Graphical Abstract

Highlights

- Research highlight 1
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Abstract

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Keywords:

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1. Introduction

Urticaria is a common condition presenting with wheals, angioedema, or both, driven by mast cell degranulation(Zuberbier et al., 2021; Radonjic-Hoesli et al., 2018; Ring and Grosber, 2012). The lifetime prevalence for acute urticaria is approximately 20% (Zuberbier et al., 2021).

Urticaria is classified based on duration and triggers. Acute urticaria lasts less than 6 weeks, often triggered by specific causes like drugs, food, or infections. While chronic urticaria lasts more than 6 weeks and can be further classified into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU)(Zuberbier et al., 2021; Ring and Grosber, 2012).

CSU is characterized by the spontaneous occurrence of wheals and/or angioedema without a specific trigger and often associated with autoimmune mechanisms(Schettini et al., 2023), while CIndU is triggered by specific stimuli like cold, heat, or pressure(Pozderac et al., 2020).

The prevalence of CSU is approximately 0.5% in general population, and is less prevalent in children compared to adults(Balp et al., 2015; Poddighe, 2019; Labbene and Tekou, 2023). Some patients with CSU experience trigger-induced wheals, angioedema, or both. Up to 36% of patients with CSU have been reported to react concomitantly to physical trigger tests(Dressler et al., 2018). These triggers are not definite, as their presence does not always induce signs and symptoms and because wheals, angioedema, or both also occur without them, that is, spontaneously. Some patients can present with more than one subtype of urticaria(Zuberbier et al., 2021).

Chronic urticaria significantly impairs quality of life, affecting work and school performance. It is considered a severe allergic disease due to its disabling nature and high disease burden(Zuberbier et al., 2021). Predicting

the duration of urticaria, particularly chronic spontaneous urticaria (CSU), is crucial for effective patient management and treatment planning.

Duration of CSU greater than 3 years are associated with better responses to second-generation antihistamines and other treatments(Chiang et al., 2022).

Several factors have been associated with the severity and duration of chronic spontaneous urticaria (CSU). Higher age at onset, female gender, longer disease duration, and hypersensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) are linked to more severe CSU and prolonged time to remission (SanchezBorges et al., 2017; Rabelo-Filardi et al., 2013).

Patients exhibiting concomitant inducible urticaria and recurrent angioedema also tend to experience longer durations of CSU (SanchezBorges et al., 2017; Curto-Barredo et al., 2018).

In pediatric cases, significant predictors of the duration of acute urticaria include age, specific clinical presentations, coexistent pyrexia or angioedema, and personal histories of allergic diseases, particularly atopic dermatitis (Lin et al., 2011). Moreover, patients with multiple allergic conditions are more likely to have prolonged episodes of urticaria (Lin et al., 2011).

Potential biomarkers for CSU severity and duration have been identified. Positive autologous serum skin test (ASST) results, basophil counts, levels of inflammatory markers, activation markers of the extrinsic coagulation pathway, immunoglobulin E (IgE), and vitamin D levels are all associated with the disease's severity and duration (SanchezBorges et al., 2017; Rabelo-Filardi et al., 2013). Specifically, plasma levels of prothrombin fragment, D-dimer, and C-reactive protein (CRP) may serve as markers of CSU severity (Rabelo-Filardi et al., 2013). Serum diamine oxidase (DAO) levels have been linked to the response to antihistamines and dietary interventions, indicating a potential role in predicting disease duration (Chiang et al., 2022).

Metabolic factors also play a role, with high waist circumference (WC), rather than high body mass index (BMI), emerging as a predictive risk factor for longer disease duration in CSU patients (Kim et al., 2021).

Machine learning models have been used in predicting duration object in circumstances such as ICU stay and COVID-19 hospitalization(Wu et al., 2021; Ghosh et al., 2022; Etu et al., 2022).

The aim of this study was to build a machine learning model for predicting the disease duration of urticaria based on clinical laboratory data and to identify the factors affecting the disease duration of chronic urticaria by analyzing the importance of variables in the model, hoping to provide a

reference for the clinical management of urticaria.

