Scientific Reports

https://doi.org/10.1038/s41598-026-39742-7

Article in Press

Ischemic stroke prediction model of sick sinus syndrome patients without atrial fibrillation: insights from atrial myopathy

Received: 6 September 2025

Accepted: 6 February 2026

Published online: 17 March 2026

Cite this article as: Yang Y., Dong H., Wang S. *et al.* Ischemic stroke prediction model of sick sinus syndrome patients without atrial fibrillation: insights from atrial myopathy. *Sci Rep* (2026). https://doi.org/10.1038/s41598-026-39742-7

Yiheng Yang, Haoyu Dong, Shihao Wang, Yushan Wei, Rongfeng Zhang, Xiaomeng Yin, Lianjun Gao, Yingxue Dong, Xiaolei Yang & Yunlong Xia

Ischemic stroke prediction model of sick sinus syndrome patients without atrial fibrillation: insights from atrial myopathy.

Yiheng Yang, MD, PhD[1*], Haoyu Dong, MD[1*], Shihao Wang, MD[1], Yushan Wei, MD, PhD[1], Rongfeng Zhang, MD, PhD[1], Xiaomeng Yin, MD, PhD[1], Lianjun Gao, MD, PhD[1], Yingxue Dong, MD, PhD[1], Xiaolei Yang, MD, PhD[1*], Yunlong Xia, MD, PhD[1*]

[1]Department of Cardiology, First Affiliated Hospital of Dalian Medical University, Dalian, China

Corresponding author: Xiaolei Yang and Yunlong Xia

Corresponding address

Department of Cardiology, First Affiliated Hospital of Dalian Medical University, No. 222. Zhongshan Road. Dalian. Liaoning Province. China,

E-mail: yunlong_xia@126.com

*Yiheng Yang and Haoyu Dong contributes equally to this work

Abstract

Sick Sinus Syndrome (SSS) has been identified as a risk factor for ischemic stroke. Thrombus assessment in SSS patients without atrial fibrillation (AF) or atrial flutter (AFL) remains underexplored. We aims to develop a predictive model for ischemic stroke risk specifically in SSS patients without AF/AFL. Patients diagnosed with SSS and without AF/AFL were consecutively enrolled from single center. Incident AF/AFL cases were excluded during follow-up period. Symptomatic ischemic stroke was confirmed by reviewing the all available medical records. After a median follow-up of 1215 days, 187 out of 1645 (11.9%) patients experienced symptomatic ischemic stroke. Key predictors identified via multivariable Cox regression included age, left atrial diameter (LAD), prolonged P-wave duration (PWD), neutrophil-lymphocyte ratio (NLR), non-AF atrial tachyarrhythmias, and prior thrombotic events. These variables were incorporated into our nomogram prediction model, which demonstrated superior calibration and performance compared to the CHA2DS2-VASc score. The incidence of

new-onset ischemic stroke in SSS patients is notably high, warranting focused attention in clinical practice. We developed the model evaluate the risk for ischemic stroke of SSS patients without AF/AFL and internally validated. This risk score performs better than CHA2DS2-VASC score and may providing evidence of thrombus assessment in patients with atrial myopathy.

Keywords: Sick sinus syndrome, Atrial myopathy, Ischemic stroke, Prediction model.

Introduction

Atrial fibrillation (AF) is widely recognized as a significant risk factor for thrombotic events. Current understanding of the mechanisms underlying atrial thrombosis suggests that pathological changes in the atrium—such as aging, inflammatory activity, hemodynamic alterations, fibrosis, and remodeling—may occur even in the absence of AF or atrial flutter (AFL) [1-3]. Consequently, atrial myopathy has been characterized as any atrial dysfunction (anatomical, electrical, hemodynamic, etc.) that contributes to clinical symptoms and outcomes. This dysfunction is considered a key etiological factor in embolic events and may also predispose individuals to the development of AF[4].

Sick sinus syndrome (SSS) represents a group of common sinus node disorders, which may or may not be accompanied by AF/AFL (referred to as isolated SSS). Isolated SSS has been associated with an increased risk of ischemic stroke due to atrial fibrosis and remodeling[5,6]. Additionally, SSS serves as a substrate for atrial myopathy, AF, stroke, and other clinical manifestations. Recent studies have reported a higher prevalence of stroke in patients with isolated SSS compared to the general population[7]. Despite these findings, there remains no well-defined tool for assessing stroke risk specifically in patients with isolated SSS. The CHA2DS2-VASc score has been extensively utilized for risk stratification for ischemic stroke. However, this scoring system focuses primarily on the accumulation of clinical diagnoses without adequately addressing the underlying atrial hemodynamics or substrate abnormalities, such as those seen in atrial myopathy. This limitation raises concerns about its applicability in assessing stroke risk in conditions like SSS, where atrial structural and functional changes may play a dominant role. To address this gap, the aim of this study is to develop and validate a risk score for predicting ischemic stroke in patients with isolated SSS.

Methods

Study populations

SSS patients were continuous enrolled in the study cohort from the first affiliated hospital of Dalian medical university during January 2011-November 2021. Exclusion criteria were as bellow: 1) Patients with prior AF/AFL 2) Patients with new onset AF/AFL during follow-up period. 2) Lost of follow-up. 3) Data missing of key variables. SSS defined as having one of the following conditions when other potential treatable or reversible etiologies are excluded 1) Persistent and severe sinus bradycardia (<50 bpm/24h) with or without sinoatrial conduction block/sinus arrest; 2) Recurrent episodes of sinoatrial conduction block/sinus arrest. 3) Tachycardia-bradycardia syndrome not attributable to AF/AFL. During the baseline enrollment and follow-up ascertainment, all participants had completed continuous ECG monitoring and 48h Holter monitoring to enable a precise diagnosis of arrhythmias, including SSS and AF/AFL. Our study conforms to the Declaration of Helsinki and was approved by the medical Ethics Committee of the first affiliated hospital of Dalian medical university. Study protocol was registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn, registration number: ChiCTR2200063702). Informed consent was exempted in accordance with the regulations of Ethics committee of

First affiliated hospital of Dalian Medical University, as this study employed a retrospective design and involved no identifiable risks to participants.

