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The Significance of Hematological Parameters in Predicting Disease Activity in Chronic Spontaneous Urticaria and Their Changes with Omalizumab: A Retrospective Cohort Study

Kronik Spontan Ürtikerde Hastalık Aktivitesini Öngörmede Hematolojik Parametrelerin Önemi ve Omalizumab ile Değişimleri: Retrospektif Bir Kohort Çalışması

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ABSTRACT Objective: To investigate the change of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), neutrophil-to-monocyte ratio (NMR), mean platelet volume (MPV), the red blood cell distribution width (RDW), C-reactive protein (CRP), and total immunoglobulin E (IgE) with omalizumab treatment in patients with chronic spontaneous urticaria (CSU). Additionally, to evaluate the relationship between complete blood cell count (CBC)-derived biomarkers and urticaria activity score (UAS7), as well as their relationship with CRP and total IgE, known indicators of disease activity in CSU. **Material and Methods:** CBC, CRP, total IgE and UAS7 values of 101 patients before and at the 12th week of treatment were analyzed retrospectively. **Results:** Before the omalizumab treatment, a significant difference was found between the mild+moderate and severe urticaria groups for the NLR (p=0.023) and NMR (p=0.019). At the 12th week of treatment; a significant increase was observed in MPV (p=0.010), LMR (p=0.031), and total IgE (p<0.001) while NLR (p<0.001), PLR (p=0.013), NMR (p<0.001) and CRP (p<0.001) significantly decreased. There was no significant correlation between CBC-derived biomarkers and UAS7 before and after the treatment. Of the CBC-derived biomarkers, only RDW and MPV showed a weak correlation with CRP. Besides, solely NMR had a weak negative correlation with total IgE just for post-treatment. **Conclusion:** NLR and NMR may reflect the severity of CSU. The inflammatory biomarkers showed a significant change during omalizumab treatment. Omalizumab inhibits inflammation as well as its anti-IgE effect. The lack of correlation between the biomarkers and UAS7 may be attributed to the involvement of different complex inflammatory pathways in the pathogenesis of urticaria.

Keywords: Chronic spontaneous urticaria; omalizumab; CBC-derived inflammatory biomarkers; C-reactive protein; total immunoglobulin E

ÖZET Amaç: Kronik spontan ürtikerli (KSÜ) hastalarda omalizumab tedavisi ile nötrofil-lenfosit oranı [neutrophil-to-lymphocyte ratio (NLR)], trombosit-lenfosit oranı [platelet-to-lymphocyte ratio (PLR)], lenfosit-monosit oranı [lymphocyte-to-monocyte ratio (LMR)], nötrofil-monosit oranı [neutrophil-to-monocyte ratio (NMR)], ortalama trombosit hacmi [mean platelet volume (MPV)], eritrosit dağılım genişliği [red blood cell distribution width (RDW)], C-reaktif protein (CRP) ve total immünglobulin E'deki (IgE) değişimleri incelemektir. Ayrıca, tam kan sayımı kaynaklı biyobelirteçlerin hastalık aktivite skoru [urticaria activity score (UAS7)] ile olan ilişkisini ve KSÜ'de hastalık aktivitesini yansıttığı bilinen CRP ve total IgE değerleri ile olan ilişkilerini değerlendirmektir. **Gereç ve Yöntemler:** Yüz bir hastanın tedavi öncesi ve tedavinin 12. haftasındaki tam kan sayımı, CRP, total IgE ve UAS7 değerleri retrospektif olarak incelendi. **Bulgular:** Omalizumab tedavisi öncesi hafif+orta ve şiddetli ürtiker grupları arasında NLR (p=0,023) ve NMR (p=0,019) açısından anlamlı fark bulundu. Tedavinin 12. haftasında; MPV (p=0,010), LMR (p=0,031) ve total IgE'de (p<0,001) anlamlı artış gözlenirken, NLR (p<0,001), PLR (p=0,013), NMR (p<0,001) ve CRP (p<0,001) anlamlı derecede azaldı. Tedaviden önce ve sonra, tam kan sayımı biyobelirteçleri ile UAS7 arasında anlamlı bir korelasyon yoktu. Tam kan sayımı biyobelirteçlerinden yalnızca RDW ve MPV, CRP ile zayıf bir korelasyon gösterdi. Ayrıca sadece tedavi sonrası için NMR'nin toplam IgE ile zayıf bir negatif korelasyonu vardı. **Sonuç:** NLR ve NMR KSÜ'nün şiddetini yansıtabilir. Omalizumab tedavisi ile inflamatuar biyobelirteçlerin anlamlı değişimi, omalizumabın anti-IgE etkisinin yanı sıra antiinflamatuar etkisini de göstermektedir. Biyobelirteçler ile UAS7 arasındaki korelasyon eksikliğinin, ürtiker patogenezinde rol alan farklı kompleks inflamatuar yolaklar ile ilişkili olabileceği düşünülmüştür.

