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Evaluation of the Relationship Between Systemic Inflammatory Markers and Biphasic Reaction in Patients Diagnosed with Anaphylaxis

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ABSTRACT

Objective: Biphasic anaphylaxis, defined as the recurrence of symptoms after initial resolution without re-exposure to the trigger, remains a significant clinical challenge. Identifying laboratory-based predictors of biphasic reactions may help optimize monitoring and management strategies. This study aimed to investigate the relationship between systemic inflammatory markers—neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic inflammation index (SII), systemic inflammatory response index (SIRI), and pan-immune-inflammation value (PIV)—and the development of biphasic reactions in adult patients presenting to the emergency department with anaphylaxis.

Materials and Methods: This retrospective observational study included adult patients diagnosed with anaphylaxis between January 1, 2024, and January 1, 2025, at the emergency department of a tertiary care hospital. Demographic data, clinical findings, laboratory values at presentation, and outcomes were collected. Biphasic reactions were defined as a recurrence of symptoms between 1 and 72 hours after initial improvement. Inflammatory markers were calculated from initial complete blood counts and compared between patients with and without biphasic reactions.

Results: A total of 142 patients were included, of whom 14 (9.9%) experienced biphasic reactions. There were no statistically significant differences in NLR, PLR, SII, SIRI, or PIV between the biphasic and non-biphasic groups ($p > 0.05$ for all). Hypotension was observed more frequently in the biphasic group, but the difference did not reach statistical significance ($p = 0.059$).

Conclusion: Systemic inflammatory markers derived from admission laboratory values were not significantly associated with the development of biphasic anaphylactic reactions. Further prospective studies are warranted to identify reliable biomarkers for early prediction and risk stratification.

Keywords: Anaphylaxis, biphasic reaction, systemic inflammatory markers, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index

INTRODUCTION

Anaphylaxis is a severe hypersensitivity reaction characterized by a rapid onset and systemic manifestations that can become life-threatening if left untreated. In adults, the most common triggers of anaphylaxis include medications, foods, and insect stings, and the majority of anaphylaxis cases can be controlled with appropriately and promptly administered intramuscular epinephrine therapy (1,2). However, in some patients, clinical scenarios such as biphasic anaphylaxis may develop. Biphasic anaphylaxis refers to a secondary phase of reaction that typically recurs within 1 to 72 hours after the resolution of initial symptoms. The unpredictable nature of biphasic reactions may adversely affect both patient safety and emergency department management (3-5).

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Anaphylactic reactions should be regarded not only as immunological events but also as processes involving a marked systemic inflammatory response. Mediators such as histamine, tryptase, prostaglandin D2, and leukotrienes, released from mast cells and basophils, initiate an inflammatory cascade resulting in vasodilation, increased vascular permeability, and fluid loss at the tissue level. In addition, the release of cytokines such as IL-6, IL-10, and TNF-α and the acute-phase response may exacerbate the clinical picture, leading to serious cardiovascular and respiratory consequences (1,2,4).

In evaluating these inflammatory processes, hematological indices derived from complete blood count parameters have garnered attention. Ratios and composite indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Systemic Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), and Pan-Immune-Inflammation Value (PIV) are calculated using the counts and proportions of neutrophils, lymphocytes, monocytes, and platelets. These indices serve as indirect markers of the intensity of systemic inflammation and the balance among immune cell types (6-11). Several studies have demonstrated the prognostic value of these parameters, particularly in allergic conditions and various inflammatory diseases (6,7,9,10). However, studies assessing their predictive power in clinically critical subgroups such as biphasic anaphylaxis remain limited.

The aim of this study was to investigate the relationship between systemic inflammatory markers—such as NLR, PLR, SII, SIRI, and PIV—and biphasic reactions in adult patients who presented to the emergency department due to anaphylaxis.

MATERIAL AND METHODS

Study Design

This retrospective observational study was conducted at the emergency department of Ankara Atatürk Sanatoryum Training and Research Hospital, an 830-bed tertiary care center located in a major provincial city, managing approximately 390,000 emergency department visits annually. Ethical approval for the study was obtained from the local ethics committee (2024-BÇEK/236). The study design adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (12).

