Development and external validation of a prediction model for venous thromboembolism in systemic lupus erythematosus

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INTRODUCTION

Various factors are related to the occurrence of VTE in patients with SLE. The proposed SLE-VTE risk score can accurately predict the risk of VTE and help identify patients with SLE with a high risk of VTE who may benefit from thromboprophylaxis.

ABSTRACT

Objective Patients with systemic lupus erythematosus (SLE) have an increased risk of venous thromboembolism (VTE). We conducted this study to develop a risk score algorithm for VTE in patients with SLE that provides individualised risk estimates. Methods We developed a clinical prediction model of VTE in 4502 patients with SLE based on the Chinese SLE Treatment and Research group cohort (CSTAR) from January 2009 to January 2020 and externally validated in 3780 patients with SLE in CSTAR from January 2020 to January 2022. Baseline data were obtained and VTE events were recorded during the follow-up. The prediction model was developed to predict VTE risk within 6 months in patients with SLE, using multivariate logistic regression and least absolute shrinkage and selection operator. SLE-VTE score and nomogram were established according to the model. Results A total of 4502 patients included in the development cohort, 135 had VTE events. The final prediction model (SLE-VTE score) included 11 variables: gender, age, body mass index, hyperlipidaemia, hypoalbuminaemia, C reactive protein, anti-β2GPI antibodies, lupus anticoagulant, renal involvement, nervous system involvement and hydroxychloroquine, with area under the curve of 0.947 and 0.808 in the development and external validation cohort (n=4502) and external validation cohort (n=3780), respectively. According to the net benefit and predicted probability thresholds, we recommend annual screening of VTE in high risk (≥1.03%) patients with SLE. Conclusion Various factors are related to the occurrence of VTE risk stratification-guided management and thromboprophylaxis have been shown to reduce the incidence of VTE in high-risk patients. Monitoring for and the prevention of VTE, and ensuring that all patients are assessed individually and given adequate thromboprophylaxis are vital to reduce the risk of VTE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with systemic lupus erythematosus (SLE) have a substantially increased risk of venous thromboembolism (VTE).

WHAT THIS STUDY ADDS

⇒ The model (nomogram and app) we have developed will help physicians and researchers to predict the risk of VTE in patients with SLE.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with systemic lupus erythematosus (SLE) have a substantially increased risk of venous thromboembolism (VTE).

WHAT THIS STUDY ADDS

⇒ We developed and externally validated a model to help predict the risk of VTE in patients with SLE based on demographic data, clinical manifestations, laboratory markers and treatment of SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The model (nomogram and app) we have developed will help physicians and researchers to predict the risk of VTE in patients with SLE.

INTRODUCTION

Population-based evidence has found that patients with systemic lupus erythematosus (SLE) have a substantially increased risk of venous thromboembolism (VTE), especially in the first year after SLE diagnosis. Pulmonary embolism (PE) is a potentially fatal complication of deep vein thrombosis (DVT) with a high mortality rate in the first 3 months after diagnosis, rendering this complication as deadly as acute myocardial infarction. VTE risk stratification-guided management and thromboprophylaxis have been shown to reduce the incidence of VTE in high-risk patients. Monitoring for and the prevention of VTE, and ensuring that all patients are assessed individually and given adequate thromboprophylaxis are vital to reduce the risk of VTE.

Given the increased incidence of VTE in patients with SLE, a risk prediction model is needed to help identify subgroups of patients who would benefit most from early prevention.


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Several clinical VTE prediction models for specific populations such as pregnant women,\textsuperscript{8} patients with cancer\textsuperscript{9} and hospitalised medical patients\textsuperscript{10} have been reported. However, patients with SLE are younger and have fewer traditional comorbidities correlated with VTE, such as tumours, surgery and respiratory failure. Furthermore, this population may have several unique risk factors such as lupus nephritis (LN), glucocorticoid exposure and antiphospholipid antibodies (aPL). As a result, these risk stratifying tools may not be ideal for patients with SLE. The Global Antiphospholipid Syndrome Score (GAPSS) can predict the risk of thrombosis in patients with SLE\textsuperscript{11}; however, GAPSS cannot distinguish the risk of arterial thrombosis and venous thrombosis. To date, there has not been a risk assessment model to assess the risk of VTE in patients with SLE.

The Chinese SLE Treatment and Research group (CSTAR) developed the first online registry of Chinese patients with lupus in 2009 in a multicentre observational study that identified major clinical characteristics of patients with SLE.\textsuperscript{12} 13 In this study, we developed a clinical prediction model of VTE in patients with SLE based on the prospective CSTAR cohort and externally validated the model using an independent cohort.

