International Archives of Allergy and Immunology

Clinical Allergy – Research Article

Int Arch Allergy Immunol 2023;184:421–432
DOI: 10.1159/000528395

Received: September 27, 2022
Accepted: November 22, 2022
Published online: January 18, 2023

In Chronic Spontaneous Urticaria, Complete Response to Antihistamine Treatment Is Linked to Low Disease Activity

Murat Türk[a] Ragıp Ertaş[b] Ümit Murat Şahiner[c] Pavel Kolkhir[d, e, f] Bülent Enis Şekerel[c] Özge Soyer[c] Atıl Avcı[b] Mustafa Atasoy[g] Kemal Özyurt[h] Yekta Türk[i] Engin Zeydan[j] Marcus Maurer[d, e]

[a]Kayseri City Education and Research Hospital, Clinic of Immunologic and Allergic Diseases, Kayseri, Turkey; [b]Health Science University, Kayseri Faculty of Medicine, Kayseri City Education and Research Hospital, Department of Dermatology, Kayseri, Turkey; [c]Hacettepe University, Division of Pediatric Allergy and Immunology, Ankara, Turkey; [d]Institute of Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; [e]Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP), Allergology and Immunology, Berlin, Germany; [f]I.M. Sechenov First Moscow State Medical University (Sechenov University), Division of Immune-mediated Skin Diseases, Moscow, Russia; [g]Biruni University, Medical Faculty, Department of Dermatology, İstanbul, Turkey; [h]Kırşehir Ahi Evran University, Department of Dermatology, Kırşehir, Turkey; [i]Aselsan Inc., Ankara, Turkey; [j]Services as Networks (SAS) Research Unit, Centre Tecnològic de Telecomunicacions de Catalunya (CTTC), Barcelona, Spain

Keywords
Chronic spontaneous urticaria · Antihistamine · Predictors · Disease activity

Abstract
Introduction: The use of predictors of response to a specific treatment in patients with chronic spontaneous urticaria (CSU) can improve disease management, help prevent unnecessary healthcare costs, and save time. In this study, we aimed to identify predictors of complete response to standard-dosed and higher than standard-dosed antihistamine treatments in patients with CSU. ***Methods:*** Medical records of 475 CSU patients, 120 of them <18 years old, from 3 different centers were analyzed. We used 15 machine learning (ML) models as well as traditional statistical methods to predict complete response to standard-dosed and higher than standard-dosed antihistamine treatment based on 17 clinical parameters. ***Results:*** CSU disease activity, which was assessed by urticaria activity score (UAS), was the only clinical parameter that predicted complete response to standard-dosed and higher than standard-dosed antihistamine treatment, with ML models and traditional statistics, for all age groups. Based on ROC analyses, optimal cut-off values of disease activity to predict complete response were UAS <3 and UAS <4 for standard-dosed (area under the ROC curve [AUC] = 0.69; $p = 0.001$) and higher than standard-dosed (AUC = 0.79; $p = 0.001$) antihistamine treatments, respectively. Also, ML models identified lower total IgE (<150 IU/mL) as a predictor of complete response to a standard-dosed antihistamine and lower CRP (<3.4 mg/mL) as a predictor of complete response to higher than standard-dose antihistamine treatment. ***Discussion:*** In this study, we showed that patients

Edited by: Zuotao Zhao, Beijing.
Murat Türk and Ragıp Ertaş contributed equally to this work.

Karger@karger.com
www.karger.com/iaa

Correspondence to:
Marcus Maurer, marcus.maurer@charite.de

with UAS <3 are highly likely to have complete response to standard-dosed AH and those with a UAS <4 are highly likely to have complete response to higher than standard-dosed AH treatment. Low CSU disease activity is the only universal predictor of complete response to AH treatment with both ML models and traditional statistics for all age groups.

Introduction

Chronic spontaneous urticaria (CSU) is a prevalent disease affecting approximately 1% of the population [1]. CSU negatively affects the quality of life (QoL) of patients; thus, the main aim of the treatment is complete response, i.e., no more signs and symptoms, normal QoL, and complete disease control, until spontaneous remission occurs [2, 3]. The current international urticaria guideline recommends the use of a second-generation antihistamine (sgAH) as the first-line treatment in all patients with CSU. Treatment should be started at standard dose, and the dose should be increased, up to 4-fold, in patients who do not achieve complete response with the standard dose [3, 4]. If complete response cannot be achieved with this within 2–4 weeks, the second- and third-line treatment options are omalizumab and cyclosporine, respectively [3, 4]. The use of this step-wise treatment approach is recommended in all patients with CSU.

CSU is a heterogeneous disease with distinct subgroups. We recently identified three different clusters of CSU patients by using machine learning (ML) algorithms [5]. One of these clusters, characterized by high IgE levels, is linked to dominant characteristics of type I autoimmune CSU, also called autoallergic CSU. Another cluster had dominant characteristics of type IIb autoimmune CSU. Patients with type I and type IIb autoimmune CSU are held to differ in their disease features, laboratory markers, and response to treatment [6]. Indeed, several studies suggest that the rates of complete response to sgAHs and omalizumab are lower in patients with type IIb autoimmune CSU [7–11]. Our study and others provided proof of concept that ML algorithms can be used to identify CSU patient clusters with distinct characteristics including some that are linked to treatment response [5, 12, 13]. Thus, it may be possible to use this approach to specifically search for predictors of patients' complete response to individual treatments. This, however, has not been done.

The use of predictors of response to a specific treatment can improve disease management, prevent unnecessary healthcare costs, and save time. As of now, there are very few studies on markers that are linked to the response of adult CSU patients to antihistamine treatment, and there are even less in children with CSU. A recent review of potential predictors of response to different CSU treatments did not demonstrate any predictors for complete response to sgAH treatment and only a few predictors for nonresponse [14]. The authors concluded that the number of studies on patients and disease markers that forecast the response to antihistamine treatment in CSU was limited and that further studies are required.

To address this unmet need, we aimed to identify predictors of complete response to standard-dosed and higher than standard-dosed antihistamine treatment in a large multicenter cohort of pediatric and adult patients with CSU. To this end, we used several ML models as well as traditional statistical methods.

Methods

Study Design

We retrospectively analyzed the medical records of patients diagnosed with CSU from all age groups treated at the Dermatology Clinic of the Kayseri City Hospital, Dermatology Clinic of Sechenov University, and Pediatric Allergy Clinic of Hacettepe University. The study was approved by the Institutional Review Board (Kayseri City Hospital, Clinical Research Ethical Committee, decision no/date: 498/November 04, 2021), and written informed consent from participants was not required in accordance with local/national guidelines.

