ORIGINAL REPORT

The Predictive Value of Serum Total IgE for Antihistamine Treatment Outcomes in Chinese Patients with Chronic Spontaneous Urticaria

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Chronic spontaneous urticaria is a common skin disorder with variable treatment responses. Second-generation H_1-antihistamines are the first-line treatment for chronic spontaneous urticaria, yet many patients fail to respond to licensed doses. Predictors of treatment response to second-generation H_1-antihistamines could help optimize disease management and minimize unnecessary healthcare costs. In this retrospective cohort study of 99 Chinese chronic spontaneous urticaria patients, higher log-transformed serum total IgE levels were significantly associated with poor response to standard-dose antihistamines (aOR = 2.09, 95% CI: 1.29–3.38, $p = 0.003$). However, this association was not observed in the subgroup of patients who required dose escalation, suggesting a more complex relationship in later treatment stages. Machine learning analysis further supported total IgE as one of the top predictors of poor response to standard-dose second-generation H_1-antihistamines. While serum total IgE may not serve as a diagnostic tool, it appears to be a helpful risk indicator for anticipating refractoriness to standard-dosed antihistamines in chronic spontaneous urticaria, particularly at the initial treatment stage.

Key words: chronic urticaria; antihistamines; immunoglobulin E; treatment outcome.

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SIGNIFICANCE

Chronic spontaneous urticaria is a challenging condition with limited treatment options, and identifying biomarkers that help stratify patients by risk of non-response is essential for improving outcomes. In this retrospective study of 99 Chinese chronic spontaneous urticaria patients, higher baseline serum total IgE levels were associated with a greater likelihood of failing to achieve symptom control on standard-dose antihistamines. While considerable overlap exists between responders and non-responders, total IgE may still serve as a useful risk indicator to prompt earlier consideration of dose escalation or alternative therapies. Integrating IgE testing into clinical assessment could help guide personalized treatment decisions, reduce unnecessary delays, and ultimately enhance quality of life for patients with refractory chronic spontaneous urticaria.

Chronic spontaneous urticaria (CSU) is defined as spontaneous episodes of urticaria rash that occur daily or almost daily for more than 6 weeks. CSU is a common disease with an overall prevalence of 0.5% to 1% (1). The disease significantly impacts patients' quality of life, with recurrent symptoms and long duration, yet treatment options remain limited. Recommendations in recent international guidelines include second-generation H_1-antihistamines (sgAHs), omalizumab, and cyclosporine. Second-generation H1-antihistamines are first-line therapy at licensed doses (1 tablet daily); updosing up to fourfold, though off-label, is recommended for non-responders (2). Although treatment with sgAHs is effective for some patients with CSU, a substantial proportion of patients remain refractory (3). A previous meta-analysis study reported a response rate of 38.6% to standard dosages of antihistamine in CSU patients, while updosing antihistamines led to a response rate of 63.2% (4). In refractory cases, alternative treatments like omalizumab or cyclosporine may be considered. Thus, identifying biomarkers or clinical factors predictive of sgAH treatment response is crucial for guiding therapy.

Immunoglobulin E (IgE) plays an important role in the pathogenesis of CSU. In CSU, elevated levels of IgE contribute to the activation and degranulation of mast cells, leading to the release of histamine and other pro-inflammatory mediators. This process is central to the development of the characteristic wheals and angioedema observed in CSU patients (5). Additionally, some patients with CSU exhibit autoreactivity, where IgE targets autoantigens, further exacerbating the inflammatory response (6). The role of IgE in CSU has been supported by the efficacy of anti-IgE therapy, such as omalizumab, which has shown significant clinical benefits in reducing symptoms and improving patients' quality of life.

Clinical and laboratory markers that may predict the response to sgAH treatment have been described. A recent systematic review demonstrated strong evidence for high UAS7, raised C-reactive protein (CRP) and raised D-dimer levels to predict non-response to sgAHs (7). Immunoglobulin E (IgE) contributes to the pathophysiology of CSU. As a target of treatment, it has been reported to be associated with CSU endotype and

disease activity (8). Lower total IgE levels are linked to poor response to omalizumab, but weak evidence was demonstrated for the association between total IgE levels and sgAH treatment response.

To address the uncertainty regarding the predictive value of total IgE for sgAH treatment response, we conducted this retrospective cohort study in Chinese patients with CSU. We aimed to assess whether serum total IgE levels could predict antihistamine efficacy, using both traditional logistic regression and machine learning (ML)-based approaches.

MATERIALS AND METHODS

Study design and patient selection

Medical records of patients diagnosed with chronic spontaneous urticaria in Beijing Tsinghua Changgung Hospital (Beijing, China) from April 2021 to April 2024 were retrospectively reviewed. Adult patients aged 18 years or older were enrolled. The diagnosis was confirmed by dermatologists according to the international EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline. Only patients with active CSU were included. Patients with concomitant diagnosis of inducible urticaria were excluded. Patients lacking information on sgAH treatment response were excluded.

