SELCUK MEDICAL JOURNAL
SELÇUK TIP DERGİSİ

DOI:http:/dx.doi.org/10.30733/std.2026.01910
Selcuk Med J 2026;42(2): 135-143

OPEN

RESEARCH ARTICLE

Elevated Baseline Systemic Inflammation Indices Predict Poor Response and Higher Relapse Risk in Chronic Spontaneous Urticaria Patients on Omalizumab

Omalizumab Kullanan Kronik Spontan Ürtiker Hastalarında Yüksek Bazal Sistemik İnflamasyon İndeksleri Zayıf Yanıtı ve Yüksek Nüks Riskini Öngörmektedir

Mehmet Emin Gerek[1], Fatih Colkesen[1], Ferhat Sagun[1], Secim Kolak[1], Tugba Onalan[2], Fatma Arzu Akkus[3], Filiz Sadi Aykan[4], Selim Kahraman[5], Sevket Arslan[1]

[1]Necmettin Erbakan University, Faculty of Medicine, Department of Internal Medicine, Division of Immunology and Allergy, Konya, Türkiye
[2]Beyhekim Training and Research Hospital, Department of Immunology and Allergy, Konya, Türkiye
[3]Konya City Hospital, Department of Immunology and Allergy, Konya, Türkiye
[4]Gülhane Training and Research Hospital, Department of Internal Medicine, Division of Immunology and Allergy, Ankara, Türkiye
[5]Hatay Training and Research Hospital, Department of Immunology and Allergy, Hatay, Türkiye

ABSTRACT

Objective: This study aims to assess how baseline Systemic Immune-Inflammation Index (SIRI) and Aggregate Index of Systemic Inflammation (AISI) values relate to six-month clinical outcomes of Omalizumab treatment in patients with chronic spontaneous urticaria (CSU). Additionally, whether these systemic inflammatory markers could serve as predictors for relapse risk following discontinuation of therapy has been evaluated.

Materials and Methods: In this single-center study, a total of 312 CSU patients who were on Omalizumab treatment have been retrospectively analyzed. The overall response to the therapy is evaluated at the end of a 6-month follow-up period, while 217 patients who gave up Omalizumab treatment after the successful control period have also been evaluated afterwards for any relapse situations over a 12-month period. A favorable response is detected as achieving a Urticaria Control Test (UCT) score ≥12. The predictive accuracy of inflammatory indices and potential relapse-related variables have also been examined in the study.

Result: It is seen that the baseline SIRI (Median 1.47 vs. 1.06; p<0.001) and AISI (Median 452.98 vs. 306.06; p<0.001) values of the non-responder group (n=38) are statistically significantly higher than those of the responder group (n=274). Both AISI (AUC=0.744) and SIRI (AUC=0.727) have demonstrated a strong performance in predicting non-response. In the relapse analysis subgroup (n=217), patients who relapsed (n=122) have had significantly higher baseline SIRI (p=0.012) and AISI (p=0.024) values compared to those who remained in remission (n=95).

Conclusion: It is concluded that baseline SIRI and AISI values are valuable, practical, and cost-effective biomarkers for predicting an inadequate response to Omalizumab treatment and the risk of post-treatment relapse in patients with CSU. They have the potential to serve as helpful tools for clinicians to guide the treatment decisions and optimize the management of patients.

Keywords: Biomarkers, Omalizumab, Recurrence, Treatment Outcome, Urticaria

ÖZET

Amaç: Kronik Spontan Ürtiker (KSÜ) hastalarında Omalizumab'a altı aylık klinik yanıtı ve tedavi kesimi sonrası uzun vadeli nüks riskini öngörmede bazal Sistemik İmmün-İnflamasyon İndeksi (SIRI) ve Agregat Sistemik İnflamasyon İndeksi'nin (AISI) prediktif performansını değerlendirmektir.

Gereç ve Yöntemler: Bu tek merkezli, retrospektif çalışmaya 312 KSÜ hastası dahil edildi; tedavisi kesilen 217 hasta nüks açısından takip edildi. Birincil sonlanım 6. ayda iyi tedavi yanıtı (Ürtiker Kontrol Testi [ÜKT] skoru ≥12), ikincil sonlanım tedavi kesimi sonrası nüks olarak tanımlandı. Performans ROC analizi ve lojistik regresyon ile değerlendirildi.

Bulgular: Yanıt vermeyen grubun (n=38) bazal SIRI (Medyan 1.47 vs. 1.06; p<0.001) ve AISI (Medyan 452.98 vs. 306.06; p<0.001) değerleri, yanıt veren gruba (n=274) göre anlamlı olarak daha yüksekti. Yanıt vermemeyi öngörmede hem AISI (AUC=0.744) hem de SIRI (AUC=0.727) güçlü performans gösterdi. Nüks alt grubunda (n=217), nüks gelişenlerin (n=122) bazal SIRI (p=0.012) ve AISI (p=0.024) değerleri remisyonda kalanlara (n=95) göre anlamlı düzeyde yüksekti.

Sonuç: Bazal SIRI ve AISI değerleri, KSÜ hastalarında Omalizumab'a yetersiz yanıtı ve nüks riskini öngörmede değerli, pratik ve uygun maliyetli biyobelirteçlerdir. Bu indeksler, tedavi kararlarına rehberlik etmede ve hasta yönetimini optimize etmede klinisyenlere yardımcı olabilir.

