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Original Article

Predictive value of baseline hematological parameters for the risk of recurrence in chronic urticaria

Weijie Chen[1*], Ming Gao[2*]

[1]Clinical Laboratory, The Third Hospital of Yinzhou District, Ningbo 315000, Zhejiang, China; [2]Department of Dermatology, The Third Hospital of Yinzhou District, Ningbo 315000, Zhejiang, China. [*]Equal contributors.

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Abstract: Objective: To investigate the predictive value of baseline hematological parameters for 1year recurrence risk of chronic urticaria (CU) and to construct a clinically practical prediction model. Methods: This retrospective study enrolled 155 newly diagnosed CU patients, with an additional 48 independent patients included for external validation. Baseline clinical characteristics and haematological parameters, including total IgE, C-reactive protein (CRP) and D-dimer (DD), were collected. Univariate and multivariate logistic regression analyses were performed to screen independent influencing factors for recurrence. A nomogram prediction model was subsequently established and comprehensively validated using receiver operating characteristic (ROC) curve, calibration curve, decision curve analysis and SHAP analysis. Kaplan-Meier survival curves and Cox regression analysis were adopted to evaluate recurrence-free survival outcomes. Results: Among the 155 enrolled patients, 41 developed disease recurrence, corresponding to a recurrence rate of 26.5%. Disease duration (OR = 1.07), total IgE level (OR = 1.01), CRP level (OR = 1.16) and DD level (OR = 1.01) were confirmed as independent predictive factors (all $P < 0.05$). The combined prediction model achieved an AUC of 0.83 (95% CI: 0.75-0.90), with favorable calibration performance (Hosmer-Lemeshow test, $P = 0.446$) and stable net clinical benefit within the risk threshold range of 10%-90%. External validation results demonstrated an accuracy of 79.2%, a specificity of 78.4% and a negative predictive value of 93.5%. Patients with disease duration ≥ 20.5 months, total IgE ≥ 173.7 KU/L, CRP ≥ 11.7 mg/L or DD ≥ 142.8 ng/mL had significantly shorter recurrencefree survival time ($P < 0.05$). Conclusion: Baseline disease duration, total IgE, CRP and D-D are independent predictors of 1-year recurrence in CU patients. The constructed nomogram model exhibits reliable predictive performance and good clinical applicability, which can serve as a convenient tool for early recurrence risk stratification and individualized clinical management of CU patients.

Keywords: Chronic urticaria, recurrence, hematological parameters, prediction model, nomogram

Introduction

Chronic urticaria (CU) is a skin disorder characterized by recurrent wheals and/or angioedema [1]. Approximately 1% of the global population suffers from CU, and its incidence is continuously rising [2, 3]. The protracted course of this disease severely impairs patients' quality of life and mental health, and also increases their social and economic burdens [4]. Although modern medicine has deepened the understanding of CU pathogenesis, especially mast cell activation, autoimmune mechanisms and chronic inflammatory mechanisms, CU still remains a tough clinical challenge [5, 6]. Disease recurrence is the primary bottleneck in CU treatment [7]. A large proportion of patients experience relapse after symptom relief when tapering or discontinuing first-line medications, which prolongs treatment courses and raises medical expenses [8]. Therefore, early identification of patients at high recurrence risk to implement individualized therapeutic adjustments and optimize long-term management strategies has become an urgent clinical problem to be solved.

CU is not merely a simple cutaneous disease. Moreover, a close correlation exists between CU and systemic inflammatory status [9, 10]. In this context, routine hematological indicators have regained scholarly attention due to their easy accessibility, low cost and favorable repeatability [11]. Previous studies have con-

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firmed that a large number of CU patients present abnormal baseline eosinophil proportion, C-reactive protein (CRP), immunoglobulin levels, and other laboratory markers [12, 13]. Although numerous studies have explored the correlations between hematological parameters and disease activity as well as treatment response of CU, few studies have focused on the predictive value of baseline hematological parameters for CU recurrence risk.

Given the above research status, this retrospective study was conducted. We collected clinical data and patients newly diagnosed with CU to analyze the correlations between routine hematological parameters and CU relapse This study aims to screen out effective predictive factors and establish a concise prediction model. Its core purpose is to identify objective and readily available biomarkers, so as to enable early clinical screening of CU patients at high recurrence risk. This strategy can further optimize diagnosis and treatment protocols, reduce recurrence rates and ultimately improve patients' long-term prognosis. The research results will also supplement the theoretical basis of CU recurrence mechanisms and provide references for subsequent precise treatment of CU.

Materials and methods

Patient population

This study was a single-center retrospective investigation. We initially screened 287 patients newly diagnosed with CU who initiated standardized treatment at the dermatology outpatient department of the Third Hospital of Yinzhou District between January 2019 and December 2022 via the electronic medical record system. Among them, 132 patients were excluded: 89 had incomplete follow-up data with less than 12 months of follow-up and no confirmed recurrence events, 35 were lost to follow-up, and 8 lacked key baseline hematological parameters. Ultimately, 155 patients were enrolled for subsequent analysis. For external validation, we recruited an independent cohort consisting of 48 consecutive CU patients diagnosed in the same hospital from January 2023 to October 2024, with identical inclusion and exclusion criteria and data collection protocols adopted as those for the modeling cohort. This study was approved by the Ethics Committee of the Third Hospital of Yinzhou District.

