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Research Paper

A nomogram to predict the risk of lupus enteritis in systemic lupus erythematosus patients with gastrointestinal involvement

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ABSTRACT

Background: Lupus enteritis (LE), a main cause of acute abdominal pain in systemic lupus erythematosus (SLE) patients, is a serious and potentially fatal complication. This study aimed to identify clinical serological indicators to establish a nomogram to assess LE in SLE patients with gastrointestinal manifestations.
Methods: The clinical and laboratory data of SLE patients with gastrointestinal manifestations that were hospitalized in the West China Hospital from January 2010 to January 2020 were retrospectively analyzed. The least absolute shrinkage and selection operator logistic regression model was used to select potentially relevant features. Subsequently, a nomogram was developed using multivariable logistic analysis. The performance of the nomogram was evaluated using a receiver operating characteristic curve, a calibration curve, and decision curve analysis (DCA).
Findings: We included a total of 8,505 SLE patients, of which 251 had experienced gastrointestinal manifestations. The patients were randomly divided into training (n = 176) and validation (n = 75) groups. The LRA (LE Risk Assessment) model consisted of 11 significantly associated variables, which included complement 4, antineutrophil cytoplasmic antibody, albumin, anion gap, age, D-dimer, platelet, serum chlorine, anti-Sjögren's-syndrome-related antigen A, anti-ribosomal P protein, and anti-ribonucleoprotein. In the training and validation cohorts, the areas under the curve were 0.919 (95% confidence interval [CI]: 0.876–0.962) and 0.870 (95% CI: 0.775–0.964), respectively. The nomogram demonstrated excellent performance in the calibration curve and DCA.
Interpretation: The LRA model exhibits good predictive ability in assessing LE risk in SLE patients with gastrointestinal manifestations.

1. Introduction

Systemic lupus erythematosus (SLE) is the most common autoimmune disease. It is characterized by the presence of a large number of autoantibodies and immune complexes and displays diverse clinical manifestations [1]. Although 50% of SLE cases exhibit gastrointestinal manifestations, the symptoms are often relatively mild, such as acid reflux, belching, or dyspepsia [2]. The most common complication of SLE-related gastrointestinal involvement is lupus enteritis (LE), a condition that is associated with poor prognosis in SLE patients, especially in adolescents and children, and may have life-threatening consequences [3]. The clinical definition of LE mainly includes the following two: (1) Clinical indications of multifocal intestinal or multiple vascular area involvement, duodenal ischemic changes, symptom improvement after intravenous steroids or immunosuppressants; or (2) Endoscope-guided biopsy pathological results showed changes in vasculitis or abdominal computed tomography (CT) found at least the following three signs: intestinal wall thickening, target sign, intestinal dilation, mesenteric vascular filling, mesenteric fat attenuation abnormal [4,5]. In a retrospective study of 706 SLE patients, 87 complained of acute abdominal pain, of which 47.1% were identified with lupus enteritis [6]. The occurrence of LE is secondary to inflammatory vasculitis caused by intestinal wall mesenteric and small blood vessel immune complexes as well as to

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intestinal vascular thrombosis caused by circulating antiphospholipid antibodies. These two microvascular dysfunctions can activate each other, resulting in the exacerbation of vasculitis and thrombosis and the thickening and occlusion of mesenteric arterioles, which ultimately leads to intestinal mucosal edema, ischemia, bleeding, obstruction, and ulcers, as well as bowel perforation [7-9]. The overall prevalence of LE in SLE is 0.2−9.7%, but the incidence is much higher in SLE patients with acute abdominal pain [6,10-12]. The age of onset of LE is approximately 33.3 years old, and it appears approximately 34.3 months after the diagnosis of SLE [13].

To diagnose LE in SLE patients clinically, abdominal computed tomography (CT), angiography, gastrointestinal endoscopy, and abdominal ultrasound are commonly used [14-16]. Abdominal CT is useful in diagnosing LE [10]. However, neither abdominal CT nor angiography is specific, and both are expensive. The early pathological changes of LE are atypical, and the fatality rate can be high when it occurs. Accordingly, its early diagnosis remains a challenge in clinical practice [17]. Its accurate diagnosis is essential for timely treatment to avoid unnecessary surgical intervention. Therefore, it is vital to develop new methods of evaluating and predicting LE in patients. To effectively assess LE risk, we used clinical and laboratory indicators to screen for features important for its clinical diagnosis and treatment.

