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Baseline systemic inflammatory indices as predictors of treatment escalation in chronic spontaneous urticaria: a cohort study

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Abstract
Management of chronic spontaneous urticaria (CSU) remains challenging due to frequent patient refractoriness to high-dose H1-antihistamines, necessitating omalizumab therapy. At diagnosis, reliable and accessible biomarkers are critical to predict which patients will require treatment escalation. This study aimed to evaluate baseline hematological parameters and derive inflammatory indices for their capacity to predict maximum H1-antihistamine dose and subsequent need for omalizumab in a homogenous CSU cohort without major comorbidities. This single-center, retrospective cohort study included 185 adult CSU patients. Baseline inflammatory markers were analyzed relative to the primary outcome of omalizumab requirement and secondary outcome of intensity of antihistamine dose. Multivariate logistic regression and receiver operating characteristic analyses identified independent predictors and optimized cut-off values. Higher baseline levels of inflammatory markers, such as white blood cell count, neutrophils, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, and aggregate index of systemic inflammation (AISI), were significantly associated with the need for four-fold antihistamine dosing. Adjusted multivariate analysis identified AISI ≥ 346.8 (adjusted odds ratio [aOR] = 7.45) as an independent predictor of omalizumab requirement, while erythrocyte sedimentation rate (ESR) > 7.5 (aOR = 0.24) was identified as an independent protective factor against omalizumab requirement. As a standalone biomarker, AISI demonstrated an area under the curve (AUC) of 0.733 and a negative predictive value (NPV) of 96.4% at this threshold. In this cohort, baseline AISI was independently associated with omalizumab requirement and appears to be a promising marker that warrants external validation, whereas elevated ESR appears protective. Given the retrospective single-center design, these findings should be interpreted cautiously. A high NPV of the AISI cut-off suggests potential clinical utility for ruling out patients unlikely to require treatment escalation.

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Introduction

Chronic spontaneous urticaria (CSU) is a debilitating inflammatory dermatosis characterized by the recurrent appearance of wheals, angioedema, or both, for a duration of 6 weeks or longer without an identifiable trigger.[1,2] Affecting approximately 0.5–1.0% of the global population,[1] CSU, which has been shown to be comparable in severity to that of patients with coronary artery disease, imposes a substantial burden on patients, leading to a profound impairment in the quality of life (QoL).[3]

The management of CSU follows a stepwise algorithm recommended by international guidelines. The first-line therapy consists of second-generation H1-antihistamines at a standard dose.[2] However, a substantial proportion of patients are refractory to this initial treatment, remaining symptomatic despite standard-dose antihistamines.[4,5] For such patients, the guidelines recommend increasing the second-generation H1-antihistamine dose up to four-fold. Patients who are refractory even to high-dose antihistamines are candidates for the third-line therapy, most notably the anti-immunoglobulin E (IgE) monoclonal antibody, omalizumab.[2] However, a critical challenge in CSU management is the inability to predict a patient's treatment response at diagnosis. Reliable and easily accessible biomarkers are therefore needed to identify individuals who potentially require escalation in treatment. Such a predictive tool could facilitate earlier, more personalized therapy, thereby reducing the burden of uncontrolled disease and its associated expenses.

In recent years, the search for such predictive biomarkers has focused on systemic inflammatory mediators. Elevated C-reactive protein (CRP), a sensitive marker of inflammation, has been consistently linked to higher disease activity and a poorer response to antihistamines in CSU patients.[6] Furthermore, parameters derived from routine complete blood counts (CBC) have emerged as cost-effective and promising candidates. The neutrophil-to-lymphocyte ratio (NLR), a well-established indicator of systemic inflammation, has been reported to be significantly higher in CSU patients who are refractory to H1-antihistamines.[7] Other leukocyte ratios, such as the eosinophil-to-lymphocyte ratio (ELR), eosinophil-to-neutrophil ratio (ENR), and eosinophil-to-monocyte ratio (EMR), have also been investigated, with some evidence suggesting their association with the severity of CSU.[8] However, the utility of these ratios in predicting the response to biologic therapy remains less clear, with some studies reporting no significant change in NLR, platelet-to-lymphocyte ratio (PLR), or eosinophil-to-lymphocyte ratio (ELR) during omalizumab treatment.[9] While these studies provide valuable insights, many focus on a single biomarker or a specific treatment outcome, and a comprehensive analysis investigating a broad panel of these markers to predict the full spectrum of treatment requirements is still lacking.