**PATIENTS AND METHODS**

**Data source and study population**

The development data of the prediction model in our study was based on the CSTAR online registry, which includes patients with SLE from 314 participating rheumatology centres among 31 provinces in China. The external validation data of the model was based on CSTAR from January 2020 to January 2022. The diagnosis of SLE was confirmed by a medical record review and based on the 1997 revised American College of Rheumatology classification criteria.\textsuperscript{2012 Systemic Lupus International Collaborating Clinic criteria for SLE.}\textsuperscript{14} 15 Patients in the CSTAR cohort are followed up regularly at intervals of 1/3/6/12 months according to their condition, and the VTE events were recorded. This study defined outcome time and baseline time. For patients without VTE, the time of the last follow-up was the outcome time. The most recent follow-up time 6 months (or >6 months) before the outcome time is the baseline time. For patients with VTE, the time of first VTE after joining the CSTAR cohort was the outcome time. The most recent follow-up visit within 6 months before the outcome time of the study was the baseline time. We included patients who had two follow-up visits that coincided with both the baseline time and the outcome time.

If the potential candidate variables (below) in baseline data were missing, the patient will not be enrolled in the study. Patients younger than 18 years and those who presented with overlapping scleroderma, dermatomyositis, rheumatoid arthritis or other diffuse connective tissue diseases at baseline will also not be enrolled. Furthermore, since we were studying the risk of the first VTE in patients with SLE, those patients who had a history of VTE at baseline and were treated with continuous or direct anticoagulants (vitamin K antagonists, heparin or new oral anticoagulants) will also not be included. Patients who developed VTE due to the following reasons were also excluded, including tumours, surgery, trauma, chronic obstructive pulmonary disease or heart diseases such as congestive heart failure (figure 1).

**Definition of outcome**

All the VTE episodes should be confirmed by imaging or angiographic studies. PE was diagnosed based on evidence of pulmonary artery obstruction or filling defect on pulmonary angiography, thrombus on a CT pulmonary angiogram (CTPA), or a high-probability ventilation-perfusion scan.\textsuperscript{16} 17 DVT was diagnosed by ultrasound or venography.

**The collection and definition of variables**

All CSTAR centres followed the same protocol to provide uniform medical records and evaluations. Investigators received the same training on diagnostic confirmation, disease activity evaluation, data input and data quality control. Demographic data at baseline time (as defined above) were collected, including gender, age at onset, age at diagnosis, age at follow-up and body mass index (BMI). Personal smoking history was defined as smoking at least one cigarette (filter or non-filter) per day for at least 3 months. Hyperlipidaemia includes hypercholes terolaemia or hypertriglyceridaemia. We assessed the symptoms and signs according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at the baseline time of this study. An item is considered positive only if present at baseline. Organ involvement at baseline time was collected including neurological involvement, vasculitis, arthritis, myositis, renal involvement, mucocutaneous involvement and fever. All symptoms and signs at baseline time (neurological involvement, vasculitis, arthritis, myositis, renal involvement, rash, oral ulceration, pleuritis, pericarditis and fever) were defined according to the SLEDAI. Laboratory data, including routine blood examination, urinalysis sediment examination, hepatic and renal function examination, C reactive protein (CRP), lipid profile, complement, anti-double-stranded DNA (anti-dsDNA) antibody and anti-extractable nuclear antigen (anti-ENA) antibodies (including anti-SSA, anti-SSB, anti-Sm, anti-RNP and anti-RNP antibody), were collected. Medical records were also reviewed for results of aPL testing, including lupus anticoagulant (LA), antcardiolipin (ACL), anti-β-2-glycoprotein I (antiβ2GP1), IgG and IgM autoantibodies. In order to ensure the accuracy and comparability of antibody test results in different clinical centres, and to promote the standardisation of database construction, CRDC initiates annual autoantibody test comparisons between laboratories and standardised quality control training in different clinical centres. Subjects were considered aPL-positive if at least one of these autoantibodies was documented at
Figure 1  Flow chart of study design. AUC, area under the curve; CSTAR, Chinese SLE Treatment and Research group; DCA, decision curve analysis; GAPSS, Global Antiphospholipid Syndrome Score; IDI, integrated discrimination improvement; NRI, net reclassification improvement; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.
least 12 weeks apart. Leucocytopenia was defined as white cell count <4.0×10^9/L, thrombocytopenia as platelets <100×10^9/L and hypoalbuminaemia as serum albumin level <35 g/L. The use of aspirin, statins, hydroxychloroquine (HCQ) and glucocorticoids was recorded at each visit.

The antinuclear antibody (ANA) was detected via indirect immunofluorescence (IIF) using HEp-2 cell substrates. The anti-dsDNA antibody was measured by IIF using flagellate protocista substrates and an ELISA. The anti-ENA antibodies were detected using an immunodiffusion assay. The IgG/IgM antibodies of ACL antibody and anti-β2GPI were measured using ELISA. Dilute Russell viper venom time (dRVVT) testing and activated partial thromboplastin time were measured, where LA was considered positive if the ratio of dRVVT time was >1.20.

