Original Investigation / *Özgün Araştırma*

DOI: 10.5578/ced.20219604 • *J Pediatr Inf 2021;15(4):e223-e228*

Investigation of the Diagnostic Value of Platelet Indices for the Diagnosis of Acute Bronchiolitis

Akut Bronşiolitin Tanısı İçin Platelet Belirteçlerinin Tanısal Değerinin Araştırılması

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Cite this article as: Seçilmiş Y, Dursun A. Investigation of the diagnostic value of platelet indices for the diagnosis of acute bronchiolitis. J Pediatr Inf 2021;15(4):e223-e238.

Abstract

Objective: We explored whether the platelet large cell ratio (PLCR), mean platelet volume (MPV), immature granulocyte number, and other complete blood count indices were diagnostic of acute bronchiolitis in children.

Material and Methods: We performed a single-center, prospective, diagnostic study of a accuracy of children who were admitted to the Pediatric Emergency Department with acute bronchiolitis between November 1, 2018 and February 28, 2019.

Results: The MPV, PLCR, platelet distribution width, and white blood cell count (WBC) were significantly higher in patients with bronchiolitis (p= 0.038, 0.001, 0.001 and 0.001), respectively. Significant correlations were evident between the Clinical Severity Score and each of the following: PLCR (p= 0.028, r= 0.160), MPV (p< 0.001, r= 0.263), and WBC (p= 0.005, r= 0.206). The largest area under the curve (AUC) was 0.656 (cutoff, 16.6) for the PLCR; the next largest AUC was 0.584 (cutoff, 8.85) for the MPV.

Conclusion: The PLCR, MPV, WBC and platelet distribution width increased in the bronchiolitis group. The PLCR and MPV can be used for differential diagnosis of bronchiolitis; the PLCR was better than the MPV for this purpose.

Keywords: Bronchiolitis, platelet large cell ratio, mean platelet volume, immature granulocyte, clinical severity score

Öz

Giriş: Trombosit: büyük hücre oranı (PLCR), ortalama trombosit hacmi (MPV), olgunlaşmamış granülosit sayısı ve diğer tam kan sayım indekslerinin çocuklarda akut bronşiolit için tanısal olup olmadığını araştırdık.

Gereç ve Yöntemler: 1 Kasım 2018 ile 28 Şubat 2019 tarihleri arasında Çocuk Acil Servisine akut bronşiyolit nedeniyle başvuran çocuklarda tek merkezli, prospektif, tanısal bir çalışma gerçekleştirdik.

Bulgular: Bronşiolitli hastalarda MPV, PLCR, trombosit dağılım genişliği ve beyaz kan hücre sayısı (WBC) anlamlı olarak daha yüksekti (sırasıyla p= 0.038, 0.001, 0.001 ve 0.001). Klinik Şiddet Skoru ile aşağıdakilerin her biri arasında önemli korelasyonlar vardı: PLCR (p= 0.028, r= 0.160), MPV (p< 0.001, r= 0.263) ve WBC (p= 0.005, r= 0.206). Eğri altındaki en büyük alan (AUC) PLCR için 0.656 (kesme değeri; 16.6) idi; bir sonraki en büyük AUC, MPV için 0.584'tür (kesme değeri; 8.85).

Sonuç: Bronşiolit grubunda PLCR, MPV, WBC ve trombosit dağılım genişliği artmıştır. PLCR ve MPV, bronşiyolitin ayırıcı tanısında kullanılabilir; PLCR, bu amaç için MPV'den daha iyi olarak saptanmıştır.

Anahtar Kelimeler: Bronşiolit, platelet large cell ratio, mean platelet volume, immatur granulosit, klinik ciddiyet skoru

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Received: 19.01.2021 **Accepted:** 30.06.2021 **Available Online Date:** 29.12.2021