Therefore, this study was designed to holistically evaluate the predictive value of a wide range of baseline hematological parameters and derive inflammatory indices. We hypothesized that a comprehensive analysis of readily available biomarkers, such as routine CBC parameters (e.g., white blood cell count [WBC] and platelet [PLT] count), derived ratios (NLR, PLR, ELR, and basophil-to-lymphocyte ratio [BLR]), and more novel systemic inflammatory indices (systemic immune-inflammation index [SII], systemic inflammation response index [SIRI], and aggregate index of systemic inflammation [AISI]), could effectively predict the subsequent treatment intensity required by CSU patients. The primary aim of our retrospective cohort study is to investigate the capacity of these baseline biomarkers to foresee the maximum required H1-antihistamine dose and the eventual need for biologic therapy in a homogenous population of CSU patients without major comorbidities.

Materials and Methods

Study design and ethical approval

This single-center, retrospective cohort study was conducted at the Allergy and Immunology outpatient clinic of Izmir City Hospital, Türkiye. The study protocol was designed in accordance with the principles of the Declaration of Helsinki and received approval from the Izmir City Hospital Non-interventional Research Ethics Committee (Decision No.: 2025/478, date: September 10, 2025). Owing to the retrospective nature of the study, which involved the analysis of fully anonymized existing clinical records, the requirement for individual patient's informed consent was waived by the Ethics Committee.

Study population and outcome definition

The study population consisted of patients aged ≥18 years who were diagnosed with and followed for CSU at our clinic between January 2024 and August 2025. The patient selection process is summarized in Figure 1.

The primary outcome of the study was the requirement for omalizumab therapy. The decision to initiate omalizumab was standardized across our center, adhering to guidelines of the international European Academy of Allergy & Clinical Immunology–Global Allergy and Asthma Excellence Network–European Guideline on Atopic Eczema–Asia Pacific Association of Allergy, Asthma, and Clinical Immunology (EAACI/GA²LEN/EuroGuiDerm/APAAACI).[2] A secondary outcome was the maximum required H1-antihistamine dose, categorized into four intensity levels (1×1, 2×1, 3×1, or 4×1 standard daily dose), reflecting the highest level of standard therapy needed for disease control.

Inclusion and exclusion criteria

Patients were included if they had a confirmed diagnosis of CSU;an initial prescription of a second-generation H1-antihistamine; and complete pre-treatment laboratory records. Key exclusion criteria were a primary diagnosis of chronic inducible urticaria or urticarial vasculitis; presence of an acute infection, known malignancy, or current use of immunosuppressive medications; and absence of major systemic comorbidities (e.g., cardiovascular, endocrinological, or other autoimmune disorders). A total of 1176 patients were screened based on the CSU diagnosis code; 185 met the predefined criteria and were included