To facilitate the application of the model in clinical practice, the appropriate classification was performed for all candidate variables, and dummy variables were used to represent the data as zero and one. Continuous variables are presented as numbers and median and IQR (P25, P75) for all other variables are presented as mean and SD for normally distributed data. Categorical variables are presented as numbers (percentages).

Univariate analysis
Student’s t-tests or Mann-Whitney U tests were used to evaluate the association between normally distributed variables and VTE. The χ² test or Fisher’s exact test was used to evaluate for categorical variables, as appropriate.

Selection of variables into the final model
The significant risk factors for VTE in patients with SLE (p<0.05) were selected as candidate variables. Literature review and expert assessments were also performed to identify candidate variables with sufficient evidence as predictors in the model. The final variable selection into the model was made by the least absolute shrinkage and selection operator (Lasso) regression to prevent overfitting. And the optimal variables for the final model were found via cross-validation.

Development of the SLE-VTE score and risk stratification
A multivariable logistic regression model was used to develop a predictive model for VTE in patients with SLE. To evaluate the model’s discrimination ability, we examined the concordance index (C index), Nagelkerke’s R² index, Brier score, Hosmer-Lemeshow goodness-of-fit test and the calibration curve.

The theoretical relationship between a range of threshold probabilities for VTE and how it affects the relative value of false-positive and false-negative results (termed net benefit) was examined through decision curve analysis (DCA).

In order to develop easy-to-use clinician and patient friendly measures to predict the VTE risk in clinical practice, we formulated a nomogram (named as the SLE-VTE score) based on the logistic regression model, and the total points of the risk score were then calculated for each patient. According to the SLE-VTE score, we classified individuals into low-risk, moderate-risk, high-risk and very-high-risk groups (stratification cut points at the 50th, 75th and 95th percentiles of probabilities distribution).

We also compared the SLE-VTE score and GAPSS through the area under the receiver-operating characteristic (ROC) curve (AUC) and calculated the integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices.

External validation of the SLE-VTE score
We applied our risk prediction model to each patient in the external validation cohort. We examined the performance of the SLE-VTE score in terms of discrimination by calculating the C statistic (AUC).

Patient and public involvement
Patients and the public were not involved in our research. Prediction models were developed and evaluated following the checklist outlined in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis statement (online supplemental file 1).18

Statistical software
R software (V.3.6.3) was used for data analysis. The glmnet package was used for Lasso regression. The rms and pROC packages were used to develop and validate the model (see online supplemental material for R code). The p value was two tailed and statistical significance was set at p<0.05.

RESULTS
Study participants
We identified 4622 patients with SLE from the CSTAR cohort of 5267 patients with SLE, in which 645 patients were not enrolled, including 336 patients missing baseline data, 188 patients younger than 18 years, 121 patients with a history of VTE or undergoing treatment with continuous or direct anticoagulants (vitamin K antagonists or low-molecular-weight heparin). During the follow-up, 117 patients were excluded from the analysis because of lost follow-up, and 3 patients due to the development of VTE associated with malignant tumour (n=3). Finally, the development cohort included 4502 patients with a clear endpoint event of VTE to develop the model, with the baseline data time from January 2009 to January 2020, the onset time of SLE from February 1982 to January 2020, and a mean age of 34.99±10.84 years at baseline (see online supplemental materials for the details of enrollment and exclusion of patients). During the follow-up, 135 patients developed their first VTE event, including 91 DVT events (53 cases diagnosed by ultrasound, 14 cases by angiography, 24 cases by both) and 84 PE events (33 cases diagnosed by ventilation-perfusion scan, 44 cases by CTPA, 7 cases by both). Among 135 patients who
developed VTE. 40 patients developed both DVT and PE. A total of 114 patients received anticoagulation therapy, and 21 patients did not receive anticoagulation therapy. The basic characteristics of the study populations are shown in table 1.

Variable selection and model development
Based on the univariate analysis (shown in table 1) and the above screening principles, 26 potential candidate variables were considered for inclusion in the SLE-VTE prediction model, including variables found to be significantly associated with VTE. BMI, high blood pressure, stroke, anti-dsDNA and the use of aspirin were also included as candidate variables, due to their previously reported associations with VTE\(^2\)\(^3\)\(^4\)\(^5\) expert assessment. Each candidate variable was classified (online supplemental table 1). Eleven variables were selected using LASSO regression to improve model accuracy and reduce model overfitting, which yielded a \(\lambda\) value of 0.007548 (online supplemental figure 1).

We then developed a logistic prediction model using 11 variables confirmed to be significant risk factors by the Lasso regression. The 11 variables in the multivariate logistic regression model included: gender, age, BMI, hyperlipidaemia, hypoalbuminaemia, CRP, renal involvement, nervous system involvement, anti-\(\beta\)-2GPI antibody positivity, LA positivity and no use of HCQ (table 2).

