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ORIGINAL RESEARCH

Prediction of Flares in Systemic Lupus Erythematosus During Post-Remission Follow-up

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Purpose: Patients at high risk of SLE flares benefit from being identified before flares; this can be done by predictors of flares. This study aimed to explore the predictive factors and model of SLE flares after remission, providing basis for clinical decision-making.

Patients and Methods: SLE patients recruited at the Peking Union Medical College Hospital (PUMCH), were all registered in the Chinese SLE treatment and research (CSTAR) registry cohort and had experienced at least one remission before December 31, 2020. Demographic, clinical, and laboratory parameters were collected through CSTAR online registry. The predictive effects of variables were analyzed using a Cox proportional hazards model. A nomogram was formulated to predict flares.

Results: A total of 359 patients were included in the analysis, among which, 108 (30.1%) patients had at least one flare. Multivariate Cox regression model showed that younger age (hazard ratio [HR], 0.97; 95% CI, 0.95–0.99), positive anti-dsDNA at remission (HR, 1.64; 95% CI, 1.08–2.51), significantly low levels of C3 and C4 (HR, 2.09; 95% CI, 1.17–3.73) were independent risk factors associated with flares. A nomogram was established based on the multivariate analysis. The internal bootstrap resampling approach suggested the nomogram has a certain degree of discriminatory power with a C-index of 0.654 (95% CI, 0.601–0.707). The calibration plots also showed good consistency between the prediction and the observation.

Conclusion: This study highlights that SLE patients with significantly low levels of C3 and C4, younger age, and elevated anti-dsDNA levels may require closer monitoring and follow-up after remission. Identifying these predictors allows clinicians to better assess the risk of flare and tailor therapeutic strategies accordingly for more effective long-term management.

Keywords: SLE, predictors, complements, model

Introduction

Systemic lupus erythematosus (SLE) is a diffuse immune-mediated, chronic inflammatory disease of the connective tissue, which leads to organ damage and low quality of life. Treatment in SLE aims at remission or low disease activity.[1] Remission in particular, is the most desirable target in the management of SLE, as it leads to a significant improvement in prognosis. Thus far, remission defined by the Definitions Of Remission In SLE (DORIS) international task force is a common goal.[2] However, relapse-remission is the nature of SLE.[3] Approximately 70% of SLE patients follow a relapsing-remitting course.[4] Therefore, how to prevent flares after remission is also a critical challenge in the management of SLE.[1] Early drug intervention has been reported to prevent severe flares in patients with serologically active, but clinically stable systemic lupus erythematosus,[5] indicating the importance of predicting flares. However, previous studies of predictive factors of flares showed contradictory findings. As widely acknowledged, both complement and anti-dsDNA play pivotal roles in the diagnosis and activity assessment of SLE.[6] They have been incorporated as scoring elements in the 2019 European Association for Rheumatology/American Society of Rheumatology classification criteria for systemic lupus erythematosus[7] and serve as indicators for evaluating SLE activity.[8] However, the clinical utility of complement and anti-dsDNA is constrained in the predictive capacity for SLE flares by

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heterogeneous results found by numerous studies.[9,10] In addition, due to the high uncertainty of the etiology of SLE flares, a singular risk factor is insufficient to comprehensively estimate the overall risk of SLE flares. Consequently, our study endeavors to investigate predictive factors for SLE flares following remission, providing foundation for informed clinical decision-making.

Patients and Methods

Study Cohort and Patients

The patients were recruited at the Peking Union Medical College Hospital (PUMCH), who were all registered in the Chinese SLE treatment and research (CSTAR) registry cohort before December 31, 2020.

All patients fulfilled either the 1997 American College of Rheumatology (ACR) Modified Classification Criteria for SLE,[11] or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria,[12] and had experienced at least one remission before December 31, 2020. After enrollment, they were followed up at the PUMCH clinic.

Declaration

Ethics approval and consent to participate. The institutional review boards (the ethics committee of Peking Union Medical College Hospital, China, no. JS-2038) approved all protocols, and all patients provided their informed consent forms. Guidelines outlined in the Declaration of Helsinki were followed. This study was performed without direct patient and public involvement. Access to private data can be granted upon request.