Anahtar Kelimeler: Kronik spontan ürtiker; omalizumab; tam kan sayımı biyobelirteçleri; C-reaktif protein; total immünglobulin E

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Urticaria is a prevalent skin disease marked by itchy, red, swollen patches and/or angioedema. The disease is categorized as either acute or chronic, based on its duration. If it persists for fewer than six weeks, it is termed acute urticaria (AU), while lasting beyond six weeks classifies it as chronic urticaria (CU).[1] The pathogenesis of CU has not been fully elucidated. Various factors, including disruptions in the intracellular signaling pathways of mast cells and basophils, autoimmunity, inflammation, and coagulation, are believed to contribute to the development of this condition.[2,3]

The basis of urticaria treatment is to eliminate the triggering cause and relieve the symptoms. Omalizumab, a humanized monoclonal anti-immunoglobulin E (anti-IgE) antibody, has proven to be both effective and well-tolerated in treating chronic spontaneous urticaria (CSU) in individuals aged 12 and above who do not respond adequately to antihistamine therapy.[4] Omalizumab binds to the Fc portion of IgE. It prevents IgE from binding to the effector cell and activating the cell and the release of cellular mediators. Recent studies showed that omalizumab is effective not only as anti-IgE but also with its inhibitory properties on inflammation and coagulation.[5]

For monitoring the general activity of the urticarial and treatment effectiveness, the urticaria activity score (UAS) is a simple and verified method. It is recommended to use UAS7 which is calculated by adding up UAS on a daily basis for seven consecutive days.[1] In addition to this scoring system, laboratory tests that can objectively measure inflammation severity and treatment response are needed.

C-reactive protein (CRP), an acute phase protein that rises during inflammatory responses, was identified as a biomarker linked to the activity and severity of CSU, as well as its response to treatment.[6] It is one of the tests recommended to be performed in the first step in patients with CSU.[1]

Total IgE, a pivotal factor in allergic conditions, has been identified as a biomarker linked to the activity, duration, and treatment response of CSU.[7,8] In the initial evaluation of patients with CSU, it is among the tests recommended to be performed.[1]

Neutrophils, lymphocytes, macrophages, and platelets have a role in provoking systemic inflammation. The neutrophil-to-lymphocyte ratio (NLR) is a calculated biomarker obtained by dividing the absolute neutrophil count by the absolute lymphocyte count. In the presence of systemic inflammation, inflammatory cytokines trigger the migration of neutrophils and increase in their numbers, leading to neutrophilia. Meanwhile, in response to physiological stress, there is an increase in neutrophil count and a decrease in lymphocyte count due to elevated endogenous cortisol levels that cause an increase in the NLR.[9,10] This ratio is commonly used as a marker in various diseases, including inflammatory conditions, infections, and malignancies. Research in the literature indicates that the NLR is elevated in patients with CSU compared to the healthy control group. Moreover, it demonstrates a decrease following treatment with omalizumab.[11,12]

The platelet-to-lymphocyte ratio (PLR) is another inflammatory marker obtained by dividing the absolute platelet count by the absolute lymphocyte count. It was reported that while megakaryocytic series proliferate in chronic inflammation, lymphocyte numbers tend to decrease. PLR can indicate the prognosis of various cardiovascular and chronic inflammatory disorders.[13] Studies reported different results in terms of change in PLR with omalizumab treatment in CSU patients.[12,14]

The neutrophil-to-monocyte ratio (NMR) is obtained by division of the absolute neutrophil count by the absolute monocyte count. Similar to the ratios discussed above, the NMR is also used to assess the inflammatory status in various diseases and conditions.[15] Research on NMR in the context of urticaria appears to be limited and in one study, a decrease in NMR with omalizumab treatment in CSU patients was reported.[5]

As another inflammatory marker, lymphocyte-to-monocyte ratio (LMR) is obtained by division of the absolute lymphocyte count by the absolute monocyte count. A limited number of studies showed that LMR does not change with omalizumab treatment in patients with CSU.[5,16]

The activation of the coagulation cascade triggers urticaria by activating mast cells. Since mean platelet volume (MPV) is a potential reflection of

platelet reactivity and inflammation, it is thought that this biomarker might be linked to the disease's activity in urticaria. Studies also showed that larger platelets are more reactive.[17]

The red blood cell distribution width (RDW) is widely used to measure the degree of erythrocyte anisocytosis, reflecting the variability in the size of circulating erythrocytes. In addition to anemia, it was reported that RDW increases in inflammatory diseases.[18] In a study, RDW was documented to exhibit elevated levels in individuals with CSU compared to those in the healthy control group.[19] In another study, no statistically significant change was observed in RDW after omalizumab treatment in CSU patients.[14]

In this study, our objective was to assess the impact of omalizumab on the abovementioned cost-effective CBC-derived biomarkers in patients who started omalizumab treatment with the diagnosis of CSU. We also intended to assess the correlation of these biomarkers with UAS7, CRP, and total IgE.