Model performance and internal validation of the logistic model
The prediction logistic model produced good discrimination (AUC=0.946, \(R^2=0.536\), Brier score=0.018) and calibration (figure 2A). After enhanced bootstrap adjustment for optimism (500 bootstrap replications), the prediction model had an AUC of 0.944 and Nagelkerke’s \(R^2\) of 0.520. There was good agreement between the predicted and actual outcomes compared with the ideal curve (45° line) in the calibration curve (figure 2A), and also in the bootstrap samples (online supplemental figure 2). We also got acceptable goodness of fit (Hosmer-Lemeshow \(\chi^2=7.179\times10^{-22}\), 8 df; \(p=1\)) in the final logistic risk model. The Brier score for the model was 0.0176, and the optimism-corrected Brier score was 0.0183.

The net benefit of the logistic model
The DCA showed that it is useful to identify patients with SLE with a VTE risk greater than 0.2%–76.7% who would benefit from thromboprophylaxis (figure 2B). According to the risk stratification, we recommend screening patients with SLE with high and very high risk (≥10.03%) of VTE. For every 5–6 patients with a high risk of VTE, one patient will benefit from the model (online supplemental figure 3). We also got acceptable goodness of fit (Hosmer-Lemeshow \(\chi^2=7.179\times10^{-22}\), 8 df; \(p=1\)) for the final logistic risk model. The Brier score for the model was 0.0176, and the optimism-corrected Brier score was 0.0183.

Development of SLE-VTE score and risk stratification
This prediction algorithm based on the logistic regression model is graphically summarised as a nomogram in figure 3A. Points can be obtained using a point calliper (figure 3A, also shown in table 2) and then summed to obtain a total score (named as the SLE-VTE score) which can be measured with the risk of scale. In order to facilitate the clinical application of the SLE-VTE score, we also developed an app based on the model parameters. Figure 3B shows the screenshot of the deployed app, which is freely available for download in the app store. The predicted risk was classified as low risk (0 to <0.022%, score 0 to <35), moderate risk (≥0.22% to <1.03%, score ≥35 to <100), high risk (≥1.03% to <12.73%, score ≥100 to <211) and very high risk (≥12.73%, score ≥211) for 2014, 2015, 2016, 2017, 2018, 2019, 2020, and 2021 patients, respectively. The incidence rate of VTE in different risk groups is shown in figure 4. Combined with the analysis results of the DCA curve, we recommend that patients with high and very high risk of VTE (≥1.03%, SLE score ≥100) receive further VTE screening or preventive anticoagulation.

Comparison between the SLE-VTE score and GAPSS
The AUC of the SLE-VTE score in the development cohort was 0.947 (95% CI 0.9241 to 0.9691). The AUC of the GAPSS was 0.680 (95% CI 0.6351 to 0.7267). The SLE-VTE score had a significantly higher AUC (0.947 vs 0.680, \(p<0.001\)) and positive predictive value of 25.3% (119/471, threshold=157.5) than the GAPSS (15.5%, 22/142, threshold=11) (online supplemental figure 3). The IDI was 0.6654 (95% CI 0.586 to 0.7448, \(p<0.001\)), and the NRI was 0.6654 (95% CI 0.5863 to 0.7445, \(p<0.001\)).

External validation of the SLE-VTE score
Three thousand seven hundred and eighty patients with SLE in CSTAR from January 2020 to January 2022 were selected as external validation cohort. A total of 119 VTE events occurred in the external validation cohort. Clinical characteristics of the external validation cohort and comparison with the development cohort are presented in online supplemental table 3. Because the population from the external validation source comes from a later period, the improvement of SLE diagnosis and treatment, and the improvement of VTE vigilance have resulted in differences in the clinical characteristics of the validation cohort and the modelling cohort. Despite this, applying the SLE-VTE score to the independent population still gave a satisfactory C statistic (AUC) of 0.808 (95% CI 0.767 to 0.849). The AUC of the GAPSS in the external validation cohort was 0.790 (95% CI 0.747 to 0.833). The SLE-VTE score had a higher AUC (0.808 vs 0.790, \(p=0.427\)), but there was no statistical difference (online supplemental figure 4). The IDI was 0.1057 (95% CI 0.0085–0.2199, \(p=0.070\)), and the NRI was 0.1057 (95% CI 0.0085–0.2199, \(p=0.070\)).
### Table 1 Patient demographics and data

