

# Prognostic Value of Platelet-to-Lymphocyte Ratio Combined with CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> Score for Nonvalvular Atrial Fibrillation Induced Cardiogenic Cerebral Embolism

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**Aim:** To determine the predictive significance of the platelet-to-lymphocyte ratio (PLR) combined with the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score for cardiogenic cerebral embolism (CCE) in patients with nonvalvular atrial fibrillation (NVAF).

**Methods:** A total of 553 patients with NVAF were included in this retrospective study. The general data, PLR, CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score and echocardiography indicators were compared. The risk factors for CCE and the predictive value of PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> were analyzed. Stratified analysis was performed based on the cut-off value. Least absolute shrinkage and selection operator (LASSO) regression analysis was utilized to build a model. The relationship between risk score and different anticoagulants was evaluated.

**Results:** Multiple regression analysis showed hypertension (OR=3.95, 95% CI=2.12–7.35,  $p=1.40\times 10^{-5}$ ), diabetes mellitus (OR=2.95, 95% CI=1.57–5.58,  $p=7.65\times 10^{-4}$ ), PLR (OR=1.01, 95% CI=1.00–1.01,  $p<10^{-6}$ ), creatinine level (OR=1.01, 95% CI=1.00–1.02,  $p=7.44\times 10^{-3}$ ), left atrial diameter (LAD) (OR=1.90, 95% CI=1.13–3.19,  $p=1.51\times 10^{-2}$ ), ejection fraction (EF) (OR=0.93, 95% CI=0.87–0.98,  $p=8.06\times 10^{-3}$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score (OR=3.79, 95% CI=2.95–4.85,  $p<10^{-6}$ ) were independent risk factors for CCE. A one-way linear analysis also showed the above seven indexes were significantly correlated with CCE ( $F=56.4$ ,  $p<10^{-6}$ ). The area under the receiver operating characteristic (ROC) curve of PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score was 0.760 (95% CI: 0.721–0.800), and 0.855 (95% CI: 0.824–0.886), respectively. Pearson correlation analysis showed that PLR was correlated with CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score ( $r=0.331$ ,  $p<10^{-6}$ ). Stratified analysis indicated there was a positive correlation between different risk group ( $p<10^{-6}$ ). Using the LASSO model, a composite indicator displayed differential power for distinguishing CCE with an AUC value of 0.884 (95% CI: 0.857–0.911). Patients with dabigatran and rivaroxaban exhibited higher risk score than those with warfarin (warfarin vs dabigatran,  $p=1.40\times 10^{-2}$ ; warfarin vs rivaroxaban  $p=3.00\times 10^{-3}$ ).

**Conclusion:** PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score are independent risk factors for CCE with NVAF, and the combination of the two indices can improve the prediction of CCE.

**Keywords:** NVAF, CCE, PLR, CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score, LASSO model

## Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice and is characterized by cardiac systolic dysfunction, rapid and disordered atrial electrical activity, and atrial mural thrombosis.<sup>1</sup> Due to the prevalence of population ageing and risk factors such as hypertension, diabetes, obesity, smoking and alcohol consumption, the prevalence of AF has been increasing significantly.<sup>2–5</sup> NVAF is one of the most common type major causes of atrial fibrillation, accounting for 65.2% of cases, and the incidence rate shows an increasing trend year by year. Thromboembolic complications are the main cause of death and disability in NVAF.<sup>6</sup> The risk

of stroke in patients suffering from NVAF is five times higher than that in the general population. NVAF causes more acute onset of cerebral infarction and higher mortality and disability than other types of cerebral infarction, and imposes a great burden on global public health.<sup>7,8</sup> Current guidelines agree that the prevention of AF-related cerebral infarction is the primary concern of comprehensive management strategy and treatment guidance for patients. Due to the seriousness of the danger of AF, early identification of high-risk patients is needed, and in addition to traditional approaches, some new clues have been gradually discovered, such as fragmented QFR.<sup>9,10</sup> The mechanism of the generation, maintenance and recurrence of AF is not completely clear, and an increasing number of studies have shown that external factors such as activation of the autonomic nervous system, activation of the renin angiotensinogen system, inflammatory factors, oxidative stress and genetic factors can interact to cause AF. The CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score is an abbreviated version of the thrombus risk assessment method based on clinical risk factors and baseline characteristics of AF patients. Although widely accepted by the Society of Cardiology, it has limitations in the use of clinical data rather than biochemical and morphological data.<sup>11,12</sup> In this context, biomarkers attempt to fill this gap by increasing dominance, expressing disease severity and duration. PLR, a new marker of the inflammatory pathway, is independently associated with adverse clinical outcomes such as cardiovascular lymphocytes. PLR also has high clinical value in evaluating the condition and prognosis of cardiovascular disease. Moreover, PLR is a comprehensive index based on the analysis of blood cells, which is more sensitive and accurate than a single complete blood count. However, there are few studies on PLR and NVAF, therefore, a case - control study was conducted to investigate the association between PLR and the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> scoring system and the occurrence of CCE in patients with AF, and to provide help for early clinical identification of patients at high risk of thrombosis.

