

Association of Serum Uric Acid to Lymphocyte Ratio with Clinical Outcomes in Cerebral Venous Sinus Thrombosis

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Purpose: The serum uric acid to lymphocyte ratio (ULR) is a systemic marker of inflammation, and it has been studied as an indicator of prognosis in cardiovascular disease. This study investigates the relationship between ULR and clinical outcomes in patients with cerebral venous sinus thrombosis (CVST).

Patients and Methods: A total of 636 patients with CVST were included in the study and randomly divided into a training set (n = 445) and a testing set (n = 119) in a ratio of 7:3. Logistic regression analysis was employed to analyze the risk factors for poor outcomes. The nomogram was established using the training dataset, and its predictive performance was assessed with the testing dataset.

Results: ULR accurately predicted poor outcomes in CVST and was linked to a higher likelihood of poor outcomes (OR=1.015, 95% CI: 1.003–1.026, $P = 0.013$). Age, infection, intracranial hypertension, coma, and intracerebral hemorrhage were independent predictors of poor outcomes in CVST. Additionally, a new nomogram incorporating ULR was constructed to predict the risk of poor outcomes in CVST patients. The nomogram demonstrated good accuracy and reliability, as shown by the receiver operating characteristic curve, calibration curve, and decision curve analysis.

Conclusion: ULR independently forecasted poor outcomes in patients with CVST. The novel nomogram incorporating ULR could provide CVST patients with personalized risk assessment and treatment plans, leading to improved patient prognosis.

Keywords: serum uric acid to lymphocyte ratio, cerebral venous sinus thrombosis, outcomes, risk factors, nomogram

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare venous thromboembolic event, accounting for less than 1% of strokes, and primarily affecting young and middle-aged individuals, and results in brain parenchymal injuries.¹⁻³ Imaging is fundamental to its diagnosis. It is well established that the current gold standard to depict CVT is the combination of conventional magnetic resonance imaging (MRI) with some kind of magnetic resonance venography, particularly with dynamic time-resolved angiographic techniques, such as time-resolved imaging of contrast kinetics (TRICKS) and time-resolved imaging with stochastic trajectories.⁴ While numerous factors contribute to CVST, the exact mechanisms are not fully understood.⁵ Indeed, growing evidence indicates that inflammation is implicated in all stages of CVST.⁶⁻⁹ Neuronal pyroptosis, induced by inflammation, is one of the key factors in CVST pathology.¹⁰ Therefore, controlling inflammation is a promising strategy to mitigate the progressive exacerbation of CVST.

Serum uric acid (SUA) is thought to have pro-inflammatory properties and is linked to various chronic inflammatory diseases.¹¹ However, elevated SUA levels not only have direct pro-inflammatory properties but also negatively impact the vasculature by inducing endothelial dysfunction and elevating oxidative stress.^{12–14} Increased neutrophil counts and decreased lymphocyte counts are indicative of systemic responses to inflammatory diseases.^{15,16} Furthermore, the neutrophil-lymphocyte ratio (NLR) and lymphocyte-monocyte ratio (LMR) are two commonly used inflammatory markers that reflect the body's inflammatory state by comparing the ratios of different white blood cell types. Studies have demonstrated a strong correlation between NLR and LMR with the prognosis of CVST patients.^{17–19} Lymphocytes are a key component of the immune system, and a decreased lymphocyte count indicates impaired immune function.^{20,21} The SUA to lymphocyte ratio (ULR) offers a comprehensive assessment by integrating serum uric acid levels and lymphocyte counts to identify health risks in patients with heart disease, cancer, and stroke.^{22–24} However, to date, studies on ULR as a predictive tool for CVST are lacking, and thus its potential clinical application remains unproven.

Consequently, this study aimed to evaluate the association between ULR and poor prognosis in patients with CVST. In addition, by incorporating ULR alongside other potential predictors, we developed an easy-to-use nomogram to help clinicians more accurately assess patients' risk.

Materials and Methods

Study Population

The data analyzed in this exploratory study were sourced from the database of the Henan CVST Registry in the First Affiliated Hospital of Zhengzhou University (Henan, China). We included 755 CVST patients at the acute/subacute phase from January 2011 to October 2023. The included CVST patients met the diagnostic criteria established by the European Academy of Neurology and American Heart Association/American Stroke Association.^{2,3} The acute phase was defined as ≤ 7 days from onset to hospitalization, and the subacute phase as ≤ 30 days.⁷ Exclusion criteria were: (1) age < 18 years; (2) onset > 30 days; (3) missing SUA or lymphocyte data at baseline; (4) loss to follow-up. Ultimately, the study encompassed 636 patients, dividing them into a training set ($n = 445$) and a testing set ($n = 191$) in a 7:3 ratio (Figure 1).

