



The Use of VACS Nomogram to Predict Atrial Fibrillation in Chinese Patients with Acute Ischemic Stroke

Linda Nyame^{1,2}
Enoch Kwaw-Nimeson³
Yang Zou⁴
Emmanuel Delali Kofi Fiagbey⁵
Yu-Kai Liu⁶
Xiang-Liang Chen⁶
Mako Ibrahim^{1,2}
Xiang Li^{1,2}
Zheng Zhao^{2,1}
Chao Sun^{1,2}
Jun-Shan Zhou⁶
Chun-Lian Jiang^{7*}
Jian-Jun Zou^{2,1*}

¹School of Basic Medicine and Clinical Pharmacy, China Pharmaceutical University, Nanjing, China;

²Department of Clinical Pharmacology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China;

³Business School, Hohai University, Nanjing, China;

⁴Faculty of Science, Melbourne University, Melbourne, VIC, Australia;

⁵Department of Herbal Medicine, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana;

⁶Department of Neurology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China;

⁷Department of Pathology, Nanjing First Hospital, Nanjing Medical University, Nanjing, China.

Abstract

Tools for the detection of atrial fibrillation (AF) in patients with acute ischemic stroke (AIS) are of great importance for identifying high-risk individuals. We aimed to develop and validate an easy-to-use model for predicting the risk of atrial fibrillation in acute ischemic stroke patients. We retrospectively collected patients who were diagnosed with AIS at the Stroke Center of the Nanjing First Hospital (China) between May 2013 and May 2019. Multivariable logistic regression analysis was used to develop the predicting model, and stepwise logistic regression with the Akaike information criterion was utilized to find the best-fit nomogram model. We assessed the discriminative performance by using the area under curve (AUC) of receiver-operating characteristic (ROC) and calibration of risk prediction model by using the Hosmer-Lemeshow test. The final study population consisted of 3,320 patients for generating the nomogram, 573 patients had AF. Four predictors, including Valvular heart disease, Age, Coronary heart disease and Sex (VACS) were incorporated to construct the nomogram model. The nomogram demonstrated good predictive performance in ROC analysis (AUC-ROC 0.767, 95% CI 0.745-0.788). Calibration was good ($p = 0.357$ for the Hosmer-Lemeshow test). Our nomogram may provide clinicians with a simple and reliable tool for predicting the risk of AF in acute ischemic stroke patients. It may be a valuable perspective to provide a reasonable approach in the prevention, increased monitoring and allocation of relevant medical resources.

Keywords

Atrial fibrillation; Acute ischemic stroke; Nomogram; Prediction

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and confers a substantial risk of mortality and morbidity from stroke and thromboembolism. Of all the aetiologies of stroke, AF is actually the most ubiquitous, accounting for about 20% to 30% of all ischemic stroke patients [1-3]. AF has substantial population health consequences, including impaired quality of life, increased hospitalization rates, stroke occurrence, and increased medical costs. Knowledge of developing AF in an acute ischemic stroke (AIS) patient is prudent to the adaptation of an appropriate scheme and achievement of an optimum outcome in the management of the patient [4], owing to the fact that AIS patients with AF require a tailored treatment strategy as early as possible.

Tools for the prediction of AF could help identify high-risk individuals and serve as a standard to test possible novel risk factors. A couple of studies have reported the development of several scores [5-10], such as CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke [2P]), extended CHA₂DS₂-VASc (vascular disease, age 65-74 years, and (female) sex category), Score for the Targeting of Atrial Fibrillation (STAF) and The LADS (left atrial diameter, age and diagnosis of stroke) scoring system, for the prognostication of AF in patients with AIS. However, the performance of these scores for individualized prediction of AF after AIS is limited by using dichotomization of continuous variables. Again, adaptability and ease of these scores in routine clinical care for predicting the risk of AF after stroke are limited by a moderate predictive performance.

Article Information

DOI: 10.31021/jnn.20203142
Article Type: Research
Journal Type: Open Access
Volume: 3 **Issue:** 1
Manuscript ID: JNN-3-142
Publisher: Boffin Access Limited
Received Date: 10 January 2020
Accepted Date: 21 January 2020
Published Date: 24 January 2020

*Corresponding author:

Jian-Jun Zou

Department of Clinical Pharmacology
Nanjing First Hospital, Nanjing Medical
University, Nanjing, China
Tel: +86-15380998951
E-mail: zoujianjun100@126.com

Chun-Lian Jiang

Department of Pathology
Nanjing First Hospital
Nanjing Medical University, China
Tel: +86-18625188095
E-mail: 675236684@qq.com

