Heart Surgery Forum 2025; 28(3): E249–E256
doi: 10.59958/hsf.8243

Article

Predictive Values of Left Atrial Appendage Function and Carotid Atherosclerotic Plaques for Ischemic Stroke in Patients with Nonvalvular Atrial Fibrillation

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Submitted: 20 November 2024 Revised: 9 January 2025 Accepted: 22 January 2025 Published: 23 March 2025

Abstract

Objective: This paper aimed to investigate the predictive values of left atrial appendage (LAA) function and carotid atherosclerotic plaques (CAPs) for ischemic stroke (IS) in patients with nonvalvular atrial fibrillation (NVAF). **Methods**: Data were retrospectively collected from 40 patients with NVAF complicated by IS (stroke group) and 160 patients with NVAF not complicated by IS (non-stroke group) during the same period. The basic data of the two groups were collected, CHA2DS2-VASc scoring was performed, and the diameter, depth, morphology, and function of the LAA (LAA peak) emptying velocity (LAA-PEV) and LAA peak filling velocity (LAA-PFV) were examined in the two groups using transesophageal echocardiography. The presence of CAPs was examined using transcranial Doppler ultrasonography. Univariate and multivariate logistic regression analyses were used to analyze the independent risk factors for IS in patients with NVAF. Spearman's correlation analysis was performed to investigate the relationship between LAA-PEV, LAA-PFV, and CAPs and the occurrence of IS in patients with NVAF. Finally, receiver operating characteristic (ROC) curves and the Delong test were used to analyze the predictive value of LAA function (LAA-PEV, LAA-PFV) and CAPs alone or in combination for the occurrence of IS in patients with NVAF. **Results**: Univariate analysis revealed that age, CHA2DS2-VASc score, and CAP incidence were higher in the stroke group than in the non-stroke group, while a history of anticoagulant drug use, LAA-PEV, and LAA-PFV were lower in the stroke group than in the non-stroke group ($p < 0.05$). Logistic regression analysis revealed that a higher CHA2DS2-VASc score and the presence of CAPs were independent risk factors for the occurrence of IS in patients with NVAF (odds ratio (OR) >1, $p < 0.05$) and history of anticoagulant drug use as well as higher LAA-PEV and LAA-PFV were protective factors against IS in patients with NVAF (OR <1, $p < 0.05$). Correlation analysis revealed that LAA-PEV and LAA-PFV were negatively linked (r = –0.373, –0.361, $p < 0.05$). In contrast, CAPs were positively related to IS in patients with NVAF (r = 0.310, $p < 0.05$). The area under the ROC (AUC-ROC) curve of LAA-PEV, LAA-PFV, CAPs, and combined examination to predict the occurrence of IS in patients with NVAF were 0.769, 0.761, 0.694, and 0.890, respectively. The area under curve (AUC) of the combined assessment was greater than that of the individual examinations of LAA-PEV, LAA-PFV, and CAPs ($p < 0.05$). **Conclusion**: LAA function and CAPs are closely associated with the occurrence of IS in patients with NVAF, and their combined examination has good predictive value for the occurrence of IS in patients with NVAF.

Keywords

nonvalvular atrial fibrillation; ischemic stroke; left atrial appendage function; carotid atherosclerotic plaque; predictive value; CHA2DS2-VASc scoring

Introduction

Non-valvular atrial fibrillation (NVAF), the most common arrhythmia, has a 1–2% prevalence in the general population. The prevalence of NVAF increases with age and its diagnostic benefits lie in the improvement and simplification of detection technology [1]. Approximately 20–30% of ischemic strokes (IS) are associated with NVAF. The risk of both recurrent IS and hemorrhagic transformation is particularly high in this situation [2]. The growing global prevalence of atrial fibrillation (AF) is a cause of concern, because these patients urgently require effective stroke prevention systems. Fortunately, over the past decade, data on novel approaches for stroke prevention in patients with NVAF have proliferated [3]. Vitamin K antagonists have long been used for NVAF therapy, but several direct oral anticoagulants (DOACs) have recently been approved for the prevention of stroke in patients with NVAF [4]. Although DOACs are highly effective, patients for whom they are considered or absolutely contraindicated owing to the risk of bleeding do not benefit from this therapy. Therefore, left atrial appendage occlusion (LAAO) is a nonpharmacological alternative for stroke prevention in these patients [5].

