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The Elevated Eosinophil Counts and Neutrophils/Lymphocytes Ratio as Predicting Biomarkers in Non-responders, Chronic Spontaneous Urticarial Patients to Cetirizine/Famotidine Treatment

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ABSTRACT

The responses of patients with chronic spontaneous urticaria (CSU) to regular therapeutic options vary. While these methods are effective for some patients, many do not respond successfully. Despite several studies conducted to identify immunologic and inflammatory biomarkers in patients that can predict response, our current knowledge is insufficient. This study aimed to identify biomarkers that may predict therapeutic response.

The present interventional study evaluated 61 moderate-to-severe CSU patients aged 20 to 50 years who presented to our clinic from January 2024 to January 2025. Peripheral blood samples, serum, and plasma were collected to measure inflammatory and immunological variables, and were analyzed at a reference laboratory. Subsequently, patients were treated with cetirizine 10 mg every 12 hours and famotidine 40 mg every night. After 1month, urticarial severity was reassessed using the same questionnaire. Severity scores were compared between patients with elevated biomarkers and those with normal levels.

Sixty-one patients with chronic spontaneous urticaria were enrolled; 77% female and 23% male. Forty-one patients experienced a good response to treatment, while 20 patients did not. The average (Urticaria Activity Score) UAS7 scores before and after treatment were 27.72 and 12.67, respectively. Among the serum biomarkers evaluated, only the neutrophil-to-lymphocyte ratio (NLR) and serum eosinophil count showed a significant relationship with treatment response.

To conclude, a high eosinophil count and NLR may serve as predictors of a poor clinical response to antihistamine therapy. However, further clinical trials are needed to confirm these findings.

Keywords: Biomarkers; Cetirizine; Chronic urticaria; Eosinophilia; Famotidine

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INTRODUCTION

The presence of hives, flare, and angioedema defines urticaria. Chronic urticaria is characterized by the

development of wheals, angioedema, or both that persist for more than 6 weeks. Autoimmunity, inflammation, and the coagulation cascade are key pathophysiologic mechanisms in chronic spontaneous urticaria (CSU). In addition to mast cell degranulation, several other immune mechanisms contribute to the pathogenesis of CSU.[1-3] Eosinophils can produce stem cell factors that promote the proliferation and differentiation of mast cells, which can contribute to the persistence of a high number of mast cells at the site of wheals and non-lesional skin. The survival of eosinophils is higher than expected in the normal skin of patients with CSU.[4] Patients with CSU respond differently to therapeutic options. This diversity in clinical outcomes is attributed to the heterogeneity of phenotypic and endotypic characteristics of CSU. Chronic spontaneous urticaria activity, disease duration, and response to treatment are related to laboratory variables and clinical characteristics. These factors can help physicians predict patients' disease duration and expected clinical response to treatment. However, none of these items is a significant predictor.[1] Recent research has focused on identifying inflammatory and immunologic biomarkers that may be associated with disease severity and could help predict therapeutic responses.[5-8] Patients with chronic spontaneous urticaria also exhibit additional immunological features at the site of wheals. In addition to mast cell degranulation, the lesions are characterized by infiltration of basophils, eosinophils, monocytes, neutrophils, and T lymphocytes. The infiltration represents a mixed inflammatory profile; T Helper 1 cells / T Helper 17 cells (TH1/TH17) responses are also present.4,9 Current studies report that immunologic and inflammatory biomarkers, such as Interleukin-6, C-reactive Protein, D-dimer, Erythrocyte Sedimentation Rate (IL-6, CRP, D-dimer, and ESR) are elevated during the active phase of CSU. Increased levels of inflammatory and coagulation factors (CRP, IL-6, prothrombin fragment, D-dimer) in the skin of patients with active CSU reflect the coagulation enzyme turnover in the pathogenesis of the disease. Thymic stromal lymphopoietic, IL-33, and IL-25 are increased in lesional versus non-lesional skin.[10,11] Several studies have demonstrated associations between these biomarkers and CSU activity and severity.[12] We aimed to evaluate the clinical response to conventional treatment in patients with moderate to severe chronic spontaneous urticaria who had elevated immunologic-inflammatory biomarkers and to compare their responses with those of patients without elevated biomarker levels.