## Methods

### Patient Selection

A total of 553 patients diagnosed with NVAF in Zhongnan Hospital of Wuhan University from January to December in 2022 were selected. A total of 236 patients were diagnosed with CCE. 317 patients were diagnosed with non-CCE matched for sex and age and not suffered from an acute stroke of patients with NVAF within the same time frame. Table 1 illustrates the detailed clinical features of the patient demographics enrolled in our research. Figure 1 shows the detailed screening procedure. This study was reviewed and approved by the Medical Ethical Committee of Zhongnan Hospital of Wuhan University.

**Table 1** Demography of Subject

Parameter	Non-CCE	CCE	$\chi^2$	p
Subject numbers	317	236	–	–
Gender (Male)	194	142	$6.01 \times 10^{-2}$	$8.06 \times 10^{-1}$
Age (years)	$71.82 \pm 12.45$	$73.51 \pm 9.70$	–	$8.29 \times 10^{-2}$
Smoking (yes/no)	58	43	$5.06 \times 10^{-4}$	$9.82 \times 10^{-1}$
HP (yes/no)	173	158	8.62	$3.32 \times 10^{-3}$
DM (yes/no)	70	74	6.04	$1.39 \times 10^{-2}$
CAD (yes/no)	121	82	0.68	$4.23 \times 10^{-1}$
Vascular disease (yes/no)	37	39	2.69	$1.01 \times 10^{-1}$
Heart failure (yes/no)	209	151	0.23	$6.53 \times 10^{-1}$
Renal failure (yes/no)	54	34	0.69	$4.03 \times 10^{-1}$
White blood count ( $\times 10^9/L$ )	$8.05 \pm 3.27$	$8.23 \pm 3.74$	–	$5.62 \times 10^{-1}$
Red blood count ( $\times 10^9/L$ )	$4.12 \pm 0.73$	$4.14 \pm 0.70$	–	$8.40 \times 10^{-1}$
Hemoglobin	$125.18 \pm 24.72$	$125.95 \pm 21.09$	–	$7.01 \times 10^{-1}$
Lymphocyte count ( $\times 10^9/L$ )	$1.39 \pm 0.69$	$0.98 \pm 0.41$	–	$< 10^{-6}$
Platelet count ( $\times 10^9/L$ )	$162.28 \pm 53.32$	$175.90 \pm 49.48$	–	$2.28 \times 10^{-3}$

(Continued)

Table I (Continued).

Parameter	Non-CCE	CCE	$\chi^2$	p
PLR	137.78±61.59	207.96±103.62	–	<10 <sup>-6</sup>
ALT (U/L)	24.76±33.58	22.94±28.44	–	5.00×10 <sup>-1</sup>
AST (U/L)	31.04±39.31	32.27±42.76	–	7.25×10 <sup>-1</sup>
Albumin (g/L)	36.49±5.09	35.52±4.23	–	1.81×10 <sup>-2</sup>
CR (mg/ dl)	79.85±20.43	89.22±45.06	–	1.11×10 <sup>-3</sup>
UA (μmol/L)	365.96±125.84	380.15±136.21	–	2.08×10 <sup>-1</sup>
D-dimer (ng/mL)	694.12±1421.77	1378.48±3240.21	–	8.56×10 <sup>-4</sup>
LAD (mm)	4.38±0.55	4.54±0.43	–	2.46×10 <sup>-4</sup>
EF (%)	59.32±5.08	57.73±3.06	–	2.20×10 <sup>-5</sup>
CHA <sub>2</sub> DS <sub>2</sub> -VAS <sub>c</sub>	3.09±1.50	5.46±1.53	–	<10 <sup>-6</sup>
Anticoagulant	310	233		4.13×10 <sup>-1</sup>

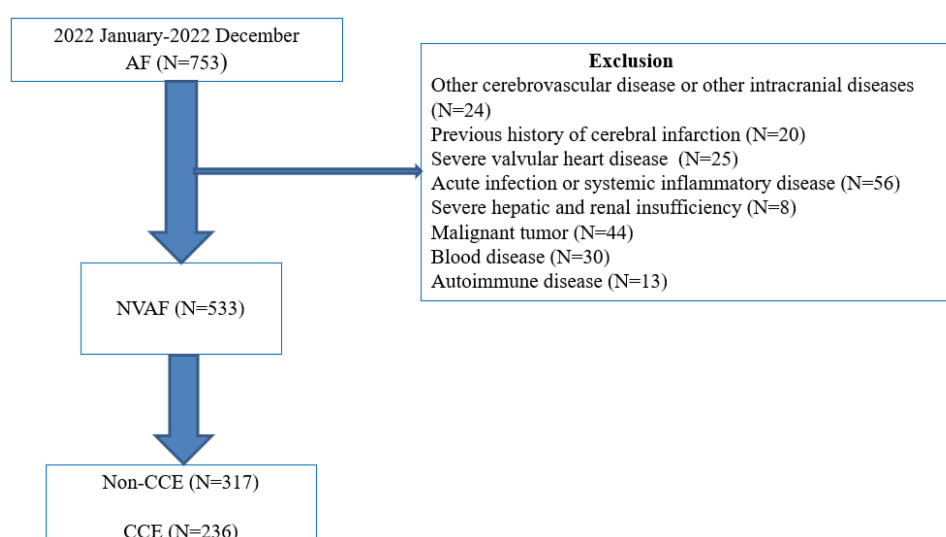
**Abbreviations:** HP, hypertension; DM, diabetes; CAD, coronary heart disease; PLR, platelet to lymphocyte ratio; CR, creatinine; UA, uric acid; LAD, left atrial diameter; EF, ejection fraction; CCE, cardiogenic cerebral embolism.

