International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Combined Predictive Value of Neutrophil-to-Lymphocyte Ratio and CHA2DS2-VASc Score for Cardiogenic Cerebral Embolism in NVAF Patients

Jie Hu[1,2,*], Jing-Jing Wang[2,3,*], Long Wang[1,2], Yong-Hong Cao[2,3], Jun-Cang Wu[1,2]

[1]Department of Neurology, Hefei Hospital Affiliated to Anhui Medical University (The Second People's Hospital of Hefei), Hefei, Anhui, 230011, People's Republic of China; [2]The Fifth Clinical Medical College of Anhui Medical University, Hefei, Anhui, 230032, People's Republic of China; [3]Department of Endocrinology, Hefei Hospital Affiliated to Anhui Medical University (The Second People's Hospital of Hefei), Hefei, Anhui, 230011, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yong-Hong Cao, Department of Endocrinology, Hefei Hospital Affiliated to Anhui Medical University (The Second People's Hospital of Hefei), Hefei, Anhui, 230011, People's Republic of China, Email fish1982cao@126.com; Jun-Cang Wu, Department of Neurology, Hefei Hospital Affiliated to Anhui Medical University (The Second People's Hospital of Hefei), Hefei, Anhui, 230011, People's Republic of China, Email wujuncang126@126.com

Aim: This study aimed to determine the identification role of neutrophil-to-lymphocyte ratio (NLR) combined with CHA2DS2-VASC score for cardiogenic cerebral embolism (CCE) in acute ischemic stroke patients with non-valvular atrial fibrillation (NVAF).

Methods: From January 2019 to August 2024, a total of 402 acute ischemic stroke patients with NVAF were enrolled in this retrospective study and were divided according to the occurrence of CCE into the CCE or non-CCE groups. Clinical data were collected from both groups, which included demographic data, medical history, CHA2DS2-VASC score, and laboratory tests (blood cell counts and blood biochemistry indicators). A predictive model based on blood indexes and the CHA2DS2-VASC score was constructed using least absolute shrinkage and selection operator (LASSO) regression analysis.

Results: Multiple regression analysis showed that the CHA2DS2-VASc score (OR = 2.95, 95% CI = 2.19–3.99, $p < 0.001$), white blood count (OR = 1.43, 95% CI = 1.15–1.78, $p = 0.001$), neutrophil-to-lymphocyte ratio (NLR; OR = 1.63, 95% CI = 1.29–2.05, $p < 0.001$), and D-dimer levels (OR = 1.56, 95% CI = 1.15–2.12, $p = 0.005$) were independent risk factors for CCE. Spearman correlation analysis showed that NLR and the CHA2DS2-VASc score had a significant positive correlation ($R = 0.449$, $p < 0.001$). The area under the receiver operating characteristic (ROC) curve (AUC) for NLR and the CHA2DS2-VASc score were 0.869 (95% CI = 0.843–0.901) and 0.859 (95% CI = 0.820–0.898), respectively. A composite index for distinguishing CCE risk was constructed using LASSO regression analysis, which yielded an AUC value of 0.924 (95% CI = 0.898–0.950).

Conclusion: NLR is an independent risk factor for CCE in NVAF patients, and combining it with CHA2DS2-VASC score provides a more useful composite index for identifying the CCE risk of patients with NVAF. This composite score may serve as a promised tool in clinical workflows, and it could even contribute to individualized anticoagulation strategies by identifying high-risk patients who may benefit from more positive preventive methods.

Keywords: non-valvular atrial fibrillation, cardiogenic cerebral embolism, CHA2DS2-VASc score, neutrophil-to-lymphocyte ratio, neutrophil extracellular traps, least absolute shrinkage and selection operator

Introduction

Stroke is the second leading cause of death worldwide and a major contributor to disability, with high incidence and disability-adjusted life years (DALYs) lost.[1,2] Cardiogenic cerebral embolism (CCE) is a pathological subtype of acute ischemic stroke, accounting for about 14–30% of cases. Compared to other subtypes of ischemic stroke, CCE often involves rapid progression, poor prognosis, and serious complications,[3,4] which often means worse outcome when occurring. Atrial fibrillation (AF), especially nonvalvular atrial fibrillation (NVAF), is the most likely cause of CCE, as it contributes to blood stasis and abnormalities in coagulation-related indexes by causing left atrial appendage systolic

Received: 18 February 2025
Accepted: 23 June 2025
Published: 27 June 2025

dysfunction, thereby increasing the likelihood of thromboembolism.[5,6] Therefore, the early diagnosis of acute stroke patients, as well as the early initiation of anticoagulation therapy and related secondary prevention, is of utmost importance.[7,8]

Due to their breadth and simplicity, the CHADS2 score and CHA2DS2-VASc score are the most common risk assessment models employed worldwide to predict the risk of acute cerebrovascular events in patients with NVAF.[9] The CHA2DS2-VASc score incorporating factors easily obtained like congestive heart failure, hypertension, age, diabetes, stroke/transient ischemic attack/thromboembolism history, vascular disease history and sex. And provide quick evaluation of high-risk patients. However, a growing number of studies have questioned these scores for the following reasons: (1) Many studies have found that these scores were still able to predict the risk of ischemic stroke without AF, and hence may not be specific to the assessment of NVAF-related stroke. (2) These scores do not include several specific factors affecting thromboembolism in patients with NVAF, such as left atrial diameter (LAD) and ejection fraction (EF) or possible biomarkers. These findings highlight the limitations of the risk stratification models, and the need for a deeper understanding of cerebral thromboembolism and NVAF.[10,11] In addition to evaluating thromboembolic events, assessing the risk of bleeding tendencies in patients receiving anticoagulation therapy is important equally. The HASBLED score is a common clinical tool included in guidelines and already proofed useful and simply predictive capacity for bleeding, which calculates the bleeding risk of severe variables: hypertension (1 point), abnormal liver/renal function (1 or 2 points), stroke (1 point), bleeding (1 point), labile international normalised ratios (1 point), elderly (>65, 1 point) and drugs/alcohol (1 or 2 points).[12,13] A comprehensive evaluation of both thrombotic and bleeding risks is essential for guiding individualized treatment strategies in patients with NVAF.

