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The Predictors of Pneumonia in Children with COVID-19

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Abstract

The purpose of this study was to evaluate the relationship between the presence of pneumonia and blood parameters in cases of Coronavirus disease (COVID-19) and to examine their predictive characteristics in terms of pneumonia. We reviewed the file records of 151 pediatric patients with a diagnosis of COVID-19 confirmed by the real time-reverse transcription polymerase chain reaction test in nasopharyngeal swabs. The patients were divided into two groups based on direct chest X-ray and computed tomography results in [Group 1 (n:41), with pneumonia findings, and Group 2 (n:110), with no pneumonia findings]. The groups' demographic data, clinical and laboratory findings were compared. Pulmonary involvement was determined in 41 (27.1%) of the 151 patients. The [body mass index (BMI) Z-score], red blood cell distribution width (RDW), mean platelet volume (MPV), neutrophil lymphocyte ratio, passive leg raise, and D-dimer levels were significantly higher in patients with pneumonia than those without pneumonia in our study. Based on multivariate logistic regression analysis, BMI Z-score, MPV, and RDW were found to be independent risk factors of pneumonia in patients. The current study showed higher levels of blood parameters in patients with coronavirus disease 2019 (COVID -19) presenting with pneumonia than those without pneumonia. We suggest that BMI-Z score and MPV value may assist in predicting pulmonary involvement in patients with COVID-19.

Keywords: Children with COVID-19, pneumonia, body mass index, hematological parameters

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Introduction

Coronavirus disease (COVID-19) has spread rapidly across the world since it was initially declared a pandemic by the World Health Organization on 11 March 2020[1]. The disease involves a wide spectrum, ranging from asymptomatic infection to severe pneumonia, acute respiratory distress syndrome, multiple organ failure, and death. In children, it is generally mild or moderate. However, pneumonia and systemic involvement have been reported in severe cases[2]. COVID-19 pneumonia is highly contagious, with a reported prevalence in children of 1.7-2.4%[3]. Due to its rapid progression and potentially fatal course, appropriate diagnostic and therapeutic approaches are of vital importance. The real-time reverse transcription-polymerase chain reaction (RT-PCR) is the primary method in the diagnosis of COVID-19. However, particularly in the early period from the disease or in the case of a low viral load, nasopharyngeal swab (RT-PCR) tests can be negative[4]. Pulmonary computed tomography (CT) and chest X-ray play an significant in the diagnosis of COVID-19, in the evaluation of the severity of pneumonia, in the detection of potential complications such as pulmonary embolism or pneumothorax, and patient follow-up[5]. A chest X-ray is the imaging method of choice for protection against radiation in children with suspected COVID-19 pneumonia. However, thoracic CT can be applied when necessary for diagnosis and treatment evaluation. Due to the low number of pediatric cases, and their milder clinical course, studies on the subject in the literature are insufficient[6]. The severe inflammatory reactions in COVID-19 can result in a cytokine storm and death. The immune response and cellular breakdown triggered by the rapid viral replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lead to monocyte and macrophage accumulation and cytokine and chemokine release. Increased release and transcription of proinflammatory cytokines result in the elevated plasma levels cytokines and may lead to a cytokine storm[7].

Highlights

- COVID-19 pneumonia in children is seen with a frequency of 1.7-2.4%, and due to its rapid progression and fatal course, appropriate diagnosis and treatment approaches are vital.
- COVID-19 pneumonia can be severe in children, and we think that high BMI Z-score, MPV, NLR, PLR and D-dimer values are very important for rapid diagnosis and guiding treatment.
- We detected BMI-Z score, MPV and RDW values as independent risk factors in predicting pulmonary involvement in children with COVID-19.

Mutual interaction has been shown between these cytokines and several blood parameters in acute inflammation[8]. The predictive rate of peripheral blood parameters, the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), red cell distribution width (RDW), and C-reactive protein (CRP) in determining the prognosis in systemic inflammatory diseases is still the subject of research. WBC count, NLR, PLR, and the lymphocyte-monocyte ratio are systemic inflammatory response markers employed as useful predictors of prognosis in viral pneumonia[9]. The aim of the study was to evaluate the association between blood parameters and pneumonia in cases of COVID-19 and to examine their predictive characteristics in terms of pneumonia.