Citation: Nyame L, Kwaw-Nimeson E, Zou Y, Fiagbey EDK, Liu YK, et al. The Use of VACS Nomogram to Predict Atrial Fibrillation in Chinese Patients with Acute Ischemic Stroke. *J Neurosci Neurosurg*. 2020 Jan;3(1):142

Copyright: © 2020 Zou JJ, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 international License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

A number of studies have demonstrated that nomograms offer better performance relative to scores that are based on risk grouping [11-16]. A nomogram is a graphical statistical instrument that incorporates variables to develop a continuous scoring system, which reflects the individual and precise risk probability. In contrast to risk groups, a nomogram offers an individualized prediction, which is entirely based on the individual's characteristics potentially increasing its practicality in both clinical trial and routine care settings. Nomograms could prove more preferable to previous prognostic models that fundamentally employ archaic risk-grouping categorization which tends to reduce the predictive accuracy.

Despite previous research reported in literature, there is currently no reported study that has focused on the use of nomogram to predict the likelihood of AF in Chinese patients with AIS. This study was therefore purposed at the development and validation of a simple and clinically useful nomogram for predicting the risk of AF in Chinese patients with AIS.

Methods

Study design and participants

The data of Chinese patients diagnosed with AIS were retrospectively collected from the Registry database of the Nanjing First Hospital (NFHSR) in China. A cohort study was then carried out on the gathered data. From the period of May 2013 to May 2019, all patients diagnosed with AIS were included in the study. As required, all patients included in the study duly granted their written informed consent. Additionally, the scientific use of the data obtained from NFHSR was approved by the Ethics Committees of Nanjing First Hospital in accordance with the Helsinki declaration and internal protocol. Multivariate parameters including baseline characteristics, demographics, comorbidities, and National Institutes of Health Stroke Scale (NIHSS) score on admission and laboratory characteristics during hospitalization were recorded.

Inclusion and exclusion criteria

The study solely included AIS patients with related exhaustive clinical, demographic and laboratory data. Patients without AF history by self-report on admission were included in the study. Principally, all patients had to be 18 years or more to be due for inclusion. The exclusion criteria included patients with a known history of AF, no prestroke modified Rankin scale (mRS) score, unexhausted data, as well as patients treated with endovascular procedure. Among the candidate variables that were assessed in this research study were demography which included age and gender; medical history which included hypertension, diabetes mellitus, hyperlipidaemia, coronary heart disease (CHD), valvular heart disease (VHD), transient ischemic attack, smoking, drinking; Baseline data which included NIHSS score, Platelet count, Urea, Uric acid, Total cholesterol, Triglyceride, Glycosylated haemoglobin, and early antiplatelet therapy. The diagnosis of AF was based on electrocardiogram (ECG) and included AF episodes of over 30 seconds [17]. The maximum monitoring duration in the study was six days. Guidelines suggest that the diagnosis of persistent or permanent AF is based on at least seven days of ECG. The ECGs were read and coded at the stroke unit using central monitoring system (TLC6000, TaiKang, China).

Clinical Outcome: Newly detected AF was defined as episodes of ECG-documented AF without a known history of AF.

The primary outcome was incident of AF, identified at follow-up by either electrocardiogram or a diagnosis of AF by two neurologists blinded to the data of this study.

Statistical Analysis

Normality was evaluated using the One-sample Kolmogorov-Smirnov test. The description of continuous variables was presented median value and interquartile range. By mathematically dividing the number of events by the total number with the exception of unknown