Clinical variables and follow-up

Assessment of covariates and follow-up of this data has been well-defined in our previous publication[8]. Patients information including demographic data, cormbid, medical history, laboratory tests at admission, examinations, CHA2DS2-VASc score were collected from electric medical history system. Standard 12-lead ECGs recorded by MAC5500 (GE Healthcare, Chicago, IL, USA) . All ECG recordings were made with 40HZ filtering which was carefully and correctly set in our GE machines. PWD was obtained from ECG database (MUSE system, GE Healthcare, Chicago, IL, USA) and prolonged PWD (pPWD) was defined as the maximum PWD≥120ms among all leads. Non-AF atrial tachyarrhythmia was defined: 1) Premature atrial contractions≥500 beats /24h; 2) Recurrent atrial tachycardia. Participants attended follow-up study visits at 1, 3, 6, 9, and 12 months after baseline assessment. Beyond the initial year, semi-annual follow-up visits were mandated. Each in-person visit including medical record of other hospital (if applicable), physical examination, potential symptoms, 12-lead ECG, 48h

Holter monitoring and cardiac implantable electronic devices (CIEDs) device programming (if applicable). New-onset AF/AFL cases were confirmed by following methods: 1) All Medical record; 2) CIED Programming records: AF/AFL was identified based on the auto mode switch (AMS) record in device programming, atrial rate was estimated to discriminate AF/AFL. AMS algorithms as follows: (1) Medtronic: AMS was confirmed if≥17 consecutive atrial intervals exceed 175 bpm. (2) Boston Scientific: AMS was confirmed when the atrial rate exceed 170 bpm, with detection initiated after 8 consecutive beats and sustained for >30 seconds. (3) Biotronik: AMS was confirmed if≥5 atrial intervals within 8 consecutive intervals≥180 bpm. (4) Abbott: the steady-state atrial interval is configured as the filtered atrial rate interval (FARI). when atrial rate changes, FARI progressively ramps up its cycle length to synchronize with atrial rate. AMS triggers when atrial rates exceed 170 bpm while FARI fail to synchronized. 3) Telephone inquiry.

Primary study endpoint was ischemic stroke. Ischemic stroke was clinically diagnosed as any neurological deficit persisting >24 hours (or until death), or deficits lasting <24 hours accompanied by a relevant brain lesion confirmed via magnetic resonance (MR) or computed tomography (CT) imaging. Ischemic stroke was confirmed

by reviewing the all available electric medical record of outpatient clinic or admission, telephone inquiry also performed again in every patient. Stroke subtypes were classified according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria to mitigate selection bias. Subjects meeting TOAST criteria for large-artery atherosclerosis or small-vessel occlusion were excluded. All patients were followed until Dec.31.2021 unless death occurred.

Model development

Total sample was randomly divided into two groups for development of the nomogram and independent validation, 70% were assigned to the development set (n = 1,196) and the remaining patients were assigned to the validation set (n = 512). For derivation of the prediction model, the Cox proportional hazard regression model was used to estimate the hazard ratio and corresponding 95% confidence interval (95% CI) for each of the potential risk factors. As the first step, each variable was successively incorporated into the univariate cox regression model, and then the significant factors were further incorporated into the multivariate cox regression model. Three variable

selection methods (forward, backward, and stepwise) were considered in the multivariate model to build the risk prediction model. The last model which was the minimum AIC (akaike information criterion) value was selected. Variables with p value <0.001 were selected from the last multifactor model results to be included in the final stroke risk model.

Model performance

Measurements of discrimination, calibration and clinical effectiveness were used for evaluation of model performance. Discrimination measures the ability to separate patients who experience stroke from those who will not. The developed models were validated with respect to their discrimination ability using C-statistics (index of concordance), NRI (net reclassification index), IDI (integrated discrimination improvement) and ROC (receiver operating characteristic) curve. Calibration plot were used to evaluate the degree of consistency between the risk predicted by the stroke prediction model and the actual risk. Clinical effectiveness was measured using a decision curve analysis that calculated the net clinical benefit. P values were two-sided, and values of<0.05 were considered statistically significant.

Statistical analysis

Continuous quantitative variables are described using median and quartiles and qualitative variables as counts and percentages. Comparisons between groups were made using $\chi 2$ tests for comparing categorical variables and the nonparametric Wilcoxon Mann-Whitney test where appropriate for continuous variables. All data analyzation and a nomogram which was generated based on the multivariate prediction model use R software version 4.1 (R foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/) mainly using packages rms, foreign and survival. Development and validation were performed in accordance with the TRIPOD statement.

Results

After a median of 1214.5 (525,2207) days follow-up, 192 patients lost of follow-up and 250 patients with new onset AF/AFL were further excluded. 1645 patients entered our final analyses and 187 (11.9%) patients experienced symptomatic ischemic events (Figure 1). After case-by-case ascertainment, the stroke subtypes were classified as follows: 104 undetermined- etiology strokes and 83 cardioembolic strokes. Baseline characteristics stratified by development and validation set were shown in Table 1. No significant differences were found

between 2 group. Of note, 23 patients were prior treated with anticoagulants therapy due to venous thrombus (N=4), pulmonary embolism (N=8) , valve or joint replacement (N=3), intracardiac thrombus (N=2) and cryptogenic stroke (N=6).