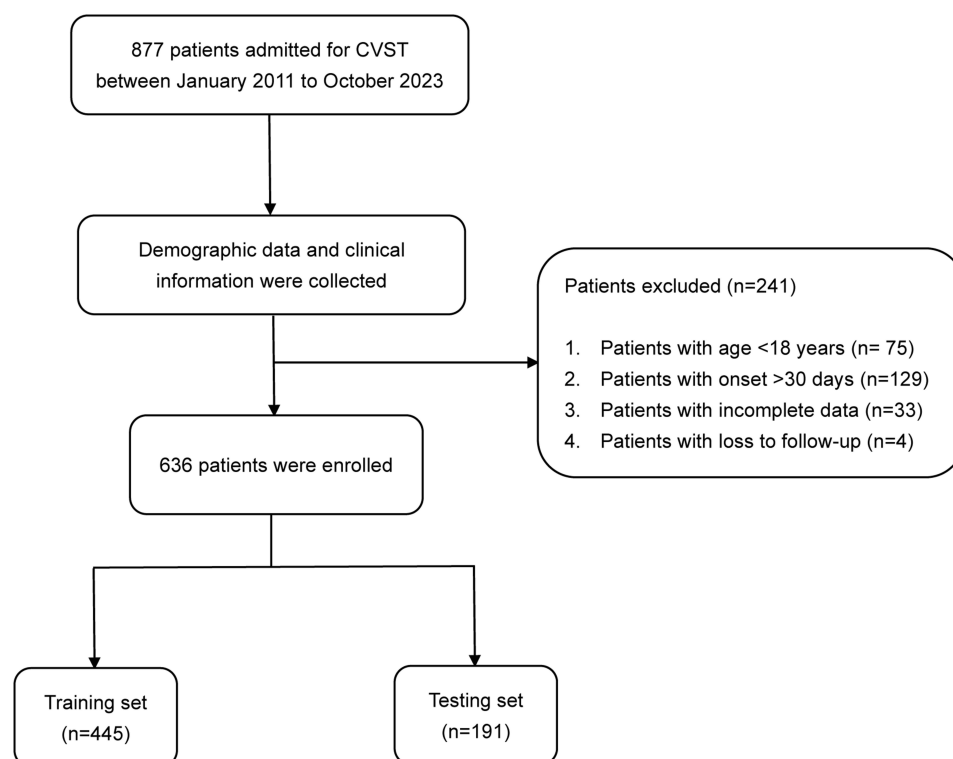


Figure 1 Flow chart of the study population in the training and testing set.

Abbreviation: CVST, cerebral venous sinus thrombosis.

The Ethics Committee of the First Affiliated Hospital of Zhengzhou University approved the study. Every participant in the study signed an informed consent form.

Data Collection

Demographic data and information, encompassing variables such as age, gender, clinical presentations, risk factors, laboratory parameters, and imaging findings, were gathered for analysis, where SUA and lymphocyte counts were assessed within 24 hours of admission in all patients.

Definitions

ULR was calculated as the ratio of SUA (mg/dL) to lymphocyte count ($\times 10^9/L$), based on previous studies.^{22–24} The International Study on Cerebral Vein and Dural Sinus Thrombosis risk score (ISCVT-RS) consists of six criteria, with a maximum score of nine. The criteria include: male (1), abnormal mental status (1), hemorrhagic lesion (1), coma (2), intracranial deep venous system thrombosis (2), and malignancy (2). Patients with an ISCVT-RS score of three or more are categorized as high-risk.²⁵

Assessment of Outcomes

Patient prognosis was assessed using the modified Rankin Scale (mRS). An mRS score of 3 or higher was characterized as a poor prognosis.²⁶

Nomogram Construction and Validation

Based on logistic regression analyses, the nomogram was constructed using the training set. Univariate analyses were performed to identify independent predictors of poor prognosis in CVST. The selected variables from the univariate analyses were then evaluated in multivariate logistic regression models. The nomogram was created using the independent predictors identified from these multivariate analyses. This tool helps estimate the total score, which can be used to predict the likelihood of poor prognosis, with higher scores indicating worse outcomes.