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio are newly discovered and readily available markers of systemic inflammation, which have recently been shown to have predictive and diagnostic value in a wide range of diseases.[14] Studies in cerebrovascular disease have shown that neutrophils are among the first cells to infiltrate damaged brain regions, inducing the production of free radical gases such as inducible nitric oxide synthase (iNOS), ultimately leading to post-ischemic brain injury and the destruction of the blood–brain barrier.[15] A higher NLR is associated with a greater incidence of cardiovascular and cerebrovascular diseases and poorer clinical outcomes. NLR can be used as a predictor of initial stroke severity, AF, and post-stroke hemorrhagic transformation.[16–20]

NLR is a composite result based on routine blood tests. Hence, it is more sensitive and valuable than individual indicators, and less affected by the processing of blood samples, reflecting the complex relationships and interactions among the autonomic nervous system, neuroendocrine system and immune system.[21] Therefore, we aimed to explore the correlation between NLR, CHA2DS2-VASc score, and NVAF-induced CCE to improve early risk identification.

Methods

Patient Selection

A total of 402 acute ischemic stroke patients diagnosed with NVAF at Hefei Hospital Affiliated to Anhui Medical University from January 2019 to August 2024 were recruited. The data above were accessed for research purposes on September 1, 2024. Of those, 196 were diagnosed with new-onset CCE (CCE group), and 206 patients were diagnosed with non-CCE matched for sex and age with NVAF within the same time frame (Non-CCE group). Figure 1 shows the screening process in detail, and Table 1 shows the detailed clinical characteristics of the demographic data for the study population.

Ethics and Statement

The research protocol was reviewed and approved by the Ethics Committee of Hefei Hospital Affiliated to Anhui Medical University, with ethical approval number: 2023-SR-006-01. All participants provided informed consent to participate and publish the clinical data in the study. Written informed consent was obtained from all participants prior to the enrollment of this study and all the data was analyzed anonymously. The study complies with the principles of the Declaration of Helsinki.

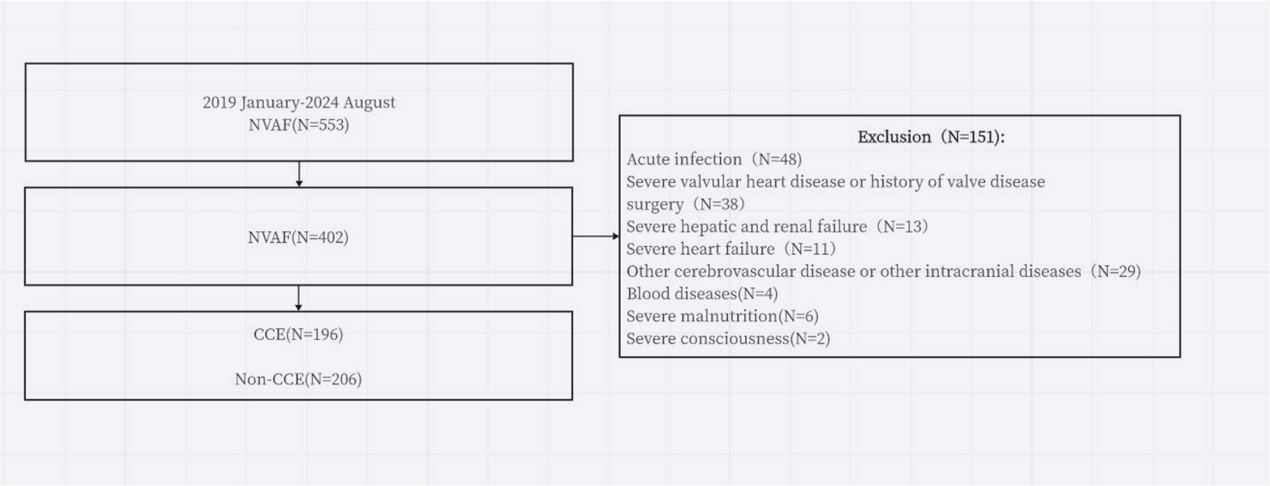

Figure 1 Study design flowchart.

Inclusion Criteria

1. NVAF was diagnosed according to the 2019 AHA/ACC/HRS guidelines for the management of patients with AF;[22]
2. Aged between 18 and 90 years;
3. Diagnosed with CCE according to the diagnostic criteria of the 2023 Chinese Guidelines for the Diagnosis and Treatment of Acute Ischemic Stroke and by head computed tomography (CT) or magnetic resonance imaging (MRI), occurring as a first-ever acute ischemic stroke;
4. Admitted to the hospital within 24 hours of onset.

Table 1 Comparison of Clinical Characteristics Between CCE with Non-CCE Patients

Variables	CCE (n = 196)	Non-CCE (n = 206)	χ^2/t	*P*
Age (years)	77.18 ± 8.20	77.35 ± 8.17	−0.20	0.839
CHA2DS2-VASc score	5.88 ± 1.16	4.07 ± 1.23	15. 11	<0.001
White blood count (×109/L)	7.51 ± 2.10	5.53 ± 1.48	10.87	<0.001
Red blood count (×109/L)	4.22 ± 0.58	4.17 ± 0.56	0.86	0.390
Hemoglobin (g/L)	127.96 ± 18.02	127.51 ± 16.62	0.26	0.796
Platelet count (×109/L)	183.20 ± 67.76	169.50 ± 50.62	2.29	0.023
Neutrophil count (×109/L)	5.71 ± 2.03	3.37 ± 1.16	14.08	<0.001
Lymphocyte count (×109/L)	1.23 ± 0.50	1.57 ± 0.57	−6.22	<0.001
NLR	5.69 ± 4. 11	2.42 ± 1.32	10.64	<0.001
CR (μmol/L)	74.36 ± 21.60	76.71 ± 23.92	−1.03	0.303
UA (μmol/L)	345.77 ± 108.38	345.72 ± 93.75	0.00	0.996
ALT (U/L)	20.53 ± 16.08	16.72 ± 9.18	2.89	0.004
AST (U/L)	28.53 ± 14.79	22.17 ± 7. 11	5.45	<0.001
TG (mmol/L)	1.15 ± 0.62	1.29 ± 0.93	−1.70	0.091
GLU (mmol/L)	6.38 ± 2.30	5.54 ± 1.41	4.36	<0.001
CYS-C (mg/L)	1.28 ± 0.40	1.31 ± 0.38	−0.85	0.395
HCY (μmol/L)	14.55 ± 5.91	14.99 ± 8.59	−0.60	0.551
CRP (mg/L)	15.56 ± 32.10	4.18 ± 9.62	4.76	<0.001
D-dimer (μg/mL)	2.94 ± 4.34	0.66 ± 0.81	7.25	<0.001

(*Continued*)

Table 1 (Continued).

