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Original Article PEDIATRICS

The association of allergic rhinitis severity with neutrophil-lymphocyte and platelet-lymphocyte ratio in children

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ABSTRACT

OBJECTIVE: The aim of the study was to investigate the relationship between the severity of allergic rhinitis (AR) and neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in pediatric patients.

METHODS: This study is a retrospective, cross-sectional, and observational study including 200 AR patients and 160 healthy controls. Of the patients, 39% were boys with a mean age of 10.5 years. The study included children with persistent and intermittent AR. Of the controls, 50.6% were boys with a mean age of 10.3 years. We compared NLR and PLR from blood test between study and control groups. They were also compared according to AR severity within the patient group.

RESULTS: The NLR was 1.64±1.29 in the study group whereas 1.18±0.31 in the control group. The PLR was 102.72±31.20 in the study group whereas 79.36±11.72 in the control group. When NLR and PLR were compared between groups, we found statistically significant differences in both NLR and PLR (p=0.003, p=0.001, respectively). We found a statistically significant difference when comparing both NLR and PLR in patients with intermittent and persistent AR. These rates increased with disease severity (p=0.000, p=0.000, respectively).

CONCLUSION: Both NLR and PLR are useful markers for the diagnosis and severity of AR. Clinicians can use these markers to assess disease severity in pediatric patients at the beginning of the diagnostic process.

Keywords: Aeroallergens; neutrophil-lymphocyte ratio; pediatric allergic rhinitis; platelet-lymphocyte ratio.

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Allergic rhinitis (AR) is a heterogeneous disorder characterized by presence of one or more of symptoms of sneezing, itching, runny nose, and nasal congestion. AR is IgE-mediated immunologic response against aeroallergens and there is systemic inflammation together with local nasal inflammation [1]. Exposure to indoor and outdoor aeroallergens causes sensitization in AR [2]. It is estimated that AR involves 15–25% of the population worldwide with increasing prevalence [3]. In our country, it affects 2.9–39.9% of pediatric population [4, 5]. AR is associated with impaired quality of life as well as emotional problems and problems in school performance, sleep-related and medical problems including chronic and acute sinusitis, serous otitis media, and exacerbation of adenoidal hypertrophy and asthma [6]. Although diagnosis of AR is based on clinical history, risk factors, characteristic signs and symptoms, serum specific IgE (spIgE) measurements, and prick tests are used to detect AR [7]. There are difficulties such as expensive laboratory spIgE measurements, inability to standardize

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skin prick tests in many centers, high false positive results, and variable sensitivity of total Ig E values. Therefore, there is a need to develop inexpensive, non-invasive, and accessible laboratory evaluations which can be used for AR diagnosis. In the previous studies, an association between systemic inflammation and AR was shown [8]. Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have been investigated as an important marker of systemic inflammation, lately. Studies have shown that NLR and PLR have prognostic significance in most diseases [9–11].

We aimed to investigate whether neutrophil: lymphocyte ratio and platelet: lymphocyte ratio, could be useful in the diagnosis and monitoring of disease severity in pediatric AR. To the best of our knowledge, this is the first study in the literature showing the relationship between AR and NLR-PLR ratios in the pediatric age group.

Highlight key points

- NLR-PLR ratios were found to be statistically significant in patients with allergic rhinitis compared to the control group. A positive correlation was obtained between high NLR-PLR values and allergic rhinitis severity.
- NRL and PRL can be used as an easy, cheap, non-invasive, and publicly available biomarker in in the diagnosis and monitoring of disease severity in pediatric allergic rhinitis.

MATERIALS AND METHODS

Overall, we included 200 patients with AR, aged 3–18 years who were diagnosed and followed up in the Mardin State Hospital Pediatric Allergy Clinic. Institutional review board approval was obtained from the Ethics Committee of Istanbul Medipol Universty Hospital. Written informed consent was obtained from the patients and/or their families.

The control group included healthy children aged 3–18 years. Patients with systemic disease, anemia/polycythemia, leukocytosis/leukopenia, thrombocytosis/thrombocytopenia, and acute-chronic infection were excluded from the study. Both intermittent and persistent AR patients were included in our study. The patient group was divided into intermittent and persistent AR.

The diagnosis and severity of AR were determined according to "AR and its impact on asthma" (ARIA) guidelines [12]. The patient group was defined as intermittent (n=113) and persistent (n=87) AR. Prick test was performed to identify allergens. While the patient group was sensitive to at least one allergen, no allergen sensitivity was detected in the control group.

