ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.300
Asthma Allergy Immunol 2023;21:135-142

RESEARCH ARTICLE

Received: 15.05.2023 • Accepted: 02.06.2023
Online Published: 11.07.2023

# Assessing Anaphylaxis Risk: A Study on Basophil-to-Lymphocyte and Eosinophil-to-Lymphocyte Ratios as Predictive Biomarkers

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## ABSTRACT

**Objective:** This study aimed to investigate the basophil-to-lymphocyte ratio (BLR) and eosinophil-to-lymphocyte ratio (ELR) as potential predictive biomarkers for anaphylaxis risk.

**Materials and Methods:** A cross-sectional study was conducted involving 66 anaphylaxis patients, 70 chronic spontaneous urticaria patients, and 65 healthy individuals. Data on demographics, clinical history, and laboratory results were collected from electronic medical records. BLR and ELR were calculated. The predictive values of BLR and ELR were evaluated using receiver operating characteristic (ROC) analysis.

**Results:** Significant differences were found in basophil and eosinophil counts among the groups with median BLR values of 0.03 (0.01), 0.02 (0.01), and 0.03 (0.01), and mean ELR values of 0.07 (0.06), 0.05 ± 0.03, and 0.06 (0.01) for groups 1 (anaphylaxis), 2 (chronic spontaneous urticaria), and 3 (healthy control) respectively. BLR comparisons between Group 1 and Groups 2 and 3 yielded p-values of <0.001 and 0.002, respectively. ELR comparisons also showed statistical significance, with p-values of <0.001 and 0.001. Multivariate binary logistic regression revealed BLR and ELR as independent predictors of anaphylaxis, with area under the curve (AUC) values of 0.69 and 0.72, respectively, indicating modest predictive capacity.

**Conclusion:** BLR and ELR present a novel avenue in assessing patients at risk for anaphylaxis. Despite their modest predictive value, these ratios could potentially be used as adjunctive tools in clinical evaluations. Further large-scale studies are needed to validate these findings and to explore their potential therapeutic implications.

**Keywords:** Anaphylaxis, basophils, blood cell count, eosinophils, lymphocytes

## INTRODUCTION

Anaphylaxis is a potentially fatal, systemic reaction involving multiple organ systems, mediated primarily by mast cells and basophils (1). Both immunologic anaphylaxis, which includes IgE-mediated, IgG-mediated, and immune complex/complement-mediated reactions, and nonimmunologic anaphylaxis, which occurs independently of immunoglobulins, are significant forms of anaphylaxis (1). Basophils, alongside mast cells, are often simultaneously activated during anaphylaxis (2). Changes in basophil numbers, IgE receptor expression, and chemokine levels have been observed in patients experiencing anaphylaxis (3, 4). With their pro-inflammatory and anti-inflammatory properties, Eosinophils may contribute to immediate and late-phase allergic responses (5). The lifetime prevalence of anaphylaxis in the general population has been estimated to be at least 1.6%, emphasizing the significance of understanding and addressing this severe allergic reaction (6, 7). With an increasing prevalence in recent years, it has become more critical than ever to devise strategies to predict and prevent anaphylactic episodes (8).

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Despite well-studied risk factors for anaphylaxis, such as older age, male sex, vigorous physical exercise, white race, cardiovascular disease, elevated serum tryptase levels, and mastocytosis, the potential of basophil-to-lymphocyte ratio (BLR) and the eosinophil-to-lymphocyte ratio (ELR) in predicting anaphylaxis risk remain unexplored (1, 9-12). As mentioned in the recent update on anaphylaxis by the European Academy of Allergy and Clinical Immunology (EAACI), a key area of focus is the requirement for biomarkers capable of predicting the risk level for individual patients (13). The diagnostic potential of baseline serum tryptase levels as a biomarker for predicting anaphylaxis is limited due to factors such as cost, lengthy laboratory turnaround times, and limited availability in all healthcare centers (14). Despite the identification of several other biomarkers for anaphylaxis, including platelet-activating factor (PAF), chymase, carboxypeptidase A3, dipeptidyl peptidase I (DPPI), basogranulin, and chemokine (C-C motif) ligand 2 (CCL-2), these are not routinely used in clinical practice due to lack of accessibility and other practical issues (15).

