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Research article

Early diagnosis and clinical application of systemic lupus erythematosus based on a nomogram model

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ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease involving multi-system and multi-organ dysfunction, and is easily misdiagnosed early in the disease course. We aimed to accurately predict early SLE nomogram to provide a reference basis for the early clinical diagnosis of SLE. **Methods**: We retrospectively analyzed 167 patients who were first diagnosed with SLE at Fengxian District Central Hospital, Shanghai, between March 2017 and October 2022. Three groups of 129 physically healthy subjects, 67 patients with rheumatoid arthritis, and 40 patients with rashes were selected as controls during the same period. Patients with SLE and control group were randomly divided into training (n = 217) and validation (n = 141) group. Univariate and multivariate analyses were used to identify independent risk factors for early SLE diagnosis. The independent risk factors for diagnosis were used to construct a nomogram to predict early SLE. **Results:** Based on the training group, three variables were identified as independently influencing early SLE: platelets (odds ratio OR = 0.993, P = 0.047), albumin (OR = 0.833, P = 0.007), and complement component 1q (OR = 0.956, P = 0.000). The precision of the nomogram was assessed using C-index values and calibration plot diagrams. The C-index values were 0.929 for training group and 0.898 for validation group. Both the training group and validation group calibration curves showed good predicted outcomes. **Conclusion:** The construction of a nomogram can accurately predict the risk of early SLE. The model showed good discriminatory power and calibration for use in the diagnosis of SLE, providing a visual tool and reference basis for the early diagnosis of SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease involving multiple systems and organ dysfunction, with complex and diverse clinical manifestations and a mostly insidious onset [1]. In China, the incidence of SLE is approximately 70 per 100,000 people, and it often affects women of childbearing age. Patients can exhibit different clinical presentations and

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autoantibodies, and no single test has sufficient sensitivity or specificity for diagnosis [2]. The diagnosis of SLE mostly depends on clinical experience and exact serological clues, leading to a high risk of underdiagnosis in early-stage patients [3], which poses a great challenge for its early diagnosis.

Nomograms have been widely used in clinical as reliable and convenient tools for quantifying risk of important factors. However, to the best of our knowledge, nomograms for predicting risk of patients with early SLE have not been reported. Therefore, in this study, we aim to analyze serum specimens from patients with SLE and a healthy population and used logistic regression analysis to screen for risk factors associated with SLE and to establish a nomogram graphical diagnostic model. And it facilitates the early identification of people at high risk of SLE in clinical practice, which can provide a reference for the development of corresponding intervention strategies and aid in the early diagnosis of SLE.

2. Methods

2.1. Participants

This retrospective analysis study was conducted at Fengxian District Central Hospital, Shanghai. Data from 122 patients with SLE diagnosed for the first time in hospitals from March 2017 to October 2022 were collected. All patients met the revised diagnostic criteria for SLE classification established by the ACR [4]. The exclusion criteria were (1) concurrent autoimmune diseases other than SLE, (2) malignancy, (3) liver disease, and (4) other infectious diseases.

During the same period, physically healthy subjects, patients with rheumatoid arthritis (RA), and patients with skin rashes were collected and defined as control groups. Peripheral blood was collected from 129 healthy subjects, including 116 women and 13 men, aged 20–69 years. Healthy subjects with normal biochemical indicators, negative autoantibodies, and no kidney disease, skin disease, diabetes, hypertension, rheumatic immunity, cirrhosis ，hematology ，or other diseases were used to identify the screening indicators. Peripheral blood was collected from 67 patients with RA attending the Rheumatology Department, including five men and 62 women, aged 33–71 years. The diagnoses were made in accordance with the 1987 ACR criteria for RA. Forty patients with skin rashes were recruited from the Dermatology Department, including three men and 37 women, aged 28–67 years. There were no statistically significant differences in age or sex between the groups. The study was approved by the Ethics Committee of Shanghai Fengxian District Central Hospital, and all subjects signed the informed consent form (Fig. 1).