2. Methods

2.1. Patients

patients with urticaria were recruited from the urticaria specialty clinic of the dermatology department of Shanghai XinHua Hospital affiliated to Shanghai Jiao Tong University School of Medicine from January 2018 to December 2024. The inclusion criteria were as follows: (1) patients diagnosed with urticaria according to the EAACI/GA2LEN/EDF/WAO guidelines(Zuberbier et al., 2021); (2) patients with complete clinical and laboratory data; (3) patients with stable follow-up indicated by at least 3 times of follow-up visits. the exclusion criteria were as follows: (1) patients with other skin diseases; (2) patients with severe systemic diseases; (3) patients with incomplete clinical data. The study was approved by the ethics committee of Shanghai XinHua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, and all patients provided written informed consent.

2.2. Data collection and processing

the data of patients with urticaria were collected from the electronic medical record system of the hospital, including demographic data, clinical data, laboratory data. the data were stored in a mysql database for subsequent analysis as follows: (1) Patients: containing basic information of each unique patient; (2) OutpatientNumbers: storing relationship between outpatient numbers with unique patient; (3) PatientVisits: containing visit events records; (4) PatientExaminations: containing the examination events records; (5) ExaminationItems: a dictionary table describing the examination items. the database schema is shown in database.dbml in supplementary materials.

2.3. Feature extraction and feature engineering

Disease duration, calculated by the difference between the first visit date and the last visit date, was the target variable. The disease duration was calculated in days. The following features were extracted from the database: (1) demographic data: gender, first visit age; (2) clinical data: concomitant inducible urticaria; (3) laboratory data: results from common blood tests, CRP, immunoglobulin,25-hydroxyvitamin D, Thyroid function, autoantibodies, coagulation function, common urine tests, and allergen specific IgE tests.

For laboratory data, 2 types of features were extracted: time-independent features and time-dependent features. Time-independent features are average values of laboratory data during the whole follow-up period, while time-dependent features are average values of laboratory data durting pre-clincial phase (before the onset of urticaria), acute phase (within 6 weeks after the onset of urticaria), and chronic phase (after 6 weeks of the onset of urticaria). 2 datasets were generated: one with time-independent features and one with time-dependent features, and were compared for prediction performance in the model development process. The sql queries for data are shown in feature_extraction.sql in supplementary materials.

2.4. Model development and comparison

Dataset was split into training set and test set with a ratio of 7:3. 5 models were adopted for comparison: Xgboost, random forest, adaboost, gradient boosting machine (GBM), and support vector machine (SVM). Hyperparameter optimization was performed using TPE algorithm by nni package in python, which is a bayesian optimization algorithm that uses tree-structured parzen estimator to model the objective function and suggest the next set of hyperparameters to evaluate based on the previous results. Internal 5 fold cross-validation was employed to discern the most suitable hyperparameters for each distinct model, individually applied to each model for enhanced performance. The performance of the model and data was evaluated by receiver operating characteristic (ROC) curve, area under the curve (AUC), accuracy, precision, recall and F1 score on different cuttoffs of disease duration. The model and data with the best performance were selected for further analysis.

2.5. feature selection

Too many features can lead to overfitting and reduce the interpretability of the model. Therefore, feature selection was performed on final model for further optimization. The feature importance was calculated by boruta algorithm, which is a wrapper algorithm that evaluate the importance of each feature by comparing it with the importance of random features. Boruta algorithm-assisted feature selection was used to restrict the number of features in accordance with feature importance rank; thereby, the final model with the best predictive ability in the process of reducing features was chosen for further analysis.

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2.6. Model explanation

The shapley value of each laboratory item in different phase of disease were compared to reveal various predicting ability of laboratory data in different phase of disease. To further verify the tendency oberserved in shapley values, kernal density estimation was used to visualize the distribution of average values of laboratory data in different phase of disease for patients with different disease duration. Shapley values together with kernal density estimation were used to explain the model and provide insights for clinical practice. Some of the features were further analyzed with different age populations to explore the potential age effect on the predicting ability of laboratory data.