2. Methods

2.1. Data sources

The corresponding authors (YL and FZ) had full access to all the data in the study, and individual participant data that underlie the results reported in this article, after de-identification can be obtained from the corresponding author upon reasonable request. We conducted a retrospective study of 8505 SLE patients who were hospitalized in West China Hospital from January 2010 to January 2020. SLE patients with the following criteria were included in the analysis: meet the 1997 American College of Rheumatology and/or the 2012 Systemic Lupus Erythematosus International Clinical Assistance Group classification criteria; [18,19]. have gastrointestinal symptoms and signs such as abdominal pain, diarrhea, nausea, vomiting, black stool, bloody stool, and fatigue as well as completed one or more abdominal CT examinations; and have complete inspection data.

LE patients that were included in this study met the following requirements: have a clear diagnosis of SLE; exhibit one of the following symptoms: abdominal pain, bloating, nausea and vomiting, or related clinical symptoms and signs such as diarrhea, melena, blood in the stool; and had abnormal abdominal CT scans indicating intestinal wall thickening, "target sign", "comb sign", intestinal dilatation, mesenteric vascular filling, or abnormal attenuation of mesenteric fat; and respond to glucocorticoid therapy.

Patient exclusion criteria included: gastrointestinal symptoms indirectly caused by other systems involved in SLE including nausea, vomiting, or abdominal pain; prior gastrointestinal diseases such as gastrointestinal perforation, bleeding, liver cirrhosis, or pancreatitis; infectious diseases including infectious peritonitis or acute gastroenteritis; malignant tumors of the digestive tract; adverse reactions caused by drugs; presence of other autoimmune diseases such as Sjogren's syndrome, scleroderma, Kawasaki disease, panniculitis, rheumatoid arthritis, inflammatory bowel disease, spondyloarthritis, or autoimmune hepatitis; and atypical digestive system symptoms with no objective (i.e., test, imaging) basis.

We collected the clinical and laboratory indicators of each eligible patient as potential predictors of LE risk. Details are provided in Supplementary Table 1.

This study was approved by the Ethics Committee on Biomedical Research at the West China Hospital of Sichuan University; the Ethics Committee waived the need for patients to give informed consent.

3. Feature selection and model establishment

Based on the split proportions in previous studies, we randomly divided the cohort into training (70%) and validation (30%) datasets [20]. To assess the risk of LE in SLE patients, we used the least absolute contraction and selection operator (LASSO) logistic regression algorithm to select LE-related feature indicators with non-zero coefficients from the laboratory test indicators [21]. Nomograms are powerful tools that, by integrating multiple risk factors, can quantify an individual's risk for a clinical disease. The risk factors selected by the LASSO regression were used to establish the model [22].

4. Model performance

A calibration curve was drawn to evaluate the nomogram. By quantifying the net benefits under different threshold probabilities in the LE cohort, the decision curve was analyzed to determine the nomogram's clinical effectiveness. The receiver operating characteristic curve was used to evaluate the diagnostic value of the nomogram in discriminating LE from non-LE and to determine the cutoff values for assessing accuracy, sensitivity, and specificity.

5. Statistical analysis

Continuous variables are expressed as the mean ± standard deviation, while categorical values are expressed in frequencies or percentages. The Student's *t*-test and Chi-square test were used to analyze differences between variances; categorical data as frequencies were analyzed using the latter. The LASSO algorithm was used to select important relevant features with non-zero coefficients from the training set. Correlation would be assessed by Spearman's test. All statistical tests were two-tailed, with $P < 0.05$ considered significant. The data were analyzed using R software (version 3.6.2) and SPSS 24.0 (IBM, USA).

6. Ethics statement

The study protocol was approved by the Ethics Committee of West China Hospital, Sichuan University with a waiver of informed consent (ethics application reference number:20,201,130).

7. Role of the funding source

This work was supported by the National Key Research and Development Program of China (Project no. 2016YFC0906201) and by the 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (Project No. ZYGD18015). All sources of funding did not have any role in the study design, collection, analysis, or interpretation of the data, the writing of this manuscript, or the decision to submit it for publication.