Data collection

Ten clinical parameters and 7 laboratory parameters were included. Clinical variables include: gender, age of onset in years, disease duration since onset (in months), presence of angioedema, presence of atopy, presence of any comorbid autoimmune disease, pruritus intensity, baseline disease activity based on Weekly Urticaria Activity Score, and response to standard- and updosed sgAH. Atopy was defined as a documented history of 1 or more atopic conditions, including allergic rhinitis, asthma, allergic conjunctivitis, or atopic dermatitis, or a family history of allergic diseases. Autoimmune diseases were defined as diagnoses of systemic or organ-specific autoimmune conditions, such as autoimmune thyroiditis, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's disease, based on clinical records. Pruritus intensity was assessed using an 11-point numerical rating scale (NRS), ranging from 0 (no itch) to 10 (worst imaginable itch). Patients were instructed to rate the peak intensity of their itch over the past 7 days (9). Intolerable itch was defined as moderate to severe pruritus, corresponding to a NRS score > 3. Blood analyses include complete blood count (CBC) with differential (lymphocytes, eosinophils, and basophils), total IgE serum levels, ANA, and positivity of thyroid immunity (IgG against Tg or TPO). Due to the skewed distribution of IgE in the cohort, we used log-transformed serum total IgE as a substitute parameter. **Table I** provides an overview of the clinical characteristics and a selection of laboratory parameters for all included patients.

Disease activity was assessed by the Weekly Urticaria Activity Score (UAS7). Patients were asked to record their symptoms for 7 consecutive days prior to day of inclusion. Disease activities were classified as follows: well-controlled (UAS7 = 0–6), mild (UAS7 = 7–15), moderate (UAS7 = 16–27), and severe (UAS7 = 28–42) (10).

To accurately determine response to H_1-antihistamines, patients were assessed for UAS7 activity index at every follow-up visit. According to the international EAACI/GA²LEN/EuroGuiDerm/APAAACI guidelines,

the aim of treatment in chronic urticaria is to achieve complete symptom control and a normalization of quality of life. Therefore, we defined an effective treatment response as achieving a continuous UAS7 score = 0 for at least 4 weeks (2). Patients were classified as good responders and poor responders. Standard-dosed and updosed sgAH intake were defined as consuming 1 tablet per day and 2–4 tablets per day, respectively.

Machine learning model

Model development was performed using Python (v3.11; https://www.python.org/downloads/) and the scikit-learn library (https://scikit-learn.org/stable/). Prior to model training, the dataset was pre-processed to reduce skewness and standardize features. Logistic regression and random forest classifiers were trained on 80% of the data, with 20% reserved for evaluation. Performance was assessed by accuracy, area under the receiver operating characteristic (ROC) curve (AUC), sensitivity, positive predictive value (PPV), and F1 score. To ensure robustness of performance estimates, 1,000 bootstrap iterations were conducted to calculate 95% confidence intervals for each metric. Feature importance for the random forest model was extracted and ranked to identify the most influential predictors. All machine learning results were interpreted alongside traditional regression analyses for consistency and clinical interpretability.

Statistical analysis

Statistical analyses were performed, and graphs created using R software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism Version 10 (GraphPad Software Inc, San Diego, CA, USA). Categorical variables were expressed as percentages, followed in brackets by the number of patients positive for this parameter. Comparative analyses were conducted using χ^2 tests for categorical variables. Continuous variables with a non-normal distribution were presented as medians with interquartile ranges (IQRs) and compared using the Mann–Whitney *U* test, while normally distributed variables were expressed as means with standard deviations (SDs) and compared using independent samples *t*-tests. The Spearman correlation

Table I. Clinical and laboratory profiles of patients stratified by response to standard- and updosed second-generation H1-antihistamines (sgAHs)