Inclusion and exclusion criteria

Inclusion criteria: (1) Aged 18 years or older; (2) Consistent with the diagnostic criteria specified in the Chinese Guidelines for the Diagnosis and Treatment of Urticaria (2022 Edition) [14], namely recurrent wheals and/or angioedema persisting for more than 6 weeks; (3) Newly diagnosed cases receiving standardized initial treatment in the mentioned hospital; (4) Complete baseline clinical data, hematological examination results and follow-up records available.

Exclusion criteria: (1) Combined with definite allergic diseases (allergic rhinitis, bronchial asthma, atopic dermatitis, allergic conjunctivitis), autoimmune diseases diagnosed in accordance with international multidisciplinary consensus, chronic inflammatory disorders or malignant tumors; (2) Suffered from acute viral, bacterial or fungal infections within 4 weeks before enrollment; (3) Received systemic glucocorticoid therapy within 4 weeks prior to baseline assessment; (4) Pregnant or breastfeeding females; (5) Accompanied by severe hepatic, renal, cardiovascular or hematological dysfunction; (6) Follow-up duration shorter than 12 months without recorded relapse. All comorbidities were strictly confirmed by two independent attending physicians by reviewing electronic medical records, past discharge notes, specialist diagnostic documents and autoimmune laboratory indicators to guarantee consistent and accurate exclusion.

Treatment regimens and definition of relapse

The Urticaria Activity Score over 7 days (UAS7) [15] was used to assess disease severity. As a validated patient-reported scale, UAS7 calculates the total score by summing daily wheal quantity scores (0-3) and pruritus severity scores (0-3) over seven days, with a total score ranging from 0 to 42. UAS7 scores were extracted from routine clinical records in this retrospective study. Patients filled out UAS7 questionnaires at home and submitted the finished forms during outpatient visits. Specially trained nurses checked the completeness of questionnaires and clarified ambiguous content together with patients, and attending dermatologists further confirmed the final scores.

Recurrence was defined as the reoccurrence of wheals and/or angioedema with a clinically meaningful UAS7 score ≥ 7 after patients achieved complete or partial remission (UAS7 ≤ 6) via initial treatment, which necessitated resumption or intensification of drug therapy. All recurrence cases were independently judged by two senior dermatologists with over five years of professional experience in CU diagnosis and management. Any inconsistent judgments were settled by a third senior dermatologist to ensure consistent and accurate assessment, and final results were verified based on follow-up clinical records. Only recurrence events occurring within 12 months after treatment initiation were included for analyzing the primary endpoint of 1-year recurrence rate. Events occurring beyond 12 months were censored in the prediction model but incorporated into overall survival analysis. All patients received standardized stepwise initial treatment, which generally began with conventional-dose second-generation H1 antihistamines. Dosage escalation or combined medication with H2 antihistamines, leukotriene receptor antagonists or omalizumab was conducted according to disease severity and therapeutic response.

Data collection

Two independent researchers retrospectively extracted all data from electronic medical records and nursing follow-up files. A third senior researcher conducted full cross-verification of all data, and inconsistencies were settled through group discussion. Inter-rater reliability was evaluated via the intraclass correlation coefficient (ICC) for continuous variables (ICC > 0.90) and the Kappa coefficient for categorical variables (Kappa > 0.85), confirming excellent inter-assessor consistency.

Baseline demographic and clinical information including age, gender, BMI, disease duration, CU subtype, presence of angioedema, baseline UAS7 score and initial treatment regimens were collected. Baseline hematological indicators were sourced from laboratory examinations completed within one week after diagnosis and prior to treatment initiation, covering total immunoglobulin E (IgE), C-reactive protein (CRP), D-dimer (D-D), eosinophil count (Eos #), basophil count (Baso #), white blood cell count (WBC), lymphocyte count (Lymph #), platelet count (PLT), and erythrocyte sedimentation rate (ESR). All laboratory results were issued by the Clinical Laboratory of The Third Hospital of Yinzhou District. Researchers only extracted these recorded data without participating in laboratory testing procedures. The laboratory adopts standardized detection protocols, regular internal quality control and instrument calibration to guarantee accurate and reliable test results.

Four-week treatment response was classified into good response (≥ 50% reduction in baseline UAS7 score or final UAS7 ≤ 6) and poor response (< 50% reduction in baseline UAS7 score). All follow-up data were retrospectively retrieved from routine clinical documents and nursing follow-up archives rather than specially organized prospective follow-up data. Routine clinical follow-up mainly included outpatient visits and telephone interviews, with follow-up intervals of 1 to 3 months within the 12-month observation period. No extra active follow-up was arranged for this study, and all adopted data were objective existing clinical records. Collected follow-up outcomes included 12-month recurrence status for model construction and overall follow-up duration for survival analysis.

Statistical analysis

All statistical analyses were conducted using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), and compared using the Student's t-test or Mann-Whitney U test, as appropriate. Categorical variables were presented as frequencies and percentages, and compared using the chi-square test.