MATERIAL AND METHODS

Our study received approval from the Clinical Research Ethics Committee of Ankara Yıldırım Beyazıt University-Faculty of Medicine (date: June 10, 2020, no: 47). The research adhered to the principles outlined in the Declaration of Helsinki, the Patient Rights Act, and ethical norms.

This retrospective study includes 101 patients, who were followed between February 2019 and September 2021, aged between 18-80. They did not have any dermatological additional diagnoses other than CSU, and they received omalizumab treatment for the first time in our clinic. Patients under 18 years of age, patients with active infection, hepatic disease, malignant disease, hematological disease, diabetes, hyperlipidemia or coronary heart disease, patients using immunosuppressants or drugs that impair platelet functions, patients who received treatment other than antihistamines and omalizumab for urticaria, and patients who received omalizumab treatment other than 300 mg every 28 days were excluded from the study.

The patients' sociodemographic characteristics (age, gender), disease and treatment information (disease duration, presence of additional systemic disease, UAS7, previous treatments for urticaria), and laboratory results were accessed using the hospital automation system. Leukocyte, platelet, neutrophil, lymphocyte, monocyte, MPV, RDW, NLR, PLR, LMR, NMR, CRP, total IgE, and UAS7 values were analyzed both before and at the 12th week of treatment. Total IgE data were unavailable for 26 patients. Correlation analysis between CBC-derived biomarkers and total IgE was conducted on 75 patients. UAS7 values were available in the system for all 101 patients included in the study. UAS7 values are used to evaluate the severity of the disease and the responses to treatments. It is obtained by scoring the number of wheals and itching severity of the patient within 24 hours and calculating the 7-day total. For a daily activity score, the patient scores wheals and itching between 0-3. The overall score of daily activity varies between 0-6, while the 7-day total varies between 0-42.[1]

Based on the literature; patients' UAS7 scores, both prior to and after a 12-week course of omalizumab treatment, were categorized into five score ranges (0, 1-6, 7-15, 16-27, 28-42). Following omalizumab treatment, patients with UAS7=0 were considered to have a complete response. UAS7 falling within the range of ≤ 6 were labeled as well-controlled, while those in the range of 7-15 were classified as mild. Scores of 16-27 were categorized as moderate, and scores ranging from 28-42 were considered severe.[20] Patients with an increase or no decrease in UAS7 were considered to be unresponsive, and UAS7 lower than the baseline but not showing complete remission were considered to have a partial response. The collected data were compared statistically.

STATISTICAL ANALYSIS

Data were summarized as mean±standard deviation and median (min-max) for continuous variables and frequencies (percentages) for categorical variables. The normality distribution of the data was examined with the Shapiro-Wilks test and, depending on the normality distribution characteristics, analysis of variance (one-way analysis of variance) or Kruskal-Wallis H test was used for comparisons of more than two independent groups. For dependent groups, the t-test (Paired t-test) or Wilcoxon test was used for comparison. Pearson or Spearman correlation coefficients

were employed to examine the association between continuous variables. Statistical analyses were conducted using IBM SPSS for Windows Version 23.0. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The study included 101 patients diagnosed with CSU who underwent omalizumab treatment. 73.3% (n=74) of the patients were female and 26.7% (n=27) were male. The mean age of the participants was 41.6±13.1 years, and the average duration of the disease was 35.5±35.6 months. While the mean UAS7 before the omalizumab treatment was 34.9, it decreased to 7.6 after the treatment (Table 1).

Based on the UAS7 before and after treatment, the patients were categorized into groups (Table 2). Patients having the complete response (UAS7=0) accounted for 18.8% (n=19) of all patients and they were included in the well-controlled group (UAS7≤6).

Here results are divided into 3 subsections namely, analysis of pre-treatment data, analysis of post-treatment data, and analysis of changes in hematological and inflammatory biomarkers with the treatment.

TABLE 1: Demographic and clinical findings of the patients.

		n	%
Gender	**Female**	**74**	**73.3**
	Male	**27**	**26.7**
	X̄±SD	**Median**	**Minimum-Maximum**
Age	41.6±13.1	40	19-75
Disease duration (months)	35.5±35.6	20	3-156
UAS7 (0th week)	34.9±6.6	36	7-42
UAS7 (12th week)	7.6	4	0-38

UAS7: Sum of daily urticaria activity scores over 7 consecutive days; SD: Standard deviation.

ANALYSIS OF PRE-TREATMENT DATA

In this section, CBC-derived biomarkers of the patients were compared considering the disease severity groups (based on UAS7), before treatment. In addition, the correlations of these biomarkers with UAS7, CRP, and total IgE were examined.

For the comparative analysis, since there were only two patients in the mild urticaria group, they were added together and a new group called mild+moderate was created. Comparative results between mild+moderate and severe urticarial groups were analyzed. There was a significant difference observed between the mild+moderate and severe urticaria groups for NLR and NMR variables ($p=0.023$, 0.019, respectively). For other variables, the difference between the mild+moderate urticaria and severe urticaria groups was not significant (Table 3).