		Standard-dose sgAHs			Updosed sgAHs		
Characteristics	Baseline ($N=99$)	Good Responders ($n=45$)	Poor responders ($n=54$)	p-value	Good Responders ($n=26$)	Poor responders ($n=28$)	p-value
Gender				0.230†			1.000†
Male	36 (36.4%)	13 (28.9%)	23 (42.6%)		11 (42.3%)	12 (57.1%)	
Female	63 (63.6%)	32 (71.1%)	31 (57.4%)		15 (57.7%)	16 (42.9%)	
Age at onset (years), median (IQR)	34.1 (26.6–46.7)	29.8 (25.5–41.1)	37.7 (28.8–58.3)	**0.006**§	42.1 (28.5–62.6)	34.0 (29.1–51.5)	0.287§
Disease duration (months), median (IQR)	10.4 (4.0–33.6)	7.4 (3.7–18.0)	13.3 (4.7–78.7)	0.062§	7.2 (3.7–30.4)	23.9 (6.1–91.3)	0.119§
Concomitant angioedema				0.335†			1.000†
Presence	11 (11.1%)	3 (6.7%)	8 (14.8%)		4 (15.4%)	4 (14.3%)	
Absence	88 (88.9%)	42 (93.3%)	46 (85.2%)		22 (84.6%)	24 (85.7%)	
History of atopy				1.000†			0.086†
Presence	41 (41.4%)	19 (42.2%)	22 (40.7%)		7 (26.9%)	15 (53.6%)	
Absence	58 (58.6%)	26 (57.8%)	32 (59.3%)		19 (73.1%)	13 (46.4%)	
Concomitant autoimmune disease				0.834†			1.000†
Presence	5 (5.1%)	3 (6.7%)	2 (3.7%)		1 (3.8%)	1 (3.6%)	
Absence	94 (94.9%)	42 (93.3%)	52 (96.3%)		25 (96.2%)	27 (96.4%)	
Pruritus intensity (NRS, 0–10)				0.891†			0.212†
0–3: mild	48 (48.5%)	23 (51.1%)	25 (46.3%)		15 (57.7%)	10 (35.7%)	
4–6: moderate	28 (28.3%)	12 (26.7%)	16 (29.6%)		7 (26.9%)	9 (32.1%)	
7–10: severe	23 (23.2%)	10 (22.2%)	13 (24.1%)		4 (15.4%)	9 (32.1%)	
UAS7, median (IQR)	15.0 (10.5–26.0)	14.0 (8.0–22.0)	18.0 (14.0–28.0)	**0.022**§	20.5 (14.0–28.0)	18.0 (13.5–29.0)	0.965§
Wheals score	7.0 (4.0–14.0)	7.0 (3.0–7.0)	9.0 (6.0–14.0)	**0.003**§	9.0 (7.0–14.0)	7.5 (4.0–14.0)	0.364§
Itching score	7.0 (6.0–14.0)	7.0 (5.0–14.0)	8.0 (7.0–14.0)	0.222§	7.0 (7.0–14.0)	9.0 (7.0–14.0)	0.477§
Activity based on UAS7				**0.025**†			0.768†
0–6: well controlled	19 (19.2%)	10 (22.2%)	9 (16.7%)		3 (11.5%)	6 (21.4%)	
7–15: mild	31 (31.3%)	20 (44.4%)	11 (20.4%)		6 (23.1%)	5 (17.9%)	
16–27: moderate	24 (24.2%)	7 (15.6%)	17 (31.5%)		9 (34.6%)	8 (28.6%)	
28–42: severe	25 (25.3%)	8 (17.8%)	17 (31.5%)		8 (30.8%)	9 (32.1%)	
Log serum total IgE (kU/L), mean (±SD)	4.7 (±1.0)	4.4 (±0.9)	5.0 (±1.1)	**0.005***	4.9 (±1.0)	5.1 (±1.1)	0.419*
Blood cells (counts/ml), median (IQR)	6.5 (5.4–7.6)	6.5 (5.3–7.2)	6.4 (5.4–7.6)	0.795§	6.6 (5.6–7.6)	6.1 (5.2–7.5)	0.516§
Lymphocytes (count/ml), median (IQR)	2.0 (1.7–2.3)	2.1 (1.8–2.3)	1.9 (1.7–2.6)	0.666§	1.8 (1.6–2.6)	2.1 (1.8–2.7)	0.139§
Eosinophils (count/ml), median (IQR)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.484§	0.1 (0.1–0.2)	0.1 (0.1 to 0.2)	0.903§
Basophils (count/ml), median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.938§	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	**0.040**§
Antinuclear antibody				0.485†			1.000†
≥1:160	4 (4.0%)	3 (6.7%)	1 (1.9%)		0 (0%)	1 (3.6%)	
≤1:80	95 (96.0%)	42 (93.3%)	53 (98.1%)		26 (100%)	27 (96.4%)	
Thyroid autoimmunity				0.978†			0.736†
Presence	12 (12.1%)	6 (13.3%)	6 (11.1%)		2 (7.7%)	4 (14.3%)	
Absence	87 (87.9%)	39 (86.7%)	48 (88.9%)		24 (92.3%)	24 (85.7%)	

IQR: interquartile range; SD: standard deviation; NRS, numeric rating scale; UAS, Urticaria activity score. Statistically significant correlations are shown in bold. P-values† calculated using the X^2 test; p-values* calculated using independent-samples t-test; p-values§ calculated using the Mann–Whitney U test.

coefficient was used to calculate correlation between variables.