<table>
<thead>
<tr>
<th>Overall (n=4502)</th>
<th>VTE negative (n=4367)</th>
<th>VTE positive (n=135)</th>
<th>P value</th>
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<tr>
<td>Female, n (%)</td>
<td>4206 (93.43)</td>
<td>4096 (93.79)</td>
<td>110 (81.48)</td>
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<td>Age at study entry (year), mean (SD)</td>
<td>34.99 (10.84)</td>
<td>34.81 (10.70)</td>
<td>4.14 (5.98)</td>
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<td>BMI (kg/m²), mean (SD)</td>
<td>23.02 (6.41)</td>
<td>23 (6.47)</td>
<td>23.48 (4.22)</td>
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<td>Ever smoker, n (%)</td>
<td>139 (3.09)</td>
<td>126 (2.89)</td>
<td>13 (9.63)</td>
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<td>Comorbidity</td>
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<td>Diabetes, n (%)</td>
<td>209 (4.64)</td>
<td>194 (4.44)</td>
<td>15 (11.11)</td>
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<td>Hypertension, n (%)</td>
<td>472 (10.48)</td>
<td>453 (10.37)</td>
<td>19 (14.07)</td>
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<td>Hyperlipaemia, n (%)</td>
<td>319 (7.09)</td>
<td>295 (6.76)</td>
<td>24 (17.78)</td>
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<td>Coronary heart disease, n (%)</td>
<td>26 (0.58)</td>
<td>23 (0.53)</td>
<td>3 (2.22)</td>
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<td>Stroke/TIA, n (%)</td>
<td>83 (1.84)</td>
<td>79 (1.81)</td>
<td>4 (2.96)</td>
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<tr>
<td>Cardiovascular</td>
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<td></td>
<td></td>
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<td>Rash, n (%)</td>
<td>397 (8.82)</td>
<td>383 (8.77)</td>
<td>14 (10.37)</td>
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<tr>
<td>Oral ulceration, n (%)</td>
<td>128 (2.84)</td>
<td>120 (2.75)</td>
<td>8 (6.3)</td>
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<td>Alopecia, n (%)</td>
<td>439 (9.75)</td>
<td>423 (9.69)</td>
<td>16 (11.85)</td>
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<td>Fever, n (%)</td>
<td>146 (3.24)</td>
<td>130 (2.98)</td>
<td>16 (11.85)</td>
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<td>Leucopenia, n (%)</td>
<td>409 (9.08)</td>
<td>394 (9.02)</td>
<td>15 (11.11)</td>
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<td>Thrombocytopenia, n (%)</td>
<td>333 (7.4)</td>
<td>302 (6.92)</td>
<td>31 (22.96)</td>
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<td>Neurological involvement, n (%)</td>
<td>163 (3.62)</td>
<td>144 (3.30)</td>
<td>19 (14.07)</td>
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<td>Renal involvement, n (%)</td>
<td>700 (15.55)</td>
<td>622 (14.24)</td>
<td>78 (57.78)</td>
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<td>Pleuritis, n (%)</td>
<td>82 (1.82)</td>
<td>67 (1.53)</td>
<td>15 (11.11)</td>
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<tr>
<td>Pericarditis, n (%)</td>
<td>86 (1.91)</td>
<td>75 (1.72)</td>
<td>11 (8.15)</td>
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<td>Arthritis, n (%)</td>
<td>497 (11.04)</td>
<td>483 (11.60)</td>
<td>14 (10.37)</td>
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<td>SLEDAI-2K, median (IQR)</td>
<td>2 (0–4)</td>
<td>2 (0–4)</td>
<td>8 (3.75–12)</td>
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<td>Laboratory variables</td>
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<tr>
<td>Hypoalbuminaemia</td>
<td>456 (10.13)</td>
<td>370 (8.47)</td>
<td>86 (63.7)</td>
</tr>
<tr>
<td>ESR&gt;20 mm/h</td>
<td>1 121 (24.9)</td>
<td>1 028 (23.54)</td>
<td>93 (68.89)</td>
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<td>CRP&gt;8 mg/L</td>
<td>404 (8.97)</td>
<td>334 (7.65)</td>
<td>70 (51.85)</td>
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<td>Hypocomplementaemia</td>
<td>1303 (28.94)</td>
<td>1235 (28.28)</td>
<td>68 (50.37)</td>
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<td>Autoantibodies (positive)</td>
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<td>ANA, n (%)</td>
<td>4340 (96.4)</td>
<td>4215 (96.52)</td>
<td>125 (92.59)</td>
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<td>anti-dsDNA, n (%)</td>
<td>1172 (26.03)</td>
<td>1128 (25.83)</td>
<td>44 (32.59)</td>
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<td>a-Sm, n (%)</td>
<td>1794 (39.85)</td>
<td>1744 (39.94)</td>
<td>50 (37.04)</td>
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<td>a-RNP, n (%)</td>
<td>1450 (32.21)</td>
<td>1402 (32.10)</td>
<td>48 (35.56)</td>
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<td>a-SSA, n (%)</td>
<td>2148 (47.71)</td>
<td>2079 (47.61)</td>
<td>69 (51.11)</td>
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<td>a-SSB, n (%)</td>
<td>755 (16.77)</td>
<td>739 (16.92)</td>
<td>16 (11.85)</td>
</tr>
<tr>
<td>a-RN;P, n (%)</td>
<td>703 (15.62)</td>
<td>681 (15.59)</td>
<td>22 (16.3)</td>
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<td>ACL, n (%)</td>
<td>541 (12.02)</td>
<td>510 (11.68)</td>
<td>31 (22.96)</td>
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<tr>
<td>Anti-IgG, n (%)</td>
<td>477 (10.6)</td>
<td>440 (10.08)</td>
<td>37 (27.41)</td>
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<td>LA, n (%)</td>
<td>466 (10.35)</td>
<td>411 (9.41)</td>
<td>55 (40.74)</td>
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<td>Treatment</td>
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<tr>
<td>Prednisone (or equivalent) (mg/d), median (IQR)</td>
<td>8 (4–13.75)</td>
<td>8 (4–12)</td>
<td>32 (5–50)</td>
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<tr>
<td>Use of HCQ, n (%)</td>
<td>3689 (81.94)</td>
<td>3647 (83.51)</td>
<td>42 (31.11)</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>442 (9.82)</td>
<td>435 (9.96)</td>
<td>7 (5.19)</td>
</tr>
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</table>