For pre-treatment correlation analysis, there was no significant correlation between CBC-derived biomarkers and UAS7. For the correlation of CRP with CBC-derived biomarkers, a weak ($0.2<r<0.4$) positive correlation was found considering MPV ($p<0.01$, $r=0.271$) and RDW ($p<0.01$, $r=0.300$). However, there was no significant correlation considering NLR, PLR, LMR, and NMR. Also, no significant correlation was observed between total IgE and CBC-derived biomarkers (Table 4).

ANALYSIS OF POST-TREATMENT DATA

In this part, post-treatment correlations of CBC-derived biomarkers with UAS7, CRP, and total IgE were examined. Between post-treatment UAS7 and post-treatment CBC-derived biomarkers, there was

TABLE 2: Distribution of the number of patients according to UAS7 before and after treatment.

	Post-treatment UAS7 (12th week)				
Pre-treatment UAS7 (0th week)	**Well-controlled**	**Mild urticaria**	**Moderate urticaria**	**Severe urticaria**	**Total**
Mild urticaria	2 (100%)	0	0	0	2
Moderate urticaria	8 (88.9%)	1 (11.1%)	0	0	9
Severe urticaria	52 (57.8%)	24 (26.7%)	8 (8.9%)	6 (6.7%)	90
Total	62	25	8	6	101

UAS7: Sum of daily urticaria activity scores over 7 consecutive days.

TABLE 3: Comparison of inflammatory biomarkers of groups classified according to disease severity before treatment.

	Mild+Moderate group, Median (Minimum-Maximum) n=11	Severe group, Median (Minimum-Maximum) n=90	p-value
MPV (fL)	8.1 (7-10)	8.4 (6.16-11.2)	0.488
RDW (%)	13.7 (11.9-19.1)	13.9 (12.1-18.4)	0.389
NLR	1.60 (0.89-3.8)	2.45 (1-7.4)	**0.023***
PLR	104.8 (67.8-165.9)	125 (11.6-258.2)	0.383
LMR	5.3 (3.40-10.2)	5.3 (1.9-19.5)	0.857
NMR	9.08 (6.8-20.6)	12.6 (5.4-43.3)	**0.019***

*p<0.05; MPV: Mean platelet volume; RDW: Red blood cell distribution width; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; NMR: Neutrophil-to-monocyte ratio.

TABLE 4: Pre-treatment correlation analysis results.

0th week		MPV	RDW	NLR	PLR	LMR	NMR
UAS7	r	0.100	-0.129	0.064	-0.099	0.172	0.173
	p value	0.319	0.199	0.528	0.323	0.086	0.084
CRP	r	**0.271**	**0.300**	0.182	0.011	0.050	0.196
	p value	**0.006***	**0.002***	0.069	0.915	0.623	0.049
Total IgE	r	0.027	-0.022	-0.113	-0.143	-0.167	-0.206
	p value	0.816	0.852	0.336	0.222	0.153	0.077

*p<0.05; MPV: Mean platelet volume; RDW: Red blood cell distribution width; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; NMR: Neutrophil-to-monocyte ratio; CRP: C-reactive protein; IgE: Immunoglobulin E; UAS7: Urticaria activity score 7; r: Correlation coefficient.

no significant correlation, similar to the pre-treatment situation. For the post-treatment correlation of CRP with CBC-derived biomarkers, a weak positive correlation was detected considering RDW ($p<0.01$, $r=0.267$). However, there was no significant correlation considering MPV, NLR, PLR, LMR, and NMR. For total IgE, a weak negative correlation was observed with post-treatment NMR ($p<0.01$, $r=-0.381$), and no significant correlation was detected with other biomarkers (Table 5).

ANALYSIS OF CHANGES IN CBC-DERIVED BIOMARKERS, CRP, AND TOTAL IGE WITH OMALIZUMAB TREATMENT

In this part, CBC-derived biomarkers, CRP, and total IgE before and at the 12th week of treatment were compared. While there was a significant increase in MPV ($p=0.010$), LMR ($p=0.031$), and total IgE ($p<0.001$); a significant decrease was observed in NLR ($p<0.001$), PLR ($p=0.013$), NMR ($p<0.001$), and CRP ($p<0.001$) with treatment. Besides, there was no significant difference between pre-treatment and post-treatment RDW (Table 6).

DISCUSSION

CSU is a common skin disease marked by the presence of pruritic urtica, angioedema, or a combination of both, persisting for a duration of six weeks or more.[1] Autoimmunity, inflammation, and the coagulation cascade are regarded as the primary factors in the pathogenesis of CSU; it is thought that different cell groups such as mast cells, basophils, neutrophils, lymphocytes, eosinophils, and platelets play a role.[2,3] Several inflammatory biomarkers have been studied to assess the inflammatory status and disease activity in CSU.

AU and CU are more common in women. Most studies found male: female ratios to be 1:2. CU is

TABLE 5: Post-treatment correlation analysis results.