Material and Method

Participants

In this retrospective study, 151 pediatric patients who were hospitalized in our Pediatrics Clinic between 01 May 2020 and 01 July 2021 and whose diagnosis of COVID-19 were confirmed by RT-PCR test on nasopharyngeal swabs were included in this retrospective study. Our study was carried out in accordance with the Declaration of Helsinki the patients and their families who participated in the study gave informed and written consent. The study protocol was approved by the local committee (Bolu Abant İzzet Baysal University Clinical Research Ethics Committee) for human studies (decision no: 2021/208, date no: 27.07.2021). Patients were seperated into two groups depending on their posterior-anterior direct chest X-ray and thoracic CT findings Group 1 (n:41) patients with pneumonia findings, and Group 2 (n:110), patients without pneumonia findings. Demographic data of patients from their file records and hemoglobin, hematocrit, mean erythrocyte volume, RDW, WBC count, neutrophil, lymphocyte and platelet counts, mean platelet volume (MPV), platelet distribution width, thrombocytcrit and glucose, aspartate aminotransferase, alanine aminotransferase, urea, creatinine, lactate dehydrogenase (LDH), fibrinogen and CRP levels at admission were evaluated. NLR and PLR values were calculated by dividing absolute neutrophil and platelet counts by lymphocyte counts, respectively, and body mass index (BMI) was calculated by dividing body weight (kg)/height^2 (m^2)[10]. The groups demographic data and clinical and laboratory findings were compared. Chest CT and chest X-ray findings were scanned and analyzed by two senior radiologists blinded to the identities and clinical data of the patients.

Statistical Analysis

Normality of variables was evaluated using the Shapiro-Wilk test. Descriptive statistics were obtained. Normally distributed continues variables were expressed as mean ± SD, while non-normally distributed numerical variables were expressed as median and interquartile range values. Categorical variables presented as number (percentages). Normally distributed continues variables were analyzed using the Student's t-test, and non-normally distributed numerical data using the Wilcoxon Rank Sum test. Categorical variables were analyzed using the chi-square (χ^2) test. Multiple explanatory variable logistic regression analysis was applied to determine the risk factors/covariates

for pneumonia. The initial model was fit including all significant independent variables. Then, a backward-elimination approach was conducted to evaluate the model for potential confounding effects. In this model, the factors/covariates were removed one at a time, starting with the factor/covariate that had the largest p value, until all remaining factors had a two-sided p value <0.05. The goodness of fit was tested using the Hosmer-Lemeshow test. Receiver-operating characteristic (ROC) curve analysis was used to determine the cutoff values of selected variables, via logistic regression, for pneumonia from the area under the curve (AUC). ROC curve analysis is carried out using "Optimal Cutpoints" library of R software. All statistical analyses were performed using the R software. A p value <0.05 were regarded as statistically significant for all analyses.

Results

COVID-19 pneumonia was present in 41 (27.2%) of the 151 patients. No pulmonary involvement was present in the other 110 (72.8%) patients. RT-PCR tests in terms of SARS-CoV-2 were positive in all patients. Ninety-three (61.6%) patients were boys, and 58 (38.4%) were girls. Pneumonia was detected in 25 (26.9%) boys and 16 (27.6%) girls. There was no significant difference between Group 1 and Group 2 in terms of the incidence of pneumonia. Unilateral right lung involvement and left lung involvement were observed in 16 (39.02%) and 6 (14.6%) on posterior-anterior chest X-rays of the 41 patients with pneumonia findings, respectively. Bilateral, predominantly peripheral multifocal involvement and consolidation areas were determined in 19 (46.34%) patients. The lower regions of the lungs were the most affected, with the right lower zone being affected in three patients (7.31%) and the left lower and left middle zones in two (4.87%). The right middle zone was affected in 13 patients (31.70%), the left middle zone in two (4.87%), and the left upper zone in two (4.87%) (**Figure 1**).

