Independent Predictors of Severity and Hospitalization in Acute Bronchiolitis: Neutrophil/Lymphocyte Ratio and Mean Platelet Volume

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Abstract

Background and Aim Acute bronchiolitis is the most common cause of hospitalization in the first year of life. The neutrophil/lymphocyte ratio (NLR) and mean platelet volume (MPV) are readily calculable laboratory markers used to evaluate systemic inflammation. We aim to evaluate the optimal values of these markers for the prediction of severity and hospitalization in infants with acute bronchiolitis.

Materials and Methods A total of 105 patients with acute bronchiolitis and 62 healthy controls aged 1 to 12 months were prospectively enrolled to the study. The patients' group was classified into two groups, namely, outpatient and inpatient, also divided into three groups according to clinical scoring: mild, moderate, and severe. The association of NLR and MPV with clinical severity and hospitalization was investigated.

Results The mean age was 7.75 $\pm$ 2.98 months in patients and 7.69 $\pm$ 2.87 months in controls. The means of NLR were 0.47 and 0.64 in controls and patients, respectively ($p = 0.032$) and of MPV were 9.64 and 8.9 ($p < 0.001$), respectively. The means of NLR were 0.73 and 0.50 in inpatient and outpatient groups, respectively ($p = 0.014$) and of MPV were 8.65 and 9.32 ($p = 0.046$), respectively. NLR of 0.64 value was calculated as a cutoff for the prediction of hospitalization with 45% sensitivity and 83% specificity (positive predictive value = 81%, negative predictive value = 19%).

Conclusion We found that blood neutrophil percentage and blood NLR are increased and also weakly predictive—but insufficient to be clinically useful—for the decision of hospitalization in acute bronchiolitis. When the positive predictive value of an NLR of 0.64 is sufficient to decide hospitalization, the negative predictive value is impractical. MPV value was less in infants with acute bronchiolitis than healthy controls and in inpatients than outpatients with acute bronchiolitis. Low MPV might be marker of inflammation in acute bronchiolitis.

Keywords
- acute bronchiolitis
- infants
- inflammation
- NLR
- MPV

Introduction

Acute bronchiolitis is a viral respiratory disease characterized by bronchiolar obstruction with edema, mucus, and cellular debris and is the most common reason for in the first year of life. In the United States, approximately 100,000 hospitalizations annually are due to bronchiolitis.[1,2] Infants

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with smaller airways and diminished lung function have a more severe course.

For identifying the most appropriate treatment, the severity of bronchiolitis should be determined. The bronchiolitis severity score has been most commonly used to determine whether patients with bronchiolitis should be treated as outpatients or inpatients.[3] Neutrophils and lymphocytes play major roles in inflammatory processes. During inflammation, the neutrophil and lymphocyte counts undergo temporary changes. During infection, depending on the severity of the inflammation, the neutrophils circulate from the marginal pool to the bone marrow and finally to the tissues. This early response increases the overall neutrophil count. Inflammation plays a major role in the pathophysiology of commonly known noninflammatory diseases, such as cancer[4] and atherosclerosis.[5] Systemic inflammation can be measured using various biochemical and hematological markers. Novel disease-specific biomarkers have been identified; however, most biomarker analyses are time-consuming and expensive. The neutrophil/lymphocyte ratio (NLR) is a readily measurable laboratory marker used for evaluating systemic inflammation. Several studies demonstrated that among many inflammatory markers, elevated NLR is a significant predictor of adverse outcomes in patients with cardiovascular disease[6] or cancer.[7] Elevated NLR is associated with increased concentration of various proinflammatory cytokines, which may cause cellular DNA damage.[4,7,8] The associations of platelet/lymphocyte ratio (PLR) with mortality in patients with acute myocardial infarction and those of mean platelet volume (MPV) with rheumatoid arthritis, ulcerative colitis, and Crohn's disease have been described.[9–11]

We assumed that systemic inflammation is also seen in acute bronchiolitis. The relevant medical literature published in either English or Turkish was searched; however, no study investigating the prognostic value of NLR and MPV in acute bronchiolitis was found. Here we aim to evaluate the relationship between acute bronchiolitis and inflammation using NLR and MPV to estimate whether these markers are reliable for predicting severity and hospitalization in infants with acute bronchiolitis.