Anahtar Kelimeler: Ürtiker, Omalizumab, Biyobelirteçler, Tedavi Sonucu, Nüks

Received: 10 November 2025 **Accepted:** 17 January 2026 **Published Online:** 17 June 2026

Corresponding Author: Mehmet Emin Gerek, Necmettin Erbakan University, Faculty of Medicine, Department of Internal Medicine, Division of Immunology and Allergy, Konya, Türkiye
e-mail: drmegerek@gmail.com

Cite this article as: Gerek ME, Colkesen F, Sagun F, Kolak S, Onalan T, Akkus FA, Sadi Aykan F, Kahraman S, Arslan S. Elevated Baseline Systemic Inflammation Indices Predict Poor Response and Higher Relapse Risk in Chronic Spontaneous Urticaria Patients on Omalizumab. Selcuk Med J 2026;42(2): 135-143

Disclosure: *Author has not a financial interest in any of the products, devices, or drugs mentioned in this article. The research was not sponsored by an outside organization. Author has agreed to allow full access to the primary data and to allow the journal to review the data if requested.*

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a long-lasting inflammatory skin disorder driven by immune dysregulation. It affects nearly 1% of people worldwide, visibly diminishing the quality of life and imposing a notable financial strain on healthcare systems (1). Although the anti-IgE monoclonal antibody Omalizumab has introduced a major therapeutic advancement for individuals unresponsive to conventional therapy, its effectiveness is not absolute. From 30% to 40% of the patients demonstrate only partial benefit, and have relapse rates between 33% and 67%. Moreover, these patients are reported as following discontinuation of the treatment (2, 3). These observations highlight that CSU continues to pose substantial difficulties in everyday clinical practice.

The pathophysiology of CSU is largely mediated through IgE-dependent mast-cell activation, which serves as the central pathway targeted by Omalizumab (4). Numerous biomarker such as C-reactive protein (CRP), total IgE, and eosinophil counts have been evaluated as potential indicators of therapeutic outcomes; nonetheless, none have shown a stable predictive value for a routine use (3). Over recent years, systemic inflammation indices based on complete blood count parameters, including the neutrophil-to-lymphocyte ratio, have been reported to correlate with disease activity and therapeutic response across multiple chronic inflammatory conditions, such as rheumatologic disorders and malignancies (5, 6).

Despite these observations, at CSU, novel composite indices readily derivable from basic laboratory data have not been sufficiently explored. To the best of our knowledge, Systemic Immune-Inflammation Index (SIRI) and Aggregate Index of Systemic Inflammation (AISI) have not been systematically evaluated yet among CSU patients regarding both treatment response and the risk of relapse concurrently. Among these, SIRI and the AISI provide an integrated reflection of systemic inflammatory status. It is seen that there is a considerable gap in literature regarding baseline markers that reliably predict long-term remission or relapse risks after the discontinuation of Omalizumab (7-10).

Accordingly, this study primarily aims to assess the predictive value of baseline SIRI and AISI levels for six-month treatment response to Omalizumab in CSU patients. The secondary objective is to explore whether these baseline inflammatory indices can estimate the likelihood of relapse following the end of therapy. It is assumed that higher baseline SIRI and AISI values are linked to suboptimal treatment outcomes and a greater relapse probability.

MATERIAL AND METHOD

Study Design

It is a retrospective and single-center study based on observational analysis. Data collection and evaluation period was from January 2021 to August 2025.

Ethical Approval

Ethical clearance for this research was granted by the Institutional Research Ethics Committee (Decision No: 2025/5983). Considering the retrospective character of the study and the use of anonymized records, the requirement for individual informed consent was waived by the committee. All study procedures adhered to the ethical standards outlined in the Declaration of Helsinki.

Study Population and Sample

• ***Participants:*** The study consists of patients aged 18 years and older who were initiated on Omalizumab therapy for a diagnosis of CSU. These patients attended the Allergy and Immunology outpatient clinic of a tertiary hospital between January 2021 and August 2025. A total of 474 patient records have been reviewed for the study.

• ***Inclusion Criteria:***

1. Age:18 and ≥ 18 years.
2. A confirmed diagnosis of CSU, by a specialist physician.
3. The initiation of Omalizumab treatment with at least a six-month follow-up period.

• ***Exclusion Criteria:***

1. The use of systemic corticosteroids within the four weeks prior to laboratory data collection (to exclude the potential confounding effect of steroids on neutrophil and lymphocyte counts).
2. The presence of an active infection or a known history of malignancy.
3. A concomitant systemic inflammatory or autoimmune disease (e.g., Lupus, Rheumatoid Arthritis).
4. Missing baseline complete blood count or 6-month Urticaria Control Test (UCT) data required for analysis.
5. The loss to follow-up.

• ***Sample Size:*** Following an initial screening of 474 patient records, 162 patients were excluded from the study regarding the exclusion criteria. The reasons for exclusion included concomitant autoimmune disease (n=32), a history of malignancy (n=3), missing data required for analysis (n=66), systemic steroid use within the preceding four weeks (n=29), and loss to follow-up (n=32). Consequently, a total of 312 patients who met all inclusion criteria have been included in the primary analysis for treatment response. A secondary analysis for relapse has been conducted on a subgroup of these patients whose Omalizumab therapy was successfully discontinued. For the relapse analysis, non-responders (n=38) and responders who were lost to follow-up or continued treatment without cessation (n=57) were excluded to isolate a cohort suitable for observing drug-free remission failures. As a result, a final cohort of 217 patients for the long-term relapse analysis have been determined. The two-stage patient selection process is shown in Figure 1.