Bilateral diffuse peripheral predominant ground-glass opacities were determined in six (54.5%) of the 11 patients who underwent pulmonary CT, and unilateral diffuse peripheral predominant ground-glass opacities in five (45.5%). In those with unilateral pulmonary involvement, a diffuse ground-glass appearance was follow up in the right lung in 3 patients and the left lung in 1 patient, and a peripheral ground glass appearance was present in the left lung in one patient (**Figure 2**).

There was no statistically significant difference between the groups in terms of age, gender, length of hospital stay, ferritin, sedimentation, CRP or LDH values. Mean BMI value, BMI Z-score, NLR, PLR, and MPV values, and D-dimer levels were significantly higher among patients with pneumonia compared to those with no pneumonia (p<0.05), while mean lymphocyte and RDW values were significantly lower (p<0.05) (**Table 1, 2** and **Table 3**).

Multivariate logistic regression analysis and ROC analyses in terms of predicting pneumonia were also performed with the BMI Z-score, MPV, and RDW parameters that differed significantly between the groups. On the basis of multivariate logistic regression analysis, BMI Z-score [odds ratio (OR): 2,946, 95%

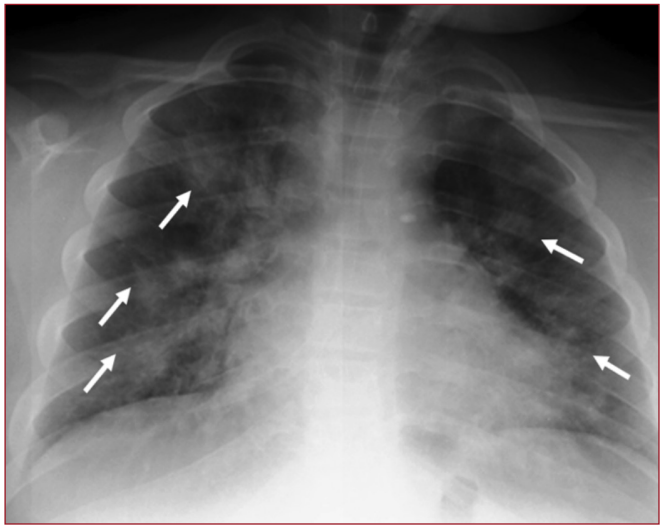

Figure 1. Posteroanterior chest X-ray showing consolidation areas (arrows) in all zones in the bilateral pulmonary parenchyma in a 10-year-old girl

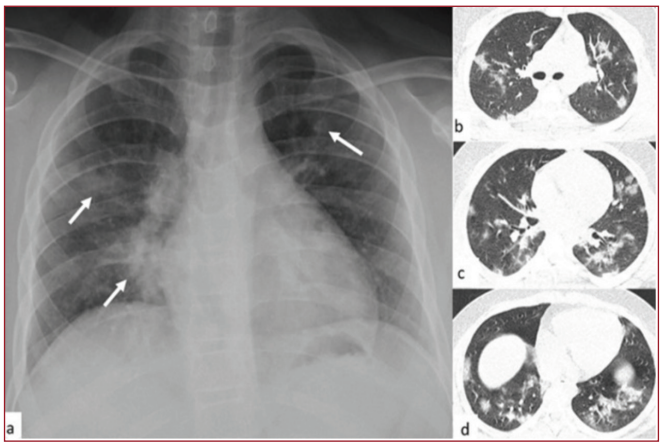

Figure 2. Posteroanterior chest X-ray and non-contrast axial CT section parenchymal window in a 15-year-old boy: Diffuse peripheral and peribronchovascular ground glass and consolidation areas in all zones of the bilateral parenchyma at lung-X-ray (a, arrow), and in the upper lobes (b), and in the middle lobe of the right lung and bilateral lower lobes (c, d) at computed tomography