Definitions

According to the 2021 DORIS definition of remission in SLE,[2] the remission was defined as follows: (1) Clinical SLEDAI (cSLEDAI-2K)=0; (2) Physician Global Assessment (PGA) <0.5 (0–3); (3) Irrespective of serology; (4) The patient may be on antimalarials, low-dose glucocorticoids (prednisolone ≤5 mg/day), and/or stable immunosuppressives including biologics.

Flares were defined as 1 or more of the following: (1) greater than a 3-point change in cSLEDAI-2K from the previous visit; (2) appearance of a new SLE clinical manifestation or worsening of a preexisting clinical manifestation that resulted in restarting or increasing corticosteroids, hydroxychloroquine, nonsteroidal anti-inflammatory drugs, or immunosuppressants after remission. (3) change in PGA score of 1.0 or more.

Hypocomplementemia was defined as C3 or C4 below the laboratory reference range. Significantly low levels of C3 or C4 were defined as C3 below 0.6655 or C4 below 0.1045 during the interval from remission to flares or the last visit (excluding data at flares or the last visit). A positive anti-dsDNA result was determined as a level exceeding the reference range established by the laboratory, in accordance with the SLICC classification criteria.

Regular follow-up refers to the follow-up of patients for more than 2 years or until the first flares with visits no more than 1 year apart. The data at remission included in the analysis were from the first remission at the beginning of regular follow-up. Disease duration was defined as the time interval from symptom onset to the first remission after regular follow-up. Follow-up duration refers to the time between the first remission after regular follow-up and the first flares for patients with flares or the last visit for patients without flares. During the follow-up period, only the first relapse was used in the analysis.

Data Collection

Demographic, clinical, and laboratory parameters were collected through CSTAR online registry, including gender, age at remission, disease duration, SLEDAI-2K at remission, and positive anti-dsDNA antibody at remission. SLE-related organ involvements before remission, such as cutaneous, arthritis, serositis, lupus nephritis (LN), neuropsychiatric SLE (NPSLE), hematological involvement (Leukopenia, thrombocytopenia, and hemolytic anemia), pulmonary arterial hypertension (PAH), were collected from the medical records of all recruited patients.

To evaluate the prognostic significance of complement levels in predicting SLE flares, a comprehensive set of data was collected, encompassing instances of hypocomplementemia at diagnosis, at remission, and during post-remission

follow-up (excluding flares or the last visit); the minimum level of C3 and C4 during the interval from remission to flares or the last visit (excluding data at flares or the last visit), as well as instances of significantly low levels of C3 and/or C4.

Statistical Analysis

Categorical variables were described as numbers (percentages) and compared using Chi-square test or Fisher's exact test. Continuous variables were presented as medians (interquartile range (IQR]) and compared using Mann–Whitney nonparametric *U*-test. A receiver operating characteristics (ROC) curve was formulated to analyze the value of the minimum level of C3 and C4 during the interval from remission to flares or the last visit (excluding data at flares or the last visit) in predicting SLE flares and to find the optimal cut-off value. Categorical variable models were further defined by the optimal cut-off value. Factors with significant differences ($P < 0.05$) in bivariate analysis were subsequently incorporated into a multivariate Cox regression analysis model. A nomogram was constructed based on the results of multivariate Cox regression analysis using the rms package in R version 4.3.2. The performance of the nomogram was measured using the Harrell concordance index (C-index), and also assessed by comparing between nomogram-predicted and observed Kaplan-Meier estimates of flare-free probability. Bootstraps of 1000 resamples were set, and calibration curves were calculated through regression analysis. All reported P values were two-sided, with the threshold for statistical significance set at $P <0.05$. All statistical analyses were performed using R version 4.3.2.

Results

Study Populations

A total of 393 cases were initially enrolled, among whom, 24 patients were excluded for insufficient follow up time and 10 cases for missing important data points. Ultimately, 359 patients were included in the analysis. As shown in Table 1, among the 359 patients, 251 (69.9%) patients had no flares during the follow-up period, and 108 (30.1%) patients had at least one flare. The median follow-up duration after remission was 3.48 years (IQR 2.63–4.49) and 1.80 years (IQR 0.95–3.26) in non-flare patients and flare patients respectively.

