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Association of severity of allergic rhinitis with neutrophil-to-lymphocyte, eosinophil-to-neutrophil, and eosinophil-to-lymphocyte ratios in adults

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Abstract

Background: Allergic rhinitis (AR) is characterized by chronic inflammation of the nasal mucosa. T-helper 2 lymphocytes, neutrophils, and eosinophils play an active role during the late-phase immune response after exposure to allergen.

Objective: We aimed to investigate the usefulness of inflammatory parameters of neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-neutrophil ratio (ENR), and eosinophil-to-lymphocyte ratio (ELR) as markers for distinction between intermittent and persistent allergic rhinitis.

Material and Methods: This was a double-center, retrospective study. Patients were enrolled after diagnosed with AR according to the Allergic Rhinitis and Its Impact on Asthma guidelines. Individuals with an active infection were excluded. A cohort of healthy subjects acted as a control group. NLR, ENR, and ELR were calculated using the results obtained from the patients' complete blood count. Descriptive statistical analysis was performed for all studied variables.

Results: In all, 205 AR patients and 49 healthy individuals were included. AR patients had significantly higher levels of absolute eosinophils, ENR, and ELR, and significantly lower levels of NLR than the healthy controls ($P<0.05$). A total of 160 (78%) patients with persistent AR had significantly higher levels of absolute eosinophils, ENR, and ELR, and significantly lower levels of NLR than patients with intermittent AR ($P<0.05$).

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Conclusion: Currently, classification of severity of AR is based on the patient's anamnesis. It has been shown in this study that serum eosinophil levels in persistent AR patients could be used as traceable parameters in evaluating severity of the disease by looking at the proportions of ENR and ELR. We anticipate that in the future this issue would be supported by a larger number of studies.
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Introduction

Allergic rhinitis (AR) is a type of immunoglobulin E (IgE)-mediated disorder of the nasal mucosa associated with symptoms such as recurrent sneezing, rhinorrhea, and nasal congestion. Patients with AR experience chronic sleep disturbances, emotional distress, and impaired social activity, resulting in impairment of both work or school performance and quality of life. It is estimated that 10–20% of population is affected by AR.[1-3]

Allergic rhinitis is characterized by chronic inflammation of the nasal mucosa. During the early phase of allergic inflammation following exposure to allergens, activated mast cells release various mediators, including histamines. These early-phase mediators trigger a late-phase response by increasing expression and activation of cellular adhesion molecules (CAMs). The late-phase response is characterized by a cell-rich environment created by eosinophil, neutrophil, and platelet chemotaxis toward the nasal mucosa. Various cytokines, chemokines, and other mediators are activated and released by T-helper 2 lymphocytes, neutrophils, and eosinophils during the late-phase immune response.[4,5]

Numerous studies have reported that neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) could be used as inflammatory markers in chronic inflammatory diseases.[6-8] Lack of data in the medical literature regarding usefulness of these markers in AR, a chronic inflammatory disease, is encountered. This study proposed to determine whether new inflammatory indicators, such as NLR, eosinophil-to-neutrophil ratio (ENR), and eosinophil-to-lymphocyte ratio (ELR) could be used in differentiating between intermittent and persistent AR.

Materials and Methods

The study was conducted at the Department of Allergy and Clinical Immunology of a tertiary teaching hospital located in Istanbul and Vakfikebir State Hospital. Data of AR patients collected between April and June 2020 were analyzed retrospectively. Individuals with a positive skin prick test and a diagnosis of AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines were included in the study group. Patients were classified as mild intermittent, moderate-severe intermittent, mild persistent, and moderate-severe persistent according to the ARIA guidelines. Intermittent AR was defined as presence of symptoms for less than 4 days in a week or for less than 4 consecutive weeks, and intermittent AR was defined as presence of symptoms for more than 4 days in a week or for more than 4 consecutive weeks. Symptoms were classified as mild if they were not causing sleep disturbances, impairment in daily activities, or impairment in work or school performance. Symptoms causing any of these impairments were classified as moderate-severe.[9]