The testing set was used to validate the prognostic nomogram. Predictive performance was assessed using receiver operating characteristic (ROC) curve analysis. Calibration curves were used to evaluate the predictive accuracy of the new nomogram. Subsequently, the predictive performance of the novel nomogram in various clinical scenarios was assessed via decision curve analysis (DCA) to ascertain its applicability and utility in clinical settings.

Statistical Analysis

We carried out statistical analyses by utilizing SPSS 27.0. Continuous data were expressed as mean $\pm$ standard deviation. Student's *t*-test was applied if the data followed a normal distribution with equal variances; otherwise, Mann–Whitney *U*-test was used. For categorical variables expressed as numbers and percentages, comparisons were made using the χ^2 test or Fisher exact test. Multivariate logistic regression analysis was employed to evaluate the impact of multiple independent variables on clinical outcomes. We developed a novel nomogram with R version 4.3.2. Statistical significance was determined at a significance level of $P < 0.05$.

Results

Baseline Characteristics

A total of 636 participants were enrolled in the current study, with 373 (58.7%) being female. The baseline characteristics of the participants can be found in [Table 1](#). The training set comprised 445 patients, while the testing set consisted of 191 patients. There were no significant discrepancies noted in the patient distribution between the training and testing sets with regard to clinical characteristics such as demographics, risk factors, clinical symptoms, venous sinus involvement, parenchymal brain lesions, and hospitalization. Additionally, no significant variances were noted in the distribution of laboratory parameters, such as lymphocyte count and uric acid levels, or in clinical outcomes between the two patient cohorts ([Table S1](#)). In comparison to the group with good outcomes, individuals with poor outcomes tended to be older

Table 1 Baseline Characteristics According to the Clinical Functional Outcome

	Good Outcome (n=570)	Poor Outcome (n=66)	P
Demographics			
Age, years, mean $\pm$ SD	36.3 $\pm$ 12.5	43.6 $\pm$ 15.4	<0.001
Female, n (%)	332(58.2)	41(62.1)	0.545
Possible Risk factors, n (%)			
Infections	99(21.5)	17(28.3)	0.230
Pregnancy/postpartum	92(16.1)	12(18.2)	0.671
Clinical symptoms, n (%)			
Intracranial hypertension	372(65.3)	45(68.2)	0.637
Seizure	138(24.2)	27(40.9)	0.003
Coma	137(24.0)	44(66.7)	<0.001
Mental status disturbance	28(4.9)	9(13.6)	0.010
Focal neurological deficits*	159(27.9)	32(48.5)	<0.001
Involved sinuses, n (%)			
Transverse sinuses	438(76.8)	42(63.6)	0.018
Sigmoid sinuses	356(62.5)	31(47.0)	0.316
Superior sagittal sinus	357(62.6)	42(63.6)	0.873
Straight sinus	107(18.8)	16(24.2)	0.287
Inferior sagittal sinus	18(6.9)	3(8.3)	0.729
Deep CVT	20(3.5)	4(6.1)	0.491
Parenchymal lesion, n (%)			
Ischemic Infarction	123(21.6)	16(24.2)	0.620
Intracerebral hemorrhage	101(17.7)	24(36.4)	<0.001
Laboratory Examinations			
SUA, mg/dL	41.4 $\pm$ 18.1	35.5 $\pm$ 19.9	0.014
Lymphocyte count, $\times 10^9$ /L	1.7 $\pm$ 0.9	1.0 $\pm$ 0.6	<0.001
ULR	29.6 $\pm$ 21.6	46.1 $\pm$ 38.0	<0.001
Hospital treatment, n (%)			
Anticoagulation	531(93.2)	59(89.4)	0.264
Endovascular Therapies	244(42.8)	32(48.5)	0.378

Notes: *Focal neurological deficits symptoms included hemiplegia and sensory changes.

Abbreviations: SD, standard deviation; CVT, cerebral venous thrombosis; SUA, serum uric acid; ULR, serum uric acid to lymphocyte ratio.

and exhibit a higher prevalence of intracranial hypertension, coma, and focal neurological deficits. They were also more likely to present with intracerebral hemorrhage and transverse sinus involvement, but had lower levels of serum uric acid and lymphocyte count (Table 2).