Variables	CCE (n = 196)	Non-CCE (n = 206)	χ^2/t	*P*
Sex, Male (%)	87 (44.39%)	109 (52.91%)	2.92	0.087
Smoking, Yes (%)	28 (14.29)	33 (16.02)	0.23	0.628
Alcohol, Yes (%)	21 (10.71)	32 (15.53)	2.04	0.153
Hypertension, Yes (%)	153 (78.06)	147 (71.36)	2.38	0.123
Diabetes mellitus, Yes (%)	40 (20.41)	57 (27.67)	2.89	0.089
Coronary disease, Yes (%)	89 (45.41)	91 (44. 17)	0.06	0.804
Anticoagulant, Yes (%)	25 (12.76)	27 (13. 11)	0.01	0.916

Exclusion Criteria

1. Patients in the acute phase of infection;
2. Acute ischemic stroke caused by other cardiogenic factors;
3. History of valvular heart disease requiring surgical intervention, patent foramen ovale closure, or prior atrial fibrillation-related surgical procedures.
4. Patients comorbid for other cerebrovascular diseases or intracranial diseases, including intracranial space-occupying lesions, craniocerebral trauma, cerebral hemorrhage and cerebrovascular malformations;
5. Patients comorbid for severe systemic diseases such as chronic infectious diseases, organ failure (including heart, liver and kidney insufficiency), hematologic diseases or rheumatic immune system diseases;
6. Severe malnutrition or impaired consciousness;
7. Incomplete clinical or imaging data.

Medical History and Data Collection

The patients' clinical data were collected retrospectively through the electronic medical records system, which included sex, age, smoking history, alcohol consumption history, history of chronic diseases (eg, hypertension, diabetes mellitus, coronary heart disease) and use of anticoagulant drugs. CHA2DS2-VASc score was calculated for all patients. Blood cell counts (eg, white blood count, neutrophil count, lymphocyte count) and blood biochemistry indicators (eg, C-reactive protein, CRP; creatinine, CR; uric acid, UA; etc) were collected within 24 h of admission, and NLR was calculated.

Statistical Analysis

Statistical analysis was performed using the SPSS 26.0 software. The Kolmogorov–Smirnov test was performed to determine the normality of data distribution, and Levene's test was performed to determine the homogeneity of variance. Normally distributed continuous data were expressed as mean ± standard deviation. Non-normally-distributed variables were expressed as median (interquartile range). Independent samples *t*-test or Mann–Whitney *U*-test was employed for the univariate analysis of continuous variables, while the chi-square test was employed for categorical variables. Correlations among variables were evaluated using Pearson or Spearman correlation coefficients. Multivariate analysis using logistic regression was performed to assess the independent risk factors for CCE in patients with NVAF. The area under the curve (AUC) was calculated, and receiver operating characteristics (ROC) curve analysis was performed to assess the predictive accuracy of NLR, CHA2DS2-VASc score, and their combination for CCE. The Youden index was used to determine the cut-off value (threshold value), sensitivity and specificity. Spearman correlation was carried out to analyze the correlation between CHA2DS2-VASc score and NLR. In addition, to assess the potential risk of CCE in patients with NVAF, the least absolute shrinkage and selection operator (LASSO) regression analysis was performed using R (4.2.1) to construct a risk score model based on NLR and CHA2DS2-VASc score. $P < 0.05$ was considered statistically significant. Besides, a power analysis was conducted to assess the adequacy of the sample size for detecting differences in the occurrence of CCE using logistic regression and LASSO regression analysis. Assuming a two-tailed test, a significance level (α) of 0.05, a power of 80%, and a medium effect size (odds ratio [OR] = 1.5), the current sample size was determined to be sufficient for detecting the expected effect. The assumed

effect size is consistent with previous studies evaluating clinical risk scores in stroke occurrence. Missing data were addressed through multiple imputation via chained equations, assuming data were missing at random (MAR).

Results

Demographic Characteristics and Inflammatory Markers

Comparison of clinical data between the two groups revealed that the CHA2DS2-VASc score, white blood count, platelet count, neutrophil count, NLR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose (GLU), CRP and D-dimer of the CCE group were higher than those of the control group, whereas the lymphocyte count was lower than that of the control group; the differences above were all statistically significant ($p < 0.05$). In contrast, the red blood count, hemoglobin, CR, UA, triglycerides (TG), cystatin C (CYS-C), homocysteine (HCY), and percentages of sex, age, smoking history, alcohol consumption history, hypertension, diabetes mellitus, coronary disease and use of anticoagulant drugs did not differ significantly between the two groups ($p > 0.05$). More details can be seen on Table 1.

Multiple Logistic Regression Analysis

Multiple logistic regression analysis was performed to comprehensively assess the association between the blood indicators above and the occurrence of CCE in patients with NVAF, and to identify the most valuable risk factors. The results indicated that CHA2DS2-VASc score (OR = 2.95, 95% CI = 2.19–3.99, $p < 0.001$), white blood count (OR = 1.43, 95% CI = 1.15–1.78, $p = 0.001$), NLR (OR = 1.63, 95% CI = 1.29–2.05, $p < 0.001$) and D-dimer (OR = 1.56, 95% CI = 1.15–2.12, $p = 0.005$) were associated with CCE. Univariate logistic regression showed that CHA2DS2-VASc score, white blood count, NLR, AST, GLU, CRP and D-dimer were highly significantly associated with CCE ($p < 0.01$), while platelet count and ALT were significantly associated with CCE ($p < 0.05$) (Table 2 and Figure 2).