Thrombosis is commonly observed in the left atrial appendage (LAA) of patients with AF due to decreased LAA contractility and blood stasis [6]. Therefore, in patients with AF, LAA function must be carefully assessed to ascertain the risk of cardioembolic complications. Owing to the close association between the LAA and thrombus formation caused by AF, catheter or surgical closure of the LAA seems to be a promising approach [7]. The LAA is a degenerated muscle extension of the left atrium located in the anterior lateral segment. Its appearance is a flat tubular structure, with the tip usually facing forward and upward, and the total average length is 25.9 $\pm$ 0.7 mm [8]. Compared to patients with sinus rhythm, patients with permanent AF have lower coverage of the pectinate muscle and a larger LAA cavity, indicating that long-term arrhythmia leads to structural remodeling [9]. Ultrasonic measurement of carotid plaques is a safe and inexpensive approach for assessing subclinical atherosclerosis because of its ease of measurement and shallow location. Adding carotid plaque measurements to the CHA2DS2-VASc score can better predict the occurrence of stroke in patients with NVAF [10,11]. Nevertheless, routine carotid ultrasound tests for all these patients will contribute significantly to the medical costs and resource consumption. As previously reported, risk factors for IS in AF patients consist of hypertension, age $\geq$75, congestive heart failure, female gender, vascular disease, diabetes mellitus, as well as previous stroke [12]. Therefore, exploring the relationship between different structural and functional parameters of the LAA and carotid atherosclerotic plaque (CAP) and the risk of stroke is of great guiding significance for clinicians in identifying IS in patients with NVAF. This study aimed to determine the predictive value of LAA function and CAP for IS in patients with NVAF.

Materials and Methods

Study Population

We retrospectively collected data from 40 patients with NVAF complicated by IS admitted to Deqing People's Hospital between May 2022 and April 2024, defined as the stroke group, and 160 patients with NVAF not complicated by IS in the same period, defined as the non-stroke group.

Inclusion Criteria

(i) All patients met the diagnostic criteria for NVAF [13]; (ii) patients in the stroke group met the diagnostic criteria for IS [14]; (iii) patients in the stroke group had a longer history of NVAF than IS and were identified using the Chinese Ischemic Stroke Subclassification as cardiogenic stroke [15]; (iv) patients provided informed consent and signed the relevant protocols; and (v) patient data were complete.

Exclusion Criteria

The following patients were excluded: (i) combination of cardiac tumor, rheumatic heart disease, congenital heart disease, cardiomyopathy, intra-atrial thrombus, cardiac valve disease, or prosthetic valve replacement; (ii) unsatisfactory image quality of imaging; (iii) combination of metabolic diseases, such as thyroid disease; (iv) severe hepatic and renal impairment or autoimmune disease; (v) hemorrhagic stroke; (vi) combination of severe infection or internal environmental disorders; and (vii) malignant tumors.

Basic Data Collection

Basic data such as age, gender, body mass index, duration of atrial fibrillation, type of atrial fibrillation, history of smoking, history of drinking, history of anticoagulant drug use, and comorbidities (hypertension, diabetes mellitus, congestive heart failure/left ventricular dysfunction, history of stroke/transient ischemic attack/thromboembolism, and vascular disorders) were acquired from both groups of patients using the hospital's computerized electronic medical record system.

CHA2DS2-VASc Score

The CHA2DS2-VASc score was performed in both groups for congestive heart failure/left ventricular dysfunction (C, 1 point), hypertension (H, 1 point), age $\geq$75 years (A, 2 points), diabetes mellitus (D, 1 point), history of stroke/transient ischemic attack/thromboembolism (S, 2 points), vascular disorders (V, 1 point), age 65–74 years (A, 1 point), and female (Sc, 1 point). The total score was 10 points, with higher scores representing a higher risk of concurrent IS in patients with NVAF [16].