In the quest for more accessible and reliable markers, the focus has turned to easily calculable and cost-effective markers of inflammation, such as the neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), and basophil-to-lymphocyte ratio (BLR), derived from complete blood cell count (CBC). These markers have shown to be valuable indicators in various chronic inflammatory diseases, making them potential candidates for predicting allergic diseases, too (16-21).

Our study addresses a significant gap in the current knowledge by examining the potential of BLR and ELR as reliable predictors of anaphylaxis risk. While previous research has explored various biomarkers for anaphylaxis prediction, ours is the first to propose specific cut-off values for BLR and ELR. Given the increasing prevalence of anaphylaxis, developing readily accessible and cost-effective predictive markers could significantly enhance patient care and facilitate timely intervention. Moreover, understanding these markers could provide new avenues for future research into managing and preventing anaphylaxis.

## MATERIALS and METHODS

### Study Design and Population

This retrospective, single-center study was conducted from April 1, 2020, through April 1, 2021. We employed a convenience sampling strategy, targeting adult patients aged between 18 and 65 who visited our clinic for anaphylaxis, chronic spontaneous urticaria (CSU), angioedema, or drug allergies.

Patients who experienced anaphylaxis within the year prior to the study were included in the study group (Group 1), according to the latest World Allergy Organization criteria (1). We chose patients with CSU as the control group (Group 2) due to previous research indicating a link between elevated NLRs and CSU, suggesting that these patients might provide a relevant comparison for our study group. The healthy control group (Group 3) comprised individuals who had visited our outpatient allergy and immunology clinic for routine screenings, including pre-employment health checks. These health screenings were unrelated to the objectives of this study, and the data were subsequently utilized for the study in a retrospective manner.

We extracted demographic, clinical, and laboratory data from electronic medical records. These data included age, gender, white blood cell (WBC), neutrophil, lymphocyte, eosinophil, basophil counts, skin prick test (SPT) results, and serum-specific IgE and serum tryptase levels. We only included routine blood analyses performed during stable phases.

Allergen-specific IgE antibody measurements were performed using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) and considered positive when levels were equal to or greater than 0.35 kU/L. The total tryptase level was measured using the Thermo Fisher Scientific ImmunoCAP™ Tryptase fluorescence enzyme immunoassay (FEIA). The neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), and basophil-to-lymphocyte ratio (BLR) were calculated for each patient.

### Inclusion and Exclusion Criteria

Patients who experienced at least one episode of anaphylaxis within the 12 months preceding the start of the study, adults diagnosed with CSU, angioedema, or drug allergies, and healthy individuals aged between 18 and 65 were included in the study. We excluded patients with acute infections, autoinflammatory or rheumatological diseases, chronic renal failure, chronic liver failure, malignancies, parasitic or hematological diseases that could alter blood lymphocyte levels, systemic mastocytosis, mast cell leukemia, acute myeloid leukemia, and patients receiving long-term systemic or oral corticosteroids. We also excluded patients who were pregnant or had renal failure.

### Patient Selection and Group Formation

The process for patient selection and the formation of the study groups is illustrated and detailed in Figure 1.

The study was approved by the Non-Interventional Clinical Research Ethics Committee, Turkey (Date: 01.06.2021, Number: 2021 – 197/27).

### Statistical Analysis

This study hypothesized that a higher BLR increased the risk of anaphylaxis. We evaluated patient characteristics in relation to sex, BLR, and the presence of specific allergic conditions. Quantitative variables were expressed as mean, SD, median, and quartiles, and qualitative variables were detailed with absolute frequencies and percentages. The normality of data distributions was evaluated