Univariate, age and sex-adjusted, and multivariate logistic regression analysis were used to identify significant factors related to sgAH treatment efficacy. Candidate variables with a p-value <0.2 on univariable analysis were included in the multivariable model. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated for efficacy. Statistical significance was defined as a two-sided p-value <0.05.

Model discrimination was assessed by calculating the area under the AUC. To evaluate the incremental value of total IgE, both Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) were calculated. Categorical NRI was computed based on predefined clinical risk thresholds, while continuous NRI and IDI were estimated using the PredictABEL package (https://www.rdocumentation.org/packages/PredictABEL/versions/1.2-4/topics/PredictABEL-package). The optimal cutoff probability for classification was determined by maximizing Youden's index from the ROC curve.

RESULTS

Patient demographics

The basic characteristics of the patients in our study cohort are presented in Table I. A total of 99 patients with CSU were included. There was a female predominance ($n=63$, 63.6%) compared with males ($n=36$, 36.4%). The median age of CSU onset was 34.1 years, and the median disease duration was 10.4 months. Angioedema was associated in 11 patients (11.1%). A total of 41 patients (41.4%) had atopy, and 5 patients (5.1%) presented with concomitant autoimmune disease. Concerning disease activity based on UAS7, 25 patients (25.3%) had severe disease, 24 patients (24.2%) had moderate disease, 31 patients (31.3%) had mild disease, and 19 patients (19.2%) were well controlled.

All the patients in the cohort were managed through the stepwise approach. Most of them received standard doses of sgAH treatment at first referral for at least 4 weeks. Two- to fourfold doses of sgAHs would be prescribed if complete response was not achieved. Finally, if CSU continued to be refractory, anti-inflammatory agents or biologics would be recommended. At the follow-up visits, 45 patients (45.5%) achieved being symptom free with the standard dose of antihistamine treatment and 54 patients (54.5%) did not reach remission. Some 28 (28.3%) patients reported inadequate improvement with up to fourfold doses of sgAHs; they received step-up treatment such as omalizumab or immunosuppressants thereafter. Among these 28 patients, 17 (60.7%) achieved symptom relief within 8 weeks, whereas the remaining 11 (39.3%) remained refractory.

Total IgE levels predict treatment response to standard-dose sgAHs, as assessed by traditional statistical methods

We compared the baseline characteristics between good and poor responders to standard-dose sgAHs.

Traditional pairwise comparisons showed that poor responders had a higher age of onset ($p = 0.006$), a higher urticaria activity score (particularly wheals score, $p = 0.003$), and higher log-transformed total serum IgE levels (4.4 [3.5–5.3] vs 5.0 [3.9–6.1], $p = 0.005$) (Table I, **Fig. 1**). Notably, despite these statistically significant differences, there was considerable overlap in IgE distributions between the 2 groups, indicating that serum total IgE alone may have limited discriminatory power at the individual patient level. Both age- and sex-adjusted and multivariable logistic regression analyses showed that higher log-transformed serum total IgE levels were significantly associated with poor response to standard-dose sgAHs. In the adjusted model, the adjusted odds ratio (aOR) was 2.09 (95% CI: 1.29–3.38, $p = 0.003$), and remained significant in the multivariable model (OR = 1.86, 95% CI: 1.13–3.07, $p = 0.015$). Additionally, an association of longer disease duration with an insufficient sgAH response was observed in our patients (OR = 1.02, 95% CI 1.0–1.03, $p = 0.019$) (**Table II**).

A subgroup of 54 patients with baseline total IgE > 100 kU/L was identified and analysed to investi-