Table 1 Comparison of Non-Flare vs Flare Patients by Bivariate Analysis

	Non-flare Patients (n=251)	**Flare Patients (n=108)**	***P* value**
Gender, F(%)	237 (94.4)	107 (99.1)	0.083
Age at remission, years, median [IQR]	35.4 [29.5, 42.1]	30.7 [27.8, 37.4]	<0.001
Disease duration, years, median [IQR]	6.80 [3.50, 11.40]	8.20 [4.0, 12.08]	0.232
Follow-up duration, years, median [IQR]	3.48 [2.63, 4.49]	1.80 [0.95, 3.26]	<0.001
Cutaneous, n(%)	123 (49.0)	60 (55.6)	0.255
Arthritis, n(%)	134 (53.4)	66 (61.1)	0.177
Serositis, n(%)	32 (12.7)	21 (19.4)	0.101
Nephritis, n(%)	102 (40.6)	47 (43.5)	0.611
Nervous system, n(%)	21 (8.4)	7 (6.5)	0.541
Hemolytic anemia, n(%)	15 (6.0)	5 (4.6)	0.610
Leukopenia, n(%)	90 (35.9)	33 (30.6)	0.332
Thrombocytopenia, n(%)	60 (23.9)	20 (18.5)	0.261
Pulmonary arterial hypertension, n(%)	25 (10.0)	12 (11.1)	0.742
SLEDAI-2K at remission, n(%)			0.059
0	174 (69.3)	67 (62.0)	
2	58 (23.1)	24 (22.2)	
4	19 (7.6)	17 (15.7)	

(*Continued*)

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Table 1 (Continued).

	Non-flare Patients (n=251)	Flare Patients (n=108)	*P* value
Positive anti-dsDNA at remission, n(%)	54 (21.5)	41 (38.0)	0.001
Hypocomplementemia at diagnosis, n(%)	189 (75.3)	85 (78.7)	0.486
Hypocomplementemia at remission, n(%)	46 (18.3)	28 (25.9)	0.103
Hypocomplementemia during post-remission follow-up, n(%)	91 (36.3)	46 (42.6)	0.257
The minimum level of C3, g/L, median [IQR]	0.82 [0.70, 0.94]	0.78 [0.64, 0.92]	0.073
The minimum level of C4, g/L, median [IQR]	0.12 [0.10, 0.16]	0.11 [0.08, 0.15]	0.006
Significantly low levels of C3 and C4, n(%)	22 (8.8)	32 (29.6)	<0.001
Significantly low levels of C3 or C4, n(%)	83 (33.1)	51 (47.2)	0.011
Dose of GCs at flares or the last visit, mg/d, median [IQR]	2.5 [0, 5.0]	2.5 [0, 5.0]	0.425
Dose of HCQ at the time of remission, g/d, median [IQR]	0.4 [0.3, 0.4]	0.4 [0.4, 0.4]	0.076
Dose of HCQ at flares or the last visit, g/d, median [IQR]	0.4 [0.4, 0.4]	0.4 [0.4, 0.4]	0.550
Immunosuppressant at the time of remission, n(%)	167 (66.5)	72 (66.7)	0.980
Immunosuppressant at flares or the last visit, n(%)	155 (61.8)	74 (68.5)	0.221

Notes: The data at remission included in the analysis were from the first remission at the beginning of regular follow-up. Disease duration: the time interval from symptom onset to the first remission after regular follow-up. Follow-up duration: the time between the first remission after regular follow-up and the first flares for patients with flares or the last visit for patients without flares. Regular follow-up: the follow-up of patients for more than 2 years or until flares with visits no more than 1 years apart. The minimum level of C3 or C4: the lowest value that occurred during the interval from remission to flares or the last visit (excluding data at flares or the last visit). Significantly low levels of C3 and C4: C3 below 0.6655 with C4 below 0.1045 during the interval from remission to flares or the last visit (excluding data at flares or the last visit). Significantly low levels of C3 or C4: C3 below 0.6655 or C4 below 0.1045 during the interval from remission to flares or the last visit (excluding data at flares or the last visit).
Abbreviations: GCs, glucocorticoids (prednisone [or equivalent]); HCQ, hydroxychloroquine.

