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Predictors of Paroxysmal Atrial Fibrillation Detected in Patients After Ischemic Cerebrovascular Stroke

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Abstract

Atrial fibrillation (AF) -related cardioembolic stroke is highly prevalent and requires specific management. Early detection of such patients will help clinicians to decide the appropriate intervention. We aimed to build up a prediction score for paroxysmal AF among patients presented with acute ischemic stroke to predict paroxysmal AF on hospital admission. A prospective case-control study was conducted at Shebin Elkom teaching hospital. Cases were 50 adult patients presented with acute ischemic stroke and developed paroxysmal AF during the hospital course, while control group included 50 adult patients with acute ischemic stroke who did not develop paroxysmal AF. All baseline data including laboratory, electrocardiography, and echocardiography data were prioritized and utilized in a prediction model using discriminant analysis and SPSS software. Univariate analysis revealed that laboratory data including free T3 level, BNP level, and neutrophils to lymphocytes ratio (N/L); electrocardiography data including P-R interval (ms) and P/v1mm*ms; echocardiography including LAD (mm) and LAVI (ml/m2) were higher among cases compared to control group. Discriminant analysis prioritized the following variables in descending order; LAVI, N/L, LAD, BNP, and P/V1; and buit a prediction equation, named PAAS. The model showed a sensitivity of 84% and specificity of 82%. The prediction model of the present can help in early prediction of paroxysmal AF among similar patients with acute ischemic stroke. The model may be tested in further studies in a larger sample size.

Keywords: Atrial fibrillation, Ischemaic Cereberovascular

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1. Introduction

Cardioembolism accounts for about 20% to 30% of all ischemic strokes. Cardiac causes of embolism include atrial fibrillation (AF), valvular heart disease, and left ventricular dysfunction [1]. The prevalence of AF varies according to age and sex. AF was found in 0.12%–0.16% of people younger than 49 years. However, it was found in 3.7%–4.2% of those aged 60–70 years and in 10%–17% of those aged 80 years or older [2]. Approximately half of them had permanent AF, 25% of them had paroxysmal AF and 25% had persistent AF. New onset paroxysmal AF associated with acute ischemic stroke, transient ischemic attack, or both was detected in 11.5% patients who underwent any cardiac monitoring for a minimum of 12 hours [3]. Moreover, undiagnosed paroxysmal AF was common among patients with a recent cryptogenic stroke or TIA who were 55 years of age or older. It was detected in 16.1% of patients with cryptogenic ischemic stroke or TIA [4]. Early detection of AF and anticoagulating AF patients with a high risk of cardioembolism to prevent ischemic stroke is highly important. However, paroxysmal AF is not that easy to be detected in routine checkup, especially asymptomatic, even long-standing ambulatory rhythm monitoring devices are limited by modest sensitivity to detect paroxysmal AF [5]. Appling implantable cardiac monitors (ICM) provide high sensitivity for AF detection, although it requires high cost and especial application setting [6]. However, to optimize its cost effectiveness, proper patient selection is required, which highlights the need for developing AF risk prediction tools. Moreover, rapid AF detection after ischemic stroke or TIA is crucial to optimize appropriate anticoagulation. Therefore, we aimed to build up a prediction score model based on noninvasive techniques to help prediction of paroxysmal AF after acute ischemic stroke, and then choosing the most appropriate thromboprotective therapy.

2. Materials and Methods

2.1. Aim of study

We aimed to build up a prediction score for paroxysmal AF among patients presented with the acute ischemic stroke to predict the paroxysmal AF on hospital admission.

2.2. Study design

This is a prospective case-controlled study of patients admitted to the Intensive Care Units, Shebein Elkom teaching Hospital, Egypt during the period from January 2019 to September 2020.

2.3. Patients

A sample size of 50 cases and 50 control would be sufficient to detect the difference in LAD and LAVI parameters between AF and non-AF groups with a power of 80% and type 1 error of 5%. Inclusion criteria of cases include intensive care units (ICU) admission with an acute ischemic stroke defined according to the World Health Organization criteria (as neurological deficit attributed to an acute focal injury of central nervous system (CNS) by a vascular cause) with a history (documented) of paroxysmal AF or who reported new onset AF after acute stroke. Inclusion criteria of control include the ICU admission with acute ischemic stroke with same definition as cases, but without AF history and no AF was reported within 48 hours from admission. Exclusion criteria: patients with the ICU length of stay < 48 hours (either due to death or transfer to other facility), Patients whose stroke is due to trauma or neoplasm, and patients below age of 18 years Old.