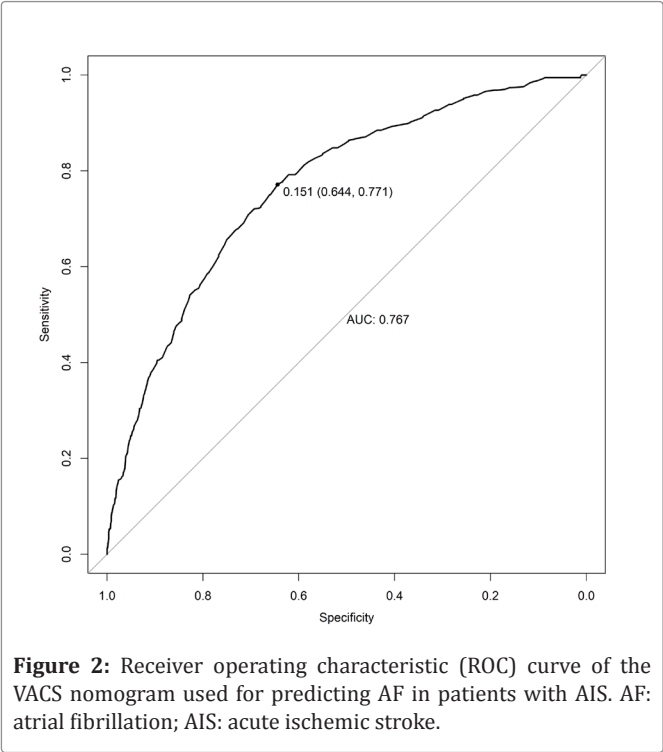
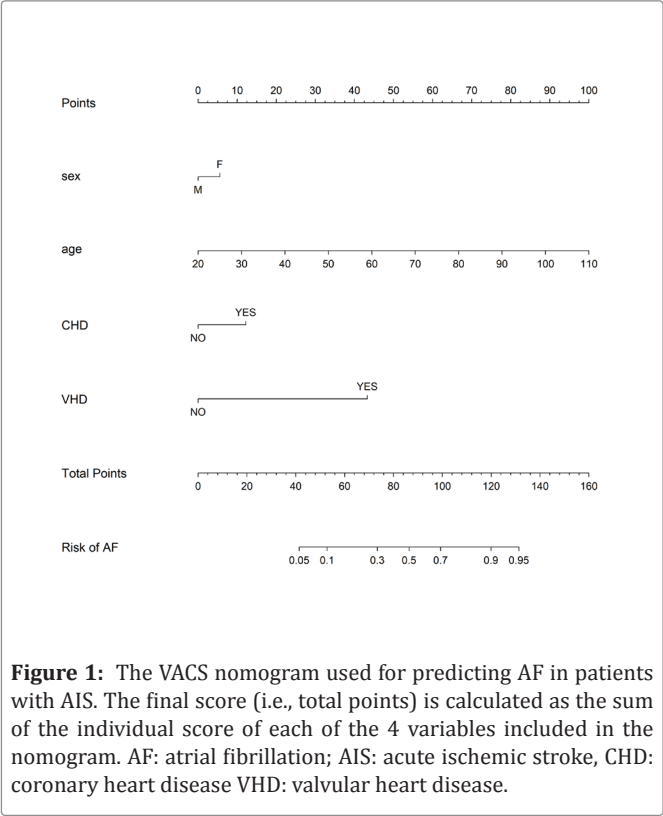
cases, ratios were rightly obtained for dichotomized variables. Using the Mann-Whitney U-test for continuous variables, various categorized sets were assessed for differences. Fisher's exact test or the χ^2 test was also used to evaluate differences between classified variables. The nomogram was generated for individual prognostication of AF in Chinese patients with AIS. The generation of the nomogram entailed the inputting of predetermined prognosticators into a logistic regression model. Upon the multivariate analysis, variables that were observed to have demonstrated a significant relationship with the primary endpoint of the analysis had OR and its 95 % CI calculated. SPSS version 22.0 (IBM Corporation, Armonk, NY, USA), Stata version 13.0 (Stata Corporation, College Station, TX, USA) statistical software, and the statistical software package R, version 3.3.3 (R Development Core Team, Auckland, New Zealand), were used to perform the statistical assessment. In order to develop the nomogram, multivariate logistic regression analysis was performed for predicting the risk of AF using a forward stepwise method that included VHD, age, CHD and sex as pre-established variables and all variables with a probability value < 0.2 in the univariate analysis. The best model was selected based on Akaike's information criterion. Collinearity of variables that entered the multivariate logistic regression analysis was assessed by the variation inflation factors (< 2 being considered non-significant) and condition index (< 30 being considered non-significant).

The prognosticative precision of the developed nomogram model was evaluated by calculating the area under curve (AUC) of the receiver-operating characteristic. Using a calibration plot of the prognosticated likelihood against the frequency of the noted unfavorable result, the calibration of the nomogram model was conducted. The prediction of a well-calibrated model should be mirrored by a 45° diagonal line. Subsequently, bootstrap sampling was employed in the validation of the model, having taken into consideration that all equations of prediction are inclined to be-fit the original sample beyond measure. All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

