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Neutrophil responses in infants with acute bronchiolitis

Neutrophils and acute bronchiolitis

Elif Çelik[1], Pınar Uysal[2], Serkan F Çelik[3], Ayşe Anık[1]
[1]Department of Pediatrics, General Pediatrics Unit,
[2]Department of Pediatric Allergy and Immunology,
[3]Department of Pediatric Cardiology, Adnan Menderes University Faculty of Medicine, Aydın, Turkey

Abstract

Aim: The role of neutrophils in acute bronchiolitis (AB) remains unclear. The present study aims to evaluate neutrophil counts and to explore its clinical significance in infants with AB.

Materials and Methods: The present study included 94 infants with AB and 52 healthy infants. The patient group was divided into two subgroups including Respiratory Syncytial virus (RSV) and Rhinovirus and divided into three bronchiolitis attack subgroups. The complete blood count indexes and correlations between patients and healthy controls were compared and clinical characteristics were analyzed. A p-value <0.05 was considered statistically significant.

Results: Neutrophil count and neutrophil to lymphocyte ratio (NLR) were higher (p=0.009 vs. p=0.003) in contrast to lower lymphocyte levels (p=0.028) in infants with AB versus healthy group. The age of hospitalization in Rhinovirus-infected infants was significantly higher than RSV infected infants (p=0.049). NLR level of 1.04 was determined as the predictive cut-off value of longer hospitalization duration in patients with AB.

Discussion: Neutrophil count and NLR level were significantly higher and NLR could predict the hospitalization duration in infants with AB.

Keywords

Bronchiolitis; Inflammation; Neutrophil

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Corresponding Author: Elif Çelik, Adnan Menderes University Faculty of Medicine, Department of Pediatrics, General Pediatrics Unit, Aydın,Turkey.
E-mail: gencelif80@yahoo.com GSM: +90 5054785518
Corresponding Author ORCID ID: https://orcid.org/ 0000-0002-0298-4088

Introduction

Acute bronchiolitis is the most common acute lower respiratory system illness in infants under 2 years and the main cause of hospitalization in infants under 6 months of age [1, 2]. Respiratory syncytial virus (RSV) is the first common and Rhinovirus is the second most common virus associated with AB [3]. Bronchiolitis occurs when viruses infect terminal bronchiolar epithelial cells, causing direct damage to the small airways, inflammation, and increased mucus production [4]. Everard et al. reported that neutrophils are the most common inflammatory cell type within the upper and lower respiratory tract in infants with bronchiolitis, accounting for around 70% of cells [5]. Moreover, there is compelling evidence that cells producing interferon-gamma may contribute to RSV-induced wheezing, possibly through induction of leukotriene release [6]. These results indicate that neutrophils probably play a major part in causing symptoms in these infants.

Neutrophil count and Neutrophil-to-Lymphocyte Ratio (NLR) can be easily evaluated in routine hematological examination [7, 8]. In many diseases, NLR has been examined as a new expression of the inflammatory biomarkers [8-11].

Although there is a limited number of studies investigating complete blood count (CBC) parameters in infants diagnosed with AB [12-16], there are only a few data that evaluated NLR levels. The current study aimed to evaluate the clinical significance of CBC parameters on patients during AB period.

Material and Methods

Study Patients

This study was conducted between September 2018 and May 2019. A total of 146 infants including 94 infants hospitalized with a diagnosis of AB according to the recommendations of the American Academy of Pediatrics (AAP) 2006 Clinical Practice Guidelines [17] and 52 healthy infants presented to our child health outpatient clinic were included in the study. Patients hospitalized with AB were recruited with informed, written, parental consent. The data of patient and control groups were collected from medical records. The patient group was divided into two subgroups including RSV and Rhinovirus and divided into three bronchiolitis attack subgroups (including mild, moderate, and severe) assessed with Wang respiratory score [18].

The infants who were hospitalized within 2 weeks before the current admission, who were born prematurely, who had bronchopulmonary dysplasia, congenital heart disease, immunodeficiency, or chronic lung disease were excluded from the study.

The complete blood count was performed by flow cytometry using the BC 6800 Mindray device analyzer. Nasopharyngeal swab samples taken before the treatment in the patient group were examined using the Multiplex Polymerase Chain Reaction method and were recorded retrospectively. NLR values were calculated by dividing the neutrophil count by the lymphocyte count. Ethics committee approval was obtained from the Local Ethics Committee of Adnan Menders University (approval number: 2019/122).