Patient Population and Measurements

The whole combined dataset from 3 centers had 1,089 patients. Since the centers' datasets differed from each other in terms of included patient characteristics, biomarkers, patient-reported outcomes, and treatment responses, we first defined the common parameters within all 3 datasets. At the end, 17 different parameters (7 continuous and 10 categorical) were included in this study. The 7 continuous variables were (1) age in years, (2) disease duration since diagnosis (in months), (3) baseline serum total IgE levels (IU/mL), (4) baseline CRP levels (mg/L), (5) baseline disease activity (baseline in-clinic urticaria activity scores [UAS]), (6) baseline blood eosinophil count (cells/mL), and (7) baseline blood basophil count (cells/mL). The 10 categorical variables were (1) gender, (2) presence of angioedema, (3) presence of CIndU, (4) presence of atopy, (5) IgG-anti-TPO positivity, (6) anti-nuclear antibody positivity, (7) presence of any comorbid autoimmune disease, (8) presence of asthma, (9) standard-dose AH response, and (10) higher than standard-dose AH response. Of all patients, 624 were missing one or more of the selected variables and were excluded. At the end, 475 patients (120 of them were <18 years old) were included in the final analyses. Clinical and laboratory parameters of the study group are presented in Table 1.

Disease activity was assessed by urticaria activity score (UAS) for the adult population and by physician global assessment, based on the results of the in-clinic UAS, for the pediatric population

Table 1. Patient characteristics

Parameters	*N* = 475
Age; years (IQR)	33 (17.5–46)
Female gender; *n* (%)	322 (67.8)
Presence of angioedema; *n* (%)	270 (56.8)
Concomitant CIndU; *n* (%)	188 (39.6)
Duration of the disease in months (IQR)	18 (6–60)
Total baseline IgE level; IU/mL (IQR)	88.5 (33.6–197)
Baseline CRP level; mg/L (IQR)	3.1 (1–5.4)
ANA positivity; *n* (%)	106 (22.4)
IgG-anti-TPO positivity; *n* (%)	94 (19.8)
Presence of any concomitant autoimmune diseases; *n* (%)	154 (32.4)
Presence of atopy; *n* (%)	200 (42.1)
Baseline disease activity (IQR)	4 (2–6)
Presence of asthma; *n* (%)	78 (16.8)

IQR, interquartile range; CIndU, chronic inducible urticaria; CRP, C-reactive protein; ANA, anti-nuclear antibody; TPO, thyroid peroxidase; UAS, urticaria activity score.

[15]. The UAS, an established measure of disease activity in CSU, assesses the severity of itch and the number of hives within the last 24 h. The total score is calculated as the sum of the severity of pruritus (0 = none; 3 = severe) and the number of hives (0 = none; 3 = severe [>50 wheals/24 h] and/or difficult to tolerate). Higher scores indicate higher disease activity (total score ranges between 0 and 6) [15].

In line with the current international urticaria guideline, standard-dose and higher than standard-dose sgAH intake were defined as 1 and 2–4 tablets of AH intake per day, respectively [3]. Complete response was defined as the absence of itchy wheals and angioedema after at least 4 weeks of treatment. All other patients, i.e., those with continued occurrence of itchy wheals, angioedema, or both despite at least 4 weeks of treatment, were defined as having insufficient response.

ML Approach

For the use of ML models for the identification of predictors of AH response, we first identified the most appropriate ML model and then characterized predictive parameters, their contribution, and possible cut-off values.

To this end, we used the Shapash Python library [16] to select ML models and interpret the results which provide comparison of models that are most representative of available ML classifiers in the literature. The Shapash Python library uses Lime and Shap as a backend to show the results. First, it compiles the elements of each step such as data preparation, feature engineering, model fitting, model evaluation, and model understanding, and then it provides a summary of explainability. For the comparison of ML models, we used the PyCaret Python library [17].

In total, using the training dataset with 10-fold cross-validation during the training phase, we compared 15 ML models; the maximum number of ML model comparisons performed by the PyCaret python library used: Linear Discriminant Analysis, Logistic Regression, Light Gradient Boosting Machine, Extra Trees Classifier, Decision Tree Classifier, Random Forest Classifier, Gradient Boosting Classifier, Naive Bayes, CatBoost Classifier, Extreme Gradient Boosting, K Neighbors Classifier, AdaBoost Classifier, Quadratic Discriminant Analysis, SVM – Linear Kernel and Ridge Classifier. The performance of each model was compared by calculating accuracy, sensitivity, positive predictive value (PPV), F1 score, and the area under the ROC curve (AUC) [18].

Accuracy, one of the most important performance indicators of ML-assisted prediction, is the proportion of correct predictions to total predictions. Sensitivity is the proportion of observed positives that were predicted to be positive, whereas the PPV is the proportion of predicted positives, which are actual positives. The F1 score is the weighted average of sensitivity and PPV. The AUC provides an aggregate measure of performance across all possible classification thresholds. It measures the quality of the model's prediction, irrespective of chosen classification thresholds. The higher the AUC value, the better the model can distinguish between two groups.

Feature importance describes which parameters are relevant for the prediction and how important they are. A higher score means that the specific parameter has a greater impact on the prediction. We used contribution plots to demonstrate how individual parameters affect the prediction and whether there are threshold effects. We used the model with the highest accuracy to obtain feature importance and generate contribution plots.

Statistical Approach

Statistical analysis was performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as frequencies and percentages, and the χ^2 test was used to compare the groups. The normality of the data was analyzed by the Kolmogorov-Smirnov test. All continuous parameters included were distributed non-normally and expressed as median (interquartile range) and compared with Mann-Whitney U test. Univariate analysis was used to determine the factors related to standard- and high-dose AH complete response separately, and the variables with statistical difference ($p < 0.2$) were included in binary logistic regression analysis to predict the odds of being a case (complete/insufficient AH response) based on the values of the independent variables, in our case predictors. Independent analyses were performed in adult and pediatric patients for higher than standard-dosed

