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The Predictive Value of Complete Blood Count Parameters in the Clinical Course of Acute Bronchiolitis: A Descriptive Study

Tam Kan Sayımı Parametrelerinin Akut Bronşiolitin Klinik Gidişatını Öngörmedeki Değeri: Tanımlayıcı Bir Araştırma

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This study was prepared based on the findings of Mustafa Orhan DUYAR's thesis study titled "Can complete blood count parameters measured at the time of admission in acute bronchiolitis be an early biomarker indicating the clinical severity and progression of the disease?" (Kayseri: Kayseri City Training and Research Hospital; 2024).

ABSTRACT Objective: Bronchiolitis is an inflammation of the bronchioles, commonly caused by viral pathogens, and is characterized by respiratory distress in children under the age of two. Early identification of disease severity is critical to initiate timely treatment and prevent clinical deterioration. This study aimed to investigate whether neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (TLR), mean platelet volume (MPV), and platelet mass index (PMI)—parameters derived from complete blood count—could serve as early biomarkers for diagnosis and clinical severity of the disease. **Material and Methods:** Patients were divided into three groups based on disease severity: outpatients (mild bronchiolitis), hospitalized patients (moderate bronchiolitis), and patients admitted to the pediatric intensive care unit (severe bronchiolitis). Age-matched healthy children with complete blood counts obtained during the same period were included as controls. Differences in CBC parameters (NLR, TLR, MPV, and PMI) at admission were compared among the groups. **Results:** NLR and TLR values were significantly higher in bronchiolitis patients compared to healthy controls ($p<0.001$). Furthermore, these values were significantly elevated in the severe bronchiolitis group compared to the mild and moderate groups ($p<0.001$). A statistically significant positive correlation was found between bronchiolitis severity and NLR (rho=0.460; $p<0.001$) and TLR (rho=0.349; $p<0.001$). MPV was significantly higher in healthy controls than in patients ($p<0.001$), while PMI showed no significant difference among the groups. **Conclusion:** This study demonstrates that complete blood count parameters, particularly NLR and TLR, may serve as early biomarkers to predict disease severity in patients with acute bronchiolitis.

Keywords: Bronchiolitis; complete blood count; lymphocyte count; neutrophil count; platelet count

ÖZET Amaç: Bronşiyolit, genellikle viral patojenlerin neden olduğu, 2 yaşın altındaki çocuklarda solunum sıkıntısı kliniği ile karakterize bir bronşiyol iltihabıdır. Hastaların klinik ciddiyetinin erken tespiti, tedaviye erken başlanarak ağır kliniğin önlenmesinde önemlidir. Bu çalışmanın amacı, tam kan sayımı ile değerlendirilebilen nötrofil/lenfosit oranı [neutrophil/lymphocyte ratio (NLR)], trombosit/lenfosit [platelet/lymphocyte ratio (TLR)] oranı, ortalama trombosit hacmi [mean platelet volume (MPV)] ve trombosit kitle indeksi [platelet mass index (PMI)] parametrelerinin hastalığın tanısı ve klinik şiddeti için erken bir biyobelirteç olup olamayacağını göstermektir. **Gereç ve Yöntemler:** Hasta grubu, pediatri polikliniklerine başvuran ve ayaktan takip edilen hastalar (hafif bronşiyolit), pediatri servisine yatırılan hastalar (orta bronşiyolit) ve pediatrik yoğun bakım ünitesine yatırılan hastalar (ağır bronşiyolit) olmak üzere 3 gruba ayrıldı. Aynı zaman aralığında tam kan sayımı alınan sağlıklı çocuklar kontrol grubu olarak dâhil edildi. Başvuru sırasında elde edilen tam kan sayımı parametrelerindeki (NLR, TLR, MPV ve PMI) değişiklikler gruplar arasında değerlendirildi. **Bulgular:** Çalışmamızda bronşiyolitli bebeklerin NLR ve TLR değerleri sağlıklı kontrollere göre anlamlı olarak yüksektir ($p<0,001$). Aynı zamanda, NLR ve TLR değerleri ağır bronşiyolit hasta grubunda diğer bronşiyolit gruplarına göre anlamlı olarak daha yüksektir ($p<0,001$). Bronşiyolit şiddeti ile NLR ve TLR düzeyleri arasında istatistiksel olarak anlamlı pozitif korelasyon vardır (rho=0,460; $p<0,001$, rho=0,349; $p<0,001$). MPV değeri sağlıklı kontrol grubunda hasta grubuna göre anlamlı olarak yüksek bulunurken ($p<0,001$), PMI parametresi gruplar arasında anlamlı bir farklılık göstermedi. **Sonuç**: Bu çalışma, tam kan sayımı parametrelerinin, özellikle NLR ve TLR'nin, akut bronşiyolitli hastalarda hastalığın prognozunu tahmin etmek için erken biyobelirteç olarak kullanılabileceğini göstermiştir.