Identification of Independent Risk Factors for SLE Flares

Flare patients were younger at remission (median age 30.7 years [IQR 27.8–37.4] versus 35.4 years [IQR 29.5–42.1], $P < 0.001$) and had higher anti-dsDNA positive rate at remission (38.0% versus 21.5%, $P = 0.001$) than non-flare patients. We did not find significant differences between non-flare and flare patients in regards to gender, SLE-DAI-2K at remission, and dose of glucocorticoids (GCs) or hydroxychloroquine (HCQ) or the use of immunosuppressant at flares or the last visit. There was no statistically significant difference between non-flare and flare patients in the incidence of hypocomplementemia at diagnosis, at remission, or during post-remission follow-up. The frequency of SLE-related organ involvements before remission in the two cohorts is also outlined in Table 1. There were no between-group differences in the prevalence of SLE-related organ involvements.

The minimum level of C4 in flare patients was slightly lower than that in non-flare patients (median level 0.11g/L [IQR 0.08–0.15] versus 0.12 g/L [IQR 0.10–0.16], $P = 0.006$), while there was no significant difference in the minimum level of C3 between groups (Table 1). The ROC analysis curve showed the optimal cut-off value for the minimum level of C3 and C4 during the interval from remission to flares or the last visit (excluding data at flares or the last visit) in predicting SLE flares as 0.6655 g/L (30.6% sensitivity and 84.9% specificity) and 0.1045 g/L (44.4% sensitivity and 74.9% specificity), respectively. The area under the curve (AUC) for the C3 model was insignificant. Although AUC for the C4 model was significant, its absolute area was relatively small, hence AUC may not be a valuable predictor (Table 2). Based on the optimal cut-off value for the minimum level of C3 and C4 in predicting SLE flares provided by

Table 2 ROC Curve Analysis of the Value of the Minimum Level of C3 and C4 in Predicting SLE Flares

Test Result Variable(s)	Area	*P value*	The Optimal Cut-off Value (g/L)	Sensitivity of the Optimal Cut-off Value	Specificity of the Optimal Cut-off Value	Youden Index
The minimum level of C3	0.560	0.072	0.6655	30.6%	84.9%	0.155
The minimum level of C4	0.592	0.006	0.1045	46.3%	73.3%	0.196

Notes: The minimum level of C3 or C4: the lowest value that occurred during the interval from remission to flares or the last visit (excluding data at flares or the last visit).

ROC curve analysis, we established two classification variables: significantly low levels of C3 and C4 and significantly low levels of C3 or C4. The incidence of significantly low levels of C3 and C4 (29.6% versus 8.8%, P < 0.001) or significantly low levels of C3 or C4 (47.2% versus 33.1%, P = 0.011) in flare patients was higher than that in non-flare patients (Table 1).

The multivariate Cox regression model displayed some independent predicted factors for flares. Younger age (hazard ratio [HR], 0.97; 95% CI, 0.95–0.99), positive anti-dsDNA at remission (HR, 1.64; 95% CI, 1.08–2.51), significantly low levels of C3 and C4 (HR, 2.09; 95% CI, 1.17–3.73) were independent risk factors associated with flares (Figure 1). Kaplan-Meier flare-free plots for these prognostic factors are shown in Figure 2.

Development of Flare Prediction Model

The nomogram for predicting the risk of flare was established based on the final multivariate model. To calculate 1-, 2-, and 3-year overall flare probability, each factor was initially identified based on the points scale at the top of the nomogram. Subsequently, the points for each factor were summed, and the 1-, 2-, and 3-year overall flare probability was obtained based on the bottom point scale of the nomogram (Figure 3). The calibration plots on bootstrap resampling validation are illustrated in Figure 4. The C-index for overall flare prediction was 0.654 (95% CI, 0.601–0.707).