ROC Curve Analysis

The AUC of the ROC curves for NLR and CHA2DS2-VASc score were 0.869 (95% CI = 0.843–0.901) and 0.859 (95% CI = 0.820–0.898), respectively. The threshold value of NLR and CHA2DS2-VASc score for predicting CCE risk in patients with NVAF was 2.989 and 4.50, respectively. The specificity was 0.832 and 0.908, respectively. The sensitivity was 0.796 and 0.665, respectively (Figure 3).

Correlation Analysis of NLR and CHA2DS2-VASc Score

Correlation analysis showed a positive correlation between NLR and CHA2DS2-VASc score ($R = 0.449$, $p < 0.001$). Furthermore, a heatmap was depicted to visualize the correlations between different variables in Figure 4 (with correlation coefficients showed in the figure).

Table 2 Multiple Logistic Analysis Results for Patients with CCE

Variables	OR	95% CI	P
CHA2DS2-VASc score	2.95	(2.19 ~ 3.99)	<0.001
White blood count (×109/L)	1.43	(1.15 ~ 1.78)	0.001
Platelet count (×109/L)	1.00	(0.99 ~ 1.01)	0.908
NLR	1.63	(1.29 ~ 2.05)	<0.001
ALT (U/L)	1.00	(0.96 ~ 1.04)	0.910
AST (U/L)	1.05	(0.99 ~ 1. 11)	0.098
GLU (mmol/L)	0.90	(0.74 ~ 1.08)	0.255
CRP (mg/L)	1.02	(0.99 ~ 1.05)	0.126
D-dimer (μg/mL)	1.56	(1.15 ~ 2. 12)	0.005

https://doi.org/10.2147/IJGM.S523480

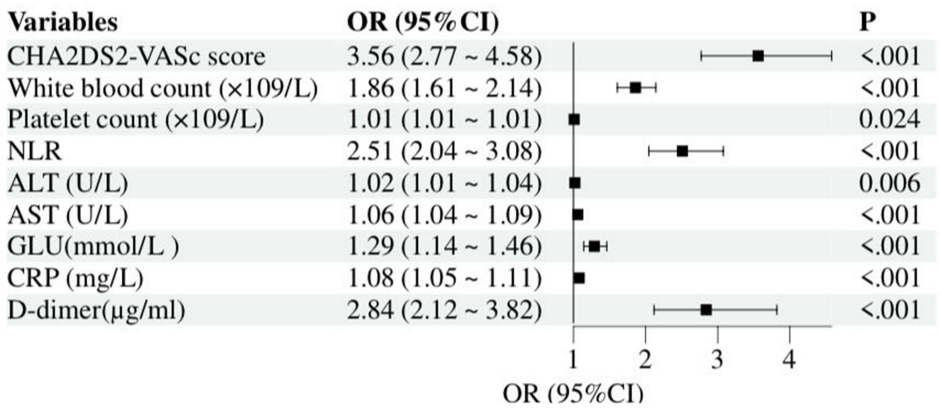

Figure 2 Independent risk factors for patients with CCE.

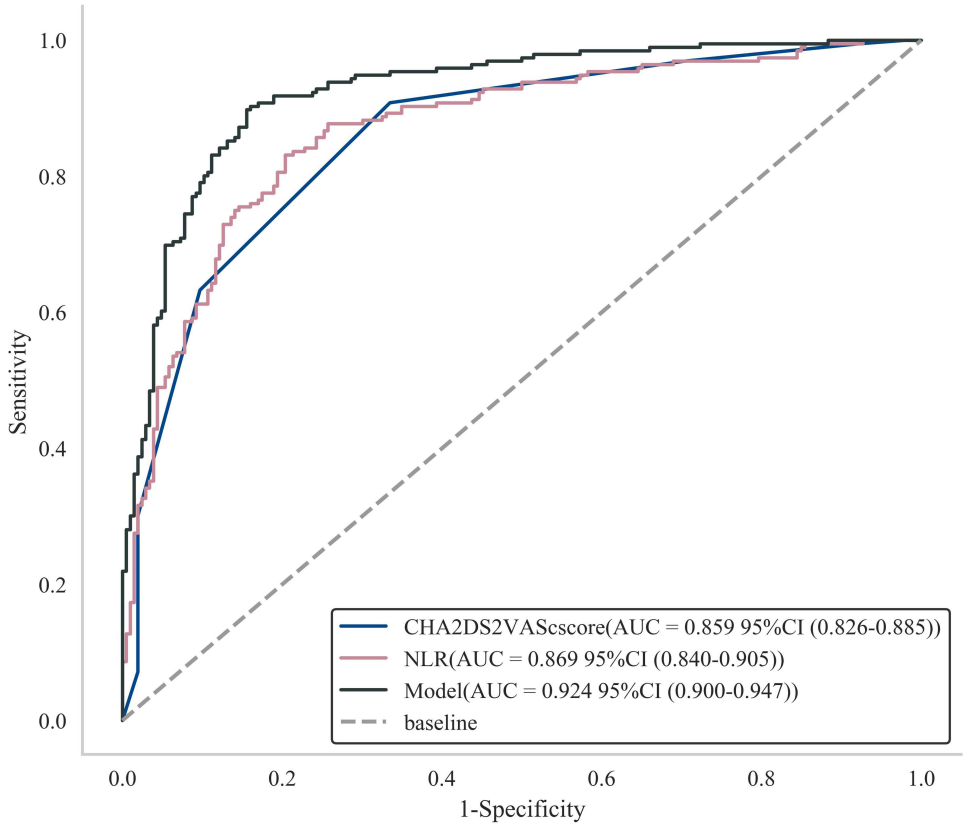

Figure 3 ROC curve analysis for NLR and CHA2DS2-VASc score.

LASSO Model Analysis

To determine the prediction of CCE risk in patients with NVAF, a composite index based on NLR and CHA2DS2-VASc score was constructed using the LASSO model. Risk score = 0.151 + 0.065 × CHA2DS2-VASc score + 0.003 × NLR. The risk score for CCE in NVAF patients was significantly higher than that of the control group, and the risk score was able to distinguish the CCE group from the Non-CCE group with an AUC of 0.924, sensitivity of 0.840, specificity of 0.903, and threshold value of 0.34 (Figures 5 and 6).