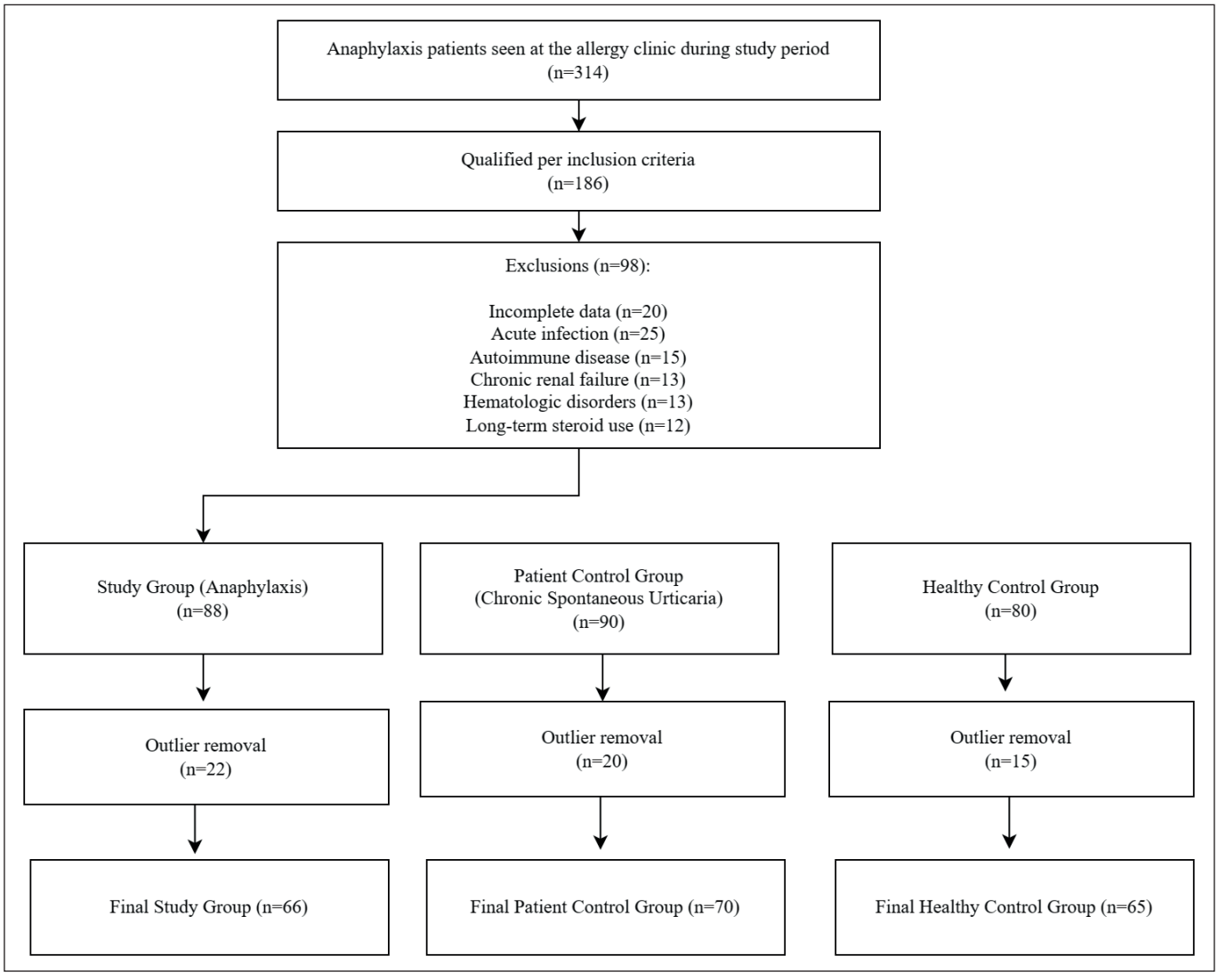


**Figure 1.** Flowchart of patient selection and grouping for anaphylaxis study.
*This figure outlines the patient selection process and formation of groups for the anaphylaxis study. Initially, 314 potential anaphylaxis patients visited our clinic during the study period. After applying the inclusion and exclusion criteria, we reduced this pool to 186 eligible patients. Following the removal of 98 patients due to various reasons such as incomplete data, presence of acute infection, autoimmune disease, chronic renal failure, hematologic disorders, and long-term steroid use, 88 anaphylaxis patients remained and formed the Study Group. Two other groups, the Patient Control Group (CSU) (n=90) and the Healthy Control Group (n=80), were formed separately from patients who met the inclusion criteria and did not meet any exclusion criteria. These participants were also age and sex-matched with the Study Group. Following outlier removal using SPSS's Explore function, the final patient groups comprised 66, 70, and 65 patients, respectively.*

using the Kolmogorov-Smirnov test. For non-normally distributed continuous data, the Kruskal-Wallis test was used, followed by a post hoc analysis with the Bonferroni-corrected Mann-Whitney U-test for significant results. Categorical variables were compared using the Chi-squared or Fisher's test. Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of laboratory parameters, and optimal cut-off values were determined using the Youden index. A multivariate binary logistic regression analysis was conducted to identify independent predictors of anaphylactic reaction outcomes. All statistical analyses were carried out with SPSS version 23, and a p-value of less than 0.05 was considered statistically significant.