2.4. Recruitment and Investigations

Eligible patients were recruited to either cases or control group according to the inclusion criteria until fulfilling the required sample in each group. Both groups were subjected to the following: Full clinical assessment, brain imaging Computed tomography (CT) or Magnetic resonance imaging (MRI) (Images and reports), full laboratory work up, electrocardiography (ECG) baseline, ECG monitoring for 48 hours, and transthoracic Echocardiography (TTE). Full laboratory works up was done for all included patients, including CBC with emphasis on absolute number of both Neutrophils and Lymphocytes and calculating Neutrophil to Lymphocyte Ratio (N/L), serum electrolytes (Na+, K+, Ca++, Mg ++), Thyroid profile and BNP. Baseline Electrocardiography (ECG) was done for all included patients and calculating P-wave duration (ms), P-R interval (ms) QRS duration (ms), Corrected QT (ms) and p wave terminal force (P/v1) in lead V1 that is defined as amplitude area of the terminal phase of P wave (the negative component when P wave was biphasic) in lead V1 (P/v1= the product of the duration and amplitude of the terminal phase of P-wave in lead V1 (in mm × ms)).

Dynamic ECG monitoring for 48 hours was done for all included patients to detect short AF episodes recorded on ICU monitors. Transthoracic Echocardiography (TTE) was done (using Vivid S5 equipment with probe 3S) by parasternal ,apical ,and subcostal views through 2D ,M mode ,pulsed wave Doppler and continuous wave Doppler for all included patients and measuring the following parameters: Left Atrium Diameter (LAD (mm)), E-velocity, Left Ventricular Ejection Fraction (LV EF %), Pulmonary Artery Systolic pressure (PASP (mmhg)), Left Ventricular End Systolic Dimension (LT VESD (mm)), Left Ventricular End Diastolic Dimension (LT VEDD (mm)), Right Atrium Pressure (RAP (mmhg)) and Left Atrial Volume Index(LAVI (ml/m2)) that is was calculated using the biplane Area-Length method.

2.5. Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Continuous data comparisons between groups were performed using independent samples t-test after ensuring normality, while categorical data comparisons were conducted using Chi square (χ^2) test Fisher exact test, which appropriate. P-values less than 0.05 were considered a statistically significant. Multivariate analyses using discriminant analysis were conducted to build up prediction models of paroxysmal AF reported with acute stroke.

3. Results and discussion

3.1. Results

3.1.1. Patients

Fifty acute ischemic stroke patients were assigned to group 1 (control) and another 50 acute ischemic stroke patients were assigned to group 2 (cases). Among the cases, 33 patients had a documented history of paroxysmal AF and 17 patients didn't have a history of paroxysmal AF and but they developed AF within 48 hours from admission.

3.1.2. Baseline factors

The distributions of sex, smoking, dyslipidemia, HTN, DM, HF, VHD, CVS/TIA, vascular disease between patients with non-AF and with AF were not significant ($P > 0.05$). However, IHD was higher in the AF group compared to normal patients ($p < 0.05$). (Table 1).

3.1.3. Laboratory factors

Free T3 and BNP were higher in the cases group than in the control group. Additionally, neutrophils to lymphocytes ratio (N/L) was also higher among patients of AF group compared to that of the control group ($p < 0.05$). (Table 2).

3.1.4. Electrocardiography parameters

P-R interval (ms) and P/v1mm*ms values were higher among AF patients compared to non-AF patients as shown in table (3).

3.1.5. Echocardiography parameters

LAD (mm) and LAVI (ml/m2) values were higher among AF patients compared to non-AF patients as shown in table (4).