3. Results

3.1. Patient characteristics

Table Appendix A and Table Appendix A provides a comparison of the baseline characteristic between the training set and external testing set data. No substantial differences were observed between the training set and the external test set across the majority of features in either time independent or time dependent data.

Table 1 and Table 2 delineates the disparities between groups regarding the disease duration of patients in dataset.

Mean Corpuscular Hemoglobin Concentration (MCHC) shows a consistent increase across both tables for patients with poor outcomes. In the time-independent dataset, the value is significantly higher in the poor outcome group (336.93 ± 11.66, $P = 0.000$) compared to the good outcome group (335.20 ± 12.03, $P = 0.000$). Similarly, in the time-dependent dataset, across all phases (acute, chronic, preclinical), the poor outcome group consistently has higher MCHC values. This suggests that **MCHC** is a reliable indicator across both time frames, indicating a similar physiological pattern regardless of time-dependent stratification.

In the time-independent dataset, the difference in **Lymphocytes Percentage** between the good and poor outcome groups is significant (28.78 ± 14.10 vs. 34.10 ± 13.86, $P = 0.000$). However, in the time-dependent dataset, more nuanced trends are observed. The values differ between preclinical, acute, and chronic phases, with significant differences seen in the acute phase (32.08 ± 12.37 vs. 33.21 ± 14.03, $P = 0.082$), while no major trend appears in

the chronic and preclinical phases. This shows that time-dependent analysis can uncover subtle temporal patterns not evident in static analysis.

In the time-independent dataset, there is a significant difference between good and poor outcomes for **Neutrophils Percentage** (63.44 ± 15.76 vs. 56.59 ± 14.96, $P = 0.000$). However, in the time-dependent dataset, the trend changes across preclinical, acute, and chronic phases. For example, in the acute phase, the difference remains significant (58.60 ± 13.68 vs. 57.78 ± 14.94, $P = 0.014$), while in the preclinical phase, the difference is less pronounced (52.85 ± 18.14 vs. 52.44 ± 17.90, $P = 0.024$), and in the chronic phase, the trend reverses with poor outcomes having higher neutrophil percentages. This highlights the importance of considering temporal variations when analyzing clinical indicators.

Characteristic	Good Outcome	Poor Outcome	P-value
Number of patients	2027	1927	
Outcome	25.37 ± 25.09	604.32 ± 437.04	$0.000 \uparrow$
Gender	0: 64.7%, 1: 35.3%	0: 61.1%, 1: 38.9%	0.023
First Visit Age	30.12 ± 21.79	28.11 ± 23.61	$0.005 \downarrow$
CI nd U	0: 99.3%, 1: 0.7%	0: 97.2%, 1: 2.8%	0.000
Lymphocytes Percentage	28.98 ± 14.05	34.02 ± 13.88	$0.000 \uparrow$
Neutrophils Percentage	63.13 ± 15.68	56.63 ± 14.97	$0.000 \downarrow$
Monocytes Percentage	6.18 ± 1.64	6.49 ± 1.67	$0.000 \uparrow$
Mean Corpuscular Hemoglobin Concentration	335.62 ± 10.51	336.93 ± 10.30	$0.000 \uparrow$
Platelet Count	263.47 ± 74.09	256.73 ± 68.96	$0.003 \downarrow$
White Blood Cell Count	10.31 ± 3.00	9.35 ± 2.39	$0.000 \downarrow$
Mean Corpuscular Hemoglobin	29.07 ± 2.33	28.98 ± 2.30	0.202
Mean Corpuscular Volume	86.66 ± 6.65	85.99 ± 6.67	$0.002 \downarrow$
Hemoglobin	130.03 ± 9.16	130.20 ± 8.46	0.546
Eosinophils Percentage	1.55 ± 2.02	2.31 ± 2.37	$0.000 \uparrow$
Basophils Percentage	0.25 ± 0.22	0.32 ± 0.24	$0.000 \uparrow$
Absolute Eosinophil Count	0.13 ± 0.20	0.18 ± 0.21	$0.000 \uparrow$
Absolute Lymphocyte Count	2.61 ± 1.12	2.83 ± 1.29	$0.000 \uparrow$
Mean Platelet Volume	9.14 ± 1.39	9.02 ± 1.39	$0.007 \downarrow$
Platelet Distribution Width	12.72 ± 1.96	12.57 ± 1.94	$0.020 \downarrow$
Eosinophil Count Absolute	128.60 ± 141.68	162.83 ± 190.02	$0.000 \uparrow$
CR eactive Protein	13.03 ± 19.62	7.71 ± 10.23	$0.000 \downarrow$
Immunoglobulin E	131.65 ± 242.00	152.28 ± 346.75	$0.029 \uparrow$
SMRNP	1.18 ± 2.16	1.22 ± 1.84	0.576
Anti SSA	1.42 ± 5.44	1.58 ± 5.68	0.363
Anti Jo 1	1.08 ± 1.77	1.12 ± 2.06	0.534
Nucleosome	0.57 ± 0.34	0.65 ± 0.43	$0.000 \uparrow$
Ribosomal PP rotein	1.07 ± 0.71	1.17 ± 2.13	0.050
Ro 52	2.10 ± 5.90	2.23 ± 6.81	0.515