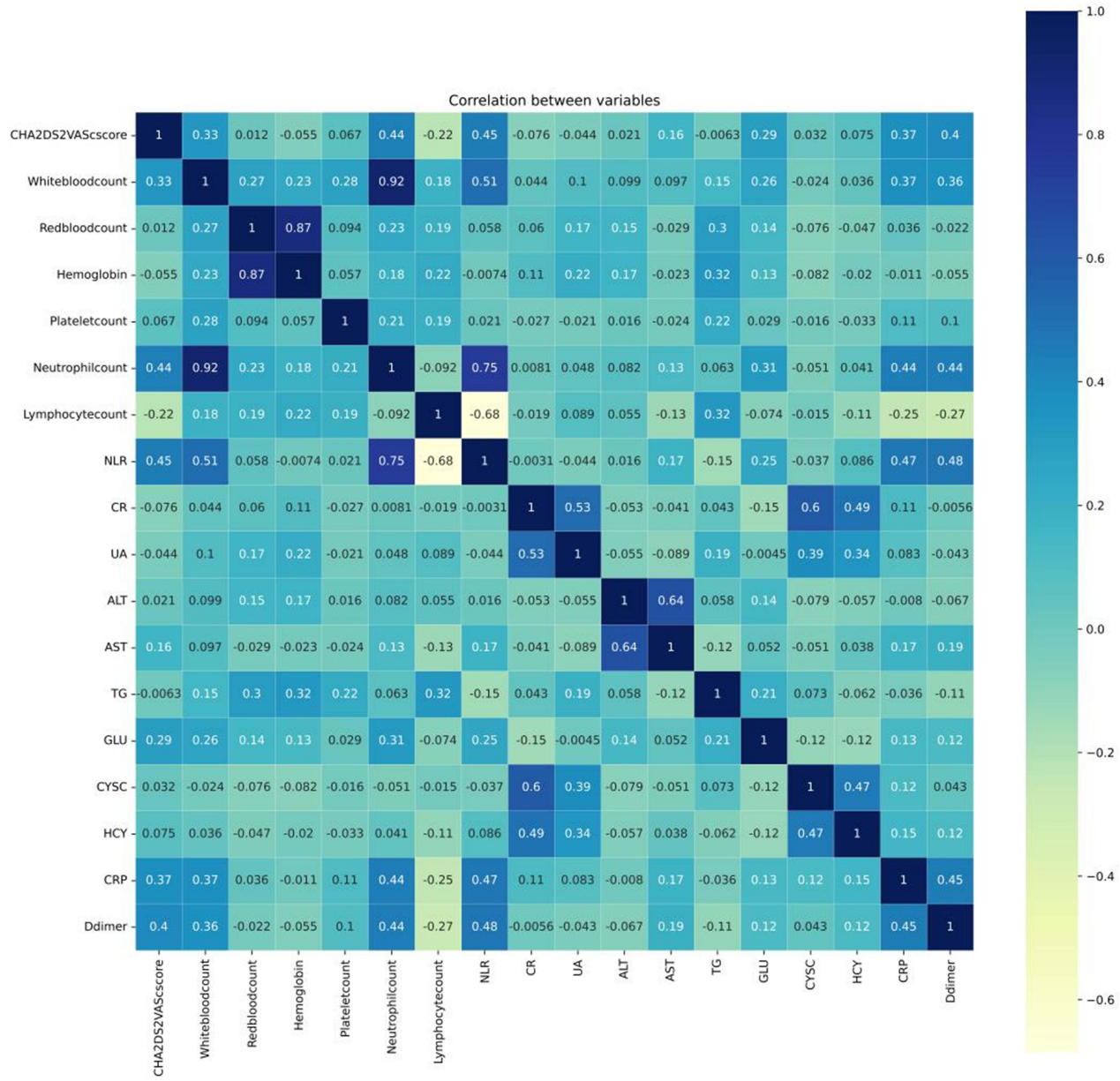

Figure 4 Correlation analysis of NLR and CHA2DS2-VASc score.

Discussion

AF is the most common type of arrhythmia observed in clinical practice, with its incidence and prevalence rising continually with age. Studies in the field of cerebrovascular disease have found that AF plays a crucial role the pathogenesis of ischemic stroke, while acute strokes caused by AF-induced cardiogenic emboli are often indicative of severe disease progression, as well as high recurrence and mortality rates.[3–5] In addition to physical factors, there is also a large body of evidence demonstrating that the inflammatory response is closely associated with triggering AF, inducing vascular endothelial cell damage, and giving rise to the subsequent process of embolus formation.[23] However, it is unclear whether the onset of AF directly activates the inflammatory response or whether the presence of a pre-existing systemic inflammatory response contributes to the persistence of AF. The two mechanisms may also interact to jointly participate in the pathogenesis of AF and its various associated complications.[24] This is the so-called "AF begets AF"