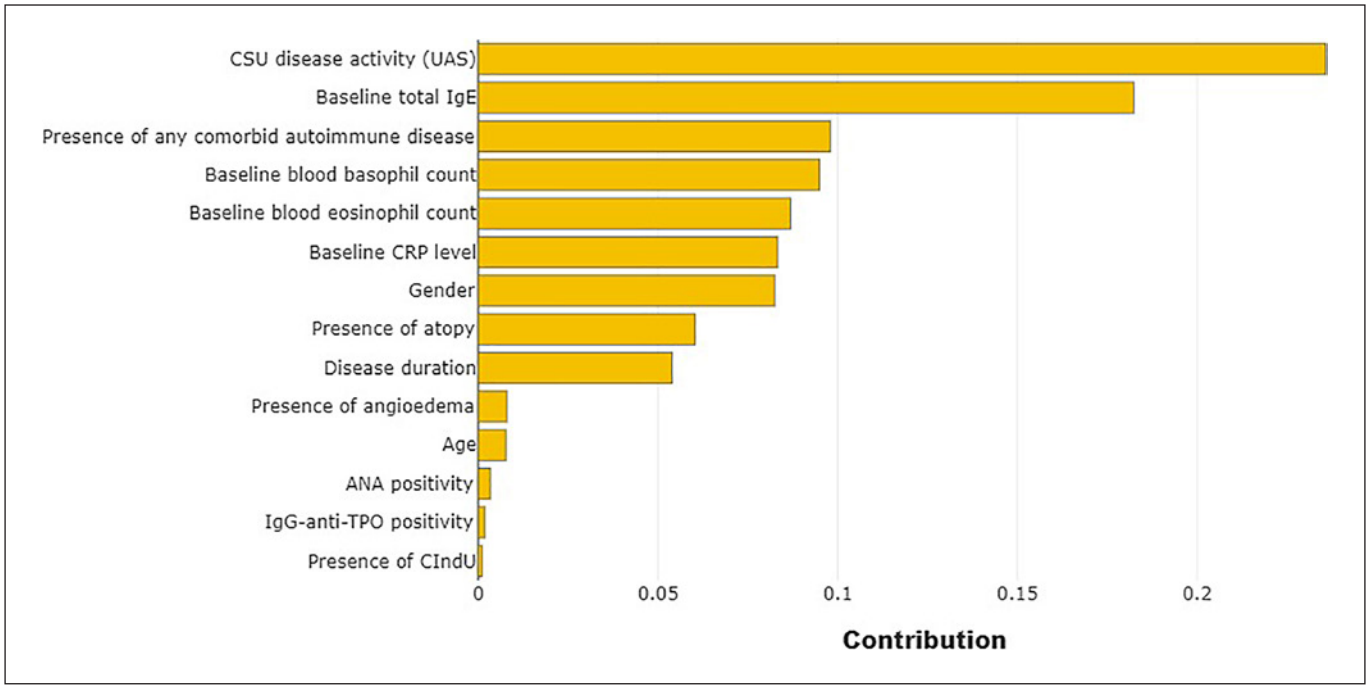

Fig. 1. Feature importance plot of features in Logistic Regression Classification model. Figure indicates that all features had a positive impact on the prediction. Disease activity and IgE levels showed the highest contribution to the standard-dosed AH complete response prediction.

AH treatment, but not standard-dosed AH treatment as the number of patients was too low. In the end, data of 112 patients were included in the standard-dosed AH response analysis, and data of 411 patients (64 patients had standard-dosed AH complete response and were not treated with higher doses and were not included in this analysis) were included in the higher than standard-dosed AH response analysis. Using ROC curves, ideal cut-off values were derived.

Results

In CSU, Low Disease Activity and Low Total IgE Predict Complete Response to a Standard-Dosed Antihistamine, as Assessed by the Use of ML Models

Of 112 CSU patients treated with a standard-dosed AH (56% female, 78% < 18 years old), 64 (57%) showed complete response (54 pediatric, 10 adult). Across 15 ML models, the "Logistic Regression Model" predicted this with the highest accuracy (0.62 ± 0.14), with a sensitivity of 0.53 ± 0.25, a PPV of 0.57 ± 0.14, F1 of 0.53 ± 0.18, and AUC of 0.64 ± 0.14.

Of 17 analyzed clinical parameters (patient and disease features), 14 contributed to the prediction of complete response. Disease activity and total IgE were the most important predictors and contributed with 24% and 18% to the overall prediction of complete response, respectively (shown in Fig. 1). Optimal cut-off values for these two parameters were 3 of 6 for disease activity and 150 IU/mL for IgE levels, with lower disease activity and lower IgE levels linked to a higher probability of complete response to standard-dosed AH treatment (shown in Fig. 2).

Low CSU Disease Activity Predicts Complete Response to a Standard-Dosed Antihistamine, as Assessed by Traditional Statistical Methods

When we compared CSU patients who experienced complete response to a standard-dosed AH with those who did not, using traditional pairwise comparison, the only differences were longer disease duration (6.4 [3–22] vs. 4.5 [1.5–11.9] months; $p = 0.035$) and lower disease activity (UAS: 2.6 [1.7–4] vs. 4 [3–6]; $p = 0.001$) in the former (Table 2). Traditional statistical methods, i.e., binary logistic regression analysis, revealed that only lower disease activity was an independent predictor of complete response to standard-dosed AH treatment ($p = 0.001$; OR: 1.477; 95% CI: 1.171–1.863) (Table 3). Binary logistic regression analysis predicted this with an accuracy