CT; Computed tomography

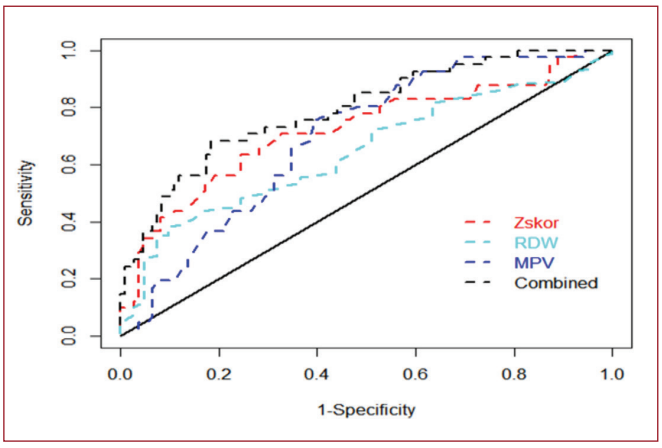

Figure 3. Receiver-operating characteristic curve for body mass index (BMI) Z Z-score, red cell distribution width (RDW), MPV and combined (MPV, RDW, BMI Z-score) parameters in the prediction of pneumonia in patients with Coronavirus Disease of 2019

MPV; Mean platelet volume, RDW; Red blood cell distribution width, BMI; Body mass index

Table 1.
Demographic, anthropometric and clinical characteristics of COVID-19 patients with pneumonia and COVID-19 patients without pneumonia

Covıd-19					
	Pneumonia-negative		Pneumonia-positive		
Variables	**n (110)**	**Median (IQR)**	**n (41)**	**Median (IQR)**	**p value**
Age (months)		60 (1-204)		120 (2-204)	0.11*
BMI		51 (3-95)		74 (6-100)	**0.00***
BMI Z-score		0.03 (-3.0-1.6)		0.6 (-1.5-3.5)	**0.00***
Hospitalization		4 (1-22)		5 (2-14)	0.14*
Gender					
Male	68		25		0.92**
Female	42		16		

*Data incompatible with normal distribution. Wilcoxon rank sum test was applied as the statistical technique, the results being expressed as median (IQR)
**The Pearson chi-square test was used in the analysis of categorical variables at two independent group analysis
IQR; Inter quantile range, BMI; Body mass index

Table 2.
Comparison of hematological parameters of COVID-19 patients with pneumonia and COVID-19 patients without pneumonia

Covıd-19					
	Pneumonia-negative		Pneumonia-positive		
Variables	**n (110)**	**Median (min.-max.)**	**n (41)**	**Median (min.-max)**	**p value**
WBC (x10^3/L)		6.56 (1.1-26.8)		6.96 (2.99-17.77)	0.85
Neutrophils (x10^3/L)		2.57 (0.27-11.3)		3.16 (0.67-15.3)	0.14
Lymphocytes (x10^3/L)		2.4 (0.54-14.5)		2.06 (0.58-7.8)	**0.043**
Hemoglobin (g/dL)		13 (8.5-18.6)		13 (10.1-19.3)	0.26
Hematocrit (%)		38 (28-62)		38 (29-66)	0.64
MCV (fl)		79 (75-101)		80 (77-101)	0.19
RDW (%)		13.1 (11.1-37.1)		12.6 (11.4-16.9)	**0.005**
PLT (x10^3/L)		299 (83.2-880)		292 (156-880)	0.96
MPV (fl)		10.2 (5.3-17.7)		11.1 (6.5-17.1)	**0.0002**
PCT (%)		0.23 (0.1-0.79)		0.26 (0.1-0.53)	0.68
PDW (%)		16.8 (8-18.60)		16.9 (15.6-18.6)	0.25
NLR (%)		1.1 (0.004-10.36)		1.6 (0.1-12.4)	**0.021**
PLR (%)		0.11 (0.01-0.59)		0.14 (0.02-0.56)	**0.027**

*Values are median (min.-max), p value obtained via Mann Withney-U test
WBC; White blood cell, MCV; Mean corpuscular volume, RDW; Red blood cell distribution width, PLT; Platelet, MPV; Mean platelet volume, PCT; Procalcitonin, PDW; Platelet distribution width, NLR; Neutrophil-lymphocyte ratio, PLR; Platelet-lymphocyte ratio, Min.-max; Minimum-maximum

Table 3.
Comparison of biochemical parameters of COVID-19 patients with pneumonia and without pneumonia