## Inclusion Criteria

(1) NVAf was diagnosed according to the 2019 AHA/ACC/HRS guidelines for the management of patients with AF, and patients with paroxysmal or persistent AF were diagnosed with a 12-lead routine ECG or a 24-hour Holter monitor, and echocardiography confirmed NVAf.<sup>13</sup> (2) According to the diagnostic criteria of the Chinese guidelines for the diagnosis and treatment of acute ischaemic stroke 2018, patients with CCE were diagnosed by cranial CT or magnetic resonance imaging. (3) Complete clinical data and biochemical test results during hospitalization.

## Exclusion Criteria

(1) Complicated by other cerebrovascular disease or other intracranial diseases. (2) Previous history of cerebral infarction or brain imaging evidence of cerebral infarction. (3) Severe valvular heart disease. (4) Patients with acute infection or systemic inflammatory disease, severe liver and renal insufficiency, malignant tumour, blood disease, autoimmune disease and other systemic diseases.



**Figure 1** Study design flowchart.

## Instruments and Methods

- (1) Clinical data collection: The basic data of patients were collected retrospectively by an electronic medical record system, including sex, age, smoking history and comorbidities (hypertension, diabetes, coronary heart disease, peripheral vascular disease, heart failure, and renal failure). Hypertension is defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg, with patients reporting a history of hypertension or being treated with antihypertensive drugs. Diabetes mellitus was determined on the basis of a previous diagnosis, fasting blood glucose  $\geq 7.1$  mmol/L, and glycated haemoglobin blood glucose (HbA1c)  $\geq 6.5\%$ , or are on glucose-lowering drugs or insulin therapy. Renal failure is defined as  $\text{eGFR} < 90 \text{ mL}/(\text{min} \cdot 1.73 \text{ m}^2)$ .<sup>14</sup>
- (2) Biochemical and echocardiography indices: peripheral venous blood was collected on an empty in the morning after admission, and routine blood tests were performed by automatic blood cell analyser, white blood cell count (WBC), red blood cell count (RBC), hemoglobin, lymphocyte count, platelet count and PLR. Liver function, renal function and D-dimer were measured by an automatic biochemical analyzer. LAD and EF% were recorded with a Philips IE33 colour Doppler imaging system.
- (3)  $\text{CHA}_2\text{DS}_2\text{-VAS}_\text{c}$  score: includes age, sex, heart failure, hypertension, diabetes mellitus, history of stroke/transient ischaemic attack/thromboembolism, and related vascular disease (myocardial infarction, composite aortic plaque, and peripheral arterial disease). Scoring criteria: ①Age  $\geq 75$  years old (2 score), age 65–74 years old (1 score). ②Female (1 score). ③Heart failure (1 score). ④Hypertension (1 score). ⑤Diabetes mellitus (1 score); ⑥History of stroke/transient ischaemic attack/thromboembolism (2 score). ⑦Related vascular disease (1 score).<sup>15</sup>

## Statistical Analysis

SPSS 21.0 software was used. The measurement data were expressed as  $\bar{X} \pm s$ , and the  $t$  test was used. The count data were expressed, and the chi-square test was used. The independent risk factors for acute cerebral infarction in patients with NVAf were analyzed by logistic regression analysis. The correlation between  $\text{CHA}_2\text{DS}_2\text{-VAS}_\text{c}$  score and PLR was analyzed by Pearson correlation. Stratified analysis was performed by the chi-square test. The area under the curve (AUC) was calculated to evaluate the predictive value of the  $\text{CHA}_2\text{DS}_2\text{-VAS}_\text{c}$  score, PLR and combined indices for CCE in NVAf patients by ROC analysis. Youden's index was used to determine the cut-off value, sensitivity and specificity. Furthermore, to assess the potential risk of CCE for NVAf patients, LASSO regression analysis was performed using R (4.2.1) software to construct a risk score model based on PLR and  $\text{CHA}_2\text{DS}_2\text{-VAS}_\text{c}$  score. Kruskal–Wallis test was used to evaluate the relationship between the risk score and different anticoagulants. The statistical power analysis was performed with a program that calculates the sample size and power (PASS 15.0).  $p < 0.05$  was considered statistically significant.