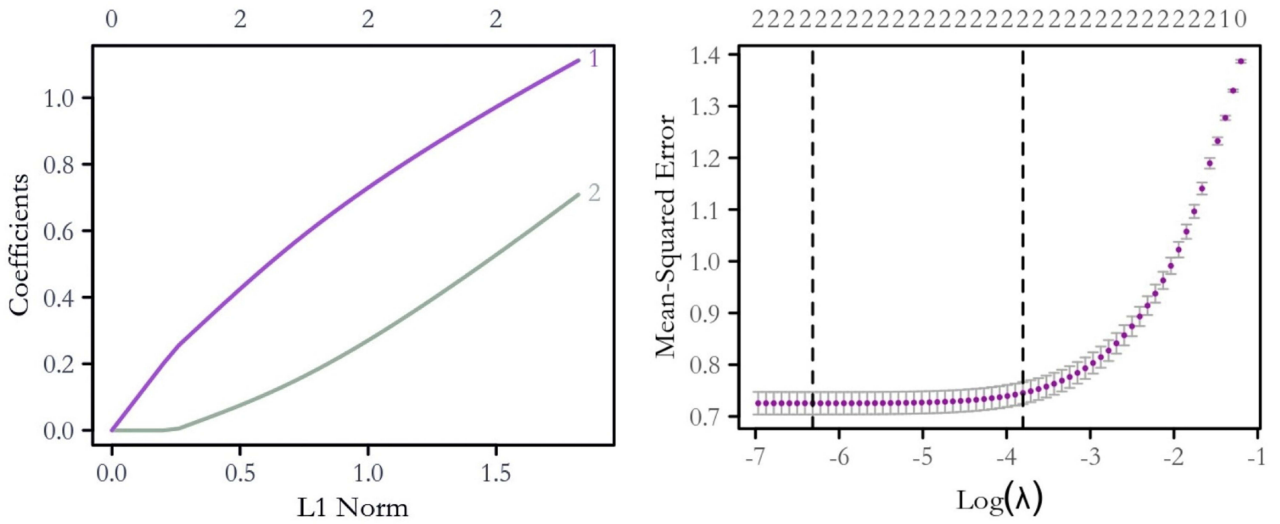

Figure 5 LASSO model based on NLR and CHA2DS2-VASc score.

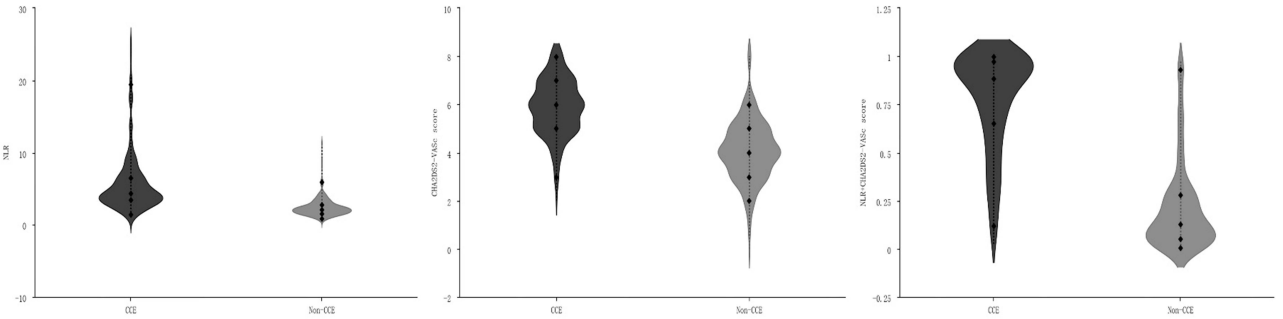

Figure 6 The association between NLR and CHA2DS2-VASc score in CCE patients.

phenomenon, in which a pre-existing inflammatory response triggers AF, while the AF-induced inflammatory response further promotes atrial remodeling and the persistence of abnormal rhythms.[22]

Previous studies have already identified numerous blood markers associated with AF and acute stroke, which not only encompass general markers, such as neutrophils, lymphocytes and platelets, but also include CRP, red cell distribution width, NT-proBNP, S100β, UA, D-dimer, as well as indexes based on routine blood indicators, such as the systemic immune-inflammation index (SII), NLR and platelet-to-lymphocyte ratio (PLR).[25–27] Our study demonstrated that NLR and D-dimer were independent risk factors for the risk of CCE occurrence in patients with NVAF, which is consistent with previous studies.[28] Despite the significant difference in CRP levels between the CCE group and the control group, in which the CCE group showed higher CRP levels, this indicator was not an independent risk factor for CCE in patients with NVAF. Previous studies have shown that CRP plays a crucial role in predicting adverse outcomes in acute stroke and can serve as an indicator of the prothrombotic state in AF patients, but there is a lack of reliable evidence demonstrating its ability to predict the risk of stroke onset.[24,29,30]

NLR is a composite index based on blood neutrophils and lymphocytes that is able to reflect the extent of the systemic inflammatory response. Thromboembolism is the most common cause of cerebrovascular occlusion, but stroke can also be a complication of systemic inflammatory responses and autoimmune processes. It participates in the pathogenesis of vascular diseases by inducing coagulation processes and altering the vascular inflammatory response. Ischemic stroke results in a sudden interruption of nutrient supply, which rapidly leads to irreversible damage to the infarct core and a series of secondary pathologies such as neuronal excitotoxicity, oxidative stress and mitochondrial

disorders, which ultimately cause an intense inflammatory response. During which, peripheral circulating cells, such as neutrophils, are recruited to the lesion site and activated, resulting in the release of cytokines, interferons and chemokines, thus leading to an imbalance between procoagulant and anticoagulant effects.[21,31]

Neutrophil extracellular traps (NETs) are extracellular DNA produced by neutrophil hyperactivation. Acute stroke can induce the production of NETs, which play a role in triggering neutrophil accumulation and producing factors that promote the disruption of the blood–brain barrier, such as reactive oxygen species (ROS), proteases and proinflammatory mediators. This, in turn, can enhance neutrophil–endothelium interactions and impair post-stroke vascular remodeling.[32,33] In addition, NETs can also promote thrombosis by recruiting coagulation factor XII and binding to tissue factor pathway inhibitor (TFPI).[34] In contrast, lymphocyte count is thought to exert neuroprotective functions that can benefit the improvement of neurological function after stroke.[21] In our study, the CCE group had a higher neutrophil count and lower lymphocyte count compared to the Non-CCE group.

Risk assessment of ischemic stroke is central to the management of NVAF. Although numerous risk assessment schemes have been proposed, the CHA2DS2-VASc score remains the most commonly used risk prediction model worldwide, most likely due to its simplicity and ease of use. Nonetheless, current stroke prediction models have significant limitations and do not incorporate other risk factors that contribute to CCE, including but not limited to: 1. NVAF-specific factors such as LAD and cardiac function; 2. potential cardiovascular and inflammatory response markers; 3. abnormal electrocardiographic findings; and 4. competing risk factors such as complex aortic plaque, carotid or intracranial artery stenosis, uncontrolled hypertension, advanced left ventricular dysfunction, or structural heart defects (eg, patent foramen ovale, atrial septal aneurysm).[10,35] A meta-analysis indicated that the predictive value of CHA2DS2-VASc score for stroke is limited when AF-related indexes are not included, and this predictive performance is similar in the presence or absence of NVAF.[11] Moreover, the combination of PLR and CHA2DS2-VASc can improve the prediction of CCE, CHA2DS2-VASc is no longer enough.[36,37] In summary, a wide range of elements should be incorporated into current risk factor-based stroke prediction models to optimize prevention practices and provide prevention and treatment recommendations for high-risk populations.