Table 1: Comparison of the characteristics between patients with good and poor outcomes in the time independent dataset
continuous variables are presented as mean $\pm$ standard deviation, categorical variables are presented as number (percentage)
good outcome is defined as visit duration < 100 days, poor outcome is defined as visit duration ≥ 100 days

Characteristic	Good Outcome	Poor Outcome	P-value
Number of patients	1202	746	
Outcome	14.68 ± 22.61	631.42 ± 448.34	0.000 ↑
Gender	0: 84.6%, 1: 15.4%	0: 77.3%, 1: 22.7%	0.000
First Visit Age	22.60 ± 21.58	22.26 ± 23.12	0.746
CI nd U	0: 99.4%, 1: 0.6%	0: 98.5%, 1: 1.5%	0.079
Lymphocytes Percentage preclinical	37.86 ± 14.45	40.34 ± 15.16	0.000 ↑
Lymphocytes Percentage chronic	35.37 ± 9.29	36.50 ± 11.95	0.019 ↑
Lymphocytes Percentage acute	32.37 ± 14.25	34.65 ± 13.91	0.001 ↑
Neutrophils Percentage chronic	54.34 ± 10.18	53.71 ± 12.76	0.229
Neutrophils Percentage acute	59.48 ± 15.77	56.92 ± 14.85	0.000 ↓
Neutrophils Percentage preclinical	51.40 ± 15.89	48.94 ± 16.49	0.001 ↓
Monocytes Percentage acute	6.23 ± 1.08	6.23 ± 1.04	0.937
Monocytes Percentage chronic	6.53 ± 0.77	6.53 ± 1.22	0.980
Monocytes Percentage preclinical	6.66 ± 1.03	6.70 ± 0.82	0.359
Mean Corpuscular Hemoglobin Concentration acute	336.49 ± 12.49	338.59 ± 12.85	0.000 ↑
Mean Corpuscular Hemoglobin Concentration chronic	333.82 ± 4.53	334.04 ± 8.74	0.457
Mean Corpuscular Hemoglobin Concentration preclinical	343.26 ± 6.90	343.88 ± 7.38	0.058
Platelet Count acute	260.29 ± 69.51	258.81 ± 62.12	0.634
Platelet Count chronic	253.50 ± 31.29	257.54 ± 57.28	0.044 ↑
Platelet Count preclinical	252.05 ± 52.40	255.30 ± 50.00	0.176
White Blood Cell Count acute	10.06 ± 3.20	9.56 ± 2.56	0.000 ↓
White Blood Cell Count preclinical	8.65 ± 2.05	8.52 ± 1.81	0.179
White Blood Cell Count chronic	8.44 ± 1.00	8.67 ± 2.31	0.003 ↑
Mean Corpuscular Hemoglobin preclinical	28.47 ± 1.63	28.30 ± 1.73	0.027 ↓

3.2. Comparison of multiple models on time-dependent and time-independent data

time independent and time dependent data were used to generate 5 machine learning models to predict the disease duration of urticaria. Among the 10 models, Xgboost model with time dependent data (AUC =) has the best predictive effect for disease duration, followed by random forest with time dependent data (AUC =) .The discriminative performances of these 10 models are listed in Supplementary Table S3, and the ROC curves for the top three best-performing ML models are presented in Fig. 2, respectively.

