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Evaluation of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as potential biomarkers of acute exacerbation in children with non-cystic fibrosis bronchiectasis

Nötrofil-lenfosit oranı ve trombosit-lenfosit oranlarının çocuklardaki kistik fibroz dışı bronşektazinin akut alevlenmesinde potansiyel biyolojik gösterge olarak değerlendirmesi

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Abstract

Purpose: Non- cyctic fibrosis bronchiectasis (non-CFBE) is a chronic inflammatory lung disease which causes significant morbidity in children. Exacerbations in non-CFBE are associated with worsening lung function. Several laboratory parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) have been suggested to be as an indicator in various chronic inflammatory diseases. We aimed to asses the value of the NLR, PLR and MPV as markers of acute exacerbation in pediatric patients with non-CFBE.

Materials and methods: The NLR, PLR, and MPV values of 55 non-CFBE patients (during exacerbation and stable state periods) and 79 healthy control subjects were analyzed.

Results: The mean ages for the patient and control group were 13.62±3.5 and 12.72±2.68 years, respectively. 64% of patients and 54% of control subjects were male. The white blood cell count, absolute neutrophil count, and NLR values were significantly higher in the exacerbation group than in the healthy control group (p<0.05). MPV and PLR values were not significantly different between the two groups. Only forced expiratory volume in one second (FEV1) and C-reactive protein (CRP) level were significantly different (p<0.001) between the acute exacerbation and stable state periods in the patient group.

Conclusion: Despite the NLR value being significantly higher in children with non-CFBE than in healthy control subjects, it did not differentiate between the steady-state and acute exacerbations periods of the disease. PLR and MPV values also cannot be used as markers of acute exacerbation in children with non-CFBE.

Key words: Bronchiectasis, non-cystic fibrosis bronchiectasis, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, mean platelet volume.

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Özet

Amaç: Kistik fibroz dışı bronsektazi (KFDBE) çocuklarda önemli morbiditeye yol açan kronik inflamatuar akciğer hastalığıdır. KFDBE'de alevlenme akciğer fonksiyonlarının kötüye gitmesi ile ilişkilidir. Nötrofil-lenfosit oranı (NLO), trombosit- lenfosit oranı (TLO) ve ortalama trombosit hacmi (OTH) gibi bazı laboratuar parametrelerinin çesitli kronik inflamatuar hastalıkları için bir gösterge olduğu öne sürülmüştür. Çalışmamızda, KFDBE'li çocuklardaki akut alevlenmede NLO, TLO ve OTH ölçümlerinin bir gösterge olarak değerlendirilmesini amaçladık.

Gereç ve yöntem: Çalışmada, akut alevlenme ve stabil dönemdeki 55 KFDBE' li hastanın ve 79 sağlıklı kontrol grubunun NLO, TLO ve OTH değerleri analiz edildi.

Bulgular: Çalışma ve kontrol grubundaki hastaların ortalama yaşları sırasıyla 13,62±3,5 ve 12,72±2,68 yıldı. Çalışma grubunun %64'ü ve kontrol grubunun %54'ü erkekti. Alevlenme dönemindeki grupta beyaz küre sayısı, nötrofil oranı ve NLO değerleri sağlıklı kontrol grubundan anlamlı olarak yüksekti (p<0,05). İki gruptaki TLO ve OTH değerleri arasında anlamli fark yoktu. Çalışma grubunun akut alevlenme ve stabil dönemleri arasında, sadece ilk bir saniyede zorlu ekspiryum hacmi (FEV1) ve c-reaktif protein (CRP) seviyeleri arasında anlamlı fark vardı (p<0,001).

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Sonuç: Her ne kadar KFDBE' li çocuklardaki NLO değeri sağlıklı kontrol grubundaki çocuklara göre anlamlı ölçüde yüksek olsa da hastalığın stabil durum ve akut alevlenme periyodu arasında NLO değeri farklılık göstermedi. TLO ve OTH değerleri, KFDBE'li çocuklardaki akut alevlenmelerde bir gösterge olarak kullanılamaz.

Anahtar kelimeler: Bronşektazi, kistik fibroz dışı bronşektazi, nötrofil-lenfosit oranı, trombosit-lenfosit oranı, ortalama trombosit hacmi.