Anahtar Kelimeler: Bronşiyolit; tam kan sayımı; lenfosit sayımı; nötrofil sayımı; trombosit sayımı

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Bronchiolitis is a clinical condition characterized by inflammation of the bronchioles, which is usually caused by viral pathogens. It increases the number of breaths per minute, retraction during respiratory function, and wheezing.[1] Radiological imaging is not required except in patients with severe clinical complications and secondary bacterial infection.[2] Additionally, laboratory tests are not routinely recommended for diagnosis and treatment.[3] Early determination of the clinical severity of acute bronchiolitis in patients who are treated as outpatients, followed up as inpatients, or who require intensive care because of respiratory failure findings is important for preventing severe disease by starting treatment early.[4]

In inflammatory diseases, the erythrocyte sedimentation rate, C-reactive protein (CRP), procalcitonin (PCT), and leukocyte count are the main acute-phase reactants. Along with these parameters, platelet parameters, including the platelet count (PLT), the platelet mass index (PMI), and the mean platelet volume (MPV), may act as acute-phase reactants in diseases characterized by inflammatory processes.[5] The MPV, which is an indicator of platelet activation and function, can affect many infectious and inflammatory events.[6] However, it was found to increase in some studies, but decrease in others.[5,7-10] The neutrophil/lymphocyte ratio (NLR) is accepted as a marker that accurately reflects the inflammatory response, and it increases in direct proportion to the severity of diseases.[11,12] The NLR plays a role in airway inflammation, and relative lymphopenia accompanies neutrophilia in infants with acute bronchiolitis.[13,14] Although lymphocyte dominance generally occurs in acute bronchiolitis of viral origin, lymphopenia may also occur in severe cases of bronchiolitis caused by respiratory syncytial virus.[15,16] In this context, parameters such as the platelet/lymphocyte ratio (TLR) obtained from the complete blood count can be used as indicators of inflammatory processes.[17] Recent studies have found that the evaluation of platelet function with the MPV or PLT alone may be insufficient and that the platelet mass is a more reliable marker. Platelet mass is determined by the PMI, which is calculated by multiplying the PLT and MPV, and younger and more active platelets were found to play a role in inflammatory processes.[18-20]

In this study, we determined whether the NLR, TLR, MPV, and PMI, which can be evaluated by complete blood count in patients with mild, moderate, and severe bronchiolitis, can be used as early biomarkers for the diagnosis and clinical severity of the disease.

MATERIAL AND METHODS

Infants (1-24 months old) who were admitted to the pediatric outpatient clinic of our hospital between 1 January 2022 and 31 December 2022 and who were admitted to pediatric intensive care and pediatric wards with a diagnosis of acute bronchiolitis or who were followed up and treated as outpatients were included in the study by retrospectively examining the file records. The Kayseri City Training and Research Hospital Ethics Committee (date: May 09, 2023, no: 835) approved the study. This study was conducted following the principles of the Declaration of Helsinki.

The patients were divided into 3 groups as follows: patients admitted to pediatric outpatient clinic and followed up as outpatients (mild bronchiolitis), patients hospitalized (moderate bronchiolitis), and patients hospitalized in the pediatric intensive care unit (PICU) (severe bronchiolitis). The patients in the intensive care unit were classified as intubated, receiving high-flow oxygen therapy, and receiving oxygen support with a diffuser mask. Within the same time interval, healthy children (1-24 months old) without any additional complaints or signs of infection, who were admitted to the pediatric outpatient clinic of our hospital and underwent complete blood count testing as part of the procedural requirements for anesthesia prior to strabismus, inguinal hernia, or circumcision surgeries, or as part of routine child health screening, were included in the control group. Patients in the PICU group consisted of patients initially admitted to the PICU or transferred to the PICU within the first 24 h after admission to the ward. No patient included in the study was transferred to the PICU 24 h after admission to the ward. For all patients included in the study, changes in complete blood count parameters (NLR, TLR, MPV, and PMI) obtained at admission were noted and evaluated among groups.