A sum of 4,184 patients with AIS was identified from the NFHSR database over the period of May 2013 to May 2019. Among the 4,184 patients registered in the NFHSR cohort, 124 (2.96%) patients lack information on atrial fibrillation on discharge. Additional patients were excluded for NIHSS unknown ($n = 429$; 10.3%) and lack of clinical information ($n = 311$; 7.4%). Therefore, the final study population consisted of 3,320 patients (median age 68 years; IQR 60-77 years). Table 1 details the clinical and demographic characteristics of the 2,747 patients in the No AF cohort and 573 patients in the AF cohort. Valvular heart disease (OR: 16.984; 95% CI: 8.982-32.113 $p < 0.0001$), Age (OR: 1.075; CI: 1.065-1.086; $p < 0.0001$), Coronary heart disease (OR 2.219; 95% CI: 1.747-2.819; $p < 0.0001$) and Sex (OR: 0.695; 95% CI: 0.569-0.848; $p < 0.0001$), (Table 2, Figure 1) (VACS) were the four pre-established prognosticators that were inputted into a logistic regression model in the multivariate analysis to develop the nomogram for the prediction of AF in patients with AIS. For any of the four pre-established predictors that were inputted into the multivariate logistic regression evaluation model, no significant statistical co-linearity was noted. The resultant logistic regression model was mathematically expressed as: $\text{Log} (p[x]/1-p[x]) = -4.514 + (0.023 \times \text{age}) + (0.170 \times \text{NIHSS score}) + (0.356 \times \text{previous mRS score}) + (0.936 \times \text{atrial fibrillation})$; where $p(x)$ was the probability of risk of AF after AIS.

In the development of the nomogram, an initial score was graphically ascribed to each of the 4 independent predictive markers with a point limit from 0 to 100. This was thereafter totalled to yield a summed score and was expressed as a percentage with a point limit from 0 to 100 after it was converted into an independent or individual risk of AF secondary to AIS. The nomogram's higher total score was prognosticated to be related to an increased tendency of AF. Meanwhile, the decreased probability of AF secondary to AIS was



prognosticated to be related to the lower total score.

The AUC-receiver operating characteristic value of the VACS nomogram was 0.767 (95% CI 0.745-0.788) in the NFHSR cohort (Figure 2). The age values exhibited a modest diagnostic accuracy for identifying patients with AF after AIS, displaying an AUC of 0.730 (95% CI 0.708-0.752; $p < 0.0001$). Valvular exhibited a good diagnostic accuracy for identifying patients with risk of developing AF, displaying an AUC of 0.526 (95% CI 0.499-0.553; $p < 0.0001$). The total number of patients with a risk probability $< 10\%$ was 1,341/3320 (40.4%), and only 74 of these had AF (0.95 sensitivity, 0.25 specificity, 0.87 negative predictive value and 0.46 positive

	Without AF	With AF	P-value
Patients, n	2747	573	
Age, years, median (IQR)	67(59-75)	77(70-83)	$<0.0001^{†*}$
Sex, n (%)			$<0.0001^*$
Male	1905(69.3)	301(52.5)	
Female	842(30.7)	272(47.5)	
Medical history, n (%)			
Diabetes Mellitus	806(29.3)	140(24.4)	0.018
Hyperlipidemia	87(3.2)	9(1.6)	0.383
Coronary Heart disease	276(10)	156(27.2)	$<0.0001^*$
Valvular heart disease	20(0.7)	34(5.9)	$<0.0001^*$
Transient ischemic attack	10(0.4)	6(1)	0.032
Drinking, n (%)			$<0.0001^*$
Never drinker	1596(58.1)	411(71.7)	
Former drinker	308(11.2)	64(11.2)	
Current drinker	843(30.7)	98(17.1)	
Smoking, n (%)			$<0.0001^*$
Never smoker	1272(46.3)	366(63.9)	
Former smoker	382(13.9)	89(15.5)	
Current smoker	1093(39.8)	118(20.6)	
Baseline data			
NIHSS score, median (IQR)	4(2-10)	11(4-17)	$<0.0001^*$
Platelet count, $10^9/L$, median (IQR)	197(163-240)	173(141-218)	<0.0001
Urea	5.5(4.5-6.76)	6(4.66-7.75)	$<0.0001^*$
Uric acid	324(257-418)	339(247-429)	0.834
TC, mmol/L, median (IQR)	4.4(3.69-5.27)	4.08(3.46-4.86)	$<0.0001^{†*}$
TG, mmol/L, median (IQR)	1.36(0.98-2.05)	1.03(0.75-1.44)	$<0.0001^{†*}$
Glycosylated hemoglobin (IQR)	6.1(5.6-7.7)	6.1(5.7-6.9)	0.545 †
Early antiplatelet therapy	445(16.2)	126(22)	$<0.0001^*$