Age, gender, platelet, neutrophil count, lymphocyte, eosinophil count, eosinophil percentage, and prick test result of the children in each group were recorded. The NLR was calculated by dividing neutrophil count with lymphocyte count while PLR was calculated by dividing the platelet count with the lymphocyte count. Neutrophil, lymphocyte, platelet, eosinophil counts, and percentages were determined by complete blood count analysis (SYSMEX XN 9000 A (Sysmex Corporation USA, Inc).

Epidermal Prick Test

Epidermal prick test was formed with the 16 most common allergens in the region [13, 14]. The Prick test panel contained aeroallergens such as house dust mites (Dermatophagoides farinae, Dermatophagoides pteronyssunus), mold fungi (Alternaria tenuis, Penisilium notatum, Aspergillus Fumigatus), tree pollen (Plane tree, Arizona cypress, Juniper, Birch, Willow tree, Olive tree), weed pollen (cereals mixture), wild herb (Wall pellitory), grass pollen (Grasses), cat (Cat epithelia), and cockroach (Blatella germanica). The cereals pollen mixture consisted of hordeleum vulgare, avea sativa, secale cereale, and triticum sativum. The grasses pollen mixture involved holcus lanatus, dactylis glomerata, lolium perenne, phleum pratense, poa pratensis, and fescuta pratensis. Histamine was used as positive control and 0.9% NaCl solution was applied for negative control. The brand of the prick test solution used was Allergopharma. The prick tests were applied to the volar side of the forearms or back region after cleaning the areas with alcohol and procedures were performed with prick test applicators (Medblue one allergy 020013, Turkiye). All epidermal prick tests were applied and evaluated by the same doctor to achieve proper standardization. The diameter of induration at 15 min of the tests was measured. An induration of 3 mm or more with respect to the negative control was considered as positive [15].

Statistical Analysis

Data analyses were performed SPSS 20 (SPSS Inc., Chicago, Illinois, USA. Continuous variables are given as mean±standard deviation (SD). Categorical variables are given as percent. The normal data distribution was tested by the Kolmogorov–Smirnov test. The continuous variables with normal distribution was tested by Student's t

Table 1. Comparison of sociodemographic features and laboratory findings between patients with allergic rhinitis and control groups

	Study group (n=200)	Control group (n=160)	p
Gender (male/female) (%)	61/39	49.4/50.6	**0.02**[a]
Age (years)			0.668[b]
Mean±SD	10.58±3.78	10.36±3	
Min–max	3–18 (10)	4–17 (10)	
Neutrophil #(10^3/μL)			**0.01**[b]
Mean±SD	44.70±20.51	48.15±12.39	
Min–max (median)	1550–12210 (3895)	2250–8420 (4825)	
Lymphocyte #(10^3/μL)			**0.01**[b]
Mean±SD	31.32±10.11	42.53±12.41	
Min–max (median)	1510–7800 (2990)	1970–8440 (4050)	
Thrombocyte #(10^3/μL)			**0.003**[b]
Mean±SD	30.2±69.5	335±102.3	
Min–max (median)	172–523 (302)	163–579 (326)	
NLR			**0.003**[b]
Mean±SD	1.642±1.295	1.18±0.315	
Min–max (median)	0.35–13.30 (1.128)	0.55–2.40 (1.20)	
PLR			**0.001**[b]
Mean±SD	102.72±31.20	79.36±11.72	
Min–max (median)	49–223.9 (98.85)	52–106 (79.2)	

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SD: Standard deviation; Min: Minimum; Max: Maximum; a: Chi-square; b: Mann–Whitney-U.

tests while those with skewed distribution were tested by Mann–Whitney U. The categorical variables were tested by Chi-square. The Spearman's correlation was used to evaluate the relationships between statistical analyses. P<0.05 was considered as statistically significant.

RESULTS

The study included 360 participants aged between 3 and 18 years; 201(55.8%) male and 159 female (44.2%). The mean age of the patients was 10.58±3.78, and the mean age of control group was 10.36±3. There is no statistically difference between AR and control groups (p=0.668; p>0.05) (Table 1). Gender ratios were F/M (122/78) in patient group and F/M (79/81) in control group (p=0.02, p<0.05). The comparison of NLR and PLR ratios, neutrophil, lymphocyte, and platelet counts of whole patient group (intermittent and persistent) and healthy control group are given in Table 1. NLR and PLR ratios in the AR group were found to be statistically significantly higher than in the healthy control group (p<0.05) (Table 1).