Patients with underlying congenital heart disease, iron deficiency anemia, a history of prematurity, a history of recurrent bronchiolitis, immunodeficiency, asthma, or any chronic disease, patients diagnosed with pneumonia as a result of acute phase elevation (significant elevation of PCT), posteroanterior chest radiography, and physical examination findings compatible with pneumonia, and patients who did not have a complete blood count at presentation were excluded. Children who were below one month or above 24 months at the time of presentation and those who received systemic steroid treatment before the complete blood count was taken were also excluded from the study.

STATISTICAL ANALYSIS

The data were analyzed using the IBM SPSS Statistics 26.0 (IBM Corp., Armonk, New York, USA) statistical package program. Descriptive statistics are presented as the number of units, percentage, mean±standard deviation, median, minimum value, maximum value, and interquartile distance values. The normal distributions of the numerical variables were evaluated by conducting the Shapiro-Wilk normality test. Differences in the CRP, PCT, PMI, NLR, TLR, and MPV among the groups were determined by conducting a Kruskal-Wallis analysis. Multiple comparisons via the Kruskal-Wallis test were performed with the Dunn-Bonferroni correction. The white blood cell (WBC) value and PLT of the groups were compared by one-way analysis of variance. The Duncan test was performed as a multiple comparison test for one-way analysis of variance. The length of hospital stay of ward and intensive care unit patients and the NLR, TLR, MPV, and PMI values of patients who received high flow nasal cannula and intubated patients were compared via the Mann-Whitney U test. The relationships between the length of hospital stay and the PMI, NLR, TLR, and MPV were evaluated by the Spearman correlation coefficient. The diagnostic performance of the NLR and TLR in predicting disease severity was evaluated using sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Optimal cut-off values for different levels of bronchiolitis severity were determined through receiver operating characteristic curve analysis. For all tests, the results were considered to be statistically significant at $p<0.05$.

RESULTS

Among the 621 patients with mild bronchiolitis who were followed up and treated in pediatric outpatient clinic during the study period, 516 patients with incomplete blood counts were excluded from the study. All inpatients in the inpatient group had a complete blood count. No significant difference was found between the infants in the acute bronchiolitis group and those in the control group in terms of mean age or sex ($p=0.147$, $p=0.078$). The general characteristics of 210 infants in the bronchiolitis group and 90 infants in the control group who met the inclusion criteria are summarized in Table 1.

The WBC value of infants with severe bronchiolitis were significantly greater than those of the infants in the control group and other bronchiolitis groups ($p<0.001$). The PLT values of the severe bronchiolitis group were significantly greater than those of the control group and the moderate bronchiolitis group ($p<0.001$). The NLR and TLR values were sig-

TABLE 1: General characteristics of the patient and control groups

Variable	n (%)
Groups	
Outpatient clinics	105 (35.0)
Pediatric ward	54 (18.0)
Intensive care	51 (17.0)
Control	90 (30.0)
Gender	
Male	182 (60.7)
Female	118 (39.3)
Type of treatment	
Oxygen with mask	60 (20.0)
High flow nasal cannula	36 (12.0)
Mechanical ventilation	9 (3.0)
Variable	**Statistics**
Age (months)	
$\bar{X}$±SD	10.1±6.1
Median (minimum-maximum)	8.7 (1-23)
Hospitalization duration (day), n=105	
$\bar{X}$±SD	4.5±5.5
Median (minimum-maximum)	3.0 (1-49)

n: number of patients; %: percentage value; SD: standard deviation

nificantly greater in the severe bronchiolitis group than in all other groups (p<0.001) and in the moderate and mild bronchiolitis groups than in the healthy control group. While the MPV of healthy infants was significantly greater than that of infants with bronchiolitis (p<0.001), no significant difference in MPV was found when the bronchiolitis groups were evaluated among themselves. When the CRP values of infants with bronchiolitis were compared, the CRP values in the group with severe bronchiolitis were significantly greater than those in the group with mild bronchiolitis (p=0.001), whereas no significant difference was found between the CRP values of infants with moderate bronchiolitis and those in the other 2 groups (Table 2). A significant moderate positive correlation was found between disease severity and the NLR, while a significant weak positive correlation was found between disease severity and the TLR (Figure 1).