Clinical Predictors of Poor Outcomes in CVST

Table 3 displayed the findings of the multivariate logistic regression analysis. A higher prevalence of infection (odds ratio [OR] = 2.464, 95% confidence interval [CI]: 1.101–5.518, $P = 0.028$) intracranial hypertension (OR = 2.583, 95% CI: 1.092–6.111, $P = 0.031$), intracerebral hemorrhage (OR = 2.743, 95% CI: 1.221–6.162, $P = 0.015$), and coma (OR = 3.908, 95% CI: 1.866–8.185, $P < 0.001$) were linked to a higher likelihood of poor outcomes. Additionally, CVST patients with poor outcomes had higher age (OR = 1.049, 95% CI: 1.022–1.077, $P < 0.001$) and ULR levels (OR = 1.015, 95% CI: 1.003–1.026, $P = 0.013$) (Table 3).

Nomogram for Poor Outcomes in CVST

Based on Table 3, a nomogram model was developed to predict poor prognosis in patients with CVST, incorporating factors such as age, infection, intracranial hypertension, coma, intracerebral hemorrhage, and ULR. Additionally, a novel nomogram was developed by integrating these factors (Figure 2). Within the training set, the nomogram model exhibited

Table 2 Baseline Characteristics According to the Clinical Functional Outcome in Training Set and Testing Set

	Training set			Testing set		
	Good Outcome (n=405)	Poor Outcome (n=40)	P	Good Outcome (n=165)	Poor Outcome (n=26)	P
Demographics						
Age, years, mean $\pm$ SD	36.1 $\pm$ 12.8	43.9 $\pm$ 16.3	<0.001	36.9 $\pm$ 11.8	43.2 $\pm$ 14.3	0.014
Female, n (%)	241(59.5)	26(65.0)	0.499	91(55.2)	15(57.4)	0.809
Possible Risk factors, n (%)						
Infections	72(17.8)	12(30.0)	0.059	27(16.4)	5(19.2)	0.935
Pregnancy/postpartum	65(16.0)	7(17.5)	0.812	27(16.4)	5(19.2)	0.935
Clinical symptoms, n (%)						
Intracranial hypertension	261(64.4)	31(77.5)	0.097	111(67.3)	14(53.8)	0.181
Seizure	98(24.2)	13(32.5)	0.247	40(24.2)	14(53.8)	0.002
Coma	96(23.7)	24(60.0)	<0.001	41(24.8)	20(76.9)	<0.001
Mental status disturbance	20(4.9)	4(10.0)	0.325	8(4.8)	5(19.2)	0.007
Focal neurological deficits*	107(26.4)	18(45.0)	0.013	52(31.5)	14(53.8)	0.026
Involved sinuses, n (%)						
Transverse sinuses	315(77.8)	26(65.0)	0.068	123(74.5)	16(61.5)	0.166
Sigmoid sinuses	208(51.4)	19(47.5)	0.641	84(50.9)	11(42.3)	0.415
Superior sagittal sinus	257(63.5)	25(62.5)	0.905	100(60.6)	17(65.4)	0.642
Straight sinus	72(17.8)	11(27.5)	0.132	35(21.2)	5(19.2)	0.817
Inferior sagittal sinus	33(8.1)	6(15.0)	0.144	18(10.9)	3(11.5)	1.000
Deep CVT	15(3.7)	2(5.0)	0.683	5(3.0)	2(7.7)	0.539
Parenchymal lesion, n (%)						
Ischemic Infarction	90(22.2)	8(20.0)	0.746	33(20.0)	8(30.8)	0.214
Intracerebral hemorrhage	71(17.5)	14(35.0)	0.007	30(18.2)	10(38.5)	0.018
Laboratory Examinations						
SUA, mg/dL	41.1 $\pm$ 18.4	31.9 $\pm$ 14.3	0.002	42.0 $\pm$ 17.1	41.2 $\pm$ 25.6	0.882
Lymphocyte count, $\times 10^9/L$	1.7 $\pm$ 0.8	1.0 $\pm$ 0.6	<0.001	1.8 $\pm$ 1.1	1.1 $\pm$ 0.5	0.002
ULR	31.0 $\pm$ 24.6	43.3 $\pm$ 31.8	0.004	30.6 $\pm$ 25.9	59.2 $\pm$ 68.8	<0.001
Hospital treatment, n (%)						
Anticoagulation	379(93.6)	37(92.5)	0.792	152(92.1)	22(84.6)	0.212
Endovascular Therapies	174(43.0)	22(55.0)	0.143	70(42.4)	9(34.6)	0.452

Notes: *Focal neurological deficits symptoms included hemiplegia and sensory changes.

Abbreviations: SD, standard deviation; CVT, cerebral venous thrombosis; SUA, serum uric acid; ULR, serum uric acid to lymphocyte ratio.