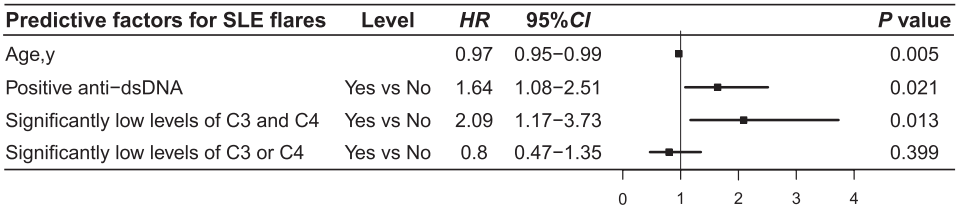

Figure 1 Risk factors for SLE flares in Cox regression model. The figure presents the HRs and the 95% CIs associated with flares. Significantly low levels of C3 and C4: C3 below 0.6655 with C4 below 0.1045 during the interval from remission to flares or the last visit (excluding data at flares or the last visit). Significantly low levels of C3 or C4: C3 below 0.6655 or C4 below 0.1045 during the interval from remission to flares or the last visit (excluding data at flares or the last visit).

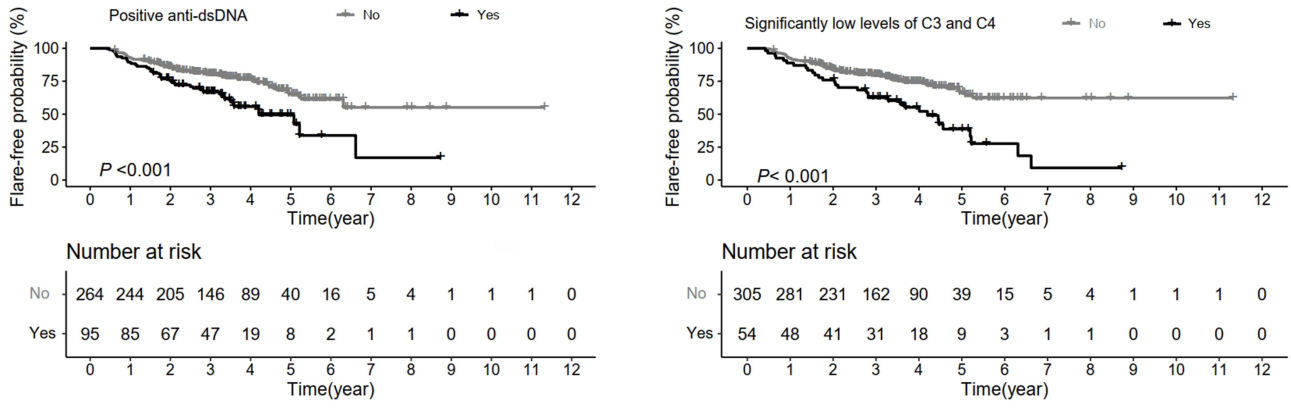

Figure 2 Kaplan-Meier flare-free plots for different prognostic factors. The figure displays the Kaplan-Meier flare-free plots according to (left) anti-dsDNA and (right) Significantly low levels of C3 and C4. Significantly low levels of C3 and C4: C3 below 0.6655 with C4 below 0.1045 during the interval from remission to flares or the last visit (excluding data at flares or the last visit).

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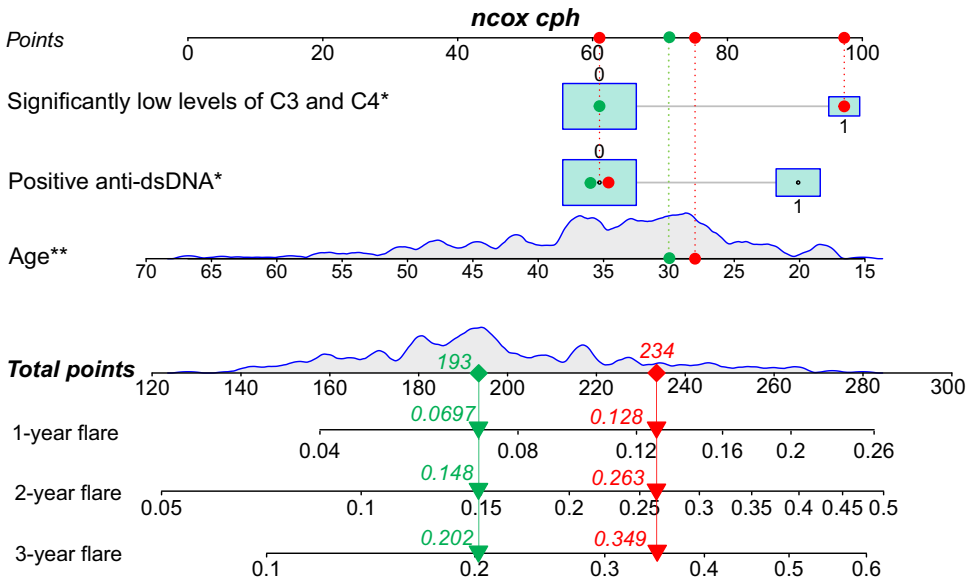