Statistical Analyses

The distribution of variables was checked with the Kolmogorov-Smirnov test. Data are expressed as the mean standard deviation (SD) or median [25–75% interquartile range (IQR)]. Categorical variables were compared using the Chi-square and the Fisher's exact test when 20% of the expected frequencies were less than five. In the analysis of the quantitative data, the Mann-Whitney U test was used for non-parametric data and the Student's t-test for parametric data. The Anova test was used for statistical analysis of parametric data and the Kruskal-Wallis for non-parametric data among mild, moderate, and severe bronchiolitis groups. Roc curve analysis was performed to determine cut-of value for long hospitalization. $P<0.05$ was considered statistically significant. The data were analyzed using the Statistical Package for the Social Sciences® (SPSS) software version 22.0 (Chicago, IL, USA).

Results

The median age of the patient group was 82 (52.2-180) days. No significant differences were found between the study and healthy groups in terms of gender or age (p=0.098, p=0.99, respectively). Neutrophil count and neutrophil to lymphocyte ratio (NLR) were higher (p=0.009, p=0.003, respectively) in contrast to lower lymphocyte levels (p=0.028) in infants with AB versus healthy group. Although, the PLR was higher in the study group with respect to the healthy group, the difference was not statistically significant (p=0.177). The demographic and laboratory characteristics of the study and control groups are given in Table 1.

The age of hospitalization in Rhinovirus infected infants was significantly higher than RSV infected infants (p=0.049). However, there was no difference in terms of bronchiolitis severity and duration of hospitalization between two groups (p=0.131 vs. p=0.453). The comparison of the parameters in the infants with RSV and Rhinovirus bronchiolitis are shown in Table 2.

The findings represented a significant difference among infants with mild, moderate, and severe acute bronchiolitis in terms of duration of hospitalization and PLR (p=<0.001, p=0.06, respectively), while other hematologic parameters including WBC, PLT, NLR, CRP were not significantly different among three subgroups (p>0.05) (Table 3).

A receiver operating characteristics curve was performed to decide the cut-off value of NLR to predict the duration of hospitalization ≥ 9 days in infants with acute bronchiolitis. A cut-off value of NLR>1.04 yielded a sensitivity of 44.4% and a specificity of 81% for predicting longer hospitalization duration in patients with acute bronchiolitis. The area under the curve (AUC) was 0.675 (95% confidence interval 0.548–0.802, p = 0.022) (Figure 1).

Discussion

In the present study, it was found that NLR and neutrophil count were significantly higher and lymphocyte levels were lower in infants with AB. Furthermore, NLR could predict the hospitalization duration in patients with AB.

Because of the physiological responses of circulating leukocytes in the human body to stress, an increase in the number of neutrophils and a decrease in the number of lymphocytes, NLR has been used as a marker for inflammation in many diseases.

Table 1. Comparison of demographics and laboratory parameters between children with bronchiolitis and healthy controls.

Parameters	Patient Group (N=94)		Healthy Group (N=52)		P- values
Demographic Parameters					
	n	%	n	%	
Gender Male Female	 54 40	 58.7 41.3	 23 29	 44.2 55.8	0.098[a]
	Mean ± SD (min – max)	**Median (25 – 75 p)**	**Mean ± SD**	**Median (25-75p)**	
Age (days)	138.3 ± 133 (33 – 575)	82 (52.2-180)	121 ± 99.3 (33- 455)	73 (55-166.5)	0.99[a]
Laboratory Parameters					
	Mean ± SD (min – max)	**Median (25 -75 p)**	**Mean ± SD (min – max)**	**Median (25-75p)**	
WBC (10^3 /µL)	11.3±4.42 (4.09-25.69)	10.6 (8.1-13.9)	10.79±3.34 (3.51-18.2)	10.1 (8.1-12.5)	0.773[a]
Lymphocyte (10^3 /µL)	5.76±2.72 (1.77-14.79)	5.2 (3.7-7.2)	6.41±2.49 (0.83-11.76)	6.1 (4.7-7.8)	0.028[a]
Neutrophil (10^3 /µL)	4.32±3.22 (0.69-16.39)	3.2 (2.1-5.7)	3.02±2.09 (0.83-14.3)	2.2 (1.8-3.5)	0.009[a]
Hb (g/ dL)	10.61±1.44 (7.8-15.7)	10.5 (9.6-11.3)	11.37±1.49 (8.5-15.8)	10.9 (10.4-129)	0.002[a]
MCV (fL)	83.31±8.83 (61.4-100.3)	84.9 (76.2-90.6)	82.28±9.13 (59.5-101.2)	81.9 (76.1-91.1)	0.471[a]
RDW	14.7±1.92 (11.8-24.6)	14.4 (13.5-15.7)	14±1.27 (11.6-17)	13.9 (13-15)	0.031[a]
MPV (fL)	8.75±0.92 (6.9-11.6)	8.7 (8-9.37)	9.08±1.15 (7-12.1)	9 (8.3-9.77)	0.059[b]
PDW	15.81±0.41 (14.9-16.9)	15.8 (15.42-16.1)	15.92±0.54 (15-17.6)	15.85 (15.5-16.3)	0.171[b]
PLT (10^3 /µL)	8.75±0.93 (6.9-11.6)	427.5 (353.7-516.2)	457.13±160.3 (67-867)	427 (364.2-552.7)	0.704[a]
NLR	0.93±1.05 (0.13-7.48)	0.65 (0.35-1.02)	0.67±1.04 (0.14-7.01)	0.42 (0.28-0.57)	0.003[a]
PLR	91.95±44.44 (20.57-235.62)	82 (61.9-109.29	84.35±48.63 (9.52-277.06)	70.1 (57.9-100.5)	0.177[a]