8. Results

8.1. Clinical characteristics

This study included 8505 SLE cases. After excluding patients who did not meet the inclusion criteria, 251 remaining cases were enrolled for the final analysis (Fig. 1). The baseline characteristics of the training and validation cohorts are listed in Table 1 and Supplementary Table S2. The training cohort consisted of 176 cases (19 males and 157 females), while the validation cohort included 75 cases (7 males and 68 females). The two cohorts did not differ in age, sex, BMI, smoking history, alcohol consumption history, diabetes, dsDNA positive rate ($P > 0.05$). However, there were significant differences in the incidence of hypertension, SM antibody positivity, C3 and C4 levels in serum between the LE and non-LE groups in the

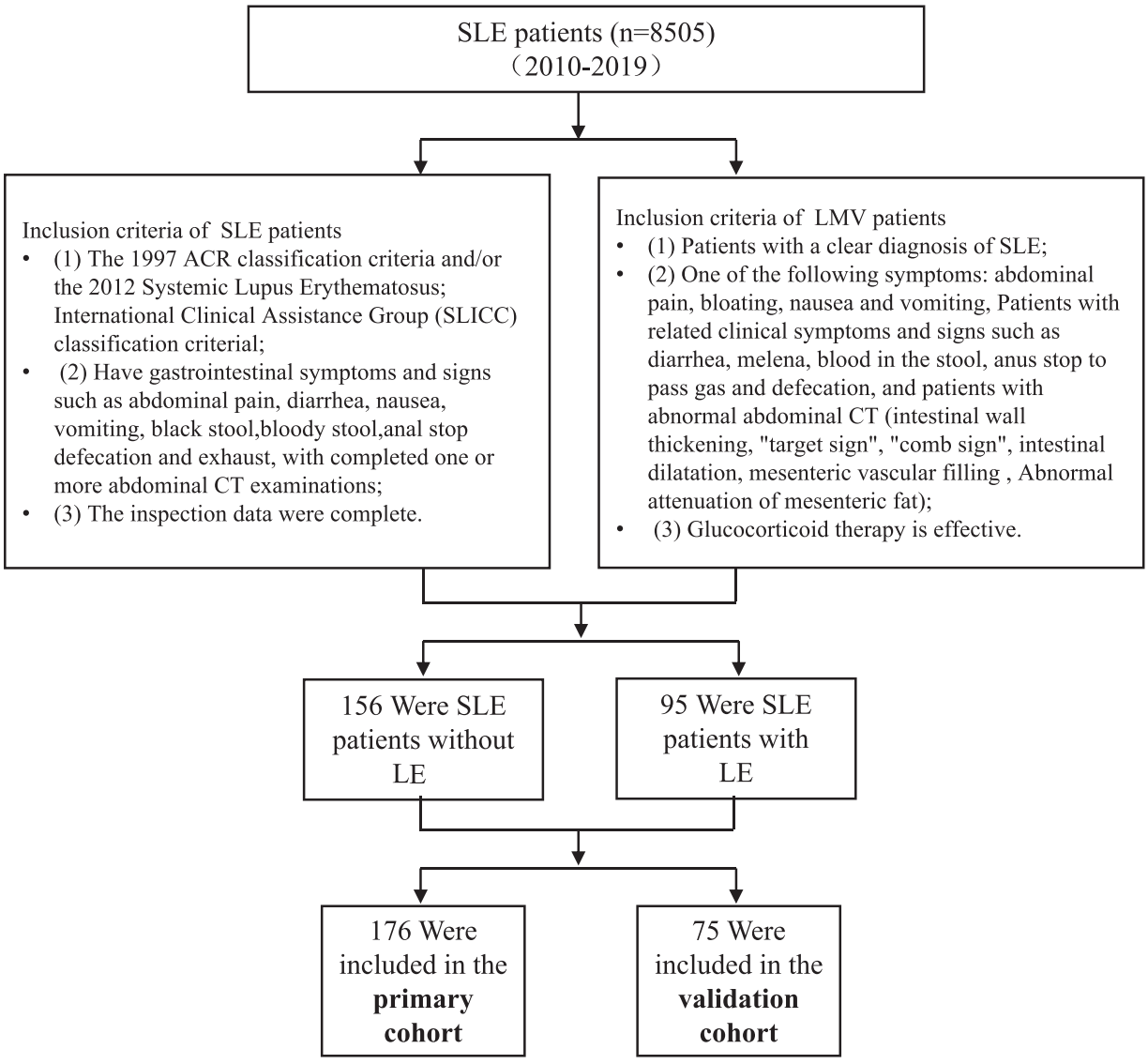

Fig. 1. Flowchart.

Table 1
Characteristics of patients included in this study.