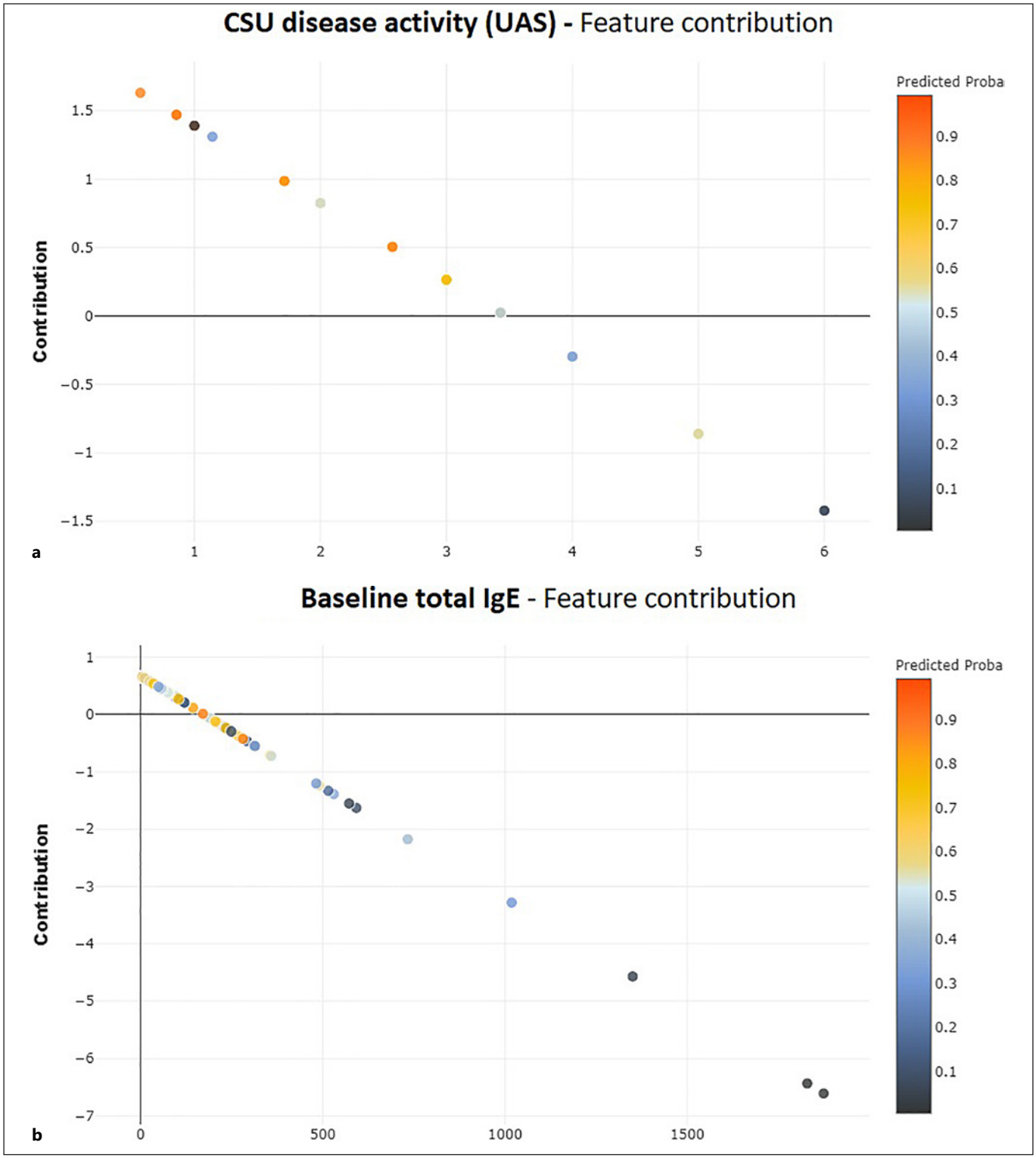

Fig. 2. Contribution plots of UAS (**a**) and total IgE (**b**) in Logistic Regression ML model. Prediction probabilities of having standard-dosed AH complete response was scaled from high average prediction probability (red points) to low prediction probability (black points). The vertical black lines where the contribution is equal to 0 are the cut-off of the features which was 3 for UAS and 150 IU/mL for total IgE. It showed that the lower disease activity scores (especially UAS <3) and lower total IgE levels (especially <150 IU/mL) increase the probability of having standard-dosed AH complete response.

Table 2. Comparison of the characteristics of the patients with standard-dosed AH complete or insufficient response

Parameters	Standard-dosed AH complete response (*n* = 64)	Standard-dosed AH insufficient response (*n* = 48)	*p* value
Age; years (IQR)	10.8 (7.7–16.5)	12.8 (10.1–23.8)	0.067
Female gender; *n* (%)	35 (55)	28 (58)	0.7
Presence of angioedema; *n* (%)	31 (48.4)	22 (45.8)	0.785
Concomitant CIndU; *n* (%)	9 (14.1)	7 (14.6)	0.938
Duration of the disease in months (IQR)	6.4 (3–22)	4.5 (1.5–11.9)	**0.035**
Total baseline IgE level; IU/mL (IQR)	61.6 (26.8–164.3)	98.9 (26.2–269.8)	0.216
Baseline CRP level; mg/L (IQR)	0.25 (0.15–0.81)	0.39 (0.15–1.16)	0.545
ANA positivity; *n* (%)	11 (17.2)	11 (22.9)	0.45
IgG-anti-TPO positivity; *n* (%)	9 (14.1)	5 (10.4)	0.564
Presence of any concomitant autoimmune diseases; *n* (%)	19 (29.7)	15 (31.3)	0.859
Presence of atopy; *n* (%)	21 (32.8)	17 (35.4)	0.773
Baseline disease activity (IQR)	2.57 (1.71–4)	4 (3–6)	**0.001**

Table 3. Binary logistic regression analysis for predicting standard-dosed AH complete response in patients with CSU

	Univariate			Multivariate		
	OR	CI (95%)	*p* value[a]	OR	CI (95%)	*p* value[b]
Age	1.015	0.984–1.047	0.34			
Female gender	0.862	0.405–1.836	0.7			
Presence of angioedema	1.160	0.545–2.470	0.7			
Presence of concomitant CIndU	1.043	0.359–3.034	0.938			
Duration of the disease in months	0.985	0.965–1.006	**0.161**			
Total baseline IgE	1.001	0.999–1.002	0.388			
Baseline CRP	0.951	0.839–1.079	0.436			
ANA positivity	1.432	0.562–3.65	0.451			
IgG-anti-TPO positivity	0.711	0.222–2.275	0.565			
Presence of any concomitant autoimmune diseases	1.077	0.478–2.426	0.859			
Presence of atopy	1.123	0.51–2.471	0.773			
Baseline disease activity	1.477	1.171–1.863	**0.001**	1.45	1.141–1.843	**0.002**
Baseline basophil count	0.992	0.975–1.010	0.387			
Baseline eosinophil count	1.001	0.998–1.005	0.462			

[a] Variables with $p < 0.2$ were included in binary logistic regression analysis. [b] $p < 0.05$ was considered significant.

of 0.66. AUC of disease activity was 0.69 ($p = 0.001$), and using a cut-off of 3 of 6, the sensitivity was 79% and the specificity was 39%, which indicates that values of less than 3 are highly likely to identify complete response to standard-dosed AH treatment.

In CSU, Low Disease Activity and Low CRP Predict Response to a Higher than Standard-Dosed Antihistamine, as Assessed by the Use of ML

Across 411 CSU patients treated with a higher than standard-dosed AH (70% female, 13% < 18 years old), 223 (54.3%) showed complete response (53 pediatric and 170 adult). Of 15 ML models, "Random Forest Classifier" predicted this with the highest accuracy (0.77 ± 0.09), with a sensitivity of 0.69 ± 0.17, a PPV of 0.76 ± 0.10, F1 of 0.72 ± 0.12 and AUC of 0.83 ± 0.07.

Almost all, i.e., 13 of 17 analyzed patient and disease features, positively contributed to this prediction. Disease activity and CRP levels were the most important parameters and contributed with 29% and 21% to the overall prediction of complete response, respectively (shown in Fig. 3). Optimal cut-off values for these two parameters were 3 of 6 for disease activity and 3.4 mg/L for CRP, and lower disease activity and lower CRP levels