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Introduction

Bronchiectasis (BE) comprises abnormal dilation and distortion of the bronchial tree caused by numerous pathophysiological mechanisms, all of which result in the weakening and collapse of the bronchial walls and the establishment of chronic inflammation and obstructive lung disease. Cystic fibrosis (CF) is the main cause of BE in children in developed countries. Adult infection and other acquired causes are more prevalent in resource-limited countries. Regardless of the etiology, a complex interplay between the host, respiratory pathogens, and environmental factors seems to be the common pathway in the pathogenesis [1]. The course of the disease is characterized by chronic disease/stability phases interrupted by acute exacerbation episodes, with the acute exacerbations leading to further decline in lung function and health-related quality of life [2]. Therefore, early detection and proper treatment of acute exacerbations are important when managing BE. Several laboratory parameters, such as C-reactive protein (CRP), amyloid, interleukin (IL)-6, and expiratory CO levels have been studied as potential markers of acute exacerbation [3, 4].

The neutrophil-to-lymphocyte ratio (NLR) has been used to detect systemic inflammation in various clinical conditions ranging from different types of cancer to bacteremia and rheumatological diseases. Many studies have suggested using the NLR as an indicator of inflammation in various types of chronic inflammatory lung diseases [5-8]. Platelets play an important role as modulators of the inflammatory response. Mean platelet volume (MPV) and the platelet-to-lymphocyte ratio (PLR), as indirect indicators of the platelet activation, are other inflammatory biomarkers that have been studied [9].

Evidence concerning the utility of these parameters in the pediatric BE population is scant. This study aims to assess the value of the PLR, NLR, and MPV as markers of acute exacerbation in pediatric patients with non-cyctic fibrosis bronchiectasis (non-CFBE).

Methods

Fifty-five patients with non-CFBE who were followed up in Istanbul University-Cerrahpasa Medical Faculty, Department of Pediatric Pulmonology in Istanbul, Turkey between January 2018 and March 2020 were included in the study. Also, 79 healthy control subjects were included in this retrospective cross-sectional study. The study protocol was approved by the medical ethics committee of Cerrahpasa Faculty of Medicine, Istanbul University. The methods were carried out in accordance with the principles stated in the Declaration of Helsinki, and informed consent was obtained from the families of all subjects.

A history of cough with chronic productive sputum that lasted at least 3 months from the diagnosis was the inclusion criterion. Patients diagnosed with CF were not included in the study group. Also, patients diagnosed with immune suppression, or the patients on immune-suppressive, anti-inflammatory or antimicrobial therapy were excluded, as this would interfere with their complete blood count (CBC) values. In addition to age, gender, age of onset of symptoms, age of diagnosis, coughing, wheezing, sputum, shortness of breath, and weakness, findings such as dyspnea, rales, and roncus were evaluated. CBC, immunoglobulin titers (IgA, IgM, IgG, and IgE), lymphocyte subgroups, chest X-ray, a chest computed tomography (CT) scan, sputum culture, and flexible bronchoscopy were performed for all patients for the diagnosis. Forced expiratory volume in one second (FEV1) and forced vital

capacity in children > 6 years of age were determined in those who were able to complete respiratory function testing. All of the subjects in the patient group were able to complete the spirometric test. Bronchoalveolar lavage analysis and culture, the skin prick test, the nitroblue tetrazolium test, an echocardiogram, and tuberculin test were performed, and the alpha-1 antitrypsin level and gastroesophageal reflux were also assessed. Pulmonary function tests were performed according to the American Thoracic Society standards.

BE was diagnosed based on a history compatible with the disease, supported by radiological findings from high-resolution CT. The results of the patient group were assessed in two subgroups: the acute exacerbation (Group 1) and stable state (Group 2) groups. An acute exacerbation was defined as a persistent (>24 h) increase in respiratory symptoms, new opacification in chest X-rays, or worsening in the chest physical examination findings [10]. Group 3 comprised healthy control subjects.

Demographic parameters and the CBC results of patients (during an acute exacerbation or in a stable state) and control subjects were accessed from the hospital database/patient files. CBC was performed via Beckman Coulter Hematology Analyzer, employing the principle of flow cytometry. NLR values were calculated by dividing the percentage of neutrophils by that of lymphocytes in the CBC. PLR values were calculated by dividing the platelet count by the absolute lymphocyte count. Additionally, CRP and the percentage of predicted FEV1% values in the patient group were obtained from patient records.