Table 3 Multivariate Logistic Regression Analysis of Predictors for Poor Clinical Outcome in CVST Patients in Training Test

Variable	OR	95% CI	P
Age	1.049	1.022~1.077	<0.001
Gender	1.554	0.715~3.379	0.266
Infection	2.464	1.101~5.518	0.028
Intracranial hypertension	2.583	1.092~6.111	0.031
Coma	3.908	1.866~8.185	<0.001
Focal neurological deficits*	1.606	0.764~3.379	0.212
Intracerebral hemorrhage	2.743	1.221~6.162	0.015
Transverse sinus	0.478	0.216~1.057	0.068
ULR	1.015	1.003~1.026	0.013

Notes: *Focal neurological deficits symptoms included hemiplegia and sensory changes.

Abbreviations: ULR, prognostic nutritional index; OR, odds ratio; CI, confidence interval.

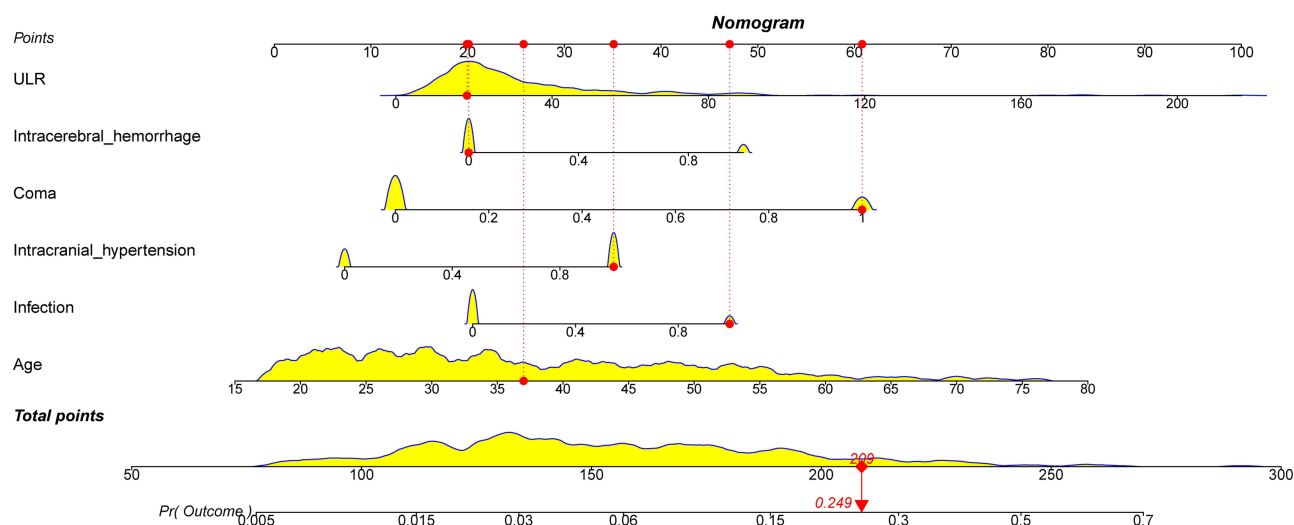


Figure 2 Nomogram for predicting the incidence of poor outcomes in CVST patients. Based on the results of multivariable logistic regression, we included age, infection, intracranial hypertension, coma, intracerebral hemorrhage and ULR in the nomogram.

Abbreviation: ULR, serum uric acid to lymphocyte ratio.