Study Population

Patients aged 18 years and older who presented to the emergency department with a diagnosis of anaphylaxis between January 1, 2024, and January 1, 2025, and who had a complete blood count (CBC) performed at the time of admission were included in the study. The diagnosis of anaphylaxis was made in accordance with the clinical criteria defined by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network (NIAID/FAAN) (2).

Patients with the following characteristics were excluded from the study: those with missing laboratory data; individuals with chronic inflammatory diseases such as rheumatoid arthritis or systemic lupus erythematosus; patients with advanced liver or kidney failure; those with active malignancy or a recent history of oncological treatment; individuals diagnosed with hematologic disorders (e.g., leukemia, lymphoma, or myeloproliferative syndromes); patients with recent major surgical procedures or severe trauma; and those receiving systemic corticosteroids or other immunosuppressive medications.

Data Collection

During the data collection process, the patients' clinical status at presentation, demographic characteristics, vital signs, triggering factors of anaphylaxis, treatment approaches, and clinical outcomes were evaluated. Biphasic reaction was defined as the recurrence of symptoms between 1 and 72 hours after initial clinical improvement. All patients were monitored in the emergency department for at least 6 hours and closely followed during this period for the development of biphasic reactions. Additionally, patients who re-presented with anaphylactic symptoms within 72 hours after discharge were also included in the assessment.

The complete blood count (CBC) results obtained at the time of admission for all included patients were recorded, and various systemic inflammatory indices were calculated using the following formulas (6-11):

- NLR (Neutrophil / Lymphocyte)
- PLR (Platelet / Lymphocyte)
- SII (Platelet × Neutrophil / Lymphocyte)
- SIRI (Neutrophil × Monocyte / Lymphocyte)
- PIV (Neutrophil × Platelet × Monocyte / Lymphocyte)

These hematological markers were analyzed to investigate their potential association with the development of biphasic reactions in the patients.

Data Analysis

All data obtained during the study and recorded on the study form were analyzed using the IBM SPSS 20.0 (Chi-

cago, IL, USA) statistical program. The distribution of discrete and continuous numerical variables was evaluated using the Shapiro-Wilk test, histogram, and Q-Q plot graphs. Descriptive statistics were presented as mean ± standard deviation (SD) or median (minimum-maximum) for continuous variables, and as frequencies and percentages for categorical variables. Categorical variables were compared using the Chi-squared test or Fisher's exact test, depending on expected cell counts. For comparison of continuous variables between two independent groups, either the independent samples t-test or the Mann-Whitney U test was used, based on distribution characteristics. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 186 patients diagnosed with anaphylaxis in the emergency department were identified during the study period. After applying the inclusion and exclusion criteria, 142 patients were deemed eligible and included in the analyses. The patient selection process is presented in a flow diagram in Figure 1.

The median age of the patients was 46 years, and 52.1% were female. The most commonly identified allergens were antibiotics (37.3%) and analgesics (34.5%). Cutaneous and/or mucosal involvement was observed in nearly all patients (99.3%), while 71.1% had hypotension, 43% experienced gastrointestinal symptoms, and 32.4% presented with respiratory findings. In the majority of cases (76.1%), a single dose of epinephrine was sufficient; however, 9.9% of patients developed biphasic reactions. The median white blood cell count was [11.65 (IQR 25-75: 9.57-13.9) $\times 10^3/\mu L$] and neutrophil count was [6.91 (IQR 25-75: 4.54-8.7) $\times 10^3/\mu L$], both exceeding the upper limits of the reference range. In contrast, lymphocyte, monocyte, eosinophil, and platelet values remained within normal limits. The median values for inflammatory parameters were as follows: NLR 1.53, PLR 80.07, SII 468.44, SIRI 0.94, and PIV 280.21. The demographic and clinical characteristics of the patients are presented in Table I.