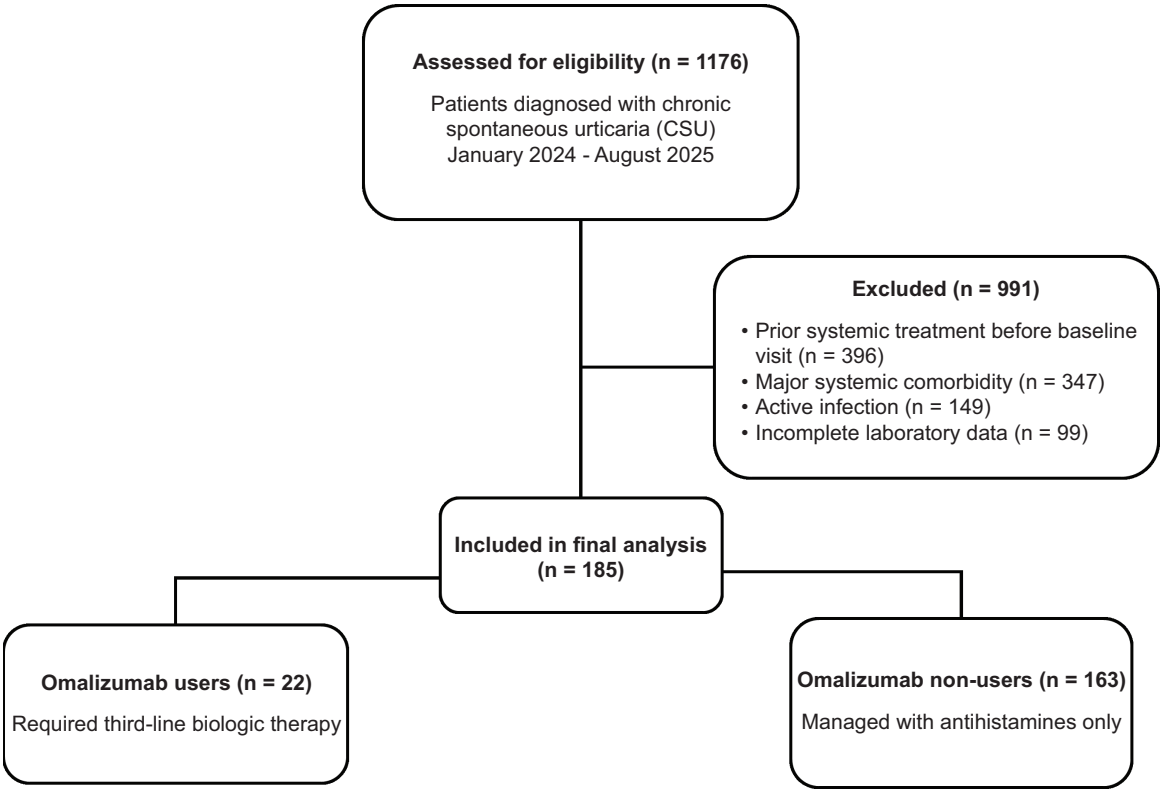

Figure 1 Flow diagram illustrating patient screening, exclusion, and final cohort inclusion. A total of 1176 CSU patients were assessed for eligibility. After applying predefined inclusion and exclusion criteria, 185 treatment-naive patients with complete baseline laboratory data were included in the final analysis.

in the final analysis (Figure 1). Skin prick test results to inhaled allergens, available in a subset of patients from prior clinical evaluations unrelated to the urticaria presentation, were recorded as descriptive data only and did not influence inclusion criteria. The diagnosis of CSU was established based on the presence of spontaneous wheals and/or angioedema for 6 weeks or longer without a clinically identifiable trigger, in accordance with international guidelines.[2]

Data collection and predictor variables

Data were retrospectively collected from the Hospital Information Management System, laboratory automation system, and electronic prescription records from the initial diagnostic visit. The predictor variables included the following: *demographic and clinical data*: age, gender, and presence of concomitant angioedema; *baseline laboratory parameters*: CBC parameters, including WBC, neutrophil (NEU), lymphocyte (LYM), eosinophil (EOS), monocyte (MONO), basophil (BASO), and PLT counts; hemoglobin (HGB) and mean platelet volume (MPV); *immunological and inflammatory markers*: CRP, erythrocyte sedimentation rate (ESR), and total IgE; and *derived Inflammatory Indices*: the following ratios and indices were calculated: NLR, PLR, ELR, (BLR), mean platelet volume-to-erythrocyte sedimentation rate (MPV–ESR) ratio, (SII), (SIRI), and (AISI). Baseline blood samples were collected at the initial visit, prior to initiation of any treatment. As per guideline recommendations, omalizumab was considered only after inadequate response to up-dosed H1-antihistamines, resulting in a typical interval of approximately 3 months between baseline sampling and initiation of omalizumab. Although disease duration varied among patients, precise onset dates could not be reliably determined due to recall bias inherent to the retrospective design. Therefore, disease duration was not included as a quantitative variable in the analysis. All patients were treatment-naive at the index visit when baseline laboratory parameters were obtained.

Statistical analysis

All statistical analyses were performed using the statistical software Jamovi 2.7 and R (version 4.3.1) via RStudio integrated development environment (IDE). A two-sided $P < 0.05$ was considered statistically significant.

The distribution of all continuous variables was assessed using the Shapiro–Wilk test. As all variables deviated from normality, they were presented as median (25th–75th percentile). Differences across antihistamine treatment-intensity groups were evaluated using the Kruskal–Wallis H test, followed by Dunn's *post hoc* test with Bonferroni correction.

For the comparison of baseline markers between patients who required and did not require omalizumab,

the Mann–Whitney U test was used. To account for multiple comparisons in this step, all P values were adjusted using the Benjamini–Hochberg procedure to control false discovery rate (FDR) at 5%; and an adjusted P (P-adj) < 0.05 was considered significant.

Receiver Operating Characteristic (ROC) curve analysis was conducted to evaluate the discriminatory ability (area under the curve [AUC]) of significant biomarkers. The optimal cut-off value was identified by maximizing Youden's index (a common summary measure of the ROC curve, J = sensitivity + specificity - 1). The stability of this optimal cut-off was assessed through a bootstrap internal validation procedure with 1000 replicates, calculating the 95% confidence interval (95% CI) for the threshold.

A multivariate binomial logistic regression model was constructed to identify independent predictors of omalizumab requirement. The model included significant biomarkers (dichotomized at their optimal cut-offs) and key clinical confounders (e.g., age, gender, and angioedema). Results are presented as adjusted odds ratios (aORs) with 95% CIs. Given the low number of events per variable (EPV), a sensitivity analysis was performed using Firth's penalized logistic regression to confirm the robustness of findings. Model fit and performance were assessed using Nagelkerke's R^2, the Hosmer–Lemeshow goodness-of-fit test, and a classification matrix. Finally, decision curve analysis (DCA) was performed to evaluate the clinical utility and net benefit of using the final predictive model.

Table 1 Baseline demographic and clinical characteristics of the study population.