The Procedure and Data Collection

As it is an observational study, no interventional procedures have been applied to the participants. The demographic, clinical, and laboratory variables have been retrospectively retrieved from the hospital's information system (HIS) and electronic medical records. The degree of the control of the disease is determined through the UCT, a valid and widely used assessment tool. All laboratory analyses have been performed in the central hospital laboratory by following standard

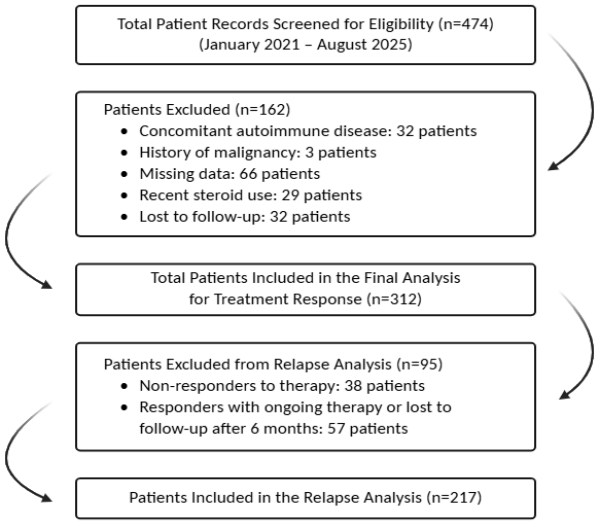

Figure 1. The flowchart of patient selection for primary and secondary analyses

procedures as a part of the routine clinical practice. All patients received subcutaneous Omalizumab at a standard dose of 300 mg every 4 weeks.

Variables and Outcomes

The basic demographic data (age and gender), the clinical characteristics (the duration of symptoms, the presence of angioedema and the initial UCT score), and laboratory parameters (complete blood count, CRP, ESR, IgE, TSH, anti-TPO, AST, ALT, Creatinine) have been collected as independent variables. SIRI is calculated by using the formula [(Neutrophil × Monocyte) / Lymphocyte], and AISI is calculated by using the formula [(Neutrophil × Monocyte × Platelet) / Lymphocyte].

• ***Primary Outcome:*** The primary outcome of the study can be stated as a good response to Omalizumab therapy at the 6-month follow-up period. A good response is defined as a UCT score ≥12. (11)

• ***Secondary Outcome:*** The secondary outcome of the study can be stated as the development of relapse in patients whose treatment was successfully discontinued. Relapses are defined as the recurrence of symptoms requiring renewed medical treatment in patients who were followed for at least one year after the end of Omalizumab therapy.

Statistical Analysis

All statistical analyses have been conducted by using SPSS Statistics software, version 25.0 (IBM Corp., Armonk, NY, USA). The statistical significance is defined as a two-tailed p value of less than 0.05. The distribution normality of continuous variables is examined by means of the Kolmogorov-Smirnov test. Variables following a normal distribution are summarized as mean ± standard deviation (SD), whereas those not normally distributed are presented as median values with interquartile ranges (25th–75th percentile). Categorical variables are shown as absolute numbers (n) and corresponding percentages (%).

The comparisons between the "responder" group and the "non-responder" group as well as the "relapser" subgroup and the "non-relapser" the subgroup are also performed. For non-normally distributed continuous data, the Mann–Whitney U test is applied. Categorical comparisons are analyzed by using either the Chi-square test or Fisher's Exact test. A complete case analysis method is adopted for the study.

The diagnostic capacity of baseline biomarkers that showed statistical significance in univariate analyses for predicting treatment response and relapse is assessed through Receiver Operating Characteristic (ROC) curve analysis. The area under the curve (AUC), its 95% confidence interval (CI), and the p value are determined for each biomarker. The optimal cutoff

Table 1. The demographic and baseline clinical characteristics of the study population (n=312)

Clinical Characteristics	Value	Laboratory Parameters	Value
Age (years)	41.0 (30.25 – 50.00)	Neutrophil (x10^3/μL)	4.60 (3.72 – 5.78)
Gender, n (%)		Lymphocyte (x10^3/μL)	2.43 (1.97 – 2.80)
Female	200 (64.1)	Monocyte (x10^3/μL)	0.56 (0.46 – 0.69)
Male	112 (35.9)	Platelet (x10^3/μL)†	295.38 ± 63.35
Symptom Duration (months)	24.0 (10.00 – 60.00)	ESR (mm/hour)	8.0 (5.00 – 11.00)
Presence of Angioedema, n (%)		CRP (mg/L)	3.0 (1.49 – 5.00)
Yes	116 (37.2)	Total IgE (IU/mL)	107.5 (30.00 – 214.00)
No 196 (62.8)		Creatinine (mg/dL)	0.76 (0.66 – 0.91)
Baseline UCT Score	4.0 (2.00 – 5.00)	AST (U/L)	15.5 (11.83 – 18.50)
6-Month UCT Score	15.0 (13.00 – 16.00)	ALT (U/L)	15.25 (11.25 – 20.35)
		TSH (μIU/mL)	1.81 (1.20 – 2.50)
		Anti-TPO (IU/mL)	11.15 (9.00 – 17.80)
		SIRI	1.10 (0.82 – 1.49)
		AISI	327.43 (221.16 – 447.90)

Numerical values are presented as Median (25th–75th percentile). Data marked with † are presented as Mean ± Standard Deviation. Categorical variables are presented as number (n) and percentage (%).

Abbreviations: UCT, Urticaria Control Test; ESR: Erythrocyte sedimentation rate CRP, C-reactive protein; IgE, Immunoglobulin E; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TSH, Thyroid-stimulating hormone; Anti-TPO, Anti-thyroid peroxidase antibody; SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation.

threshold is obtained by using Youden's Index (J = sensitivity + specificity – 1).

Finally, a multivariable binary logistic regression model is constructed in order to determine the independent predictors associated with treatment response and relapse. Variables identified as significant in univariate analyses are included in the model. The outcomes are reported as odds ratios (ORs) together with their 95% confidence intervals (CIs). SIRI and AISI are included in separate multivariable logistic regression models to avoid multicollinearity, given their mathematical derivation from shared blood parameters.