Materials and Methods

In total, 105 patients with acute bronchiolitis and 62 healthy controls were enrolled to the study from pediatric outpatient and emergency clinics between January 1, 2015 and January 1, 2016. On admission, patients were evaluated for enrollment by one physician (B.A.S.) using a standardized questionnaire and by clinical evaluation. In children < 1 year, at least one of the signs of increased respiratory effort such as wheezing, rhonchi, prolonged expiration, tachypnea, or intercostal or subcostal retractions as well as findings of upper respiratory tract infections such as fever, nasal discharge, and cough helped in diagnosing acute bronchiolitis.[12] Patients showing recurrent wheezing episodes, cardiopulmonary disease, immunodeficiency, congenital anomalies, prematurity, cystic fibrosis, and bronchopulmonary dysplasia were excluded. In addition, patients showing any consolidation on the chest X-ray or any other sign of bacterial infection were excluded. Although routine blood culture or urine analysis was not performed in all infants, those having inflammation (as per their history, physical examination, and laboratory findings) were also excluded. Controls healthy for acute bronchiolitis were obtained from well child visits; infants with any other infections were excluded. Subject data and characteristics were extracted from our past study.[13] The blood samples were collected in the emergency or outpatient clinic on admission before initiating any treatment. The patients who received any treatment before admission to the hospital were not enrolled into the study. Demographic, clinical data, laboratory results, and radiological findings were recorded. The patients were classified into two groups according to the hospitalization: outpatient and inpatient. The patients were also divided into three groups according to the clinical severity score: mild, moderate, and severe.[3] The clinical severity score (►**Table 1**), based on respiratory rate, wheezing, retraction, and general condition (irritability, poor feeding, and lethargy), was assessed on admission. The approved criteria for hospitalization were age < 3 months, gestational age at birth < 34 weeks, respiratory rate > 70 breaths per minute, lethargic appearance, wheezing and respiratory distress associated with oxygen saturation $< 92\%$ on room air, moderate or severe disease according to the clinical severity score, and atelectasis on chest radiography.[14] Based on these two classifications, the specificity, sensitivity, and positive and negative predictive values of NLR for hospitalization risk were calculated.

Furthermore, the association of NLR and MPV with clinical severity and hospitalization was investigated. The hospitalization duration was extracted from electronic health

Table 1 Clinical severity scores[a]

Variables	Score			
	0	1	2	3
Respiratory rate (breaths/min)	< 30	30–45	46–60	> 60
Wheezing	None	Terminal respiratory or only with stethoscope	Entire expiration or audible on expiration without stethoscope	Inspiration and expiration without stethoscope
Retraction	None	Intercostal only	Tracheosternal	Severe with nasal flaring
General condition	Normal	Mild irritable	İrritable, poor feeding	Noon-feeding, alteration in consciousness

[a]From Wang et al.[3]
According to these clinical severity scores, disease severity was described as mild disease: 1–3 scores, moderate disease: 4–8 scores, severe disease: 9–12 scores.

records. The study protocol was in accordance with the Helsinki Declaration of the World Medical Association and ethical standards, and the study was approved by the Ethics Committee of Gaziosmanpasa University School of Medicine (15-KAEK-040). Informed consent was obtained, and questionnaires used to gather information were answered by the parents.

Laboratory Tests

White blood cell count (WBC) and C-reactive protein (CRP) levels were determined before hospitalization or treatment. Total WBC; neutrophil, lymphocyte, and platelets counts; MPV; and red blood cell distribution width (RDW) were determined using an automated blood cell counter (Sysmex XN-1000; Hematology Analyzer). NLR and PLR were obtained by dividing the neutrophil and platelet counts by the lymphocytes count, respectively. The CRP levels were measured using an automated latex-enhanced turbidimetric immunoassay.

Statistical Analysis

Descriptive analyses were performed to obtain the general characteristics of the study population. A one-way analysis of variance was used to compare continuous data among the groups. Tukey's honest significant difference test was used for multiple comparisons. Continuous variables are presented as means ± standard deviations and categorical variables as numbers and percentages. The chi-square test was used to compare categorical variables between groups. ROC analysis was used for performance measurements. Pearson correlation coefficient was used for correlation between variables. A p-value of <0.05 was considered significant. Analyses were performed using SPSS 19 (IBM SPSS Statistics 19, SPSS Inc., IBM Co., Somers, New York, United States).