Covıd-19					
	Pneumonia-negative		Pneumonia-positive		
Variables	**n (110)**	**Median (min.- max.)**	**n (41)**	**Median (min.-max)**	**p value**
CRP (mg/dL)*		0.7 (0.1-96)		2.31 (0.1-160)	0.24
LDH (U/L)*		260 (150-625)		311 (143-726)	0.18
D-dimer (mg/L)*		0.40 (0.16-11)		0.5 (0.19-8.86)	**0.01**
AST (U/L)*		30 (9-214)		32 (12-77)	0.92
ALT (U/L)*		18 (6-94)		18 (7-179)	0.50
Urea (mg/dL)*		21 (4-50)		19 (9-39)	0.74
Creatinine (mg/dL)**		0.53 (±0.12)		0.57 (±0.14)	0.08
Glucose (mg/dL)*		91 (57-149)		95 (69-148)	0.21
Ferritin* (µg/L)		32 (4.6-794)		42 (5.7-820)	0.12
Sedimentation*(mm/h)		13 (1-32)		15 (2-51)	0.05
CK* (U/L)		97 (18-4,267)		86 (29-701)	0.15

*: Values are median (min.-max.), P value obtained via Mann Withney-U test
**: Values are mean ± SD, P value obtained via t-test
CRP; C-reactive protein, LDH; Lactate dehydrogenase, CK; Creatine kinase, Min.- max.; Minimum-maximum

confidence interval (CI): 1.701-5.668, p=0.00), MPV (OR: 1.219, 95% CI: 1.026-1.461, p=0,001), and RDW (OR: 0.617, 95% CI: 0.429-0.835, p=0.001) were independent risk factors of pneumonia in patients with COVID-19. ROC curve analysis showed that the AUC of MPV in group pneumonia was 0.694 (95% CI: 0.607-0.782), with the diagnostic sensitivity 75.60% and specificity 60.55%; AUC of BMI-Z score was 0.721 (95% CI: 0.621-0.821), with sensitivity 63% and specificity 75%; AUC of RDW was 0.646 (95% CI: 0.554-0.739), with sensitivity 81% and specificity 90%; AUC of BMI-Z score, RDW combined with MPV

was 0.792 (95% CI: 0.71-0.874), with the diagnostic sensitivity 95.40% and specificity 80%. The optimal cut-off values for the MPV, BMI-Z score and RDW and to be able to differentiate pneumonia patients were 10.5, 0.42 and 14.2, respectively. (**Figure 3**)

Discussion

COVID-19 infection is generally milder in children. This may be due to the lower social isolation, frequencies of comorbidity, and low smoking rates among children compared to adults, together with their greater pulmonary regeneration capacity and lower angiotensin converting enzyme expression[11]. A study involving 2,143 children in China reported that severe and critical cases were observed at rates of 10.6% in patients aged under one year, 7.3% in those aged 1-5 years, 4.3% in those aged 6-10, 4.1% in those aged 11-15, and 3% in children aged over 16[12]. Pulmonary involvement can be detected in most children hospitalized for follow-up. Pneumonia was detected in 81 (65.8%) out of 123 children who underwent CT of the lung in a study from China. Right lung involvement was observed in 17 (13%) of these 81 children, left lung involvement in 35 (28%), and bilateral pulmonary involvement in 29 (23%)[13]. In the present study, pulmonary involvement was detected in 41 (27.1%) patients assessed by means of chest X-ray and/or CT. Bilateral peripheral predominant multifocal involvement and consolidation areas were present in 19 (46.35%) of these patients. Moreover when patients who had undergone pulmonary CT were considered merely, bilateral involvement was determined in six (54.5%) of these patients Chest CT has a important for diagnosis of COVID-19. Most children with COVID-19 experience mild illness. Pulmonary involvement on CT is often less extensive than in adults[14]. For these reasons, in order to balance the risk of radiation and necessity for chest CT, we performed chest CT in selected patients who had had increased breath rate with a blood oxygen saturation at rest < 92% or those with disease progression during hospitalization[15].