3.3. Feature selection and final model

Xgboost with time dependent data, as the best performing model, was selected for further optimization. During the process of reducing features based on the feature important rank calculated by boruta algorithm, the changes in AUCs for the model shows that the model maintain robust performance unitil the number of features reduced to less than 10. The performance of the RF model with varied numbers of features is displayed in Fig. 2C and Supplementary Table S4. The sensitivity, specificity, PPV, NPV, accuracy, and F1 score were calculated at the optimal cutoff value that maximized the Youden index.

3.4. Model explanation

4. Discussion

Although the pathogenesis of CSU is not yet fully understood, it is well established that its signs and symptoms are due to the activation of mast cells and basophils, leading to the release of histamine and other inflammatory mediators(Zuberbier et al., 2021).

Based on recent evidence, it is known that the causes of CSU include autoimmunity Type I (CSUaiTI, or "autoallergic CSU"; with IgE autoantibodies to self-antigens) and autoimmunity Type IIb (CSUaiTIIb; with mast cell–directed activating autoantibodies). In CSU due to unknown cause (CSUuc), as of yet unknown mechanisms are relevant for the degranulation of skin MC(Sella et al., 2023; Maronese et al., 2023).

The results of the basic tests performed in CSU can point to CSUaiTI vs CSUaiTIIb, with CRP more often elevated and eosinophil and basophil levels more often reduced in CSUaiTIIb(Xiang et al., 2023). Other underlying causes include active thyroid disease, infections, inflammatory processes,
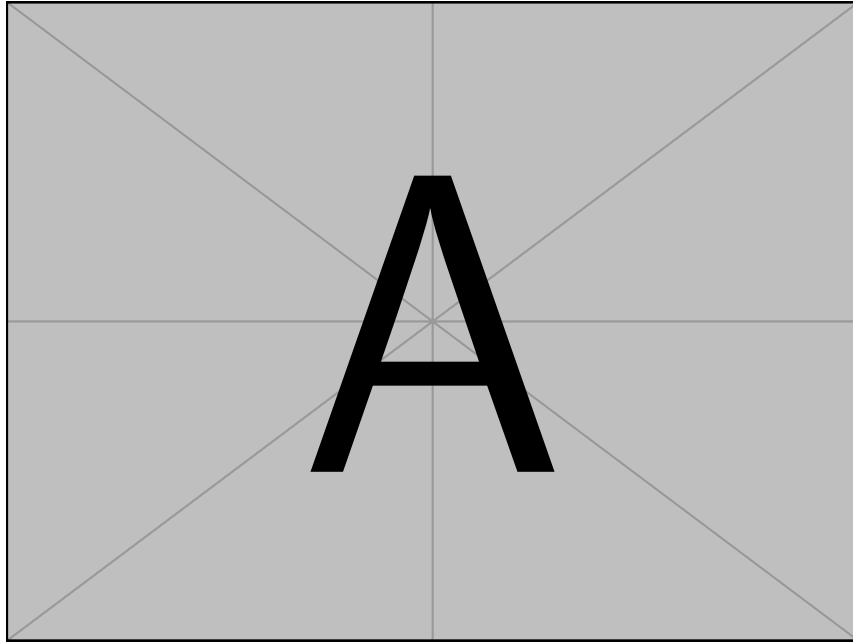
Figure 1: Figure Caption

food, and drugs but these can be both cause as well as only aggravating factor(Kolkhir et al., 2021)

Appendix A. Supplementary data

Supplementary Table1: Comparison of the characteristic between the training set and external testing set data in the time independent dataset

Supplementary Table2: Comparison of the characteristic between the training set and external testing set data in the time dependent dataset

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