3.1.6. AF prediction model

We included 5 variables in the discriminant model, named "Prediction of AF in Acute Stroke PAAS", based on a structure matrix cutoff of 0.3 (Table 5 & figure 1). The canonical discriminant function has Eigen value of 0.894, canonical correlation of 0.687, and Wilk lambda of 0.528 ($p < 0.001$). The cross-validated grouped cases correctly classified is 79 % which is less than the accuracy rate obtained by chance which equals 62.5 %. (Sensitivity = 84% and specificity = 82%). (Table 5 and figure 1). Discriminant score = -5.427 + .112 (LAVI) + .681 (N/L) -0.198 (LAD) + 0.001 (BNP) + 8.849 (P/V1). Score above zero is considered AF patient, otherwise, they would be classified as non-AF based on centroids of non-AF and AF patients = -0.953 and 0.953 respectively.

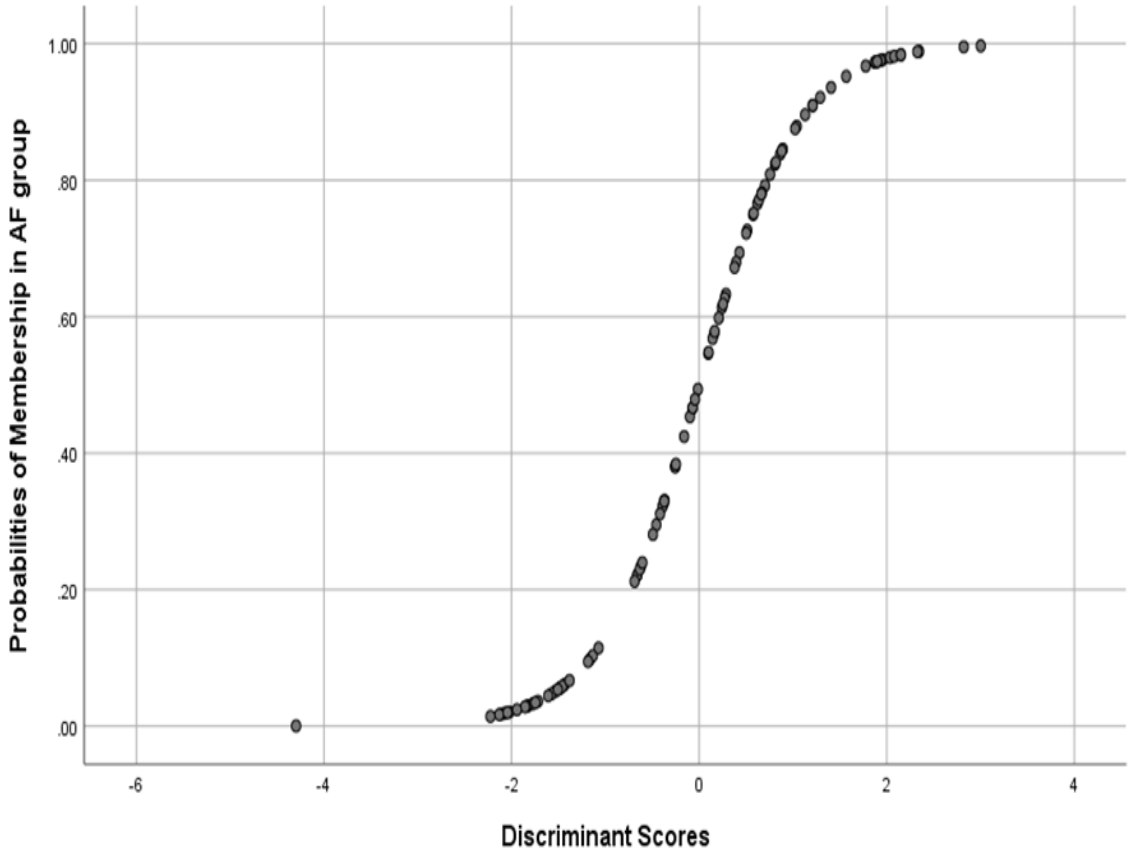

Figure 1: The relationship between discriminant scores and probability of atrial fibrillation among the study patients.

Table 1: Distribution of baseline and clinical risk factors among the study groups regarding AF status.