The patient group is divided into intermittent (Group I) and persistent (Group II). Comparison of sociodemographic characteristics, clinical, and laboratory findings of Group 1 and Group 2 is given in Table 2. AR group consisted of 113 (56.5%) intermittent and 87 (43.5%) persistent patients. NLR and PLR values were significantly higher in persistent AR group compared to the intermittent AR group (p<0.05) (Table 2). Distribution of mean NLR and PLR between intermittent and persistent groups (Fig. 1).

Comparison of aeroallergen sensitivity of Group I and Group II patients is given in (Table 3). According to our results, grass pollen (n=158, 79%) was found to be most common aeroallergen in AR patients. Monosensitisation rate (n=46, 23%), and polysensitization rate (n=154, 77%) were found in AR. Grass pollen in Group I (n=89, 78.8%) and Group II (n=69, 79.3%) was the most common aeroallergen. No statistically significant correlation was found between the number of allergens to which the patients sensitive and the severity of disease (p>0.05). Sensitivity to pollens (grass, weed, and tree pollens), sensitivity to house dust mite, mold fungus, and cockroach did not differ between the groups (p>0.05) (Table 3).

TABLE 2. Comparison of sociodemographic features, clinical, and laboratory findings of the patient with intermittent (Group I) and persistent AR (Group II)

	Group 1 (n=113)	Group 2 (n=87)	p
Gender (male) %	60.2	62.1	0.786[a]
Age (years)			**0.03**[b]
Mean±SD	9.88±3.90	11.48±3.42	
Minimum–maximum (median)	3–18 (10)	6–17.5 (11)	
Familial atopy (P/A) (%)	30/70	49/51	**0.008**[a]
Exposure to smoke (P/A) (%)	36 /64	55 /45	**0.01**[a]
The presence of asthma (P/A) (%)	30/70	39/61	0.23[a]
The percentage of eosinophil			**0.036**[b]
Mean±SD	3.94±3.21	4.60±3.33	
Minimum–maximum (median)	0–27.2 (3.5)	0–22 (4.3)	
Eosinophil count (10^3/μL)			**0.04**[b]
Mean±SD	362±336	495±409	
Minimum–maximum (median)	0–3090 (320)	0–2450 (460)	
Neutrophil count (10^3/μL)			**0.000**[b]
Mean±SD	3391±852,8	5872±2295	
Minimum–maximum (median)	1550–7070 (3280)	2120–12210 (5330)	
Lymphocyte count (10^3/μL)			**0.000**[b]
Mean±SD	3571±1029	256.1±633.2	
Minimum–maximum (median)	2090–7800 (3290)	1510–4160 (2500)	
Thrombocyte count (10^3/μL)			
Mean±SD	29.4±66.3	312.4±72.5	0.085[b]
Minimum–maximum (median)	172–515 (295)	188–523 (306)	
NLR			**0.000**[b]
Mean±SD	0.98±0.26	2.49±1.58	
Minimum–maximum (median)	0.35–1.68 (1)	1.02–13.30 (2.09)	
PLR			**0.000**[b]
Mean±SD	85.1±18.8	125.5±29.2	
Minimum–maximum (median)	49–169 (84)	68.6–223.9 (122.4)	

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; SD: Standard deviation; Min: Minimum; Max: Maximum; a: Chi-square; b: Mann–Whitney-U.

DISCUSSION

There are numbers of studies about the relationship between the ratio of NLR and PLR and various inflammatory diseases in childhood. As far as we concern, our study is the first in the literature examining the relationship between AR severity and NLR and PLR in this age group. We presented a cross-sectional analysis of a cosmopolitan urban population.

Although there are studies on the relationship between NLR and PLR ratio in the pediatric population in atopic dermatitis [8], inflammatory diseases [16], pediatric trauma [17], and facial paralysis [18], asthma [19], and hearing loss in serous otitis media patients [10] as a prognostic marker, NLR and PLR, and disease severity in pediatric AR patients has not been observed together in the literature.

Theoretically, it is known that neutrophils are known to take part in acute bacterial inflammation. However, recent innovations about neutrophil subgroups are promising. Neutrophils can be divided into subgroups in their maturation process of which have versatile immunoregulatory functions [20]. Locally activated neutrophils in the upper airways have ability to mediate inflammatory processes in allergy by influencing suppressor T cell function, priming T cell and attracting eosinophils [21]. In normal nasal cytological examination, pseudo stratified columnar epithelium and neutrophils are seen [22].