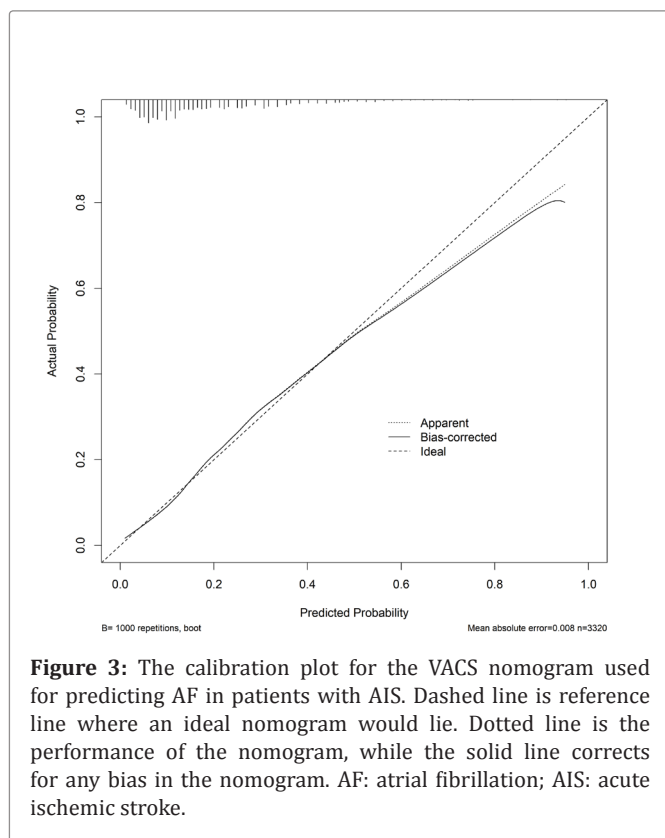
NIHSS: National Institutes of Health Stroke Scale; TC: Total cholesterol; TG: Triglyceride;

* included in the multiple logistic regression models.

† Calculated using Mann-Whitney U test.

Table 1: Clinical, demographic and laboratory data of the study population stratified according to risk of Atrial Fibrillation after acute ischemic stroke in Chinese patients.

predictive value). The total number of patients with a risk probability $< 40\%$ was 3,055/3,320 (92%), 437 of whom had AF (0.86 sensitivity, 0.51 specificity, 0.24 negative predictive value and 0.95 positive predictive value). Finally, the total number of patients with a high-risk probability (i.e., $> 80\%$) was 13/3,320 (0.4%), the vast majority of whom (9/13; 62.2%) had a poor prognosis (0.83 sensitivity, 0.70 specificity, 0.01 negative predictive value and 0.99 positive predictive value). The model was internally validated using 2,000 bootstrap samples to calculate the discrimination with accuracy, and the good



predictive performance of the nomogram was confirmed, yielding a notable AUC of 0.767 (95% CI 0.745- 0.788; $p < 0.0001$; Figure2). The bias-corrected calibration plot for the nomogram model showed adequate agreement between predictors calculated with the VACS nomogram and actual unfavorable outcomes at the end of the follow-up period (Figure 3). Calibration graphic revealed adequate fit of the model predicting the risk of AF. The Hosmer-Lemeshow goodness-of-fit test showed good calibration of the nomogram ($p = 0.357$).

Discussion

Many strokes which are initially diagnosed as cryptogenic may actually be due to underlying paroxysmal atrial fibrillation that was not detected during hospitalization. Currently, antiplatelet drugs [18] are employed in the treatment of cryptogenic strokes. However, in instances where cryptogenic stroke results from unidentified AF, the use of oral anticoagulation is employed to ensure improved protection. Hence, early identification of patients that have been diagnosed with AIS and consequently have increased risk of AF following stroke could be a valuable perspective to provide a reasonable approach in the prevention, raised monitoring and apportioning of necessary medical resources.

There has been the development of various prognostic scores [5-10] to prognosticate the development of AF in stroke patients. CHADS2 (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke [2P]) and the extended CHA2DS2-VASc (vascular disease, age 65-74 years, and (female) sex category) scores have been used to predict the presence of AF in patients with ischemic stroke [5,6]. Nonetheless, clinical outcomes are not consistent. Also, extra effort and cost may be required in identifying at-risk patients on the account that a lot of the markers and risk scores need more diagnostic workup such as serum testing [10,20] as well as imaging analysis [10,21]. According to a study by Douen et al. [22], 70% of outpatients with AIS and transit ischemic attack (TIA) undergo transthoracic echocardiography and Holter monitoring and thereby attributed to an estimated 94% of total cardiovascular expenditure.

The VACS nomogram offers an individualized prediction of AF which is solely founded on the individual's characteristics latently increasing its ability to be practically applied in the undertaking

	OR	Error	Wald	P	95% CI
Valvular heart disease	16.984	5.519	8.982	$P < 0.0001$	8.982 -32.113
Age	1.075	0.005	14.390	$P < 0.0001$	1.065-1.086
Coronary heart disease	2.219	0.271	6.530	$P < 0.0001$	1.747-2.819
Sex	0.695	0.706	-3.580	$P < 0.0001$	0.569-0.848

CI: confidence intervals

Table 2: Significant predictors of Atrial Fibrillation in patients with acute ischemic stroke

of clinical trials and also in the dispensary of regular procedural care. Furthermore, the VACS nomograms provide a more improved prognosticative efficiency for AF as compared to models based on risk grouping owing to its ability to integrate all essential and informative prognosticators of a patient. Simultaneously, the discriminative performance of the VACS nomogram was excellent.