	Training cohort			Validation cohort		
	Non-LE (*n* = 104)	LE (*n* = 72)	*P*	Non-LE (*n* = 52)	LE (*n* = 23)	*P*
Age, mean (SD), years	44.15 (15.98)	35.39 (13.26)	0.08	43.73 (13.97)	37.39 (12.56)	0.60
Male	50.67 (16.50)	31.75 (19.72)		31.00 (15.95)	N	
Female	43.06 (15.72)	35.60 (12.96)		45.71 (12.72)	37.39 (12.56)	
Gender, n (%)			0.06			0.07
Male	15 (14.42)	4 (5.56)		7 (13.46)	0 (0)	
Female	89 (85.58)	68 (94.44)		45 (86.54)	23 (100)	
BMI, mean (SD)	21.34 (4.27)	21.27 (4.21)	0.921	20.95 (2.83)	21.69 (2.56)	0.288
Smoking history, n (%)	8 (7.7)	4 (5.6)	0.76	5 (9.6)	1 (4.3)	0.660
Alcohol consumption history, n (%)	7 (6.7)	4 (5.6)	–	3 (5.8)	1 (4.3)	–
Diabetes, n (%)	5 (4.8)	1 (1.4)	0.40	4 (7.7)	0 (0)	0.306
Hypertension, n (%)	18 (17.3)	1 (1.4)	0.001	8 (15.4)	1 (4.3)	0.26
ANA-positive, n (%)	104 (100)	72 (100)	–	52 (100)	22 (95.7)	0.307
dsDNA-postive, n (%)	56 (53.8)	35 (48.6)	0.494	26 (50)	10 (43.5)	0.602
SM-positive, n (%)	10 (9.6)	23 (31.9)	0.000	8 (15.4)	7 (30.4)	0.209
C3, mean (SD)	0.54 (0.22)	0.43 (0.22)	0.002	0.50 (0.24)	0.42 (0.22)	0.166
C4, mean (SD)	0.14 (0.07)	0.11 (0.07)	0.003	0.13 (0.08)	0.11 (0.10)	0.418