Skin prick tests were performed using standard commercially available allergen extracts (grasses mix, cereals mix, tree mix, dermatophagoides (D) pteronyssinus, D. farinae, acarus siro, cockroach, cat epithelia, dog epithelia, aspergillus fumigatus, alternaria, clodosporium, lepidoglypus destructor, tyrophagus putrescentiae, artemisia vulgaris, parietaria officinalis, plantago lanceolata, ambrosia artemisiifolia, corylus avellana, alder, olea europaea, ash, oak, populus alba, and betula alba). The skin test allergen panel has been created according to the prevailing geographical and climatic conditions. Skin prick tests were performed on both forearms in accordance with international guidelines. Histamine (10 mg/mL) was used as a positive control, and sterile saline 0.09% as a negative control. A wheal diameter of ≥3 mm, greater than the negative control, was considered as a positive prick test.[10] Data were collected pertaining to demographics (age and gender), severity of rhinitis, duration of the disease, other atopic diseases (asthma, allergic contact eczema, etc.), comorbidities, family history, and serum total IgE levels. NLR, ENR, and ELR were calculated for each patient. Individuals with an active infection were excluded. Healthcare personnel who underwent annual medical checkup during the study period acted as the control group; however, those with any chronic diseases or active infections were excluded. Diseases, such as parasitic disease, allergic bronchopulmonary aspergillosis, Churg–Strauus syndrome, blood malignancies, etc., which would affect serum eosinophilia levels in our patients were excluded. Cut-off values were as follows: eosinophils, $\geq 0.2 \times 10^3/\mu L$ (normal range: $0–0.2 \times 10^3/\mu L$); neutrophils, $\geq 4.8 \times 10^3/\mu L$ (normal range: $2.2–4.8 \times 10^3/\mu L$); lymphocytes, $\geq 2.0 \times 10^3/\mu L$ (normal range: $1.3–2.0 \times 10^3/\mu L$); platelets, $\geq 400 \times 10^3/\mu L$ ($130–400 \times 10^3/\mu L$); and IgE, ≥100 UI/mL (normal range: 0–100 UI/mL).

Statistical Analysis

Descriptive statistical analysis was performed for all studied variables. Compatibility with normal distribution of data obtained by measurements was assessed using the Kolmogorov—Smirnov test. Student's *t*-test was used to analyze normally distributed data; the Mann–Whitney U test was used for non-normally distributed data; and the

Chi-square (χ^2) test was used to compare categoric variables. Data obtained from measurements are expressed as mean±standard deviation (SD). Data obtained by counting are expressed as numbers (%); analyses were performed using the Chi-square test. Correlation analysis was performed using Pearson's correlation test or Spearman's correlation test. Receiver operating characteristic (ROC) analysis was performed to calculate the sensitivity, specificity, and negative predictive value (NPV) and positive predictive value (PPV) of statistically significant variables. $P<0.05$ was considered statistically significant.

Results

In all, 205 patients were in the AR group and 49 participants in the control group. Groups were similar pertaining to demographics. Comparing with healthy controls, patients with AR had significantly higher levels of absolute eosinophils, ENR, and ELR, and significantly lower levels of NLR ($P<0.05$) (Table 1). ROC curve analysis was performed. An ELR cut-off value of >0.067 had 76.6% sensitivity, 69.4% specificity, and 89% PPV for predicting AR with an AUC of 0.746. An NLR cut-off value of ≤1.7 had 42.8% sensitivity, 73.5% specificity, and 86.5% PPV for predicting AR with an AUC of 0.602. An ENR cut-off value of >0.034 had 76.6% sensitivity, 65.3% specificity, and 87.7% PPV for predicting AR with an AUC of 0.778 (Table 2). Among AR patients, 160 (78%) had persistent AR. Symptom severity was moderate-severe in 70% of the patients with persistent AR, and 44.4% of the patients with intermittent AR ($P<0.001$). Persistent and intermittent AR patients had similar demographic and clinical characteristics. Patients with persistent AR had significantly longer duration of symptoms ($P=0.013$). Patients with persistent AR had significantly higher absolute eosinophils, and ENR and ELR values, and significantly lower NLR value ($P<0.05$) (Table 3). For predicting persistent AR, an ELR cut-off value of >0.15 had 85.7% specificity and 90.7% PPV with an AUC of 0.746; an NLR cut-off value of ≤1.62 had 88.1% specificity and 92.5% PPV with an AUC of 0.602; and an ENR cut-off value of >0.041 had 73.2% sensitivity and 84.9% PPV with an AUC of 0.659 (Table 4).