The tendency of developing AF is widely known to rise with age [23,24]. In the proposed predictive model, we found that advancement in age was related to an increased likelihood of developing AF. Age was the strongest, significant, independent predictor for AF and it maintained a significant impact following alteration of other demographic and clinical factors. This finding is consistent with previous reports [23,25-27]. In the Framingham Study [26], the incidence of AF increases by twice with each advancing decade of age > 50 yr and reaches almost 10% in octogenarians. This relationship has been explained to be attributable to age-related structural changes in the atrium such as dilation, stiffness of the left atrium, muscle atrophy, decreased conduction tissue, but also electro anatomical changes and fibrosis [28-30]. Again, old age is associated with one or more cardiovascular diseases such as coronary artery disease, high blood pressure, high cholesterol, heart failure, peripheral artery disease, and cerebral amyloid angiopathy.

The established cardiac conditions associated with AF are various types of VHD (especially mitral regurgitation), acute myocardial infarction, cardiomyopathy (all forms), congenital heart disease, hypertensive cardiovascular disease, and CHD. VHD and CHD were associated with the risk of incident of AF in our study. Similar findings have been reported for both VHD and CHD in previous studies [31,32]. In the Framingham Study [31], VHD was associated with an increased risk of developing AF (odds ratio of 1.8 in men and 3.4 in women). A study by Muscari et al. [32] found mild to moderate mitral and tricuspid regurgitation to be significantly associated with first diagnosed AF in ischemic stroke patients. AF prevalence was 9.1% in patients with mild-to-moderate aortic stenosis and 33.7% as observed for those with severe stenosis [33,34].

CHD was associated with an increased risk of atrial fibrillation in previous studies as well as in the present one [32]. Having both CHD and AF was found in the Framingham study to adversely influence prognosis regarding total mortality and stroke [35]. CHD manifests as angina, silent ischemia, unstable angina, myocardial infarction, arrhythmias, heart failure, and sudden death. Possibly, the notion that coronary artery disease is a ubiquitous cause of atrial fibrillation is rooted in the fact that many congestive cardiomyopathies are related to AF. Reports from the coronary care units that acute myocardial infarctions complicated by congestive heart failure are frequently associated with AF strengthens the notion of CHD resulting in atrial fibrillation.

The prevalence of AF differs with age and sex. In our study sex was also related to the detection of AF, which is consistent with previous studies [31,36,37]. In addition, AF is known to occur more frequently in men. In spite of the high prevalence in men, women represent the bulk of patients with AF owing to their longer survival [37-39]. Interestingly, in our study, the incidence of AF was observed in both men and women.

In the present study, a $> 80\%$ risk limit was deduced from the

nomogram. This risk limit was related to a positive predictive value of 0.99. This positive predictive value thereby allowed a more precise prognostication of risk of AF after AIS. Contrary to the nomogram-derived >80% risk limit, risk cut-off of <10% significantly demonstrated a negative prognostic value of 0.87. This negative prognostic value enabled the precise exclusion of the likelihood of developing AF after AIS. The use of a VACS nomogram could aid the notification of physicians to adopt preventive measures in patients with raised suspicious, follow-up counseling and patient counseling. Also, early intervention and distribution of medical resources may decrease the likelihood of AF and improve prognosis after AIS. More so, the VACS nomogram is a readily interpretable and widely available tool that can be easily used at patient-level to enhance improvements in these risk factors.

The current study has a number of strengths. First, our study is novel. In that, the VACS nomogram is the foremost graphic prognostic model developed with the purpose of particularly predicting individualized risk of AF in patients with AIS. By integrating relevant clinical variables, the VACS nomogram has the capability to generate an individual risk of developing AF in patients with AIS. Additionally, the nomogram prognostications are customized to suit the probable adverse effects posed by the characteristics of an individual's stroke. Comparatively, this is more significant against the results of the general group peers.

We acknowledge that this study has limitations. First, our data are retrospectively collected in a single-center, causing much data lost which might have influenced the final outcomes. Second, the diagnosis of AF was based on just a six-day ECG monitoring period; a longer monitoring period might have identified more cases of AF and the results might be different. Finally, external validation in an entirely different cohort of patients is vehemently recommended.