MATERIALS AND METHODS

Patients

In this interventional study, 61 CSU patients aged 20 to 50 years were selected from Shahid Sadoughi Hospital and Khatam Al-Ambia Clinic (Yazd, Iran) between January 2024 and January 2025. Before sample collection and treatment initiation, informed consent was obtained from all participants. A detailed medical history, including their previous medical history including clinical examination was then recorded. Patients with moderate to severe chronic spontaneous urticaria were identified using the Urticaria Activity Score (UAS7) questionnaire. If the patients met our inclusion criteria, a peripheral blood sample, serum, and plasma were collected to measure inflammatory and immunological variables. All patients were examined and interviewed before enrollment in the study by an immunologist specialist based on their past medical history and documents. Individuals with chronic inflammatory diseases, such as rheumatologic disorders, metabolic disorders such as diabetes, and individuals with a history of atopy (e.g., asthma, allergic rhinitis, or atopic dermatitis) were excluded. Patients showing evidence of recent infection or who had taken antibiotics or corticosteroids for at least 1 month prior to enrollment were also excluded.

Sample Collection and Intervention

The selected CSU patients were interviewed, and whole blood was collected and sent to a reference laboratory (Central Lab, Yazd, Iran) before and after receiving any intervention. Blood samples were collected using appropriate collection tubes, selected according to the type of each test. For the complete blood count with differential (CBC diff), PLT/LYM ratio, eosinophil count (EOS), and platelet count (PLT), whole blood was drawn into EDTA tubes. For the ESR test, whole blood was collected in sodium citrate tubes with a 1:4 citrate-to-blood ratio, as recommended for accurate ESR determination. CRP, anti-TPO, and IgE levels were measured from serum samples obtained from the patients. For the D-dimer test, plasma samples were used as the test material. Blood was collected in sodium citrate tubes (Fartest/Iran). To minimize pre-analytical errors, each patient's sample was tested immediately upon their arrival at the clinic.

Subsequently, the patients were treated with cetirizine 10 mg twice daily and famotidine 40 mg

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nightly. Patients were allowed to use any accessible brands of these medications, and no specific brand was mandated or required for participation in the study. After one month, their urticaria severity was reassessed using the same questionnaire. Severity scores were compared between the high-level biomarker group and the normal-level group. A reduction of a 10 points urticaria score was considered a therapeutic response.

Laboratory Experiments

CBC diff was performed using a Mindray BC-5000 (China) and a VisionC ESR Analyzer (China) for ESR, CRP, and D-dimer tests, which were conducted on a Roche Hitachi 917 analyzer Machine (Japan). To evaluate the anti-TPO Pishtazteb (IRAN) and DiaZist (IRAN) ELISA kits for determining IgE level, they were used, and their serum level was assessed by BioTek800 ELISA reader (China). ELISA kits (Pishtaz Teb Diagnostics) were used to measure T3, T4, TSH, anti-TPO, and IgE levels, following manufacturer instructions, while the AST and ALT biochemistry kit (Iric Tashkhis, Iran) was used with a BT1500 analyzer (Biotechnical, Italy). The normal range and elevated values of our experimental variables were based on the kits and reference values from Khatamalanbia Central Lab, Yazd, Iran (Table 1).

Table 1. Normal range and elevated values of the investigated variables based on their kits and Khatam Al-Anbia Central Lab, Yazd, Iran, reference values.