Characteristic	Total population (N = 185)
Age, years (median [IQR])	33.0 (25.0–43.0)
Gender, n (%)	
Female	138 (74.6)
Males	47 (25.4)
Angioedema, n (%)	
Present	43 (23.2)
Absent	142 (76.8)
Antihistamine treatment group, n (%)	
1×1	104 (56.2)
2×1	39 (21.1)
3×1	15 (8.1)
4×1	27 (14.6)
Atopy (Prick test), n/N (%)	
Positive	31/57 (54.4)
Negative	26/57 (45.6)
ANA, n/N (%)	
Positive	32/167 (19.2)
Negative	135/167 (80.8)

Notes: Data are presented as n (%) or median (25th–75th percentile).
IQR: interquartile range; ANA: antinuclear antibody.

Results

Baseline characteristics of the study cohort

The study included 185 patients with CSU. The baseline demographic and clinical characteristics of the cohort are presented in Table 1. The population had a median age of 33.0 years (interquartile range [IQR]: 25.0–43.0) with a predominancy of females (74.6%). Concomitant angioedema was reported in 23.2% of patients. Regarding the required treatment intensity, 56.2% of patients were controlled on a standard single daily dose (1×1) of H1-antihistamines, whereas 14.6% required up-dosing to a four-fold daily dose (4×1) for management of symptoms.

Association of baseline inflammatory markers with antihistamine treatment intensity

To investigate the relationship between baseline inflammatory status and the subsequent need for intensified antihistamine therapy, we compared hematological and derived inflammatory markers across the four treatment groups (Table 2). The Kruskal–Wallis H test revealed statistically significant differences for a range of key inflammatory markers, including WBC, NEU, basophil (BASO), and monocyte (MONO) counts as well as several derived inflammatory indices (P < 0.05 for all).

Post hoc analyses with Bonferroni correction demonstrated a clear association between higher inflammation and greater treatment intensity. Notably, the group requiring a four-fold antihistamine dose (4×1) exhibited significantly higher median counts of WBC and NEU, compared to both standard-dose (1×1) and double-dose (2×1) groups. Similarly, the composite inflammatory indices, such as NLR, SII, SIRI, and AISI, were significantly elevated in the 4×1 group compared to the 1×1 group.

Baseline biomarkers as predictors of Omalizumab requirement

We next compared the baseline parameters of patients who eventually required third-line therapy with omalizumab (n = 22) to those managed with antihistamines alone (n = 163). To account for multiple comparisons, P values were adjusted using the Benjamini–Hochberg procedure (FDR). As shown in Table 3, a distinct pro-inflammatory baseline profile was significantly associated with the future need for omalizumab. After FDR correction, patients who later required omalizumab had significantly higher median NEU counts (P-adj = 0.004) and AISI (P-adj = 0.005). Conversely, the median ESR was significantly lower in patients requiring omalizumab (P-adj = 0.032).

A Multivariate predictive model for Omalizumab requirement and its validation

To identify independent predictors for the requirement of omalizumab, a multivariate binomial logistic regression analysis was constructed, including significant biomarkers (categorized at their optimal cut-offs) and key clinical

Table 2 Comparison of baseline inflammatory markers across antihistamine treatment intensity groups.

Parameter	1×1 Group (n = 104)	2×1 Group (n = 39)	3×1 Group (n = 15)	4×1 Group (n = 27)	Overall P value*
WBC (10^9/L)	7.03 (6.08–8.08)	7.13 (5.98–8.13)	7.26 (6.64–7.92)	9.30 (7.37–10.3)[a,b]	<0.001
NEU (10^9/L)	4.03 (3.35–4.82)	4.15 (3.55–4.84)	4.32 (3.69–5.36)	5.74 (4.79–6.83)[a,b]	<0.001
BASO (10^9/L)	0.04 (0.03–0.05)	0.03 (0.02–0.05)	0.02 (0.02–0.03)	0.02 (0.01–0.05)	0.005
MONO (10^9/L)	0.52 (0.42–0.63)	0.50 (0.42–0.57)	0.57 (0.50–0.66)	0.64 (0.49–0.78)[b]	0.030
NLR	1.84 (1.45–2.36)	2.20 (1.52–2.59)	1.89 (1.83–2.57)	2.25 (1.99–3.27)[a]	0.012
SII	554 (369–666)	548 (415–758)	516 (377–720)	732 (564–999)[a]	0.002
SIRI	0.91 (0.68–1.34)	1.03 (0.80–1.39)	1.28 (0.93–1.41)	1.35 (1.06–2.22)[a]	0.004
AISI	266 (165–409)	276 (196–367)	294 (222–424)	446 (372–572)[a,b]	<0.001

NotesL Data are presented as median (25th–75th percentile).
Overall P values were derived from the Kruskal–Wallis H test.
IQR: interquartile range; WBC: white blood cell; NEU: neutrophil; BASO: basophil; MONO: monocyte; NLR: neutrophil-to-lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation.
[a]P < 0.05 vs. 1×1 group (Dunn's *post hoc* test with Bonferroni correction).
[b]P < 0.05 vs. 2×1 group (Dunn's *post hoc* test with Bonferroni correction).
Although the overall group difference for basophil count was significant, no individual pairwise comparisons remained significant after Bonferroni correction.