Statistical analyses

MedCalc Statistical Software version 12.7.7 (MedCalc Software, Ostend, Belgium; http://www.medcalc.org; 2013) was used to analyze the data. Descriptive statistics (mean, standard deviation, range, and median) were calculated for continuous variables. As our data were not distributed normally, the Mann–Whitney *U*-test was used to compare two independent groups, whereas the Wilcoxon test was used to compare two dependent groups. Spearman's rho coefficient was used to evaluate the correlation between two continuous variables. A p value <0.05 was considered to denote significance.

Results

The mean age was 13.62±3.5 years in the patient group and 12.72±2.68 years in the control group. Approximately 64% of the patients and 54% of the control subjects were male. There was no statistically difference between the groups regarding to age and gender (p>0.05).

Selected CBC parameters (including the calculated NLR and PLR), CRP, and FEV1% values for groups are shown in Table 1. The white blood cell count (WBC), absolute neutrophil count (ANC), and NLR values were significantly higher in the exacerbation group than in the healthy control group (p=0.036*, p*=0.02*, and p*=0.012*,* respectively). Absolute lymphocyte and platelet counts in the non-CFBE group were significantly lower than in the control group during the stable state (p=0.021 *and p*=0.04*,* respectively). MPV and PLR values were not significantly different between the two groups. Only FEV1% and CRP levels were significantly different (p<0.001) between the acute exacerbation and stable state periods in the patient group (Table 1).

We analyzed the correlation between inflammatory markers (MPV, PLR, and NLR) and established markers, such as ANC and CRP, during the acute exacerbation and stable state periods (Table 2). The NLR was strongly correlated with the ANC in the exacerbation (*Spearman's* rho=0.791, p<0.001) and stable state (rho=0.894, p<0.001) groups. The PLR was moderately correlated with the ANC during the stable state period (*Spearman's* rho=0.556*,* p<0.001). None of the tested markers was significantly correlated with the CRP level in either group.

Table 1. Difference of laboratory parameters between groups

	Group 1 n=55	Group 2 n=55	Group 3 n=79	Gr 1-2	Gr 1-3	Gr 2-3
	Mean±SD Mdn (Min-Max)	Mean±SD Mdn (Min-Max)	Mean±SD Mdn (Min-Max)	p^1	p^2	p^3
WBC (×10³/µl)	8.5±2 8.4 (4.2-15.4)	8.4±2.5 7.8 (5-19)	7.8±1.6 7.5 (5-11.8)	0.740	**0.036**	0.349
ALC (×10³/µl)	2.8±0.8 2.6 (0.9-5.2)	2.5±1.1 2.2 (0.6-5.5)	2.9±0.9 2.7 (1.5-5.1)	0.213	0.528	**0.021**
ANC (×10³/µl)	4.8±1.8 4.7 (2.2-9.6)	4.9±2.7 3.8 (1.1-15.2)	4.1±1.3 3.7 (2.3-7.9)	0.799	**0.020**	0.217
Plt (×10³/µl)	308±125 300 (33-640)	296±1000 273 (157-559)	313±68 302 (167-522)	0.394	0.558	**0.040**
MPV (fL)	8.15±0.85 8 (6.3-10.3)	8.2±1.01 8.1 (6.4-10.4)	8.41±1.02 8.3 (6.5-13.4)	0.954	0.167	0.272
NLR	1.95±1.08 1.75 (0.54-5.82)	2.78±3.22 1.75 (0.42-14.67)	1.53±0.68 1.37 (0.53-4.16)	0.431	**0.012**	0.085
PLR	114.08±38.39 113.87 (10.52-222.08)	147.13±112.08 118.5 (46.57-551.67)	114.95±34 107.89 (54-206.09)	0.123	0.944	0.347
FEV1%	86.8±65.44 77 (40-533)	85.71±25.18 87 (44-126)	-	**<0.001**	-	-
CRP (mg/L)	36.69±22.82 34 (8-121)	3.02±4.39 1.6 (0.03-21)	-	**<0.001**	-	**-**

p¹; Group 1 and 2 (Wilcoxon test), *p²*; Group 1 and 3 (Mann-Whitney U test), *p³*; Group 2 and 3 (Mann-Whitney U test)
N: number, Gr: Group, SD: Standart Deviation, Mdn: Median, Min-Max: Minimum-Maximum, WBC: white blood cell count, ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, Plt: Platelet count, MPV: Mean platelet volume, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, FEV1: Forced expiratory volume in one second, CRP: C-reactive protein