Univariate and multivariate logistic regression models were applied to screen independent predictors of 1-year recurrence, and results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). The variance inflation factor (VIF) was used to detect multicollinearity, and VIF < 5 indicated no obvious multicollinearity. A nomogram was established based on the finalized multivariate regression model. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive efficacy of single indicators and the combined

model, and inter-group differences were compared using the DeLong test. Model calibration was verified via calibration curves and the Hosmer-Lemeshow test, while decision curve analysis was used to assess clinical net benefit. SHapley Additive exPlanations (SHAP) analysis was performed to interpret model outputs.

Kaplan-Meier survival curves combined with the log-rank test were used to compare recurrence-free survival stratified by optimal cut-off values determined via the Youden index. Bootstrap resampling with 1000 iterations was performed for internal validation to stabilize these cut-off values, and their 95% CIs were calculated based on bootstrap distributions. A multivariate Cox proportional hazards regression model was used to explore the independent correlation between continuous predictors and recurrence risk. A two-tailed *P* value < 0.05 was defined as statistically significant.

Results

Baseline characteristics of the study population

A total of 155 CU patients were enrolled, among whom 41 (26.5%) developed recurrence within one year. Compared with the non-relapsed group (n = 114), patients with recurrence had significantly longer disease duration (20.54 ± 8.70 vs. 16.48 ± 7.84 months, P = 0.007), higher baseline UAS7 scores (25.68 ± 4.52 vs. 23.26 ± 5.84, P = 0.008), inferior 4-week treatment response (P = 0.041), and higher proportion of receiving combined antihistamine therapy (P = 0.014). Baseline levels of total IgE, CRP and D-D were markedly elevated in the relapsed group (all P < 0.05, **Table 1**).

Identification of independent predictors for 1-year recurrence

Univariate logistic regression revealed that poor 4-week treatment response, combined antihistamine therapy, longer disease duration, higher baseline UAS7 score, as well as elevated IgE, CRP and D-D were correlated with increased 1-year recurrence risk (all P < 0.05, **Table 2**). Subsequent multivariate logistic regression screened out independent risk factors: disease duration (OR = 1.07, 95% CI: 1.01-1.13, P = 0.015), IgE (OR = 1.01, 95% CI: 1.01-1.02, P < 0.001), CRP (OR = 1.16, 95% CI: 1.04-1.28, P = 0.005), and D-D (OR = 1.01, 95% CI: 1.01-1.02, P = 0.007) (**Table 2**). All variables included in the multivariate model had VIF values < 5, indicating no significant multicollinearity.

Construction of the nomogram prediction model

On the basis of the four confirmed independent predictors, a nomogram (**Figure 1**) was constructed to calculate individual 1-year relapse probability. The logistic regression formula of this nomogram was as follows: Logit(P) = -7.25 + 0.08 × CU disease duration (months) + 0.01 × IgE (KU/L) + 0.14 × CRP (mg/L) + 0.01 × D-D (ng/mL).

ROC curve analysis was performed to assess the predictive efficiency of single indicators and combined models (**Figure 2**), and corresponding AUC values are summarized in **Table 3**. Among single indicators, total IgE exhibited the best discriminative ability (AUC = 0.70, 95% CI: 0.60-0.79). The combined model of three hematological indicators (IgE+CRP+D-D) yielded an AUC of 0.78 (95% CI: 0.70-0.87). The full combined model integrating the three hematological indicators and disease duration achieved the optimal predictive performance with an AUC of 0.83 (95% CI: 0.75-0.90). DeLong test results indicated that the AUC of the full combined model was significantly higher than that of all single predictors and the three-indicator hematological model (all P < 0.05), except for a marginal difference with the hematological combined model (P = 0.063). **Table 3** shows the accuracy, sensitivity, specificity, PPV, NPV and optimal cut-off values of each model.

Model calibration, clinical utility, and interpretation

Calibration of the full combined model was verified via calibration curves (**Figure 3A**), which showed favorable consistency between predicted and actual recurrence risks, consistent with the non-significant result of the Hosmer-Lemeshow test (P = 0.446). Decision curve analysis (**Figure 3B**) indicated that this model provided a superior net clinical benefit compared with the treat-all and treat-none strategies within the risk range of approximately 10% to 90%. SHAP analysis was adopted to improve model inter-

Table 1. Comparison of baseline characteristics and hematological parameters between relapsed and non-relapsed groups within one year