Table 3 Comparison of baseline parameters between patients who received and did not receive omalizumab therapy.

Parameter	Omalizumab non-users (n = 163)	Omalizumab users (n = 22)	P-adj*
WBC (10^9/L)	7.13 (6.25–8.25)	8.54 (7.28–10.2)	0.011
NEU (10^9/L)	4.16 (3.44–4.91)	5.60 (4.88–6.54)	0.004
ESR (mm/h)	7.00 (5.00–13.0)	5.00 (4.00–7.00)	0.032
NLR	1.98 (1.47–2.50)	2.35 (1.97–4.11)	0.038
MPV/ESR	1.44 (0.86–2.21)	2.26 (1.45–2.60)	0.038
SII	548.0 (391–720)	732.0 (555–1009)	0.013
SIRI	1.03 (0.71–1.39)	1.32 (1.06–2.22)	0.031
AISI	275.7 (182–415)	445.6 (371–544)	0.005

Notes: Data are presented as median (25th–75th percentile) values.
*P-adj: P values derived from the Mann–Whitney U test and adjusted for multiple comparisons using the Benjamini–Hochberg (FDR) procedure.
WBC: white blood cell; NEU: neutrophil; ESR: erythrocyte sedimentation rate; NLR: neutrophil-to-lymphocyte ratio; MPV/ESR: mean platelet volume to erythrocyte sedimentation rate; SII: systemic immune-inflammation index; SIRI: systemic inflammation response index; AISI: aggregate index of systemic inflammation.

confounders (age, gender, and angioedema). The overall model was statistically significant ($\chi^2(6) = 31.9$, $P < 0.001$) and explained 30.6% of the variance in omalizumab requirement (Nagelkerke R^2). The model also demonstrated good calibration (Hosmer–Lemeshow test, $\chi^2(8) = 6.67$, $P = 0.572$). No significant multicollinearity was detected among predictors (VIF range: 1.07–1.25). As detailed in Table 4, the analysis confirmed two independent predictors: A baseline AISI value ≥ 346.8 was the strongest predictor, independently increasing the odds of requiring omalizumab by over seven-fold (aOR = 7.45; 95% CI, 2.027–27.382; P = 0.002). A baseline ESR > 7.5 was identified as an independent protective factor, reducing the odds of requiring omalizumab by approximately 76% (aOR = 0.24; 95% CI, 0.066–0.879; P = 0.031). Age, gender, angioedema, and NLR were not significant independent predictors in the adjusted model. Given the low number of EPV, a sensitivity analysis was performed using Firth's penalized logistic regression to assess the robustness of these findings. This analysis confirmed that both AISI ≥ 346.8 (P = .005) and ESR > 7.5 (P = .002) remained significant independent predictors, thereby supporting the stability of primary conclusions. The final model's overall predictive accuracy was 89.2%; however, a classification matrix revealed a high specificity (98.8%) but a low sensitivity (18.2%).

Table 4 Multivariate logistic regression analysis of categorized baseline predictors for omalizumab requirement.

Predictor	Adjusted odds ratio (aOR)	95% Confidence interval (CI)	P value
Biomarkers			
AISI ≥ 346.8 (vs. <346.8)	7.45	2.027-27.382	**0.002**
ESR > 7.5 (vs. ≤7.5)	0.24	0.066-0.879	**0.031**
NLR ≥ 3.06 (vs. <3.06)	1.99	0.631-6.268	0.240
Clinical confounders			
Age (per year of increase)	1.03	0.983-1.074	0.230
Gender (female vs. male)	0.50	0.174-1.412	0.189
Angioedema (present vs. absent)	1.89	0.564-6.357	0.301

Notes: The overall model was statistically significant ($\chi^2(6) = 31.9$, $P < .001$) and explained 30.6% of variance in omalizumab requirement (Nagelkerke R^2). No multicollinearity was detected among variables (VIF range: 1.07-1.25).
aOR: adjusted odds ratio; CI: confidence interval; AISI: aggregate index of systemic inflammation; NLR: neutrophil-to-lymphocyte ratio; ESR: erythrocyte sedimentation rate.

Diagnostic performance and clinical utility of AISI as a standalone biomarker

Given that AISI emerged as the most potent independent predictor, its performance as a standalone biomarker was evaluated in detail (Table 5). ROC curve analysis confirmed that baseline AISI has a good discriminatory ability to predict the need for omalizumab, with AUC = 0.733 (95% CI, 0.623–0.843).