Ultrasonography

Transesophageal echocardiography (TEE) was performed to examine the diameter, depth, morphology, and function of the left atrial appendage (LAA) in both groups. A Philips IU Elite Ultrasound Diagnostic Instrument (Shanghai Qiwei Medic Co., Ltd., Shanghai, China) was used to detect the LAA using S5-1 through a transthoracic echocardiography (TTE) probe (frequency 1 MHz~5 MHz) and X7-2t through a real-time three-dimensional transesophageal echocardiography (RT-3DTEE) probe (frequency 2 MHz~7 MHz). Image acquisition: The ultrasonographer successively performed TTE and RT-3DTEE; the patient fasted for 4 h before the examination, and 2% lidocaine hydrochloride gel (10 g) was administered 15 min be-

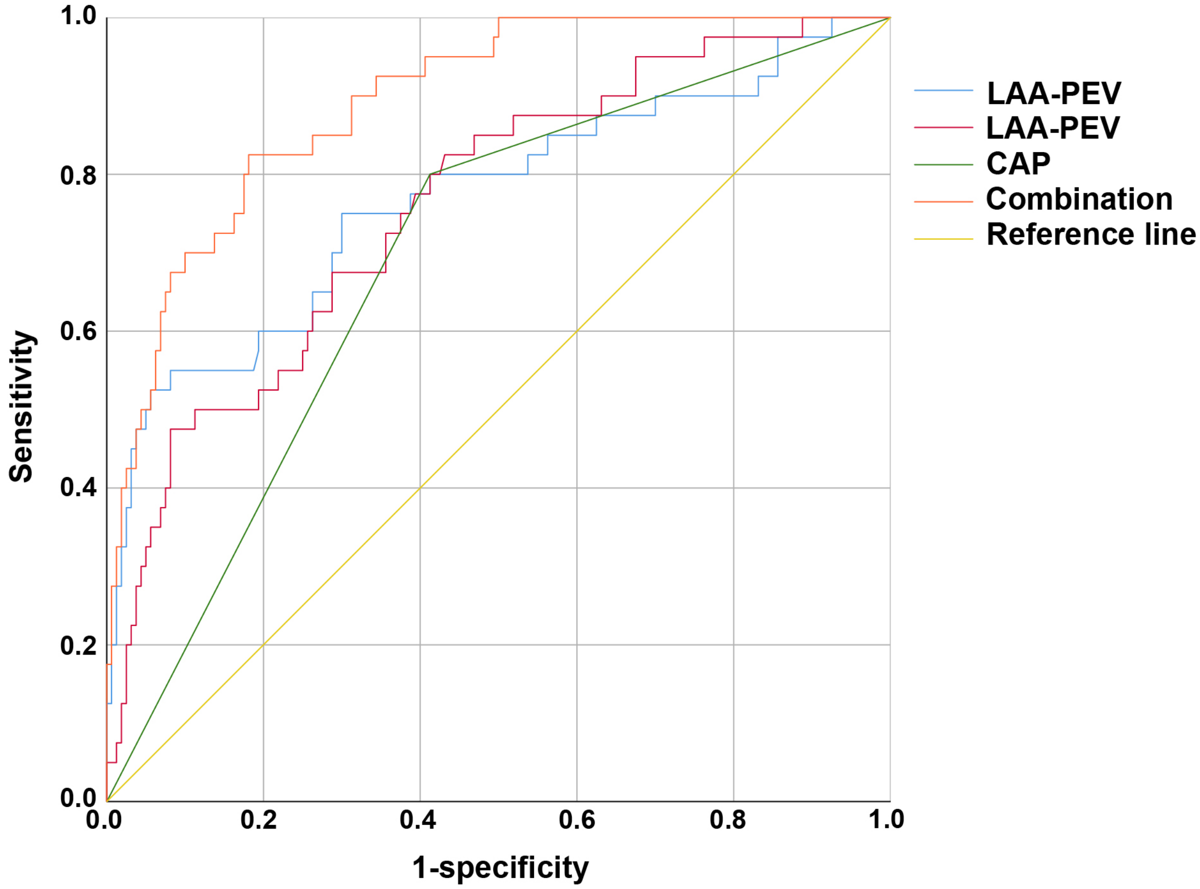

Fig. 1. ROC curve of LAA function and CAP predicting the occurrence of IS in patients with NVAF. ROC, receiver operating characteristic; LAA, left atrial appendage; LAA-PEV, LAA peak emptying velocity; LAA-PFV, LAA peak filling velocity; CAP, carotid atherosclerotic plaque; IS, ischemic stroke; NVAF, nonvalvular atrial fibrillation.

fore the examination for pharyngeal local anesthesia. Subsequently, the false tooth was removed before the examination, and the patient was assisted in assuming the left lateral position and then connected to an electrocardiogram. Next, the probe was placed into the esophagus through an occluder to show the short-axis view of the base of the heart at a distance of 30–40 cm from the incisal teeth, and the LAA was swept over a range of 0° to 180° to clearly show the coronal view of the LAA at 45°, and the sagittal view of at 90°, to determine the