Data are presented as mean±SD or as median with range. P<0.05 was considered significant. Significant values were expressed in bold. WBC: White Blood Cells, Hb: Hemoglobin, MCV: Mean Corpuscular Volume, RDW: Red cell distribution volume, MPV: Mean platelet volume, PDW: Platelet Distribution Width, PLT: Platelet, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-Reactive Protein, fL: Femtoliter, mg: milligram, dL: deciliter, L: liter, g:gram, µL: microliter; a Mann-Whitney U test, b Student- t test was performed.

Previously more specifically, NLR has been used to determine the severity of inflammation in respiratory tract [19-21]. Lee et al. determined NLR as a useful parameter in determining the severity of pneumonia [22]. Neutrophils produce so many inflammatory products, including proteolytic enzymes and oxidants, and have been contained in the formation of acute and chronic lung disease [23].

When evaluated together with the results of this study, NLR may be a marker to evaluate disease severity in patients with AB with an inflammatory pattern. There is an increasing argument that in respiratory viral infections, neutrophils may have a main role in host defense [24]. A recent study has confirmed that neutrophil numbers correlate with IL-8 levels and that both IL-8 levels and neutrophil numbers correlate closely with symptom severity during respiratory viral infections obtained from samples of nasal secretions [25]. In term and preterm infants, chemotaxis and adherence of neutrophils are impaired [26]. This may be an explanation for the higher risk of acute bronchiolitis that infants appear to have in the first month of life and tend to be severe in those with symptoms.

In addition, we found a cut-off value of NLR>1.04 yielded a sensitivity of 44.4% and a specificity of 81% for predicting longer hospitalization duration in patients with AB. In some studies, AB with RSV and Rhinovirus have been reported to lead to more severe clinic events [27,28]. Moreover, some authors claimed that RSV-related bronchiolitis had a longer hospital stay and higher baseline score than Rhinovirus- related bronchiolitis [27]. Similar to our study, Calvo et al. found no

Table 2. Comparison of demographics and laboratory parameters between children with RSV vs Rhinovirus bronchiolitis.