Variables	Total (n = 155)	Non-relapsed group (n = 114)	Relapsed group (n = 41)	Statistic	*P*
Age (year), Mean ± SD	43.84 ± 11.24	43.74 ± 11.53	44.12 ± 10.49	t = -0.19	0.851
BMI, Mean ± SD	24.58 ± 3.55	24.73 ± 3.45	24.19 ± 3.85	t = 0.83	0.406
Duration of CU (months), Mean ± SD	17.55 ± 8.24	16.48 ± 7.84	20.54 ± 8.70	t = -2.76	0.007
CU subtype, n (%)				χ^2 = 0.58	0.445
CSU	118 (76.13)	85 (74.56)	33 (80.49)		
CIU	37 (23.87)	29 (25.44)	8 (19.51)		
Baseline UAS7 score, Mean ± SD	23.90 ± 5.61	23.26 ± 5.84	25.68 ± 4.52	t = -2.71	0.008
Gender, n (%)				χ^2 = 0.93	0.334
Female	112 (72.26)	80 (70.18)	32 (78.05)		
Male	43 (27.74)	34 (29.82)	9 (21.95)		
Combined angioedema, n (%)				χ^2 = 0.32	0.570
No	89 (57.42)	67 (58.77)	22 (53.66)		
Yes	66 (42.58)	47 (41.23)	19 (46.34)		
Omalizumab treatment, n (%)				χ^2 = 0.59	0.442
No	122 (78.71)	88 (77.19)	34 (82.93)		
Yes	33 (21.29)	26 (22.81)	7 (17.07)		
Response after 4-week treatment, n (%)				χ^2 = 4.17	0.041
Good	89 (57.42)	71 (62.28)	18 (43.90)		
Poor	66 (42.58)	43 (37.72)	23 (56.10)		
Treatment plan, n (%)				χ^2 = 5.98	0.014
Antihistamine monotherapy	110 (70.97)	87 (76.32)	23 (56.10)		
Antihistamine combination	45 (29.03)	27 (23.68)	18 (43.90)		
IgE, M (Q_1, Q_3)	133.11 (71.23, 184.05)	127.61 (61.35, 159.86)	174.33 (107.21, 240.95)	Z = -3.71	< 0.001
CRP, M (Q_1, Q_3)	5.05 (2.66, 8.32)	4.42 (2.37, 7.57)	6.18 (3.60, 12.07)	Z = -2.40	0.016
D-D, M (Q_1, Q_3)	171.00 (118.89, 210.58)	162.24 (104.28, 206.17)	179.23 (154.64, 231.06)	Z = -2.96	0.003
Eos #, M (Q_1, Q_3)	0.21 (0.11, 0.27)	0.21 (0.11, 0.25)	0.22 (0.13, 0.29)	Z = -1.54	0.124
Baso #, M (Q_1, Q_3)	0.03 (0.01, 0.07)	0.03 (0.01, 0.07)	0.03 (0.02, 0.05)	Z = -0.32	0.748
WBC, M (Q_1, Q_3)	7.36 (5.58, 8.92)	7.22 (5.58, 8.80)	7.69 (6.02, 9.46)	Z = -1.19	0.233
Lymph #, M (Q_1, Q_3)	2.42 (1.74, 3.26)	2.42 (1.69, 3.25)	2.69 (1.85, 3.36)	Z = -0.85	0.395
PLT, M (Q_1, Q_3)	241.22 (194.95, 285.11)	241.11 (194.84, 278.80)	261.83 (195.82, 296.06)	Z = -0.74	0.462
ESR, M (Q_1, Q_3)	11.00 (7.00, 17.00)	10.50 (6.00, 17.00)	11.00 (8.00, 19.00)	Z = -0.90	0.366

Abbreviations: CU, chronic urticaria; UAS7, urticaria activity score over 7 days; BMI, body mass index; IgE, immunoglobulin E; CRP, C-reactive protein; D-D, D-dimer; Eos #, eosinophil count; Baso #, basophil count; WBC, white blood cell count; Lymph #, lymphocyte count; PLT, platelet count; ESR, erythrocyte sedimentation rate.

Table 2. Univariate and multivariate logistic regression analyses for predicting 1-year recurrence risk in CU patients

Variables	Univariate logistic				Multivariate logistic			
	β	OR	95% CI	*P*	β	OR	95% CI	*P*
Response after 4-week treatment								
Good		Ref	Ref			Ref	Ref	
Poor	0.75	2.11	1.02-4.35	0.043	0.72	2.05	0.84-5.00	0.116
Treatment plan								
Antihistamine monotherapy		Ref	Ref			Ref	Ref	
Antihistamine combination	0.92	2.52	1.19-5.35	0.016	0.62	1.86	0.73-4.76	0.193
Duration of CU	0.06	1.06	1.02-1.11	0.008	0.07	1.07	1.01-1.13	0.015
Baseline UAS7 score	0.08	1.08	1.01-1.16	0.020	0.06	1.06	0.97-1.15	0.173
IgE	0.01	1.01	1.01-1.02	< 0.001	0.01	1.01	1.01-1.02	< 0.001
CRP	0.15	1.16	1.06-1.27	< 0.001	0.15	1.16	1.04-1.28	0.005
D-D	0.01	1.01	1.01-1.02	0.003	0.01	1.01	1.01-1.02	0.007

Abbreviations: CU, chronic urticaria; OR, odds ratio; CI, confidence interval; IgE, immunoglobulin E; CRP, C-reactive protein; D-D, D-dimer; UAS7, urticaria activity score over 7 days. The outcome variable was recurrence within one year (1 = Yes, 0 = No).