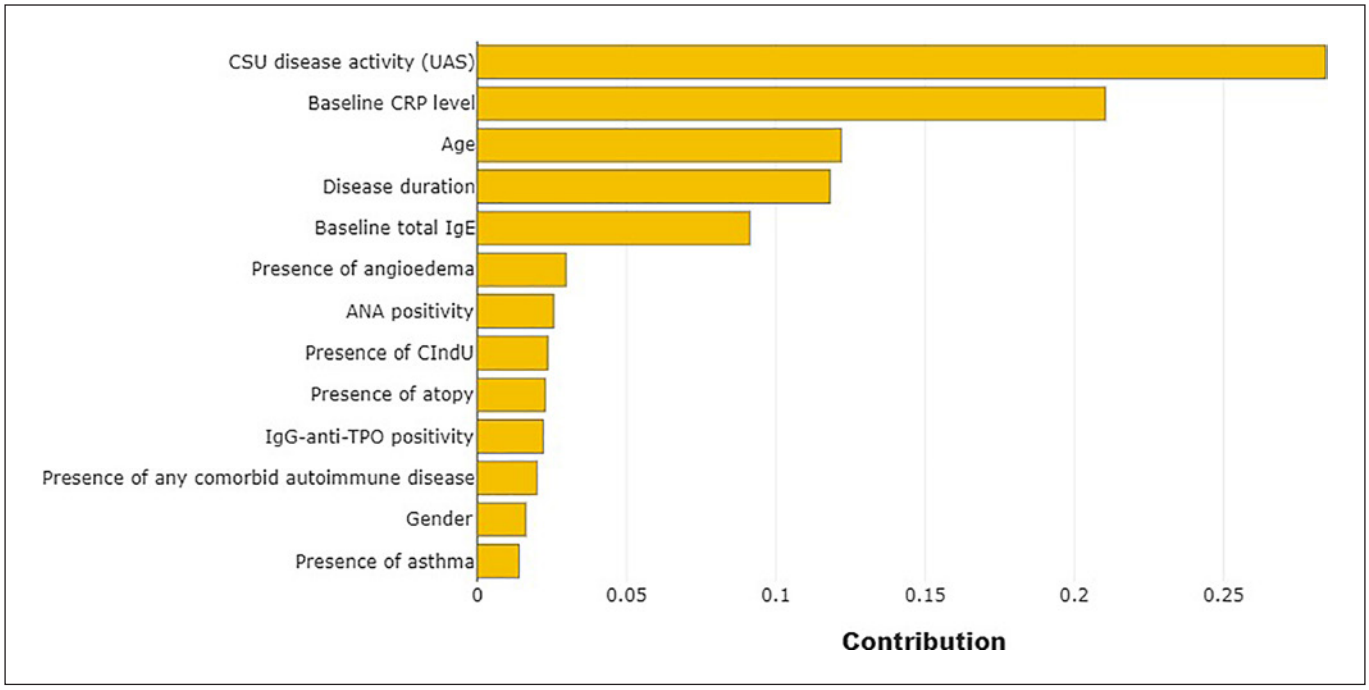

Fig. 3. Feature importance plot of all features used in Random Forest ML model. Figure indicates that all features had a positive impact on the prediction. Disease activity and CRP levels showed the highest contribution to the higher than standard-dosed AH complete response prediction.

were linked to a higher probability of complete response to higher than standard-dosed AH treatment (shown in Fig. 4).

We also performed independent analyses for pediatric and adult patients. The ML model "Linear Discriminant Analysis" worked best for the adult (338 patients) dataset and identified lower disease activity, lower total IgE levels, and younger age as the most important drivers of complete response prediction. In contrast, "Extreme Gradient Boosting Analysis" worked best for the pediatric dataset (127 patients) and showed that lower disease activity, lower IgE and CRP levels were linked to a higher probability of complete response to higher than standard-dosed antihistamine treatment.

Low CSU Disease Activity, Age, Absence of Angioedema, and Total IgE Predict Complete Response to a Higher than Standard-Dosed Antihistamine, as Assessed by Traditional Statistical Methods

By paired comparisons, patients with complete response to a higher than standard-dosed AH were younger (34 [19-47] years vs. 38 [28.3–47] years; $p = 0.013$); showed lower rates of angioedema (51.6 vs. 66%; $p = 0.001$) and IgG-anti-TPO positivity (16.6 vs. 25.5%; $p = 0.005$); and had shorter disease duration (12 [4–48] months vs. 36 [12–96] months; $p < 0.001$), lower CRP levels (3.02 [1.7–4.29] vs. 3.31 [3–7.84]; $p < 0.001$), and lower disease activity (UAS: 3 [2–5] vs. 5 [4–6]; $p < 0.001$) (Table 4).

Binary logistic regression analysis identified younger age ($p = 0.009$; OR: 1.019; 95% CI: 1.005–1.034), absence of angioedema ($p = 0.042$; OR: 1.621; 95% CI: 1.018–2.582), lower total IgE ($p = 0.03$; OR: 1.001; 95% CI: 1–1.002), and lower disease activity ($p < 0.001$; OR: 2.009; 95% CI: 1.713–2.356) to be independent predictors of complete response to higher than standard-dose AH treatment (Table 5), with an accuracy of 0.74. AUC of disease activity was 0.79 ($p = 0.001$), and using a cut-off of 4 of 6, the sensitivity was 90% and the specificity was 57%, which indicates that UAS values of less than 4 are highly likely to identify complete response to higher than standard-dosed AH treatment.

With further analyses in pediatric and adult patients separately, paired comparisons showed that only disease activity was significantly lower in pediatric patients who showed complete response to a higher than standard-dosed AH (4 [1.8–6] vs. 5.2 [3.8–6]; $p = 0.045$). In contrast,