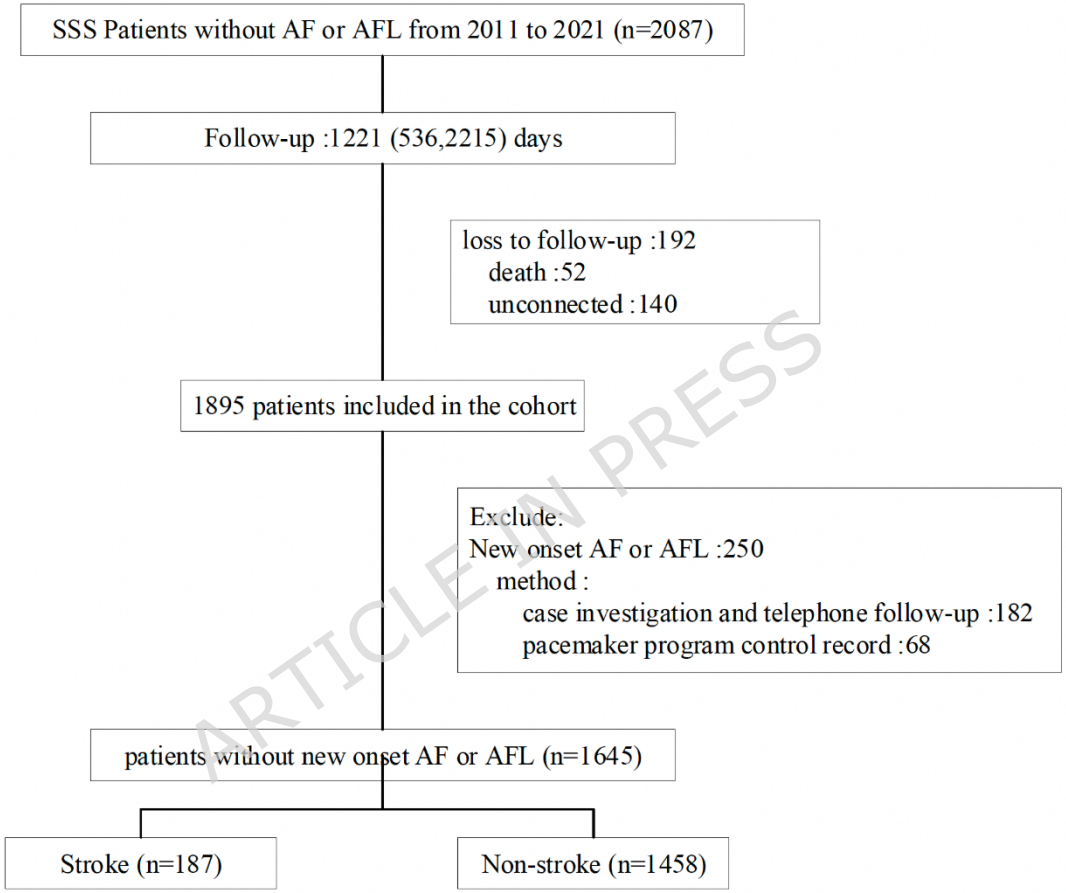


Figure 1. Baseline screening and follow-up of study

Table1 Baseline characteristics in the development and validation sets

Variables	Development set (n = 1,153)	Validation set (n = 492)	P value
Follow-up (days, median(Q1, Q3))	1263(531,2251)	1166(537,2150)	0.348
Demographic data			
Age（years, median(Q1, Q3)）	66(58,75)	67(59,74)	0.814
Female (N,%)	635(55.100)	261(53.000)	0.934
Current smoker (N,%)	234(19.565)	118(23.047)	0.103
Current drinker (N,%)	187(15.635)	77(15.039)	0.755
Comorbidities			
Anticoagulant treatment (N,%)	18(1.600)	5(1.000)	0.389
Pacemaker (N,%)	607(52.600)	277(56.300)	0.173
Hypertension (N,%)	501(43.500)	225(45.700)	0.394
Diabetes (N,%)	145(12.600)	71(14.400)	0.308
Heart failure (N,%)	92(8.000)	41(8.300)	0.809
Non-AF atrial tachycardia (N,%)	398(34.500)	166(33.700)	0.761
Vascular disease (N,%)	176(15.300)	69(14.000)	0.518
Prior stroke/TIA/thrombotic events (N,%)	173(15.000)	77(15.700)	0.738
New-onset stroke/TIA/thrombotic events (N,%)	134(11.622)	53(10.772)	0.274
LAD（mm）	36(34,39)	36(34,39)	0.705
CHA2DS2-VASc score (median(Q1, Q3))	2(1,4)	2(1,4)	0.895
Biomarkers			
NLR (median(Q1, Q3))	1.683(1.260,2.328)	1.738(1.297,2.348)	0.434
Uric acid (mmol/L,median(Q1, Q3))	319(264,371)	314(267,371)	0.887

LDL-C□mmol/L,median(Q1, Q3)□	2.59(2.15,3.10)	2.54(2.01,3.08)	0.083
Prolonged PWD (N,%)	84(64,106)	81(64,104)	0.552

LAD: Left atrial diameter
NLR: Neutrophil lymphocytes ratio
PWD: P wave duration

Risk factors and development of prediction model

In univariate analysis, age, smoking, drinking, pacemaker, hypertension, diabetes mellitus, heart failure, non-AF atrial tachyarrhythmia, vascular disease, history of stroke/ thrombotic events, LAD, NLR, LDL-C and prolonged PWD were significantly associated with overall stroke risk (Table 2). Multivariate analyses were further performed using the significant risk factors determined in the univariate analysis. Finally, age, non-AF atrial tachyarrhythmia, prior stroke/thrombotic events, LAD and PWD were selected as significant independent factors for model development (P□0.0001). Based on these factors screened by multivariable regression, a nomogram prediction model was established to predict 3, 5,10-year overall stroke risk in SSS patients (Figure 2). Each factor corresponds to specific point by drawing a line straight upward to the points axis. After sum of the points is

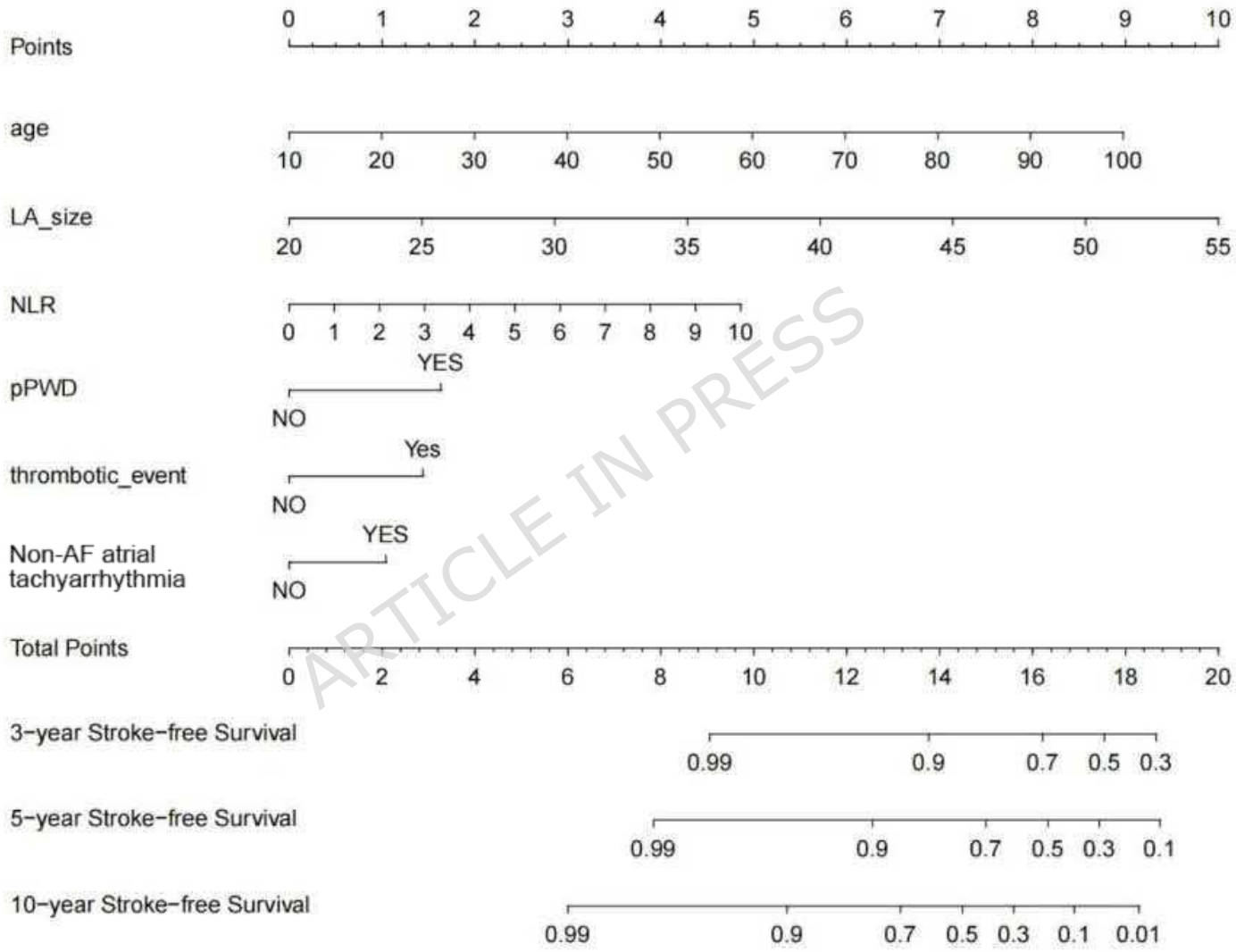
located on the total points axis, the sum represents the probability of 3-year, 5-year and 10-year free of stroke by drawing straight down to the 3-year, 5-year and 10-year axis.