## RESULTS

The study involved a total of 201 participants with a median age of 35.0 years (range: 18-71), including 140 (69.7%) females and 61 (30.3%) males. The Anaphylaxis Study Group (Group 1) showed significant differences in basophil and eosinophil counts compared to the CSU Patient Control Group (Group 2) and the Healthy Control Group (Group 3). Notably, no such difference was observed between Group 2 and Group 3. Table I provides a detailed breakdown of patients' baseline characteristics and laboratory values across the three groups.

Within Group 1, comorbidities included allergic rhinitis (31.8%), chronic urticaria (12.1%), and asthma (9.1%). The prevalence of atopy among the patients was 53%, with pollen atopy being the most common at 24.2%. The rates of diagnosed allergies included food allergies (40.9%), venom allergies (24.2%), latex allergies (4.5%), and animal allergies (3.0%). Anaphylactic reactions were most frequently triggered by food intake (37.9%), followed by drug intake and venom allergies, each responsible for 22.7% of the cases. Exercise-induced anaphylaxis was the least common trigger at 1.5%, and for 15.2% of the patients, the cause remained undetermined.

Table II demonstrates significant associations between basophil-to-lymphocyte ratio (BLR) and eosinophil-to-lymphocyte ratio (ELR) with anaphylactic reactions across the three groups.

### ROC analysis

Using receiver operating characteristic (ROC) analysis, we evaluated the predictive value of laboratory values for anaphylactic reactions (Figures 2 and 3). The analysis suggested that both BLR and ELR could be useful for predicting anaphylaxis, albeit with moderate accuracy. The area under the curve (AUC) values for BLR and ELR were 0.69 and 0.72, respectively.

**Table I: Baseline characteristics and laboratory values of the patients.**

| | Group 1 (n=66) | Group 2 (n=70) | Group 3 (n=65) | P-value |
|---|---|---|---|---|
| Age, years | 37 (18) | 30 (23) | 48 (26) | NS |
| Female (n/%) | 39 (59.1) | 53 (75.7) | 48 (73.8) | NS |
| Tryptase (ng/mL) | 4.8 (3.3) | 4.5 (2.1) | NA | NS |
| Total IgE (kU/L) | 87.5 (156) | 72.0 (76) | NA | <0.001 *,† / NS‡ |
| White Blood Cells (/mm$^3$) | 7245(2025) | 7650 (3218) | 5260 (3020) | NS |
| Basophil (/mm3) | 80 (40) | 70 (50) | 70 (30) | <0.001 *,† / NS‡ |
| Eosinophil (/mm$^3$) | 170 (143) | 115 (140) | 120 (80) | <0.001 *,† / NS‡ |
| Lymphocyte (/mm$^3$) | 2395 (1105) | 2520 (860) | 1870 (460) | NS |
| Neutrophil (/mm$^3$) | 3960 (1520) | 4235 (2438) | 3140 (2260) | NS |
| Monocyte (/mm$^3$) | 560 (230) | 540 (230) | 460 (140) | NS |
| Platelets (x10$^3$/mm$^3$) | 251 (85) | 275 (97) | 260 (93) | NS |

Data are median (IQR). **NA:** Not available, **NS:** Non-significant, The parameters' pre and post-values were compared using the Kruskal–Wallis test with Bonferroni-corrected multiple comparisons.
Group 1: The study group, Group 2: The Patient Control Group (CSU), Group 3: The healthy control group,
Symbols define the significant P-values of pairwise comparisons:
* denotes the comparison of Group 1 vs. Group 2
† denotes the comparison of Group 1 vs. Group 3
‡ denotes the comparison of Group 2 vs. Group 3

### Multivariate binary logistic regression

The multivariate binary logistic regression analysis found that baseline BLR and ELR levels independently predicted anaphylactic reaction outcomes, regardless of potential confounding variables. In simpler terms, patients with higher BLR and ELR levels were at an elevated risk of an anaphylactic reaction. The final prediction model included these two ratios, with adjusted odds ratios (ORs) of 1.715 (95% CI, 1.207-2.437) and 1.213 (95% CI, 1.103-1.334) for BLR and ELR, respectively, as shown in Table III.