## Results

### Demographic Characteristics

The two groups of patients were compared in terms of baseline data. The proportion of hypertension and diabetes mellitus, lymphocyte count, platelet count, PLR, albumin, creatinine, D-dimer, LAD, EF% and  $\text{CHA}_2\text{DS}_2\text{-VAS}_\text{c}$  score in the CCE group were higher than those in the non-CCE group, and the difference was statistically significant ( $p < 0.05$ ). However, there were no significant differences in sex, age, smoking history, proportion of coronary heart disease, proportion of peripheral vascular disease, proportion of heart failure, proportion of renal failure, WBC, RBC, haemoglobin, platelet count, lymphocyte count, ALT, AST and UA ( $p > 0.05$ ). The sample size provided a statistical power of 98.9%. See Table 1.

### Multiple Logistic Regression Analysis

To comprehensively evaluate the association between confounding factors and the occurrence of CCE in NVAf patients and determine the most valuable risk factors, a multiple regression analysis was performed, and the results showed that hypertension ( $\text{OR} = 3.95$ , 95%  $\text{CI} = 2.12\text{--}7.35$ ,  $p = 1.40 \times 10^{-5}$ ), diabetes mellitus ( $\text{OR} = 2.95$ , 95%  $\text{CI} = 1.57\text{--}5.58$ ,  $p = 7.65 \times 10^{-4}$ ), creatinine level ( $\text{OR} = 1.01$ , 95%  $\text{CI} = 1.00\text{--}1.02$ ,  $p = 7.44 \times 10^{-3}$ ), PLR ( $\text{OR} = 1.01$ , 95%  $\text{CI} = 1.00\text{--}1.01$ ,  $p < 10^{-6}$ ), LAD ( $\text{OR} = 1.90$ , 95%  $\text{CI} = 1.13\text{--}3.19$ ,  $p = 1.51 \times 10^{-2}$ ), ejection fraction (EF) ( $\text{OR} = 0.93$ , 95%  $\text{CI} = 0.87\text{--}0.98$ ,

**Table 2** Multiple Logistics Analysis Result of CCE in NVAF

Parameter	OR	95% CI	p
HP	3.95	2.12–7.35	$1.40 \times 10^{-5}$
DM	2.95	1.57–5.58	$7.65 \times 10^{-4}$
PLR	1.01	1.00–1.01	$<10^{-6}$
Albumin	1.04	0.99–1.10	$1.40 \times 10^{-1}$
CR	1.01	1.00–1.02	$7.44 \times 10^{-3}$
D-dimer	1.00	1.00–1.00	$4.74 \times 10^{-1}$
LAD	1.90	1.13–3.19	$1.51 \times 10^{-2}$
EF	0.93	0.87–0.98	$8.06 \times 10^{-3}$
CHA <sub>2</sub> DS <sub>2</sub> -VAS <sub>c</sub>	3.79	2.95–4.85	$<10^{-6}$

**Abbreviations:** HP, hypertension; DM, diabetes; PLR, platelet to lymphocyte ratio; CR, creatinine; LAD, left atrial diameter; EF, ejection fraction; CCE, cardiogenic cerebral embolism; NVAF, nonvalvular atrial fibrillation.

$p=8.06 \times 10^{-3}$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score (OR=3.79, 95% CI=2.95–4.85,  $p<10^{-6}$ ) were associated with CCE. A one-way linear analysis also showed that the above seven indexes were significantly correlated with CCE ( $F=56.4$ ,  $p<10^{-6}$ ). See Table 2 and Figure 2.

### ROC Curve Analysis

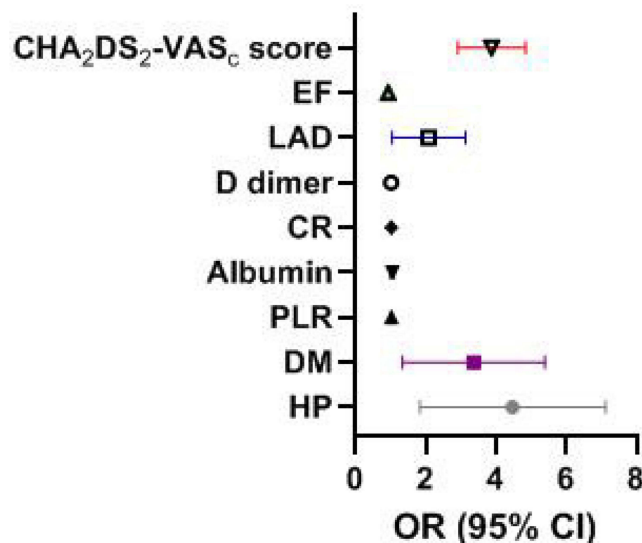
The ROC curves of PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score were 0.760 (95% CI: 0.721–0.800), and 0.855 (95% CI: 0.824–0.886) respectively. The cut-off values of PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score for predicting CCE in NVAF patients were 150.7 and 5.0 respectively. The sensitivity was 0.712 and 0.742 and the specificity was 0.729 and 0.814 respectively. See Figure 3.