Figure 3 Prognostic nomogram for predicting the flare probability of SLE patients. Prognostic patient's value is located on each variable axis, and a line is drawn upward to determine the number of point nomogram for predicting overall flare probability of patients with SLE. The sum of these numbers is located on the Total points axis, and a line is drawn downward to the flare axes to determine the likelihood of 1-year, 2-year, and 3-year flare. *P<0.05; **P<0.01. Significantly low levels of C3 and C4: C3 below 0.6655 with C4 below 0.1045 during the interval from remission to flares or the last visit (excluding data at flares or the last visit). Eg the red point represents a patient with significantly low levels of C3 and C4 (value = 1, corresponding to 97 points), no positive anti-dsDNA (value = 0, corresponding to 61 points), and 28 years old (corresponding to 76 points). The total score is 234 points, which predicts probabilities of flares at 1 year, 2 years, and 3 years as 0.128, 0.263, and 0.349, respectively. The green point represents a patient with no significantly low levels of C3 and C4 (value = 0, corresponding to 61 points), positive anti-dsDNA (value = 0, corresponding to 61 points), and 30 years old (corresponding to 71 points). The total score is 193, which predicts probabilities of flares at 1 year, 2 years, and 3 years as 0.0697, 0.148, and 0.202, respectively.

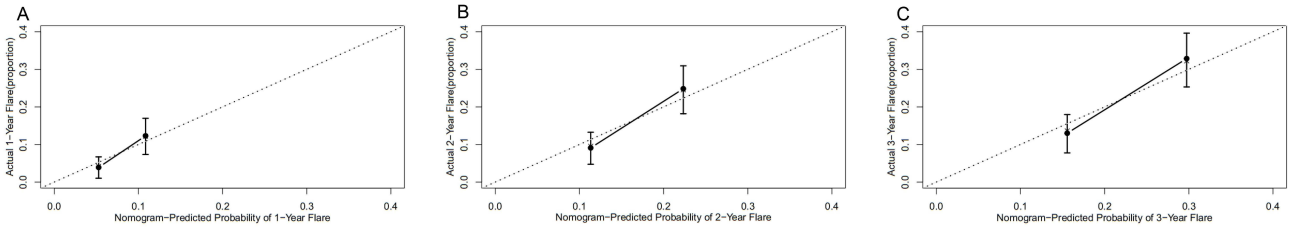

Figure 4 Calibration curves of the nomogram predicting flares in SLE patients. Calibration curves of the nomogram predict 1-year (**A**), 2-year (**B**), and 3-year (**C**) overall flare in patients with SLE. Nomogram-predicted probability of overall flare is plotted on the x-axis; actual overall flare is plotted on the y-axis.

Discussion

To our knowledge, this is the first study to show that younger age at remission, positive anti-dsDNA at remission and significantly low levels of C3 and C4 were independent predictors of SLE flares after remission. Introduced as a predictive factor for the first time, significantly low levels of C3 and C4 increased the risk of flares by 109% through the cox regression analysis. Additionally, this study pioneers the application of prediction model for SLE flares based on the results of multivariate Cox regression analysis, which provides a visual assessment for risk of flare.