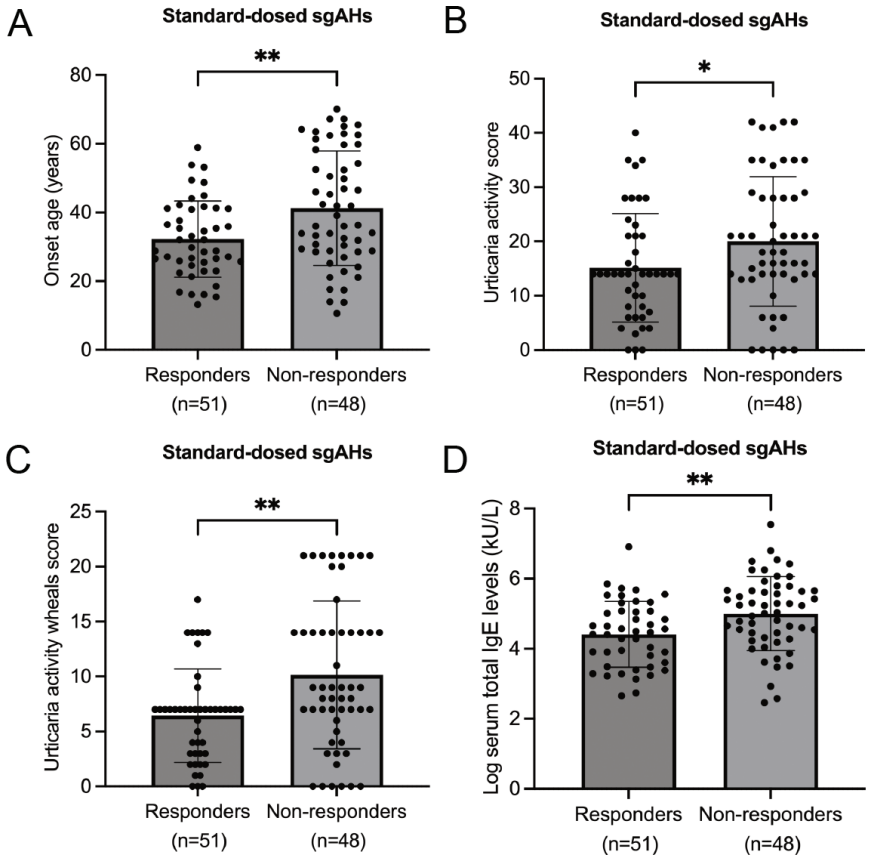

Fig. 1. Comparison of clinical and laboratory characteristics between responders and non-responders to standard-dosed second-generation H1-antihistamines (sgAHs) in patients with chronic spontaneous urticaria (CSU). (A) Age of onset was significantly higher in non-responders than in responders ($p = 0.006$). (B) Urticaria activity score (UAS7) was significantly higher in non-responders ($p = 0.022$). (C) Wheals score (component of UAS7) was significantly higher in non-responders ($p = 0.003$). (D) Log-transformed serum total IgE levels were significantly elevated in non-responders compared with responders ($p = 0.005$). Notably, there was considerable overlap in IgE values between response categories, which may limit the test's utility in individual-level clinical decision-making. Bars represent mean ± standard deviation. Each dot represents an individual patient. Significance was determined using the Mann–Whitney *U* test. ns: not significant.

Table II. Logistic regression analyses for the identification of predictor of standard-dosed second-generation H1-antihistamine (sgAH) treatment efficacy in patients with chronic spontaneous urticaria

	Crude		Age- and sex-adjusted		Multivariate	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male gender	1.83 (0.79–4.23)	0.160	–	–	1.23 (0.46–3.29)	0.680
Age at onset	**1.04 (1.01–1.08)**	**0.004**	–	–	**1.07 (1.03–1.11)**	**<0.001**
Disease duration	**1.01 (1.00–1.03)**	**0.025**	**1.02 (1.01–1.03)**	**0.005**	**1.02 (1.00–1.03)**	**0.019**
Concomitant angioedema	2.43 (0.61–9.79)	0.210	3.63 (0.81–16.36)	0.093		
History of atopy	0.94 (0.42–2.10)	0.882	0.89 (0.38–2.10)	0.798		
Concomitant autoimmune disease	0.54 (0.09–3.37)	0.508	0.63 (0.09–4.26)	0.637		
Intolerable itching	1.21 (0.55–2.68)	0.633	0.94 (0.40–2.21)	0.880		
UAS7	**1.04 (1.00–1.08)**	**0.036**	1.03 (0.99–1.08)	0.105	1.03 (0.98–1.07)	0.252
Log serum total IgE levels	**1.80 (1.18–2.76)**	**0.007**	**2.09 (1.29–3.38)**	**0.003**	**1.86 (1.13–3.07)**	**0.015**
Blood cells	1.05 (0.83–1.32)	0.691	1.03 (0.81–1.32)	0.789		
Lymphocytes	1.14 (0.55–2.38)	0.729	1.13 (0.51–2.51)	0.765		
Eosinophils	3.16 (0.27–37.07)	0.360	4.63 (0.32–67.41)	0.262		
Low basophils	1.08 (0.49–2.39)	0.854	0.99 (0.42–2.32)	0.984		
ANA ≥1:160	0.26 (0.03–2.63)	0.256	0.21 (0.02–2.26)	0.196		
Thyroid autoimmunity	0.81 (0.24–2.72)	0.736	0.68 (0.19–2.45)	0.557		

UAS: urticaria activity score; ANA: antinuclear antibody; OR: odds ratio; CI: confidence interval. Odds ratios with a *p*-value <0.05 are shown in bold.

gate factors associated with treatment response in the high-IgE population. Traditional pairwise comparisons showed that poor responders had a longer disease duration (25.2 [6.6–99.7] vs 7.0 [3.7–17.5], $p=0.036$) and higher UAS7 scores (22.8 ± 12.3 vs 12.4 ± 9.6, $p=0.002$). There was a significant trend towards more severe pruritus among poor responders compared with good responders ($p=0.033$), with a higher proportion of poor responders reporting moderate to severe symptoms. Log-transformed IgE levels did not differ significantly between groups ($p=0.107$) (Table SI). Univariable and age- and sex-adjusted logistic regression analyses indicated that higher UAS7 was associated with poor response to standard-dose sgAHs (OR = 1.09, 95% CI: 1.02–1.15, $p=0.006$; aOR = 1.08, 95% CI: 1.01–1.15, $p=0.018$) (Table SII). Due to limited sample size, multivariable regression was not performed in this subgroup.

