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The evaluation of eosinophil-to-lymphocyte, eosinophil-to-neutrophil, and neutrophil-to-lymphocyte ratios in adults with allergic/non-allergic rhinitis

Ali Selçuk[1], Metin Keren[2]

[1]*Malatya Training and Research Hospital, Clinic of Allergy and Immunology, Malatya, Türkiye*

[2]*University of Health Sciences Türkiye, Sureyyapasa Training and Research Hospital, Clinic of Allergy and Immunology, Istanbul, Türkiye*

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Corresponding Author:
Ali Selçuk, M.D., Malatya Training and Research Hospital, Clinic of Allergy and Immunology, Malatya, Türkiye
draliselcuk@gmail.com

ORCID:
orcid.org/0000-0003-4089-7564

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ABSTRACT

Aims: This study investigated the usefulness of inflammatory parameters such as eosinophil-to-lymphocyte ratio (ELR), eosinophil-to-neutrophil ratio (ENR), and neutrophil-to-lymphocyte ratios (NLR) as markers for the diagnosis of patients with allergic rhinitis (AR) and non-AR (NAR).

Methods: This retrospective study included patients admitted to the allergy and immunology outpatient clinic with symptoms of chronic rhinitis. Subjects were divided into AR and NAR groups based on the skin prick test, serum total/allergen-specific immunoglobulin E level, and complete blood count. Subjects who underwent a medical check-up were included as healthy controls. ELR, ENR, and NLR were calculated using the results from complete blood counts.

Results: The study included 121 patients with AR [mean±standard deviation (SD) age: 30.6±7.5 years, female: 68.6%], 101 patients with NAR (mean±SD age: 31.6±10.3 years, female: 72.3%), and 116 control subjects (mean±SD age: 31.1±9.8 years, female: 62.9%). Mean age and sex ratios were similar across the groups. Patients with AR had significantly higher serum eosinophil counts, ELR, and ENR than healthy controls (mean±SD 0.22±0.17 vs. 0.15±0.12; 0.10±0.10 vs. 0.08±0.06; and 0.06±0.04 vs. 0.04±0.04, respectively, $p<0.05$). ENR >0.0684 showed 31.4% sensitivity and 82.9% specificity to predict AR. ELR was higher in NAR patients compared with the healthy controls (mean±SD 0.10±0.10 vs. 0.08±0.06, $p<0.05$). There was no difference in NLR across the three groups.

Conclusions: Our study showed that serum eosinophil counts, ELR, and ENR values were higher in AR patients compared to healthy controls, while ELR values were higher in NAR patients compared to healthy controls.

Introduction

Chronic rhinitis is an inflammation of the nasal mucosa characterized by symptoms of nasal congestion, rhinorrhea (anterior or posterior), sneezing, and nasal/ocular itching. Patients with chronic rhinitis have two nasal symptoms that last at least 12 weeks per year and at least 1 h per day (1). Worldwide, chronic rhinitis is becoming more common, with an estimated 30% prevalence rate across the entire population. This trend is on the rise throughout the world (1). Chronic rhinitis is a clinical manifestation with a high economic burden that can lead to sleep disturbance, fatigue, irritability, decreased school/work performance, and deterioration in the quality of life (2).

Generally, chronic rhinitis is categorized into four main groups according to etiology: allergic, non-allergic, infectious, and mixed (2,3). The diagnosis of allergic rhinitis (AR) is diagnosed according to the symptoms that occur after inhalation of at least one aeroallergens and positive skin prick test (SPT) and/or serum allergen-specific IgE (sIgE) tests revealing allergic sensitization (4). Non-AR (NAR) is the absence of any signs of infection and systemic aeroallergens sensitization (sIgE and/or a positive SPT), often as a diagnosis of exclusion (3).

The pathophysiology of NAR is unclear, although it is generally considered non-IgE. In NAR, there is an excessive response to non-allergic environmental triggers such as physical

(cold air, weather changes) or chemical (perfume, odorants, etc.) stimuli. It is thought that neurogenic mechanisms such as nociceptive dysfunction and autonomic nervous dysregulation may be responsible for this response (5). AR is an IgE-mediated type 1 hypersensitivity reaction to aeroallergens. Mast cells, lymphocytes, eosinophils, neutrophils, and various cytokines and mediators released from these cells are involved in the mucosal inflammation observed in the AR (1).

Several studies have shown that eosinophil-to-lymphocyte ratio (ELR), eosinophil-to-neutrophil ratio (ENR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are correlated with chronic inflammatory diseases such as atopic dermatitis, asthma, and sinonasal polyps (6-9). However, there are few studies in the literature investigating these inflammatory markers in both AR and NAR patients.

Rapid, minimally invasive, and inexpensive parameters must enable high identification of patients with AR and NAR. In this study, we investigated whether easily accessible ELR, ENR, and NLR could be used as novel inflammatory markers in the diagnosis of AR and NAR.