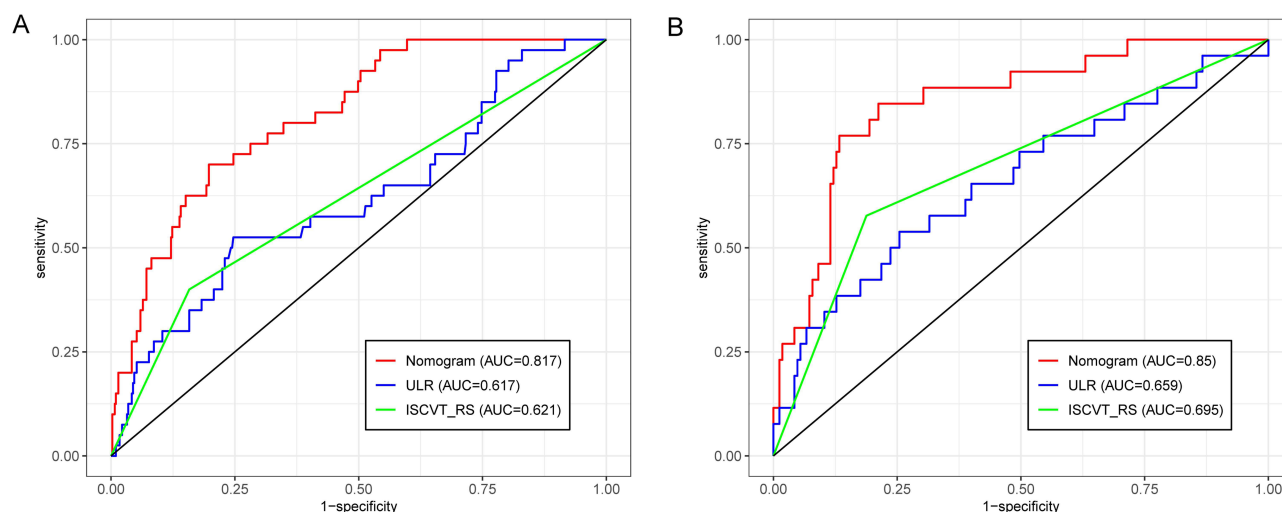


Figure 3 ROC curves of the nomogram (red), ULR (blue), ISCVT_RS (green) for the prediction of poor outcomes in CVST patients in the training (A), and testing (B) sets. **Abbreviations:** ROC, receiver operating characteristic; CVST, cerebral venous sinus thrombosis; ULR, serum uric acid to lymphocyte ratio; ISCVT_RS, International Study on Cerebral Vein and Dural Sinus Thrombosis risk score.

markedly superior predictive performance for identifying the risk of adverse outcomes in CVST patients compared to ULR (area under the curve [AUC], 0.817 vs 0.617) and ISCVT-RS (AUC, 0.817 vs 0.621) (Figure 3A). Similar findings were observed in the testing set, with the nomogram demonstrating superior performance compared to ULR (AUC, 0.850 vs 0.659) and ISCVT-RS (AUC, 0.850 vs 0.695) (Figure 3B). The nomogram exhibited excellent performance in both stratifying patients into high-risk and low-risk categories (Figure 3) and accurately predicting individual patient risks (training set: $P = 0.880$; test set: $P = 0.915$) (Figure 4). Furthermore, the DCA outcomes indicate the substantial practical value of nomograms in clinical practice, offering valuable guidance across various therapeutic thresholds (Figure 5).

Discussion

Our study examined potential independent predictors of poor outcomes in 636 CVST patients. Among these, ULR demonstrated a strong ability to predict poor outcomes in CVST (OR = 1.015, 95% CI: 1.003–1.026, $P = 0.013$). The research further revealed a positive association between increasing ULR and the incidence of poor outcomes in CVST.

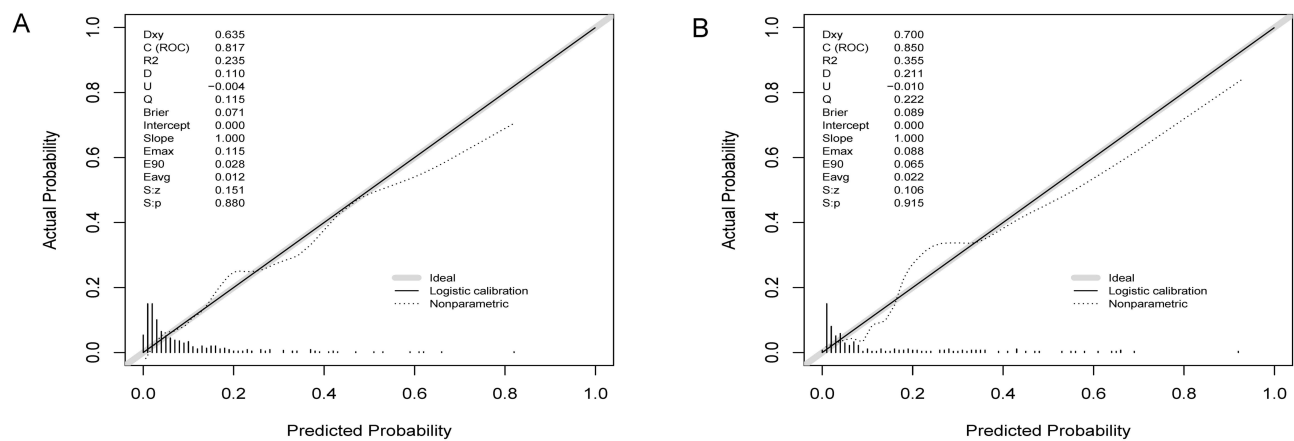


Figure 4 Calibration curves of the nomogram in the training (A), and testing (B) sets. The idea line is the calibration curve for the ideal case, indicates that the predicted probability is exactly equal to the probability of the actual occurrence. The logistic calibration is a logistic regression based method for calibrating predictive models. Nonparametric line is a non-parametric method that does not rely on specific statistical distribution assumptions.