## DISCUSSION

Our study has unveiled distinct differences in the basophil and eosinophil counts among anaphylaxis patients, chronic urticaria patients, and a healthy control group. Notably, our results suggest that the basophil-to-lym-

**Table II: Laboratory value ratios and their association with anaphylactic reaction outcomes across three groups.**

| | Group 1 (n=66) | Group 2 (n=70) | Group 3 (n=65) | P-value |
|---|---|---|---|---|
| BLR | 0.03 (0.01) | 0.02 (0.01) | 0.03 (0.01) | <0.001 * /0.002 † NS‡ |
| ELR | 0.07 (0.06) | 0.05 (0.03) | 0.06 (0.01) | <0.001 *,† NS‡ |
| NLR | 1.69 (0.95) | 1.72 (0.92) | 1.61 (1.55) | NS |
| MLR | 0.24 (0.10) | 0.22 (0.09) | 0.23 (0.92) | NS |
| PLR | 109 (52) | 115 (35) | 132 (64) | NS |

Data are median (IQR). **NS:** Non-significant, **BLR:** Basophil-to-lymphocyte ratio), **ELR:** Eosinophil-to-lymphocyte ratio, **NLR:** Neutrophil-to-lymphocyte ratio, **MLR:** Monocycte-to-lymphocyte ratio, **PLR:** Platelet-to-lymphocyte ratio.
The parameters' pre- and post-values were compared using the Kruskal–Wallis test with Bonferroni-corrected multiple comparisons. Group 1: The study group, Group 2: The Patient Control Group (CSU), Group 3: The healthy control group,
Symbols define the significant P-values of pairwise comparisons:
* denotes the comparison of Group 1 vs. Group 2
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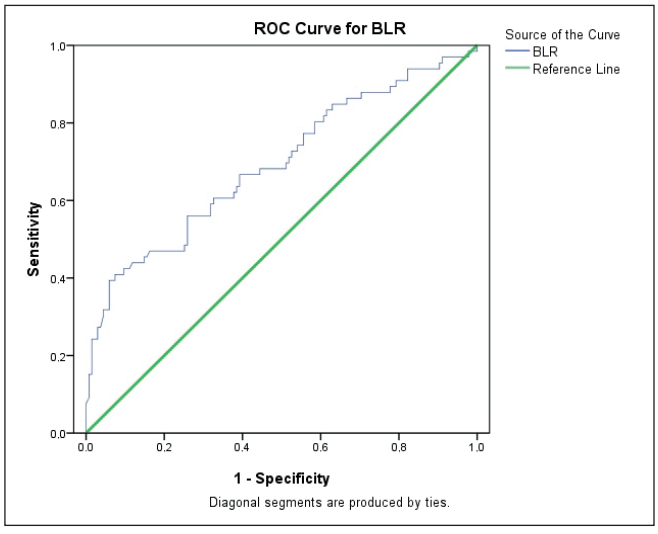


**Figure 2.** Predictive value of basophil-to-lymphocyte ratio (BLR) for anaphylactic reaction outcomes.
*Receiver operating characteristic (ROC) curve illustrating the predictive value of the basophil-to-lymphocyte ratio (BLR) for anaphylactic reaction outcomes. The area under the curve (AUC) is 0.69 (95% CI: 0.61-0.77), with a sensitivity of 62.1% and a specificity of 62.2% at a BLR threshold of 0.030.*