Discussion

Allergic rhinitis is a complex inflammatory disease of the respiratory tract. Mast cells, eosinophils, T lymphocytes, dendritic cells, macrophages, and neutrophils play a major role in progress of the disease.[5] Although not a life-threatening condition, this widespread disease significantly affects patients' quality of life. If left untreated, persistent AR causes upper and lower respiratory tract symptoms that deteriorate activities of daily life. Therefore, effective management of AR is crucial. Growing evidence shows that absolute neutrophil, lymphocyte, and neutrophil counts and their respective ratios could be used to assess severity of AR.[11,12]

In this study, 160 patients (78.0%) had persistent AR. Istanbul and Trabzon, where the research was conducted, have zero altitude and have a climate with an average relative humidity of 80-85%[13]. For this reason, a high rate of

Table 1 Demographic and laboratory findings of patients with allergic rhinitis and healthy controls.

	Allergic rhinitis group, n=205	Control group, n=49	P
Age (years)	32.2±11.5	27.7±1.8	0.116
Females	132 (64.4%)	32 (65.3%)	0.904
Neutrophil count ($10^3/\mu L$)	4189±1262	4531±1393	0.098
Lymphocyte count ($10^3/\mu L$)	2127±502	1990±647	0.172
Platelet count ($10^3/\mu L$)	268517±55627	257347±66557	0.226
Platelet-lymphocyte ratio	133.2±39.3	145.5±69.9	0.243
Eosinophil count ($10^3/\mu L$)	315±239	147±126	<0.001*
ELR (range)	0.14±0.1 (0.02-0.59)	0.078±0.07 (0.01-0.32)	<0.001*
NLR (range)	2.07±0.8 (0.97-5.76)	2.62±1.9 (1.15-5.91)	0.028*
ENR (range)	0.08±0.07 (0.01-0.33)	0.034±0.03 (0.01-0.13)	<0.001*

ELR: eosinophil-to-lymphocyte ratio; ENR: eosinophil-to-neutrophil ratio; NLR: neutrophil-to-lymphocyte ratio.
*P<0.05.

Table 2 Receiver operating characteristic curve analysis data obtained to determine the diagnostic efficacy of eosinophil-to-lymphocyte ratio (ELR), neutrophil-to-lymphocyte ratio (NLR), and eosinophil-to-neutrophil ratio (ENR) in allergic rhinitis.

Parameters	Cut-off	AUC	AUC 95% CI	Sensitivity	Specificity	PPV	NPV	P
ELR	>0.067	0.746	0.681-0.804	76.6	69.4	89.0	47.9	<0.001*
NLR	≤1.7	0.602	0.5367-0.664	42.8	73.5	86.5	24.5	0.024*
ENR	>0.034	0.778	0.715-0.832	76.6	65.3	87.7	46.4	<0.001*

AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value.
*P<0.05.

Table 3 Demographic, clinical, and laboratory findings of patients with persistent and intermittent allergic rhinitis.