2.2. Baseline characteristics and laboratory parameters

All patients had 3 mL of venous blood drawn on an empty stomach, and the specimens were centrifuged (4000 rpm for 15 min) within 2 h of collection to obtain serum and plasma for testing each test index. Immunoglobulin A (IgA), IgG, IgM, IgE2, complement C3 (C3), and complement C4 (C4) levels were analyzed using a Siemens BNII Automated Protein Analyzer. White blood cells (WBC), red blood cells (RBC), platelet (PLT) , lymphocytes (LY), neutrophils (NE), hemoglobin (HGB), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were measured using a Sysmex Series XN3000 automated blood cell analyzer. Blood urea nitrogen (BUN), creatinine (CR), cystatin C (CYCS), uric acid (URIC), total protein (TP), ALB, globulin, estimated glomerular filtration rate, α-L-fucosidase (AFU) , retinol binding protein (RBP) , and C1q on a Beckman AU5800 fully automated biochemistry analyzer.

2.3. Statistical analysis

The data were statistically analyzed using SPSS version 26.0 a $\overline{n}$ d R version 4.0.3, and a small amount of missing data was performed mean interpolation to complete the analysis. The eligible patients (n = 358) were randomly divided into two groups using the function “sample.int” in R: a training group (n = 217) and a validation group (n = 141). Normal data are expressed as mean ± standard deviation (x ± s) and analyzed using independent-samples analysis of variance; skewed data are expressed as median (quartiles) [M

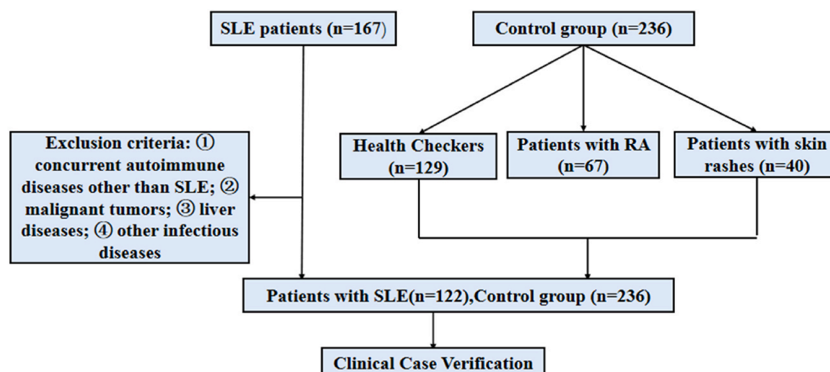

Fig. 1. Schematic diagram depicting the study selection workflow.

(P25–P75)] and analyzed using the Kruskal-Wallis test. The data of each index were screened using logistic single-factor and multi-factor variable regression analyses to obtain significant risk factors for the early diagnosis of SLE. Finally, the associated factors identified by the multivariate analysis through logistic regression were used to construct a nomogram for early diagnosis of SLE using the R package "rms." To ensure the predictive accuracy of the nomogram, we validated the models internally (1000 bootstrap resamples in the training group) and externally (in the validation group). The degree of fit was assessed using calibration diagrams and C-index values. Differences were considered statistically significant at $P < 0.05$.

Table 1
Patients' demographics and clinical indicators.