A significant, weak positive correlation was found between the length of hospitalization of pa-

TABLE 2: Comparison of complete blood count parameters of the groups

	Mild Bronchiolitis n=105	Moderate Bronchiolitis n=54	Severe Bronchiolitis n=51	Control n=90	p value
WBC (10^3/μL)	10.90±4.07[a]	11.07±4.25[a]	14.82±6.29[b]	9.41±2.17[a]	<0.001‡
PLT (10^3/μL)	417.2±129.9[ab]	396.0±181.7[a]	455.2±119.8[b]	385.2±108.6[a]	<0.001‡
NLR	0.83 (0.53)[b]	0.84 (1.36)[b]	2.00 (3.61)[c]	0.34 (0.26)[a]	<0.001†
TLR	77.19 (52.37)[b]	85.93 (45.72)[b]	134.0 (93.6)[c]	66.89 (32.49)[a]	<0.001†
MPV (fL)	9.10 (0.85)[b]	9.20 (1.05)[b]	9.10 (1.10)[b]	9.70 (1.50)[a]	<0.001†
PMI (fL/nL)	3637.2 (1387.0)	3476.0 (1627.5)	4130.8 (1735.3)	3729.3 (1365.7)	0.060†
CRP (mg/L)	3.80 (9.50)[a]	5.65 (16.97)[ab]	8.60 (25.53)[b]	-	0.001

†: Kruskal-Wallis analysis; ‡:one-way analysis of variance; a, b, and c superscripts indicate the difference between groups in each row. There is no significant difference between the groups ith the same letters.

WBC: White blood count; PLT: Platelet value; NLR: Neutrophil/lymphocyte ratio; TLR: Platelet/lymphocyte ratio; MPV: Mean platelet volume; PMI: Platelet mass index; CRP: C-reactive protein

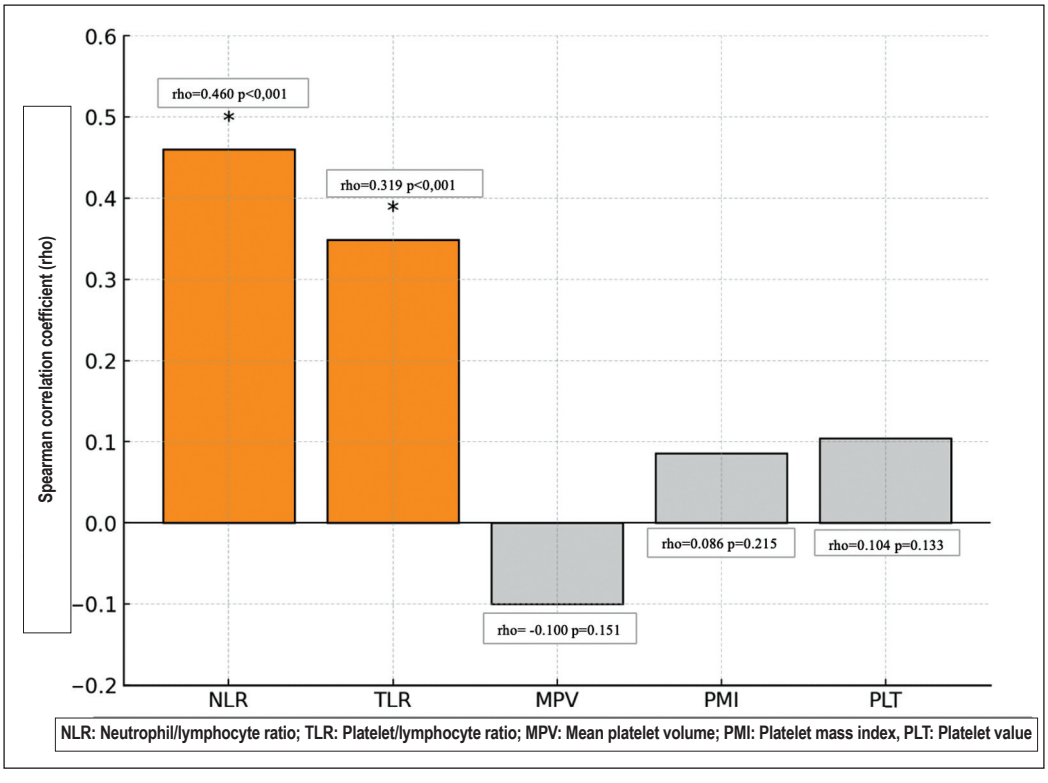

FIGURE 1: Relationships between disease severity and the NLR, TLR, MPV, PMI, and PLT