Variables	Normal range	Elevated group
WBC	4000-11000 Cells/µL	>11000 Cells/µL
HB	Male: 13.5-17.5 g/dL	Male: >17.5 g/dl
	Female: 12-16 g/dL	Female: >16 g/dl
MCV	80-96 fl	>96 fl
Plt	150000-450000 Cells/µL	>450000Cells/µL
Lymphocyte	30-40%	>40%
Neutrophil	40-75%	>75%
CRP	3 mg/mL>	> 3 mg/mL
ESR	For children: 0-10 mm/hour	>10 mm/hour
	For females under 50 years old: 0-20 mm/hour	>20 mm/hour
	For males under 50 years old: 0-30 mm/hour	>30 mm/hour
	For females over 50 years old: 0-30 mm/hour	>30 mm/hour
	For males over 50 years old: 0-20 mm/hour	>20 mm/hour
NLR	1-3	>3
Eosinophil	400 Cells/µL>	>400 Cells/µL
TSH	0.32-5.2 mIU/L	>5.2 mIU/L
T4	4.7-12.5 µg/dL	>12.5 µg/dl
T3	0.6-2.1 ng/mL	>2.1 ng/ml
Anti-TPO	12 IU/ml>	>12 IU/ml
ALT	Female: 0-31 U/L	>31 U/L
	Male: 0-41 U/L	>41 U/L
AST	Female: 0-31 U/L	>31 U/L
	Male: 0-35 U/L	>35 U/L
D-dimer	500 ng/mL FEU (Fibrinogen Equivalent Units)	>500 ng/mL FEU

WBC: White Blood Cells; HB: Hemoglobin; MCV: Mean Corpuscular Volume; PLT: Platelet; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; NLR: Neutrophil-to-lymphocyte ratio; TSH: Thyroid Stimulating Hormone; T4: Thyroxine (Tetraiodothyronine); T3: Triiodothyronine; Anti-TPO: Anti–Thyroid Peroxidase antibody; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; µL: microliter; g: gram; mg: milligram; dl: deciliter.

To describe our data, the mean and standard deviation were calculated. First, the normality of all data has been evaluated using the Kolmogorov-Smirnov tests. As the data did not follow a normal distribution, nonparametric tests (Mann-Whitney pair-wise tests) were used to compare mean of variables including hemoglobin; platelets; lymphocyte count and percentage of neutrophils between responder and nonresponder patients. Categorical variables (normal CRP, elevated CRP, normal ESR, elevated ESR, normal anti-TPO, elevated anti-TPO, normal PLT/LYM, elevated PLT/LYM, normal NLR, elevated NLR, normal EOS, elevated EOS, normal D-dimer, elevated D-dimer, normal IgE, elevated IgE, normal PLT, elevated PLT, duration <1 year, duration ≥1 year, no hypothyroidism, hypothyroidism, gender, and age) were analyzed using Fisher's exact test ;Fisher exact test was applied when the expected frequency in any cell was≤5, as appropriate. We used Spearman's rank correlation coefficient tests to examine the relationships of NLR, eosinophil count, age, and gender with treatment response. Additionally, logistic regression analysis was used to investigate the relationships of NLR, eosinophil count, age and gender with treatment response. In all analyses, we considered $p<0.05$ (95% CI) as statistically significant. GraphPad Prism software (version 8.2.1) and IBM SPSS Statistics (version 26.0) were used to draw graphs and compare data.

RESULTS

The study involved 61 chronic spontaneous urticaria patients; 77% were women and 23% were men. The participants' ages varied from 20 to 50, averaging 36.82 (SD, 10.7). Of the 61 individuals, 41 patients demonstrated a good response to treatment, while 20 patients showed no significant response. The mean duration since disease onset was 15.69 months. The average UAS7 scores before and after treatment were 27.72 and 12.67, respectively. The minimum and maximum of UAS7 scores before treatment were 16 and 40, while the range of UAS7 scores after treatment was 1 to 35. Of the 61 patients in our study, 14 had a history of hypothyroidism and were being treated with levothyroxine. Among the serum biomarkers evaluated, only the NLR and serum eosinophil levels showed a significant relationship with treatment response (Figures 1 and 2).