There have been numerous advancements in the treatment of SLE in recent years, making remission as treatment target for SLE easier to be achieved. Our study, for the first time, explored predictive factors of flares in patients after remission as defined by DORIS, which determines its value in the context of SLE treatment strategies targeting remission. Previous study showed that progressive reductions in serum C3 and C4 levels was a risk factor for SLE flares,[13] suggesting that hypocomplementemia at different disease stages or the degree of complement decline may have different value in predicting SLE flares. Therefore, our study comprehensively compared the incidence of hypocomplementemia at different disease stages to predict SLE flares, and introduced significantly lower levels of complement as novel categorical variables, providing a more nuanced exploration of their predictive value. Our previous study showed that hypocomplementemia at entry was not a risk factor for SLE flare.[14] In the current study, our results further revealed that hypocomplementemia at diagnosis, remission, and post-

remission follow-up were not predictors of SLE flares (Table 1). Despite low value of hypocomplementemia in predicting SLE flare, multivariate Cox regression analysis showed that significantly low levels of C3 and C4 was an independent predictor of flares, which showed higher specificity (91.2%) and positive predicted value (59.3%) (not shown directly in tables). This suggests that drug dosage should be reduced with caution when significantly low complement level appears at remission or during the follow-up. Dose elevation should also be considered to reduce flares.

In our previous study,[14] age was analyzed as a categorical variable, showing that younger age was a significant risk factor for flares. In contrast, this study analyzed age as a continuous variable and found that each additional year of age slightly reduced the risk of flares (OR = 0.962; 95% CI, 0.937–0.988; P = 0.005). This provides a complementary perspective on the role of age, offering a nuanced understanding of its impact on flare risk. The hazard ratio for age (HR, 0.97; 95% CI, 0.95–0.99) indicates that younger age is associated with a higher risk of flares. These findings suggest that younger patients require closer monitoring and tailored management during remission to mitigate their higher flare risk. In addition, positive anti-dsDNA at remission (HR, 1.64; 95% CI, 1.08–2.51), a known marker of lupus activity, were also associated with increased relapse risk. Consistent with our findings, Fatemi et al identified younger age and elevated anti-dsDNA levels as significant predictors of severe lupus flares in a prospective study.[15] These results emphasize the importance of age and serological markers in predicting relapse risks and guiding management strategies.

As we know, maintaining stable disease conditions may help reduce risks of irreversible organ damage and mortality.[16] Therefore, it is necessary to ongoing assessment of the dynamic changes in flare risk throughout patient follow-up in order to reduce SLE flares. Thus, our study developed a nomogram model to predict flares of SLE patients after remission based on individual characteristic risk factors. While the C index is not highly satisfactory, the model still shows positive prediction value combined with judgment from the calibration plots and Kaplan-Meier flare-free plots. The calibration curves for flare probability also showed consistent alignment between predictions and observations. Moreover, the nomogram model provides an intuitive patient-specific flare risk assessment, facilitating convenient clinical evaluation. This nomogram model allows for ongoing assessment of the dynamic changes in flare risk throughout patient follow-up. In other words, our study provides a simple yet valuable prediction model of SLE flares in the context of SLE treatment strategies targeting remission and provides a reference for clinical decision-making in the course of post-remission follow-up.

Several limitations should be noted in the interpretation of our results. Firstly, the patients in our study were single-center data from PUMCH. Therefore, the identification of more sensitive and specific indicators is crucial for predicting SLE flares. Additionally, this study was conducted in an ethnically homogeneous population, primarily consisting of Chinese patients. The findings may not be fully generalizable to other ethnic groups, as genetic, environmental, and sociocultural factors can influence disease presentation and outcomes. Future studies involving multi-ethnic cohorts are essential to validate these findings and assess their applicability across diverse populations.

Conclusion

In conclusion, this study stands as the first to investigate predictors of flares in patients achieving DORIS-defined remission. The presence of significantly low levels of C3 and C4, younger age, and elevated anti-dsDNA levels emerge as key predictors for SLE flares during follow-up. Furthermore, the nomogram model provides a simple and convenient platform for clinical assessment of flare risk. These findings equip clinicians with valuable insights to identify patients at greater risk of SLE flares and facilitate convenient assessment of flare risk after remission.

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Disclosure

The authors report no conflicts of interest in this work.

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