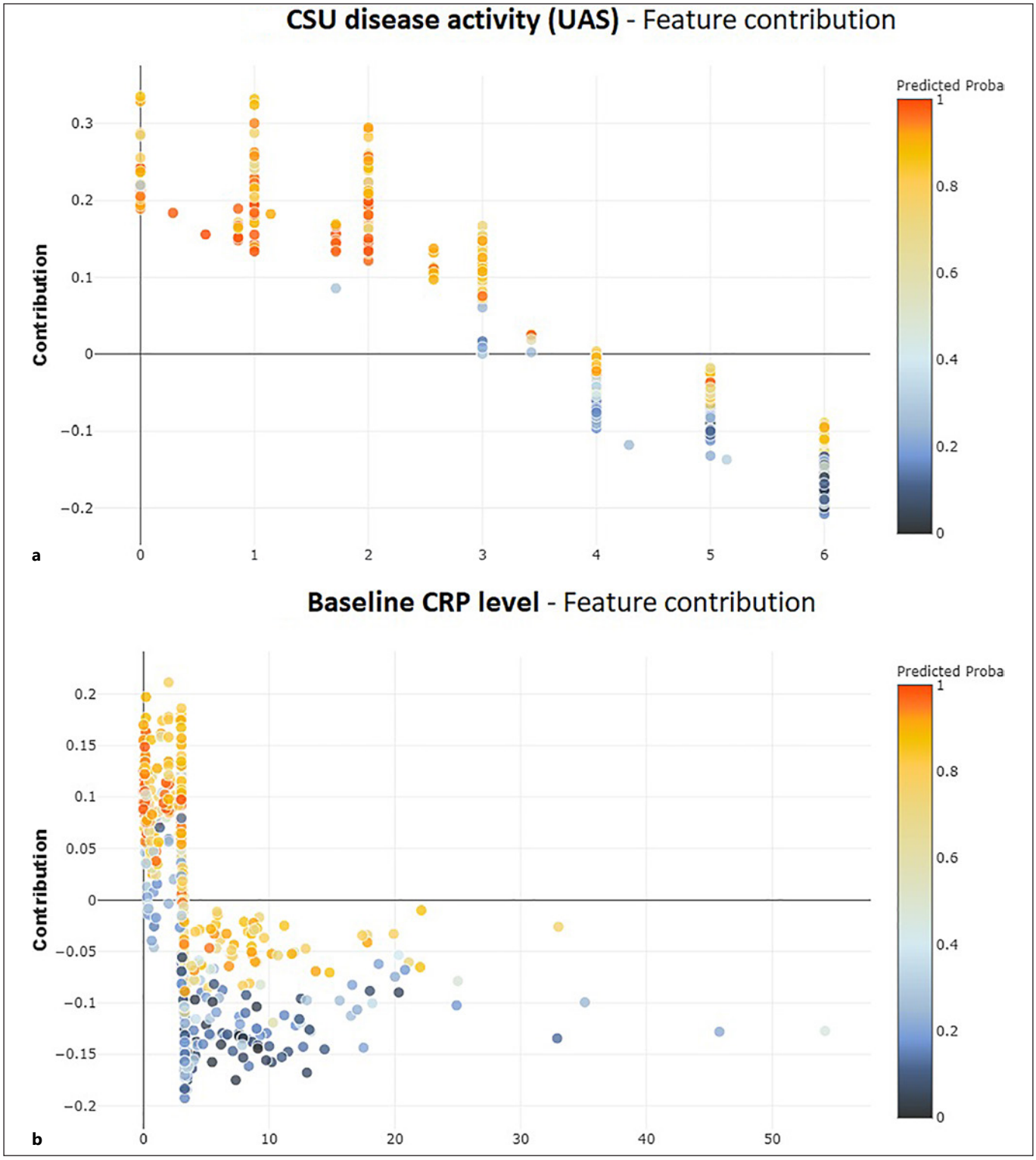

Fig. 4. Contribution plot of UAS (**a**) and CRP (**b**) in Random Forest ML model. Prediction probabilities of having higher than standard-dosed AH complete response were scaled from high average prediction probability (red points) to low prediction probability (black points). The vertical black lines where the contribution is equal to 0 are the cut-offs of the features which was 3 for UAS and 3.4 mg/mL for CRP. We found that higher disease activity (especially UAS >3) and CRP levels (especially >3.4 mg/mL) increased the probability of having higher than standard-dosed AH insufficient response.

Table 4. Comparing characteristics of the patients with higher than standard-dosed AH complete or insufficient response

Parameters	Higher than standard-dosed AH complete response (n = 223)	Higher than standard-dosed AH insufficient response (n = 188)	p value
Age	34 (19–47)	38 (28.3–47)	**0.013**
Female gender	155 (69.5)	132 (70.2)	0.877
Presence of angioedema	115 (51.6)	124 (66)	**0.001**
Concomitant CIndU	102 (45.7)	77 (41)	0.330
Duration of the disease in months	12 (4–48)	36 (12–96)	**<0.001**
Total baseline IgE level; IU/mL	90 (28.5–182.1)	99.2 (38–232.3)	0.178
Baseline CRP level; mg/L	3.02 (1.7–4.29)	3.31 (3–7.84)	**<0.001**
ANA positivity	53 (23.8)	42 (22.3)	0.733
IgG-anti-TPO positivity	37 (16.6)	48 (25.5)	**0.005**
Presence of concomitant autoimmune diseases	70 (31.4)	65 (34.6)	0.493
Presence of atopy	98 (43.9)	81 (43.1)	0.861
Baseline disease activity	3 (2–5)	5 (4–6)	**<0.001**
Presence of asthma	41 (18.4)	30 (16)	0.517

Table 5. Binary logistic regression analysis for predicting higher than standard-dosed AH complete response in patients with CSU

	Univariate			Multivariate		
	OR	CI (95%)	p value[a]	OR	CI (95%)	p value[b]
Age	1.017	1.004–1.029	**0.008**	1.019	1.005–1.034	**0.009**
Female gender	1.034	0.677–1.579	0.877			
Presence of angioedema	1.82	1.22–2.714	**0.003**	1.621	1.018–2.582	**0.042**
Presence of concomitant CIndU	0.823	0.556–1.218	0.33			
Duration of the disease in months	1.004	1.001–1.006	**0.008**			
Total baseline IgE	1.001	1–1.001	**0.154**	1.001	1–1.002	**0.03**
Baseline CRP	1.059	1.020–1.100	**0.003**			
ANA positivity	0.923	0.582–1.464	0.733			
IgG-anti-TPO positivity	1.724	1.065–2.79	**0.027**			
Presence of any concomitant autoimmune diseases	1.155	0.764–1.745	0.494			
Presence of atopy	0.966	0.653–1.428	0.861			
Baseline disease activity	1.978	1.697–2.307	**<0.001**	2.009	1.713–2.356	**<0.001**

[a] Variables with $p < 0.2$ were included in binary logistic regression analysis. [b] $p < 0.05$ was considered significant.

complete control in adult high-dose AH complete responders was linked to lower rates of angioedema (38 vs. 62%; $p = 0.008$), less disease activity (3 [2–5] vs. 5 [4–6]; $p < 0.001$), and lower CRP levels (3.1 [2.2–5.8] vs. 3.5 [3.2–8.2]; $p < 0.001$). When we performed binary logistic analyses in pediatric and adult patients separately, lower disease activity ($p = 0.05$; OR: 1.377; 95% CI: 0.996–1.903) was the only predictor in children with CSU, whereas the absence of angioedema ($p = 0.029$; OR: 1.779; 95% CI: 1.060–2.988) and lower disease activity ($p < 0.001$; OR: 2.213; 95% CI: 1.841–2.660) were independent predictors of higher than standard-dosed AH complete response in adults.

Discussion

In this study, low CSU disease activity, which was assessed by UAS, emerged as the only universal predictor of complete response to AH treatment across all clinical and laboratory parameters included, using ML models and traditional statistics, in children and adults, for standard and higher than standard doses. We also identified optimal cut-off values for disease activity to predict complete response to standard-dosed (UAS <3) and higher than standard-dosed (UAS <4) antihistamine treatment.

Our findings complement those of earlier studies that link CSU disease activity and response to antihistamine treatment [19–21]. In their recent comprehensive review on predictors of treatment failure in CSU, Fok and coworkers showed that high disease activity, high baseline CRP and D-dimer levels are markers of nonresponse or poor response to treatment with sgAHs [14]. In our study, low disease activity was linked to high response rates, and, vice versa, high disease activity had a 1.5-fold increased risk for standard-dose AH resistance and nearly 2-fold increased risk for high-dose AH resistance. Since CSU is a disease with fluctuating disease activity, it has been advised to record daily UAS values for at least 4 consecutive days or 7 days if possible, which the retrospective design of our study did not permit us to do [22]. Rather, disease activity in our study was determined by a single in-house UAS documentation. Although other studies used the UAS7 and found high values to be predictive of AH resistance, we will need prospective studies to show that the UAS7 or other validated tools like urticaria control test (UCT), when low, predict AH complete response [23–25].