RESULT

Baseline Characteristics of the Groups

The basic demographic and clinical characteristics of the study population are summarized and shown in Table 1. The median age of the 312 included patients is 41.0 (30.25–50.00) years, and 64.1% (n=200) are female. The median duration of symptoms before Omalizumab treatment is 24.0 (10.00–60.00) months, and 37.2% of the patients (n=116) have had a history of angioedema.

Primary Outcome: Response to Omalizumab Therapy

For the study, the baseline characteristics of patients who responded (responders, n=274) and did not respond (non-responders, n=38) to Omalizumab therapy have been compared. It is seen that the median baseline SIRI value of the non-responder group is statistically significantly higher than that of the responder group (1.47 vs. 1.06; p<0.001). Similarly, AISI is also found to be significantly higher in the non-responder group (452.98 vs. 306.06; p<0.001). A detailed comparison of the groups is presented in Table 2.

The performance of baseline SIRI and AISI values in predicting non-response to therapy is evaluated with ROC curve analysis. The performance of AISI (AUC=0.744; 95% CI: 0.665–0.824; p<0.001) is slightly superior to that of SIRI (AUC=0.727; 95% CI: 0.648–0.806; p<0.001) in predicting non-response. The optimal cutoff values and diagnostic performance metrics for these biomarkers are summarized in

Table 2. The comparison of basic demographic, clinical, and laboratory characteristics of the patients according to the treatment response status

Clinical / Laboratory Characteristic	Non-responder Group (n=38)	Responder Group (n=274)	p-value
Age (years)	40.0 (28.75 – 51.00)	42.0 (30.75 – 50.00)	0.427
Gender, female, n (%)	26 (68.4)	174 (63.5)	0.554
Symptom duration (months)	17.0 (8.00 – 51.00)	24.0 (10.00 – 60.00)	0.896
Presence of angioedema, n (%)	18 (47.4)	100 (36.5)	0.195
Baseline UCT Score	4.0 (1.75 – 4.00)	4.0 (2.00 – 5.00)	0.083
Neutrophil ($x10^9$/L)	6.00 (4.79 – 6.87)	4.42 (3.66 – 5.58)	<0.001
Lymphocyte ($x10^9$/L)	2.25 (1.80 – 2.87)	2.44 (2.00 – 2.80)	0.377
Monocyte ($x10^9$/L)	0.60 (0.47 – 0.77)	0.56 (0.46 – 0.68)	0.260
Platelet ($x10^9$/L)	303.0 (277.5 – 328.0)	288.5 (250.0 – 335.0)	0.071
ESR (mm/hour)	8.0 (5.0 – 12.75)	8.0 (5.0 – 11.0)	0.258
CRP (mg/L)	4.05 (2.74 – 6.00)	3.00 (1.36 – 5.00)	0.309
Total IgE (IU/mL)	61.5 (18.75 – 169.75)	109.0 (45.0 – 214.0)	0.096
Creatinine (mg/dL)	0.80 (0.66 – 0.87)	0.76 (0.66 – 0.91)	0.980
AST (U/L)	15.15 (12.0 – 17.60)	15.50 (11.80 – 18.63)	0.332
ALT (U/L)	15.10 (10.30 – 19.40)	15.30 (11.50 – 20.50)	0.504
TSH (μIU/mL)	1.84 (1.20 – 2.59)	1.76 (1.20 – 2.49)	0.849
Anti-TPO (IU/mL)	13.0 (9.0 – 36.0)	12.1 (9.0 – 18.8)	0.076
SIRI	1.47 (1.22 – 2.07)	1.06 (0.81 – 1.44)	<0.001
AISI	452.98 (388.57 – 646.50)	306.06 (213.68 – 427.74)	<0.001

Data are presented as Median (25th–75th percentile) for continuous variables and as number (n) and percentage (%) for categorical variables. P-values are calculated by using the Mann-Whitney U test for continuous variables and the Chi-Square test for categorical variables. Statistically significant p-values (p < 0.05) are highlighted in bold.

Abbreviations: UCT, Urticaria Control Test; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; IgE, Immunoglobulin E; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TSH, Thyroid-stimulating hormone; Anti-TPO, Anti-thyroid peroxidase antibody; SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation.

Table 3. The performance of baseline SIRI and AISI in predicting non-response to omalizumab therapy

Biomarker	AUC (Area Under the Curve)	95% Confidence Interval	p-value	Optimal Cutoff Value	Sensitivity (%)	Specificity (%)
SIRI	0.727	0.648 – 0.806	<0.001	>1.285	65.8	68.2
AISI	0.744	0.665 – 0.824	<0.001	>349.87	68.4	60.9

Abbreviations: SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation; AUC, Area Under the Curve; CI, Confidence Interval. Optimal cutoff values were determined using Youden's Index.

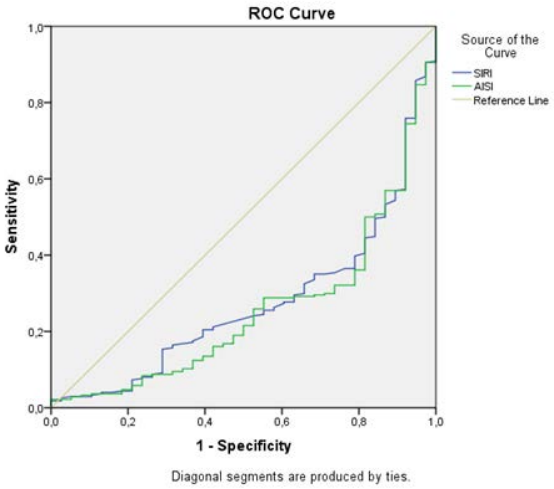

Figure 2. The receiver operating characteristic (ROC) curve for predicting non-response to omalizumab therapy
The ROC curve illustrates the diagnostic performance of the baseline Systemic Immune-Inflammation Index (SIRI) and the Aggregate Index of Systemic Inflammation (AISI) in distinguishing between patients who responded and those who did not respond to Omalizumab treatment.