The cut-off points for CRP and eosinophils were 3 mg/mL and 400 cells/mL, respectively. Other biomarkers, including ESR, D-dimer, anti-TPO, PLT/LMP, and IgE, were not significantly associated with clinical response. Twenty-three patients had elevated anti-TPO concentration, and 14 had hypothyroidism. Thirty-six patients had high serum IgE levels (IgE>100 IU/mL) (Figure 3).

Patients were categorized into three age groups: 20–30, 31–40, and 41–50 years. The highest response rate was observed in the 41–50-year group, and the lowest in the 31–40year group. However, the association between age group and treatment response was not statistically significant ($p=0.056$). This lack of significance may be due to the limited sample size. Furthermore, the treatment response rate did not differ significantly between males and females ($p=0.352$). The details of serum biomarkers and other variables are presented in Table 2 and the Mean and Standard deviation of hematologic variables in responder and non-responder CSU patients presented in Table 3.

Our results demonstrated a no significant association between treatment response and mean hemoglobin, platelet, neutrophil, and lymphocyte counts. Table 2 illustrates the average hematologic variables for both responder and nonresponder groups. Spearman correlation analysis illustrated significant correlation between NLR and treatment response (Spearman correlation coefficient = −0.296, $p=0.020$) and between eosinophil count and treatment response (Spearman correlation coefficient = −0.366, $p=0.004$), Furthermore, logistic regression between NLR and treatment response (OR = 0.178, $p=0.047$) and between eosinophil count and treatment response (OR = 0.185, $p=0.013$) were significant (Supplementary Tables 1 and 2). In contrast, neither age nor gender were significantly correlated with treatment response (age: ρ=0.050, $p=0.702$; gender: ρ=-0.132, $p=0.310$). These variables were also not significant predictors in the logistic regression model (age: OR=0.989, $p=0.677$; gender: OR=1.973, $p=0.347$) (Supplementary Tables 3 and 4).

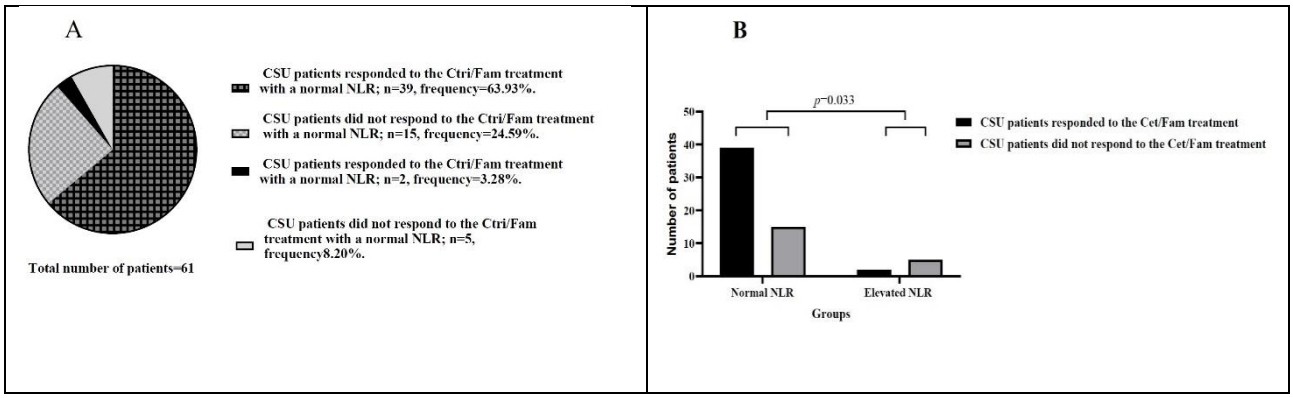

Figure 1. The results of NLR in the responder and nonresponder CSU patients to Cet/Fam treatment. (A) Frequency of responder and nonresponder CSU patients based on NLR under treatment with Cet/Fam. (B) The number of patients who responded or did not respond to treatment is shown for normal and elevated NLR groups. Statistical significance was assessed using Fisher's exact test, which was significant (p=0.033, confidence interval=95%) .NLR: Neutrophil-to-Lymphocyte Ratio; CSU: Chronic Spontaneous Urticaria; Cet/Fam: Cetirizine/Famotidine.