The optimal cut-off value, determined by maximizing the Youden's Index (J), was 346.8. The stability of this threshold was confirmed through a bootstrap internal validation procedure (1000 replicates), which yielded 95% CI, 341.5–443.8 for cut-off. At this threshold, AISI demonstrated a sensitivity of 81.8% and a specificity of 65.6%.

Most notably for clinical application, the test showed a very high negative predictive value (NPV) of 96.4%. Furthermore, a DCA was performed to assess the clinical utility of this threshold. The analysis demonstrated that using the AISI ≥ 346.8 biomarker provided a clear net benefit over the default strategies of treating all or no patients across a wide and clinically relevant range of threshold probabilities (approximately 10–75%) (Figure 2).

Table 5 Diagnostic performance of optimal baseline AISI cut-off value for predicting the requirement of omalizumab therapy.

Performance metric	Value (95% confidence ınterval)
Area under the curve (AUC)	0.733 (0.623-0.843)
Optimal cut-off value*	346.8
Sensitivity	81.8% (59.7-94.8%)
Specificity	65.6% (57.8-72.9%)
Positive predictive value (PPV)	24.3% (19.4-30.0%)
Negative predictive value (NPV)	96.4% (91.6-98.5%)

Notes: The optimal cut-off value was determined by maximizing Youden's Index (J = 0.4746) from the ROC curve analysis.
AISI: aggregate index of systemic inflammation.

Discussion

This retrospective cohort study aimed to determine the predictive utility of baseline hematological parameters and derived inflammatory indices for subsequent treatment requirements in patients with CSU. Our principal findings demonstrate that a state of heightened systemic inflammation at diagnosis is significantly associated with both need for high-dose H1-antihistamine therapy and eventual requirement of omalizumab. Crucially, we identified a baseline AISI ≥ 346.8 as an independent predictor for omalizumab requirement and established its clinical utility, most notably through its excellent NPV.

The association between systemic inflammation and severity of CSU is well established. Our results, showing elevated levels of WBC, NEU, and a panel of inflammatory indices (NLR, SII, SIRI, and AISI) in patients requiring fourfold antihistamine doses, align with and expand upon this literature. For instance, Qiu et al. have reported a strong association between a higher NLR and H1-antihistamine resistance in CSU, a finding our bivariate analyses corroborate.[7] Our study contributes to this body of evidence by showing that composite indices such as SII and AISI, which integrate multiple cell lineages, were significantly associated with the need for intensified standard therapy. This suggests that the underlying inflammatory process in treatment-refractory CSU is complex and may involve extensive crosstalk between different arms of the immune system, which these composite markers are better suited to capture than single-cell ratios.

The most significant finding of our study is the identification of baseline AISI as an independent predictor for the future need of omalizumab. To our knowledge, while individual ratios, such as NLR, have been explored, this is one of the first studies to establish a clinically relevant, validated cut-off value for a composite index such as AISI in predicting treatment escalation to biologics in CSU.

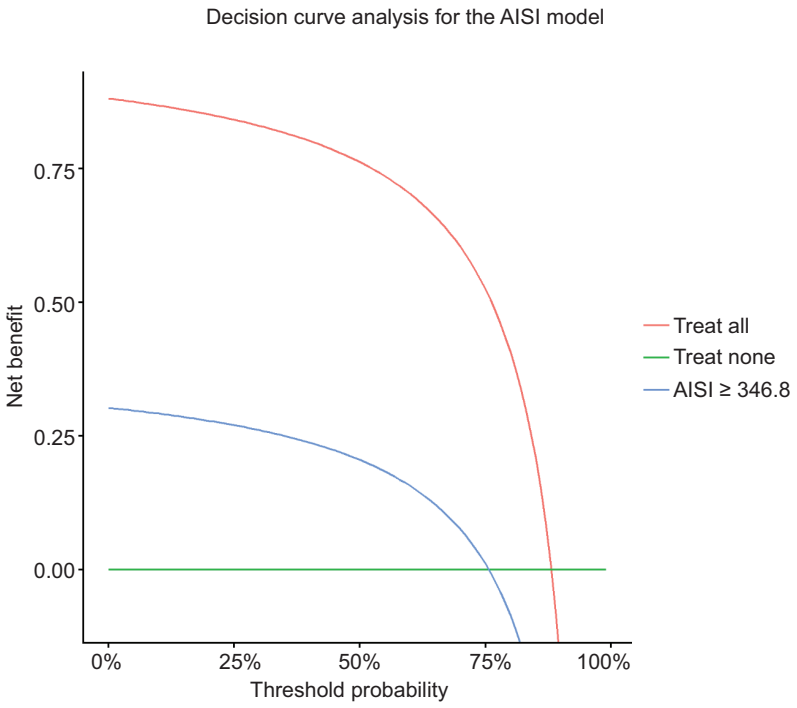

Figure 2 Decision curve analysis (DCA) for the AISI ≥ 346.8 model. The *y*-axis represents the net benefit. Blue line (AISI 346) shows the net benefit of using biomarker strategy (treat if AISI ≥ 346.8). Red line (treat all) represents the strategy.