Conclusion

In conclusion, the VACS nomogram is a promising tool that provides a new and improved model of predicting AF in AIS patients. Additionally, the VACS nomogram is an easily interpretable and widely available tool that can be easily applied at the patient-level to encourage improvements in these risk factors.

Author Contributions

Linda Nyame, Enoch Kwaw-Nimeson and Yang Zou contributed equally to this work. Jian-jian Zou, Jun-shan Zhou and Chun-Lian Jiang conceived, designed and supervised the study. Jun-shan Zhou, Xiang-Liang Chen, and Yu-Kai Liu acquired the data. Linda Nyame, Enoch Kwaw-Nimeson, Xiang Li, Chao Sun and Zheng Zhao analyzed and interpreted the data, provided statistical analysis, had full access to all of the data in the study, and are responsible for the integrity of the data and the accuracy of the data analysis. Linda Nyame, Mako Ibrahim and Emmanuel Delali Kofi Fiagbey drafted the manuscript, Jian-jian Zou, Chun-Lian Jiang and Yang Zou critically revised the manuscript for important intellectual content.

Acknowledgments

We acknowledge the Nanjing first Hospital, relevant clinicians, and investigators for their participation.

Funding

This study was supported by the National Natural Science Foundation of China grant 81673511, Jiangsu key Research and Development Plan grant BE2017613, Jiangsu Six Talent Peaks Project grant WSN-151, and Nanjing Medical Science and Technique Development Foundation grant QRX17020 and ZKX15027.

Disclosure statement

The authors have declared that they have no conflicts of interest regarding the content of this article.

References

1. Ihle-Hansen H, Thommessen B, Wyller TB, Engedal K, Fure B. Risk factors for and incidence of subtypes of ischemic stroke. *Funct Neurol*. 2012 Jan-Mar;27(1):35-40.
2. Lip GY, Lim HS. Atrial fibrillation and stroke prevention. *Lancet Neurol*. 2007 Nov;6(11):981-993.
3. Hannon N, Sheehan, O, Kelly L, Marnane M, Merwick A, et al. Stroke associated with atrial fibrillation--incidence and early outcomes in the north Dublin population stroke study. *Cerebrovasc Dis*. 2019Dec;29(1):43-49.
4. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, et al. Uncovering Atrial Fibrillation Beyond Short-Term Monitoring in Cryptogenic Stroke Patients: Three-Year Results From the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial. *CircArrhythmElectrophysiol*. 2016 Jan;9(1):e003333.
5. Suissa L, Bertora D, Lachaud S, Mahagne MH. Score for the targeting of atrial fibrillation (STAF): a new approach to the detection of atrial fibrillation in the secondary prevention of ischemic stroke. *Stroke*. 2009 Aug;40(8):2866-2868.
6. Malik S, Hicks WJ, Schultz L, Penstone P, Gardner J, et al. Development of a scoring system for atrial fibrillation in acute stroke and transient ischemic attack patients: the LADS scoring system. *J Neurol Sci*. 2011 Feb;301(1-2):27-30.
7. Horstmann S, Rizos T, Güntner J, Hug A, Jenetzky E, et al. Does the STAF score help detect paroxysmal atrial fibrillation in acute stroke patients? *Eur J Neurol*. 2013 Jan;20(1):147-152.
8. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010 Feb;137(2):263-272.
9. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, et al. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: the ATRIA study stroke risk score. *J Am Heart Assoc*. 2013 Jun;2(3):e000250.
10. Seo WK, Kang SH, Jung JM, Choi JY, Oh K. Novel composite score to predict atrial Fibrillation in acute stroke patients: AF predicting score in acute stroke. *Int J Cardiol*. 2016 Apr;209:184-189.
11. Shariat SF, Capitanio U, Jeldres C, Karakiewicz PI. Can nomograms be superior to other prediction tools? *BJU Int*. 2009 Feb;103(4):discussion 495-497.
12. Chun FK, Karakiewicz PI, Briganti A, Walz J, Kattan MW, et al. A critical appraisal of logistic regression-based nomograms, artificial neural networks, classification and regression-tree models, look-up tables and risk-group stratification models for prostate cancer. *BJU Int*. 2007 Apr;99(4):794-800.
13. Kattan MW. Nomograms are superior to staging and risk grouping systems for identifying high-risk patients: preoperative application in prostate cancer. *Curr Opin Urol*. 2003 Mar;13(2):111-116.
14. Kattan MW. Comparison of Cox regression with other methods for determining prediction models and nomograms. *J. Urol*. 2003 Dec;170 (6 pt 2):S6-S9 discussion S10.
15. Shariat SF, Karakiewicz PI, Palapattu GS, Amiel GE, Lotan Y, et al. Nomograms provide improved accuracy for predicting survival after radical cystectomy. *Clin. Cancer Res*. 2006 Nov;12(22):6663-6676.
16. Song BL, Liu YK, Nyame L, Chen XL, Jiang T, et al. A COACHS nomogram to Predict the Probability of Three- Month Unfavorable Outcome after Acute Ischemic Stroke in Chinese Patients. *Cerebrovasc. Dis*. 2019 Mar;47(1-2):80-87.
17. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on