When the 14 patients who developed biphasic reactions were compared with the 128 who did not, no statistically significant differences were found in terms of age, sex, symptom onset time, vital signs, or history of allergy and anaphylaxis. The most common triggering agents in both groups were antibiotics and analgesics. In terms of clinical findings, hypotension was more frequently observed in

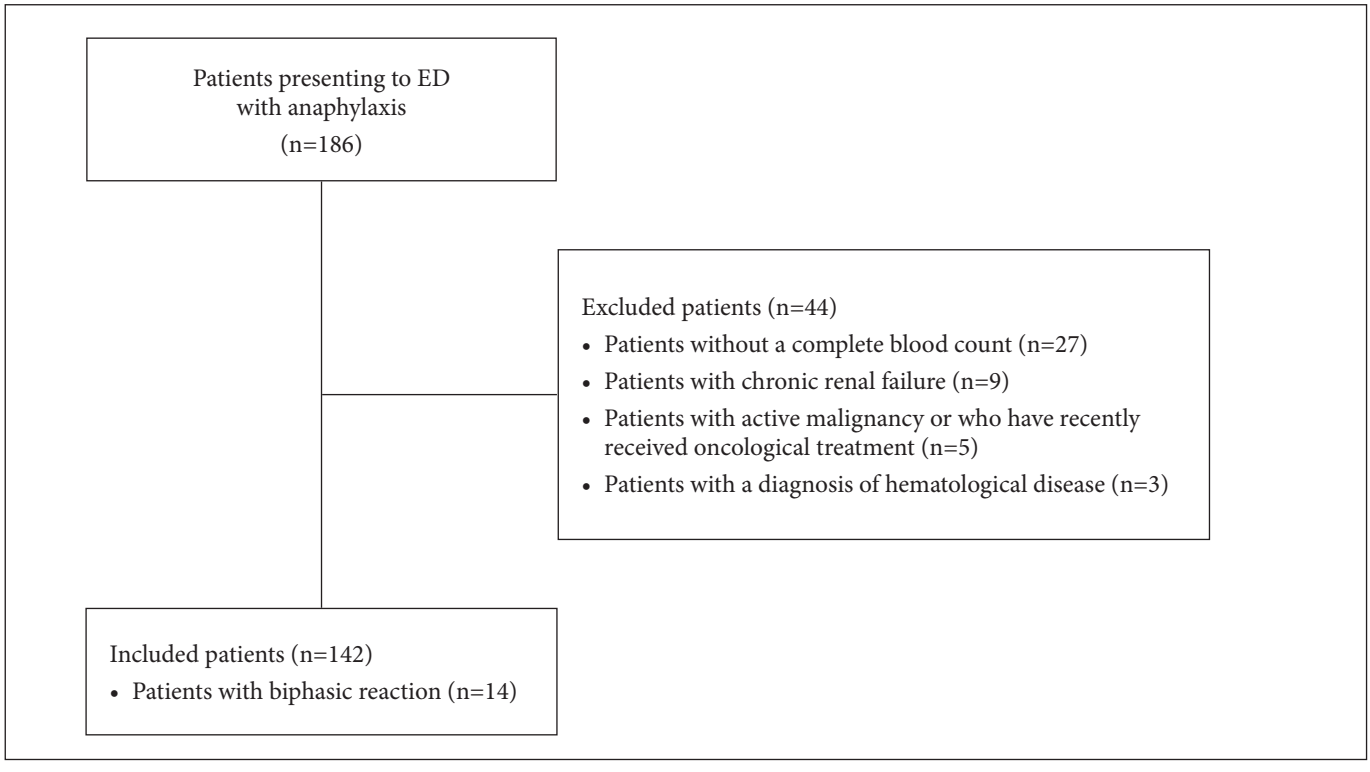

Figure 1. Flowchart of the patients

Table 1. Demographic and clinical characteristics of the patients

Demographic and clinical characteristics, n(%)	All patients (n=142)
Gender n(%)	
Female	74 (52.1)
Age median, (IQR[1], 25-75)	46 (34-53.25)
Time to onset of symptoms (minutes), (IQR, 25-75)	30 (23.75-45)
Vital signs, (IQR, 25-75)	
Pulse	91 (84-105)
Saturation	96 (94-98)
Systolic BP[2]	85 (80-100.75)
Diastolic BP	50 (40-60)
History of allergy	69 (48.6)
History of anaphylaxis	17 (12)
Possible allergen, n(%)	
Antibiotics	53 (37.3)
Analgesics	49 (34.5)
Unknown	10 (7)
Proton pump inhibitors	10 (7)
Food	6 (4.2)
Multidrug	5 (3.5)
Bee stings	4 (2.8)
Contrast agent	2 (1.4)
Hair dye	2 (1.4)
Pastille	1 (0.7)
Skin/mucosal tissue involvement	141 (99.3)
Respiratory compromise	46 (32.4)
Reduced BP	101 (71.1)
Gastrointestinal symptoms	61 (43)
Syncope	11 (7.7)
1 dose of epinephrine	108 (76.1)
2 doses of epinephrine	29 (20.4)
3 doses of epinephrine	5 (3.5)
Epinephrine infusion	3 (2.1)