Methods

Study groups and classifications

In this study, we retrospectively analyzed the medical records of patients (aged 18 years and over) admitted to the University of Health Sciences Erzurum Region Training and Research Hospital Allergy and Immunology Department between February 2017, and March 2019. Patients with chronic rhinitis symptoms were divided into two groups: patients with a positive SPT and/or serum sIgE test were classified as AR (n=121), while patients with a negative SPT and serum sIgE test were classified as NAR (n=101). Participants who underwent medical a check-up during the study period acted as the control group (n=116). Age, gender, complete blood count parameters, aeroallergens sensitivity, serum total/sIgE and SPT results of the participants were recorded. Also, aged <18 years, patients with systemic/chronic diseases, acute/chronic infections, obesity, pregnancy, and patients receiving systemic corticosteroids, anti-inflammatory or anticoagulant drugs were excluded from the study.

Laboratory

Complete blood count parameters, serum total IgE, SPT and allergen-sIgE tests were performed simultaneously for each patient. ELR, ENR, NLR and PLR were calculated for each patient. Complete blood count parameters were studied on a Sysmex XN-10 (Sysmex Comp., Kobe, Japan) device for each participant in the study. Serum total IgE and sIgE tests were analyzed by chemiluminescence immunometric system (Immulite 2000 Siemens, Erlangen, Germany) for each patient with chronic rhinitis. The serum sIgE panel contained grass mix *(Dactylis glomerata, Lolium temulentum, Phleum pratense, Poa pratensis, Panicum miliaceum),* trees-mix *(Acer negundo, Betula pendula, Quercus macrolepsis, Ulmus laevis, Juglans orientis)*, mite-mix *(Dermatophagoides pteronyssinus, Dermatophagoides farinae, Lepidoglyphus destructor, Euroglyphus maynei, Tyrophagus putrescentiae, Blomia tropicalis, Glycphagus domesticus, Dermatophagoides microcereas)* and mold-mix *(Cladosporium herbarum, Aspergillus fumigatus, Penicillium notatum, Candida albicans, Alternaria tenuis)*. sIgE ≥0.35 kU/L is defined as a positive result.

All patients underwent SPTs with the positive control (histamine), negative control (physiological saline), house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), grasses mix, cereal pollen mix, tree mix, weed mix, Alternaria alternata, cockroaches, cat dander, and dog dander (Lofarma Allergeni, Milan, Italy). We performed SPTs using the same antigens in all patients. About 15 to 20 min after the application of the inhalant prick panel on the forearm, aeroallergens with a wheal ≥3 mm diameter were recorded as positive. The same observer evaluated the SPTs.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 25.0 (IBM Corp., Armonk, NY, USA) software package. Descriptive statistics were presented as frequencies, percentages, means, and standard deviations (SD). Categorical variables were compared using the chi-square test. The normality of numerical variables was tested using the Kolmogorov-Smirnov test. The Mann-Whitney U test or Kruskal-Wallis test with Tamhane post-hoc comparisons was used to compare numerical variables between the groups. Receiver operating characteristic (ROC) analysis was performed for numerical variables to reveal cut-off points in differentiating patients with AR from the control group. The area under the curve (AUC), sensitivity, and specificity values were calculated. The level of statistical significance was set at $p<0.05$.

Results

The study included 121 patients with AR (mean±SD age: 30.6±7.5 years, female: 68.6%), 101 patients with NAR (mean±SD age: 31.6±10.3 years, female: 72.3%), and 116 control subjects (mean±SD age: 31.1±9.8 years, female: 62.9%) (Table 1). Mean age and sex ratios were similar across the groups. The most common inhalant allergen sensitivity in AR patients was pollens (n=79, 65.3%), followed by house dust mites (n=64, 52.9%).

There were no significant differences in the mean age or sex of the groups. Eosinophils, ELR, and ENR values were significantly different between the groups. Measured only in the AR and NAR groups, serum total IgE values were significantly higher in the AR group (Table 1).

We performed ROC analyses using eosinophil count, ELR, and ENR variables. The highest AUC was observed for the eosinophils variable (Figure 1, Table 2). Cut-off studies have revealed that an eosinophil count >0.325 (x10^3/mL) could predict AR with a sensitivity of 20.7% and a specificity of 88.9% (likelihood ratio=1.86), while an ENR >0.0684 could predict AR with a sensitivity of 31.4% and a specificity of 82.9% (likelihood ratio=1.84).

Discussion

This study showed that serum eosinophil count, ENR, and ELR were higher in AR patients compared to healthy controls and ELR were higher in NAR patients compared to healthy controls. Additionally, total serum IgE levels were higher in the AR group than in the NAR group.