12th week		MPV	RDW	NLR	PLR	LMR	NMR
UAS7	r	0.029	0.037	0.100	0.178	0.013	0.179
	p value	0.774	0.710	0.321	0.075	0.894	0.073
CRP	r	-0.009	**0.267**	0.125	0.092	-0.052	0.149
	p value	0.931	**0.007***	0.214	0.359	0.608	0.136
Total IgE	r	-0.037	-0.158	-0.187	-0.069	-0.062	**-0.381**
	p value	0.755	0.176	0.108	0.557	0.595	**0.001***

*p<0.05; MPV: Mean platelet volume; RDW: Red blood cell distribution width; NLR: Neutrophil-to- lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; NMR: Neutrophil-to-monocyte ratio; CRP: C-reactive protein; IgE: Immunoglobulin E; UAS7: Urticaria activity score 7; r: Correlation coefficient.

TABLE 6: Analysis of changes in CBC-derived biomarkers, CRP, and total IgE.

	X̄±SD	Median (Minimum-Maximum)	p-value
MPV (fL) 0th week	8.50±1.06	8.30 (6.16-11.20)	**0.010***
MPV (fL) 12th week	8.76±1.18	8.60 (6.90-12.30)	
RDW (%) 0th week	14.15±1.39	13.80 (11.90-19.10)	0.152
RDW (%) 12th week	14.06±1.53	13.80 (11.30-19.90)	
NLR 0th week	2.63±1.16	2.40 (0.89-7.40)	**<0.001***
NLR 12th week	2.08±0.94	1.83 (0.70-7.40)	
PLR 0th week	130.53±46.21	124.80 (11.60-258.20)	**0.013***
PLR 12th week	124.16±49.78	119.30 (11.80-308.10)	
LMR 0th week	5.58±2.48	5.30 (1.90-19.50)	**0.031***
LMR 12th week	5.82±2.16	5.50 (1.70-17.80)	
NMR 0th week	13.55±6.58	11.90 (5.40-43.30)	**<0.001***
NMR 12th week	11.10±3.61	10.80 (4.60-26)	
CRP (mg/L) 0th week	7.06±11.35	3.80 (0.30-77.80)	**<0.001***
CRP (mg/L) 12th week	3.85±4.09	2.10 (0.30-15.60)	
Total IgE (IU/mL) 0th week	153.93±211.15	64.30 (1-1156.40)	**<0.001***
Total IgE (IU/mL) 12th week	263.78±335.97	132.80 (3-2235)	

*p<0.05; MPV: Mean platelet volume; RDW: Red blood cell distribution width; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio; NMR: Neutrophil-to-monocyte ratio; CRP: C-reactive protein; IgE: Immunoglobulin E; SD: Standard deviation.

most frequently reported between the ages of 25 and 55 years.[20] In our study, the male: female ratio was 1:2.7 and the average age was 41.6±13.1 years, similar to the literature.

Based on the double-blind placebo-controlled studies including over a thousand patients, the effectiveness of omalizumab in urticaria was approved and it was added to the treatment algorithm in CSU guidelines.[21] In one of these studies, ASTERIA I, the initial mean UAS7 of patients in the 300 mg omalizumab group was found to be 31.3±5.8. At the 12th week, 35.8% achieved a complete response (UAS7=0), and 51.9% were classified as well-controlled (UAS7≤6). These rates were more than four times higher than the rates in the placebo group.[22] In a review of five randomized controlled trials, 43% of patients on 300 mg omalizumab for 24 weeks achieved complete response (UAS7=0), compared to 9% in the standard urticaria treatment group.[23] In our study, we found the initial mean UAS7 to be 34.9±6.6, similar to that in ASTERIA I. After treatment, 61.4% of the patients had a well-controlled disease response including an 18.8% complete response rate. Compared to the literature our complete response rate (18.8%) was lower. However, the well-controlled disease response rate (61.4%) was observed to be high compared to the literature. Overall, our findings showed consistent results with the literature considering the effectiveness of omalizumab in reducing the patients' symptom scores.

Autoimmunity, inflammation, and coagulation processes are involved in the pathogenesis of CU, thus different inflammation biomarkers have been studied to evaluate the inflammatory status and disease activity. These biochemical and hematological biomarkers might be time-consuming and expensive to use in all clinical cases. However, some biomarkers can be easily acquired from a complete blood count to monitor the status and disease activity.[5,14] NLR is a practical method to predict the prognosis of various diseases which also increases in some dermatological conditions like atopic dermatitis and psoriasis, and this increase is associated with disease activity.[9,10,24,25] PLR can be used as an indicator of systemic inflammation and indicate the prognosis of various disorders including psoriasis and atopic dermatitis.[13,24,26] LMR and NMR were also presented as prognostic indicators of some dermatological diseases.[27,28] MPV is a potential indicator of platelet reactivity and inflammation, which might be associated with disease activity in urticaria.[17] Lastly, CRP is a known inflammatory biomarker in many diseases, which is recommended to be examined as a routine diagnostic test in CU.[1]

The study by Tat et al. found a significant increase in NLR in CU patients compared to the control group, but no significant difference in NLR among different disease severity groups.[29] Another study noted higher NLR and CRP in CSU patients, with CRP being significantly higher in severe cases.[30] Cosansu reported elevated NLR and RDW and lower MPV in CSU patients, with no significant difference in PLR. Furthermore, there were no significant differences in these markers between different disease severity subgroups.[19] To the best of our knowledge, there is no study investigating the correlation between NMR and LMR with urticaria disease severity. Different from some studies in the literature, there was no control group in our study, instead the patients were stratified into two groups (mild+moderate/severe) based on the severity of the disease. In our study, both NLR and NMR were significantly elevated in the severe disease group compared to the mild and moderate disease group. Thus, we believe that both NLR and NMR could serve as potential biomarkers capable of indicating the severity of the disease.