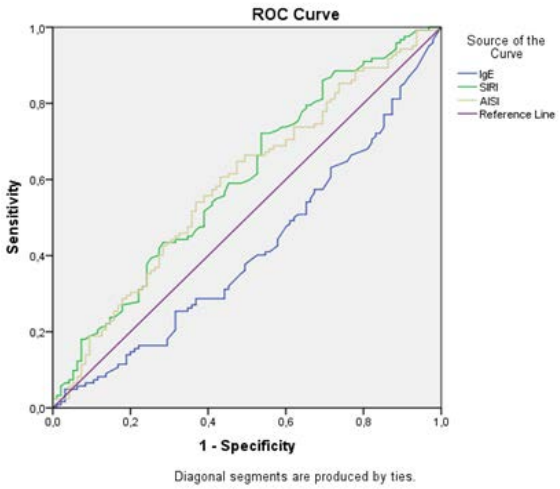

Figure 3. The receiver operating characteristic (ROC) curve for predicting relapse after treatment discontinuation
The ROC curve illustrates the diagnostic performance of baseline Total Immunoglobulin E (IgE), the Systemic Immune-Inflammation Index (SIRI), and the Aggregate Index of Systemic Inflammation (AISI) in predicting disease relapses after Omalizumab cessation.

Table 4. The binary logistic regression analysis of independent factors predicting response to omalizumab therapy

Model	Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Model 1	SIRI	0.466	0.305 – 0.713	<0.001
	Age	1.008	0.982 – 1.036	0.542
	Baseline UCT	1.143	0.975 – 1.338	0.099
Model 2	AISI	0.997	0.996 – 0.999	<0.001
	Age	1.009	0.982 – 1.037	0.520
	Baseline UCT	1.147	0.978 – 1.345	0.091

The analysis identifies independent predictors for a good response to Omalizumab therapy, defined as a 6-month Urticaria Control Test (UCT) score ≥ 12. Two separate multivariable models are constructed to avoid multicollinearity between SIRI and AISI. Statistically significant p-values ($p < 0.05$) are highlighted in bold.
Abbreviations: SIRI, Systemic Immune-Inflammation Index; UCT, Urticaria Control Test; AISI, Aggregate Index of Systemic Inflammation; OR, Odds Ratio; CI, Confidence Interval.

Table 3, and the corresponding ROC curves are shown in Figure 2.

In the multivariable binary logistic regression analysis performed to identify independent risk factors for non-response, an increased SIRI value is found to be an independent factor that reduced the likelihood of a good treatment response (Odds Ratio [OR]: 0.466; 95% CI: 0.305–0.713; p<0.001). AISI, which has been examined in a separate model, is similarly identified as an independent risk factor (OR: 0.997; 95% CI: 0.996–0.999; p<0.001). The results of the analysis are presented in Table 4.

Secondary Outcome: Relapse after Treatment Discontinuation

During the long-term follow-up of 217 patients whose Omalizumab therapy was successfully discontinued, relapse is observed in 56.2% of the patients (n=122), while 43.8% (n=95) remained in remission. When the baseline characteristics of the relapsing and non-relapsing groups are compared, it is determined that the baseline SIRI (Median 1.29 vs. 1.17; p=0.012) and AISI (Median 357.38 vs. 302.65; p=0.024) values are significantly higher in the group that relapsed. Conversely, the median baseline Total IgE is significantly lower in the relapsing group compared to the non-relapsing group (Median 94.05 vs. 119.0; p=0.026). The comparison results are presented in Table 5.

The performance of these three biomarkers in predicting relapses has been evaluated with ROC curve analysis. SIRI

Table 5. The comparison of baseline demographic and clinical characteristics of patients according to relapse status

Variable	Non-relapser Group (n=95)	Relapser Group (n=122)	p-value
Age (years)	42.0 (31.0 – 49.0)	42.0 (33.0 – 52.0)	0.477
Gender, female, n (%)	54 (56.8)	79 (64.8)	0.086
Symptom Duration (months)	15.0 (8.00 – 48.00)	24.0 (12.00 – 60.00)	0.080
Presence of Angioedema, n (%)	28 (29.5)	50 (41.0)	0.080
Baseline UCT Score	4.0 (3.00 – 4.00)	4.0 (3.00 – 5.00)	0.340
Neutrophil ($x10^9$/L)	4.25 (3.60 – 5.00)	4.64 (4.00 – 5.70)	0.446
Lymphocyte ($x10^9$/L)	2.43 (2.00 – 2.82)	2.43 (1.97 – 2.80)	0.137
Monocyte ($x10^9$/L)	0.56 (0.48 – 0.68)	0.56 (0.46 – 0.68)	0.080
Platelet ($x10^9$/L)	288.5 (250.0 – 331.0)	293.0 (253.0 – 334.5)	0.854
ESR (mm/hour)	8.0 (5.00 – 12.00)	9.0 (5.00 – 15.00)	0.657
CRP (mg/L)	3.00 (1.26 – 4.26)	3.07 (1.80 – 5.00)	0.390
Total IgE (IU/mL)	119.0 (56.00 – 241.50)	94.05 (41.98 – 192.00)	0.026
Creatinine (mg/dL)	0.78 (0.70 – 0.91)	0.77 (0.65 – 0.89)	0.240
AST (U/L)	14.90 (12.25 – 18.10)	15.50 (13.18 – 18.43)	0.120
ALT (U/L)	14.80 (11.45 – 19.85)	15.75 (11.98 – 20.43)	0.477
TSH (µIU/mL)	1.55 (1.02 – 2.50)	1.88 (1.21 – 2.59)	0.125
Anti-TPO (IU/mL)	13.00 (9.00 – 22.72)	11.00 (9.00 – 18.76)	0.569
SIRI	1.17 (0.87 – 1.47)	1.29 (1.02 – 1.66)	0.012
AISI	302.65 (220.19 – 405.05)	357.38 (264.12 – 451.33)	0.024