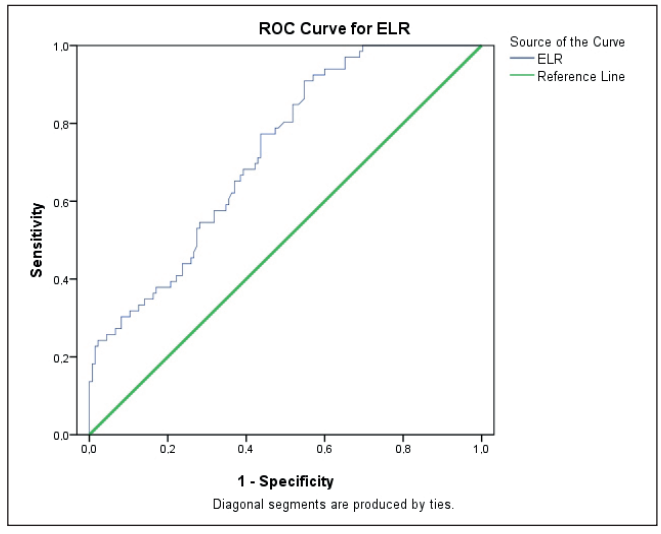


**Figure 3.** Predictive value of eosinophil-to-lymphocyte ratio (ELR) for anaphylactic reaction outcomes.
*Receiver operating characteristic (ROC) curve demonstrating the predictive value of the eosinophil-to-lymphocyte ratio (ELR) for anaphylactic reaction outcomes. The area under the curve (AUC) is 0.72 (95% CI: 0.65-0.79), with a sensitivity of 63.6% and a specificity of 63.0% at an ELR threshold of 0.062.*

**Table III: Predicting risk factors for the anaphylactic reaction outcome by binary logistic regression analysis.**

| | Regression coefficient | SEM | Wald | P-value | OR (95% Cl) |
|---|---|---|---|---|---|
| BLR | 0.539 | 0.179 | 9.053 | **0.003** | 1.715 (1.207 – 2.437) |
| ELR | 0.193 | 0.049 | 15.752 | **<0.001** | 1.213 (1.103 – 1.334) |

Data are median (IQR). **BLR:** Basophil-to-lymphocyte ratio, **ELR:** Eosinophil-to-lymphocyte ratio, **SEM:** Standard error of mean

phocyte ratio (BLR) and eosinophil-to-lymphocyte ratio (ELR) could potentially serve as biomarkers for identifying individuals at increased risk of anaphylaxis. While not guaranteeing absolute precision in predicting anaphylactic outcomes, these ratios offer an inexpensive, rapid screening tool to identify individuals who may be more susceptible to anaphylaxis.

Anaphylaxis is a complex immunological response that is primarily triggered by antigen interaction with allergen-specific immunoglobulin E (IgE) bound to the receptor Fc-epsilon-RI on mast cells or basophils. The exact mechanisms of anaphylaxis and the roles of peripheral blood basophil counts remain to be fully understood (22). Previous studies, though limited, have highlighted associations between anaphylaxis and peripheral basophil counts, functionality, and significant migration of circulating basophils during reactions (23). In a study involving 31 patients with acute anaphylaxis, blood samples collected during and after have revealed significantly lower circulating basophil numbers during reactions compared to those seen 7 and 30 days later (3). However, no differences were observed in the absolute counts of eosinophils and lymphocytes. Unlike our study, which measured baseline levels, these studies measured basophil levels during the reaction, potentially explaining the differing observations. Similarly, although known to play a role in allergic reactions and associated with various allergic diseases, eosinophils remain underexplored in the context of anaphylaxis (24, 25).

Distinct from previous research, our study specifically focused on the ELR and BLR in anaphylaxis patients and found no significant difference between the groups for other studied ratios, such as NLR, MLR, and PLR. This is notable as earlier retrospective work reported higher neutrophil counts and NLR in acute allergy patients compared to controls (26). However, it was not specified whether patients who had received corticosteroids, a standard treatment for allergic reactions known to increase the neutrophil count and blood sugar levels quickly, were excluded. This factor and the observed elevated blood sugar levels in the acute allergy group could potentially explain the discrepancy. Moreover, the inflammatory cell count can fluctuate in acute exacerbations of chronic urticaria, suggesting that the value of the NLR ratio may be limited in acute situations.

Moreover, considering that chronic urticaria is a systemic chronic inflammatory condition, it is not surprising that the NLR ratio could be high even at baseline. Several studies have found higher NLRs in chronic spontaneous urticaria (CSU) patients compared to controls (21, 27). Additionally, a study has found a positive correlation between NLR and CSU, suggesting that an elevated NLR may be associated with a poor prognosis in CSU patients (18). Given these studies highlighting the relationship between NLR and CSU and acute allergic reactions, we evaluated the subjects' blood samples at a baseline while conducting our study. We also deemed it appropriate to include a control group consisting of CSU patients who had not experienced anaphylaxis. Despite this, our study did not detect any significant differences in other ratios, such as neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) between the groups. Interestingly, one study found that lower, not higher, NLRs were associated with anaphylaxis resistant to treatment, even after adjusting for potential covariates (20). Although the pathophysiological mechanism between low NLR and refractory anaphylaxis could not be fully elucidated, the researchers concluded that NLR could be used as an easy and inexpensive test to predict resistant anaphylaxis. Compared with our study's results, it is impossible to make a similar interpretation about NLR, unlike ELR and BLR.