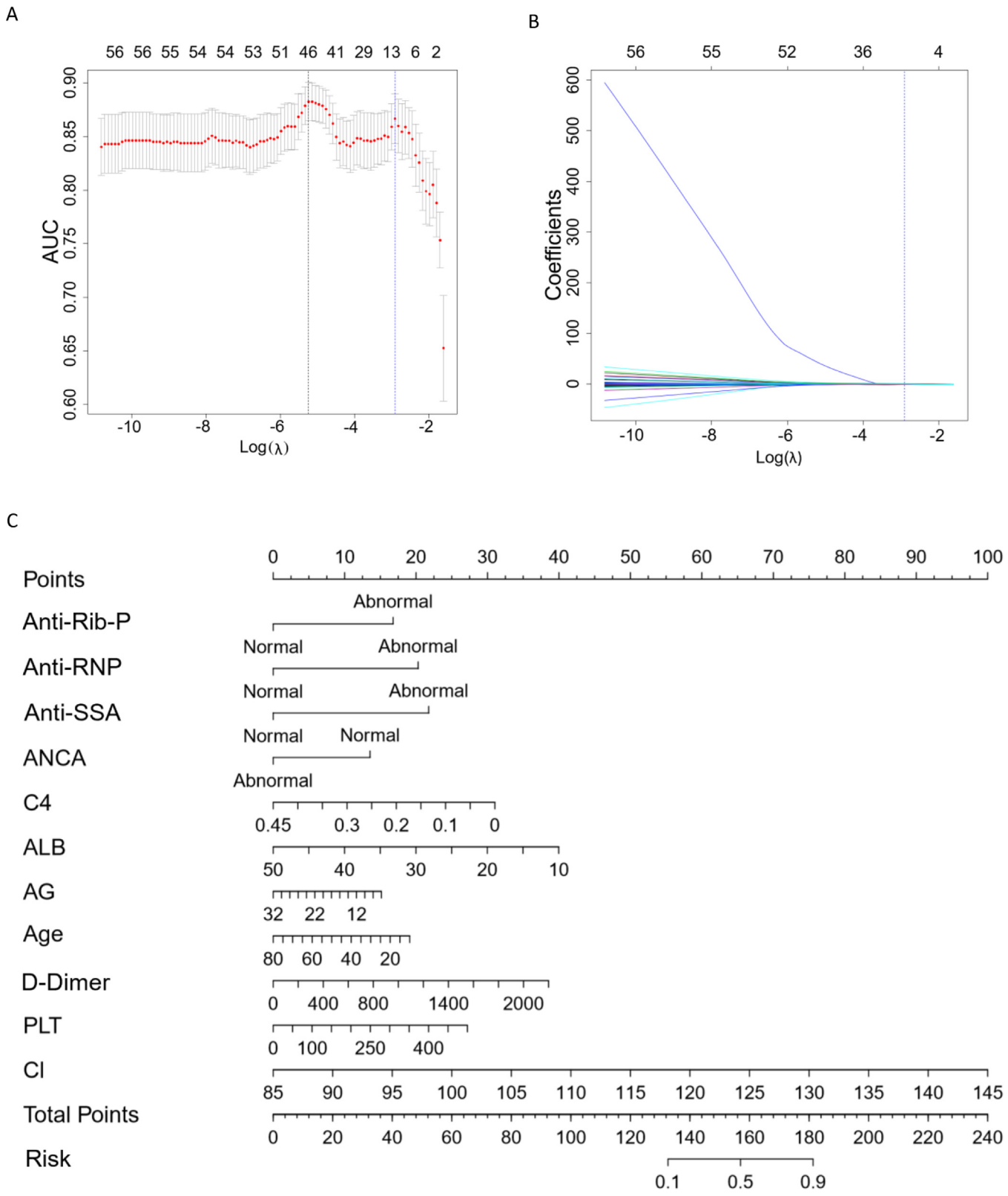

Fig. 2. Clinical feature selection and model establishment. A. Optimal parameter (lambda) selection by LASSO used tenfold cross validation via minimum criteria. The average number of predicted variables is expressed as a number along the upper x-axis. The average deviation of each model is represented by a red dot, and the upper and lower limits of the deviation are represented by vertical lines passing through the red dot. The best value of lambda is defined by a vertical black line (λ=0.054). B. LASSO coefficient profiles of the 71 variables plotted against the log(lambda) sequence. Drawing vertical lines by optimum lambda values of eleven nonzero coefficients through tenfold cross-validation. C. The LRA model was developed with C4, ANCA, ALB, AG, age, D-dimer, PLT, serum chlorine (Cl), anti-SSA, anti-Rib-P and anti-RNP. The scale of the line segment corresponding to each variable in the prediction model indicates the possible value range of the variable, and the length of the line segment indicates the influence of the factor on the outcome event. Point represents the individual score corresponding to each variable under different values, and the total score is obtained by adding the individual scores of all variables. Risk represents the risk of LE in SLE patients with gastrointestinal manifestations. Anti.Rib-P, anti-Rib-P antibody; anti.RNP,anti-RNP antibody; anti.SSA, anti-SSA antibody; ANCA, antineutrophil cytoplasmic antibody; C4,complement 4; ALB, albumin; AG, anion gap; PLT,blood platelet; Cl,serum chlorine; SLE, Systemic lupus erythematosus; LE, Lupus enteritis.