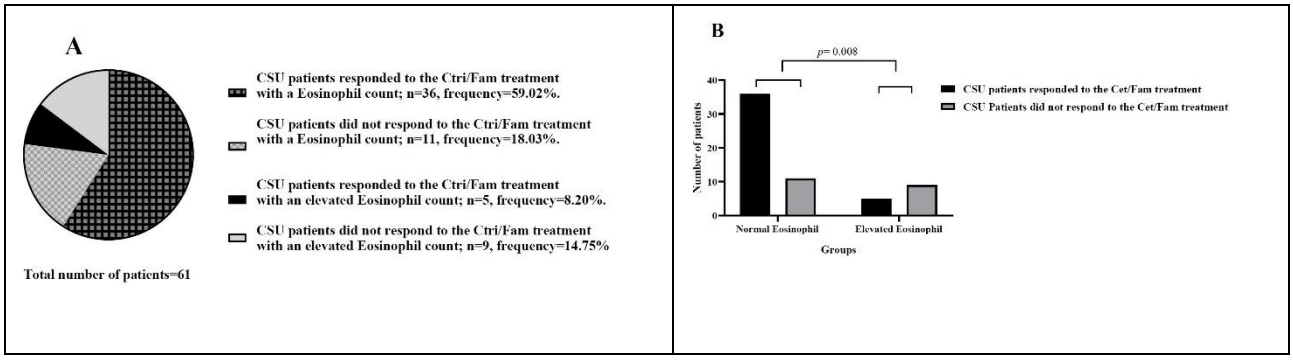

Figure 2. The results of eosinophil count in the responder and nonresponder CSU patients to Cet/Fam treatment. (A) The Frequency of responder and nonresponder CSU patients based on eosinophil counts under treatment with Cet/Fam treatment. (B) The number of patients who responded or did not respond to treatment is shown for the normal and elevated eosinophil counts groups. Statistical significance was assessed using Fisher's exact test, which was significant (p=0.008, confidence interval=95%). CSU: Chronic Spontaneous Urticaria; Cet/Fam: Cetirizine/Famotidine.

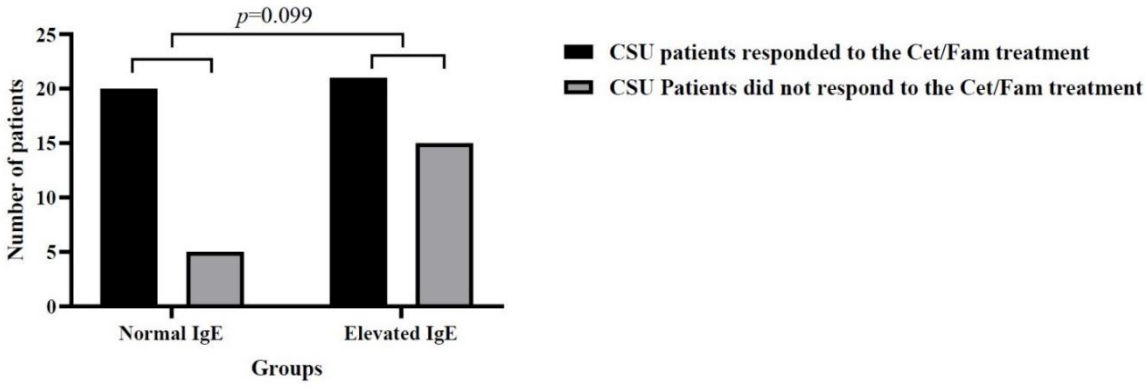

Figure 3. The results of IgE levels in responder and nonresponder CSU patients to Cet/Fam treatment. IgE levels did not show significant differences between the patients who responded to Cet/Fam treatment and those who did not (p= 0.099, 95% confidence interval, sample size of normal IgE group = 25, elevated IgE group = 36). Statistical significance was assessed using Fisher's exact test. CSU: Chronic Spontaneous Urticaria; Cet/Fam: Cetirizine/Famotidine.