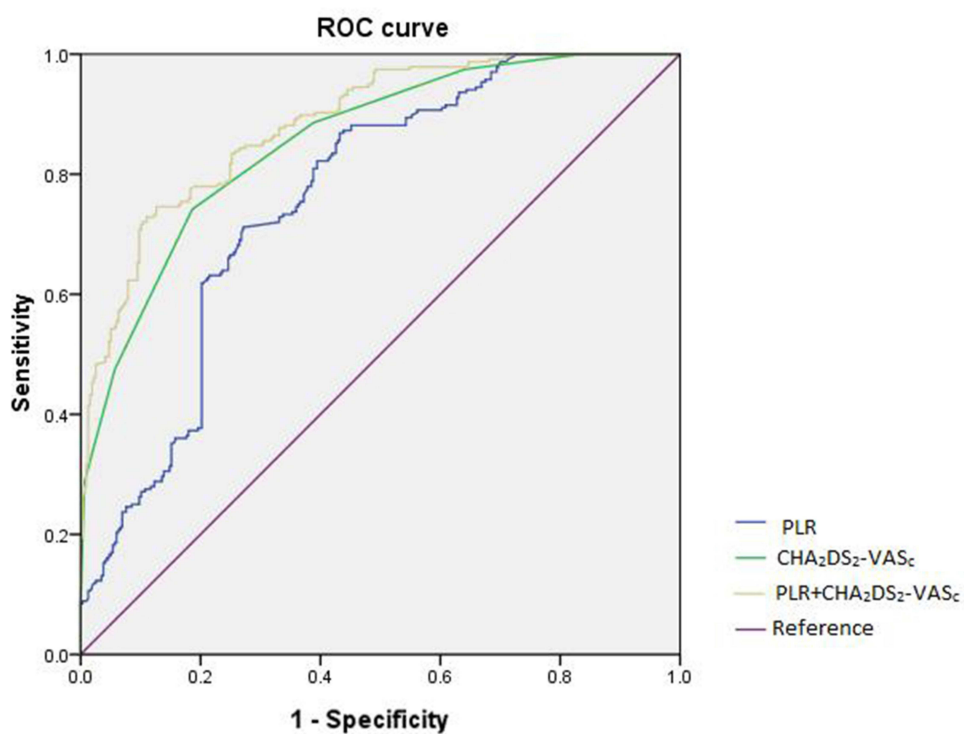
### Correlation Analysis of PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> Score

Pearson correlation analysis showed that the PLR level was positively correlated with the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score ( $r = 0.331$ ,  $p<10^{-6}$ ). See Figure 4.

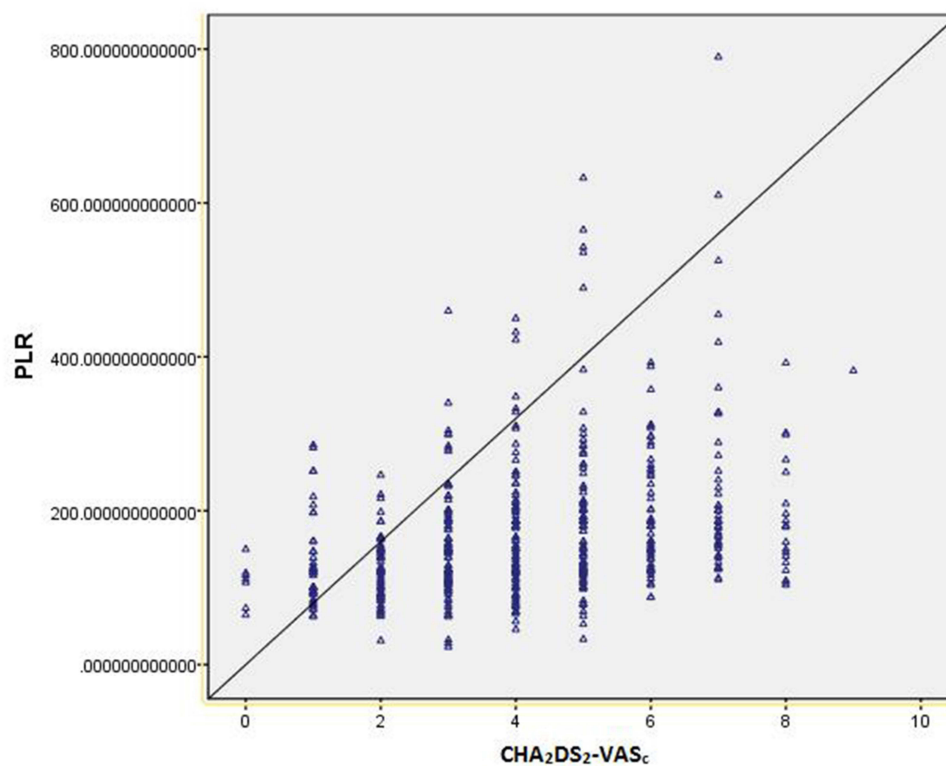
### Stratified Analysis of CCE Risk in NVAF

Risk stratification of patients with NVAF was performed using the cut-off values of PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score. The stratification criteria were: PLR<150.7 and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score<5 was low-risk group (263 cases). PLR≤150.7 and