Results

In total, 167 infants were enrolled, of which, 105 were patients with acute bronchiolitis and 62 were controls. The mean age was 7.75 ± 2.98 months in patients and 7.69 ± 2.87 months in controls ($p = 0.901$). ►**Table 2** shows the demographic features and clinical and laboratory findings of patients with acute bronchiolitis and controls. Regarding inflammatory markers, NLR was significantly higher ($p = 0.032$) and MPV was lower ($p < 0.001$) in infants with acute bronchiolitis than in controls (►**Table 2**).

A total of 65 infants were hospitalized for 8.4 ± 3.2 days (range: 2–18 days). None of the infant required mechanical ventilation and no death occurred in the study. ►**Table 3** shows the means of quantitative variables in the patient groups according to hospitalization and severity. NLR was higher ($p = 0.014$) and MPV was lower ($p = 0.046$) in the inpatient group than in the outpatient group. The predictive capacity of the NLR values was evaluated by the area-under-the-curve (AUC) analysis (►**Table 4**). An NLR value of 0.64 was considered as the cutoff for predicting hospitalization with 45% sensitivity and 83% specificity ([positive predictive value = 81%, negative predictive value = 19%; AUC = 0,622; [95% confidence interval, CI: 0.513–0.731]; $p = 0.037$]). However, no significant difference in the PLR values ($p = 0.143$) was observed between the inpatient and outpatient groups. In addition, no significant differences were

Table 2 The means of quantitative and descriptive variables in all study groups

		Total ($n = 167$)	Controls ($n = 62$)	Patients ($n = 105$)	p-Value
Age (months)		7.73 ± 2.93	7.69 ± 2.87	7.75 ± 2.98	0.901
MPV		9.18 ± 1.49	9.64 ± 0.93	8.9 ± 1.68	< 0.001
RDW		14.47 ± 2.28	14.46 ± 2.59	14.47 ± 2.1	0.971
Platelet/mm^3		377.93 ± 110.67	393.3 ± 112.33	368.86 ± 109.2	0.169
NLR		0.58 ± 0.5	0.47 ± 0.35	0.64 ± 0.56	0.032
PLR		70.58 ± 38.75	64.85 ± 26.91	73.96 ± 44.05	0.143
Lymphocyte/mm^3		6.2 ± 2.33	6.67 ± 2.3	5.93 ± 2.31	0.044
Neutrophil/mm^3		4.04 ± 2.4	2.74 ± 1.49	4.81 ± 2.51	< 0.001
WBC		10.75 ± 3.13	10.74 ± 2.76	10.75 ± 3.34	0.988
Birth weight		3107.19 ± 453.63	3065.97 ± 435.76	3131.52 ± 464.18	0.368
Gender	Female	71(42.5)	27(43.5)	44(41.9)	0.836
	Male	96(57.5)	35(56.5)	61(58.1)	
Type of labor	Vaginal	65(38.9)	25(40.3)	40(38.1)	0.775
	C/S	102(61.1)	37(59.7)	65(61.9)	

Abbreviations: C/S, cesarean section; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; PLR, platelets/lymphocyte ratio; RDW, red cell distribution width; WBC, white blood cell count.
The data were illustrated as standard mean ± standard deviation.
Bold type indicates statistically significant difference.

Table 3 The means of quantitative variables in patients according to hospitalization and severity groups