Table 3. Comparison of aeroallergen sensitivity between of the patients with intermittent (Group I) and persistent AR (Group II)

	Group 1 (intermittent) n=113	Group 2 (persistent) n=87	p
The number of positive sensitivity			
Monosensitization (%)	26.5	18.3	0.11[a]
Polysensitization (%)	73.5	81.7	
Sensitivity to pollens (%)			
Grass pollen (S/NS) (%)	78.8/21.2	79.3/20.7	0.534[b]
Weed pollen (S/NS) (%)	51.3/48.7	51.7/48.3	0.535[b]
Tree pollen (S/NS) (%)	31/69	41/59	0.85[b]
Sensitivity to house dust mite (S/NS) (%)	16.8/83.2	19.5/80.5	0.37[b]
Sensitivity to mold fungus (S/NS) (%)	7.1–92.9	11.5–88.5	0.20[b]
Sensitivity to cockroach (S/NS) (%)	0/100	2.3/97.7	0.18[b]
Sensitivity to pet (S/NS) (%)	11.5/88.5	14.9/85.1	0.30

a: Chi-square; b: Mann-whitney-U; AR: Allergic rhinitis; S: Sensivite; NS: Nonsensivite.

In AR, it is believed that the early-phase reaction results from IgE-dependent histamine release from mast cells. There was increased eosinophils and neutrophils in nasal fluid appear in both early phase and late phase of AR, which implies that the pathogenetic mechanisms could be more complex [23]. Local allergic rhinitis (LAR) with unsolved immunopathology is a phenotype of AR characterized by the presence of a positive response to nasal allergen provocation test (NAPT) and local production of specific IgE (sIgE) antibodies. Therefore, LAR is characterized by a localized nasal allergic response and the absence of systemic atopy since specific IgE antibodies are not produced locally rather than systemically [24].

In the literature, there are various clinical trials about NLR ratio in children. Doğru et al. [19] examined NLR ratio and its association to severity of asthma in children. Mean NLR was found to be higher in asthmatic children compared to control group. In another study by Doğru et al. [25], the mean NLR in children with atopic dermatitis was not found statistically significant compared to control group. This result is attributed to small sample size of the study. Cayir et al. [18] in their comparison of recovered and no recovered group of pediatric facial paralysis patients found that NLR was higher in Bell paralysis group indicating poor prognosis. Esmaeilzadeh et al. [26] in their cross sectional study of hospitalized and no hospitalized asthmatic patients NLR was found to be higher in hospitalized patients of asthma. Our results, similar to these studies, showed that the NLR rate was significantly higher in the patient group compared to the healthy controls.

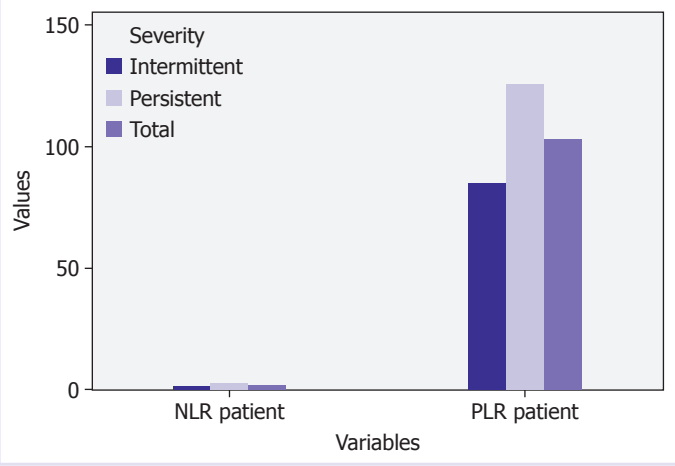

Figure 1. Distribution of mean NLR and PLR between AR and control group.

NLR: Neutrophil–lymphocyte ratio; PLR: Platelet–lymphocyte ratio.