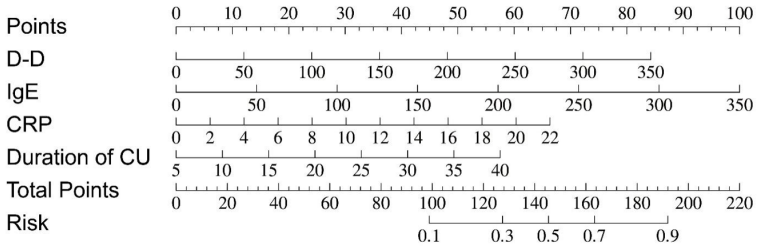

Figure 1. Nomogram for predicting the individual probability of 1-year recurrence in chronic urticaria patients.

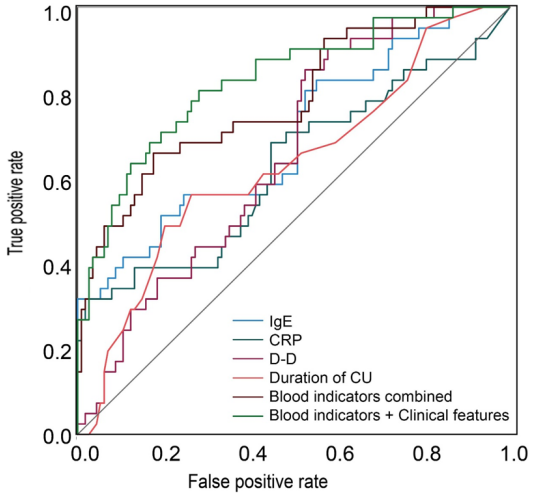

Figure 2. ROC curves of individual predictors and combined models for predicting 1-year recurrence. ROC, Receiver operating characteristic; IgE, immunoglobulin E; CRP, C-reactive protein; D-D, D-dimer; CU, chronic urticaria. The "Hematological Combination" model includes IgE, CRP, and D-D. The "Total Combined" model includes the three hematological parameters plus disease duration.

pretability. The feature importance ranking plot (**Figure 4A**) showed total IgE exerted the strongest predictive effect, followed by D-D, disease duration and CRP. The SHAP waterfall plot (**Figure 4B**) visualized the contribution of each indicator to recurrence risk prediction in individual patients, and the beeswarm plot (**Figure 4C**) displayed the overall distribution and action direction of SHAP values of all indicators in the whole cohort.

External validation of the prediction model

External validation was conducted in an independent cohort consisting of 48 patients enrolled. No significant differences in age, gender composition, disease duration and baseline UAS7 scores were observed between the validation cohort and primary cohort (all P > 0.05). Model predictive results were compared with clinical diagnostic outcomes confirmed by follow-up records (**Table 4**). The model demonstrated an accuracy of 79.2% (38/48), sensitivity of 81.8% (9/11), specificity of 78.4% (29/37), PPV of 52.9% (9/17) and NPV of 93.5% (29/31). The prediction results were in moderate agreement with clinical judgments, with a Cohen's kappa coefficient of 0.51.

Survival analysis based on stratified analysis based on predictors

The median follow-up duration of all enrolled patients was 15 months, and a total of 69 patients (44.52%) experienced recurrence during follow-up. All four continuous predictors were stratified according to the optimal cut-off values determined by the Youden index, and Kaplan-Meier survival curves were plotted accordingly (**Figure 5**). Patients with disease duration ≥ 20.5 months (HR = 1.89, 95% CI: 1.17-3.04, P = 0.006), total IgE ≥ 173.65 KU/L (HR = 2.25, 95% CI: 1.39-3.67, P < 0.001), CRP ≥ 11.66 mg/L (HR = 4.72, 95% CI: 2.57-8.68, P < 0.001) and D-D ≥ 142.84 ng/mL (HR = 2.13, 95% CI: 1.26-3.62, P = 0.003) had significantly shorter recurrence-free survival time (**Figure 5**; **Table 5**).

Multivariate Cox proportional hazards regression analysis

A multivariate Cox proportional hazards regression model was established with the four indicators included as continuous variables. The results confirmed that longer disease duration (HR = 1.03, 95% CI: 1.01-1.06, P = 0.015), higher total IgE level (HR = 1.01, 95% CI: 1.01-1.01, P < 0.001), higher CRP level (HR = 1.08, 95% CI: 1.02-1.14, P = 0.006) and higher D-D level (HR = 1.01, 95% CI: 1.01-1.01, P = 0.006) were independent risk factors for increased recurrence hazard (**Table 6**).

Discussion

This study performed a retrospective analysis on 155 CU patients and external validation in another 48 independent patients, aiming to explore the predictive value of baseline hema-

Table 3. Performance comparison of different prediction models

Models	AUC (95% CI)	Accuracy	Sensitivity	Specificity	PPV	NPV	Cut off	DeLong's test	
								Z value	*P* value
IgE	0.70 (0.60-0.79)	0.73	0.51	0.81	0.49	0.82	173.7 (158.4-189.2)	-2.90	0.004
CRP	0.63 (0.52-0.74)	0.81	0.32	0.98	0.87	0.80	11.7 (9.8-13.5)	-4.28	< 0.001
D-D	0.66 (0.57-0.75)	0.57	0.85	0.47	0.37	0.90	142.8 (128.6-157.3)	-3.21	0.001
Hematological Combination	0.78 (0.70-0.87)	0.78	0.66	0.82	0.57	0.87	-	-1.86	0.063
Duration of CU	0.63 (0.53-0.73)	0.69	0.56	0.74	0.43	0.82	20.5 (18.2-22.8)	-3.77	< 0.001
Total Combined Model	0.83 (0.75-0.90)	0.74	0.80	0.72	0.51	0.91	-	Ref	Ref

Abbreviations: AUC, area under the receiver operating characteristic curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; IgE, immunoglobulin E; CRP, C-reactive protein; D-D, D-dimer; CU, chronic urticaria. The "Hematological Combination" model includes IgE, CRP, and D-D. The "Total Combined" model includes the three hematological parameters plus disease duration.