Values in bold are statistically significant at p<0.05.

ACL, anticardiolipin; ANA, antinuclear antibodies; anti-dsDNA, anti-double-stranded DNA; anti-RNP, anti-ribonucleoprotein; anti-RN;P, anti-ribosomal RNP; anti-Sm, anti-Smith; anti-SSA, anti-SSA/Ro; anti-SSB, anti-SSB/La; anti-IgG, anti-IgG-2-glycoprotein I; BMI, body mass index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; HCQ, hydroxychloroquine; LA, lupus anticoagulant; SLEDAI, SLE Disease Activity Index.
You H, et al. RMD Open 2023;9:e003568. doi:10.1136/rmdopen-2023-003568

**Table 2** Logistic analysis for venous thromboembolism risk in patients with SLE before and after adjustment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before adjustment</th>
<th>After adjustment</th>
<th>β coefficients</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.234</td>
<td>0.621</td>
<td>&lt;0.001</td>
<td>0.621</td>
<td>0.061</td>
<td>26</td>
</tr>
<tr>
<td>Age at study entry(≥50)</td>
<td>1.192</td>
<td>1.038</td>
<td>&lt;0.001</td>
<td>1.038</td>
<td>0.002</td>
<td>35</td>
</tr>
<tr>
<td>BMI≥25</td>
<td>1.093</td>
<td>0.838</td>
<td>&lt;0.001</td>
<td>0.838</td>
<td>0.006</td>
<td>35</td>
</tr>
<tr>
<td>Hyperlipaemia</td>
<td>2.942</td>
<td>2.163</td>
<td>&lt;0.001</td>
<td>2.163</td>
<td>&lt;0.001</td>
<td>91</td>
</tr>
<tr>
<td>Hypoalbuminaemia</td>
<td>2.565</td>
<td>1.452</td>
<td>&lt;0.001</td>
<td>1.452</td>
<td>&lt;0.001</td>
<td>61</td>
</tr>
<tr>
<td>hsCRP&gt;3mg/L</td>
<td>2.565</td>
<td>2.382</td>
<td>&lt;0.001</td>
<td>2.382</td>
<td>&lt;0.001</td>
<td>61</td>
</tr>
<tr>
<td>β2GPI</td>
<td>1.215</td>
<td>1.013</td>
<td>&lt;0.001</td>
<td>1.013</td>
<td>0.001</td>
<td>43</td>
</tr>
<tr>
<td>Nervous system</td>
<td>1.79</td>
<td>1.599</td>
<td>&lt;0.001</td>
<td>1.599</td>
<td>0.001</td>
<td>33</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>2.109</td>
<td>2.382</td>
<td>&lt;0.001</td>
<td>2.382</td>
<td>&lt;0.001</td>
<td>61</td>
</tr>
<tr>
<td>No use of hydroxychloroquine</td>
<td>1.79</td>
<td>1.599</td>
<td>&lt;0.001</td>
<td>1.599</td>
<td>0.001</td>
<td>33</td>
</tr>
</tbody>
</table>

Values in bold are statistically significant at p<0.05.

**DISCUSSION**

We devised a simple point score algorithm, the SLE-VTE score, with the potential to detect patients with SLE who are at a high risk of developing VTE within 6 months. We then externally validated this model in an independent cohort and got favourable calibration and discrimination. To the best of our knowledge, this is the first analysis of a prediction scoring algorithm of VTE in patients with SLE. This model is based on demographic data (gender, age and BMI), clinical manifestations (hyperlipidaemia, renal involvement and nervous system involvement), laboratory markers (hypoalbuminaemia, CRP, aPL) and treatment (HCQ) of a very large population. As the SLE-VTE score uses easily accessible demographic, clinical and laboratory variables, it can be directly applied in clinical practice and is readily amenable to further external validation in other cohorts with routine data available. And the scoring algorithm is also available for clinical use as a printed nomogram or as a mobile phone app. This scoring algorithm provides a more evidence-based approach to VTE prevention in patients with SLE that can be implemented as part of clinical practice guidelines.