Table 2 Risk factors related to ischemic stroke in SSS patients by Cox regression

	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Demographic data						
Age	1.085	1.065-1.105	<0.001	1.052	1.031-1.072	<0.001
Female	1.023	0.727-1.439	0.896			
Current smoking	1.225	0.816-1.840	0.328			
Current Drinking	2.169	1.464-3.214	<0.001	1.823	1.208-2.750	0.004
Comorbidities						
LAD	1.201	1.165-1.237	<0.001	1.146	1.106-1.187	<0.001
Anticoagulant	1.847	0.588-5.807	0.294			
Hypertension	1.951	1.384-2.750	<0.001			
Diabetes	2.151	1.400-3.307	<0.001			
Non-AF atrial tachycardia	1.833	1.306-2.572	<0.001	1.794	1.270-2.533	<0.001
Heart failure	2.382	1.465-3.871	<0.001			

Vascular disease	2.003	1.344-2.983	<0.001			
Thrombotic event	3.312	2.316-4.735	<0.001	1.990	1.377-2.876	<0.001
Pacemaker	1.803	1.268-2.565	0.001			
Biomarkers						
NLR	1.463	1.354-1.582	<0.001	1.273	1.158-1.399	<0.001
LDL-C	1.264	0.993-1.610	0.057			
Uric Acid	1.005	1.003-1.007	<0.001	1.003	1.001-1.005	0.006
Prolonged PWD	4.495	3.050-6.625	<0.001	2.056	1.351–3.127	<0.001

LAD: Left atrial diameter
NLR: Neutrophil lymphocytes ratio
PWD: P wave duration



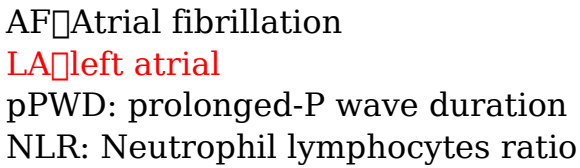


Figure 2. Nomogram risk model predicting stroke in SSS patients. Each factor corresponds to specific point by drawing a line straight upward to the points axis. After sum of the points is located on the total points axis, the sum represents the probability of 3-year, 5-year and 10-year free of stroke by drawing straight down to the 3-year, 5-year and 10-year axis. For example, a 65-year-old individual (5.5 points) experienced non-AF atrial tachyarrhythmia (1 point), LAD 40mm (5.75 points) and the PWD was≥120ms (1.75points). Total point equals 14 and corresponding 3-year, 5-year, 10-year free of stroke risk is approximately 90%, 80%, 60%, respectively.

Validation and performance

Internal validation was performed by evaluating the performance of the model with respect to its discrimination, calibration abilities and clinical effectiveness. The new model's C-index, which indicated discrimination ability, was 0.910 (95% CI, 0.890–0.931) in development set and 0.897 (95% CI, 0.864–0.930) in validation set. By contrast, in validation set, the C-index of CHA2DS2-VASc score which was 0.739 (95% CI, 0.671–0.807) is

significantly lower than the new model's ($P < 0.001$, a Student t test for dependent samples). Moreover, similar tendency was observed across the time node between the new model and CHA2DS2-VASc in the validation set (Figure 3). As for the ROC, the AUC of the new model performs better than that of CHA2DS2-VASC score in predicting 3-year, 5-year and 10-year risk (Figure 4)

IDI and NRI value were performed to evaluate the ability of identify risk (Table 3). Compared to CHA2DS2-VASC score, the new model significantly improved the discrimination ability of 3-year stroke risk and 5-year stroke risk in the validation cohort by 26.3% and 33.1%, respectively. Regarding the NRI statistics, the new model significantly improved its ability to classify stroke risk at 3 and 5 years in the validation set (49.3% and 50.2%, respectively). The calibration plot shows an adequate calibration of the predicted probabilities stroke free survival proportions in development and validation set at 3-year, 5-year and 10-year stroke risk (Figure 5). In addition, the decision curve analyses based on the new model and CHA2DS2-VASc score were drawn in Figure 6. In validation set, the analysis revealed that the new model generally had a higher net benefit, especially at a threshold probability of 0 to 50% (3-year node) and at a threshold probability of 0 to 75% (5-year node).

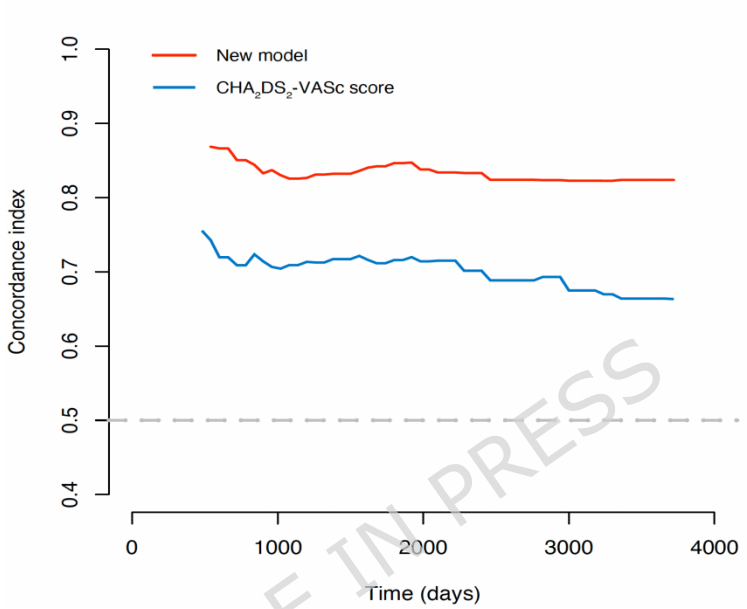


Figure 3. Concordance index (C-index) of CHA2DS2-VASc score and new model.