**Figure 2** Independent risk factors for CCE in NVAF patients.

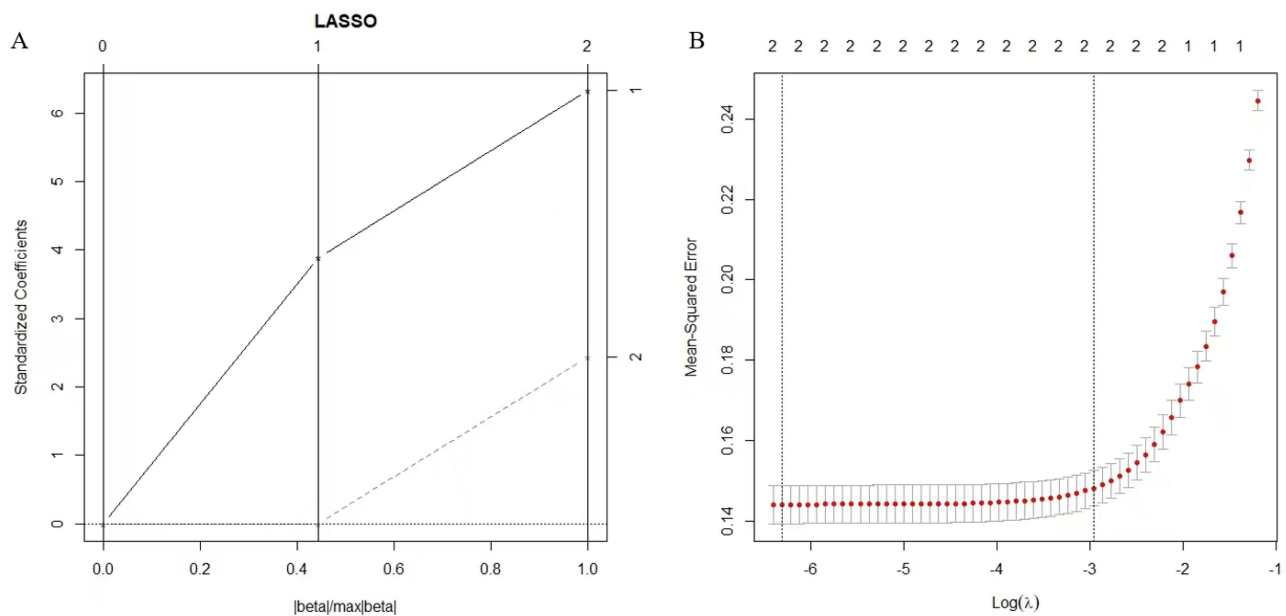


**Figure 3** ROC curve analysis.



**Figure 4** Spearman correlation analysis of PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score.



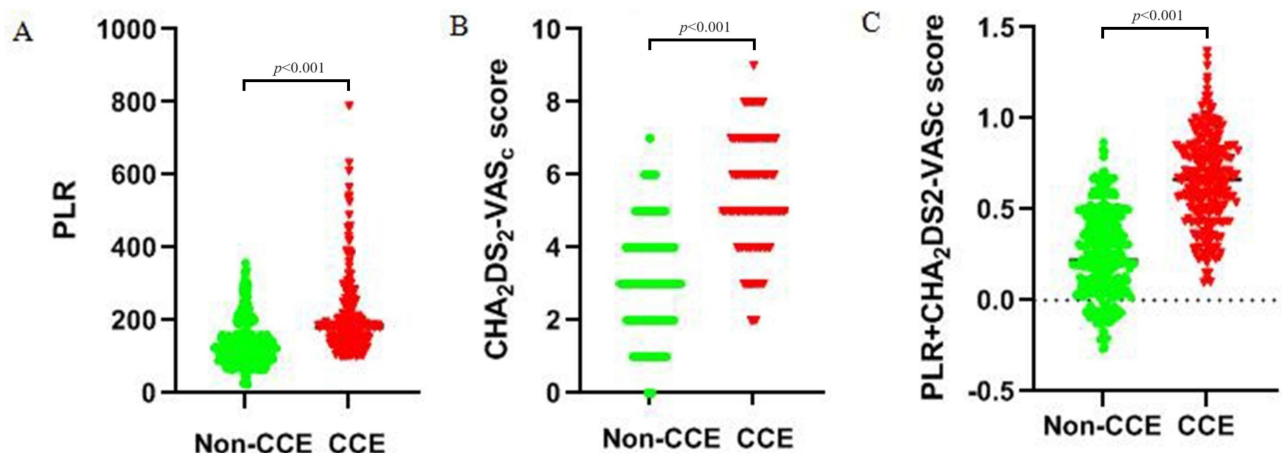


**Figure 5** LASSO model based on PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score. (A) The coefficients of each variate in the model (1: PLR; 2: CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score). (B) The mean-squared error of the model.

