lung lesions and severe presentation.<sup>20</sup> In our study, in addition to the literature, fibrinogen, and ferritin levels were also significant markers of lung involvement. We hypothesize that this finding is a result of the cytokines produced by macrophages, which constitute the highest number of immune cells in lung parenchyma.<sup>21</sup>

During viral infections, the fever is a manifestation of the body's immune response to the viral replication to augment immunity.<sup>22</sup> However, if the viral infection is not restricted by the initial immune response, the course of the disease is complicated by the dysregulated inflammatory state and cytokine storm, manifested by persistent fever. On this basis, persistent high fever in COVID-19 is considered an indicator of severe infection and is associated with a higher likelihood of acute respiratory distress syndrome.<sup>23</sup> In our

study, fever was not a factor affecting pulmonary involvement. The possible reason was that the fever response in all patients was short-term and not persistent.

This study has several limitations. First, as a result of the retrospective design of the study, only the parameters obtained at the time of admission could be evaluated. Although the sample size is statistically sufficient, the study should be repeated in larger patient groups. Second, as this was a cross-sectional and retrospective study, ongoing changes in the laboratory parameters and CT images could not be evaluated.

In conclusion, fibrinogen may be useful to predict pulmonary involvement of COVID-19 in children. Restricting radiological imaging such as CT scans to patients with significant symptoms and high fibrinogen levels might be helpful in children with COVID-19 infections.

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#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

#### AUTHOR CONTRIBUTIONS

**Elif Böncüoğlu:** data curation (lead); writing original draft (lead); writing review & editing (equal). **Mehmet Coşkun:** data curation (equal); methodology (equal). **Elif Kıymet:** data curation (supporting); writing original draft (supporting). **Şahika Şahinkaya:** data curation (supporting). **Ela Cem:** data curation (supporting). **Mine Düzgöl:** data curation (supporting). **Kamile Ötiken Arıkan:** data curation (equal). **Nuri Bayram:** methodology (equal); writing original draft (equal); writing review & editing (equal). **İlker Devrim:** formal analysis (lead); methodology (equal); project administration (lead); supervision (lead); writing review & editing (equal).

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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