Atopic history, but not total IgE levels, predict refractoriness to updosed sgAHs after standard-dose failure

For the updosed sgAH model, we included only patients who did not achieve symptom control with standard doses and subsequently received dose escalation. In this refined cohort, multivariable logistic regression analysis revealed that only a history of atopy was significantly associated with poor response to higher-dose treatment (aOR = 3.64, 95% CI: 1.06–12.47, $p=0.040$) (**Table III**). Neither log-transformed total IgE levels nor disease duration remained significant predictors in this subgroup. These findings suggest that in patients who failed standard-dose sgAHs, baseline IgE may be less predictive of treatment refractoriness than clinical atopic status. However, this lack of statistical significance may also be due to the relatively small sample size, which limits the statistical power to detect weaker associations in the updosed group.

Total IgE levels predict treatment response to sgAHs, as determined by machine learning models

In addition to traditional statistical analyses, we applied supervised machine learning (ML) models to identify key predictors of sgAH treatment outcomes in CSU. Among all tested algorithms, the random forest classifier achieved the highest predictive performance for both standard- and high-dose response classification.

Table III. Logistic regression analyses for the identification of predictor of updosed second-generation H1-antihistamine (sgAH) treatment efficacy in patients with chronic spontaneous urticaria

	Crude		Age- and sex-adjusted		Multivariate	
Variable	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Male gender	1.02 (0.35–3.01)	0.968	–	–		
Age at onset	0.98 (0.95–1.01)	0.238	–	–		
Disease duration	1.01 (1.00–1.02)	0.162	1.01 (1.00–1.02)	0.226	1.01 (1.00–1.02)	0.195
Concomitant angioedema	0.92 (0.20–4.12)	0.910	0.87 (0.19–4.02)	0.861		
History of atopy	**3.13 (1.00–9.81)**	**0.050**	**3.36 (1.04–10.87)**	**0.043**	**3.64 (1.06–12.47)**	**0.040**
Concomitant autoimmune disease	0.93 (0.05–15.61)	0.957	0.77 (0.04–13.20)	0.855		
Intolerable itching	2.45 (0.82–7.35)	0.109	2.99 (0.93–9.60)	0.066	2.18 (0.65–7.28)	0.205
UAS7	1.00 (0.95–1.04)	0.880	1.00 (0.95–1.05)	0.966		
Log serum total IgE levels	1.24 (0.74–2.09)	0.413	1.20 (0.68–2.11)	0.530		
Blood cells	0.94 (0.70–1.26)	0.664	0.93 (0.68–1.26)	0.620		
Lymphocytes	1.79 (0.69–4.67)	0.235	1.68 (0.62–4.58)	0.309		
Eosinophils	7.24 (0.21–248.62)	0.272	5.81 (0.18–188.43)	0.321		
Low basophils	0.41 (0.14–1.22)	0.109	0.42 (0.13–1.32)	0.137	0.45 (0.14–1.47)	0.184
Thyroid autoimmunity	2.00 (0.33–11.97)	0.448	2.16 (0.35–13.22)	0.405		

UAS: urticaria activity score; ANA: antinuclear antibody; OR: odds ratio; CI: confidence interval. Odds ratios with a *p*-value <0.05 are shown in bold.

In the prediction of standard-dose sgAH response, log-transformed serum total IgE emerged as the second most important predictor (importance score = 0.167, **Fig. 2**A-B), following age of onset. In the updosed response model, which focused on patients unresponsive to standard doses, log-transformed IgE again ranked within the top 5 most informative features (Fig. 2C, D). These consistent findings highlight the central role of IgE in CSU pathophysiology and support its utility as a predictive biomarker for treatment planning. Our machine learning results reinforce the statistical findings, suggesting that elevated IgE levels are strongly associated with refractoriness to sgAHs, particularly at standard doses.