	Persistent allergic rhinitis, n=160	Intermittent allergic rhinitis, n=45	P
Moderate-severe symptoms	112 (70%)	20 (44.4%)	<0.001*
Age (years)	32.3±11.7	31.8±11.2	0.848
Females	100 (62.5%)	32 (71.1%)	0.374
Urticaria	14 (8.8%)	6 (13.3%)	0.528
Pruritus	51 (31.9%)	17 (37.8%)	0.573
Eczema	35 (21.9%)	9 (20.0%)	0.948
Asthma	62 (38.8%)	18 (40.0%)	0.879
Comorbidity (Diabetes mellitus [DM], migraine, hypertension, etc.)	21 (13.1%)	10 (22.2%)	0.204
Family history of allergic disease	132 (82.5%)	35 (77.8%)	0.615
Duration of symptoms (years)	8.4±8.0	5.9±7.2	0.013*
Neutrophil count ($10^3/\mu L$)	4147±1291	4338±1153	0.387
Lymphocyte count ($10^3/\mu L$)	2147±507	2055±483	0.294
Platelet count, $10^3/\mu L$	266338±57074	276267±49968	0.291
Platelet-lymphocyte ratio	131.2±40.4	140.4±34.4	0.181
IgE	237.2±361.6	187.3±332.2	0.242
Eosinophil count ($10^3/\mu L$)	339±246	232±195	0.005*
ELR (range)	0.15±0.1 (0.03-0.59)	0.11±0.08 (0.02-0.46)	0.013*
NLR (range)	2.04±0.8 (0.97-5.76)	2.17±0.6 (1.35-3.98)	0.043*
ENR (range)	0.09±0.07 (0.02-0.33)	0.06±0.05 (0.01-0.30)	0.004*
Grasses mix	55 (34.4%)	21 (46.7%)	0.182
Mites	135 (84.4%)	32 (71.1%)	0.043*
Cat-dog hair	33 (20.6%)	12 (26.7%)	0.387
Mold	16 (10.0%)	4 (8.9%)	0.542
Pollens	59 (36.9%)	22 (48.9%)	0.145

ELR: eosinophil-to-lymphocyte ratio; ENR: eosinophil-to-neutrophil ratio; IgE: Immunoglobulin E; NLR: neutrophil-to-lymphocyte ratio.
*P<0.05.

Table 4 Receiver operating characteristic curve analysis data obtained to determine the diagnostic efficacy of eosinophil-to-lymphocyte ratio (ELR), neutrophil-to-lymphocyte ratio (NLR), and eosinophil-to-neutrophil ratio (ENR) in persistent allergic rhinitis.

Parameters	Cut-off	AUC	AUC 95%CI	Sensitivity	Specificity	PPV	NPV	P
ELR	>0.15	0.637	0.557-0.712	39.8	85.7	90.7	28.8	0.006*
NLR	≤1.62	0.602	0.529-0.671	40.8	88.1	92.5	29.1	0.016*
ENR	>0.041	0.659	0.580-0.733	73.2	54.3	84.9	36.5	0.003*

AUC: area under curve; PPV: positive predictive value; NPV: negative predictive value.
*P<0.05.

mite sensitivity is observed. The fact that the majority of our patients were in the persistent AR group was the result of geographic structure and climate difference. The present study shows that absolute eosinophils, and ENR and ELR values were higher, with lower NLR values in AR patients versus healthy controls as well as in persistent AR patients versus intermittent AR patients. Eosinophils are the most predominant cells in the pathogenesis of allergic inflammation. Their numbers increase in blood and nasal secretion of atopic individuals. In this study, we observed that both persistent and intermittent AR patients had increased blood eosinophil counts, with a more pronounced increase in persistent AR patients. Previous research studies have demonstrated that eosinophilia is associated with allergen sensitization and could be used as a sensitivity marker.[14-18] However, none of these reports proposed cut-off values for practical clinical use.[14-18] As a result, there is a trend for using respective ratios of eosinophils, lymphocytes, and neutrophils instead of their absolute or relative values.

Yenigun and colleagues have reported that children with AR had significantly increased levels of eosinophils and lower levels of lymphocytes, and that ELR could be used for the diagnosis and clinical follow-up of pediatric AR patients.[19] However, they did not report a cut-off level for this diagnostic marker.[19] A study conducted by Ekici revealed that an ELR of ≥0.09 had 61.8% sensitivity and 73.3% specificity to determine sensitization of allergen in children.[20] In the present study, an ELR cut-off value of >0.067 had 76.6% sensitivity, 69.4% specificity, and 89% PPV for predicting AR with an AUC of 0.746. Additionally, an ELR cut-off value of >0.15 had 85.7% specificity and 90.7% PPV with an AUC of 0.746 for predicting persistent AR.