Studies assessing the relationship between allergic diseases and ELR are fewer than those involving NLR. A study of 695 children with allergic rhinitis found that ELR in sensitized patients was significantly higher than non-sensitized patients. The authors concluded that ELR could be employed as an adjunctive tool for clinical follow-up (16). A two-center study comparing adult AR patients with healthy controls reported that AR patients had significant-

ly higher levels of absolute eosinophils, eosinophil-to-neutrophil ratio (ENR), and ELR and significantly lower levels of NLR (19). The authors also proposed a diagnostic cut-off level for ELR. They concluded that although a patient's comorbidities could easily alter ELR, it could be used to differentiate between intermittent and persistent AR (19). In a different study involving 97 patients, the researchers reported that ELR was significantly higher in patients with nonsteroid exacerbated respiratory disease (NERD) than in other types of immediate nonsteroid anti-inflammatory drug (NSAID) hypersensitivity reactions (17). The authors attributed their results to the pathophysiology of NERD and concluded that ELR might help differentiate various types of immediate hypersensitivity to NSAIDs (17). As allergic rhinitis is characterized by chronic inflammation of the nasal mucosa, it would be inaccurate to suggest that the results of these studies are predictive of anaphylaxis. While the relationship between anaphylaxis and ELR found in our study might be partially explained by the fact that approximately one-third of the patients in the anaphylaxis group were also diagnosed with allergic rhinitis, further studies may be required to clarify this issue. Similarly, studies involving BLR are scarce, with some evidence suggesting its potential role in predicting the recurrence of chronic rhinosinusitis with nasal polyps (CRSwNP) in asthmatic patients (28).

The modest predictive value of BLR and ELR identified in our study can offer an additional perspective in clinical evaluations of patients potentially at risk for anaphylaxis. They represent a fast, inexpensive tool that could aid in gauging anaphylaxis risk and influence clinical decisions, such as prescribing adrenaline auto-injectors to high-risk patients. Our study uniquely provides potential cut-off values for BLR and ELR, specifically in the context of anaphylaxis prediction.

However, our study has limitations. The relatively small sample size of the groups could have influenced the statistical power of the results, reducing the certainty with which we can make inferences and potentially limiting the generalizability of our findings. Furthermore, the single blood count measurement, lack of a follow-up evaluation, absence of basophil activation biomarkers like CD63 or CD203c in the analysis, and potential for unmeasured confounding variables inherent to any observational study design also need to be taken into account when interpreting our results.

Future research should address these limitations by incorporating larger sample sizes, multiple measurements, follow-up evaluations, and more comprehensive basophil assessments using specific basophil activation biomarkers such as CD63 or CD203c. We recommend repeating the study in larger populations and conducting prospective randomized controlled studies that will look at ELR and BLR ratios more than once and confirm them with basophil activation by flow cytometry analysis.

## CONCLUSION

In conclusion, our study presents evidence of a modest predictive value of the basophil-to-lymphocyte ratio (BLR) and eosinophil-to-lymphocyte ratio (ELR) in the context of anaphylaxis risk. While our study has shed light on potential biomarkers for anaphylaxis, it is clear that more research is required to fully understand the roles of basophils and eosinophils in this complex immunological response. Despite the limitations, our findings contribute to the growing body of knowledge on anaphylaxis, offering a foundation for future studies to build upon and, ultimately, improving patient care.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**Financial Support**

The authors received no financial support for this article's research, authorship, and/or publication.

**Statement of Ethics**

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the Non-Interventional Clinical Research Ethics Committee, Turkey (Date: 01.06.2021, Number: 2021 – 197/27).

**Acknowledgments**

The authors express their sincere gratitude to all those who contributed to its successful completion.

**Authorship Contributions**

Concept: **Pamir Cerci,** Design: **Pamir Cerci,** Data collection or processing: **Pamir Cerci, Anıl Ucan,** Analysis or Interpretation: **Anıl Ucan,** Literature search: **Pamir Cerci, Anıl Ucan,** Writing: **Pamir Cerci, Anıl Ucan,** Approval: **Pamir Cerci, Anıl Ucan.**

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