Refractory anaphylaxis	7 (4.9)
Biphasic anaphylaxis	14 (9.9)
Koinus syndrome	4 (2.8)
Laboratory findings, (IQR, 25-75)	
White Blood Cell, (4-10 $x10^3/\mu L$)*	11.65 (9.57-13.9)
Lymphocyte, (0.8-4 $x10^3/\mu L$)*	3.77 (2.2-5.05)
Monocyte, (0.12-1.2 $x10^3/\mu L$)*	0.6 (0.35-0.75)
Neutrophil, (2-7 $x10^3/\mu L$)*	6.91 (4.54-8.7)
Eosinophil, (0.02-0.7 $x10^3/\mu L$)*	0.09 (0.05-0.17)
Basophil, (0-0.1 $x10^3/\mu L$)*	0.02 (0.02-0.04)
Platelet, (150-450 $x10^3/\mu L$)*	288 (237-329)
NLR[3]	1.53 (1.01-4.11)
PLR[4]	80.07 (56.09-128.99)
SII[5]	468.44 (263.31-1198.48)
SIRI[6]	0.94 (0.50-1.81)
PIV[7]	280.21 (129.97-562.12)

IQR[1]: Inter Quartile Range, **BP[2]:** Blood pressure, **NLR[3]:** Neutrophil-to-Lymphocyte Ratio, **PLR[4]:** Platelet-to-Lymphocyte Ratio, **SII[5]:** Systemic Immune-Inflammation Index, **SIRI[6]:** Systemic Inflammation Response Index, **PIV[7]:** Pan-Immune-Inflammation Value, *The values in parentheses indicate the reference ranges for the respective parameters in the general adult population.

the biphasic reaction group (92.9% vs. 68.8%), although this difference was of borderline statistical significance (p = 0.059). Regarding laboratory parameters, there were no significant differences between the groups in systemic inflammatory markers such as NLR, PLR, SII, SIRI, and PIV. Comparative data of patients with and without biphasic reactions are presented in Table II.