Numerical values are presented as Median (25th–75th percentile), while categorical variables are presented as n (%). P-values were calculated using the Mann-Whitney U test for continuous variables and the Chi-Square test for categorical variables. Statistically significant p-values ($p < 0.05$) are highlighted in bold.
Abbreviations: UCT, Urticaria Control Test; ESR, Erythrocyte Sedimentation Rate; CRP, C-reactive protein; IgE, Immunoglobulin E; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; TSH, Thyroid-stimulating hormone; Anti-TPO, Anti-thyroid peroxidase antibody; SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation.

Table 6. The univariate and multivariate analyses of baseline biomarkers for predicting relapse after treatment discontinuation

Variable	Univariate ROC Analysis		Multivariate Logistic Regression Analysis	
	AUC (95% CI)	p-value	Odds Ratio (OR) (95% CI)	p-value
Total IgE	0.587 (0.511 – 0.663)	0.029	0.999 (0.998 – 1.000)	0.056
SIRI	0.599 (0.523 – 0.675)	0.012	1.863 (0.860 – 4.034)	0.115
AISI	0.589 (0.513 – 0.665)	0.024	1.001 (0.999 – 1.003)	0.434

The multivariable logistic regression analysis identifies independent predictors for relapse after Omalizumab discontinuation; this model included all three variables (Total IgE, SIRI, and AISI) together. Optimal cutoff values from the univariate ROC analysis are: Total IgE ≤ 94.05 (Sensitivity 50.0%, Specificity 62.1%); SIRI > 1.165 (Sensitivity 59.8%, Specificity 50.5%); and AISI > 357.38 (Sensitivity 50.0%, Specificity 64.2%).
Abbreviations: IgE, Immunoglobulin E; SIRI, Systemic Immune-Inflammation Index; AISI, Aggregate Index of Systemic Inflammation; OR, Odds Ratio; CI, Confidence Interval; AUC, Area Under the Curve.

(AUC=0.599; p=0.012), AISI (AUC=0.589; p=0.024), and Total IgE (AUC=0.587; p=0.029) all demonstrated a statistically significant but weak performance in predicting relapses. These results are summarized in Table 6, and the corresponding ROC curves are shown in Figure 3.

In the multivariable logistic regression model, which included these three factors, has found to be significant in the univariate analysis and none of the variables are identified as statistically significant, independent predictors of relapse (p>0.05 for all). The results are presented in Table 6.

DISCUSSION

The primary finding of this study is that baseline systemic inflammation indices, specifically SIRI and the AISI, are found to be valuable biomarkers in patients with CSU. These indices, derived from the complete blood count, can predict both the initial response to Omalizumab therapy and the long-term risk of relapse after treatment discontinuation. Our study confirmed the hypothesis that higher baseline systemic inflammatory activity is associated with both a poorer initial response to Omalizumab and a higher risk of post-treatment relapse.

In this study, patients exhibiting an inadequate clinical response to Omalizumab have demonstrated significantly elevated baseline SIRI and AISI levels. This reinforces the notion that CSU represents not only a localized cutaneous condition but also encompasses a systemic inflammatory component. This aligns with previous investigations reporting increased systemic inflammatory mediators, including C-reactive protein and interleukin-6, among individuals with CSU (12-14). To date, the neutrophil-to-lymphocyte ratio (NLR) has been the most extensively studied neutrophil-derived index linked to CSU activity (15-17). The present study contributes to the existing literature by emphasizing that broader and composite

indices such as SIRI and AISI, which incorporate monocyte and platelet parameters, are also relevant in CSU. Indeed, these results are in parallel with findings from rheumatologic and oncologic research, where elevated SIRI and AISI values have been associated with unfavorable prognosis and diminished therapeutic responsiveness (18). Our findings are partly consistent with large-scale real-world studies. For instance, Marzano et al. identified high baseline UAS7 and IgE levels as predictors of relapse, whereas this study highlights the role of systemic inflammation indices (10). Similarly, Kucharczyk et al. emphasized the complexity of predicting relapse, which supports our finding that traditional markers alone might be insufficient without composite indices like SIRI (7).

Notably, more conventional inflammation markers such as CRP and eosinophil count are not found to be as significant predictors of Omalizumab response in this study. This is consistent with the conflicting results in the literature; while some studies report a weak association with these markers, many, like ours, have not detected a significant relationship (19). A possible reason for this discrepancy might be that composite indices like SIRI and AISI better reflect the complex interaction and balance between different arms of the immune system, such as innate and adaptive immunity, than a single biomarker does. The logistic regression analysis, which demonstrated SIRI and AISI as independent predictors, statistically substantiates the importance of this immune balance concept. Although the Odds Ratio for AISI is found to be 0.997, suggesting a minimal effect per unit, it can be interpreted in the context of the index's wide numerical range (often 0–1000+). Therefore, larger fluctuations in AISI values are required to reflect clinically significant changes in inflammatory status.

The analysis of relapses after treatment discontinuation provided some of the most novel insights of the study. The association between high baseline SIRI and AISI and an increased risk of relapse suggests that persistent subclinical systemic inflammation might be a factor that prevents sustained remission even after treatment is stopped. It is conceptually consistent with the reports from other autoimmune diseases, such as rheumatoid arthritis, where the risk of relapse after discontinuing biological therapy is associated with high baseline inflammatory activity. For instance, in patients with inflammatory bowel disease (IBD), the risk of relapsing after stopping biological therapy increases significantly with clinical indicators of active inflammation, such as steroid dependency or perianal disease (20). Similarly, in patients with autoimmune hepatitis, high levels of active CD4□T-peripheral helper cells, CD8□T cells, and BAFF levels before treatment cessation have been identified as strong biomarkers for relapse (21). These data reveal that in various autoimmune diseases, the risk of relapsing after discontinuing biological therapy is closely related to the levels of inflammatory activity before or during the treatment.