Mast cells, T-helper 2 lymphocytes, eosinophils, and neutrophils play a major role in AR (1). Previous studies have shown that eosinophilia is associated with allergen sensitization and can be used as a sensitization marker (10-12). Liu et al. (12) observed higher eosinophil counts in the AR group than in the control group. In our study, eosinophil count and ELR were higher in patients with AR compared to the control group. Similarly, Yenigun et al. (13) reported that both eosinophil count and ELR were higher in children with AR and that ELR could be used together with SPTs to diagnose AR. However, in the same study, the eosinophil count and ELR in patients with nonsensitized rhinitis were similar to those in the control group. Meanwhile, in our study, ELR was higher in patients with NAR than in controls. However, their study group included pediatric patients and used only SPT for the diagnosis of AR and did not use sIgE tests.

The prognostic significance of ELR was higher in patients with nasal polyps with chronic rhinosinusitis who had disease recurrence after endoscopic sinus surgery (14). Besides, in pediatric patients with atopic dermatitis, ELR and ENR were higher than in the control group (6). Likewise, in our study, ENR was higher in patients with AR than in the control group. Previous studies have shown increased ENR in nasal secretion in allergic conditions (15,16). Furthermore, blood eosinophil counts correlated with eosinophil counts in sputum and bronchoalveolar lavage (17). Zhang et al. (7) reported a correlation between blood ENR and sputum eosinophil count, and a cut-off >0.05 for blood ENR had a sensitivity of 89.6% and a specificity of 77.0% in predicting eosinophilic asthma. Lee et al. (16) found that the ENR level in nasal secretion was higher than 0.1 in patients with AR. In this study, an ENR cut-off >0.0684 could predict AR with a sensitivity of 31.4% and a specificity of 82.9%. To our knowledge, this is the first report of a blood ENR cut-off in patients with AR. Considering all these data, we thought that ENR levels in nasal secretion and blood ENR might correlate in patients with AR.

NLR is a valuable inflammatory marker (6,8,14). However, studies on the correlation between NLR and AR have reported conflicting results (18,19). In our study, there was no difference between both the AR and NAR groups and the healthy control group in terms of NLR. Ha et al. (18) showed higher eosinophil counts and lower NLR in children with AR compared to the control group. In the same study, there was no difference in both eosinophil count and NLR in children with NAR compared with the control group. Their results for patients with NAR were similar to those of our study. In this study, although the number of patients and healthy controls was similar to that in our study, only SPT was used to demonstrate allergen sensitization, and no information was given about SPT results. Dogru et al. (19) found that NLR was higher in children with AR compared with the control group. However, different from the current work, that

Table 1. Comparison of demographic and laboratory findings of patients with AR, NAR and healthy controls

	AR (n=121)	NAR (n=101)	Controls (n=116)	Test	p
Sex, female, n (%)	83 (68.6)	73 (72.3)	73 (62.9)	2.220*	0.330
Age, years, mean±SD	30.6±7.5	31.6±10.3	31.1±9.8	0.189#	0.910
Platelets (x10^3/mL), mean±SD	283.68±63.30	287.10±54.42	276.22±54.69	3.916#	0.141
Leukocytes (x10^3/mL), mean±SD	7.57±1.78	7.29±1.28	7.33±1.48	1.096#	0.578
Neutrophils (x10^3/mL), mean±SD	4.40±1.51	4.35±1.06	4.42±1.33	0.121#	0.941
Lymphocytes (x10^3/mL), mean±SD	2.24±0.68	2.03±0.55	2.12±0.58	4.468#	0.107
Eosinophils (x10^3/mL), mean±SD	0.22±0.17^a	0.21±0.25^{a,b}	0.15±0.12^b	11.326#	**0.003**
ELR, mean±SD	0.10±0.10^a	0.10±0.10^a	0.08±0.06^b	8.209#	**0.017**
ENR, mean±SD	0.06±0.04^a	0.05±0.08^{a,b}	0.04±0.04^b	10.745#	**0.005**
NLR, mean±SD	2.17±1.15	2.35±1.01	2.27±0.98	4.543#	0.103
PLR, mean±SD	136.51±44.37	150.76±46.90	141.40±52.31	5.649#	0.059
Total IgE (U/mL), mean±SD	192.53±251.29	56.59±63.51		6.840**	**<0.001**

Different superscript letters in the cells denote categories whose column proportions do not differ significantly from each other at the 0.05 level, *chi-square test value, #Kruskal-Wallis test value, **Mann-Whitney U test value.
ELR: Eosinophil-to-lymphocyte ratio, ENR: Eosinophil-to-neutrophil ratio, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SD: Standard deviation, AR: Allergic rhinitis, NAR: Non-AR

study included chronic inflammatory atopic diseases (eczema and asthma). Additionally, the sensitivity of house dust mites in patients with AR was 52.9% in our study, whereas it was higher in their study (85.1%). In the literature, neutrophil dominance has been reported in nasal cytology in patients with house dust mite-sensitive AR (20). However, it may also be present in peripheral blood, similar to nasal cytology in patients with AR. Considering all these data, further studies may investigate the clinical significance of NLR in AR and NAR patients.