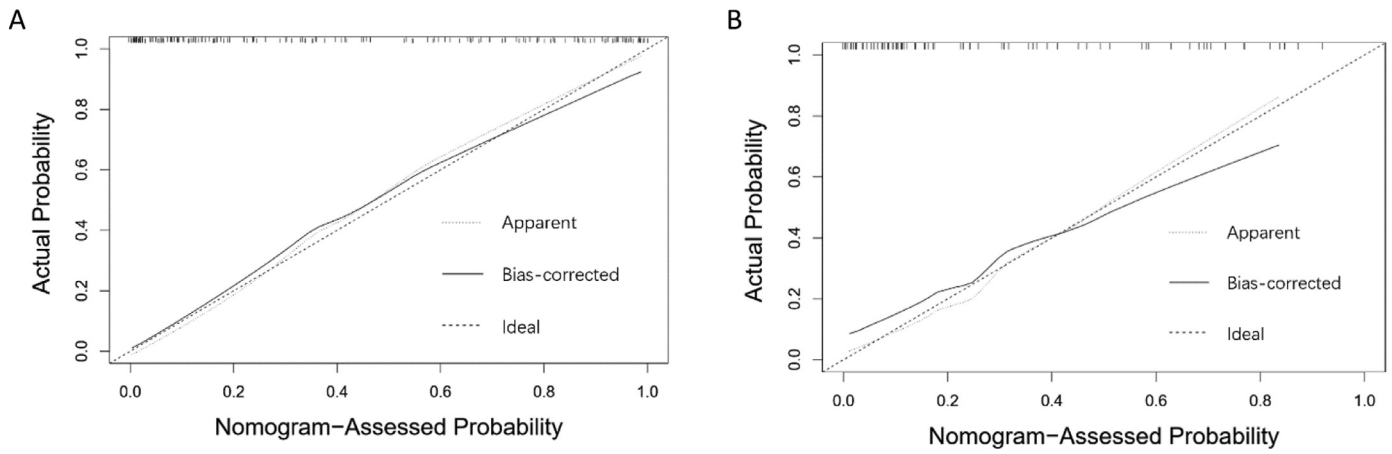

Fig. 3. Calibration curve the LRA model. A. Calibration curve of the training cohort. "Apparent" is the uncalibrated prediction curve, "Bias-correctrd" is the calibrated prediction curve, and "Ideal" is the standard curve, which represents the perfect prediction of the ideal model. Based on the consistency between the predicted risk of LE and the observed results of LE, the scale curve describes the scale of each model. B. Calibration curve of the validation cohort. The Y-axis represents the actual prevalence of LE. The X-axis represents the predicted risk of LE in the cohort. SLE, Systemic lupus erythematosus; LE, Lupus enteritis.

training cohort (P<0.05), but not in the validation cohort. Typical images of SLE patients with LE are shown in Supplementary Figure S1.

8.2. Feature selection and model development

Seventy-one features were used in the LASSO logistic regression. Eleven potential predictors with non-zero coefficients were subsequently selected; the optimal lambda (λ) value was 0.054 (log [λ] = −2.912; Fig. 2A and 2B). Based on the 11 independent predictors, the nomogram, coined the "LRA (LE Risk Assessment) model", was constructed (Fig. 2C). The 11 features were: complement 4 (C4), antineutrophil cytoplasmic antibody (ANCA), albumin (ALB), anion gap (AG), age, D-dimer, platelet (PLT), chlorine (Cl), anti-Sjögren's-syndrome-related antigen A (SSA), anti-ribosomal P protein (Rib-P), and anti-ribonucleoprotein (RNP).

Supplementary Figure S2 and Supplementary Table 3 display the contribution of each variable in the model to the outcome variable. Among them, C4, anti-SSA, anti-Rib-P, and anti-RNP had the highest contribution. C4 was a protective factor (odds-ratio [OR]: 0.2, 95% confidence interval [CI]: 0.07−0.56), while anti-SSA (OR: 1.29, 95% CI: 1.09−1.51), anti-Rib-P (OR: 1.38, 95% CI: 1.18−1.61), and anti-RNP (OR: 1.49, 95% CI: 1.31−1.70) were risk factors. Among the indicators included in the model, C4, ANCA, ALB, AG, and age were negatively correlated with the occurrence of LE, while anti-RNP, anti-Rib-P, anti-SSA, Cl, D-dimer, and PLT were positively correlated (Supplementary Fig. S3).

8.3. Predictive ability and performance of the LRA model

The LE risk prediction model exhibited good consistency between predictions and actual observations in both the training and validation cohorts (Fig. 3). The area under the curve (AUC) were 0.919 (95% CI: 0.876−0.962) and 0.870 (95% CI: 0.775−0.964) in the training and validation cohorts, respectively. The two cohorts did not significantly differ (P = 0.356; Fig. 4A). The accuracy of the training and validation cohorts were 0.864 (95% CI: 0.862−0.865) and 0.840 (95% CI: 0.836−0.844), the sensitivity specificity of these two cohorts were