Introduction

Bronchiolitis is a common lower respiratory tract infection that primarily affects the small airways (bronchioles) and is the leading cause of hospitalization in early childhood. In the first year of life, the disease affects approximately 20-30% of children, particularly those younger than five months of age (1). In the U.S.A., 3% of healthy children receive bronchiolitis treatment annually; the financial and parental labor costs are high (2,3). The pathogenesis includes edema, cell destruction, increased mucus secretion, and bronchial obstruction. The disease is typically mild and resolves without treatment. The condition begins with symptoms of upper respiratory tract infection (runny nose and cough), followed by fever and respiratory distress. Diagnosis should be based on clinical symptoms and their severity (4). Various scoring systems have been developed. However, no system has become widely accepted for the evaluation of bronchiolitis severity; a rapid, inexpensive, and simple tool is therefore required. Today, automated analyzers measure various complete blood cell (CBC) indices including the mean platelet volume (MPV), platelet large cell ratio (PLCR), and immature granulocyte count. Previous studies showed that the MPV was inversely associated with the extent of inflammation, as well as the inflammatory process and disease activity (4-6). The PLCR is the platelet percentage in a volume >12 fL and contains more detailed data regarding inflammation, compared with the MPV. Any relationship between the PLCR and bronchiolitis remains unexplored. Here, we investigated whether the MPV, PLCR, immature granulocyte count, and/or another CBC index might be useful for diagnosis of acute bronchiolitis, and we explore the clinical significance of our findings.

Materials and Methods

Study Population

We conducted a single center prospective diagnostic accuracy study with children who were admitted to the Pediatric Emergency Department with acute bronchiolitis between November 1st, 2018 and February 28th, 2019. The study was approved by the local ethics committee (Number: 2018/18-193). Written informed consent was obtained from all parents/guardians.

Bronchiolitis was defined according to the recommendations of American Academy of Pediatrics guidelines (7). At least 2 of the following signs: chest retractions, tachypnea, and wheezing or rales on auscultation was diagnosed bronchiolitis in children less than 24 months of age (excluding newborns). Infants those who had underlying cardiac or neuromuscular disease or those who had a known history of bronchopulmonary dysplasia or history of previous antibiotic use or chronic lung disease or premature infants were excluded from the study and the patients who had known any chronic disease were also excluded.

All patients underwent a routine clinical evaluation in the emergency department by the solely pediatrician. Patients were divided into three groups as mild, moderate and severe according to the clinical severity score (CSS) of acute bronchiolitis which was previously described by Wang EE et al. (Table 1) (8). Acute bronchiolitis was defined as either mild (total score ≤4), moderate (score between 5 and 9), or severe (score ≥10).

The control group was conducted from children who presented to Pediatric General Policlinics for routine health control or vaccination in the same period.

Data Collecting and Blood Samples

On admission all patients were performed CBC for using a commercially available analyzer (CELL-DYN Ruby, Abbott Park, Illinois, U.S.A). Each sample of whole blood was collected in tubes containing ethylenediaminetetraacetic acid and processed within one hour. The age, sex, respiratory scores and clinical findings were evaluated and laboratory parameters were recorded from each patient's chart. White blood cell count (WBC), IG, PLCR and MPV were obtained from the CBC without receiving any treatment such as steroids.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0. (IBM Corp. Armonk, NY: USA. Released 2013). For the normality analysis of the parametric data, the Shapiro Wilk test was used. Numerical variables were specified as mean ± SD and median (Q1-Q3). Student's t-test was used to compare the groups with normal distribution. Mann-Whitney U test was used to compare non-normal-

Table 1. The classification of the clinical severity score

	One point	2 point	3 point
Respiratory rate /min	31- 45	46-60	>60
Wheezing	At terminal expiration using a stethoscope	During the entire expiration or audible on expiration without stethoscope	Inspiratory and expiratory wheezing without stethoscope
Retraction	intercostal	Tracheo sternal	Severe retraction with nasal flaring
General Condition	normal	stable	Irritability and lethargy

ly distributed groups. Comparison between groups for data that did not show a normal distribution were performed using Kruskal-Wallis Test. The receiver operating characteristic (ROC) curve was used to evaluate the optimal cut-off points of the parameters for which significant differences were found. Sensitivity, specificity, cut-off points, negative predictive value (NPV), positive predictive value (PPV) and the area under the curve (AUC) were calculated for these parameters. The results were analyzed within a 95% confidence interval. A value of p< 0.05 and AUC> 0.600 was considered statistically significant. The bivariate correlation tests were used to analyze the correlations.