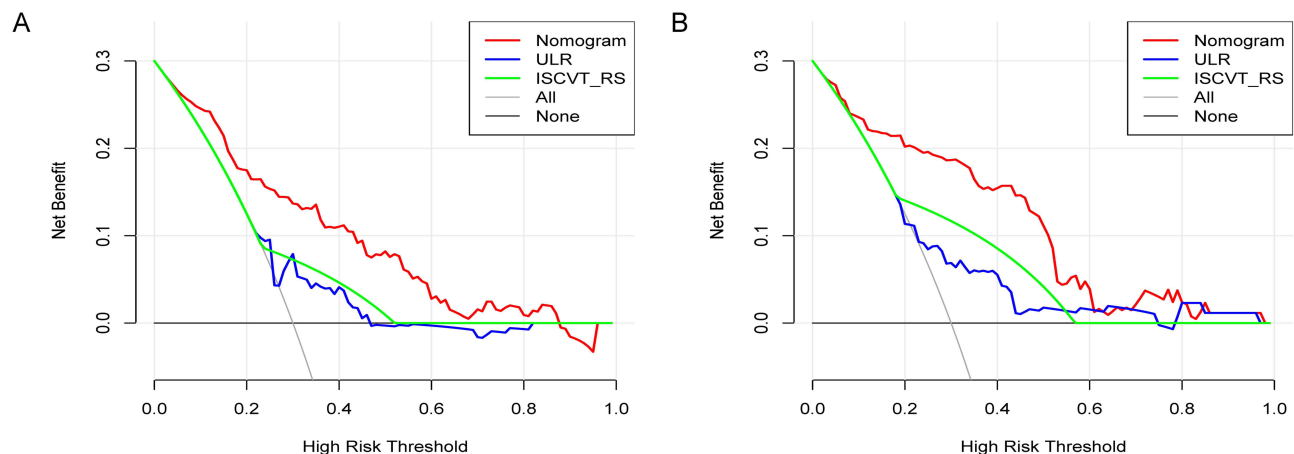


Figure 5 Decision curve analysis (DCA) of the training (A), and testing (B) sets. The red line indicates Nomogram, the blue line indicates ULR, the green line indicates ISCVT_RS, the All line indicates an intervention against anyone, and the None line indicates a not intervention against anyone.

Abbreviations: ULR, serum uric acid to lymphocyte ratio; ISCVT_RS, International Study on Cerebral Vein and Dural Sinus Thrombosis risk score.

Additionally, we developed a new nomogram model incorporating ULR based on the aforementioned findings. The model demonstrated precise discriminative power in both the training and testing datasets, and its favorable clinical performance was validated through calibration curve and DCA analyses.

Lymphocytes have been implicated in mediating the inflammatory response by upregulating anti-inflammatory cytokines and suppressing pro-inflammatory cytokines.²⁷ Inflammatory mechanisms are essential for the initiation and advancement of ischemic cerebrovascular disease.^{28–30} Lymphocytes proliferate, differentiate, and release cytokines, thus recruiting monocytes, promoting macrophage maturation, and facilitating the removal of damaged tissues through phagocytosis and secretion of protein hydrolases.³¹ The post-thrombotic inflammatory response is essential for bodily repair.^{32–34} Lymphocytes play a vital role in the progression of CVST, reflecting the inflammatory response and stress stage of the body.¹⁸ During stress, levels of catecholamines and cortisol rise. Studies have demonstrated that these hormones can induce lymphocyte apoptosis, and physical stress during a stroke may exacerbate immune suppression, resulting in decreased lymphocyte counts.³⁵ Furthermore, decreased lymphocyte counts are linked to an unfavorable outlook in individuals with myocardial infarction and ischemic stroke.³⁶ Animal models have demonstrated that stroke-induced immunosuppression can result in lymphocytopenia and alterations in the ratio of helper T cells.^{37,38} Thus, lower lymphocyte counts may predict poor outcomes.