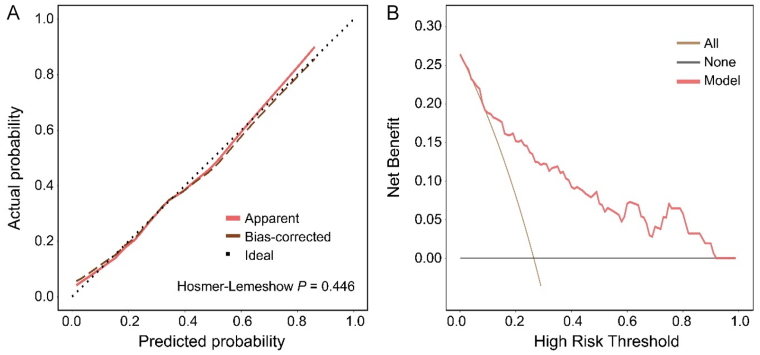

Figure 3. Calibration and clinical utility of the Total Combined prediction model. A. Calibration curve of the Total Combined model; B. Decision curve analysis for the Total Combined model.

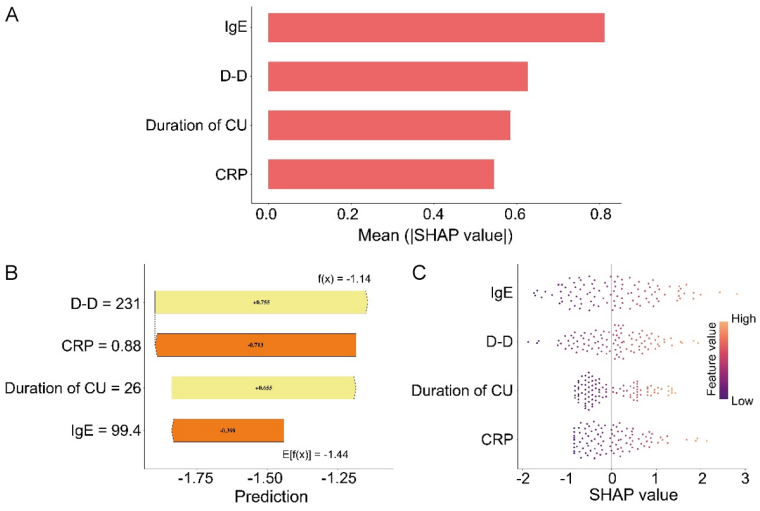

Figure 4. SHAP analysis for interpreting the Total Combined prediction model. A. Feature importance plot; B. Waterfall plot for an individual patient; C. Beeswarm plot summarizing the SHAP values for all patients. SHAP, SHapley Additive exPlanations; IgE, immunoglobulin E; D-D, D-dimer; CRP, C-reactive protein; CU, chronic urticaria.

tological indicators for 1-year recurrence risk. The main results were as follows. CU disease duration, IgE, CRP and D-D were independent risk factors for 1-year recurrence in CU patients. The combined prediction model established based on these four indicators achieved satisfactory predictive performance with an AUC of 0.83, and its reliability and clinical practicability were validated via calibration curves, decision curve analysis and external clinical verification. SHAP analysis indicated that total IgE exerted the strongest predictive impact within the model. Survival analysis further confirmed that patients with indicators above the optimal cut-off values had markedly shorter recurrence-free survival. Multivariate Cox regression also validated the independent prognostic role of these markers in predicting recurrence risk.

Total IgE serves as a core mediator in allergic responses, and its value in predicting CU recurrence has been validated in previous studies [16]. IgE binds to high-affinity FcεRI receptors to trigger mast cell and basophil degranulation, which is a key pathological process in CU progression [17, 18]. Bakay et al. [12] found a significant correlation between serum IgE levels and miR-155 expression in CU patients. miR-155 can regulate cytokine secretion by modulating mast cell FcεRI signaling pathways, thereby facilitating disease aggravation [19]. This study also

Table 4. Clinical validation of the 1-year recurrence risk prediction model

Model	Clinical diagnosis		Total
	Recurrence	No recurrence	
Recurrence	9	8	17
No recurrence	2	29	31
Total	11	37	48

Model performance metrics: Accuracy = 79.2%, Sensitivity = 81.8%, Specificity = 78.4%, PPV = 52.9%, NPV = 93.5%, Kappa = 0.51.

confirmed that IgE levels were positively correlated with disease activity; patients with severe CU had obviously higher median IgE levels than those with mild-to-moderate conditions, which was consistent with the elevated IgE levels observed in the relapse group in our cohort. Ertas et al. [20] also reported that baseline total IgE levels were negatively associated with recurrence interval in CU patients receiving omalizumab therapy. We further determined the optimal IgE cutoff value of 173.65 KU/L, providing a precise reference threshold for clinical early identification of high recurrence risk.