Parameters	RSV Group (n=47)		Rhinovirus Group (n=47)		P-values
Demographic parameters					
	n	%	n	%	
Gender Male Female	 25 22	 53.2 46.8	 30 17	 63.8 36.2	0.295[a]
	Mean ± SD (min – max)	Median (25 – 75 p)	Mean ± SD	Median (25-75p)	
Age of diagnosis	97.44±68.63	71	176.02±165.61	90	0.049[a]
(days)	33-330	47-120	35-575	54-270	
Bronchiolitis score	6.67±2.57 (2-12)	6 (5-9)	5.84±2.62 (2-11)	6 (3-8)	0.131[b]
Duration of hospitalization (days)	6.39±3.7 (2-26)	6 (4-8)	5.82±3.48 (2-15)	5.5 (3-7.25)	0.453[b]
Laboratory parameters					
	Mean ± SD (min – max)	Median (25 -75 p)	Mean ± SD (min – max)	Median (25-75p)	
WBC (103 /µL)	10.47±3.72 (4.09-20.12)	10.19 (7.46-12.55)	12.15±4.85 (5.55-25.69)	10.85 (8.15-15.9)	0.144[a]
Lymphocyte (103 /µL)	5.74±2.75 (1.77-14.79)	5.22 (3.71-7.21)	5.83±2.7 (1.83-14.68)	5.27 (3.74-7.31)	0.759[a]
Neutrophil (103 /µL)	3.56±2.17 (0.69-10.78)	3.07 (1.85-4.21)	4.99±3.88 (0.79-16.39)	3.84 (2.3-6.98)	0.112[a]
Hb (g/ dL)	10.53-1.38 (7.9-14)	10.7 (9.6-11.3)	10.64±1.5 (7.8-15.7)	10.5 (9.6-11.3)	0.925[a]
MCV (fL)	84.94-8.23 (67-100.12)	87.4 (78.3-90.9)	82.08±9.29 (61.4-100.3)	84.1 (74.1-89.8)	0.125[a]
RDW	14.81±1.95 (11.9-22.6)	15 (13.3-15.9)	14.59±1.87 (11.8-24.6)	14.3 (13.6-15)	0.55[a]
MPV (fL)	8.85±0.99 (7.5-11.6)	8.6 (8-9.5)	8.65±0.84 (6.9-10.4)	8.7 (8-9.3)	0.312[a]
PDW	15.89±0.41 (15.2-16.9)	15.9 (15.6-16.2)	15.73±0.39 (14.9-16.8)	15.7 (15.4-16)	0.054[a]
PLT (103 /µL)	446.23±127.74 (218-764)	424 (351-545)	457.7±139.62 (223-826)	455 (368-508)	0.623[a]
NLR	0.75±0.6 (0.13-3.28)	0.58 (0.35-1)	1.11±1.34 (0.13-7.48)	0.74 (0.39-1.15)	0.32[a]
PLR	91.99±44.52 (31.08-211.05)	77.8 (58.95-112.20)	91.91±44.83 (20.57-235.62)	82.77 (62.94-103.98)	0.818[a]
CRP (mg/dL)	7.1±13.45 (1-72.9)	1 (1-6.1)	9.87±17.57 (1-80)	1 (1-9.9)	0.745[a]

Data are presented as mean±SD or as median with range. P<0.05 was considered significant. Significant values were expressed in bold. WBC: White Blood Cells, Hb: Hemoglobin, MCV: Mean Corpuscular Volume, RDW: Red cell distribution volume, MPV: Mean platelet volume, PDW: Platelet Distribution Width, PLT: Platelet, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-Reactive Protein, fL: Femtoliter; mg: milligram, dL: deciliter, L: liter, g: gram, µL: microliter, aMann-Whitney U test, bStudent- t test was performed.

difference between viral agents in this respect [29]. On account of hospital length-of-stay (LOS), the median LOS was 2,3 days among infants with RSV-only bronchiolitis, versus 1,4 days among infants with Rhinovirus-only bronchiolitis. Marguet et al. showed in infants with their first bronchiolitis hospitalization that the infants with rhinovirus-only infections had lower odds of staying in the hospital for more days compared with infants with RSV [27]. Recently, Mansbach et al. showed in US infants aged <2 years that those with sole Rhinovirus-induced bronchiolitis had shorter hospital LOS than those with only RSV. Consistent with the literature, when we compare the demographics and laboratory parameters between infants with RSV and Rhinovirus bronchiolitis, we showed no statistically significant differences between two patient groups, except for the age of diagnosis days [30,31].

Our laboratory findings such as leukocyte count and CRP did not differ between viral agents. These findings support the recommendations of the American Academy of Pediatrics at evidence B level in 2014 for laboratory tests in AB [4]. Also, in the present study, patients were divided into three groups according to the severity of the disease. When we compare laboratory parameters among infants with mild, moderate, and severe bronchiolitis, no statistical difference was found. However, the severity of AB determines not only the specific

Table 3. Comparison of laboratory parameters among children with mild, moderate and severe bronchiolitis.