Variables	All patients (n = 358)		Training group (n = 217)		Validation group (n = 141)	
	Control group (n = 236)	SLE patients (n = 122)	Control group (n = 144)	SLE patients (n = 73)	Control group (n = 92)	SLE patients (n = 49)
Gender (male/female)	21/215	11/111	13/131	9/64	9/84	2/47
Age	45.00 (37.00,53.00)	42 (32,54)	43 (36.25,50)	43.37 ± 14.23	47.38 ± 12.49	42.16 ± 14.86
IgA(g/L)	2.54 (2.00,3.13)	2.65 (1.95,3.56)	2.58 ± 0.78	2.7 (2.12,3.75)	2.49 (2.01,3.15)	2.67 ± 1.06
IgG (g/L)	13.50 (12.10,15.10)	13.9 (10.8,16.85)	13.5 (12.2,15.45)	14.61 ± 4.57	13.5 (11.99,14.58)	13.6 (10.3,16.4)
IgM(g/L)	1.11 (0.82,1.52)	0.85 (0.56,1.31)	1.20 ± 0.50	0.87 (0.52,1.36)	1.08 (0.83,1.34)	0.84 (0.59,1.24)
IgE2(g/L)	62.17 (19.04,127.04)	50.59 (12.12,173.63)	69.4 (22.76,127.15)	50.84 (12.49,173.9)	54.6 (14.68,106.85)	44 (11.17,174.55)
C3 (g/L)	0.99 ± 0.16	0.77 (0.57,0.9)	0.99 (0.89,1.09)	0.74 ± 0.26*	1.01 ± 0.15	0.74 ± 0.24*
C4 (g/L)	0.21 (0.18,0.25)	0.15 (0.09,0.19)	0.21 (0.18,0.25)	0.14 (0.08,0.19) *	0.21 (0.18,0.26)	0.17 (0.11,0.2)
WBC($\times 10^{9}$/L)	5.75 (4.83,6.67)	6.1 (4.1,7.89)	5.78 (4.83,6.6)	6.06 (4.15,7.96)	5.65 (4.84,6.98)	6.17 (3.97,7.94)
RBC($\times 10^{12}$/L)	4.45 (4.14,4.76)	3.94 ± 0.67	4.43 (4.12,4.76)	3.92 ± 0.73*	4.46 ± 0.43	4.07 (3.72,4.39) *
PLT ($\times 10^{9}$/L)	239.00 (201.00,286.75)	195 (131.75,238.25)	237.5 (202.25,285)	191.55 ± 71.32*	244.5 (194.25,288.75)	188 (124.5238.5) *
Lym ($\times 10^{9}$/L)	1.73 (1.41,2.11)	1.38 (1.02,1.82)	1.73 (1.49,2.1)	1.37 (0.89,1.8) *	1.7 (1.36,2.12)	1.47 ± 0.63*
NEUT ($\times 10^{9}$/L)	3.36 (2.62,4.47)	3.76 (2.34,5.64)	3.27 (2.63,4.34)	3.82 (2.43,5.55)	3.4 (2.56,4.68)	3.66 (2.27,5.84)
HGB (g/L)	131.00 (123.00,140.75)	118.5 (99,130.25)	130 (122,140)	112.11 ± 28.13*	132.63 ± 13.35	123 (106.5132) *
CRP (mg/L)	2.69 (1.33,6.78)	4 (1.3,6.65)	2.35 (1.33,5.95)	4.4 (1.75,7.41)	2.78 (1.33,7.48)	2.8 (1,6.15)
ESR (mm/h)	14.00 (7.00,22.00)	16.71 (8,31.25)	13 (7,22)	18 (10.5,34)	14.5 (8,22)	16.71 (8,19)
BUN (mmol/L)	4.93 (4.20,5.70)	5.1 (3.9,6.53)	4.9 (4.3,5.9)	5.2 (4,6.9)	4.96 (4,5.6)	4.9 (3.6,6.1)
CR (umol/L)	59.00 (53.00,66.75)	63 (54,74)	59 (52.25,67)	64 (54,75.5)	57.75 (53,64.41)	59 (52,71)
URIC (umol/L)	280.60 (240.00,329.00)	309 (252.75,364.5)	278 (247.75,323)	315 (258.5375)	291.20 ± 76.53	304 (241.5357)
CYSC (mg/L)	0.87 (0.76,1.13)	1.1 (0.92,1.25)	0.87 (0.76,1.17)	1.11 (0.93,1.32)	0.88 (0.77,1.08)	1.05 (0.91,1.25)
TP (g/L)	72.03 (69.6,74.88)	65.65 (58.13,71.8)	72.03 (69.6,74.88)	66.1 (58,72.6) *	71.84 ± 4.76	63.21 ± 10.32*
ALB (g/L)	42.60 (40.50,44.9)	36.15 (30.28,40.7)	42.2 (40.4,44.6) *	36.7 (30.35,41)	42.8 (40.55,45.2)	35.6 (30.1,39.8) *
GLO (g/L)	29.2 (27.2,31.55)	27.8 (25.08,34.4)	29.35 (27,31.95)	28.7 (25.3,34.6)	29.05 (27.33,30.73)	26.5 (24.55,33)
eGFR (ml/min/1.73 m^2)	117.69 (102.67,134.52)	120.43 (102.69,132.2)	117.4 (101.5134.84)	120.43 (96.14,131.74)	117.88 (103.24,133.66)	120.43 (108.44,135.55)
RBP(mg/L)	34.75 (30.43,40.45)	37.75 (33,44.3)	34.7 (30.4,40.23)	37.75 (34.45,42.8)	35.5 (30.83,42.05)	37.75 (31.85,44.6)
AFU(U/L)	26.55 (24.00,32.00)	24 (19.75,26.3)	26.3 (24,31.93)	25 (20,26.3)	27.89 ± 6.08	24.10 ± 7.41
C_1q (mg/L)	173.80 (162.00,190.24)	142.75 (125.53,163.25)	173.35 (164.83,189.88) *	145.2 (126.9164)	177.72 ± 22.18	141.26 ± 30.69*
NLR	1.93 (1.41,2.56)	2.58 (1.83,4.14)	1.89 (1.38,2.42)	2.73 (1.94,3.87)	1.98 (1.49,2.79)	2.36 (1.62,4.85)
PLR	139.45 (110.43,174.57)	143.63 (93.04,194.44)	138.1 (110.43,173.92)	148.35 (93.65,199.94)	140.9 (109.46,174.76)	131.66 (92.71,176.97)