In this study, the LASSO regression-based risk score constructed using NLR and CHA2DS2-VASc score achieved an accuracy of 0.924 in predicting the CCE risk of patients with NVAF. This was higher than the accuracy of each index alone, despite the relatively high predictive accuracies of NLR and CHA2DS2-VASc score (0.869 and 0.859, respectively). Therefore, we recommend applying this risk score to the screening of patients with NVAF who are at high risk for CCE. Spearman correlation analysis revealed a positive correlation between NLR and CHA2DS2-VASc score. This may be because NLR, as a composite index of systemic inflammatory response, elevated the risk of NVAF patients through the "AF begets AF" phenomenon, thereby increasing their CHA2DS2-VASc score. Although we have fully investigated and explored the potential risk factors for NVAF-associated CCE and constructed a prediction model, this study still has some limitations: 1. This was a single-center retrospective study, which may have led to some bias. Thus, a multicenter study will be planned in the future to further confirm the feasibility and accuracy of this model in disease prediction. 2. This study did not follow up on the CCE patients. Future studies should focus on constructing a model for predicting the risk of secondary CCE or screening high-risk groups for CCE, while also taking into account other types of acute stroke or CCE caused by valvular AF. 3. The blood samples in this study were collected only once within 24 h of admission, whereas NLR is a dynamically changing blood index. Future studies should focus on the association between the changes in NLR levels at various phases in the pathogenesis of stroke and disease. Only CRP was included in this study, and the correlation between NLR and other inflammatory markers could not be compared. Future studies should add multiple inflammatory markers to comprehensively assess the role of the inflammatory response in CCE onset among patients with NVAF. 5. This study only analyzed whether anticoagulant therapy was performed in the two groups, without further examining the specific medications administered and timing of medications. Subsequent studies should further evaluate the impact of different anticoagulant drugs on the risk of CCE and the prediction model. 6. Although this composite score demonstrated great performance in CCE risk assessment, external validation in independent cohorts is necessary for generalization. 7. This study did not distinguish the impact of paroxysmal atrial fibrillation and permanent atrial fibrillation on clinical outcomes. However, previous study has already demonstrated that, compared to paroxysmal atrial

fibrillation, patients with permanent atrial fibrillation experience a higher risk of cardiogenic embolism and related complications.[38] Future studies should focus on exploring the effects of different atrial fibrillation episodes.

Conclusion

Our study found that the composite score which combined NLR and CHA2DS2-VASc score was more valuable than each index alone in identifying the CCE risk of patients with NVAF. The LASSO prediction model constructed based on NLR and CHA2DS2-VASc score had an accuracy of 0.924, which will enable the early identification of high-risk groups for CCE among NVAF patients and provide suggestions of anticoagulants strategies.

Data Sharing Statement

Origin data of this study are available from the corresponding author on reasonable request.

Acknowledgments

This study was supported by the Hefei Health and Wellness Applied Medicine Program (No. Hwk2023zd022) and the Natural Science Research Project of Anhui Universities (No. KJ2021A0349).

Funding

This study was funded by the project of "Hefei 2022 Key Common Technology Research and Development Project" of the science and technology innovation policy (GJ2022SM07).

Disclosure

The authors declare that they have no known competing interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Hankey GJ. Stroke. *Lancet*. 2017;389(10069):641–654. doi:10.1016/S0140-6736(16)30962-X
2. Li X, Kong X, Yang C, et al. Global, regional, and national burden of ischemic stroke, 1990–2021: an analysis of data from the global burden of disease study 2021. *eClinicalMedicine*. 2024;75:102758. doi:10.1016/j.eclinm.2024.102758
3. Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. *Curr Cardiol Rev*. 2010;6(3):150–161. doi:10.2174/157340310791658730
4. Bjerkreim AT, Khanevski AN, Thomassen L, et al. Five-year readmission and mortality differ by ischemic stroke subtype. *J Neurol Sci*. 2019;403:31–37. doi:10.1016/j.jns.2019.06.007
5. Ferro JM. Brain embolism. *J Neurol*. 2003;250(2):139–147. doi:10.1007/s00415-003-1017-0
6. Kamel H, Healey JS. Cardioembolic Stroke. *Circ Res*. 2017;120(3):514–526. doi:10.1161/CIRCRESAHA.116.308407
7. Tu WJ, Dong X, Zhao SJ, et al. Prognostic value of plasma neuroendocrine biomarkers in patients with acute ischaemic stroke. *J Neuroendocrinol*. 2013;25(9):771–778. doi:10.1111/jne.12052
8. Chamorro A, Vila N, Saiz A, Alday M, Tolosa E. Early anticoagulation after large cerebral embolic infarction: a safety study. *Neurology*. 1995;45(5):861–865. doi:10.1212/wnl.45.5.861
9. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation. *Chest*. 2018;154(5):1121–1201. doi:10.1016/j.chest.2018.07.040
10. Saliba W, Gronich N, Barnett-Griness O, et al. Usefulness of CHADS2 and CHA2DS2-VASc scores in the prediction of new-onset atrial fibrillation: a population-based study. *Am J Med*. 2016;129(8):843–849. doi:10.1016/j.amjmed.2016.02.029
11. Siddiqi TJ, Usman MS, Shahid I, et al. Utility of the CHA2DS2-VASc score for predicting ischaemic stroke in patients with or without atrial fibrillation: a systematic review and meta-analysis. *Eur J Prev Cardiol*. 2022;29(4):625–631. doi:10.1093/eurjpc/zwab018
12. Claridge SB, Kanaganayagam GS, Kotecha T. Atrial fibrillation guidelines. Don't forgetHASBLED score. *BMJ*. 2011;342:d3205. doi:10.1136/bmj.d3205
13. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. *J Am Coll Cardiol*. 2011;57(2):173–180. doi:10.1016/j.jacc.2010.09.024
14. Kamel H, Okin PM, Elkind MSV, et al. Atrial fibrillation and mechanisms of stroke: time for a new model. *Stroke*. 2016;47(3):895–900. doi:10.1161/STROKEAHA.115.012004
15. Chen C, Gu L, Chen L, et al. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as potential predictors of prognosis in acute ischemic stroke. *Front Neurol*. 2021;11:525621. doi:10.3389/fneur.2020.525621
16. An C, Shi Y, Li P, et al. Molecular dialogs between the ischemic brain and the peripheral immune system: dualistic roles in injury and repair. *Prog Neurobiol*. 2014;115:6–24. doi:10.1016/j.pneurobio.2013.12.002