Variables		Non- AF		AF		P-value
		No.	%	No.	%	
Sex	Male	35	70.0	33	66.0	0.67
	Female	15	30.0	17	34.0	
Smoking	No	37	74.0	35	70.0	0.65
	Yes	13	26.0	15	30.0	
Dyslipidemia	No	27	54.0	25	50.0	0.69
	Yes	23	46.0	25	50.0	
HTN	No	21	42.0	22	44.0	0.84
	Yes	29	58.0	28	56.0	
DM	No	21	42.0	29	58.0	0.11
	Yes	29	58.0	21	42.0	
HF	No	44	88.0	44	88.0	1
	Yes	6	12.0	6	12.0	
VHD	No	36	72.0	35	70.0	0.95
	Yes	14	28.0	14	28.0	
IHD	No	36	72.0	27	54.0	0.04
	Yes	13	26.0	23	46.0	
CVS/TIA	No	24	48.0	21	42.0	0.55
	Yes	26	52.0	29	58.0	
Vascular	No	46	92.0	43	86.0	0.34
	Yes	4	8.0	7	14.0	

P-values were obtained from Chi-square test. *: Significant p-value at 0.05 level of significance

Table 2: Comparison between the study groups regarding age, laboratory factors, and other clinical factors

Variables	Non-AF		AF		P-value
	Mean	SD	Mean	SD	
Age	62.8a	13.2	60.64	13.032	0.41
BMI	29.36	4.6	29.8	4.7	0.62
CHA2DS2-VASC	4	(2 – 5)	4	(2 – 5)	0.83
HAVOC	3	(2 – 5.3)	3	(2 - 6)	0.82
Na	136.72	5.831	136.56	7.360	0.9
K	3.9596	.55704	3.7816	.43935	0.08
Ca++mmol/l	1.2676	.46996	1.1484	.13746	0.09
Mg (mg/dl)	1.9240	.25917	1.8944	.26941	0.58
TSH (mu/ml)	2.0126	1.21373	1.9326	1.41919	0.76
FT3 (pg/ml)	2.8994	.61269	3.2136	.69013	0.02*
FT4 (ng/dl)	1.5490	.44570	1.7610	.71542	0.08
BNP	107.24	108.377	228.82	225.350	0.001*
NEUTROPHILS	5928.0	1902.74	6090.00	1642.702	0.65
LYMPHOCYTES	2824.00	1216.479	2342.00	1762.082	0.12
N/L	2.33ab	.84593	3.1358	.95688	0.00*

The independent samples t-test was conducted for all variables except for CHA2DS2-VASC and HAVOC, where Mann-Whitney test was used. *: significant p-value at 0.05 level of significance

Table 3: Comparison between AF roups regarding ECG parameters

Variables	Non-AF		AF		P-value
	Mean	SD	Mean	SD	
P-wave duration (ms)	82.50	3.929	83.92	5.465	0.14
P-R interval (ms)	119.82	18.550	128.98	21.728	0.026
P/v1mm*ms	.04328	.046424	.06312	.014499	0.005
QRS duration (ms)	94.56	12.289	99.68	47.549	0.46
Corrected QT (ms)	424.44	64.289	420.40	30.280	0.69

The independent samples t-test was conducted for all variables except for CHA2DS2-VASC and HAVOC, where Mann-Whitney test was used. *: significant p-value at 0.05 level of significance.

Table 4: Comparison between AF groups regarding Echocardiography parameters

Variables	Non-AF		AF		P-value
	Mean	SD	Mean	SD	
LAD (mm)	3.44ab	.8428	4.200	.9012	0.00
E-velocity	1.1820	2.49122	.7976	.23804	0.28
LAVI (ml/m2)	27.61	8.8754	38.640	6.5831	0.00
LV EF %	56.12	12.223	55.12	13.017	0.69
PASP (mmhg)	29.350	10.7020	32.500	9.8130	0.13
LT VESD (mm)	36.06	6.082	35.72	6.263	0.78
LT VEDD (mm)	51.70	5.339	50.26	6.124	0.21
RAP (mmhg)	5.74	2.117	5.64	1.735	0.8

The independent samples t-test was conducted for all variables except for CHA2DS2-VASC and HAVOC, where Mann-Whitney test was used. *: significant p-value at 0.05 level of significance.