Note: ①*is a statistically significant result of Kruska-Wallis test between SLE disease group and control group; ②Control group include healthy subjects、RA and skin rashes patients.

3. Results

3.1. Patient characteristics

A total of 167 patients initially suspected to have SLE were identified from the renal rheumatology patients, 45 of whom were excluded because of other autoimmune diseases, oncologic disease, and other infectious diseases. Thus, 122 patients were included in the analysis. General information and clinical characteristics and clinical tests were collected for the SLE affected group and the three control groups (Sup Table 1) .The patients and control group were randomly divided into a training group and a validation group (Table 1).

3.2. Univariate and multivariate analyses in the training group

Univariate and multivariate logistic regression analyses were performed for the SLE prevalence and control groups. For the training group, 27 laboratory indices were subjected to one-way logistic regression analysis, and statistical significance was set at $P < 0.05$. The results showed that nine of these indicators (C3, C4, RBC, PLT, Lym, HGB, TP, ALB, C1q) were significantly different and thus included in a logistic multi-factorial regression model. The multi-factorial regression model showed that PLT (odds ratio [OR] = 0.993, P = 0.047), ALB (OR = 0.833, P = 0.007), and C1q (OR = 0.956, P = 0.000) were independent factors that influenced SLE (Table 2). At the same time, collinearity was excluded before conducting multiple factor analysis on the data (Sup Table 2).

3.3. Development of a nomogram model for early diagnosis of SLE risk

Based on three independent influences (ALB, C1q, and PLT) from the logistic multi-factor regression analysis, a prediction model was constructed for the training group (Fig. 2). The logistic regression model was described as a series of straight lines with a common linear scale in the nomogram, and the scale factors of the individual lines were provided by the coefficients (beta) of the covariates in the model. The distribution of each variable is superimposed onto each scale.

3.4. Validation of the diagnostic nomogram model for early risk of SLE

Validation of the nomogram was performed both training groups and validation groups. In the model validation, the C-index was come from the training data. In the training group, the C-index values of the nomograms were 0.929 (95%CI, 0.841–0.977). The cut-off value were 0.3, and the receiver operating characteristic curve had a sensitivity of 99.8 % and specificity of 73.5 %. In the validation group, the C-index values of the nomograms were slightly lower at 0.898 (95 % CI, 0.848–0.948). The cut-off value were 0.41, and the sensitivity of 90.3 % and specificity of 80.8 %. Both the training group and validation group calibration curves showed good predicted outcomes. (Fig. 3).

4. Discussion

SLE is a chronic autoimmune inflammatory disease with insidious early onset and a variety of clinical manifestations, mostly mild symptoms such as arthritis, skin rash, and occult nephritis, which can easily lead to misdiagnosis and underdiagnosis [5]. SLE can involve multiple systems, and the initial symptoms are complex and varied and can be easily combined with a variety of hematological abnormalities [6]. Early diagnosis of SLE uses a positive antinuclear antibodies titer as the main indicator; however, the quantification of antinuclear antibodies potentially varies among laboratories, which may provide inconsistent experimental results and make the diagnosis of early SLE difficult [7]. The most commonly used classification standard for SLE is the ACR classification standard developed in 1982 [8] and revised in 1997 [4]. The survival rate of patients with SLE has improved significantly in the last few decades, but morbidity and mortality rates remain high; the main causes of morbidity are the lack of timely diagnosis and treatment and prolonged disease activity [9]. Therefore, early diagnosis and treatment of the disease and maintenance of sustained remission are

Table 2
Univariate and multivariate analyses of SLE in the training group.