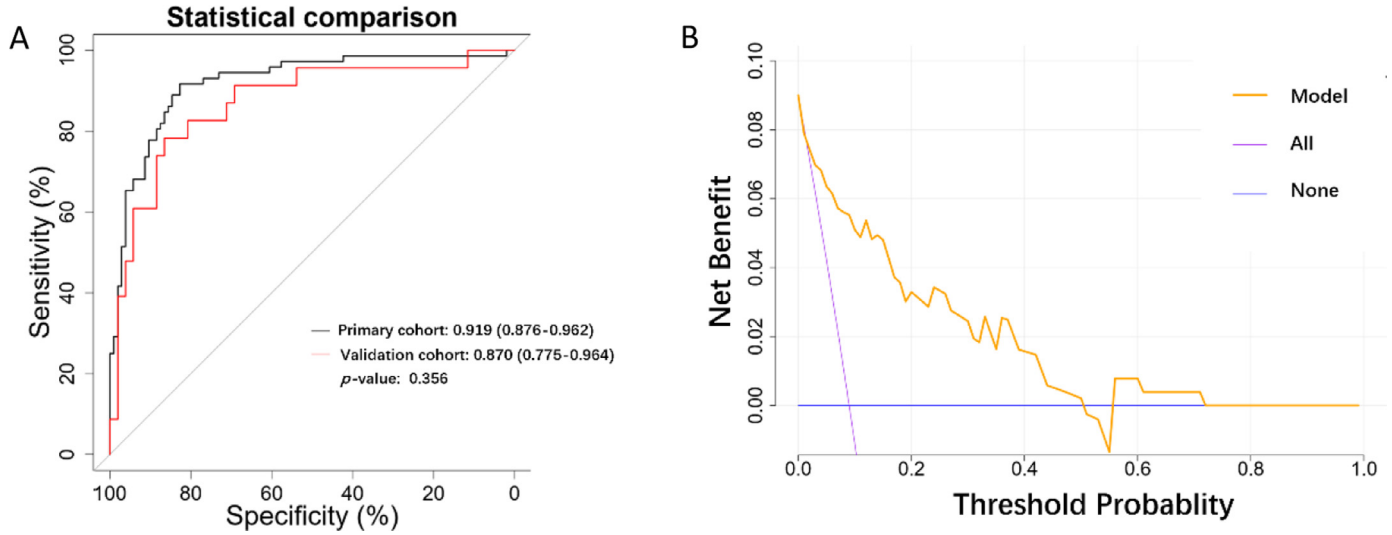

Fig. 4. Performance verification of the LRA model. A. ROC curve of the LRA model. The X-axis is the sensitivity of the model to predict LE, and the Y-axis is the specificity of the model to predict LE. The upper left grid represents the number of non-LE cases predicted by the LRA model from non-LE patients in the validation cohort. The upper right grid represents the number of LE cases predicted from non-LE patients in the validation cohort using the LRA model. The lower left grid represents the number of non-LE cases predicted by the LRA model from LE patients in the validation cohort. The lower right grid represents the number of LE cases predicted by the LRA modeln from LE patients in the validation cohort. B. Decision curve analysis (DCA) for the LRA model. The yellow line represents the LRA model. The purple line represents the assumption that all patients had LE, and the blue line represents the assumption that no patients had LE. The Y-axis measures net benefit. SLE, Systemic lupus erythematosus; LE, Lupus enteritis.

Table 2
Accuracy, senstivity and specificity of this prediction nomogram.

	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Training cohort	0.864 (0.862–0.865)	0.917 (0.853–0.981)	0.827 (0.754–0.900)
Validation cohort	0.840 (0.836–0.844)	0.783 (0.614–0.951)	0.865 (0.773–0.958)

0.917 (95% CI: 0.853–0.981) and 0.783 (95% CI: 0.614–0.951), and the specificity of these two cohorts were 0.864 (95% CI: 0.754–0.900) and 0.865 (95% CI: 0.773–0.958; Table 2). The results suggest that the LRA model was consistent and had good predictive capabilities.

The results of the decision curve analysis (DCA) revealed that using the LRA model to predict LE risk in SLE patients confers a net benefit, which highlights its clinical application value in LE risk prediction (Fig. 4B), which showed when the threshold probability of a doctor or patient was in the range of 0–0.5, the model achieved more net benefits than the "full treatment" or "no treatment" strategy.

9. Discussion

LE is a serious and potentially fatal complication and is the main cause of acute or chronic abdominal pain in SLE [23]. However, due to the lack of specificity in its clinical manifestation, patients often experience a delay in diagnosis and treatment, which can result in serious complications or death. In our study, we developed a LRA model and validated its ability to predict LE based on the clinical features of SLE patients with gastrointestinal manifestations. This model may be a new method to diagnose LE. The internal validation and DCA confirmed the model's discrimination and calibration capabilities; in particular, the AUC and matrix diagrams confirmed that the nomograph can be used clinically. Its use will increase the possibility of early intervention in high-risk patients, especially in primary hospitals in areas where medical resources are unevenly distributed.

A retrospective study analyzed 62 SLE patients with gastrointestinal manifestations and found that decreases in C4 levels in LE patients may be related to active mesenteric vascular lesions and the activation of the complement pathway [13]. In our study, similar to the aforementioned results, we found that C4 was negatively correlated with LE risk.