Results

A total of 257 infants (55.6% boys and 44.4% girls) were enrolled: 187 (115 boys, 61.5%; 72 girls, 38.5%) in the bronchiolitis group and 70 (42 boys, 60%; 28 girls, 40%) in the control group. Of the 187 patients, 107 (57.2%) were hospitalized, and the remaining patients were followed up in the emergency department and discharged. The median ages of infants were 12 (6-20) months in the bronchiolitis group and 12 (8-22.50) months in the control group. Table 2 lists the demographic and laboratory characteristics of the two groups; the demographic characterisitcs did not differ between the groups (p> 0.05). Based on the CSS, 26, 87, and 74 patients had mild, moderate, and severe bronchiolitis, respectively. In the mild group, 10 patients (38.5%) were girls and 16 patients (61.5%) were boys. In the moderate group, 35 patients (40.2%) were girls and 52 patients (59.8%) were boys. In the severe group, 27 (36.5%) were girls and 47 patients (63.5%) were boys. The sex ratio did not differ between the groups (p= 0.381). The median MPVs of the healthy and bronchiolitis groups were 8.8 (8.50-9.10) and 9 (8.50-9.40) fL, respectively (p= 0.038). The white blood cell count (WBC), PLCR, and platelet distribution width (PDW) were significantly higher in the bronchiolitis group than in the control group. The median platelet, plateletcrit, and immature granulocyte counts did not differ between the groups (Table 2). The MPV, PLCR, and PDW findings, stratified by the CSS, are listed in Table 3. The median MPVs were 8.6 (8.00-9.20), 8.9 (8.60-9.30), and 9.2 (8.60-9.60) fL in the mild, moderate, and severe bronchiolitis groups, respectively; the median MPVs were greater in the moderate and severe bronchiolitis groups than in the mild group (p< 0.001, p= 0.029, respectively). In the mild, moderate, and severe bronchiolitis groups, the median PDWs were 8.7 (7.90-9.40), 9.0 (8.50-9.70), and 9.1 (8.40-9.70), respectively (p= 0.225). The median PLCRs were 12.9 (10.80-17.80) in the mild bronchiolitis group, 16 (13-18.60) in the moderate bronchiolitis group, and 19.3 (15.1-22.9) fL in the severe bronchiolitis group. Significant correla-

Table 2. Comparison of the demographic and laboratory characteristics of the patients

	Bronchiolitis group (n= 187)	Control group (n= 70)	p
Age, months [Median, (IQ1-IQ3)]	12 (6-20)	12 (8-22.25)	
Sex, n (%)			
Male	115 (61.5)	42 (60)	
Female	72 (38.5)	28 (40)	
Laboratory findings	median (min-max)	median (min-max)	
White blood cell (µL)	10210 (8100-13100)	7945 (6552-9355)	**<0.001***
Platelet (µL)	352000 (275000-421000)	3545000 (309750-420500)	
Platelet distribution width (fL)	9.0 (8.4-9.7)	9.9 (8.87-11.3)	**<0.001***
Immature granulocyte (µL)	20 (10-40)	20 (10-32.5)	
Mean Platelet Volume (fL)	9 (8.5-9.4)	8.8 (8.5-9.1)	**0.038***
Platelet Large Cell Ratio (%)	16.7 (13.0-20.5)	13.2 (11.7-16.6)	**<0.001***
Platelecrit (%)	0.32 (0.26-0.38)	0.34 (0.28-0.39)	

min: Minumum value, max: Maximum value, *(p< 0.05), statistically significant.

Table 3. The differences in the measurements of MPV, PLCR and PDW levels according to CSS

Variable	Mild Median (Q1-Q3)	Moderate Median (Q1-Q3)	Severe Median (Q1-Q3)	p
MPV (fl)	8.6 (8.0-9.2)[b]	8.9 (8.6-9.3)[a]	9.2 (8.6-9.6)[a]	**0.02***
PLCR (fl)	12.9 (10.8-17.8)[b]	16 (13-18.6)[ab]	19.3 (15.1-22.9)[a]	**<0.001***
PDW	8.7 (7.9-9.4)	9.0 (8.5-9.7)	9.1 (8.4-9.7)	

*: (p< 0.05), statistically significant. Different letters on the same line represent statistically different groups. MPV: Mean platelet volume, PLCR: Platelet large cell ratio, PDW: Platelet distribution width.