We observed no significant differences in PLR between the groups. Several studies have investigated PLR as an inflammatory marker (21,22). NLR and PLR were higher in children with atopic dermatitis compared to the control group, and both markers reflected the severity of the disease in these patients (8).

We also found that the mean serum total IgE level was higher in patients with AR than in patients with NAR. Serum total IgE measurement is considered unuseful in the diagnosis of AR and is primarily associated with SPT/sIgE (1). Min et al. (10) found higher serum total IgE in patients with AR compared with patients with NAR in a study conducted on adult patients. Since NAR is a group of non-IgE-mediated inflammatory diseases, we think that serum total IgE levels may be useful in the differential diagnosis of AR.

Study Limitations

This study has several potential limitations. Firstly, we could not exclude patients with local AR to diagnose NAR. However, in most previous clinical studies, the definition of NAR is considered chronic rhinitis with negative SPT and/or sIgE results. In our study, we defined patients who had chronic rhinitis but who had negative tests as NAR. Nasal sIgE and nasal allergen provocation tests are recommended for diagnosing local AR. However, routine use of these tests is challenging for both patients and clinicians. Another limitation of this study was that it was retrospective. However, similar studies in the literature investigating complete blood count parameters are mostly retrospective.

Conclusion

In conclusion, we suggest that SPT, allergen sIgE, ELR, and ENR could be used to diagnose AR in adult patients. Moreover, increased serum total IgE levels in patients with

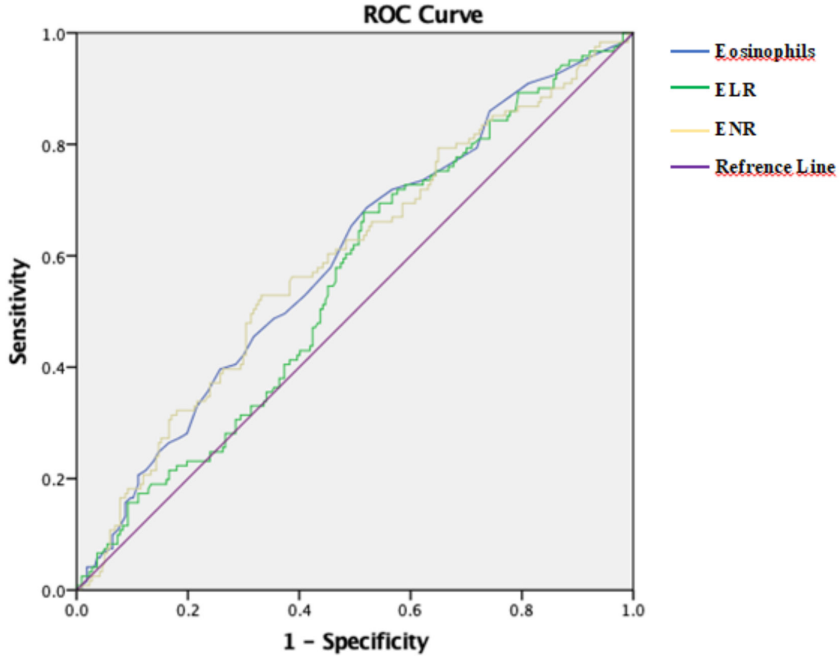

Figure 1. ROC curves for the eosinophils (x10³/mL), ELR, and ENR variables
ELR: Eosinophil-to-lymphocyte ratio, ENR: Eosinophil-to-neutrophil ratio, ROC: Receiver operating characteristic

Table 2. ROC analysis results for the eosinophils (x10³/mL), ELR, and ENR variables

	AUC	p	95% confidence interval	
			Lower bound	Upper bound
Eosinophils (x10³/mL)	0.594	**0.004**	0.532	0.657
ELR	0.556	0.085	0.494	0.619
ENR	0.593	**0.004**	0.530	0.657

AUC: Area under the curve, ELR: Eosinophil-to-lymphocyte ratio, ENR: Eosinophil-to-neutrophil ratio, ROC: Receiver operating characteristic

AR compared with patients with NAR may also be used in the differential diagnosis. Further studies are needed to investigate inflammatory markers, including ELR, ENR, and NLR, which can be measured with a complete blood count and nasal cytology.

Ethics

Ethics Committee Approval: This study was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Erzurum Ataturk University Faculty of Medicine (approval number: 04, date: 13.03.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.S., M.K., Design: A.S., M.K., Data Collection or Processing: A.S., Analysis or Interpretation: A.S., M.K., Literature Search: A.S., M.K., Writing: A.S., M.K.

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