Table 2. The frequency and comparison of measured variables between the CSU responder and non-responder patients and demographic data.

Variables	Response to the treatment	No response to treatment	Total number	Chi-square p^*	Fisher's exact test p^*
Normal CRP	12 (57.1%)	9 (42.9%)	21		
Elevated CRP	29 (72.5%)	11 (27.5%)	40	0.225	
Normal ESR	28 (73.7%)	10 (26.3%)	38		
Elevated ESR	13 (56.5%)	10 (43.5%)	23	0.168	
Normal Anti-TPO	26 (68.4%)	12 (31.6%)	38		
Elevated Anti-TPO	15 (65.2%)	8 (34.8%)	23	0.796	
Normal PLT/LYM	34 (64.2%)	19 (35.8%)	53		
Elevated PLT/LYM	7 (87.5%)	1 (12.5%)	8		0.253
Normal NLR	39 (72.2%)	15 (27.8%)	54		
Elevated NLR	2 (28.6%)	5 (71.4%)	7		0.033
Normal EOS	36 (76.6%)	11 (23.4%)	47		
Elevated EOS	5 (35.7%)	9 (64.3%)	14		0.008
Normal D-dimer	18 (69.2%)	8 (30.8%)	26		
Elevated D-dimer	23 (65.7%)	12 (34.3%)	35	0.772	
Normal IgE	20 (80%)	5 (20%)	25		
Elevated IgE	21 (58.3%)	15 (41.7%)	36		0.099
Normal PLT	41(69.5%)	18 (30.5%)	59		
Elevated PLT	0 (0.00%)	2 (100%)	2		0.103
Duration< one year	21 (65.6%)	11 (34.4%)	32		
Duration>=0ne year	20 (69%)	9 (31%)	29	0.781	
No Hypothyroidism	29 (61.7%)	18 (38.3%)	47		
Hypothyroidism	12 (85.7%)	2 (14.3%)	14		0.115
Female	30 (63.8%)	17 (36.2%)	47		
Male	11 (78.6%)	3 (21.4%)	14		0.352
Age (20-30)	13 (81.3%)	3 (18.8%)	16		
Age (31-40)	9 (47.4%)	10 (52.6%)	19	0.056	
Age (41-50)	19 (76%)	6 (24%)	25		

*Fisher's exact test was employed for cells with expected counts of 5 or fewer, while the Chi-square test was applied to the remaining cells, and $p<0.05$ was considered statistically significant (CI=95%).

CRP: C-reactive protein, ESR: Erythrocyte Sedimentation Rate, Anti-TPO: Anti-thyroid peroxidase, PLT: Platelet, LYM: Lymphocyte, NLR: Neutrophil-to-lymphocyte ratio, EOS: Eosinophil

Table 3. The Mean and Standard deviation of hematologic variables in responder and non-responder CSU patients.

Variables	Response to the treatment	Mean ± Standard deviation	p^*
Hemoglobin	Responder[#]	13.25 ± 1.88	0.546
	Non-responder[#]	12.94 ± 1.78	
Platelet	Responder	253146 ± 67468	0.475
	Non-responder	267150 ± 79301	
Neutrophils (%)	Responder	55.43% ± 11.53	0.912
	Non-responder	55.02% ± 17.18	
Lymphocyte (count)	Responder	2353 ± 817	0.105
	Non-responder	2692 ± 605	

[*]Statistical comparisons between the two groups were performed using the Mann-Whitney U test, with a $p<0.05$ was considered statistically significant (CI=95%). [#]The Responder group comprised 41 patients, and the non-responder group comprised 20.