Variables	Univariate analysis				Multivariate analysis			
	β	P	OR	95%CI	β	P	OR	95%CI
C3 (g/L)	−5.732	<0.001***	0.003	0.001–0.020	−1.119	0.473	0.327	0.015–6.967
C4 (g/L)	−16.575	<0.001***	0.000	0.000–0.000	−8.091	0.063	0.000	0.000–1.562
RBC($\times 10^{12}$/L)	−1.513	<0.001***	0.220	0.125–0.388	−0.186	0.669	0.831	0.355–1.944
PLT ($\times 10^{9}$/L)	−0.014	<0.001***	0.986	0.981–0.991	−0.007	0.047*	0.993	0.985–1.000
Lym ($\times 10^{9}$/L)	−0.935	<0.001***	0.393	0.230–0.669	−0.196	0.547	0.822	0.434–1.557
HGB (g/L)	−0.043	<0.001***	0.958	0.942–0.974	−0.014	0.295	0.986	0.960–1.012
TP (g/L)	−0.119	<0.001***	0.888	0.848–0.929	0.021	0.647	1.021	0.934–1.116
ALB (g/L)	−0.211	<0.001***	0.810	0.756–0.868	−0.183	0.007**	0.833	0.728–0.952
C_1q (mg/L)	−0.053	<0.001***	0.948	0.933–0.964	−0.045	<0.001***	0.956	0.937–0.975

Notes: *Two-sided P-values <0.05; **two-sided P-values <0.01; ***two-sided P-values <0.001.

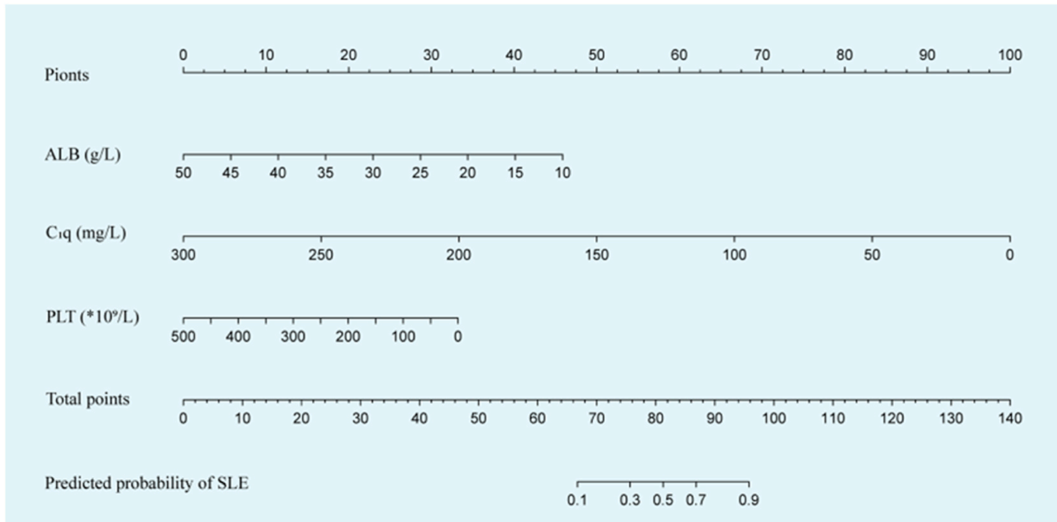

Fig. 2. SLE early risk nomogram prediction model.