In our multivariate model, adjusted for key demographic and clinical confounders, including age, gender, and the presence of angioedema, a baseline AISI ≥ 346.8 increased the odds of requiring omalizumab by more than seven-fold. This finding is particularly relevant as it identifies a distinct inflammatory phenotype at diagnosis that is less likely to be controlled by antihistamines alone. While NLR was significantly elevated in omalizumab users in our initial comparison, it lost its independent predictive value in the final multivariate model. This suggests that AISI, which incorporates monocytes and platelets in addition to NEU and LYM, provides a more comprehensive measure of the pan-immune inflammatory state, thereby subsuming the predictive information carried by NLR.

This finding gains biological plausibility if considered in the context of emerging concepts in CSU pathogenesis. Contemporary research has highlighted the role of coagulation cascade and endothelial dysfunction in CSU.[10,11] By incorporating platelet count, AISI may better reflect the intricate crosstalk between systemic inflammation and coagulation pathways, which is increasingly recognized as a key feature in severe CSU. The increasing recognition of distinct inflammatory endotypes in CSU, namely Type I (autoallergic) and Type IIb (autoimmune), provides a potential framework for our findings.[12] It is plausible that an elevated AISI reflects the underlying pathophysiology of the Type IIb autoimmune endotype, which is often associated with a more severe and treatment-refractory disease course.

Interestingly, our multivariate model identified a baseline ESR > 7.5 as an independent protective factor. This finding appears counterintuitive, as ESR is a nonspecific marker of inflammation. However, Kolkhir et al. also reported that CRP is a more reliable inflammatory marker than ESR in CSU,[6] with many patients having elevated CRP despite normal ESR. One hypothesis for our finding could be that the specific inflammatory pathways driving ESR elevation (e.g., those involving fibrinogen) may be distinct from the cellular inflammatory pathways captured by AISI that characterize the omalizumab-refractory phenotype. This exploratory finding warrants further mechanistic investigation.

From a clinical utility perspective, the performance of AISI as a standalone biomarker is highly promising. We identified an optimal cut-off AISI value of 346.8, which was confirmed to be stable through bootstrap internal validation. While its positive predictive value was modest, a reflection of the low prevalence of omalizumab use in the cohort, its NPV was exceptionally high at 96.4%. The clinical significance of this high NPV is substantial: a patient with a baseline AISI below this threshold is highly improbable to require omalizumab in near future. The clinical utility of this threshold was further supported by DCA, which demonstrated a clear net benefit over default clinical strategies. The value of AISI is further underscored, compared to other proposed biomarkers, such as low total IgE or positive autologous serum skin tests, which may require more specialized or expensive testing.[13] AISI's derivation from a routine, universally available CBC makes it an ideal, cost-effective tool for risk stratification, especially in resource-limited settings.

Strengths and Limitations

The present study has several methodological strengths that enhance the validity of its findings. A key strength is its rigorous statistical methodology, which began with the appropriate use of non-parametric tests justified by normality testing. Crucially, we proactively addressed the issue of multiple comparisons in our bivariate analyses by adjusting P values with the Benjamini–Hochberg (FDR) procedure. Our primary predictive model was not only adjusted for key demographic and clinical confounders (age, gender, and angioedema) but also subjected to a comprehensive performance evaluation. Furthermore, by focusing on a homogenous patient population without major systemic comorbidities, we minimized the influence of external factors on inflammatory markers, allowing for a clearer interpretation of their predictive roles.

The most significant methodological strength lies in how we addressed the inherent statistical challenges of the dataset. Recognizing that the small sample size of the omalizumab group resulted in a low number of EPV, we performed a sensitivity analysis using Firth's penalized logistic regression. This advanced method, specifically designed for such conditions, confirmed that our primary predictors (AISI and ESR) remained significant, thereby supporting the stability of our conclusions. Additionally, we validated the optimal cut-off for AISI using a bootstrap internal validation procedure and assessed its clinical utility with DCA, moving beyond simple statistical significance to demonstrate its potential for real-world clinical benefits.

Nevertheless, we must acknowledge several limitations. The primary limitation is the retrospective, single-center design and the modest sample size of the omalizumab-user group (n = 22). Although the robustness of our main predictors was confirmed with Firth's regression, the low EPV directly impacted the model's classification performance. While our model demonstrated good calibration (Hosmer–Lemeshow test, P = 0.572) and high overall accuracy (89.2%), its clinical utility is characterized by a high specificity (98.8%) but a low sensitivity (18.2%). This imbalance, a common consequence of analyzing datasets with rare events, makes the model highly effective for 'ruling out' the need for omalizumab (as supported by high NPV) but unreliable for prospectively 'ruling in' individual patients for therapy.