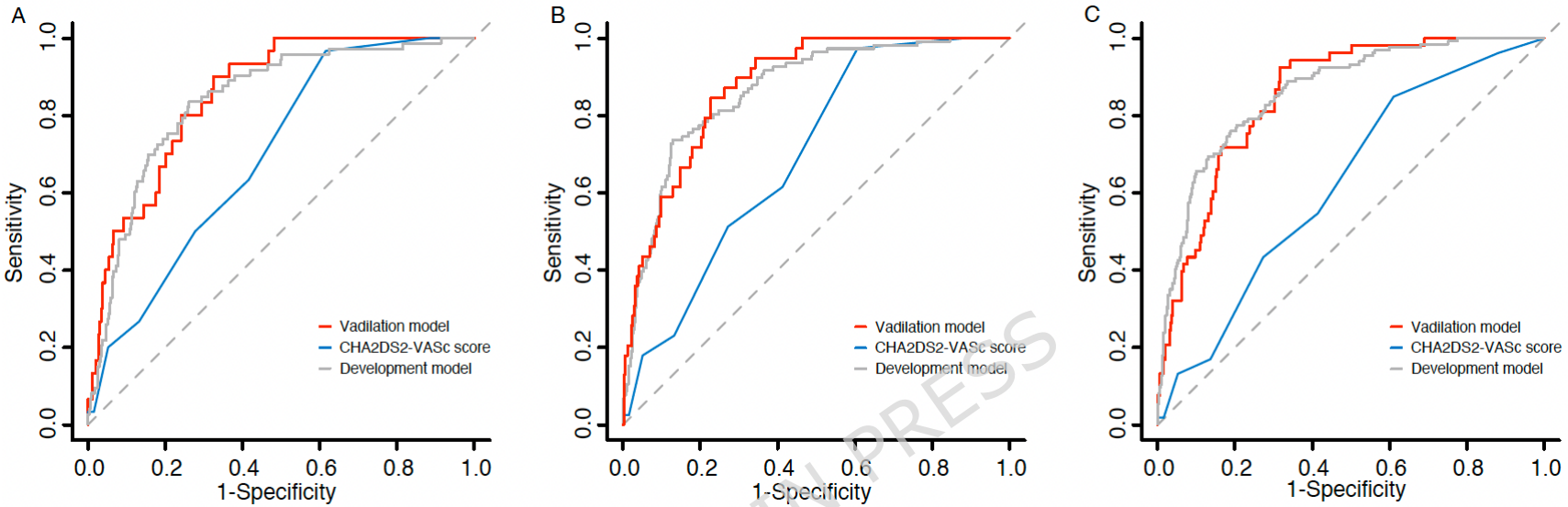


Figure 4. ROC showed the accuracy of CHA2DS2-VASc score and new model at risk for 3 year (A), 5 year (B) and 10 year (C)

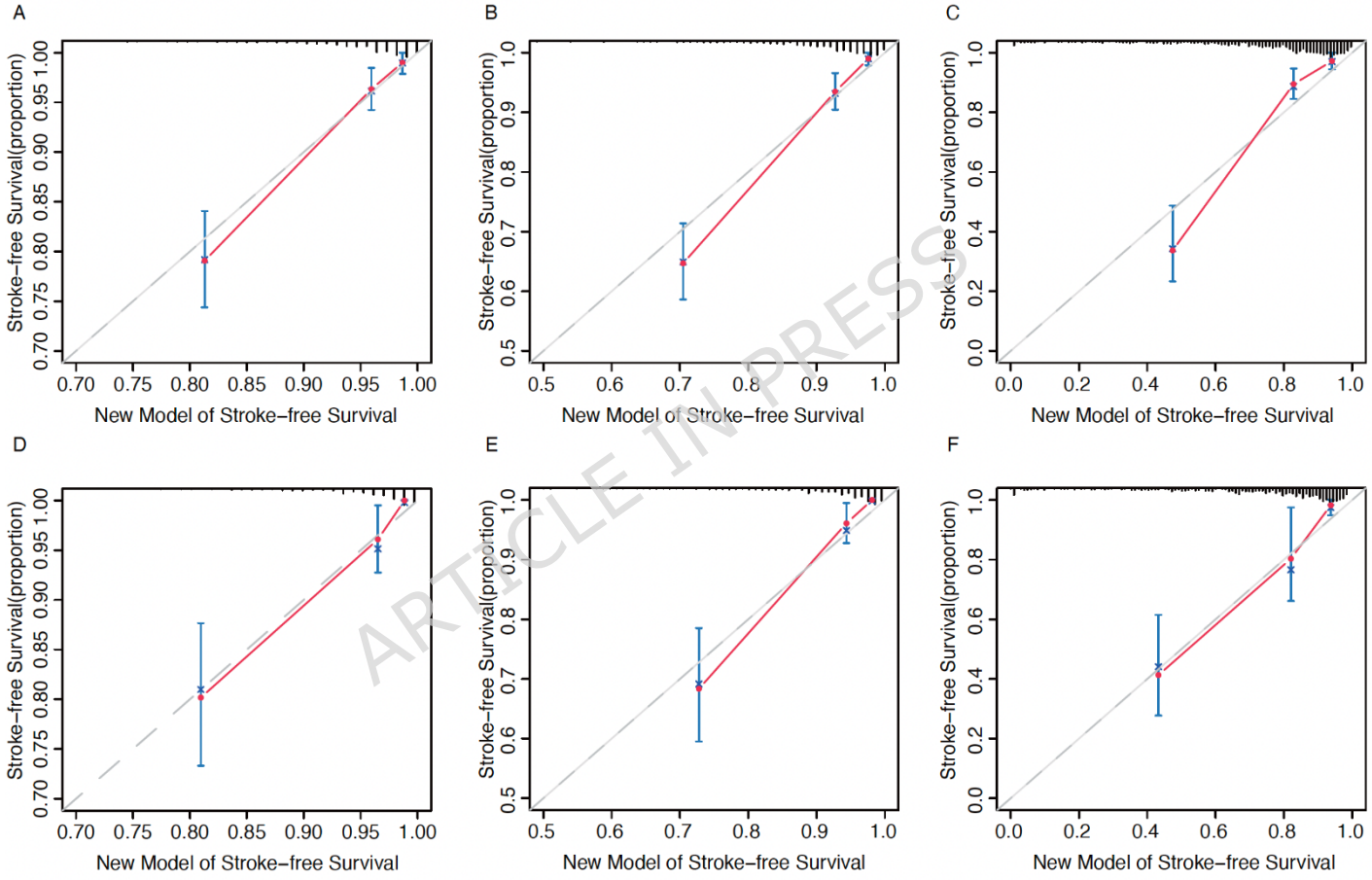


Figure 5. Calibration plot showed the risk of stroke free survival in development(A, B, C) and validation (D, E, F) set at 3,5,10-years.

Table 3 The IDI and NRI statistics of the development and validation set

	3-year node	5-year node	10-year node
	Development set		
IDI statistics			
IDI event (95% CI)	0.166 (0.127,0.206)	0.216 (0.172,0.261)	0.269 (0.224,0.313)
IDI non event (95% CI)	-0.039 (-0.044,-0.034)	-0.061 (-0.068,-0.054)	-0.093 (-0.106,0.081)
IDI (95% CI)	0.205 (0.161,0.250)	0.278 (0.226,0.329)	0.362 (0.305,0.419)
P Value	<0.001	<0.001	0.020
NRI statistics			
NRI (95% CI)	0.554 (0.409,0.664)	0.601 (0.481,0.670)	0.715 (0.345,1.032)
P Value	<0.001	<0.001	<0.001
	Validation set		
IDI statistics			
IDI event (95% CI)	0.221 (0.153,0.290)	0.267 (0.187,0.347)	0.332 (0.250,0.414)
IDI non event	-0.041 (-0.050,-	-0.064 (-0.076,-	-0.093 (-0.114,-

(95% CI)	0.033)	0.052)	0.072)	
IDI (95% CI)	0.263	0.331	0.425	
	(0.186,0.340)	(0.239,0.423)	(0.322,0.528)	
P Value	<0.001	<0.001	0.109	
NRI statistics				
NRI (95% CI)	0.493	0.502	0.632	(-
	(0.319,0.691)	(0.388,0.697)	0.173,1.390)	
P Value	<0.001	<0.001	0.060	