diameter, depth, morphology (chicken-winged, weathervane, cactus, and cauliflower), and function [LAA peak emptying velocity (LAA-PEV) and LAA peak filling velocity (LAA-PFV)] of LAA. The presence of CAP was examined using a color ultrasound transcranial Doppler blood flow analyzer (model: BT1000, Xuchang Beishida Trading Co., Ltd., Henan, China), which performs a longitudinal and transverse sweep of the common carotid artery to the extracranial segment of the internal carotid artery. Carotid atherosclerosis (CAS) was defined as intima-media thickening and plaque formation. Diagnostic criteria for intima-media thickening: protruding intima-media surface or intima-media thickness (IMT) of 1.0~1.5 mm; diagnostic criteria for plaque: protruding intima-media surface or IMT >1.5 mm [17].

Statistical Analysis

Data were processed using SPSS 26.0 software (IBM Corp., Chicago, IL, USA). Qualitative data were described by [n (%)] with a χ^2 test. Normally distributed quantitative data were described by $\pm$ s for the independent samples *t* test, and skewed quantitative data were described by M (P25, P75) for the Mann–Whitney U test. Statistically significant indicators from univariate analyses were included in the binary logistic regression analyses. Spearman's correlation analysis was performed to analyze the correlation between LAA-PEV, LAA-PFV, and CAP and the occurrence of IS in patients with NVAF. Finally, the receiver operating characteristic (ROC) curve and Delong test were used to analyze the predictive value of LAA function (LAA-

Table 1. Results of a univariate analysis of the occurrence of IS in patients with NVAF.