Importantly, our study offers important insights on CSU in children, an under-researched population. CSU is as frequent in pediatric patients as it is in adults [26], and the international urticaria guideline advises the same treatment plan for children as for adults [3]. As of now, data on predictors of response to antihistamines in the pediatric CSU population are very limited. In our study, nearly one-fourth of patients were children. As shown by both traditional statistical methods and ML model, low disease activity was, like in adults with CSU, the only common parameter that predicted complete response to a high-dosed antihistamine. Similar to our findings, Park et al. [27] showed that higher initial UAS values can predict inadequate treatment response in children. Both studies, the one by Park and coworkers as well as ours, indicate the need for disease activity to be regularly monitored with a validated tool in this population. The challenge with this is that we do not have such a tool as the UAS7 is not yet validated for use in children with CSU.

We also demonstrate that ML models that jointly consider several patient and disease features can offer an innovative way to predict the response of treatment and can be applied to CSU. Importantly, individual models, in our case, Linear Regression and Random Forest Classifier models, can show better accuracy and F1 scores than others, so various models should be compared for their outcomes. Our study also showed some differences between the outcomes of the use of traditional statistical and ML methods for both standard-dosed and higher than standard-dosed AH response predictors. Even though method comparison was not an aim of this study, one can ask whether the predictions with one method are superior to other one. Here, it is important to note that there is no strict boundary between the two. Statistics and ML are both used for predicting future behavior. The focus of the former is to infer, e.g., to identify how a disease behaves by quantifying how strongly parameters are linked. Its strength lies with datasets where the number of patients is greater than the number of variables, as is the case in our study. In contrast, ML models focus on the identification of generalizable predictive patterns, and the primary concern is an accurate prediction. They work best where the number of parameters analyzed exceeds the number of patients [28]. Clearly, with larger datasets available, ML has become a valuable tool [29, 30]. The accuracy of predicting standard and higher than standard-dosed AH responses was quite similar for both traditional statistical and ML methods in our study (62 vs. 66% for standard dose and 77 vs. 74% for high dose), and it is not possible for us to identify results from one method as superior. Importantly, both models consistently demonstrated low CSU disease activity as a predictor and support each. ML, which is becoming more widely utilized in medicine and clinical research, is not a magical technology but rather a potential natural extension of existing statistical methods [30]. In future studies, the results of both methods should be carefully analyzed in order to obtain more valid and robust data.

How can the results of our study help improve the management of CSU? First, our results stress the importance of assessing disease activity in all patients, ideally every day and with the help of validated tools such as the UAS7. Complete response, the explicit aim of treatment, can only be secured when properly measured. Second, our report increases awareness of this, i.e., the importance of aiming for complete response rather than "benefit" or "improvement." Third, we emphasize the need to closely monitor treatment responses in patients with high disease activity and to step up treatment as needed in these patients with their increased risk of not achieving complete response. Finally, and most importantly, our findings enable physicians who treat patients with CSU to better predict who will show complete response. When communicated upon starting antihistamine treatment, this may lead to increased patient confidence that their treatment will work, which may translate to improved outcomes.

Our study has some limitations. (1) The retrospective nature of the study led to a limited range of possible predictive parameters and loss of patient data due to missing values. (2) The standalone use of UAS-based physician global assessment for assessing disease activity does not bring on board the angioedema component of CSU. Thus, we cannot say if disease activity in CSU patients who only or predominantly exhibit angioedema (rather than whealing) predicts antihistamine complete response. Also, future prospective studies should include UAS7 documentation for determining disease activity before and after the initiation of treatment. (3) Complete response, defined here as the absence of itchy wheals and angioedema, could be argued to include normal QoL and complete control, which are linked with but not identical to zero disease activity. This should be addressed through the use of patient-reported outcome measures that assess QoL impairment and disease control in future studies. (4) Low AUC and specificity scores might limit the clinical application of our results. Even though we had a quite large patient population, we believe future studies with larger cohorts may overcome this limitation.

The strengths of this study are that it was a multicenter, multinational study that included both pediatrics and adults, and the consistency of the results was tested with different methods such as ML models and traditional statistical methodology. In conclusion, we found lower CSU disease activity to universally predict complete response to AH treatment, and all patients of all ages should, therefore, be assessed for their disease activity at every visit. Although the new international urticaria guideline comes with a more dynamic treatment decision and adjustment approach [3], it still recommends a fixed treatment algorithm with fixed intervals for all patients. Our increasing knowledge of predictors of complete response and treatment resistance to specific treatments could help develop more targeted treatment algorithms based on patient and disease parameters. Our study encourages physicians to consider advising and counseling patients with low baseline disease activity differently than those with high baseline disease activity, which may improve compliance and other outcomes.

Statement of Ethics

The study was approved by the Institutional Review Board (Kayseri City Hospital, Clinical Research Ethical Committee, decision no/date: 498/November 04, 2021), and written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

Murat Türk has no relevant conflict of interest in relation to this work. Outside of it, Murat Türk is or recently was a speaker and/or advisor for Novartis. Ragıp Ertaş has no relevant conflict of interest in relation to this work. Outside of it, Ragıp Ertaş is or recently was a speaker and/or advisor for Novartis, AbbVie, Janssen, and Pfizer. Pavel Kolkhir has no relevant conflict of interest in relation to this work. Outside of it, Pavel Kolkhir is or recently was a speaker and/or advisor for Novartis. Ümit Murat Şahiner has no relevant conflict of interest in relation to this work. Outside of it, Ümit Murat Şahiner is or recently was a speaker and/or consultant for Expansiense Lab Mustela. Bülent Enis Şekerel has no relevant conflict of interest in relation to this work. Outside of it, Bülent Enis Şekerel is or recently was a speaker and/or advisor for Abdi İbrahim, Novartis, Sandoz, Sanofi, and Synevo Laboratories. Özge Soyer has no relevant conflict of interest in relation to this work. Outside of it, Özge Soyer was a speaker and/or advisor for CSL Behring, Novartis, GSK, and AstraZeneca. Atıl Avcı has no relevant conflict of interest in relation to this work. Outside of it, Atıl Avcı is or recently was a speaker and/or advisor for Novartis, AbbVie, and Janssen. Mustafa Atasoy has no relevant conflict of interest in relation to this work. Kemal Özyurt has no relevant conflict of interest in relation to this work. Yekta Türk has no relevant conflict of interest in relation to this work. Engin Zeydan has no relevant conflict of interest in relation to this work. Marcus Maurer has no relevant conflicts of interest in relation to this work. Marcus Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, Argenx, AstraZeneca, Celldex, Centogene, CSL Behring, FAES, Genentech, GIInnovation, Gilead, Innate Pharma, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Roche, Sanofi/Regeneron, Third Harmonic Bio, UCB, and Uriach.