Omalizumab is a fast-acting treatment agent with high treatment efficacy in patients with CSU who do not respond to high-dose antihistamines. Omalizumab shows its general effects by stopping the degranulation of mast cells, reducing the secretion of mediators, cytokines, and chemokines, and with additional anti-inflammatory effects.[5,31] In our study, we found that MPV, LMR, and total IgE increased with treatment while NLR, PLR, NMR, and CRP decreased with treatment. However, we did not observe any significant changes in RDW. Our findings generally support the literature findings, on the other hand, we had conflicting results regarding the response of PLR and LMR to omalizumab treatment. Different studies showed that PLR decreased after omalizumab treatment or its change was not significant, and the change in LMR was not significant.[5,12,14,16,32-34]

As for the pre-treatment correlation analysis, CBC-derived biomarkers did not show a correlation with UAS7, consistent with the findings in Cosansu's study.[19] This might be explained by the different inflammatory pathways involved in the complex urticaria pathogenesis and by only including the patients under omalizumab treatment in our study. We also analyzed the correlation of CBC-derived biomarkers with CRP and total IgE, which are biomarkers considered indicators of disease activity (according to previous studies' results) and recommended as routine tests in the guidelines.[1,6-8] In our results, MPV and RDW showed weak correlations with CRP, while NLR, PLR, LMR, and NMR did not correlate supporting the findings of Akca and Tuncer Kara.[35] In addition, CBC-derived biomarkers also showed no significant correlation with total IgE in our study.

To our knowledge, there is no research examining the correlation between complete blood count biomarkers and CRP/total IgE/UAS after omalizumab treatment. In our study, these biomarkers and UAS7 did not correlate in post-treatment analysis, as well as pre-treatment analysis. While they may not directly correlate with the disease activity score, it is important to note that NLR and NMR might be higher in individuals with severe urticaria. We also found that CRP had a weak correlation with RDW, while it did not correlate with other biomarkers. Among the CBC-derived biomarkers, only NMR showed a weak correlation with total IgE. This situation was similar to the pre-treatment correlation analysis. Among the existing literature, best of our knowledge, our study is the most comprehensive one analyzing the correlations of CBC-derived biomarkers and the disease activity both before and after treatment.

Our study has limitations such as its retrospective design and lack of a control group.

CONCLUSION

PLR, LMR, MPV, and RDW may not be reliable markers for predicting disease activity because they neither showed significant differences between severity groups nor correlated with UAS7 in the pre- and post-treatment analysis. Besides UAS7, these biomarkers did not show a correlation either with total IgE and CRP (only a weak correlation for MPV and RDW). However, NLR and NMR might reflect disease severity because of the significant differences between severity groups. The lack of correlation between these CBC-derived biomarkers and UAS7 might be attributed to the involvement of different complex inflammatory pathways in the pathogenesis of urticaria. A significant elevation in MPV, LMR, and total IgE, along with a reduction in NLR, PLR, NMR, and CRP following treatment indicates that omalizumab possesses not only an anti-IgE effect but also exerts inhibitory effects on inflammation and coagulation processes.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Cansu Altınöz Güney, Akın Aktaş;* ***Design:*** *Cansu Altınöz Güney, Akın Aktaş;* ***Control/Supervision:*** *Akın Aktaş;* ***Data Collection and/or Processing:*** *Cansu Altınöz Güney;* ***Analysis and/or Interpretation:*** *Cansu Altınöz Güney, Akın Aktaş;* ***Literature Review:*** *Cansu Altınöz Güney, Akın Aktaş;* ***Writing the Article:*** *Cansu Altınöz Güney, Akın Aktaş;* ***Critical Review:*** *Cansu Altınöz Güney, Akın Aktaş;* ***References and Fundings:*** *Cansu Altınöz Güney, Akın Aktaş;* ***Materials:*** *Cansu Altınöz Güney, Akın Aktaş.*