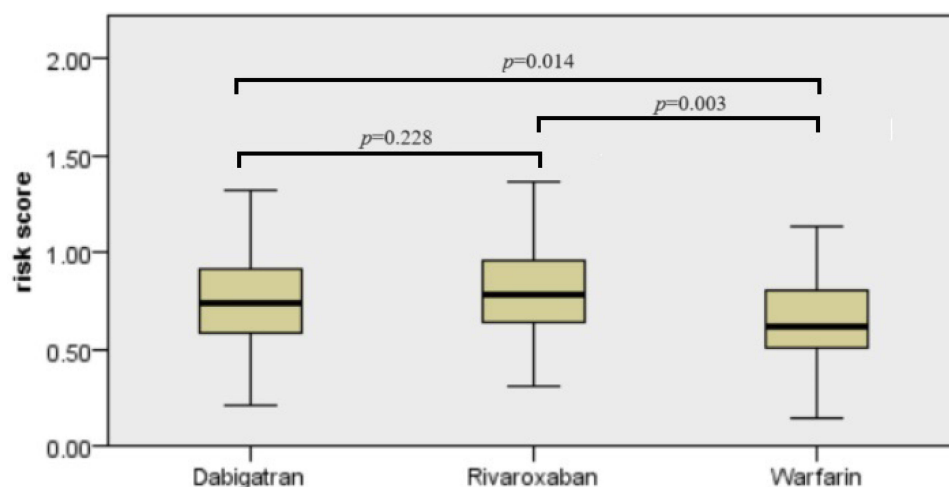
CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score  $\geq 5$  or PLR  $\geq 150.7$  and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score  $\leq 5$  were medium-risk group (N=204). PLR  $> 150.7$  and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score  $> 5$  was high-risk group (N=86). Chi-square test analysis showed that the risk of CCE in high-risk group was higher than that in low-risk and medium-risk group ( $\chi^2=160.7$ , 26.9, both  $p<10^{-6}$ ), and the medium-risk group was higher than that in low-risk group ( $\chi^2=95.2$ ,  $p<10^{-6}$ ).

## LASSO Model Analysis

To identify a comprehensive risk index to predict the occurrence of CCE in NVAf, we built a composite indicator based on the PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score. The risk score of the LASSO model was calculated as follows: risk score = the level of PLR  $\times 1.149289e^{-03}$  + the level of CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score  $\times 1.40295668e^{-01} - 0.341324479$  (see Figure 5). The results showed that the risk score was significant for CCE in NVAf patients and the risk score could differentiate CCE patients from patients in the NVAf group with an AUC of 0.884 (sensitivity=74.6%, specificity=87.4%, cut-off value=0.504). See Figures 3 and 6.



**Figure 6** The association between PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score in CCE patients and non-CCE patients. (A) The significant difference in the PLR between CCE patients and non-CCE patients. (B) The significant difference in the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score between CCE patients and non-CCE patients. (C) The significant difference in the PLR combined with CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score between CCE patients and non-CCE patients.



**Figure 7** The association between the risk score and different anticoagulants in CCE patients.

## Difference of the Risk Score Among Different Anticoagulants in CCE Patients

Furthermore, in the CCE group, patients received different anticoagulation therapy (warfarin: 59 cases; dabigatran: 92 cases; rivaroxaban: 82 cases). Results showed that there were significant differences in the risk score among three groups ( $H=12.38$ ,  $p=2.00 \times 10^{-3}$ ). Patients with non-vitamin K antagonist oral anticoagulants (dabigatran and rivaroxaban) exhibited significantly higher risk score than those with warfarin (dabigatran vs warfarin,  $p=1.40 \times 10^{-2}$ ; rivaroxaban vs warfarin  $p=3.00 \times 10^{-3}$ ). However, there was no significant association between dabigatran and rivaroxaban in risk scores ( $p=2.28 \times 10^{-1}$ ). See Figure 7.

## Discussion

NVAF is the unsynchronized contraction of the left atrium leading to the loss of mechanical function of the atrium, which causes blood to form eddies in the atrium, leading to thrombosis.<sup>16–18</sup> To date, the mechanism of NVAF remains unclear, but a large number of studies have shown that inflammatory reactions are closely related to the triggering and maintenance of atrial fibrillation. Inflammation can increase the risk of atrial fibrillation in various cardiovascular diseases such as coronary heart disease, heart failure, and hypertension and the anti-inflammatory effect of glucocorticoids can reduce the risk of recurrence of atrial fibrillation within 3 days after radiofrequency ablation.<sup>19</sup> Inflammatory conditions can also lead to a decrease in intracellular calcium currents. Inflammatory mediators cause apoptosis of atrial myocytes, which in turn leads to electrical and structural remodeling of the atria through activation of the fibrotic pathway of fibroblasts, ultimately leading to AF. AF may further aggravate the inflammatory state of the body.<sup>20,21</sup>