Performing early risk stratification by evaluating abnormal clinical findings and laboratory findings together in COVID-19 patients will enable at risk of respiratory failure, multiple organ failure, and even death[16]. Indeed, BMI Z-score, MPV, NLR, PLR, and D-dimer levels were significantly higher in patients with pneumonia. While there was no significant difference between the patient groups in terms of CRP, LDH and ferritin levels, mean CRP, LDH and ferritin levels were found to be higher in patients with pneumonia. Based on our multivariate logistic regression analysis results, we found that BMI Z-score, MPV, and RDW were independent risk factors for pneumonia in COVID-19 patients. Obesity exacerbates the risk of serious COVID-19 in children. The impaired pulmonary functions in obesity, immune and thrombogenic responses to pathogens are also compromised[17]. One multicenter study reported a high rate of obesity among children hospitalized due to COVID-19[18]. In this study, BMI Z-scores were significantly higher in patients with pneumonia. A positive correlation was observed between BMI Z-score and inflammatory markers. We think that obesity increases the severity of inflammation and induces disease progression in children patients with COVID-19. Several studies have reported that hematological markers, the peripheral blood levels of cytokines, and coagulation parameters such as CRP, neutrophil count, D-dimer, NLR, and PLR increase considerably in contrast with T lymphocytes in severe forms of COVID-19[19].

However, the majority of laboratory data in COVID-19-associated pediatric patients comes from case reports or a small number of observational studies. The most frequently reported coagulation/fibrinolytic abnormality associated with COVID-19 is an increase in D-dimer levels[20]. D-dimer is a cross-linked fibrin degradation product produced when plasmin breaks down fibrin to break up clots. D-dimer reflects the functioning normally of coagulation and fibrinolysis systems[21]. Recent studies have reported that severity of the disease and prognosis are associated with D-dimer level elevation in patients hospitalized due to severe COVID-19[22].

COVID-19, infection of bone marrow increased platelet breakdown due to immune system activation, and greater platelet accumulation in the lungs leads to thrombocytopenia[23]. A decreased platelet count increases platelet production and the proportion of more functionally active young platelets. MPV rises as a result. It has been found that there is an increase in MPV values in severe COVID-19 patients, particularly those with risk of mortality[24]. A study involving adult patients with COVID-19 reported that a one-unit increase in MPV resulted in a 1.76-fold increase in the risk of mortality[25]. Similarly in this study, MPV values were significantly higher in patients with COVID-19-associated pneumonia. We suggest that the higher levels of D-dimer together with higher values of MPV and LDH might be highlighting the possibility of more obvious activation of the coagulation system induced by prominent inflammatory responses and dysfunction of endothelial cells in patients with pneumonia in our study. RDW indicates heterogeneity in size of erythrocytes and anisocytosis in red blood cells. Anisocytosis may present with impaired erythropoiesis in inflammation-related diseases and renal dysfunction with insufficient erythropoietin production[26].

An association between increased mortality in COVID-19 patients and decreased RDW levels has been reported[27]. Low RDW values have been reported in COVID-19 patients with severe pneumonia, while RDW levels increase together with improvement[28]. In this study, RDW was significantly lower in patients without pneumonia, but the mean RDW values of both groups were within normal limits. This finding, which emerged in our study, may indicate that the severity of inflammation did not increase at a level that would affect RDW in patients with pneumonia. Due to the cross-sectional and single-center nature of this study, the small number of patients in the groups, and the fact that the number of patients without pneumonia was 2.68 times higher than that of those with pneumonia, the lower mean RDW value in patients with pneumonia should be interpreted with caution. We did not study procalcitonin levels, a potential marker of secondary bacterial infection in patients included in this study. Hence, the higher levels

of inflammatory markers in patients with pneumonia might have been partially related to secondary bacterial infections.

Conclusion

The current study showed higher levels of inflammatory, coagulation and hematological parameters in patients with COVID-19 presenting with pneumonia. We suggest that BMI-Z score and MPV value may assist in predicting pulmonary involvement in patients with COVID-19.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee Clinical Researches (Decision no: 208, Date: 27.07.2021).

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: No conflict of interest was declared by the authors.

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