TABLE 3: Relationship between length of hospitalization and hemogram parameters

	Length of stay			
	Pediatric ward (moderate bronchiolitis) n=54		Intensive care (severe bronchiolitis) n=51	
	rho	p value	rho	p value
NLR	0.013	0.927	-0.194	0.174
TLR	0.108	0.435	0.017	0.907
MPV (fL)	0.022	0.878	0.295	0.036
PMI (fL/nL)	0.181	0.194	0.391	0.005

rho: Spearman correlation coefficient; NLR: Neutrophil/lymphocyte ratio; TLR: Platelet/lymphocyte ratio; MPV: Mean platelet volume; PMI: Platelet mass index

tients with severe bronchiolitis and the MPV (ρ=0.295; p=0.036), and a significant moderate positive correlation was found between the PMI (ρ=0.391; p=0.005). Thus, as the MPV and PMI increased, the duration of inpatient treatment in the intensive care unit increased (Table 3).

The diagnostic performance of the NLR and TLR was evaluated in terms of their ability to predict disease severity. The sensitivity was 77%, the specificity was 80%, the PPV was 43%, and the NPV was 94% for the threshold NLR≥1 in severe bronchiolitis patients. The sensitivity was 73%, the specificity was 69%, the PPV was 32%, and the NPV was 92% for the threshold TLR≥90. In patients with mild bronchiolitis, the diagnostic performance of the NLR and the TLR is limited. The sensitivity, specificity, PPV, and NPV data of the NLR and TLR in severe, moderate, and mild bronchiolitis patients are presented in Table 4.

TABLE 4: Predictive values of NLR and TLR for the disease severity

	Sensitivity	Specificity	PPV	NPV
*Severe vs others				
NLR≥1	77	80	43	94
TLR≥90	73	69	32	92
Moderate vs control				
NLR≥0.5	74	71	61	83
TLR≥75	65	62	51	75
Mild vs control				
NLR≥0.4	73	59	68	65
TLR≥70	59	57	61	54

*Severe vs others comparison includes patients with severe bronchiolitis versus a combined group of moderate, mild, and control subjects. PPV: Positive Predictive Value; NPV: Negative Predictive Value; NLR: Neutrophil/lymphocyte ratio; TLR: Platelet/lymphocyte ratio.

DISCUSSION

In this study, we evaluated the role of complete blood count parameters in predicting clinical severity in patients with acute bronchiolitis. WBC value, PLT, and the NLR and TLR values of infants with severe bronchiolitis were significantly greater than those of healthy controls. Moreover, the NLR and TLR values were significantly greater in the severe bronchiolitis patient group than in the other bronchiolitis groups. While the MPV was significantly greater in the healthy control group than in the patient group, the PMI did not significantly differ between the groups.

The NLR, which is considered to be a new biomarker in systemic inflammatory disorders, can reflect the immune response to various stress stimuli.[11] In patients with bronchiolitis/bronchitis, the NLR increased significantly as the clinical condition worsened, and WBC and CRP values were not correlated with disease severity.[21] The NLR was reported to be related to disease severity in patients with CAP and was significantly correlated with the pneumonia severity index score.[22] A similar study revealed that the NLR may be useful in determining the severity of pneumonia.[23] Studies evaluating NLR changes in acute inflammatory lung diseases are extremely rare in infants. These data indicate that the NLR may be a useful biomarker for the recognition of acute bronchiolitis and the early prediction of its clinical severity. The NLR is a simple, accessible, and inexpensive method that can be measured with hemogram parameters recorded at admission, especially in predicting the progression of severe, moderate, and mild

bronchiolitis, increasing its clinical value. In this study, the NLR of infants with severe bronchiolitis receiving treatment in the intensive care unit was significantly greater than that of the infants in the control group and those with mild and moderate bronchiolitis. The NLR of infants with mild and moderate bronchiolitis was also greater than that of healthy infants in the control group. In this case, the NLR increased with an increase in disease severity. Additionally, the high negative predictive value of the NLR (94%) was important in differentiating cases of severe bronchiolitis. This finding indicates that the chance of a severe course is very low in patients with an NLR<1. The high sensitivity (77%) and specificity (80%) also make the NLR an effective biomarker for the exclusion of severe bronchiolitis.