REFERENCES

1. Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734-66. PMID: 34536239.
2. Bracken SJ, Abraham S, MacLeod AS. Autoimmune theories of chronic spontaneous urticaria. Front Immunol. 2019;10:627. PMID: 30984191; PMCID: PMC6450064.
3. Akelma AZ, Mete E, Cizmeci MN, Kanburoglu MK, Malli DD, Bozkaya D. The role of mean platelet volume as an inflammatory marker in children with chronic spontaneous urticaria. Allergol Immunopathol (Madr). 2015;43(1):10-3. PMID: 23969073.
4. Ertas R, Ozyurt K, Atasoy M, Hawro T, Maurer M. The clinical response to omalizumab in chronic spontaneous urticaria patients is linked to and predicted by IgE levels and their change. Allergy. 2018;73(3):705-12. PMID: 29083482.
5. Önder S, Ozturk M. How does omalizumab affect the immunoinflammatory response in patients with chronic spontaneous urticaria? Cutan Ocul Toxicol. 2020;39(1):31-5. PMID: 31642341.
6. Yan S, Chen W, Su J, Chen M, Zhu W, Zhang J, et al. [Association between C reactive protein and clinical characteristics in patients with chronic spontaneous urticaria]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2017;42(2):168-72. Chinese. PMID: 28255118.
7. Altrichter S, Fok JS, Jiao Q, Kolkhir P, Pyatilova P, Romero SM, et al. Total IgE as a marker for chronic spontaneous urticaria. Allergy Asthma Immunol Res. 2021;13(2):206-18. PMID: 33474856; PMCID: PMC7840871.
8. Kessel A, Helou W, Bamberger E, Sabo E, Nusem D, Panassof J, et al. Elevated serum total IgE--a potential marker for severe chronic urticaria. Int Arch Allergy Immunol. 2010;153(3):288-93. PMID: 20484928.
9. Jung J, Park SY, Park SJ, Park J. Prognostic value of the neutrophil-to-lymphocyte ratio for overall and disease-free survival in patients with surgically treated esophageal squamous cell carcinoma. Tumour Biol. 2016;37(6):7149-54. PMID: 26662960.
10. Demirkol S, Balta S, Kucuk U, Kucuk HO. The neutrophil lymphocyte ratio may be useful inflammatory indicator before applying other expensive and invasive procedures. Indian J Nephrol. 2014;24(1):65-6. PMID: 24574639; PMCID: PMC3927199.
11. Sarac G, Mantar İ, Sener S, Cenk H, Kapicioglu Y. Assessment of change in neutrophil-lymphocyte ratio, platelet-lymphocyteratio in patients with acute and chronic urticaria. Ann Med Res. 2018;25(4):719-22. https://annalsmedres.org/index.php/aomr/article/view/1097
12. Ertaş R, Özyurt K, Karakükçü Ç, Akkuş MR, Özlü E, Avcı A, et al. Evaluation of platelet parameters and neutrophil/lymphocyte ratio during omalizumab treatment in patients with severe chronic spontaneous urticaria. Turk J Med Sci. 2018;48(6):1255-62. PMID: 30541255.
13. Toprak E, Bozkurt M, Dinçgez Çakmak B, Özçimen EE, Silahlı M, Ender Yumru A, et al. Platelet-to-lymphocyte ratio: a new inflammatory marker for the diagnosis of preterm premature rupture of membranes. J Turk Ger Gynecol Assoc. 2017;18(3):122-6. PMID: 28890425; PMCID: PMC5590207.
14. Acer E, Kaya Erdogan H, Yüksel Çanakçı N, Saracoglu ZN. The effect of omalizumab on hematological and inflammatory parameters in patients with chronic spontaneous urticaria. Cutan Ocul Toxicol. 2019;38(1):5-8. PMID: 29969297.
15. Rizo-Téllez SA, Méndez-García LA, Flores-Rebollo C, Alba-Flores F, Alcántara-Suárez R, Manjarrez-Reyna AN, et al. The neutrophil-to-monocyte ratio and lymphocyte-to-neutrophil ratio at admission predict in-hospital mortality in Mexican Patients with severe SARS-CoV-2 infection (Covid-19). Microorganisms. 2020;8(10):1560. PMID: 33050487; PMCID: PMC7600553.
16. Tamer F. Omalizumab does not lead to a distinct alteration in hematological parameters and complete blood count-derived inflammation biomarkers except for basophil count. Cutan Ocul Toxicol. 2020;39(3):229-32. PMID: 32380865.
17. Čavčić A, Ivković-Jureković I, Trkulja V. Higher mean platelet volume is associated with paediatric chronic spontaneous urticaria and with a more severe disease in the affected children. Australas J Dermatol. 2019;60(3):e263-e6. PMID: 30790277.
18. Gisondi P, Geat D, Lippi G, Montagnana M, Girolomoni G. Increased red blood cell distribution width in patients with plaque psoriasis. J Med Biochem. 2021;40(2):199-201. PMID: 33776570; PMCID: PMC7982291.
19. Cosansu NC. Evaluation of new inflammatory parameters in patients with chronic spontaneous urticaria: a new predictor of refractoriness to antihistamine treatment. Namık Kemal Tıp Derg. 2020;8(3):404-11. https://dergipark.org.tr/tr/download/article-file/1085495
20. Stull D, McBride D, Georgiou P, Zuberbier T, Grattan C, Balp M. Measuring patient severity in chronic spontaneous/idiopathic urticaria (CSU/CIU) as categorical health states: efficient and informative? Allergy. 2014;69(Suppl s99):317. https://www.rti.org/publication/measuring-patient-severity-chronic-spontaneousidiopathic-urticaria-csuciu-categorical-health-states
21. Koncatürk Göncü E, Aktan Ş, Atakan N, Bülbül Başkan E, Erdem T, Koca R, et al. Türkiye Ürtiker Tanı ve Tedavi Kılavuzu-2016 [The Turkish Guideline for the Diagnosis and Management of Urticaria-2016]. Turkderm-Turkish Arch Dermatology Venereol. 2016;50:82-98. https://jag.journalagent.com/turkderm/pdfs/TURKDERM_50_3_82_98.pdf
22. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bülbül Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. J Invest Dermatol. 2015;135(1):67-75. Erratum in: J Invest Dermatol. 2015;135(3):925. PMID: 25046337; PMCID: PMC4269803.
23. Agache I, Rocha C, Pereira A, Song Y, Alonso-Coello P, Solà I, et al. Efficacy and safety of treatment with omalizumab for chronic spontaneous urticaria: a systematic review for the EAACI Biologicals Guidelines. Allergy. 2021;76(1):59-70. PMID: 32767573.
24. Jiang Y, Ma W. Assessment of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in atopic dermatitis patients. Med Sci Monit. 2017;23:1340-6. PMID: 28306706; PMCID: PMC5367851.
25. Sen BB, Rifaioglu EN, Ekiz O, Inan MU, Sen T, Sen N. Neutrophil to lymphocyte ratio as a measure of systemic inflammation in psoriasis. Cutan Ocul Toxicol. 2014;33(3):223-7. PMID: 24147939.
26. Ünal M, Küçük A, Ünal GÜ, Balevi Ş, Tol H, Aykol C, et al. Psoriasiste ortalama trombosit hacmi, nötrofil/lenfosit oranı ve trombosit/lenfosit oranı [Mean platelet volume, neutrophil to lyphocyte ratio and platelet to lymphocyte ratio in psoriasis]. TURKDERM-Turkish Arch Dermatology Venereol. 2015;49(2):112-6. https://jag.journalagent.com/turkderm/pdfs/TURKDERM_49_2_112_116.pdf
27. Schildbach VAS, Horn S, Hidalgo-Gadea G, Johannis W, Mauch C, Franklin C. C-reactive protein and lymphocyte-to-monocyte ratio predict recurrence in stage III melanoma patients with microscopic sentinel lymph node metastasis. Cancers (Basel). 2023;15(3):702. PMID: 36765660; PMCID: PMC9913855.
28. Albayrak H. Neutrophil-to-lymphocyte ratio, neutrophil-to-monocyte ratio, platelet-to-lymphocyte ratio, and systemic immune-inflammation index in psoriasis patients: response to treatment with biological drugs. J Clin Med. 2023;12(17):5452. PMID: 37685519; PMCID: PMC10488109.
29. Tat TS. Kronik ürtikerli hastalarda troid otoimmünitesi ve artmış nötrofil lenfosit oranı [Thyroid autoimmunity and increased neutrophil lymphocyte ratio in patients with chronic urticaria]. Turkish J Clin Lab. 2019;10(1):52-6. https://doi.org/10.18663/tjcl.521024