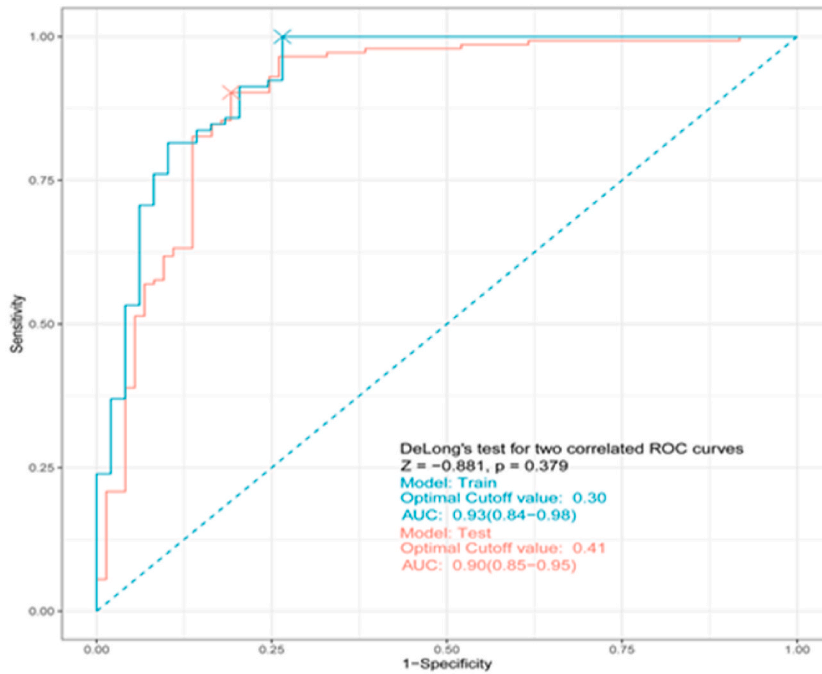

Fig. 3. ROC curve performance SLE evaluation of Nomogram.

critical to patient care and prognosis.

The combination of logistic regression analysis and nomograms can be used to identify and visualize risk factors for diseases [10]. To improve the sensitivity and specificity of early diagnosis of SLE, the study of the risk of early-onset SLE relied on variables selected by logistic regression as predictors to assess between-group differences in clinical characteristics [4]. Our study comparing patients with SLE with control groups identified C1q, ALB, and PLT as independent factors that contributed to the construction of the SLE nomogram. We included these risk factors in the construction of nomogram, and both the C-index values and the calibration diagrams showed satisfactory robustness when applied to both training group and validation group.

Inflammation in patients with SLE involves many components of the immune system during the ongoing autoimmune process. Although most patients with SLE do not have an inherited C1q deficiency, there is indirect evidence of the importance of C1q in the inflammatory process of the disease. Low levels of classical complement pathway components, including C1q, are frequently observed in patients with SLE, which can be attributed to complement activation during disease exacerbation [11]. C1q is found in

electron-dense deposits in the renal subendothelial space and/or glomerular basement membrane and is a specific histological manifestation of severe lupus nephritis (LN) [12]. Autoantibodies against C1q (anti-C1q), which are strongly associated with disease activity and hypocomplementemia, are detected in approximately one-third of patients with SLE and in more than 90 % of patients with proliferative LN, and these anti-C1q antibodies are strongly associated with disease activity and hypocomplementemia [13]. Studies have shown that C1q plays a key role in the clearance of apoptotic cells, and it has been suggested that C1q binds to apoptotic cells through interactions with ribosomes, leading to the exposure of new epitopes recognized by anti-C1q antibodies in patients with SLE [14]. In this model, C1q can be used as a test for the early prediction of SLE, and complement C1q can be used as a marker for active LN and SLE disease activity [15].

Serum ALB is often considered a biomarker of nutritional status and the systemic inflammatory response. The liver can be involved in systemic immune diseases because of its role in inducing immune tolerance and as a target organ for immune-mediated damage, which may lead to reduced ALB synthesis [16]. Immune complex formation and deposition are important mechanisms underlying LN. The infiltration of inflammatory cells and release of inflammatory factors cause kidney damage, resulting in decreased concentrations of ALB [17]. Yip et al. found that ALB levels were lower in patients with LN than in those without LN and negatively correlated with systemic lupus erythematosus disease activity index in both [18]. Liu et al. found that low ALB in patients with active SLE was strongly associated with poor prognosis in patients with SLE and that ALB-globulin may also be a strong predictor of developing LN [19]. In this model, the ALB level could be used as an independent influencing factor for the early prediction of SLE.