A particularly noteworthy finding from the data is that lower baseline Total IgE levels have predicted an increased risk of relapse. Although this might seem contradictory to the pathophysiology of CSU at first glance, it is consistent with current literature suggesting the disease's heterogeneous nature and its different immunological subtypes. It is reported that CSU comprises at least two distinct endotypes, type I (IgE-mediated autoallergic) and type IIb (IgG-mediated autoimmune), and that these subtypes exhibit significant differences in disease severity, treatment response, and biomarker levels (22, 23). It is suggested that patients with low IgE levels might belong to the type IIb autoimmune CSU subtype, which is characterized by mast cell activation primarily driven by functional IgG autoantibodies (24). In this patient group, the therapeutic effect of Omalizumab is thought to occur through non-IgE-mediated mechanisms, such as down-regulating the expression of high-affinity IgE receptors (FcεRI) on mast cells and basophils, rather than by neutralizing free IgE (25). Therefore, these underlying autoimmune processes might make disease recurrence more likely upon treatment cessation. Clinically, this suggests that while low Total IgE alone is a risk factor, its evaluation in conjunction with elevated SIRI/AISI could better identify patients with 'autoimmune-enriched' endotypes who are prone to rapid relapse. In such cases, the decision to discontinue treatment should be taken into consideration with a greater caution. These findings contribute to the identification of biomarkers that can predict relapses after Omalizumab and highlight the importance of a personalized approach in CSU treatment.

The findings of this study are believed to hold important practical implications for the clinical management of CSU patients. SIRI and AISI values, which can be easily calculated from a routine complete blood count before treatment, can offer clinicians the opportunity to identify patients with a potentially lower response to Omalizumab at an early stage. This 'at-risk' patient group might be a candidate for closer monitoring or for alternative treatment combinations that can be developed in the future. Similarly, the presence of high SIRI/AISI or very low Total IgE values in a patient for whom treatment discontinuation is planned can be considered as a warning sign of a high relapse risk. This might warrant a reconsideration of the decision to discontinue therapy.

This study has several strengths that contribute significantly to literature. Firstly, the large sample size of over 300 patients and the ability to analyze long-term relapse data in a subgroup of this population (n=217) have increased the statistical potency of the study. The most important methodological strength can be considered as the control for the known effects of systemic corticosteroids on neutrophil-based markers. It is achieved by using the recent use of steroids as an exclusion criterion. This approach has strengthened the likelihood that our findings are directly related to the disease's underlying inflammatory activity.

On the other hand, the present study also has certain limitations. The primary limitation stems from its retrospective design, which might have introduced information bias due to non-standardized documentation in patient records. This also restricts the ability to establish a clear causal relationship for the observed associations. Additionally, as the study is carried out at a single center, the external validity and generalizability

of the findings to broader populations might be constrained.

Consequently, the inability to demonstrate statistically independent effects for individual markers in the multivariable relapse analysis warrants careful interpretation. This outcome might be primarily attributed to the multicollinearity between SIRI and AISI, as they are mathematically derived from shared hematological parameters. Furthermore, the multifactorial nature of relapse mechanisms suggests that other unmeasured variables are likely to influence the remission durability. Finally, the relatively limited sample size of the relapse subgroup might have restricted the statistical strength of the study that is necessary to isolate these independent associations.

CONCLUSION

In brief, the findings of this study indicate that baseline SIRI and AISI levels represent a practical, reliable, and cost-efficient biomarkers to estimate both inadequate therapeutic response to Omalizumab and the likelihood of relapses after treatment withdrawal in patients with CSU. These might serve as valuable adjunctive tools to assist clinicians in guiding treatment strategies and improving overall patient management. Future prospective, multicenter studies with larger cohorts are required to validate these cut-off values and confirm the clinical utility of these biomarkers in routine practice.

DECLARATIONS

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declare that there is no financial conflict of interest related to this study.

Acknowledgements: Not applicable.
Funding: No financial support is received for this study.

Author Contributions: Concept: M.E.G., Ş.A.; Design: M.E.G., Ş.A.; Data Collection or Processing: F.S., S.KO., T.Ö., F.A.A., F.S.A., S.KA.; Analysis or Interpretation: F.Ç., M.E.G., Ş.A.; Literature Search: M.E.G., S.KA.; Writing: M.E.G., Ş.A.

Address correspondence to: *Mehmet Emin Gerek, Necmettin Erbakan University, Faculty of Medicine, Department of Internal Medicine, Division of Immunology and Allergy, Konya, Türkiye*
e-mail: *drmegerek@gmail.com*