IDI: Integrated discrimination improvement
NRI: Net reclassification improvement

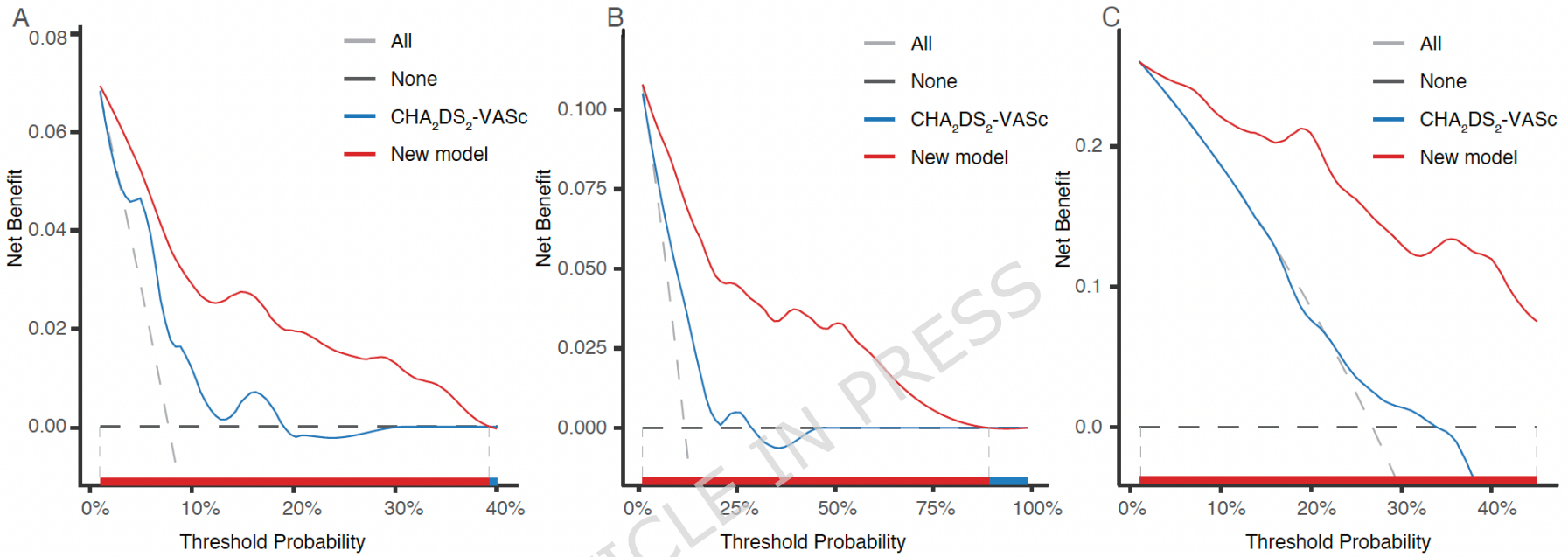


Figure 6.Model performance evaluated by decision curve analyses at risk for 3 year (A), 5 year (B) and 10 year (C), the horizontal dashed line

and the slanted dashed line indicate theoretically that no patient experiences ischaemic stroke events and all patients experience ischaemic stroke

events, respectively.

Discussion

In our study, a nomogram prediction model was developed to evaluate the risk of ischemic stroke in patients with isolated SSS. Multiple aspects including common cardiovascular comorbidity, modifiable lifestyles and atrial substrates were covered in our analyses. Additionally, almost all atrial substrates factors were finally selected to establish the model and well validated and calibrated. Suggesting the risk assessment of isolated SSS in patients was not merely traditional clinical factors but especially electrophysiological substrates that reflect atrial hemodynamic dysfunction and structural remodeling. Further external validation in different cohort and stroke prevention are needed in future study.

Population characteristics

Although a European national cohort study demonstrated that patients with SSS have a higher incidence of ischemic stroke compared to those with other cardiovascular diseases [7]. The 2.8% annulized stroke rate observed in this study was notably comparable to the 2.1% in SSS cohort [1], slightly higher than 1-2% reported

by clinical trial of anticoaguation drugs [9,10]. This results may be attributed to key population differences. Contrasting with community-based cohorts, participants were recruited from a tertiary cardiology department with high cardiovascular comorbidity burden (hypertension: 44%; current smoking: 20.6%; diabetes: 13.8%). Stroke rates in SSS-related studies [11,12] from various regions are consistently high (ranging from 4.8% to 9.6%) and the 1-year cumulative stroke rate in anticoagulation cohorts for AF is close to 7% [13]. These findings are comparable to our results. Moreover, the competing risks in this study may also have contributed to the relatively high stroke rate. We excluded all-cause deaths through the medical insurance system. This approach ensured that the cohort used to assess stroke incidence consisted solely of individuals who remained alive and under observation for the entire period, thereby eliminating death as a competing risk for stroke in our primary analysis. Nevertheless, during follow-up only a small proportion of patients were lost to follow-up (N = 140), among whom there may have been non-fatal competing risks (such as relocation, end-stage disease, malignancy, severe cardiovascular events, etc.) that could have led to a relative overestimation of the stroke rate

in this study. However, the incidence of these conditions is relatively low. We believe its impact on the study results is limited.

As for risk factor management, Anticoagulation therapy was not administered to these patients and post-hospitalization interventions targeting modifiable risk factors (e.g., blood pressure control, smoking cessation) were not systematically implemented. Further, most cases presented as either "slow-fast syndrome" or isolated severe bradycardia, with 55.9% receiving permanent dual-chamber pacemakers at baseline. Long-term atrial pacing may exacerbate pre-existing atrial fibrosis [14], a plausible contributor to thromboembolic risk.

Notably, the median CHA2DS2-VASc score in both groups was 2, which underestimates stroke risk in this population. These findings underscore the necessity of incorporating quantitative atrial substrate evaluation—including electrophysiological and structural markers—rather than relying solely on traditional CHA2DS2-VASc parameters for risk stratification in isolated SSS patients. In addition, the baseline characteristics demonstrated no significant differences between the development and validation sets, indicating well-balanced cohort matching, which ensures the quality of the study and enhances the credibility of the results.

SSS and stroke

Association between SSS and ischemic stroke in ARIC study (Atherosclerosis Risk in Communities) and the CHS (Cardiovascular Health Study) were not reach the significance due to limited sample size [15]. Consistent with our results, A large-scale European registry study (N = 1.6 million) recently demonstratedthe incidence of ischemic stroke higher in SSS patients when compare to control population [7], but the risk factors and risk assessment were not further explored. Atrial myopathy has recently been focused and was described as the main risk factor to incident AF and cardio-embolism even prior to AF occurrence, characterized by the increased left atrial size, elevated biomarker, conduction delay of atrial depolarization and non-AF atrial tacharrhythmia, reflecting the remodeling and fibrosis of atrial [16]. It may relate to endocardial dysfunction and consequently lead to pre-thrombotic state, providing substrate of both AF and stroke. SSS was also considered as the diffuse atrial lesions. Consequently, we collected the isolated SSS patients and their clinical information including CHA2DS2-Vasc score and thereby take into account metric of atrial myopathy. As expected, crucial contributors including

age, non-AF atrial tacharrhythmia, history of stroke/thrombotic events, LAD and prolonged PWD showed their role on progress of atrial myopathy.

