

## Graphical Abstract

## Highlights

- Research highlight 1
- Research highlight 2

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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 during pre-clinical 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 cutoffs 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.

1	2	3
4	5	6
7	8	9

Table 1: Table Caption

## 2.6. Model explanation

## 3. Results

### 3.1. Patient characteristics

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

### 3.3. Feature selection and final model

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

## Appendix A. Example Appendix Section

Appendix text.

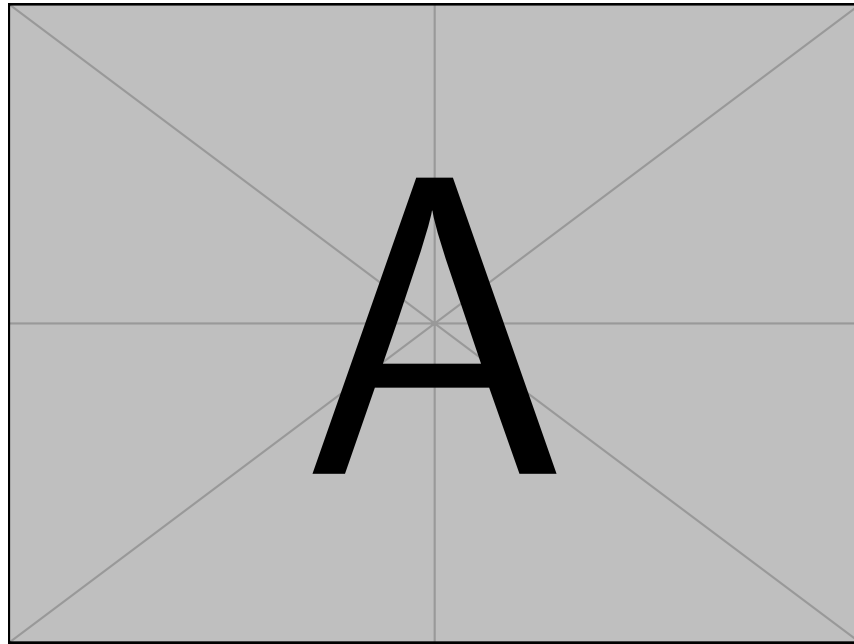


Figure 1: Figure Caption

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