Table 2. Correlation analyses of inflammatory markers during the acute exacerbation and stable state periods

	Group 1 n=55	Group 2 n=55	Group 3 n=79	Gr 1-2	Gr 1-3	Gr 2-3
	Mean±SD Mdn (Min-Max)	Mean±SD Mdn (Min-Max)	Mean±SD Mdn (Min-Max)	*p¹*	*p²*	*p³*
WBC (×10³/µl)	8.5±2 8.4 (4.2-15.4)	8.4±2.5 7.8 (5-19)	7.8±1.6 7.5 (5-11.8)	0.740	**0.036**	0.349
ALC (×10³/µl)	2.8±0.8 2.6 (0.9-5.2)	2.5±1.1 2.2 (0.6-5.5)	2.9±0.9 2.7 (1.5-5.1)	0.213	0.528	**0.021**
ANC (×10³/µl)	4.8±1.8 4.7 (2.2-9.6)	4.9±2.7 3.8 (1.1-15.2)	4.1±1.3 3.7 (2.3-7.9)	0.799	**0.020**	0.217
Plt (×10³/µl)	308±125 300 (33-640)	296±1000 273 (157-559)	313±68 302 (167-522)	0.394	0.558	**0.040**
MPV (fL)	8.15±0.85 8 (6.3-10.3)	8.2±1.01 8.1 (6.4-10.4)	8.41±1.02 8.3 (6.5-13.4)	0.954	0.167	0.272
NLR	1.95±1.08 1.75 (0.54-5.82)	2.78±3.22 1.75 (0.42-14.67)	1.53±0.68 1.37 (0.53-4.16)	0.431	**0.012**	0.085
PLR	114.08±38.39 113.87 (10.52-222.08)	147.13±112.08 118.5 (46.57-551.67)	114.95±34 107.89 (54-206.09)	0.123	0.944	0.347
FEV1%	86.8±65.44 77 (40-533)	85.71±25.18 87 (44-126)	-	**<0.001**	-	-
CRP (mg/L)	36.69±22.82 34 (8-121)	3.02±4.39 1.6 (0.03-21)	-	**<0.001**	-	**-**

*Spearman's rho correlation coefficient
WBC: white blood cell count, ALC: Absolute lymphocyte count, ANC: Absolute neutrophil count, Plt: Platelet, MPV: Mean platelet volume, NLR: Neutrophil lymphocyte ratio,
PLR: Platelet lymphocyte ratio, FEV1: Forced expiratory volume in one second,
CRP: C-reactive protein

Discussion

In the present study, several inflammatory markers were evaluated for their potential to differentiate between stable state and acute exacerbation periods in non-CFBE in children. The main outcomes of this study are: Leukocyte counts, ANCs, and NLRs were significantly higher in non-CFBE patients than in healthy control subjects during acute exacerbation; NLR, MPV, and PLR values in non-CFBE patients did not differ significantly between the stable state and acute exacerbation periods of the disease; FEV1% was significantly higher and CRP levels significantly lower during the stable state of the disease than during the acute exacerbation period; and none of the studied markers (i.e., MPV, NLR, and PLR) was correlated with serum CRP, a marker of systemic inflammation.

Acute stress activation of the sympathetic system results in a surge of adrenal hormones (e.g. epinephrine and cortisol), which increase the number of circulating neutrophils and decrease the number of circulating lymphocytes within the leukocyte pool. These bidirectional changes make the NLR an even better indicator of acute stress/inflammation than either ANC or acute lymphocyte count alone. The role of the NLR in prognosis/detection of a vast variety of clinical conditions has been studied, including bacterial infections/sepsis, cardiovascular diseases, different types of cancers, and rheumatological diseases [10-15].

Among chronic inflammatory lung diseases, the use of the NLR has been mostly studied in adults with chronic obstructive pulmonary disease (COPD). In a meta-analysis that enrolled 5140 COPD patients who participated in nine studies by Ye et al. [6], the NLR was an independent predictor for the incidence of exacerbation, and higher NLR values were associated with higher mortality. Coban and Gungen [16] studied the correlation between the NLR and BE scoring systems, namely BSI and FACED, in 117 stable adult BE patients. Their results showed that the WBC and NLR failed to capture systemic inflammation in patients with stable BE. Conversely, another Turkish study by In et al. [17] reported that the NLR values of patients with COPD (both acutely exacerbated and stable) were significantly higher than those of the control subjects. They also calculated an NLR cutoff value of 3.34, which had 78.7% sensitivity and 73.2% specificity for detecting a COPD exacerbation. Similar results were demonstrated by Gunay et al. [18], in that NLR values of stable COPD patients were significantly higher than those of the control subjects, and there was a further increase during acute exacerbation compared to the stable period.