17. Bhat T, Teli S, Rijal J, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. *Expert Rev Cardiovasc Ther*. 2013;11(1):55–59. doi:10.1586/erc.12.159
18. Brooks SD, Spears C, Cummings C, et al. Admission neutrophil–lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy. *J Neurointerv Surg*. 2014;6(8):578–583. doi:10.1136/neurintsurg-2013-010780
19. Nam KW, Kim TJ, Lee JS, et al. Neutrophil-to-lymphocyte ratio predicts early worsening in stroke due to large vessel disease. *PLoS One*. 2019;14(8):e0221597. doi:10.1371/journal.pone.0221597
20. Kundnani NR, Sharma A, Lighezan DF, et al. Use of neutrophil-to-lymphocyte ratio to predict in-hospital mortality in patients admitted with acute decompensation of atrial fibrillation. *J Clin Med*. 2024;13(16):4719. doi:10.3390/jcm13164719
21. Gong P, Liu Y, Gong Y, et al. The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-thrombolysis early neurological outcomes in patients with acute ischemic stroke. *J Neuroinflammation*. 2021;18(1):51. doi:10.1186/s12974-021-02090-6
22. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. *Bratisl Lek Listy*. 2021;122(7):474–488. doi:10.4149/BLL_2021_078
23. Dolu AK, Akçay FA, Atalay M, Karaca M. Systemic immune-inflammation index as a predictor of left atrial thrombosis in nonvalvular atrial fibrillation. *J Tehran Heart Cent*. 2023;18(2):87–93. doi:10.18502/jthc.v18i2.13317
24. Engelmann MDM, Svendsen JH. Inflammation in the genesis and perpetuation of atrial fibrillation. *Eur Heart J*. 2005;26(20):2083–2092. doi:10.1093/eurheartj/ehi350
25. Harpaz D, Bajpai R, Ng GJL, et al. Blood biomarkers to detect new-onset atrial fibrillation and cardioembolism in ischemic stroke patients. *Heart Rhythm*. 2021;18(6):855–861. doi:10.1016/j.hrthm.2021.01.032
26. Bai J, Sun H, Xie L, et al. Detection of cardioembolic stroke with B-type natriuretic peptide or N-terminal pro-BNP: a comparative diagnostic meta-analysis. *Int J Neurosci*. 2018;128(11):1100–1108. doi:10.1080/00207454.2017.1408612
27. He H, Guo J, Zhang A. The value of urine albumin in predicting thromboembolic events for patients with non-valvular atrial fibrillation. *Int J Cardiol*. 2016;221:827–830. doi:10.1016/j.ijcard.2016.07.145
28. Shi Y, Xuan C, Ji W, et al. Combination of platelet-to-lymphocyte ratio and D-dimer for the identification of cardiogenic cerebral embolism in non-valvular atrial fibrillation. *Front Neurol*. 2023;14:1069261. doi:10.3389/fneur.2023.1069261
29. Hu L, Qiao Z, Xu M, et al. Establishment and validation of a 3-month prediction model for poor functional outcomes in patients with acute cardiogenic cerebral embolism related to non-valvular atrial fibrillation. *Front Neurol*. 2024;15:1392568. doi:10.3389/fneur.2024.1392568
30. Geng HH, Wang XW, Fu RL, et al. The relationship between C-reactive protein level and discharge outcome in patients with acute ischemic stroke. *Int J Environ Res Public Health*. 2016;13(7):636. doi:10.3390/ijerph13070636
31. Macrez R, Ali C, Toutirais O, et al. Stroke and the immune system: from pathophysiology to new therapeutic strategies. *Lancet Neurol*. 2011;10(5):471–480. doi:10.1016/S1474-4422(11)70066-7
32. Denorme F, Portier I, Rustad JL, et al. Neutrophil extracellular traps regulate ischemic stroke brain injury. *J Clin Invest*. 2022;132(10):e154225. doi:10.1172/JCI154225
33. Rachieru C, Luca CT, Văcărescu C, et al. Future perspectives to improve CHA2DS2VASc score: the role of left atrium remodelling, inflammation and genetics in anticoagulation of atrial fibrillation. *Clin Interv Aging*. 2023;18:1737–1748. doi:10.2147/CIA.S427748
34. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease. *Nat Rev Immunol*. 2018;18(2):134–147. doi:10.1038/nri.2017.105
35. Alkhouli M, Friedman PA. Ischemic stroke risk in patients with nonvalvular atrial fibrillation. *J Am Coll Cardiol*. 2019;74(24):3050–3065. doi:10.1016/j.jacc.2019.10.040
36. Reiffel JA. CHA2DS2-VASc is no longer enough. *Europace*. 2022;24(7):1195. doi:10.1093/europace/euac018
37. Fan Q, Gao L, Wang Z, Ndjana Lessomo FY, Wang G. Prognostic value of platelet-to-lymphocyte ratio combined with CHA2DS2-VASc score for nonvalvular atrial fibrillation induced cardiogenic cerebral embolism. *J Inflamm Res*. 2023;16:5937–5947. doi:10.2147/JIR.S431149
38. Rosca CI, Sharma A, Nisulescu DD, et al. Prevalence of cardio-embolic brain complications in permanent and paroxysmal atrial fibrillation patients. *Healthcare*. 2023;11(2):175. doi:10.3390/healthcare11020175