DISCUSSION

Our findings reinforce the role of serum total IgE as a clinically meaningful risk indicator in CSU, particularly for predicting refractoriness to standard-dose sgAH therapy. The integration of machine learning models allowed for a more nuanced analysis of nonlinear associations, strengthening the predictive value of IgE. In both statistical and ML-based approaches, log-transformed total IgE consistently ranked among the top predictors of poor treatment response, especially in patients who failed to achieve symptom control with standard dosing. However, as shown in **Fig. 1**D and Table I, there is considerable overlap in IgE values between responders and non-responders, which limits its utility as a standalone diagnostic test. Thus, total IgE should be interpreted as 1 component of a broader risk stratification strategy rather than a definitive clinical marker. In addition, within the high-IgE subgroup (defined as total IgE > 100 kU/L), the discriminatory value of IgE diminished. This attenuation likely reflects the compressed distribution of IgE values in this subgroup, where most patients exhibited similarly elevated levels. In this high-IgE population, UAS7 emerged as the principal factor distinguishing poor responders from good responders. This observation is consistent with previous findings of Fok et al., which highlighted UAS7 as a robust clinical indicator of antihistamine resistance (7, 11, 12).

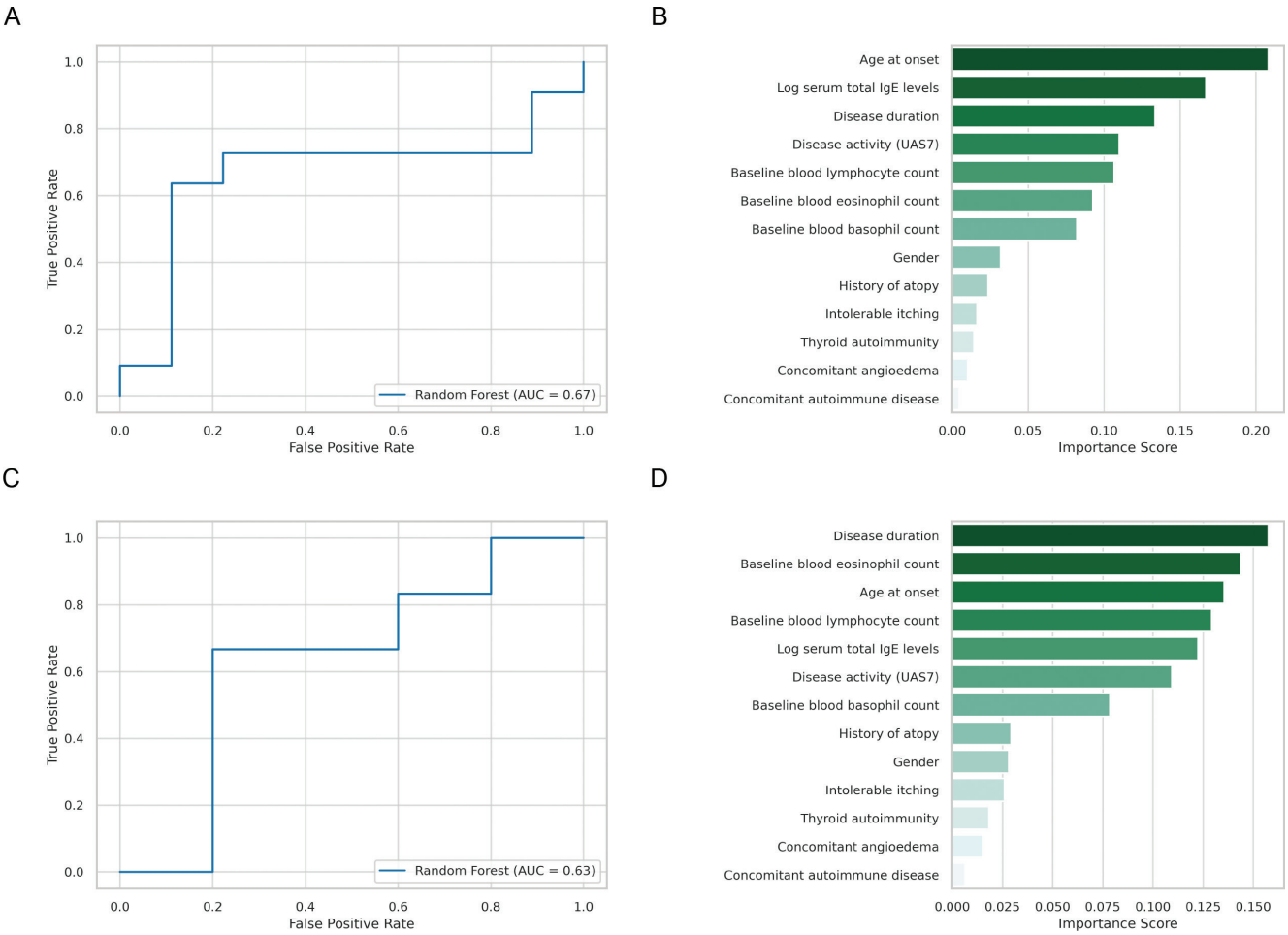

Fig. 2. Machine learning model performance and feature importance in predicting treatment response to standard and updosed second-generation H1-antihistamines (sgAHs) in patients with chronic spontaneous urticaria (CSU). (A) Receiver operating characteristic (ROC) curve of the random forest model for predicting refractoriness to standard-dose sgAHs. (B) Feature importance plot from the standard-dose response model, ranked by mean decrease in impurity. (C) ROC curve of the random forest model for predicting refractoriness to updosed sgAHs in patients who failed standard treatment. (D) Feature importance plot from the updosed sgAH response model. AUC: area under the ROC curve.

The management of CSU can be time-consuming, leading to significant psychological and economic burdens on patients. Second-generation H_1-antihistamines remain the first-line therapy according to guideline for urticaria, yet a substantial proportion of patients show inadequate response to licensed doses, resulting in delayed escalation (3). Thus, identification of reliable predictive markers of treatment efficacy can inform individualized therapy decisions, saving time and costs. Our findings suggest that patients with elevated serum IgE levels are less likely to respond to standard-dose sgAHs and may benefit from earlier dose escalation or consideration of biologic therapy. Conversely, those with lower IgE levels are more likely to achieve remission with standard-dose treatment. Nonetheless, given the overlapping distributions, clinicians should combine IgE results with other clinical indicators – such as disease duration and UAS7 score – when counselling patients on the likelihood of response. These results support the potential clinical utility of baseline IgE testing in guiding personalized treatment strategies. Our study encourages physicians to discuss the risk of poor sgAH response in advance with those patients who have longer disease duration, higher UAS7 score, or higher serum IgE levels.