SUA is the final product of purine metabolism and possesses dual roles as both pro-oxidant and anti-oxidant properties.³⁹ Elevated SUA levels, acting as pro-oxidants, are associated with inflammatory stress⁴⁰ SUA activates inflammatory pathways, resulting in the activation of chemokines and inflammatory markers (eg, monocyte chemoattractant protein-1, C-reactive protein), thereby triggering vasoconstrictor mediators (eg, endothelin-1, angiotensin II) and the release of growth factors. Upregulation of oxidative enzymes is a critical aspect of hyperuricemia pathophysiology. Oxidase inhibitors effectively mitigate damage to vascular endothelial cells caused by oxygen radicals and reduce inflammatory responses.^{41,42} Population studies have shown that elevated SUA levels are linked to a heightened risk of recurrent stroke. Tu et al concluded that asymptomatic hyperuricemia is linked to a two-fold increased risk of stroke within three years, thus suggesting its potential as a strong predictor of stroke.⁴³ On the contrary, SUA also acts as a potent natural antioxidant, mitigating cellular oxidation. Aliena-Valero et al demonstrated that SUA attenuates oxidative stress in hyperperfused rats following ischemic stroke.⁴⁴ A meta-analysis published in 2021 demonstrated that SUA improved outcomes in rodent models of ischemic stroke by reducing infarct size, enhancing the integrity of the blood-cerebrospinal fluid barrier, and improving neurological function.⁴⁵ Liu et al concluded that low SUA levels predict poor outcomes and death in men with ischemic stroke, whereas high SUA levels predict mortality in women with stroke. A J-shaped relationship was observed between SUA levels and poor short-term prognosis in patients with acute ischemic stroke.⁴⁶ Consistent with our previous findings, there may be a sex-based disparity in how SUA levels are linked to clinical prognosis in CVST patients. High SUA significantly reduces the risk of poor prognosis in female CVST patients, whereas this relationship does not exist in male CVST patients.⁴⁷ This conflicting characteristic may reduce SUA's effect on the risk of poor CVST prognosis.

ULR combines SUA levels and lymphocyte counts, both of which are associated with the body's inflammatory state and immune response. Elevated SUA levels are frequently linked to an elevated risk of cardiovascular disease, whereas decreased lymphocyte counts may indicate compromised immune function. Therefore, ULR, a ratio that integrates these two parameters, may theoretically offer valuable insights into a patient's inflammatory status and associated health risks. The ULR was initially introduced by Wei et al in their study.²³ ULR exhibits greater prognostic value in elderly patients with rheumatic heart disease undergoing valve replacement surgery.²³ Likewise, ULR may serve as a prognostic predictor in early-stage non-small cell lung cancer.²² Based on our results, there is a notable link between elevated ULR levels and an increased risk of poor prognosis in CVST after adjusting for other potential confounders. Furthermore, the nomogram prediction model based on ULR demonstrated superior predictive value compared to the conventional ISCVT-RS model. Taken together, these findings lend support to the hypothesis that elevated ULR levels may correlate with an unfavorable prognosis in patients with CVST.

A nomogram is a graphical predictive tool used to integrate multiple variables into a unified predictive model.⁴⁸ In this study, we developed a novel nomogram by incorporating ULR and five additional risk factors for adverse outcomes. The model exhibits excellent clinical predictive performance and utility, resulting in greater net benefit and clinical efficiency in guiding clinical decision-making. Consequently, the model aids physicians in accurately predicting patient prognosis, facilitating the formulation of patient-centered decisions.

Our study has a few limitations. Firstly, the study's focus on a single center may limit the generalizability of the results. Therefore, these findings should be interpreted with caution. Future research should aim to explore these associations in a multicenter prospective cohort study to validate and expand upon our findings. Secondly, the absence of external validation for the nomogram highlights the need to assess its performance in a broader and more diverse population, ensuring the robustness and applicability of the model across different settings. A third limitation of this study is the lack of assessment of the predictive value of ULR in combination with other known factors, which may affect the breadth and accuracy of its use in clinical practice.

Conclusion

A high ULR level may serve as an independent risk factor for poor outcomes in CVST patients. Additionally, the newly developed nomogram presented in this study offers an effective predictive tool for managing CVST, potentially enhancing patient outcomes and showing the potential of precision medicine.

Data Sharing Statement

Study data are available from the corresponding author upon request.

Ethics Approval

The study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University (approval number: 2024-KY-0838-001). Our study was complied with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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