This study also confirmed the predictive roles of systemic inflammatory marker CRP and coagulation-fibrinolysis marker D-D. As a typical acute-phase reactant, elevated CRP levels reflect underlying low-grade systemic inflammation [21]. Our results identified baseline CRP as an independent recurrence predictor (OR = 1.16). Accumulating evidence has proven that CU is not merely a localized cutaneous disorder but closely linked to systemic inflammatory status [22]. Nearly one-third of CU patients present elevated CRP levels, which are correlated with disease activity and impaired quality of life [23]. Inflammatory cytokines can recruit mast cells and form an inflammatory microenvironment prone to disease recurrence [24]. Relevant studies have confirmed that inflammatory cytokines including IL-4, IL17, and IL31 are closely associated with CU severity, and serum IL-6 levels can well reflect UAS scores [24, 25]. Our findings are in line with these conclusions and further expand the prognostic application value of CRP, confirming that baseline CRP can independently predict CU recurrence risk.

D-D is a specific fibrin degradation product [26]. In CU patients, elevated D-D levels imply pathological changes beyond simple coagulation disorders. A systematic review including 71 studies and 5,606 participants conducted by Qin et al. [27] demonstrated that D-D is the most extensively investigated coagulation-related indicator in CU research. Its level is positively correlated with disease severity, rising during acute exacerbations and declining in remission stage. The present study firstly incorporated D-D into the CU recurrence prediction model and confirmed its independent predictive efficacy. Patients with D-D ≥ 142.84 ng/mL had significantly higher recurrence risk, which supports the view that D-D can be used to evaluate CU disease status. The underlying mechanism may involve vascular endothelial injury. Inflammatory factors can upregulate endothelial tissue factor expression and activate the extrinsic coagulation pathway [28, 29]. Thrombin induces mast cell degranulation via PAR-2, and local microthrombosis aggravates tissue hypoxia and inflammation, eventually forming an inflammation-coagulation vicious cycle [30]. Nevertheless, we did not conduct relevant correlation analyses between D-D and CRP or IgE in this study, so the above mechanistic speculations need further experimental verification.

Moreover, disease duration ≥ 20.5 months was identified as another independent recurrence risk factor. A prolonged disease course usually indicates sustained chronic inflammatory activation, which contributes to higher recurrence tendency, consistent with previous research findings [31]. Since we did not detect immune memory-related markers such as memory B cells or basophil activation indicators in this study, the relevant mechanistic interpretation remains preliminary and requires further laboratory evidence for confirmation.

The prediction model established in this study possesses prominent clinical application value. First, all included indicators are routine laboratory items that are easily accessible and incur no extra examination costs, making the model applicable to primary medical institutions and routine clinical practice. Designed exclusively for newly diagnosed CU patients, it only requires baseline routine laboratory data without additional complicated tests. Compared with traditional subjective clinical assessment, this model enables quantitative, visualized and repeatable risk stratification with higher objectivity and consistency. Since it relies solely on routine blood parameters, it barely increases med-

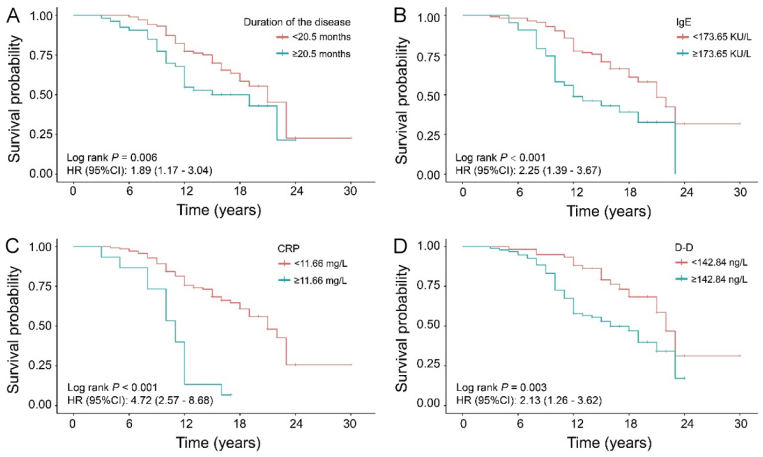

Figure 5. Kaplan-Meier survival curves for recurrence-free survival stratified by dichotomized predictors. A. Stratified by disease duration of CU; B. Stratified by total IgE level; C. Stratified by CRP level; D. Stratified by D-D level. CU, chronic urticaria; IgE, immunoglobulin E; CRP, C-reactive protein; D-D, D-dimer.

ical expenses and presents favorable cost-effectiveness in clinical settings.