In CSU, immunoglobulin E (IgE) is involved in the activation and degranulation of mast cells, and anti-IgE antibodies like omalizumab have become licensed treatment recommendations in patients refractory to sgAHs (2). Elevated serum IgE is considered a potential marker for severe chronic urticaria (13). Given its crucial role in CSU, IgE has been investigated for its predictive value in treatment outcomes. Studies have shown that low total IgE levels are associated with poor response to omalizumab treatment and good response to cyclosporine (5, 14–16). However, existing literature examining the relationship between IgE levels and antihistamine response has yielded mixed results. For example, a systematic review by Fok et al. reported that in several cohorts there was no significant difference in total IgE between antihistamine responders and non-responders (7). Similarly, a review by Altrichter et al. pointed out that total IgE does not appear to predict the response to antihistamine treatment (8). In contrast, Türk et al. found lower total IgE as a predictor of complete response to standard-dose antihistamine treatment (17). Our data suggest that elevated IgE levels are indeed associated with poor response to standard-dose sgAHs. The discrepancies between these studies may be due to differences in patient endotypes, geographic or genetic factors, and sample size. Consequently, our findings should be interpreted with caution; prospective, multicentre studies with rigorous phenotyping are needed to validate total IgE as a reliable risk indicator for antihistamine response.

The heterogeneity of CSU endotypes may, at least in part, account for the discrepancies observed between our findings and those of previous studies. Recent advances in the pathogenesis of CSU have emphasized the significance of autoimmunity, leading to the emergence of 2 distinct endotypes: type I autoimmune CSU (aiCSU) and type IIb autoimmune CSU (18). Type I autoimmune CSU (aiCSU), or autoallergic CSU, is characterized by IgE-mediated mast cell activation, whereas type IIb aiCSU involves IgG/IgM autoantibodies and generally exhibits lower IgE levels (8, 18). In our cohort, the majority of patients could be classified as type I CSU based on autologous serum skin test/basophil activation test (ASST/BAT) screening and clinical features, with only a small number potentially falling under type IIb. Therefore, our study conclusions were primarily applicable to the population of type I CSU patients. To validate this, we conducted a separate analysis focusing exclusively on the classic type I CSU patients within the cohort. The results were consistent with the previous findings (Tables SIII–IV).

Our study has some limitations. First, its retrospective, single-centre design restricted the range of available parameters and led to missing data. Some important laboratory tests such as D-dimer and C-reactive protein levels were unavailable in most patients and thus excluded. Second, the modest sample size restricted the number of variables in multivariate models and reduced statistical power in subgroup analyses. In particular, ANA positivity was rare and excluded from machine learning analysis. Third, detailed CSU endotyping was not performed, and triple testing to identify type IIb aiCSU was lacking. Further prospective studies with larger, well-phenotyped cohorts and broader biomarker panels – such as D-dimer, CRP, ASST, BAT, and FcεRI expression – are warranted to refine predictive models for antihistamine response.

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The authors have no conflicts of interest to declare.

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