Indicator	Stroke group (n = 40)	Non-stroke group (n = 160)	$\chi^2/t/Z$	*p*
Age (n)			12.195	0.002
≤64 years	1 (2.50)	22 (13.75)	-	-
65∼74 years	6 (15.00)	54 (33.75)	-	-
≥75years	33 (82.50)	84 (52.50)	-	-
Female (n)	21 (52.50)	66 (41.25)	1.648	0.199
BMI (kg/m^2)	24.71 ± 2.86	24.41 ± 3.35	0.516	0.606
Type of atrial fibrillation (n)			1.915	0.166
Persistent	19 (47.50)	57 (35.62)	-	-
Paroxysmal	21 (52.50)	103 (64.38)	-	-
History of smoking (n)	12 (30.00)	38 (23.75)	0.667	0.414
History of drinking (n)	9 (22.50)	31 (19.38)	0.195	0.659
Hypertension (n)	30 (75.00)	102 (63.75)	1.805	0.179
Diabetes mellitus (n)	12 (30.00)	35 (21.88)	1.175	0.278
Congestive heart failure/left ventricular dysfunction (n)	12 (30.00)	39 (24.38)	0.533	0.465
History of stroke/transient ischemic attack/thromboembolism (n)	13 (32.50)	32 (20.00)	2.867	0.090
Vascular disorders (n)	21 (52.50)	74 (46.25)	0.501	0.479
History of anticoagulant drug use	8 (20.00)	60 (37.50)	4.367	0.037
CHA2DS2-VASc score (point)	4.50 (4.00, 6.00)	4.00 (3.00, 4.75)	–3.865	<0.001
Left atrial appendage diameter (mm)	21.00 (20.00, 22.00)	20.50 (19.00, 22.00)	–1.600	0.110
Left atrial appendage depth (mm)	29.00 (26.00, 31.00)	28.00 (25.00, 32.00)	–0.551	0.582
Left atrial appendage morphology (n)			0.422	0.936
Chicken-Winged	17 (42.50)	66 (41.25)	-	-
Weathervane	8 (20.00)	37 (23.13)	-	-
Cactus	9 (22.50)	38 (23.75)	-	-
Cauliflower	6 (15.00)	19 (11.88)	-	-
LAA-PEV (cm/s)	26.09 (18.65, 38.70)	40.38 (35.26, 44.97)	–5.258	<0.001
LAA-PFV (cm/s)	27.56 ± 8.62	36.14 ± 8.22	–5.848	<0.001
CAP (n)	32 (80.00)	66 (41.25)	19.228	<0.001

BMI, Body Mass Index.

Table 2. Logistic regression analysis of the occurrence of IS in NVAF patients.

Variable	B	Standard error	Wald	*p*	OR	95% Confidence interval
Age	0.470	1.154	0.166	0.684	1.601	0.167–15.361
CHA2DS2-VASc score	0.628	0.203	9.579	0.002	1.875	1.259–2.791
History of anticoagulant use	–1.207	0.586	4.234	0.040	0.299	0.095–0.944
PEV	–0.123	0.028	19.725	<0.001	0.884	0.837–0.934
PFV	–0.114	0.031	13.359	<0.001	0.893	0.840–0.949
CAP	1.952	0.585	11.140	0.001	7.042	2.238–22.155

OR, odds ratio.

PEV and LAA-PFV) and CAP alone or in combination for the occurrence of IS in patients with NVAF. $p < 0.05$ was considered as statistically significant difference.

Results

Univariate Analysis of the Occurrence of IS in Patients with NVAF

Univariate analysis revealed that age, CHA2DS2-VASc score, and CAP incidence were higher in the stroke group than in the non-stroke group, while history of anticoagulant drug use, LAA-PEV, and LAA-PFV were lower in the stroke group than in the non-stroke group ($p < 0.05$). No significant differences were observed in the other indicators between the two groups ($p > 0.05$) (Table 1).

Logistic Regression Analysis of IS Occurrence in Patients with NVAF

Considering that patients with NVAF developed IS as the dependent variable and statistically significant variables from Table 1 (age (0–75 years, 1–75 years), CHA2DS2-VASc score, history of anticoagulant drug use (0 = no, 1 = yes), LAA-PEV (cm/s), LAA-PFV (cm/s), CAP (0 = no, 1 =

yes)) as independent variables, we entered them into a multivariate logistic regression equation. Logistic regression analysis revealed that a higher CHA2DS2-VASc score and the presence of CAP were independent risk factors for IS in patients with NVAF, with odds ratios (OR) of 1.875 and 7.042, respectively ($p < 0.05$). Additionally, a history of anticoagulant use, higher LAA-PEV, and higher LAA-PFV were protective factors against IS in patients with NVAF, with OR of 0.299, 0.884, and 0.893, respectively ($p < 0.05$) (Table 2).

Correlation of LAA Function, CAP, and IS Occurrence in Patients with NVAF

Spearman's correlation analysis revealed that both LAA-PEV and LAA-PFV were negatively associated with the occurrence of IS in patients with NVAF (r = –0.373 and –0.361, $p < 0.001$), and CAP was positively associated with the occurrence of IS in patients with NVAF (r = 0.310; $p < 0.001$).