The anti-RNP, anti-SSA, and anti-Rib-P antibodies have been reported as specific autoantibodies of SLE and are related to its diagnosis and differential diagnosis [24]. We found that anti-RNP, anti-Rib-P, and anti-SSA antibodies were positively correlated with the occurrence of LE. Among them, anti-RNP antibodies were the highest risk factor. Chen's study revealed that the positive rate of anti-SSA and anti-RNP antibodies in SLE patients can be greater than 50% [25] Therefore, anti-SSA and anti-RNP antibodies may be related to the condition of SLE patients with LE. Others have reported that in SLE patients, the anti-RNP antibody is related to symptoms such as Raynaud's phenomenon, pulmonary hypertension, hemolytic anemia, leukopenia, and mental symptoms; [24,26] the association with Raynaud's phenomenon and pulmonary hypertension suggests that it may be related to vascular disease [27]. Positive anti-RNP antibodies have also been found to be an independent risk factor for death in patients with SLE and thrombotic microangiopathy [28]. Although the anti-RNP antibody's role in LE is unclear, it is associated with thrombosis in SLE patients, especially in the presence of lupus anticoagulant antibodies [29]. However, in this study, we did not find a link between lupus anticoagulant and LE. The anti-SSA antibody is associated with various autoimmune diseases, including Sjogren's syndrome, SLE, and primary biliary cirrhosis as well as with pulmonary hypertension, and neonatal heart block [24,30-32].

Anti-Rib-P antibody is a specific autoantibody that has diagnostic value for SLE and is related to disease activity and early onset [33,34]. However, the association between anti-Rib-P and LE is unclear. Anti-Rib-P antibodies can specifically bind to Rib-P antigens as well as to ribosomal proteins within cells and prevent protein synthesis [33,35]. Moreover, it can enhance the production of tumor necrosis factor and interleukin-6 and upregulate their mRNA expression in activated monocytes [36].

ANCA is an autoantibody considered to be closely related to multiple clinical small vasculitis diseases [37]. The research on the relationship between ANCA and SLE is still lacking. However, our results suggest that ANCA is negatively correlated with LE in SLE patients (Supplementary Fig. S2), which has yet to be reported in the literature. Therefore, we speculate that ANCA may be a risk factor for digestive system involvement in SLE, but this association needs further verification via basic experiments and clinical practice.

Although our study was well-designed, several limitations should be emphasized. This study was retrospective and involved a single center with a relatively small number of patients, which may result in reduced generalizability of the LRA model. Thus, to improve its performance, in future studies we plan to expand the sample size of SLE patients by using data from multiple hospitals and further optimizing the selection of statistically and clinically significant predictors based on current research findings.

In conclusion, we have established a prediction model based on clinical and serological indicators that predicts the occurrence of LE in SLE patients with gastrointestinal manifestations; this model may assist clinically in early intervention.

10. Evidence before this study

Lupus enteritis (LE) is a rare but fatal complication in patients with systemic lupus erythematosus (SLE). We searched PubMed for articles published in English on LE and found that although abdominal CT can bring some hints to the diagnosis of lupus LE, it still lacks effective and convenient diagnostic tools, and this difficulty poses a challenge for the development of clinical work.

11. Added value of this study

We established a prediction model of LE by LASSO regression analysis and a total of 11 variables were included in this model, of which complement 4 (OR: 0.2, 95% CI: 0.07–0.56), anti-Sjögren's-syndrome-related antigen A (OR: 1.29, 95% CI: 1.09–1.51), anti-ribosomal P protein (OR: 1.38, 95% CI: 1.18–1.61), and anti-ribonucleoprotein (OR: 1.49, 95% CI: 1.31–1.70) contributed most to the prediction model. These variables are all common tests for patients with SLE and are easy to obtain clinically and convenient to use.

12. Implications of all the available evidence

Clinically, the diagnosis of LE is often easily delayed. However, our model has a good predictive ability and provides clues and rationale for the development of LE in patients with SLE

Author contributions

ZH-L, MG and YR-C were responsible for experiment design, data analysis, and writing the manuscript. YZ were responsible for experiment design, acquisition and analysis of data. FX-Z and YL were responsible for revising the manuscript. All authors read and approved the final manuscript.

Data sharing statement

All data will be available upon reasonable request to the corresponding author, and it will be shared according to the standards of ethical policies regulating data sharing of human subjects.

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Declaration of Competing Interest

All the authors declare that this work was supported by the National Key Research and Development Program of China (Project no. 2016YFC0906201) and by the 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (Project No. ZYGD18015). All the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2021.100900.

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