Furthermore, the established optimal risk thresholds enable clinicians to rapidly identify patients at high recurrence risk. For instance, patients with IgE ≥ 173.65 KU/L and CRP ≥ 11.66 mg/L should avoid premature dose reduction or treatment discontinuation. Instead, individualized interventions such as prolonged maintenance therapy and combined targeted medications can be adopted. For low-risk patients, treatment can be adjusted following standard protocols. Such strategy realizes precise stratified management and reduces both overtreatment and undertreatment. Meanwhile, the high negative predictive value (93.5%) ensures reliable negative prediction results, which can effectively ease psychological burden among low-risk patients and improve treatment adherence. This excellent negative predictive value confirms the model's stable performance in screening patients with low relapse possibility, facilitating patient reassurance and rational clinical decision-making. The relatively low positive predictive value is mainly attributed to the low recurrence rate and limited sample size of the validation cohort. Further studies based on larger multicenter cohorts and more prognostic variables are expected to improve the positive predictive efficiency.

This study also has several limitations. First, it is a single-center retrospective investigation with a modest sample size of 155 enrolled patients, and all participants were recruited from a single hospital, which may cause selection bias. Although external validation was performed, the validation cohort only contained 48 patients from the same center, which restricts the generalizability of our findings. Large-sample multicenter prospective studies are required to verify the model's applicability across different regions, ethnic groups and clinical settings, and further optimize risk stratification cut-off values. Second, data on allergen detection results, concomitant medications and lifestyle factors were not collected in this study. It is well acknowledged that allergen sensitization, regular medication use, smoking, drinking and psychological stress can affect CU disease activity and recurrence risk. These factors will be included as covariates in subsequent studies, and advanced statistical methods including extended multivariate regression and machine learning will be applied to clarify their independent effects so as to further elevate model accuracy and generalizability. Third, dynamic monitoring of predictive indicators was not performed; hence, the correlation between longitudinal changes of these indicators and disease recurrence remains unclear. Long-term follow-up studies are warranted to explore whether dynamic fluctuations in IgE, CRP and other markers can serve as early warning signals of recurrence during treatment. Additionally, this study did not differentiate chronic spontaneous urticaria from chronic inducible urticaria, which may have distinct recurrence mechanisms. Subgroup analyses based on clinical subtypes should be carried out to establish more targeted prediction models.

In terms of the D-dimer cut-off value of 142.84 ng/mL, this value is lower than the median level in both groups due to the considerable overlap of D-D distribution between relapsed and non-relapsed patients. This threshold was optimized to achieve high sensitivity (85%) for minimizing missed high-risk cases, accompanied by moderate specificity (47%), which is

Table 5. Comparison of recurrence-free survival between patients grouped by different indicator levels

Indicators	Group[a]	N	Events	Median recurrence-free survival (months)	Log-rank x^2	*P* value
IgE	< 173.7 KU/L	112	42	21.00	11.98	< 0.001
	≥ 173.7 KU/L	43	27	12.00		
CRP	< 11.7 mg/L	140	55	21.00	31.62	< 0.001
	≥ 11.7 mg/L	15	14	11.00		
D-D	< 142.8 ng/mL	60	19	22.00	8.69	0.003
	≥ 142.8 ng/mL	95	50	18.00		
Duration of CU	< 20.5 months	102	39	21.00	7.41	0.006
	≥ 20.5 months	53	30	16.00		

[a]Groups were defined using the cut-off value corresponding to the maximum Youden index. Abbreviations: CU, chronic urticaria; IgE, immunoglobulin E; CRP, C-reactive protein; D-D, D-dimer.

Table 6. Multivariable Cox proportional hazards model analysis for recurrence risk

Variables	β	HR	95% CI	*P*
Duration of CU	0.03	1.03	1.01-1.06	0.015
IgE	0.01	1.01	1.01-1.01	< 0.001
CRP	0.08	1.08	1.02-1.14	0.006
D-D	0.01	1.01	1.01-1.01	0.006

Abbreviations: HR, hazard ratio; CI, confidence interval; CU, chronic urticaria; IgE, immunoglobulin E; CRP, C-reactive protein; D-D, D-dimer. All variables were included as continuous variables in the model.

suitable for screening-based clinical risk stratification. Finally, UAS7 is a patient-reported scale with inherent subjectivity. Although UAS7 scores were verified by nurses and physicians during outpatient visits in this retrospective study, standardized guidance for patients and dual independent verification of assessment records were not implemented. Future prospective research shall combine physician-assessed objective indicators such as wheal quantity and size with patient-reported scores to improve evaluation accuracy.

Conclusion

In conclusion, this study has confirmed that baseline disease duration, total IgE, CRP and D-D are core independent predictors of 1-year recurrence in CU patients. The prediction model constructed based on these indicators exhibits favorable predictive accuracy and clinical practicability. This study provides objective and convenient biomarkers for early recurrence risk assessment of CU, which helps optimize individualized treatment regimens and lower overall recurrence rates. Further multicenter prospective studies are needed to validate the external efficacy of this model, and in-depth research is required to clarify the molecular mechanisms underlying inflammation and coagulation disorders involved in CU recurrence, so as to lay a theoretical foundation for developing novel targeted therapeutic strategies.

Disclosure of conflict of interest

None.

Address correspondence to: Ming Gao, Department of Dermatology, The Third Hospital of Yinzhou District, No. 18, Renmin Road, Ningbo 315000, Zhejiang, China. Tel: +86-0574-88098990; E-mail: gm66gmgm@163.com

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