	Total ($n = 167$)	Hospitalization group		*p*-Value	Severity group			*p*-Value
		Outpatient	Inpatient		Mild	Moderate	Severe	
		($n = 40$)	($n = 65$)		($n = 58$)	($n = 15$)	($n = 9$)	
Age (month)	7.75 ± 2.98	8 ± 2.62	7.6 ± 3.19	0.506	8.12 ± 2.94	8.09 ± 2.56	5.6 ± 3.22	0.009
MPV (fL)	8.90 ± 1.68	9.32 ± 1.54	8.65 ± 1.72	0.046	9.04 ± 1.53	8.96 ± 1.79	8.26 ± 1.95	0.268
RDW (%)	14.47 ± 2.10	14.23 ± 1.53	14.62 ± 2.38	0.348	14.62 ± 2.36	14.44 ± 1.63	13.98 ± 1.93	0.584
Platelets/mm^3	368.86 ± 109.20	349.82 ± 107.56	380.57 ± 109.38	0.162	373.48 ± 110.75	363.98 ± 117.92	361.38 ± 87.52	0.890
NLR	0.64 ± 0.56	0.50 ± 0.3	0.73 ± 0.66	0.014	0.57 ± 0.42	0.79 ± 0.82	0.63 ± 0.28	0.192
PLR	73.96 ± 44.05	65.01 ± 28.46	79.46 ± 50.78	0.103	72.81 ± 45.84	79.5 ± 48.79	66.58 ± 21.36	0.621
Lymphocyte count/mm^3	5.93 ± 2.31	5.98 ± 2.13	5.89 ± 2.42	0.839	6.1 ± 2.39	5.65 ± 2.28	5.86 ± 2.11	0.675
WBC/mm^3	10.75 ± 3.34	10.94 ± 3.19	10.64 ± 3.45	0.657	10.79 ± 3.4	10.85 ± 3.46	10.39 ± 3.03	0.902
Lymphocyte (%)	55.60 ± 15.03	56.58 ± 15.79	55 ± 14.65	0.603	56.9 ± 14.67	53.44 ± 17.72	55.19 ± 9.48	0.580
Neutrophil (%)	43.94 ± 15.59	42.75 ± 16.44	44.67 ± 15.13	0.544	42.56 ± 15.12	46.35 ± 18.33	44.14 ± 10.51	0.548
CRP (mg/dL)	5.71 ± 8.58	5.58 ± 9.38	5.79 ± 8.12	0.902	5.52 ± 8.42	5.55 ± 9.79	6.79 ± 6.62	0.872
Birth weight (g)	3131.52 ± 464.18	3262 ± 403.49	3051.23 ± 483.45	0.023	3173.62 ± 459.04	3086.87 ± 494.85	3064 ± 428.53	0.584
Respiratory rate/min	43.68 ± 9.59	38.45 ± 6.42	46.89 ± 9.84	<0.001	37.52 ± 5.19	48.97 ± 7.58	56.2 ± 7.59	<0.001
Heart rate/min	109.42 ± 20.14	99.78 ± 7.83	115.35 ± 22.97	<0.001	97.84 ± 7.95	115.88 ± 17.25	140.4 ± 20.42	<0.001
spO_2	94.02 ± 9.47	97.83 ± 1.88	91.68 ± 11.36	0.001	97.57 ± 2.02	89.69 ± 15.29	89.53 ± 3.87	<0.001
CS score	4.39 ± 2.96	2.28 ± 1.11	5.69 ± 2.99	<0.001	2.09 ± 0.73	6.13 ± 1.34	9.6 ± 0.91	<0.001

Abbreviations: CRP, C-reactive protein; CS, clinical severity; MPV, mean platelet volume; NLR, neutrophil/lymphocyte ratio; PLR, platelets/lymphocyte ratio; RDW, red cell distribution width; spO_2, oxygen saturation; WBC, white blood cell count.
The data were illustrated as standard mean ± standard deviation.

Table 4 ROC analysis for predictive values of NLR, sensitivity, and specificity

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood	Negative likelihood
NLR > 0.61	0.46	0.75	0.75	0.25	1.85	0.72
NLR > 0.62	0.45	0.78	0.76	0.24	1.98	0.71
NLR > 0.63	0.45	0.80	0.78	0.22	2.23	0.69
NLR > 0.64	0.45	0.83	0.81	0.19	2.55	0.67
NLR > 0.65	0.43	0.83	0.80	0.20	2.46	0.69
NLR > 0.68	0.42	0.83	0.79	0.21	2.37	0.71
NLR > 0.70	0.40	0.83	0.79	0.21	2.29	0.73

Abbreviations: AUC, area under curve; CI, confidence interval; NLR, neutrophil/lymphocyte ratio.
For that 0.64 value of NLR cutoff point (AUC = 0.622; 95% CI: 0.513–0.731; $p = 0.037$).

found between the severity groups with respect to the NLR, MPV, PLR, and RDW values. NLR showed a weak but significant correlation with hospitalization duration ($r = 0.261$, $p = 0.007$).

Discussion

We found that the neutrophil count and NLR increase in acute bronchiolitis and are predictive markers; however, they are insufficient to be clinically useful for determining hospitalization. Acute bronchiolitis usually involves local inflammation; systemic inflammatory markers have not been investigated in acute bronchiolitis. These results suggest that blood count can be useful for determining the need for hospitalization in infants with acute bronchiolitis. We also identified some additional findings, namely reduced lymphocytes and increased NLR in acute bronchiolitis, which may reflect systemic inflammation. In community-acquired pneumonia, basic blood count could provide parameters such as NLR, which shows a high predictive capacity for mortality.[15] High NLR value is suggested as an inflammation marker in childhood brucellosis.[16] Özer et al suggested that the cutoff value for NLR can be used for detecting subclinical inflammation.[17]