Funding Sources

No funding was received for this study.

Author Contributions

Murat Türk, Ragıp Ertaş, Marcus Maurer, Engin Zeydan, and Yekta Türk designed this study. Murat Türk, Ragıp Ertaş, Ümit Murat Şahiner, and Pavel Kolkhir managed data entry and prepared the datasets. Murat Türk and Ümit Murat Şahiner performed statistical analysis. Engin Zeydan and Yekta Türk performed machine learning analysis. Murat Türk and Engin Zeydan wrote the manuscript. Marcus Maurer, Bülent Enis Şekerel, Özge Soyer, Atıl Avcı, Mustafa Atasoy, and Kemal Özyurt edited the manuscript. All authors provided critical feedback and helped shape the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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.
2 Maurer M, Abuzakouk M, Bérard F, Canonica W, Oude Elberink H, Giménez-Arnau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. Allergy. 2017;72(12):2005–16.
3 Zuberbier T, Abdul Latiff AH, Abuzakouk M, Aquilina S, Asero R, Baker D, et al. The international EAACI/GA2LEN/EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734–66.
4 Türk M, Yılmaz İ, Şahiner ÜM, Kocatürk E, Şekerel BE, Zuberbier T. Experience-based advice on stepping up and stepping down the therapeutic management of chronic spontaneous urticaria: where is the guidance? Allergy. 2022;77(5):1626–30.
5 Türk M, Ertaş R, Zeydan E, Türk Y, Atasoy M, Gutsche A. Identification of chronic urticaria subtypes using machine learning algorithms. Allergy. 2022;77(1):323–6.
6 Maurer M, Eyerich K, Eyerich S, Ferrer M, Gutermuth J, Hartmann K, et al. Urticaria: collegium internationale allergologicum (CIA) update 2020. Int Arch Allergy Immunol. 2020;181(5):321–33.
7 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.
8 Magen E, Waitman DA, Dickstein Y, Davidovich V, Kahan NR. Clinical-laboratory characteristics of ANA-positive chronic idiopathic urticaria. Allergy Asthma Proc. 2015;36(2):138–44.
9 de Montjoye L, Darrigade AS, Giménez-Arnau A, Herman A, Dumoutier L, Baeck M. Correlations between disease activity, autoimmunity and biological parameters in patients with chronic spontaneous urticaria. Eur Ann Allergy Clin Immunol. 2021;53(2):55–66.
10 Marzano AV, Genovese G, Casazza G, Fierro MT, Dapavo P, Crimi N, 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.
11 Gericke J, Metz M, Ohanyan T, Weller K, Altrichter S, Skov PS, et al. Serum autoreactivity predicts time to response to omalizumab therapy in chronic spontaneous urticaria. J Allergy Clin Immunol. 2017;139(3):1059–61.e1.
12 Sardina DS, Valenti G, Papia F, Uasuf CG. Exploring machine learning techniques to predict the response to omalizumab in chronic spontaneous urticaria. Diagnostics. 2021;11(11):2150.
13 Ye YM, Yoon J, Woo SD, Jang JH, Lee Y, Lee HY, et al. Clustering the clinical course of chronic urticaria using a longitudinal database: effects on urticaria remission. Allergy Asthma Immunol Res. 2021;13(3):390–403.
14 Fok JS, Kolkhir P, Church MK, Maurer M. Predictors of treatment response in chronic spontaneous urticaria. Allergy. 2021;76(10):2965–81.
15 Maurer M, Mathias SD, Crosby RD, Rajput Y, Zazzali JL. Validity and responsiveness of the urticaria activity and impact measure: a new patient-reported tool. Ann Allergy Asthma Immunol. 2018;120(6):641–7.
16 Shapash Python library (November-2021). Available from: https://github.com/MAIF/shapash.
17 PyCaret: an open source, low-code machine learning library (November-2021). Available from: https://pycaret.org/.
18 Luo W, Phung D, Tran T, Gupta S, Rana S, Karmakar C, et al. Guidelines for developing and reporting machine learning predictive models in biomedical research: a multidisciplinary view. J Med Internet Res. 2016;18(12):e323.
19 Magen E, Mishal J, Zeldin Y, Schlesinger M. Clinical and laboratory features of antihistamine-resistant chronic idiopathic urticaria. Allergy Asthma Proc. 2011;32(6):460–6.
20 Kolkhir P, Pogorelov D, Olisova O. CRP, D-dimer, fibrinogen and ESR as predictive markers of response to standard doses of levocetirizine in patients with chronic spontaneous urticaria. Eur Ann Allergy Clin Immunol. 2017;49(4):189–92.
21 Ayse Ornek S, Orcen C, Church MK, Kocaturk E. An evaluation of remission rates with first and second line treatments and indicators of antihistamine refractoriness in chronic urticaria. Int Immunopharmacol. 2022;112:109198.
22 Młynek A, Zalewska-Janowska A, Martus P, Staubach P, Zuberbier T, Maurer M. How to assess disease activity in patients with chronic urticaria? Allergy. 2008;63(6):777–80.
23 Curto-Barredo L, Archilla LR, Vives GR, Pujol RM, Giménez-Arnau AM. Clinical features of chronic spontaneous urticaria that predict disease prognosis and refractoriness to standard treatment. Acta Derm Venereol. 2018;98(7):641–7.
24 Ulambayar B, Yang EM, Cha HY, Shin YS, Park HS, Ye YM. Increased platelet activating factor levels in chronic spontaneous urticaria predicts refractoriness to antihistamine treatment: an observational study. Clin Transl Allergy. 2019;9:33.
25 Trinh HK, Pham DL, Ban GY, Lee HY, Park HS, Ye YM. Altered systemic adipokines in patients with chronic urticaria. Int Arch Allergy Immunol. 2016;171(2):102–10.
26 Balp MM, Weller K, Carboni V, Chirilov A, Papavassilis C, Severin T, et al. Prevalence and clinical characteristics of chronic spontaneous urticaria in pediatric patients. Pediatr Allergy Immunol. 2018;29(6):630–6.
27 Park YM, Oh MS, Kwon JW. Predicting inadequate treatment response in children with chronic spontaneous urticaria. Pediatr Allergy Immunol. 2020;31(8):946–53.
28 Bzdok D, Altman N, Krzywinski M. Statistics versus machine learning. Nat Methods. 2018;15(4):233–4.
29 Beam AL, Kohane IS. Big data and machine learning in health care. JAMA. 2018;319(13):1317–8.
30 Rajkomar A, Dean J, Kohane I. Machine learning in medicine. N Engl J Med. 2019;380(14):1347–58.