Table 2. Comparison of patients with and without biphasic reaction

	Patients with biphasic reaction (n=14)	Patients without biphasic reaction (n=128)	p
Gender, n(%)			
Female	10 (71.4)	64 (50)	0.128
Age median, (IQR[1], 25-75)	53 (43-61.5)	45 (34-52)	0.055
Time to onset of symptoms (minutes), (IQR, 25-75)	30 (15-48.75)	30 (25-45)	0.816
Vital signs, (IQR, 25-75)			
Pulse	92.5 (82.75-104.25)	91 (84-105)	0.795
Saturation	96.5 (90.75-98.25)	96 (94-98)	0.664
Systolic BP[2]	80 (80-88.5)	85 (80-108.5)	0.183
Diastolic BP	50 (40-55.25)	49.5 (40-60)	0.607
History of allergy	8 (57.1)	61 (47.7)	0.500
History of anaphylaxis	3 (21.4)	14 (10.9)	0.377
Possible allergen, n(%)			
Antibiotics	6 (42.9)	47 (36.7)	
Analgesics	5 (35.7)	44 (34.4)	
Unknown	0 (0)	10 (7.8)	
Proton pump inhibitors	1 (7.1)	9 (7)	0.691
Food	1 (7.1)	5 (3.9)	
Multidrug	0 (0)	5 (3.9)	
Bee stings	0 (0)	4 (3.1)	
Contrast agent	1 (7.1)	1 (0.8)	
Hair dye	0 (0)	2 (1.6)	
Pastille	0 (0)	1 (0.8)	
Skin/mucosal tissue involvement	14 (100)	127 (99.2)	0.740
Respiratory compromise	4 (28.6)	42 (32.8)	0.747
Reduced BP	13 (92.9)	88 (68.8)	0.059
Gastrointestinal symptoms	4 (28.6)	57 (44.5)	0.394
Syncope	1 (7.1)	10 (7.8)	1.000
Laboratory findings, (IQR, 25-75)			
White Blood Cell	11.25 (9.32-14.25)	11.75 (9.52-13.9)	0.956
Lymphocyte	4.23 (2.34-6.74)	3.75 (2.2-5.01)	0.165
Monocyte	0.63 (0.51-0.69)	0.60 (0.35-0.77)	0.926
Neutrophil	7.1 (5.2-8.1)	6.91 (4.47-9.1)	0.878
Eosinophil	0.08 (0.05-0.13)	0.09 (0.05-0.17)	0.745
Basophil	0.03 (0.02-0.03)	0.02 (0.02-0.04)	0.373
Platelet	320 (217-365.75)	286 (238.75-329)	0.730
NLR[3]	1.23 (0.88-3.47)	1.55 (1.04-4.15)	0.305
PLR[4]	54.95 (49.76-112)	80.75 (58.22-129.37)	0.112
SII[5]	328.9 (265.5-962.1)	496.8 (260.7-1247.6)	0.331
SIRI[6]	0.74 (0.52-1.87)	0.95 (0.50-1.76)	0.676
PIV[7]	195.9 (175.2-376.2)	299.4 (127.8-597.1)	0.400

IQR[1]: Inter Quartile Range, **BP[2]:** Blood pressure, **NLR[3]:** Neutrophil-to-Lymphocyte Ratio, **PLR[4]:** Platelet-to-Lymphocyte Ratio, **SII[5]:** Systemic Immune-Inflammation Index, **SIRI[6]:** Systemic Inflammation Response Index, **PIV[7]:** Pan-Immune-Inflammation Value

DISCUSSION

In this study, the relationship between systemic inflammatory markers (NLR, PLR, SII, SIRI, and PIV) and the development of biphasic reactions was retrospectively evaluated in patients diagnosed with anaphylaxis in the emergency department. Our findings demonstrated that these inflammatory markers did not provide a significant predictive value for the occurrence of biphasic reactions.

Early identification of biphasic reactions is of critical importance in the management of anaphylaxis, as these reactions may progress into severe and potentially life-threatening conditions even after an initial favorable response to epinephrine. The reported incidence of biphasic reactions in the literature varies widely, ranging from 0.5% to 20%. This broad range is thought to result primarily from differences in the definitions of anaphylaxis and biphasic reactions, as well as variability in the diagnostic criteria employed across studies (2-5,13-15). In our study, biphasic reactions were identified in line with the criteria proposed by NIAID/FAAN, and their incidence was determined to be 9.9%, aligning with previously published findings.

Although the exact pathophysiology of biphasic reactions remains unclear, several risk factors have been identified in the literature. In particular, delayed or insufficient administration of epinephrine during the initial episode, severe manifestations in the first phase, parenteral exposure to the triggering agent, and delayed presentation to the hospital have been associated with the development of biphasic responses. Additionally, some studies suggest that immunological mechanisms—such as the sustained effects of mediators released from mast cells, a late-phase inflammatory response, and prolonged persistence of the triggering agent in the body—may contribute to the occurrence of biphasic reactions (2,3,13-15). However, these risk factors are not sufficient to reliably predict biphasic reactions in every patient, highlighting the need for new markers, particularly those that are readily accessible and objective.