Considering all the likelihood ratios for the aforementioned positive and negative predictions, an NLR value of 0.64 seems to be the most useful cutoff value for determining hospitalization in infants with acute bronchiolitis. When the positive predictive value is sufficient to decide hospitalization, the negative predictive value is unpractical. We applied the age criterion of < 3 months for hospitalization; therefore, it is possible that the negative predictive value can be used if the number of study group and the age of subject are increased. Furthermore, we could not find any research about the association of NLR with acute bronchiolitis; therefore, we could not compare our findings with those from any other study. However, in acute appendicitis, an NLR value of 3.5 has been accepted for predicting surgery.[18] Given the suspected viral etiology acute bronchiolitis and inevitable physiological lymphocytosis in infants, the cutoff value of NLR might be lower in our patients than in those with appendicitis. Conversely, an NLR value of 0.76 is suggested as the cutoff value in community-acquired pneumonia for predicting mortality.[15]

MPV is one of the widely used markers of platelet function and has been shown to reflect inflammatory loading in several chronic disorders.[10,17,19] MPV values were found to be significantly lower in patients with familial Mediterranean fever during attack than during attack-free period. In addition, the severity score negatively affected MPV.[20] Moreover, low MPV values were reported in childhood brucellosis.[16] Ergül et al reported that MPV was decreased in infants with acute bronchiolitis.[21] Similarly, in the present study, MPV values were lesser in infants with acute bronchiolitis than in healthy controls and in inpatients than in outpatients with acute bronchiolitis. The platelet volume was effective in not only identifying the inflammation but also in determining its severity. Gasparyan et al suggested that when the inflammation severity increases because of evaluating only circulating platelets' volume, MPV decreases by the migration of activated large thrombocytes to the site of inflammation.[22] However, we did not find any significant differences between the severity groups of acute bronchiolitis. Thus, lower MPV values might be associated with systemic inflammation in infants with acute bronchiolitis, and some cytokines elevated during acute illness may influence platelets and their volumes.[20] In patients with cancer, IL-6 was shown to increase the platelet count and decrease MPV.[23] Inflammatory cytokines and immune response play important roles in the pathophysiology of acute bronchiolitis.[12] Low MPV values might be due to the effect of cytokines in acute bronchiolitis.

Moreover, we found that the NLR values correlated with the hospitalization duration, although it was not associated with disease severity. NLR might be a useful marker for prediction and hospitalization duration. Further investigations are needed to confirm our findings.

Our study has some limitations. First, the present study was an extension of our previous study on acute bronchiolitis. We believe that, in the future, designing studies to determine the usefulness of these markers in infants with acute bronchiolitis would provide more sensitive and accurate results. In addition, we employed strict hospitalization criteria for infants, whereas, in reality, some cases requiring

hospitalization may not meet these conservative criteria. Moreover, atopy is questionable, albeit not acceptable as an exclusion criterion. On the other hand, the diagnosis of acute bronchiolitis, determination of the severity score, and prediction of hospitalization by the same pediatrician are the strengths of the present study.

Although acute bronchiolitis is an acute inflammatory injury of the bronchioles, high NLR and low MPV values were determined as markers of systemic inflammation. However, we could not explore whether the low-grade inflammation was a cause or an effect of comorbid conditions. Therefore, although there is no proven effective treatment for acute bronchiolitis, new therapeutic strategies that suppress systemic inflammation are promising.

Conclusion

We found that infants with acute bronchiolitis are significantly more likely to have higher NLR and lower MPV values as markers of systemic inflammation. High NLR values are associated with clinical outcomes, particularly with prediction and hospitalization duration. Future research is needed to investigate this relationship using longitudinal data to clarify the association between these variables.

What Is Known?

- Acute bronchiolitis (AB) is the most common reason of hospitalization in infants.
- Local inflammation in bronchioles has an important role in AB.
- The neutrophil/lymphocyte ratio (NLR) and mean platelet volume (MPV) are readily calculable markers used to evaluate systemic inflammation.
- Prediction of hospitalization is important for management of AB.

What Is New?

- In the present study, we found that NLR and MPV are correlated with clinical severity score.
- Also, high NLR values are associated with clinical outcomes, especially with decision to and duration of hospitalization.
- NLR of 0.64 seems to be useful cutoff value in the determination of hospitalization in infants with AB.

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