Two specific clinical manifestations of SLE were included in the model: nervous system and renal involvement. Neurological involvement in lupus is a serious manifestation of SLE involving ischaemic and inflammatory mechanisms. Patients with nervous system involvement often need to be immobilised during treatment, promoting thrombosis. LN has been reported to be a significant risk factor for vascular thrombosis in patients with SLE, especially those with heavy proteinuria. The inflammatory status in active SLE may affect vascular homeostasis or elevate blood coagulability through vascular endothelial dysfunction. Hypoalbuminaemia has been reported to be correlated with VTE. Insufficient blood volume resulting from hypoproteinemia and the use of diuretics may also be involved in the process of thrombosis. Positive aPL is known to be an independent risk factor for thrombosis, and aPL is also an important part of the GAPSS score. We did not include antibodies to phosphatidylserine-prothrombin complex (aPS/PT) in our model, as this examination is not routinely performed for patients with SLE. A previous study in our centre reported that patients with SLE have a series of risk factors related to thrombosis. We found that inflammation state, hypoalbuminaemia, short SLE disease course and other factors are risk factors for VTE.
Figure 2  Calibration curve and decision curve of the logistic model to predict VTE in patients with SLE. (A) Calibration curve comparisons between the CSTAR cohort-based and SLE-VTE logistic model-based risk of VTE in development cohort. The y-axis represents the observed VTE rate. The diagonal grey 45° line represents good prediction by the ideal model. The concordance index (C) represents the area under the curve (AUC). R^2 represents Nagelkerke’s R^2; Emax represents the maximum absolute difference in predicted and loess-calibrated probabilities. The histograms represent the predicted probabilities of the models that display the density distribution of the predicted risks, indicating relative frequency. (B) Decision curve for the logistic model to predict VTE in patients with SLE. The expected net benefit per patient relative to a ‘treat none’ approach is shown. The curve for the prediction model (blue line) showed a positive net benefit for probability thresholds between 0.2% and 76.7% compared with screening in patients with SLE as if they will all have VTE (grey line) or screening them as if none of them will have VTE (black line). The unit is in terms of VTE found: a model with a net benefit of 0.1 is the equivalent of a strategy that treats 10 men per 100 with no wrong treatment. ROC, receiver-operating characteristic; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.
Figure 3  Nomogram and app (SLE-VTE score) for predicting the 6 months risk of venous thromboembolism in patients with SLE. (A) Nomogram predicting the probability of VTE in patients with SLE. Points for gender, age, BMI, hyperlipidaemia, hypoalbuminaemia, CRP, anti-β2-glycoprotein I antibody, lupus anticoagulant, renal involvement, nervous system involvement and no use of hydroxychloroquine can be obtained using a point calliper (also shown in table 2) and then summed to obtain a total score which can be measured with the risk of scale. The predictive scoring algorithm was formulated as: 

\[26 \times \text{gender} + 35 \times \text{age} (\geq 50) + 33 \times \text{BMI} (\geq 25 \text{kg/m}^2) + 35 \times \text{hyperlipidaemia} + 91 \times \text{hypoalbuminaemia} + 61 \times \text{CRP} (+ > 8 \text{mg/L}) + 43 \times \text{anti-β2-glycoprotein I antibody} + 65 \times \text{lupus anticoagulant} + 100 \times \text{renal involvement} + 74 \times \text{HCQ}.\]

(B) The ‘SLE-VTE score’ can be freely available for download in the app store or can be downloaded by scanning the QR code. BMI, body mass index; ALB, albumin; CRP, C reactive protein; HCQ, hydroxychloroquine; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.
in patients with SLE during hospitalisation.2 Deranged intravascular and systemic immune homoeostasis in lupus patients likely synergises with adverse effects of drugs and traditional cardiovascular risk factors to promote vascular injury, contribute to a prethrombotic state and lead to acute thrombosis.27

In our cohort, the SLE-VTE score might add more valuable parameters to the GAPSS score in predicting the risk of VTE in patients with SLE. GAPSS is a risk score based on a cross-sectional study to predict the risk of thrombosis or pregnancy loss in patients with SLE.11 GAPSS has been well externally validated in several studies,28–30 most of which include patients with APS. However, the GAPSS was not originally designed for patients with SLE, suggesting that GAPSS may not be fully applicable to predict VTE in patients with SLE. The SLE-VTE score was based on a large multicentre and longitudinal cohort of patients with SLE. And we included several specific indicators of SLE in the model, which allow the SLE-VTE score to more specifically predict the risk of VTE in patients with SLE.