It has also been reported that NLR value could be used for diagnosis and predicting severity of symptoms in AR. In addition to neutrophil and lymphocyte counts, NLR has been shown to be valuable as an inflammatory marker.[21] However, use of NLR as a prognostic marker for inflammation is debatable. NLR was proposed to have a prognostic value in cardiovascular diseases, hypertension, diabetes mellitus, Bell's palsy, sensorineural hearing loss, familial Mediterranean fever, chronic tonsillitis, cirrhosis, and malignancies.[22-25] It is possible that a parameter affected by these many conditions may not be sensitive enough to be used as an inflammatory marker. Nevertheless, studies about correlation between NLR and AR report diverse outcomes. A study conducted by Dogru et al. has revealed higher NLR values in children with AR versus healthy controls.[26] Ha and colleagues demonstrated significantly lower values of NLR in patients with AR when compared with healthy controls.[11] Similar to the results of the study conducted by Ha and colleagues,[11] we also observed significantly lower levels of NLR in AR patients versus the control group. An NLR cut-off value of ≤1.7 had 42.8% sensitivity, 73.5% specificity, and 86.5% PPV for predicting AR with an AUC of 0.602. Additionally, in the present study, patients with persistent AR had significantly lower levels of NLR than patients with intermittent AR. An NLR cut-off value of ≤1.62 had 88.1% specificity and 92.5% PPV with an AUC of 0.602 for predicting persistent AR. In the study conducted by Dogru and colleagues, difference between NLR ranges was rather substantial, with 1.77–1.67 (0.15–15.9) in the AR group, and 1.70–1.65 (0.32–10.7) in the control group.[26] This difference could have been caused by bacterial or viral infections in the patient group. Patients with AR have an increased incidence of infectious diseases, which often alter blood parameters. Shinogi and colleagues showed alterations in both neutrophil and eosinophil counts in infectious illnesses.[27] Bouldoires et al. reported that eosinopenia could be used for early diagnosis of bacterial infections.[28] In spite of the studies considered, and because of an extensive list of medical conditions that affect NLR levels, clinical significance of correlation between NLR and AR remains controversial.

It has been shown that blood eosinophil counts correlate with sputum, bronchoalveolar lavage, and submucosal eosinophil counts.[29] Previous studies have revealed that ENR levels increase in nasal secretions during allergic conditions.[12,27,30] Zhang and colleagues have reported increased ENR levels in complete blood counts of asthma patients.[31] The present study is the first one to report a cut-off value of ENR in AR patients. It demonstrated that an ENR cut-off value of >0.034 had 76.6% sensitivity, 65.3% specificity, and 87.7% PPV for predicting AR with an AUC of 0.778. Also, an ENR cut-off value of >0.041 had 73.2% sensitivity and 84.9% PPV with an AUC of 0.659 for predicting persistent AR. It has to be considered whether these cut-off values are altered during infectious conditions.

Conclusion

To conclude, patients with persistent AR experience almost year-round symptoms associated with chronic inflammation of the nasal mucosa. Accordingly, the present study observed higher absolute eosinophils, ENR, and ELR levels and lower NLR levels in patients with persistent AR compared to patients with intermittent AR. These novel inflammatory markers, which could be easily obtained by a complete blood count, are parameters that could be used in the differentiation of intermittent and persistent AR. However, it has to be remembered that these parameters could be easily altered by patient's comorbidities. In the future, a larger number of studies could support this issue.

Conflict of Interest

The authors have no conflicts of interest to declare. There was no financial support rendered to this study.

Statement of Ethics

The study protocol was approved by the local ethical committee (protocol number: 30.12.2020/514/192/10).

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