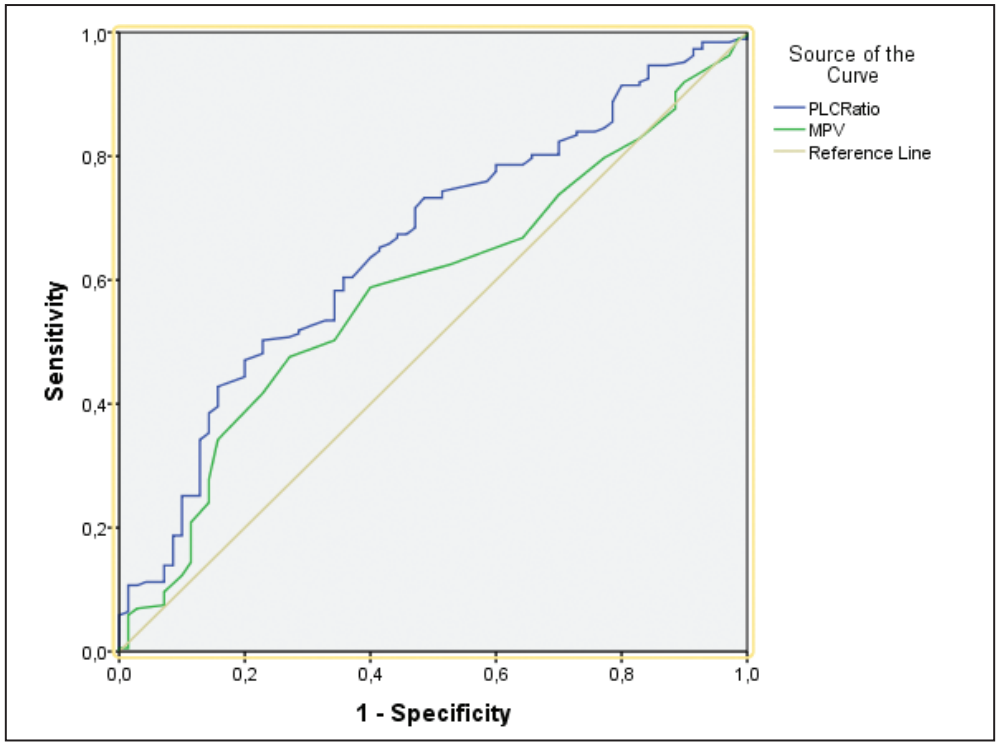

Figure 1. ROC curve was used for MPV and PLCR to differentiate bronchiolitis and control groups.

Table 4. Sensitivity, Specificity, PPV and NPV of markers

Markers	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PLCR	50.3	78.1	85.5	36.7
MPV	58.8	60.0	82.4	34.9
PPV: Positive predictive value, NPV: Negative predictive value, MPV: Mean platelet volume, PLCR : Platelet large cell ratio.				

Table 5. Area under the ROC curves, cut-off values and P-values of each tested markers

Markers	Cut-off	AUC	p	% 95 CI
PLCR	16.6	0.656	0.001	0.582-0.729
MPV	8.85	0.584	0.038	0.509-0.659
PLCR: Platelet large cell ratio, MPV: Mean platelet volume, AUC: Area under the receiver operating characteristic curve, CI: Confidence interval.				

tions were evident between the CSS and PLCR (p= 0.028, r= 0.160), the CSS and MPV (p< 0.001, r= 0.263), and the CSS and WBC (p= 0.005, r= 0.206).

ROC curves of the MPV and PLCR for differentiating the bronchiolitis and control groups are shown in Figure 1. The sensitivities, specificities, positive predictive values, and negative predictive values of the MPV and PLCR were calculated using these curves (Table 4). The optimal cutoffs and areas under the curves (AUCs) are shown in Table 5. The largest AUC was 0.656 (PLCR), while the AUC for MPV was 0.584.