Regarding the mechanisms, inflammatory factors activity and myocardial fibrosis are commonly observed in aging heart [17]. Present study selected the NLR as an inflammatory biomarker to predict stroke. Many studies have also reported that in patients with sinus rhythm or after AF ablation, elevated NLR levels are associated with delayed atrial electromechanical activity, AF incidence or recurrence [18-20]. These findings confirm that elevated NLR remains linked to atrial electromechanical dysfunction, and such mechanistic associations support the conclusion of our study regarding the predictive value of NLR for ischemic stroke in patients with isolated SSS. In addition, after adjusting for multiple confounders including age, smoking, heart failure, hypertension, and diabetes, NLR remained significantly associated with the outcome. This indicates that NLR is an important factor that cannot be ignored in our study. Notably, NLR is more readily available, requiring only a routine complete blood count, is less costly and can be obtained in hospitals at various levels and in different regions.

Non-AF atrial tacharrhythmias, such as frequent atrial premature beats and atrial tachycardia has been demonstrated as an independent marker of ischemic stroke in patients with CIEDs, independent of occurrence of AF/AF[21, 22]. In this study, atrial arrhythmias were confirmed by reviewing the holter report and atrial high-rate episode (AHRE) in programming report. Atrial rate during AHRE could be recorded to differential the AF/AFL and non-AF atrial tacharrhythmias. Moreover, LAD indicate structural remodeling of atrial, series studies has been reported that increased LAD was independently associated to ischemic stroke in non-valvular AF patients[23]. However, left atrial enlargement also found to be an important marker reflecting the atrial dysfunction in patients with sinus rhythm [24]. Accordance with this knowledge of atrial myopathy, patients in the stroke group exhibited significantly larger left atrial diameters compared to the stroke-free group (40mm vs. 36mm, $p<0.05$). Additionally, indirect marker for electric remodeling of atrial is prolonged atrial conduction time, represent by prolonged PWD, P wave terminal force in lead V1 (PtfV1) and P wave dispersion[25]. PtfV1 was thought to be a marker to predict the ischemic stroke, whereas PWD is easier to obtain than other markers in clinical utility.

Clinical Implications

The developed nomogram provides a clinically practical tool that integrates biomarkers of subclinical cardiovascular dysfunction, particularly atrial electromechanical parameters—into a dynamic risk assessment framework. Unlike traditional diagnostic approaches focused on overt disease states, this model quantifies atrial hemodynamic derangements and electrophysiological remodeling, enabling early identification of high-risk SSS patients who may benefit from anticoagulant interventions. The parsimonious structure (6 variables) facilitates rapid risk stratification during routine cardiology consultations, particularly for pacemaker-implanted patients requiring long-term monitoring. It is important to note that our primary endpoint was deliberately limited to symptomatic ischemic strokes excluding those classified as large-artery atherosclerosis or small-vessel occlusion according to the TOAST criteria. By doing so, our outcome measure was enriched for cardioembolic and undetermined ischemic strokes, which are more likely to be associated with atrial thromboembolic mechanisms, particularly in the context of SSS and underlying atrial myopathy. While this approach enhances the specificity of our model for detecting atrial-derived stroke risk, it also limits the generalizability of our findings to all ischemic

stroke subtypes. Future studies should aim to validate our model in broader stroke populations and explore its utility across different stroke subtypes. Moreover, the proposed dynamic risk model could enable continuous thromboembolic risk stratification across multiple clinical settings such as anti-arrhythmia treatment, different CIEDs settings and shortening PWD with different pacing site [14]. Furthermore, it may help refine thromboprophylaxis thresholds for borderline cases (e.g., patients with CHA2DS2-VASc scores of 1). The model reflects the atrialmyopathy-stroke continuum, addressing the gap of the CHA2DS2-VASc score in atrialmyopathy.

At present, there are multiple assessment methods for atrial myopathy, including electrocardiography, biomarkers, echocardiography, intracardiac high-density mapping, cardiac magnetic resonance imaging. The best way to measure and define it is still to be established. In this study, from the perspective of clinical availability, we selected relatively easily obtainable parameters including ECG, echocardiography and biomarkers. Similar, recent study focused on atrial myopathy and stroke have also employed indicators similar to ours [26]. Establishing a precise definition of atrial myopathy and developing specific quantitative measures remain important directions for future research.

Limitation

This study has several limitations that warrant consideration. First, the single-center design may introduce selection bias, as participants were recruited from a tertiary cardiology department with high prevalence of cardiovascular comorbidities, potentially limiting generalizability to community-based populations. Second, while internal validation showed satisfactory calibration, external validation across diverse ethnic and clinical settings is to confirm the nomogram's robustness. Despite the implementation of rigorous follow-up and comprehensive electrocardiographic monitoring to excluded new-onset AF/AFL, the presence of asymptomatic atrial arrhythmia cannot be entirely detected in SSS patients without CIEDs. the differences in monitoring methods may lead to a potential bias when evaluating the association between non-AF atrial tachyarrhythmias and stroke. We included pacemaker implantation as a variable in the multivariable regression model to minimize this bias. Additionllay, the pacemaker's algorithm for detecting AMS relies on atrial rate and duration. This approach may lead to erroneous exclusion of patients with atrial arrhythmia episodes exhibiting heart rates exceeding 170-180 bpm.

Conclusions

The incidence of new-onset ischemic stroke in SSS patients is notably high, warranting focused attention in clinical practice. We developed the model evaluate the risk for ischemic stroke of SSS patients without AF/AFL and internally validated. This risk score performs better than CHA2DS2-VASC score and may providing evidence of thrombus assessment in patients with atrial myopathy.

Reference

[1].Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J. 42(5), 373-498 (2021).

[2].Goldberger JJ, Arora R, Green D, Greenland P, Lee DC, Lloyd-Jones DM, et al. Evaluating the Atrial Myopathy Underlying Atrial Fibrillation: Identifying the Arrhythmogenic and Thrombogenic Substrate. Circulation.132(4), 278-91 (2015).

[3].Piccini JP, Daubert JP. Atrial fibrillation and stroke: it's not necessarily all about the rhythm. Heart Rhythm. 2011;8(9):1424-5.

[4].Shen MJ, Arora R, Jalife J. Atrial Myopathy. JACC Basic Transl Sci. 4(5), 640-54 (2019).

[5].Kottkamp H. Fibrotic atrial cardiomyopathy: a specific disease/syndrome supplying substrates for atrial fibrillation, atrial tachycardia, sinus node disease, AV node disease, and thromboembolic complications. J Cardiovasc Electrophysiol. 23(7), 797-9 (2012).

[6].Sanders P, Morton JB, Kistler PM, Spence SJ, Davidson NC, Hussin A, et al. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: evidence of diffuse atrial remodeling. Circulation. 109(12), 1514-22 (2004).

[7].Bodin A, Bisson A, Gaborit C, Herbert J, Clementy N, Babuty D, et al. Ischemic Stroke in Patients With Sinus Node Disease, Atrial Fibrillation, and Other Cardiac Conditions. Stroke. 51(6), 1674-81 (2020).

[8]. Dong H, Zhang Y, Sun D, et al. Refining prediction of stroke in sinus node dysfunction patients without atrial fibrillation using a P-combined score: a multi-centre study. Eur J Prev Cardiol. 31(5), 507-518 (2024).

[9].Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. Eur Heart J. 35(28), 1864-72 (2014).