DISCUSSION

Patients with CSU have variable clinical responses to treatment due to heterogeneity of clinical phenotypes and endotypes.[5] Recently research has focused on finding biomarkers to predict treatment outcomes. Some studies have shown that low serum levels of IgE are associated with a poor response to omalizumab in patients with CSU.[13] Another study reported that low IgE levels predict a positive response to cyclosporine treatment.[14] Furthermore, a systematic review found that high disease activity, increased CRP and D-dimer levels, and a previous history of corticosteroid use were associated with poor and nonresponsive to second generation antihistamines.[15] In our study, we aimed to identify hematologic and immunologic-inflammatory biomarkers that predict response to a combination of H1 and H2 second-generation antihistamines in patients with moderate-to-severe chronic spontaneous urticaria. Among the evaluated variables, elevated eosinophil counts and NLR was associated with a positive clinical response. In our study, the eosinophil count cut-off for analysis was set at > 400 cells/μL (the definition of eosinophilia varies: EOS>400, EOS>440, and EOS>500 cells/μL). An NLR≥3, derived from previous studies, was used as an inflammatory marker. The normal range is between 1–2 and values higher than 3 are pathological.[16,17] Although many inflammatory and allergic diseases are associated with blood eosinophilia but eosinopenia is observed in many patients with CSU. The possible mechanism is emigration of peripheral eosinophils into the skin during active disease and their immunologic destruction in the peripheral blood. According to this theory, eosinopenia is a good predictor of high disease activity and poor response to antihistamines.[18,19] However, as demonstrated in our study, peripheral eosinophilia was identified as a risk factor for poor clinical response, which is not consistent with this theory. Our findings align with previous investigations that have evaluated eosinophilia as a prognostic factor in patients treated with omalizumab. The overall results on the potential role of a T_H2/T_H17 imbalance as a predictor in CSU patients are illustrated in Figure 4.

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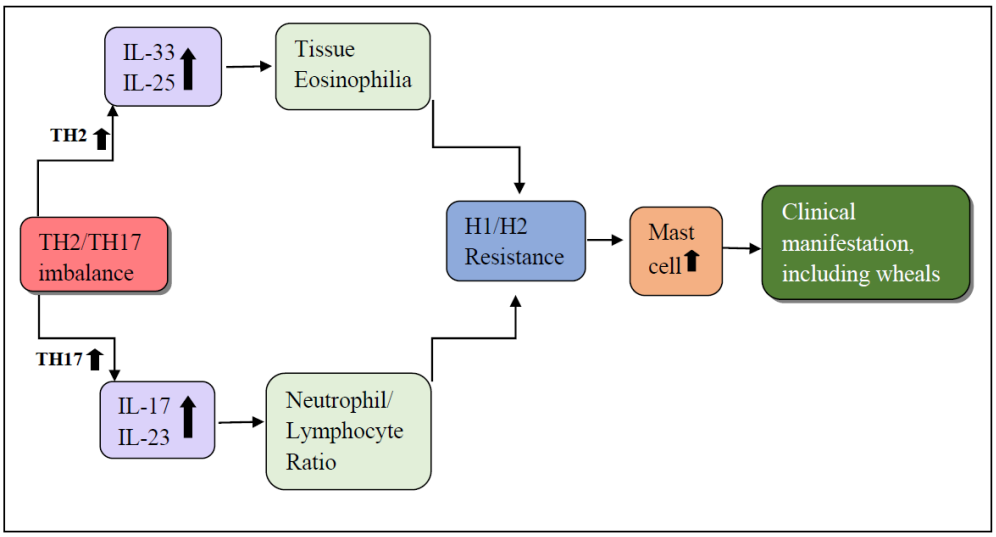

Figure 4. schematic representation of TH2/TH17 imbalance as a predictor of anti-histamine non-response in chronic spontaneous urticaria (CSU). Elevated levels of TH2 and TH17 cause clinical manifestations such as wheals.