The Value of LAA Function and CAP in Predicting the Occurrence of IS in Patients with NVAF

The ROC curves indicated that the area under the ROC curve (AUC) for predicting IS in patients with NVAF using LAA-PEV was 0.769, with a 95% CI of 0.676 to 0.862. The Youden index was 0.469, with a sensitivity of 55.00% and a specificity of 91.90%. The AUC for LAA-PFV was 0.761, with a 95% confidence interval (CI) of 0.678–0.843. The Youden index was 0.394, with a sensitivity of 47.50% and a specificity of 91.90%. The AUC for CAP was 0.694, with a 95% confidence interval (CI) of 0.607–0.781. The Youden index was 0.387, with a sensitivity of 80.00% and a specificity of 58.70%. When combining LAA-PEV, LAA-PFV, and CAP, the AUC for predicting IS in patients with NVAF was 0.893, with a 95% CI of 0.843 to 0.943. The Youden index was 0.644, with a sensitivity of 82.50% and a specificity of 81.90%. Delong's test demonstrated that the AUC of the combined examination was greater than that of the individual examinations of LAA-PEV (Z = 2.950, p = 0.003), LAA-PFV (Z = 3.383, p = 0.001), and CAP (Z = 5.518, $p < 0.001$) (Fig. 1).

Discussion

NVAF is a frequent arrhythmia with high incidence and heavy economic burden [4]. This disease increases the risk of stroke by three–five times, particularly among elderly patients, placing a huge burden on the healthcare system and negatively influencing patients' lives [18]. Because some patients with AF have an insidious onset and do not pay enough attention to it, some do not receive adequate treatment and develop serious complications, therefore, finding a sensitive and specific evaluation index is crucial for clinical work. This study revealed the predictive value of LAA function and CAP for IS in patients with NVAF.

We initially identified several risk factors for IS in patients with NVAF, including age, CHA2DS2-VASc score, incidence of CAP, history of anticoagulant use, and LAA functional parameters (LAA-PEV and LAA-PFV). Furthermore, logistic regression analysis revealed independent risk factors (higher CHA2DS2-VASc scores and the presence of CAP) and protective factors (history of anticoagulant use and higher LAA-PEV and LAA-PFV) in patients with NVAF.

The CHA2DS2-VASc score has been shown to improve IS risk stratification in lower-risk individuals, and anticoagulation therapy can be safely suspended in low-risk individuals [19]. Several components of the CHA2DS2-VASc score (advanced age, hypertension, as well as diabetes mellitus), have been indicated to be risk factors for carotid plaque formation [20,21]. Yukina *et al.* [22] also stated that age affects LAA morphology, as aging leads to cardiac remodeling, endocardial elastic fiber degeneration, and a lack of supportive tissue around the LAA wall, causing changes in LAA volume and morphology. In addition, LAA morphology is associated with AF rhythm, with patients with chronic AF having a larger LAA diameter, area, and volume than patients with paroxysmal AF [23]. Meanwhile, patients with NVAF and carotid plaque are at a higher risk of stroke, and the presence of carotid plaque is significantly associated with a 56% increased risk of stroke according to the ARIC study [11]. Becattini *et al.* [24] found that after adjusting for the CHA2DS2-VASc score, CAS was associated with a significantly elevated risk of IS, transient ischemic attack, or death. A recent meta-analysis revealed that AF and carotid stenosis usually coexist, with approximately one in ten patients with AF having carotid stenosis, and vice versa. Approximately 50% of the patients with AF have non-stenotic carotid disease [25].