[10]. Mahaffey KW, Stevens SR, White HD, Nessel CC, Goodman SG, Piccini JP, et al. Ischaemic cardiac outcomes in patients with atrial fibrillation treated with vitamin K antagonism or factor Xa inhibition: results from the ROCKET AF trial. Eur Heart J. 35(4), 233-41 (2014).

[11] Mo BF, Lu QF, Lu SB, Xie YQ, Feng XF, Li YG. Value of Combining Left Atrial Diameter and Amino-terminal Pro-brain Natriuretic Peptide to the CHA2DS2-VASc Score for Predicting Stroke and Death in Patients with Sick Sinus Syndrome after Pacemaker Implantation. Chin Med J (Engl). 2017;130(16):1902-1908.

[12] Dong H, Chen H, Hidru TH, Xia Y, Yang X. Sinus node dysfunction and stroke risk: a systematic review and meta-analysis. BMJ Open. 2023 Nov 17;13(11):e076499.

[13] Benz AP, Hohnloser SH, Eikelboom JW, Carnicelli AP, Giugliano RP, Granger CB, Harrington J, Hijazi Z, Morrow DA, Patel MR, Seiffge DJ, Shoamanesh A, Wallentin L, Yi Q, Connolly SJ. Outcomes of patients with atrial fibrillation and ischemic stroke while on oral anticoagulation. Eur Heart J. 2023 May 21;44(20):1807-1814.

[14]. Lau CP, Tachapong N, Wang CC, Wang JF, Abe H, Kong CW, et al. Prospective randomized study to assess the efficacy of site and rate of atrial pacing on long-term progression of atrial fibrillation in sick sinus syndrome: Septal Pacing for Atrial Fibrillation Suppression Evaluation (SAFE) Study. Circulation. 128(7), 687-93 (2013).

[15]. Alonso A, Jensen PN, Lopez FL, Chen LY, Psaty BM, Folsom AR, et al. Association of sick sinus syndrome with incident cardiovascular disease and mortality: the Atherosclerosis Risk in Communities study and Cardiovascular Health Study. PLoS One. 9(10), e109662 (2014).

[16]. Goette A, Kalman JM, Aguinaga L, Akar J, Cabrera JA, Chen SA, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: Definition, characterization, and clinical implication. Heart Rhythm. 14(1), e3-e40 (2017).

[17]. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circ Res. 110(8), 1097-108 (2012).

[18]. Lekkala SP, Mellacheruvu SP, Gill KS, Khela PS, Singh G, Jitta SR, Patel M, Hingora MJ, Desai R. Association between preablation and postablation neutrophil-lymphocyte ratio and atrial fibrillation recurrence: A meta-analysis. J Arrhythm. 2024 Jan 28;40(2):214-221. v

[19]. Shao Q, Chen K, Rha SW, Lim HE, Li G, Liu T. Usefulness of Neutrophil/Lymphocyte Ratio as a Predictor of Atrial Fibrillation: A Meta-analysis. Arch Med Res. 2015;46(3):199-206.

[20]. Yilmaz A, Can S, Perincek G, Kahraman F. Atrial electromechanical delay, neutrophil-to-lymphocyte ratio, and echocardiographic changes in patients with acute and stable chronic obstructive pulmonary disease. J Res Med Sci. 2022;27:64.

[21]. Binici Z, Intzilakis T, Nielsen OW, Kober L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation. 121(17), 1904-11 (2010).

[22]. Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation. J Am Coll Cardiol. 66(3), 232-41 (2015).

[23]. Ogata T, Matsuo R, Kiyuna F, Hata J, Ago T, Tsuboi Y, et al. Left Atrial Size and Long-Term Risk of Recurrent Stroke After Acute Ischemic Stroke in Patients With Nonvalvular Atrial Fibrillation. J Am Heart Assoc. 6(8), e006402 (2017).

[24]. Zhou D, Yang W, Yang Y, Yin G, Li S, Zhuang B, et al. Left atrial dysfunction may precede left atrial enlargement and abnormal left ventricular longitudinal function: a cardiac MR feature tracking study. BMC Cardiovasc Disord. 22(1), 99 (2022).

[25]. Kelmanson IA. Increased P-wave dispersion in patients with obstructive sleep apnea syndrome: a meta-analysis. Sleep Breath. 27(1), 291-301 (2023).

[26] Kamel H, Elkind MS, Kronmal RA, et al. Atrial cardiopathy biomarkers and atrial fibrillation in the ARCADIA trial. Eur Stroke J. 2025;10(2):495-501.

Figure legends:

Figure 1. Baseline screening and follow-up of study.

Figure 2. Nomogram risk model predicting stroke in SSS patients. Each factor corresponds to specific point by drawing a line straight upward to the points axis. After sum of the points is located on the total points axis, the sum represents the probability of 3-year, 5-year and 10-year free of stroke by drawing straight down to the 3-year, 5-year and 10-year axis. For example, a 65-year-old individual (5.5 points) experienced non-AF atrial tachyarrhythmia (1 point), LAD 40mm (5.75 points) and the PWD was≥120ms (1.75points). Total point equals 14 and corresponding 3-year, 5-year, 10-year free of stroke risk is approximately 90%, 80%, 60%, respectively.

Figure 3. Concordance index (C-index) of CHA2DS2-VASc score and new model.

Figure 4. ROC showed the accuracy of CHA2DS2-VASc score and new model at risk for 3 year (A), 5 year (B) and 10 year (C).

Figure 5. Calibration plot showed the risk of stroke free survival in development(A, B, C) and validation (D, E, F) set at 3,5,10-years.

Figure 6 .Model performance evaluated by decision curve analyses at risk for 3 year (A), 5 year (B) and 10 year (C), the horizontal dashed line

and the slanted dashed line indicate theoretically that no patient experiences ischaemic stroke events and all patients experience ischaemic stroke

events, respectively.

Acknowledgements

We are grateful to all the physicians involved in patients management and device programming

Funding: This work was supported by National Key Research and Development Program of China (Grant number 2022YFC2405002).

Author Contributions

Conceptualization: Yiheng yang and Yunlong Xia; Data curation: Haoyu Dong and Yiheng Yang; Methodology and formal Analysis: Yiheng Yang and Haoyu Dong; Statistical Analysis, Haoyu Dong and Yiheng Yang; Investigation: Haoyu Dong, Shihao Wang and Rongfeng Zhang; Resource: Yingxue Dong, Xiaomeng Yin Software: Yushan Wei; Writing—Original Draft Preparation: Haoyu Dong; Writing—Review and Editing: Yiheng yang and Xiaolei Yang ; Validation: Lianjun Gao. Supervision: Yunlong Xia and Xiaolei Yang . Funding acquisition: Yunlong Xia; Visualization: Xiaolei Yang and Yiheng Yang. Project administration: Xiaolei Yang and Yiheng Yang. All authors have reviewed and agreed to the published version of the manuscript.

Ethics statement

All patient information in the database is anonymized and therefore does not require informed consent according the regulations of Ethics committee of First affiliated hospital of Dalian Medical University. Study protocol adheres to the principles of Helsinki Declaration, and has been approved by the Ethics committee of First affiliated hospital of Dalian Medical University (PJ-KS-KY-2022-306).

Data statement: The data presented in this study are available upon request from the corresponding author.

Declaration of Interests: None declared