Previous studies have shown that many inflammatory markers are associated with AF, including CRP, IL-6, and IL-8. CRP, a marker reflecting systemic nonspecific inflammation, is now recognized as a valid marker for determining cardiovascular disease risk grading and plays a bridging role in the process of inflammation promoting the development of AF. Similar studies have been conducted on some new inflammatory markers such as red blood cell distribution width, neutrophil lymphocyte ratio (NLR) and PLR. Predictive analysis based on clinical data has been widely used in cardiovascular diseases, such as acute coronary syndrome, peripheral artery disease, and pulmonary embolism.<sup>22–24</sup> PLR is a new inflammatory indicator that has been used to evaluate the inflammatory status of patients with acute coronary syndrome, type 2 diabetes and other diseases. At present, the relationship between PLR and the pathophysiological mechanism of AF is still controversial. Chen et al found that PLR is an independent risk factor for left atrial thrombosis in patients with NVAF, and it is associated with the severity of stroke neurological impairment, which can be used as a predictor of short-term prognosis.<sup>25</sup> In addition, Gary et al found that high PLR levels may damage blood viscosity, thereby damaging the oxygen supply of myocardial tissue.<sup>26</sup> However, the result from a recent study was different from those of previous studies, suggesting that PLR levels are not associated with AF in 1982 subjects.<sup>27</sup> Our



findings indicate that the PLR level in the CCE group is higher than that in the non-CCE group. The ROC curve suggests that the AUC value of PLR predicting CCE occurrence in NVAf patients is 0.760, and the cut-off value is 150.4. When the PLR of NVAf patients is greater than 150.4, it can better predict the risk of CCE occurrence. The mechanism may be that in the infarcted area, macrophages are activated by inflammatory mediators, resulting in the production of a large number of activated platelets that can release proinflammatory factors to regulate the permeability of endothelial cells, which in turn recruit monocytes for migration and aggregation, leading to the progression of the inflammatory response. This is related to the key pathogenesis of platelet-forming stroke through the activation of the GP Ib-vascular haemophilia factor-GPVI axis, and triggering of the GP Ib-vascular haemophilia factor-GPVI coagulation factor XII pathway may promote the progression of inflammatory reactions.<sup>28–30</sup>

The CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score system is currently one of the more reliable methods commonly used to assess the risk of stroke in patients with NVAf. Patients with a high CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score often have a high risk of bleeding, and antithrombotic treatment based solely on the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score is not comprehensive. Some studies have optimized the risk stratification of acute cerebral infarction by combining other biochemical indicators, which has played an important guiding role in clinical antithrombotic treatment.<sup>31</sup> The results of our study showed that PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score have predictive value for the risk of CCE with NVAf, and the predictive value of the combined index is significantly higher than that of the independent index. The ROC curve suggests that the AUC value of the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score predicting CCE occurrence in NVAf patients is 0.855. However, the PLR combined with the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score index showed an AUC value of 0.884. Pearson correlation analysis showed that PLR was positively correlated with CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score. This may be because elevated PLR levels reflect the inflammatory state of the body, increasing the risk of patients with related diseases, and thereby improving the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score. PLR may be more clinically relevant for patients with CCE as a complementary stratification marker for the CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> score. In addition, we further analyzed the influence of different anticoagulant drugs on the incidence of CCE, and the results showed that our conclusions were consistent with those of previous studies, indicated that non-vitamin K antagonist oral anticoagulants may have better effect for stroke prevention than warfarin in NVAf, which provided a good inspiration for our clinical drug selection.<sup>32,33</sup>

Although we have fully evaluated the potential clinical significance of NVAf related CCE risk scores, some limitations could be noted, and the retrospective nature of this investigation could have given rise to some biases. First, because the selected patients were all inpatients in the department of cardiology of our hospital, there is a selection bias. Second, the sample size of this study was small and from a single center, and the research results are one-sided, requiring greater sample size verification in the future. Third, due to the lack of data on inflammatory markers such as CRP, IL-8, and TNF, it is impossible to compare the correlation between PLR and these inflammatory markers. Finally, there is no further dynamic monitoring of the PLR of patients and evaluation of its relationship to the severity of NVAf and CCE.

## Conclusion

Our study found that PLR and CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> showed greater value for identifying the occurrence of CCE in NVAf patients, which supported that inflammation and thrombosis were associated with CCE. Furthermore, PLR combined with CHA<sub>2</sub>DS<sub>2</sub>-VAS<sub>c</sub> based on the LASSO model and ROC curve analysis demonstrated better performance with an accuracy of 88.4% and can be used as an indicator for predicting and evaluating CCE in NVAf patients than the single index, assessing the risk of CCE in NVAf patients and providing targeted prevention. Furthermore, non-vitamin K antagonist oral anticoagulants can lower risk scores compared to warfarin. This study has important implications for the early identification of CCE high-risk groups in NVAf patients and the selection of anticoagulants.

## Patient Privacy Protection Statement

We desensitized all the data that can be used to identify patient personal information, such as their names, hospitalization ID and telephone numbers, to protect the privacy of patients.

## Data Sharing Statement

The authors declare that all data supporting the findings of this study are available within the article or from the corresponding author (Gang Wang).

## Ethical Approval and Consent to Participate

The studies involving human participants were reviewed and approved by the Medical Ethics Committee, Zhongnan Hospital of Wuhan University (2022157K). As this study is retrospective and presents no risk of harm to subjects, and no privacy of individuals is exposed, informed consent was waived. All procedures adhered to the ethical standards and the Helsinki Declaration (as revised in 2013).

## 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.

## Funding

There is no funding to report.

## Disclosure

The authors declare that they have no competing interest in this work.

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