Early anticoagulant therapy reduces the recurrence of ischemic stroke [26]. DOACs are recommended for preventing thromboembolism in patients with AF [27]. Anticoagulant use had a significant impact on the study results. First, anticoagulants can reduce the risk of thrombus formation, thereby lowering the risk of stroke in patients with AF. Therefore, the incidence of ischemic stroke may decrease in patients using anticoagulants. Second, anticoagulant use may affect LAA function and CAP development. Anticoagulants can inhibit thrombus formation, potentially mitigating pathological changes in the LAA and slowing the progression of CAPs. However, the use of anticoagulants carries certain risks, such as bleeding. The LAA is a therapeutic target for cardioembolic stroke prevention in patients with NVAF. The large opening of the LAA restricts percutaneous closure of the LAA [28]. Thrombus formation is not only related to the structural characteristics of the LAA, but also to certain functional indicators of the LAA, namely the ejection fraction and blood flow velocity of the LAA, which are independent risk factors for atrial thrombus formation. Tokunaga *et al*. [29] have supported that examination using the speckle tracking technique revealed significantly lower LAA strainability and strain rate in patients with thromboembolism, which is a vital monitor for predicting IS in patients with AF, with predictive ability similar to that of the CHA2DS2-VASc score.

Our study also found that the LAA-PEV and LAA-PFV were negatively correlated with the occurrence of IS in patients with NVAF, suggesting that decreased LAA function was associated with an increased risk of IS. This finding indicates that LAA function may be an important predictor of IS in patients with NVAF. In other words, reductions in the LAA-PEV and LAA-PFV were associated with an increased risk of IS. This finding has important clinical significance, as it provides additional biomarkers that can help identify patients with NVAF at a higher risk of IS. Furthermore, as direct indicators of LAA function, the LAA-PEV and LAA-PFV can reflect the hemodynamic state within the LAA. The LAA is the primary site of thrombus formation during AF; therefore, changes in its function may have an important effect on the occurrence of IS. By monitoring these parameters, doctors can more accurately assess the IS risk of the patient and develop personalized anticoagulant treatment plans. Additionally, CAP was positively correlated with the occurrence of IS in patients with NVAF, indicating that patients with CAP have an increased risk of IS. The results of the ROC curve analysis revealed that LAA-PEV, LAA-PFV, and CAP has predictive abilities for IS in patients with NVAF. When LAA-PEV, LAA-PFV, and CAP were combined, the AUC for predicting IS in patients with NVAF significantly improved, indicating that the combined use of these predictors can significantly enhance predictive accuracy.

Moreover, the left atrial reservoir strain in patients with NVAF is closely related to the left atrial wall velocity and strain characteristics. Providência *et al*. [30] indicated that assessing left atrial mechanical dysfunction through speckle tracking may help predict left atrial stasis in patients with AF. Kupczynska *et al*. [31] suggested that speckle-tracking transthoracic echocardiography can be used to describe left atrial reservoir and conduit function during AF, thereby identifying patients at higher risk of left atrial fibrillation and providing incremental value over the CHA2DS2-VASc score. Sonaglioni *et al*. [32] revealed that combining transthoracic echocardiography with left atrial mechanics analysis using speckle-tracking echocardiography can improve the assessment of thrombosis risk in patients with NVAF. However, one limitation of our study is the lack of myocardial strain parameters in patients with NVAF using speckle-tracking echocardiography. Further explorations in this area will be conducted in the future.

Conclusion

In conclusion, this paper highlights that LAA function and CAP are closely related to the occurrence of IS in patients with NVAF, and their combined detection has good predictive value for IS in patients with NVAF, suggesting that the above mentioned parameters need to be adequately assessed and preventive measures need to be taken to reduce the risk rate of IS occurrence when performing the treatment of patients with NVAF. Nevertheless, this study had some limitations. First, it was a single-center retrospective study with a limited sample size, which may affect the generalizability of the results; larger multicenter studies are needed in the future to reduce such bias. Second, considering that this was an observational study, further multicenter prospective studies are required to assess the true values of these indicators.

Availability of Data and Materials

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

XC and FQ finished the conception and design, XF and HX finished the acquisition and analysis of data, XS and FH finished interpretation of the data for the work. All authors have participated sufficiently in the work. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Deqing People's Hospital (approval number: 2022025). Written informed consent was obtained from all participants.

Acknowledgment

We thank the associate editor and the reviewers for their useful feedback that improved this paper.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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