Various immune mechanisms that may play a role in the development of anaphylaxis have been described in the literature. Although anaphylaxis is generally recognized as a process involving mast cell and basophil degranulation, some studies have suggested that neutrophils may also contribute to this condition. Experimental studies in mice have shown that both active and passive systemic anaphylaxis can occur in the absence of mast cells or basophils, with neutrophils mediating the response. In these models, IgG antibodies were found to activate neutrophils via FcγRIIIA and FcγRIV receptors, leading to the release of platelet-activating factor (PAF) and the subsequent development of anaphylactic shock. It was reported that depletion of neutrophils prevented anaphylaxis, whereas the condition could be reproduced through the transfer of human or murine neutrophils (16,17). In another study, an increase in leukocyte and neutrophil percentages and a decrease in eosinophil percentage were observed in patients with anaphylaxis; these changes were thought to be associated with stress responses and elevated catecholamine levels (18). In our study, the median leukocyte counts in anaphylaxis patients were above the normal reference range, while the median values for neutrophils, lymphocytes, basophils, eosinophils, monocytes, and platelets remained within normal limits. These findings suggest that hematologic changes during anaphylaxis may vary among individuals and may not always correspond to a pronounced inflammatory response.

NLR, PLR, SII, SIRI, and PIV are biomarkers that can be easily calculated from complete blood count parameters and are commonly used to predict the severity and prognosis of various infectious and non-infectious inflammatory conditions. These parameters reflect the systemic inflammatory burden by showing changes in situations where the cellular balance of the immune system is disrupted. In rapidly progressing, immune-mediated hypersensitivity reactions such as anaphylaxis, it has been suggested that these markers may also fluctuate and reflect the intensity of the immune response. One study reported that elevated NLR and PLR levels were significantly associated with the development of refractory anaphylaxis and could be considered independent predictors (9). In contrast, another study found that NLR levels were lower in cases of refractory anaphylaxis, proposing that this could be explained by alternative immune response pathways, such as the NO-cGMP axis (19). These two studies, presenting opposing results, indicate that the clinical implications of inflammatory markers in anaphylaxis may be influenced by numerous factors, including the subtype of anaphylaxis, its timing, and individual immune response patterns.

In our study, no statistically significant association was found between systemic inflammatory markers such as NLR, PLR, SII, SIRI, and PIV and the development of biphasic reactions. This finding suggests that the emergence

of biphasic reactions may be influenced not only by the peripheral inflammatory burden but also by factors such as the type of allergen, timing of epinephrine administration, individual immunological susceptibility, and other environmental variables. Furthermore, considering the complex pathophysiology of biphasic reactions, the predictive value of such hematological parameters alone may be limited.

Limitations

This study was retrospective and single-centered. Although patients were monitored in the emergency department for at least 6 hours to detect the development of biphasic reactions, and those who re-presented within 72 hours were included in the evaluation, it is possible that biphasic reactions occurring outside the hospital and not reported may have been missed. Additionally, the inflammatory markers were calculated based solely on blood samples obtained at the time of presentation, without accounting for their dynamic changes over time. The relatively limited total number of patients included in the study, particularly the small number of cases with refractory anaphylaxis, restricted the ability to perform subgroup analyses regarding the relationship between inflammatory markers and this condition.

CONCLUSION

In this study, it was demonstrated that systemic inflammatory markers—namely NLR, PLR, SII, SIRI, and PIV—did not show a statistically significant association with the development of biphasic reactions in adult patients presenting to the emergency department with anaphylaxis. These findings suggest that the complex and multifactorial pathophysiology of biphasic anaphylaxis may not be sufficiently explained by peripheral hematologic markers alone.

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Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Author Contributions

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