We assessed the clinical utility of our model using DCA21 and found the risk stratification strategy based on the SLE-VTE score provided further benefit for patients with a high risk of VTE. According to the risk stratification, patients with lupus are stratified into different risk groups for VTE based on their risk levels. Screening for VTE is recommended in these high-risk and very-high-risk groups (≥1.03%, SLE score ≥100). The model predicts 1 out of 5–6 high-risk patients will benefit from screening using this approach. This risk-stratified method may improve the precision and efficiency of screening VTE in patients with SLE and enable physicians to consider prophylactic anticoagulation therapy as early as possible. There are no standard preventive treatment guidelines for patients with SLE who are at high risk of VTE. Currently, most of the preventive anticoagulation we can take comes from clinical experience. Prophylactic doses of heparin, vitamin K antagonist or rivaroxaban can be options. For patients with positive aPL antibodies, heparin or vitamin K antagonists may be a better choice.32 There is limited evidence on the safety and effectiveness of aspirin as a sole prophylactic agent. The CRISTAL Randomised Trial found that in patients undergoing hip or knee arthroplasty for osteoarthritis, aspirin compared with enoxaparin resulted in a significantly higher rate of symptomatic VTE.33 The selection of these anticoagulation regimens requires further clinical studies to confirm.

DCA is a novel method that overcomes problems associated with other evaluation methods and has been applied in a series of studies. However, further research is needed to assess the benefit of thromboprophylaxis in patients with SLE as the concept of net benefit in DCA is a mathematically derived definition that is difficult to apply clinically. Despite this, the SLE-VTE Score had a high positive predictive value both in the development cohort and validation cohort. These results prove the effectiveness of the SLE-VTE score and indicate the benefits of preventive anticoagulation to high-VTE-risk patients.

This study has several limitations. First, some important variables that are not routine test items for patients with SLE were not included, such as APS/PT, D-dimer and fractures. Second, the baseline data of the cohort include both baseline data collected during hospitalisation and baseline data during outpatient follow-up. Inpatients and outpatients may represent different disease states, but we do not distinguish between inpatients and outpatients. Inpatients tend to be more severely ill, and their disease conditions change more quickly. In the future, specific prediction models for inpatients and outpatients can be developed separately. Another limitation is that when building the model, in order to facilitate clinical use, all continuous variables were converted into categorical variables, including age, BMI, etc. This results in a loss of information to a certain extent and will affect the accuracy of the model. Even so, the model still achieved relatively satisfactory evaluation results in the development cohort and external validation cohort. The temporal external validation is also a limitation of this study. Some information, including coding of data and participant characteristics, is similar in the later (post-2020) data. Nonetheless, comparative analysis between the development cohort and the validation cohort showed that most variables were different, suggesting that the two cohorts were not exactly similar. However, more different external validation cohorts are still needed to verify the model later. Future research with a large patient population is needed to further externally validate and update.
our SLE-VTE scoring algorithm and to establish whether other factors are independently associated with VTE in addition to those already in the model. Furthermore, long-term risks remain to be quantified, as the survival time of patients with SLE is increasing. Because this is an observational study to establish a diagnostic predictive model, studies of the benefits of preventive anticoagulation are also needed in the future. Last but not least, patients and the public did not participate in this study, which will play a really important role in helping to identify relevant predictor variables and in helping shape how these models can be used in practice. We will involve patients and the public in improving the model in future studies.

In conclusion, we developed and externally validated a clinical scoring algorithm for predicting VTE in patients with SLE. Various factors are related to the occurrence of VTE in SLE. Using clinical and laboratory variables, the calculated SLE-VTE score can accurately predict the risk of VTE in individual patients and may help to identify those who have a high risk of VTE, and patients would benefit from the control of those risk factors of VTE and thrombophrophylaxis.

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Correction notice This article has been corrected since it was first published online. The corresponding author list has been updated to include Xiaofeng Zeng.

Acknowledgements We thank all authors for their continuous and excellent support with patient data collection, data analysis, statistical analysis and valuable suggestions for the article.

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Funding This work was supported by research grant from the Chinese National Key Technology R&D Program, Ministry of Science and Technology (grant numbers 2021YFC2501030, 2017YFC0907600); CAMS Innovation Fund for Medical Sciences (CIFMS) (grant number 2021-I2M-1-005); Fundamental Research Funds for the Central Universities (grant number 3332018039); Beijing Municipal Science & Technology Commission (grant number Z201100005520023, Z201100005520027); the special Financial Grant from the China Postdoctoral Science Foundation (grant number 2021T100134); Natural Science Foundation of Jiangsu Province (grant number BK20210864); National Natural Science Foundation of China (NSFC) (grant number 82302041); Doctoral Program of Entrepreneurship and Innovation in Jiangsu Province (grant number JSSCBS20211479).

Disclaimer No author has been paid to write this article by a pharmaceutical company or other agency. The funders/ sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study protocol was approved by the Medical Ethics Committee of Peking Union Medical College Hospital with reference number JS-2038. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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