In addition to platelets "role in thrombosis and hemostasis, they also play an important role in a number of inflammatory diseases, including allergic inflammation and asthma, eczema by their and rich source of biologically active materials capable of promoting allergic inflammatory responses. Such materials have been demonstrated to be stored in alpha granules. As allergen activates platelets; platelets recruit to lungs and tissue migration occurs, then direct release of plasminogen's and hypertrophic and extracellular modifying factors leading to smooth muscle contraction, smooth muscle hyperplasia and collagen deposition in airways. Activation of inflammatory

cells release free radicals and basic proteins causing tissue damage and mucus production. Furthermore, role of platelets in the pathogenesis of allergy and related changes of platelets in allergic patients have been mentioned in the literature [27]. In a study by Bozlu et al. [28], in children with Kawasaki disease with coronary abnormalities have lower PLR compared to children without coronary abnormalities. Arcagok et al. [29] observed that PLR can be used as a parameter in prediction of neonatal sepsis. In our study, we found that the rate of PLR was significantly higher in the patient group compared to the control group. This ratio increased in direct proportion to the severity of the disease and showed that the PLR ratio could be a biomarker in determining the severity of AR.

Yukkaldiran et al. [10] in their pediatric serous otitis media patients found NLR and PLR valuable in diagnosing serous otitis media and predicting hearing loss. Ha et al. [30] in their study of idiopathic hearing loss in children compared patients as no recovery, intermediate recovery, and complete recovery. They saw that NLR was statistically higher in no recovery and intermediate recovery group. PLR results in complete recovery group were different statistically but in other two group, results were not found significant. In a study by Celik et al. [31] complicated appendicitis had higher NLR and PLR values than uncomplicated acute appendicitis. Our results showed that the ratio of NLR and PLR in pediatric patients with AR was statistically significantly higher than in healthy controls. The results of our study are similar to the results of other studies in which these two ratios are examined together.

AR is caused by sensitization to at least one aeroallergen or more. Kim et al. [32] concluded that the symptom scores and levels of total IgE were higher in polysensitized children than in monosensitized children. In study by Bot et al. [33], polysensitization was at 69% of children. Sensitization was more common between ages 9–13 years than 5–8 years of children. Due to 1st year data of our newly established clinic, our patients included in the study vary in a wide age range between 3 and 18 years of children. This may have affected the number of sensitive antigens and the distributions in the severity of disease. Rate of overall polysensitization is 77% which is parallel with the literature. Fereidouni et al. [34] showed that overall sensitivity to aeroallergens was 81% and 76% of them were polysensitized. Similar to these studies, we found the polysensitization rate as 78%. Pollen (grass, cereal, tree, and weed) is found in different densities in different regions depending on factors such as geographical features, climate, and vegetation [35]. Although, the previous studies from different cities of Turkey revealed that pollen was the second most common aeroallergens, we found them as primer allergen [36, 37]. Our study, grass pollen and weed pollen are most prevalent aeroallergens 79% and 51.5%, respectively. This difference may be related to the inability of mites to survive due to the mentioned conditions of the region, as well as the increase in pollens with the increase in planting in parks, gardens in recent years. Besides, the high density of grain cultivation in the region may explain the high rate of cereals pollen mixture.

Severity measurements used in the literature are VAS visual analog score, acoustic rhinometry, nitric oxide (NO) levels, and nasal cytology [38]. We can advise NLR and PLR as a marker of pediatric AR severity because it is easy, cheap, non-invasive, and publicly available.

We have some limitations. Our data cover a single center experience with a cross-sectional design. Besides, being a newly established clinic forced us to include all patients with a wide age range between 3 and 18 years which had a potential effect on the number of sensitive allergens and the severity of disease. Our results can be supported by long-term longitudinal multicenter studies.

Conclusion

NLR-PLR ratios were found to be statistically significant in patients with AR compared to the control group. A positive correlation was obtained between high NLR-PLR values and AR severity. To the best of our knowledge, this is the first study in the literature showing the relationship between AR and NLR–PLR in the pediatric age group. NLR and PLR values can be used in the diagnosis and determination of AR severity, especially in patients with persistent AR. NRL and PRL can be used as an easy, cheap, non-invasive, and publicly available biomarker in in the diagnosis and monitoring of disease severity in pediatric AR. Our study should be supported by additional studies involving different inflammatory markers (nasal cytology, NO etc.) in a longer-term prospective study of a larger patient population.

Ethics Committee Approval: The Istanbul Medipol Universty Hospital Clinical Research Ethics Committee granted approval for this study (date: 03.06.2021, number: 587).

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Authorship Contributions: Concept – MC, NS; Design – MC, NS; Supervision – MC, NS; Fundings – MC; Materials – MC; Data collection and/or processing – MC; Analysis and/or interpretation – MC, NS; Literature review – MC, NS; Writing – MC, NS; Critical review – MC, NS.

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