Second, the retrospective nature of the study precluded the systematic collection and analysis of disease activity scores, such as the Urticaria Activity Score (UAS7), which could have provided an additional layer of stratification for treatment resistance. Finally, while our findings are internally robust, the generalizability of our results, particularly the proposed AISI cut-off value of 346.8, needs to be confirmed in larger, multi-center, and prospective studies to ensure its applicability across different patient populations. Additionally, disease duration could not be systematically quantified due to retrospective design and patient recall bias.

Conclusion

Our study demonstrates that baseline systemic inflammatory indices, derived from routine CBC, can effectively stratify patients with CSU according to their future treatment requirements. A baseline AISI ≥ 346.8 was identified as an independent predictor of omalizumab requirement in this cohort, even after adjusting for age, gender, and the presence of angioedema. Conversely, ESR > 7.5 was found to be an independent protective factor. From a clinical perspective, high NPV (96.4%) of AISI cut-off is the most significant finding, suggesting that it can serve as a valuable, practical biomarker to confidently identify patients who are highly improbable to require treatment escalation. These easily calculated, cost-effective markers have the potential to aid clinicians in early risk stratification and contribute to a more personalized treatment approach in the management of CSU. However, these findings should be considered hypothesis-generating and require confirmation in prospective multicenter studies with external validation.

Mandatory Disclosure on Use of Artificial Intelligence

The authors declare that no AI-assisted tools were used in the preparation of this manuscript. All references have been manually verified for accuracy and relevance.

Author Contributions

All authors contributed equally to this article.

Conflict of Interest

The authors declared no potential conflict of interest with respect to research, authorship, and/or publication of this article.

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References

1. Fricke J, Ávila G, Keller T, Weller K, Lau S, Maurer M, et al. Prevalence of chronic urticaria in children and adults across the globe: Systematic review with meta-analysis. Allergy. 2020;75(2):423–32. https://doi.org/10.1111/all.14037
2. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734–766. https://doi.org/10.1111/all.15090
3. O'Donnell BF, Lawlor F, Simpson J, Morgan M, Greaves MW. The impact of chronic urticaria on the quality of life. Br J Dermatol. 1997;136(2):197–201. https://doi.org/10.1111/j.1365-2133.1997.tb14895.x
4. Hiragun M, Hiragun T, Mihara S, et al. Prognosis of chronic spontaneous urticaria in 117 patients not controlled by a standard dose of antihistamine. Allergy. 2013;68:229–35. https://doi.org/10.1111/all.12078
5. Saini SS, Bindslev-Jensen C, Maurer M, 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;135:67-75. https://doi.org/10.1038/jid.2014.512
6. Kolkhir P, Altrichter S, Hawro T, Maurer M. C-reactive protein is linked to disease activity, impact, and response to treatment in patients with chronic spontaneous urticaria. Allergy. 2018;73(4):940-8. https://doi.org/10.1111/all.13352
7. Qiu X, Ran Q, Pan J, Tan G. 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. https://doi.org/10.4103/ijd.ijd_558_22
8. Weissmann S, Burrack N, Babyev AS, Gordon M, Golan-Tripto I, Horev A. Eosinophil-lymphocyte ratio, eosinophil-neutrophil ratio, and eosinophil-monocyte ratio in chronic and severe urticaria. Am J Clin Dermatol. 2023;24:669-71. https://doi.org/10.1007/s40257-023-00781-9
9. Branicka O, Rymarczyk B, Gawlik R, Glück J. Assessment of ELR, PLR, NLR and BLR ratios during omalizumab treatment of chronic spontaneous urticaria. J Clin Med. 2024;13:4287. https://doi.org/10.3390/jcm13154287
10. Cugno M, Tedeschi A, Borghi A, et al. Activation of blood coagulation in two prototypic autoimmune skin diseases: A possible link with thrombotic risk. PLoS One. 2015;10(6):e0129456. https://doi.org/10.1371/journal.pone.0129456
11. Deza G, Giménez-Arnau AM. The coagulation system in chronic spontaneous urticaria. Curr Opin Allergy Clin Immunol. 2017;17(4):284-93.
12. Asero R, Ferrer M, Kocaturk E, Maurer M. Chronic spontaneous urticaria: The role and relevance of autoreactivity, autoimmunity, and autoallergy. J Allergy Clin Immunol Pract. 2023;11(8):2302-8. https://doi.org/10.1016/j.jaip.2023.02.022
13. Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. Allergy. 2021;76(10):2965-81. https://doi.org/10.1111/all.14757