Studies have found that thrombocytopenia in patients with SLE is associated with humoral (B cell-mediated) and cellular (T cell-mediated) mechanisms that may lead to the overproduction of antiplatelet antibodies [20]. One study also pointed out that thrombocytopenia was an independent predictor of death in patients with SLE [21], which is consistent with our findings. Jallouli et al. examined 182 patients with SLE and found that thrombocytopenia significantly increased the risk of splenomegaly, neurological lupus erythematosus, kidney disease, and mortality, as assessed using multivariate logistic regression [22]. Jung et al. retrospectively evaluated 230 patients with SLE and noted that thrombocytopenia was a useful prognostic factor for predicting survival and mortality during complete remission after thrombocytopenia treatment, showing that mortality was significantly lower than that in patients who did not achieve complete remission [23]. In this model, the PLT count could be used as an independent influencing factor for the early prediction of SLE.

This study further developed a nomogram to predict the risk of early SLE and visualized an onset risk model [24]. The proportion of the line segment corresponding to each variable in the model indicated the range of possible values for that variable, and the length of the line segment indicated the effect of that factor on the outcome event. The points represent the individual scores corresponding to each variable at different values, and the total score was obtained by summing the individual scores of all variables. This study aimed to develop a weighted scoring system to provide a more comprehensive and holistic assessment of the early stages of SLE and facilitate its early diagnosis. The model had good predictive power. The area under the receiver operating characteristic curve was as high as 0.929, and the specificity and sensitivity were 99.8 % and 73.5 %, respectively, indicating that the model had good discriminative power and calibration performance, which could be visualized in the nomogram to predict the early occurrence of SLE.

We later recruited three patients with suspected SLE to validate the model. Patient #1 was recruited for 30 days of recurrent pain in the small joints of both hands with morning stiffness that improved with activity and was accompanied by dry mouth, dry eyes, rash, and mouth ulcers; patient #2 came to the hospital with swollen and painful joints with puffiness; and patient #3 came to the hospital with a facial rash. The C1q levels were 121.3mg/L, 179 mg/L, 158.3 mg/L, corresponding to scores of 60, 40, 51, respectively; the PLT levels were 228×10^9/L, 171×10^9/L, 125×10^9/L, corresponding to scores of 19,24, 26, respectively; and the ALB levels were 38 g/L, 35 g/L, 35.6 g/L, corresponding to scores of 15, 19, 18, respectively. Mapping the experimental data for each patient onto the Nomogram eventually yields respective total scores of 94, 83, and 95, corresponding to probabilities of 91 %, 80 %, and 89 %, respectively. The final follow-up of three patients with a final diagnosis of SLE, that shows the model has a good predictive efficiency.

At the same time, 12 primary glomerulonephritis patients with low albumin were recruited. As a control supplement group to test model specificity. The mean ALB of patients with primary glomerulonephritis is 34.66 g/L. The average score is 72.61, and the average predicted risk probability is 25 % (Sup Table 2). This indicates that the model has good specificity in predicting the risk of SLE.

5. Conclusion

We analyzed the potential independent risk factors for early SLE and developed a nomogram risk model with good predictive ability and performance to predict the risk of early SLE in patients. Early identification of patients with SLE allows for early intervention and improved quality of life. This nomogram can be used as a convenient screening tool in clinical practice to guide follow-up, aid accurate prognostic assessment, and facilitate early intervention in clinical settings. Although the model exhibited good predictive power and performance, it had several limitations. This study was retrospective and involved a single center with a relatively small number of patients, which may have led to a lower generalizability of the model. Further multicenter prospective studies are required to confirm the reliability of this model.

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Ethics statement

This study was approved by Medical Ethics Committee of Shanghai Fengxian District Central Hospital, China (2021-KY-03).

Data availability statement

Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Yalin Yang: Writing – original draft. **Dingding Huang:** Writing – original draft, Data curation. **Cuicui Liu:** Formal analysis. **Ningxuan Zhong:** Data curation. **You Peng:** Methodology. **Lulu Wang:** Software. **Linlin Xiao:** Writing – review & editing. **Weiwei Zhao:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Weiwei Zhao reports financial support was provided by Fengxian District Science and Technology Commission Project. Linlin Xiao reports financial support was provided by Shanghai Municipal Health Commission Youth Project. Weiwei Zhao reports a relationship with Fengxian District Science and Technology Commission Project that includes: consulting or advisory, funding grants, non-financial support, paid expert testimony, speaking and lecture fees, and travel reimbursement. Linlin Xiao reports a relationship with Shanghai Municipal Health Commission Youth Project that includes: consulting or advisory, funding grants, non-financial support, paid expert testimony, speaking and lecture fees, and travel reimbursement. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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