Parameters	Mild Bronchiolitis (n=17)	Moderate Bronchiolitis (n=53)	Severe Bronchiolitis (n=24)	P-value
Age of diagnosis (days)	68 (50.75-110)	90 (53.5-193.5)	71 (50-180)	0.623[a]
Duration of hospitalization (days)	3.5 (2-5)	6 (3.5-6.5)	9 (6-12)	<0.001[a]
WBC (103 /µL)	8.07 (6.23-14.1)	11.15 (8.18-14.82)	10.19 (8.81-11.63)	0.219[a]
Lymphocyte (103 /µL)	5.03 (3.74-5.98)	5.38 (3.77-7.77)	5.98 (3.81-8.65)	0.169[a]
Neutrophil (103 /µL)	2.67 (1.36-4.86)	3.34 (2.27-6.08)	3.84 (2.4-5.92)	0.184[a]
Hb (g/ dL)	10.6 (9.9-11.07)	10.6 (9.7-11.5)	10.4 (9-11.2)	0.644[a]
MCV (fL)	83.8 (80.6-92.12)	83.1 (74.2-90.1)	86.1 (77.2-90.6)	0.44[a]
RDW	13.7 (13.05-14.32)	14.7 (13.4-15.9)	15 (14-15.8)	0.032[a]
MPV (fL)	8.96±0.86 (7.2-10.6)	8.75±0.86 (7.2-10.6)	8.61±1.09 (6.9-11.6)	0.523[b]
PDW	15.95 (15.52-16.27)	15.8 (15.4-16.05)	15.7 (15.4-16.1)	0.357[a]
PLT (103 /µL)	460 (399.25-646.25)	419 (345.5-501.5)	428 (346-516)	0.213[a]
NLR	0.42 (0.34-0.82)	0.66 (0.32-1)	0.74 (0.45-1.61)	0.162[a]
PLR	97.94 (74.62-112.44)	76.26 (52.53-98.3)	87.61 (76.36-130.46)	0.06 [a]
CRP (mg/dL)	1 (1-2.87)	1 (1-11.4)	1 (1-6.5)	0.32[a]

Data are presented as mean±SD or as median with range. P<0.05 was considered significant. Significant values were expressed in bold. WBC: White Blood Cells, Hb: Hemoglobin, MCV: Mean Corpuscular Volume, RDW: Red cell distribution volume, MPV: Mean platelet volume, PDW: Platelet Distribution Width, PLT: Platelet, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, CRP: C-Reactive Protein, fL: Femtoliter, mg: milligram, dL: deciliter, L: liter, g: gram, µL: microliter; aKruskal-Wallis test, bANOVA was performed.

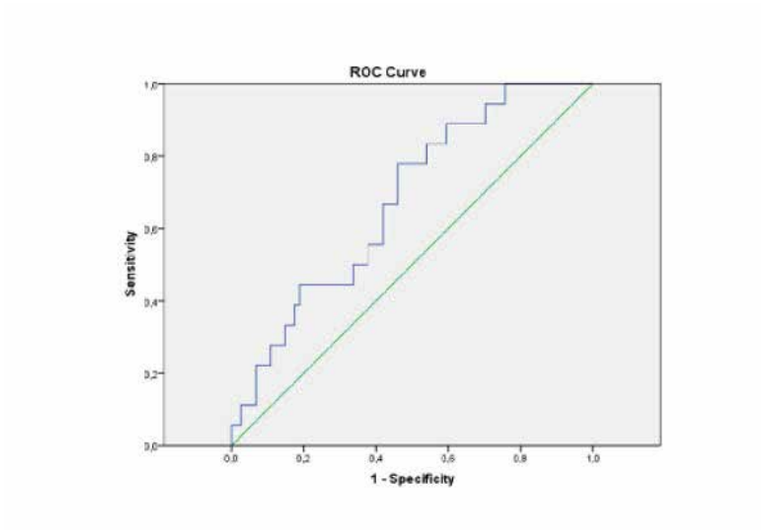

Figure 1. A receiver operating characteristics curve was performed to determine the cut-off value of NLR to predict long duration of hospitalization (≥9 days) in children with acute bronchiolitis.

immunological susceptibility but also the type of disease observed with factors such as the presence of inflammation spreading to the lower respiratory tract, relative airway size and the age of the baby.

There are some limitations in this study. Firstly, it included only one season; secondly, the sample size was relatively small. Prospective studies involving larger patient numbers are needed to assess the role of neutrophil values in the AB patients.

In conclusion, the present study has demonstrated that NLR was increased in all infants with AB, and NLR could predict the hospitalization duration. For this reason, clinicians who evaluate CBC which is often ordered should not disregard evaluating the NLR in infants with AB.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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