The platelet counts also showed a significant correlation with clinical response, though this finding is unreliable due to the small number of patients with thrombocytosis. D-dimer, serum IgE level, anti-TPO antibody, platelet/lymphocyte ratio (PLR), ESR, and CRP showed no significant correlation with clinical responsiveness in our study. In previous studies, to assess the relationship between CRP, ESR, and IL-6 with disease activity, IL-6 was a better indicator for once-daily UAS. At the same time, ESR was a good indicator for UAS7, and CRP did not correlate with disease severity.[12] In a study, CSU patients (n = 5 021) demonstrated higher neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, as well as elevated serum IgE levels, compared to acute urticaria patients (n = 8 520). Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were higher in adults and patients with severe disease. They concluded that these simple biomarkers may predict higher urticaria scores and severe chronic urticaria.[20] These results appear to be consistent with our study. We found that patients with elevated NLR and PLR responded poorly to antihistamine therapy. This suggests that patients with high ratios have severe chronic urticaria unresponsive to treatment. Karman et al[21] found that elevated neutrophil counts and a high NLR was associated with disease duration and poor outcome. Haruka Watanabe et al[22] conducted a study that enrolled 58 patients treated with omalizumab for 3 months. Good prognostic biomarkers included shorter disease duration, a higher absolute eosinophil count after omalizumab initiation, and serum IgE levels of <100 IU/mL before treatment. However, in our study, an elevated eosinophil count was a negative prognostic factor for treatment response. This discrepancy may be due to differences in therapeutic approaches.

Hao Trong Nguyen et al[23] concluded in a case-control study that D-dimer levels were higher in patients with CSU than in controls and correlated significantly with disease severity. In another case-control study, there were significantly elevated levels of D-dimer, CRP, the D-dimer/albumin ratio, and the fibrinogen/albumin ratio in the CSU group. However, there was no significant correlation between these variables and UAS7. They concluded that D-dimer and CRP can be useful variables in the assessment of chronic urticaria.[24] Roberta Fachini Criado et al[25] showed that patients with severe disease and those who are difficult to treat had higher levels of D-dimer and CRP, and there is a weak correlation between CRP level and disease activity. In our study of moderate to severe CSU, we observed similarly elevated levels of CRP and D-dimer in the majority of participants. However, there was no significant correlation with treatment response. The authors of the current study suggest a similar study with a larger population sample.

In the study by Pavel Kolkhir, patients with high anti-TPO and low IgE levels had a lower clinical response to antihistamine treatment. Total IgE has been identified as a biomarker predicting a specific endotype

with a favorable response to omalizumab.[26,27] While, elevated levels of anti-TPO had a significant correlation with poor omalizumab response.[28] In contrast to these findings, our study did not find a significant correlation between high IgE or anti-TPO levels and antihistamine therapy. According to these studies, therapeutic options, clinical responses, and evaluated biomarkers are highly variable. Therefore, the results of these studies may suggest different conclusions. Based on Spearman correlation tests and logistic regressions, as an elevated NLR and eosinophilia are associated with a poorer response to cetirizine/famotidine treatment.

In this study, we found that high eosinophil counts and a NLR may serve as predictors of poor clinical response to antihistamine therapy. Despite a significant relation between the PLR ratio and treatment response, this biomarker is not a valuable parameter for clinical outcomes due to the low number of patients involved. Given the heterogeneity in published findings, alongside the limitations of our study-including a limited sample size, lack -of extended follow-up, and potential confounding factors such as lifestyle, we recommend that additional clinical trials are necessary to identify reliable hematologic biomarkers for predicting clinical outcomes.

STATEMENT OF ETHICS

The study was approved by the ethics committee of Shahid Sadoughi University of Medical Sciences (IR.SSU.MEDICIN.REC.1403.218). Patient-identifiable information was kept confidential.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

AI ASSISTANCE DISCLOSURE

Not applicable.

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