NLR values were also positively correlated with serum CRP levels. However, we failed to show a correlation in either disease state in children with non-CFBE. A study by Nacaroglu et al. [19] with pediatric non-CFBE patients and healthy control subjects concluded that the NLR can be used to reveal chronic inflammation in non-CFBE, as well as detect acute exacerbations. We could not confirm this finding in the present study. Although the NLRs in the exacerbation group were different from those in the healthy control group, no significant difference was observed when the ratios were compared to those for patients at the stable state of the disease. Different inclusion and exclusion criteria for the study populations can be the cause of the conflicting findings. As numerous factors alter NLR value it might be challenging to control all of the confounders while designing a study. This once again may limit the use of NLR in clinical practice. Also it should be noted that there are very few studies in pediatric NCFBE population assessing NLR, so accumulating data will improve our understanding of the issue.

Beside from their role in primary hemostasis, platelets modulate the inflammatory response. Increased levels of proinflammatory cytokines, such as tumor necrosis factor-alpha and IL-6, in patients with inflammatory diseases, affect megakaryopoiesis and platelet volume [20]. On the other hand, hypoxemia and hypercapnia, which may accompany lung diseases, enhance platelet aggregation [20, 21].

MPV and the PLR are simple, inexpensive, and rapid markers that reflect inflammation and platelet activation [22]. Wang et al. [20] studied MPV in COPD patients and reported that participants with a COPD exacerbation had a lower MPV and higher CRP, WBC, and fibrinogen levels compared with patients at the stable phase of COPD and control subjects. The MPV was also lower in patients with stable-phase COPD compared with the control subjects. Uysal et al. [23] compared the MPV

values in 81 children with BE to those of healthy control subjects. The MPV values were similar for steady-state patients, whereas a significant difference was observed during exacerbation periods.

The prognostic value of the PLR has been studied in several health conditions, mainly cardiovascular diseases [24-26]. Karadeniz et al. [27] compared the PLR in steady-state and acute exacerbation groups of adults with COPD to that of healthy control subjects. They found that there was a higher platelet count, platelet distribution width, and PLR as well as lower MPV values in the exacerbation group. A negative correlation was detected between FEV1% and the PLR in COPD patients. By contrast, Nacaroglu et al. [19] concluded that neither MPV nor the PLR differentiates between exacerbation and steady-state periods in children with non-CFBE. Many other studies with equivocal results have indicated that MPV is an unreliable marker for routine use in the early detection of acute exacerbations in BE in children [19, 23, 28]. Differences in the laboratory methods used to detect MPV and the heterogeneity of the study populations may be confounding factors responsible for these findings. Relatively few studies have been conducted regarding PLR in this patient group, and the results are ambiguous. Our study adds to the growing body of evidence regarding the use of these three markers for diagnosing acute exacerbations in children with non-CFBE.

In the present study, only CRP and FEV1% values were significantly different between the acute exacerbation and stable state periods of the disease. CRP is a quick and easy marker of systemic inflammation that is already widely used in clinical practice. However, FEV1% values are determined using spirometric measurements, which require patient compliance, adequate equipment, and specialized professionals to interpret the test results, thus making it an impractical tool for routine use, particularly in the pediatric population.

The limitations of this study include the small sample size and the retrospective design. Also, confounding factors, such as corticosteroid use, were not considered in the patient group. Larger studies or meta-analyses are needed to determine the utility of and cut-off values for these parameters (i.e., NLR, PLR, and MPV).

In conclusion, despite the NLR being significantly higher in children with non-CFBE than in healthy control subjects, it could not differentiate between steady-state and acute exacerbations periods of the disease. PLR and MPV values also cannot be used as markers of acute exacerbation in children with non-CFBE.

Conflict of interest: No conflict of interest was declared by the authors.

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Author contributions

AAK, GA, NK and HC contributed substantial contributions to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work. AAK, GA and NK made drafting the work and revising it critically for important intellectual content. AAK and HC made final approval of the version to be published.

GA, NK and HC contributed to agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. All co-authors take full responsibility for all aspects of the study and the final manuscript.