- practice guidelines and the Heart Rhythm Society. *Circulation*. 2014 Dec;130(23):2071-2104.
18. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014 Jul;45(7):2160-2236.
19. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001 Jun;285(22):2864-2870.
20. Naess H, Andreassen UW, Thomassen L, Kvistad CE. A score for paroxysmal atrial fibrillation in acute ischemic stroke. *Int J Stroke*. 2018 Jul;13(5):496-502.
21. Baturova MA, Sheldon SH, Carlson J, Brady PA, Lin G, et al. Electrocardiographic and Echocardiographic predictors of paroxysmal atrial fibrillation detected after ischemic stroke. *BMC CardiovascDisord*. 2016 Nov;16(1):209.
22. Douen A, Pageau N, Medic S. Usefulness of cardiovascular investigations in stroke management: clinical relevance and economic implications. *Stroke*. 2007 Jun;38(6):1956-1958.
23. Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *Lancet*. 2015 Jul;386(9989):154-162.
24. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014 Feb;129(8):837-847.
25. Favilla CG, Ingala E, Jara J, Fessler E, Cucchiara B, et al. Predictors of finding occult atrial fibrillation after cryptogenic stroke. *Stroke*. 2015 May;46(5):1210-1215.
26. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991 Aug;22(8):983-988.
27. Jeong JH. Prevalence of and risk factors for atrial fibrillation in Korean adults older than 40 years. *J Korean Med Sci*. 2005 Feb;20(1):26-30.
28. Kistler PM, Sanders P, Fynn SP, Stevenson IH, Spence SJ, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am CollCardiol*. 2004 Jul;44(1):109-116.
29. Boyd AC, Schiller NB, Leung D, Ross DL, Thomas L. Atrial dilation and altered function are mediated by age and diastolic function but not before the eighth decade. *JACC Cardiovasc Imaging*. 2011 Mar;4(3):234-242.
30. Spach MS, Heidlage JF, Dolber PC, Barr RC. Mechanism of origin of conduction disturbances in aging human atrial bundles: experimental and model study. *Heart Rhythm*. 2007 Jul;4(2):175-185.
31. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. *JAMA*. 1994 Mar;271(11):840-844.
32. Muscari A, Bonfiglioli A, Faccioli L, Ghinelli M, Magalotti D, et al. Usefulness of the MrWALLETS Scoring System to Predict First Diagnosed Atrial Fibrillation in Patients With Ischemic Stroke. *Am J Cardiol*. 2017 Apr;119(7):1023-1029.
33. Greve AM, Gerdtts E, Boman K, Gohlke-Baerwolf C, Rossebø AB, et al. Prognostic importance of atrial fibrillation in asymptomatic aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis study. *Int J Cardiol*. 2013 Jun;166(1):72-76.
34. Stortecky S, Buellesfeld L, Wenaweser P, Heg D, Pilgrim T, et al. Atrial fibrillation and aortic stenosis: impact on clinical outcomes among patients undergoing transcatheter aortic valve implantation. *Circ Cardiovasc Interv*. 2013 Feb;6(1):77-84.
35. Kannel WB, Abbott RD, Savage DD, McNamara PM. Coronary heart disease and atrial fibrillation: the Framingham Study. *Am Heart J*. 1983 Aug;106(2):389-396.
36. Kokubo Y, Watanabe M, Higashiyama A, Nakao Y, Kusano K, et al. Development of a Basic Risk Score for Incident Atrial Fibrillation in a Japanese General Population - The Suita Study. *Circ J*. 2017 Oct;81(11):1580-1588.
37. Friberg L, Bergfeldt L. Atrial fibrillation prevalence revisited. *J Intern Med*. 2013 Nov;274(5):461-468.
38. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace*. 2013 Apr;15(4):486-493.
39. Zoni-Berisso M, Filippi A, Landolina M, Brignoli O, D'Ambrosio G, et al. Frequency, patient characteristics, treatment strategies, and resource usage of atrial fibrillation (from the Italian Survey of Atrial Fibrillation Management [ISAF] study). *Am J Cardiol*. 2013 Mar;111(5):705-711.