30. Aktaş Karabay E, Aksu Çerman A, Kivanç Altunay I. Serum C-reactive protein, neutrophil-lymphocyte ratio and uric acid levels in chronic spontaneous urticaria. Turkiye Klin Dermatoloji. 2016;26(3):125-31. doi: 10.5336/dermato.2016-52709

31. Kaplan AP, Giménez-Arnau AM, Saini SS. Mechanisms of action that contribute to efficacy of omalizumab in chronic spontaneous urticaria. Allergy. 2017;72(4):519-33. PMID: 27861988; PMCID: PMC5915348.

32. Çildağ S, Şentürk T. The effect of omalizumab treatment on IgE and other immunoglobulin levels in patients with chronic spontaneous urticaria and its association with treatment response. Postepy Dermatol Alergol. 2018;35(5):516-9. PMID: 30429712; PMCID: PMC6232555.

33. Akdogan N, Demirel Ogut N, Dogan S, Atakan N. Long-term effects of omalizumab on peripheral blood cells and C-reactive protein levels in patients with chronic spontaneous urticaria. Dermatol Ther. 2019;32(4):e12966. PMID: 31087491.

34. Celik E, Dirican E. Can we predict the duration of treatment requirement by complete blood count in chronic spontaneous urticaria patients receiving omalizumab? Dicle Med J. 2020;47(3):568-77. https://doi.org/10.5798/dicletip.799661

35. Akca HM, Tuncer Kara K. Correlation of urticaria activity score in chronic spontaneous urticaria with serum C-reactive protein level and neutrophil/lymphocyte ratio. Dermatol Ther. 2020;33(6):e14532. PMID: 33176046.