Recent studies have suggested that the TLR, obtained by dividing the number of platelets measured in a complete blood count by the number of lymphocytes, strongly affects the pathogenesis of the systemic inflammatory response and can be used as an indicator of inflammation.[17] In the adult age group, the TLR and NLR were interpreted as predictive in terms of diagnosis in coronavirus disease-2019 (COVID-19) (novel coronavirus disease) patients, and the TLR and NLR were found to be high in patients under intensive care hospitalization.[24] In pediatric patients undergoing curative surgery for acute appendicitis, high NLR and TLR parameters were found to be indicators of the risk of developing complications.[25] The TLR was found to be greater in neonates hospitalized in the neonatal intensive care unit with suspicion or evidence of early neonatal sepsis than in healthy controls.[26] Additionally, TLR, which increases in the presence of disease in patients with acute bronchiolitis, was found to increase with increasing clinical severity.[27] In this study, the findings that the TLR of patients with severe bronchiolitis was significantly greater than that of the patients in all other study groups and that the TLR of patients with moderate and mild bronchiolitis was significantly greater than that of the patients in the control group support these studies. These findings suggest that in the presence of acute bronchiolitis and as the severity of the disease increases, the TLR increases. The NPV of the TLR is highly valuable in the differential diagnosis of severe bronchiolitis (92%), but it has a lower PPV (32%) and specificity (69%) than the NLR. These findings suggest that the TLR alone may have limited diagnostic value and that it may be used for evaluation in combination with the NLR. Like the NLR, the TLR is an inexpensive and easily obtainable parameter. Therefore, prospective studies involving more patients are needed for its routine use.

The MPV is an indicator of platelet activation and function.[6] While the MPV was found to be lower in patients with a diagnosis of acute bronchiolitis than in the healthy control group, in other similar studies, the MPV of patients with acute bronchiolitis was reported to be greater than that of the patients in the control group, and no difference in MPV was found within the patient groups.[7-9] While higher MPV values were found in patients hospitalized with a diagnosis of community-acquired pneumonia than in outpatients, lower MPV values were recorded in outpatients than in healthy controls.[5] In children with lower respiratory tract infections diagnosed with asthma, both pretreatment and post-treatment MPV values were significantly greater in the patient group than in the control group. Moreover, it was found that MPV values decrease after treatment compared to pretreatment.[28] In a study conducted in adults, the MPV was reported to be negatively correlated with the severity of sepsis, and in a review study, it was reported that the MPV may first increase with mild inflammation but may decrease as the severity of sepsis worsens in the clinic.[10,29] In this study, the MPV of healthy infants in the control group was greater than that of patients with severe, moderate, or mild bronchiolitis. However, no significant change in MPV was observed as the severity of bronchiolitis increased in our patient group. This may be related to the small number of patients in the bronchiolitis group.

Some studies have suggested that it would be more accurate to evaluate platelet function with the PMI obtained by multiplying the PLT count and MPV.[18,19] In term infants diagnosed with neonatal transient tachypnoea, a low PMI is associated with prolonged duration of tachypnoea in the patient and thus prolonged respiratory support treatment.[30,31] Moreover, the PMI is lower in COVID-19 patients

than in healthy controls.[32] There is no PMI comparison study conducted in the pediatric age group specifically for acute bronchiolitis. In this study, no significant difference was found between bronchiolitis subgroups and the control group, contrary to the studies conducted in the neonatal period.

CONCLUSIONS

Early recognition of bronchiolitis, which is one of the important causes of morbidity and mortality and is especially common in infants under 2 years of age, early initiation of treatment, and prediction of clinical progression are highly important. This study revealed that the NLR and TLR, especially complete blood count parameters, may be useful in this respect. However, the fact that this was a retrospective study performed in a single center with a few patients is an important limitation. Another limitation of the study is that complete blood count examinations were not available for all patients who were followed up with a diagnosis of mild bronchiolitis. Multicenter prospective studies with more patients are needed to determine the relationships between complete blood count parameters, which are inexpensive and easily accessible tests, and the clinical progression of acute bronchiolitis.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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