Discussion

To the best of our knowledge, this study is the first to show that the PLCR and other CBC indices are diagnostic of acute bronchiolitis and can predict its severity. Early diagnosis in the Pediatric Emergency Department is based on the clinical course; however, the symptoms (chest retraction, tachypnea, wheezing, and rales) are nonspecific. Distinctive markers are required to optimize diagnosis and treatment. Platelets are key components of hemostasis, which play important roles in airway inflammation and bronchial hyperresponsiveness (9). The MPV is immediately available from a CBC, which enables calculation of platelet volume; the MPV is a key indicator of platelet activity. The MPV serves as a marker of platelet function in patients with various inflammatory diseases including cystic fibrosis, familial Mediterranean fever, and sepsis (10-12). Recently, Tuncel et al. compared control participants (n= 49) and patients with asthma (n= 100); the MPV was not

significantly higher in patients with asthma either during or between attacks (13). In contrast, Gökçe et al. demonstrated a higher MPV in patients with acute bronchiolitis than in control participants. At a cutoff of 6.0 fL, the sensitivity was 90% and the specificity was 28% (14). We found that the MPV was higher in patients with acute bronchiolitis than in control participants. At a cutoff of 8.85 fL, the sensitivity was 58.8% and the specificity was 60.0% (AUC=0.584, p= 0.038). Patients with severe and moderate bronchiolitis exhibited significantly higher MPVs, compared with patients who had mild bronchiolitis. The PLCR may be more informative than the MPV in terms of platelet size and reactivity during inflammation (15). A retrospective study by Tamelyte et al. compared patients with severe bacterial infections with the viral infections. They found that the platelet/mpv ratio was statistically significantly higher in patients with severe bacterial infections compared to viral infections. In our study, while platelet levels were not high, MPV levels were found to be higher in the group with bronchiolitis. However, we did not evaluate the platelet/mpv ratio (16).

We studied the physiopathogenesis of inflammation and found that platelets become activated; change in shape; increase in size; exhibit enhanced metabolic activity; and secrete enzymes, cytokines, and other mediators. Among patients with sepsis, the PLCR was significantly higher in those who died than in those who survived (17). In a study conducted by Ekici-Günay et al. in patients with primary immunodeficiency, showed that platelet markers, especially PLCR increased during the infections. Ekici-Günay et al. evaluated that it is related to increased platelet turnover and mediator production. These data are correlated with our study (18).

This is the first study to assess the diagnostic and prognostic utilities of the PLCR in the context of bronchiolitis. The PLCR was higher in patients with acute bronchiolitis than in control participants. At the optimal cutoff of 16.6, the sensitivity was 50.3% and the specificity was 78.1%. The diagnostic utility of the PLCR was higher than that of the MPV; the AUCs were 0.656 and 0.584, respectively.

The PDW indicates changes in platelet size and reactivity; an increase in the PDW indicates an increased number of immature platelets (19). The PDW varies among patients with different conditions. Dinc et al. showed that the PDW increased significantly in patients with acute appendicitis, but decreased in patients with invasive fungal disease (20,21). We found that the PDW was significantly greater in patients with bronchiolitis than in control participants. However, the immature granulocyte counts did not differ between the groups.

Our study was limited in that it was a single-center observational study with a small number of patients. Further work is therefore required.

Increased levels of PLCR, MPV and PDW were observed in the bronchiolitis group. PLCR and MPV may be used for the differential diagnosis of bronchiolitis and PLCR had a better predictive capacity than that of the MPV. Moreover, PLCR appeared to be increased in the bronchiolitis group and with the clinical severity compared to non-infected children. The AUC values we detected are below the significant values. However, high statistics rate and PPV values showed the effectiveness of the parameters we used in diagnosis.

Ethics Committe Approval: The study was approved by the Health Sciences University Erzurum Regional Training and Research Hospital Clinical Research Ethics Committee (Date: 2018/18/193, 19.11.2018).

Informed Consent: Patient consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - YS, AD; Design - YS, AD; Supervision - YS, AD; Resource - YS; Data Collection and/or Processing - YS, AD; Analysis and/or Interpretation - AD; Literature Search - YS; Writing - YS, AD; Critical Review - AD.

Conflict of Interest: All authors declare that they have no conflicts of interest or funding to disclose.

Financial Disclosure: The authors declared that this study has received no financial support.

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