REFERENCES

1. Maurer M, Abuzakouk M, Bérard F, et al. The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. Allergy. 2017;72(12):2005-16. doi:10.1111/all.13209
2. Curto-Barredo L, Silvestre JF, Giménez-Arnau AM. Update on the treatment of chronic urticaria. Actas Dermosifiliogr. 2014;105(5):469-82. doi:10.1016/j.ad.2012.12.019
3. Folci M, Heffler E, Canonica GW, et al. Cutting edge: biomarkers for chronic spontaneous urticaria. J Immunol Res. 2018;2018:5615109. doi:10.1155/2018/5615109
4. Beck LA, Bernstein JA, Maurer M. A review of international recommendations for the diagnosis and management of chronic urticaria. Acta Derm Venereol. 2017;97(2):149-58. doi:10.2340/00015555-2496
5. Liu X, Li J, Sun L, et al. The association between neutrophil-to-lymphocyte ratio and disease activity in rheumatoid arthritis. Inflammopharmacology. 2023;31(5):2237-44. doi:10.1007/s10787-023-01273-2
6. Mercan R, Bitik B, Tufan A, et al. The association between neutrophil/lymphocyte ratio and disease activity in rheumatoid arthritis and ankylosing spondylitis. J Clin Lab Anal. 2016;30(5):597-01. doi:10.1002/jcla.21908
7. Kucharczyk A, Marczyk K, Kucharczyk B, et al. Predicting relapse in chronic spontaneous urticaria: A retrospective cohort study evaluating omalizumab withdrawal regimens. Allergy. 2024;79(9):2554-57. doi:10.1111/all.16194
8. Foti C, Romita P, Ambrogio F, et al. Analysis of clinical factors as possible predictors of response to omalizumab and relapse after treatment discontinuation in chronic spontaneous urticaria. Dermatol Ther. 2022;35(2):e15248. doi:10.1111/dth.15248
9. Soegiharto R, Alizadeh Aghdam M, Sørensen JA, et al. Multinational drug survival study of omalizumab in patients with chronic urticaria and potential predictors for discontinuation. JAMA Dermatol. 2024;160(9):927-35. doi:10.1001/jamadermatol.2024.2056
10. Marzano AV, Genovese G, Casazza G, et al. Predictors of response to omalizumab and relapse in chronic spontaneous urticaria: A study of 470 patients. J Eur Acad Dermatol Venereol. 2019;33(5):918-24. doi:10.1111/jdv.15350
11. Zhang DG, Sørensen JA, Ghazanfar MN, et al. EXtending omalizumab treatment Intervals in patients with chronic spontaneous urticaria (EXOTIC): Protocol of a multicentre, randomised, open-label, non-inferiority trial. BMJ Open. 2025;15(1):e084987. doi:10.1136/bmjopen-2024-084987
12. Kuna M, Štefanović M, Davidović L, et al. Chronic urticaria biomarkers IL-6, ESR and CRP in correlation with disease severity and patient quality of life-a pilot study. Biomedicines. 2023;11(8):2232. doi:10.3390/biomedicines11082232
13. Kasperska-Zajac A, Grzanka A, Damasiewicz-Bodzek A. IL-6 transsignaling in patients with chronic spontaneous urticaria. PLoS One. 2015;10(12):e0145751. doi:10.1371/journal.pone.0145751
14. Grzanka R, Damasiewicz-Bodzek A, Kasperska-Zajac A. Interplay between acute phase response and coagulation/fibrinolysis in chronic spontaneous urticaria. Allergy Asthma Clin Immunol. 2018;14:27. doi:10.1186/s13223-018-0255-8
15. Karabay EA, Çerman A, Altunay I. Serum c-reactive protein, neutrophil-lymphocyte ratio and uric acid levels in chronic spontaneous urticaria. Turkiye Klinikleri J Dermatol. 2016;26(3):125-31. doi:10.5336/DERMATO.2016-52709
16. Qiu X, Ran Q, Pan J, et al. Neutrophil/lymphocyte ratio as a biomarker of response to H1-antihistamine therapy in patients with chronic spontaneous urticaria. Indian J Dermatol. 2024;69(5):367-70. doi:10.4103/ijd.ijd_558_22
17. Coşansu NC. Evaluation of new inflammatory parameters in patients with chronic spontaneous urticaria: A new predictor of refractoriness to antihistamine treatment. Namik Kemal Med J. 2020;8(3):404-11. doi:10.37696/nkmj.731617
18. Bakay OSK, Kacar N, Gul B, et al. What can be learned from real-world data about chronic spontaneous urticaria? Allergy Asthma Proc. 2024;45(4):255-61. doi:10.2500/aap.2024.45.240041
19. Atik Ö, Tepetam FM, Özden Ş, et al. Eosinophilic cationic protein and D-Dimer are potential biomarkers to predict response to antihistamines but not to omalizumab in chronic spontaneous urticaria. Libyan J Med. 2024;19(1):2420483. doi:10.1080/19932820.2024.2420483

20. Miyatani Y, Kobayashi T. Evidence-based approach to the discontinuation of immunomodulators or biologics in inflammatory bowel disease. Digestion. 2022;104(1):66-73. doi:10.1159/000527776
21. Imbert A, Gavlovsky P-J, Judor J-P, et al. T cell immunophenotyping : a source of predictive biomarkers for autoimmune hepatitis relapse. Sci Rep. 2024;14(1):24448. doi:10.1038/s41598-024-75624-6
22. Asero R, Ferrer M, Kocaturk E, et al. Chronic spontaneous urticaria: The role and relevance of autoreactivity, autoimmunity, and autoallergy. J Allergy Clin Immunol Pract. 2023;11(8):2302-8. doi:10.1016/j.jaip.2023.02.022
23. Asero R, Tedeschi A. Chronic spontaneous urticaria: from the hunt for causes and pathogenesis to the identification of different endotypes. Eur Ann Allergy Clin Immunol. 2023;55(6):253-60. doi:10.23822/EurAnnACI.1764-1489.307
24. Sella JA, Ferriani MPL, Melo JML, et al. Type I and type IIb autoimmune chronic spontaneous urticaria: Using common clinical tools for endotyping patients with CSU. J Allergy Clin Immunol Glob. 2023;2(4):100159. doi:10.1016/j.jacig.2023.100159
25. Wong D, Waserman S, Sussman GL. Endotypes of chronic spontaneous urticaria and angioedema. J Allergy Clin Immunol. 2025;156(1):17-23. doi:10.1016/j.jaci.2025.04.004