Table 5: Discriminant analysis model of atrial fibrillation prediction among the study patients

Predictors	Structure matrix	Coefficients	Wilks' Lambda	P value
LAVI	.740	.112	.663	<0.001*
N/L	.468	.681	.831	<0.001*
LAD	.456	-.198	.839	<0.001*
BNP	.361	.001	.892	0.001*
P/V1	.303	8.849	.922	0.005*
Constant		-5.427		

Coefficient: Canonical discriminant function coefficients.
We included 5 variables in the model based on a structure matrix cutoff of 0.3
The canonical discriminant function has Eigen value of 0.894, canonical correlation of 0.687, and Wilk lambda of 0.528 ($p < 0.001$).
The cross-validated grouped cases correctly classified is 79 % which is less than the accuracy rate obtained by chance which equals 62.5 %. (sensitivity = 84% and specificity = 82%)
Discriminant score = -5.427 + .112 (LAVI) + .681 (N/L) -0.198 (LAD) + 0.001 (BNP) + 8.849 (P/V1)
Score above zero is considered AF patient, otherwise, they would be classified as non-AF based on centroids of non-AF and AF patients = -0.953 and 0.953 respectively.

3.2. Discussion

We offered a comprehensive prediction model based on medical history, laboratory, electrocardiographic, and echocardiographic parameters to choose the most predictive factors to be integrated in one model to predict paroxysmal AF detected after acute stroke regardless the onset of the first attack because the diagnosis of paroxysmal AF is missed in many patients [7]. AF is being increasingly identified after transient ischemic attack and acute ischemic stroke and its diagnosed is so heterogeneous that no currently used medical terminology fits adequately [8]. Our prediction model is based on 5 independent variables; 2 echocardiography-based LAD and LAVI, one ECG-based P/v1mm*ms, and 2 laboratory-based BNP and N/L ratio and has sensitivity and specificity of 84 and 82%, respectively. Several scores have been developed to predict post stroke AF such as a simple score developed by Fujii et al which has 0-5 scores and composes of NIHSS, mitral valvular diseases, LAD, and BNP variables. The score had sensitivity of 78% and specificity of 83% for a cut-off value of 2 [9]. Another score named Acute Stroke AF Score (ASAS) is built on age, NIHSS, and left atrium enlargement [10]. The score had a sensitivity of 82% and specificity of 52% with a cut-off for a probability value of 0.09. Another score named iPAB Score is built on three variables: BNP, LAD, and history of arrhythmia or antiarrhythmic agent use.

It had values of 0 – 7 and for a total score 2 or more, the sensitivity and specificity were 93% and 71%, respectively [11]. It had area under the curve of 0.93 (0.88 – 0.98) which was higher than that of Fujii et al which was 0.81 (0.68 – 0.95) with p-value of 0.01 [9] and higher than that of STAF score which was 0.77 (0.66 – 0.88) with p-value of < 0.001 [12]. A Score for the Targeting Atrial Fibrillation (STAF) score was also developed to detect AF after ischemic stroke which includes 4 variables: age, NIHSS, LAD, and absence of symptomatic intra or extracranial stenosis ≥ 50%, or clinico-radiological lacunar syndrome. The possible total scores are 0 – 8. A sensitivity of 89% and a specificity of 88% for a cut-off value of ≥ 5 [12]. Our model does not include demographic or clinical factors such as age, sex,diabetes mellitus(DM), hypertension (HTN), heart failure (HF), valvular heart disease (VHD), ischemic heart disease IHD, dyslipidemia, smoking, vascular disease, HAVOC, CHA2DS2-VASC and baseline electrolyte levels because their low predictivity. Consistently, a study aimed to predict AF post stroke and did not find predictive values for DM, HTN, IHD, CHA2DS2-VASC compared to patients without AF [13]. On the contrary, a study reported significant association between post stroke AF and DM in the prediction of post stroke AF [9].

Another large study published by American Heart Association found an association between post stroke AF and higher age, female sex, HTN, DM, coronary artery disease, valve disease, dyslipidemia, vascular disease, COPD, renal dysfunction, hyperthyroidism, thyroid disease, HF, and CHA2DS2-VASC score [14]. The too large sample size might explain the difference with our findings. BNP was found a significant predictor of AF in the present study. Consistently, the iPAB Score identified BNP as significant predictive variable of post stroke AF in the logistic regression [11]. N/L ratio is another variable of our prediction model. In agreement with our findings, a meta-analysis built on 11 studies reported that the baseline high N/L ratio was associated with increased risk of new onset AF [15]. P-wave terminal force in Lead V1, defined as duration in milliseconds of the terminal part of the P wave multiplied by its depth in millimeters [16], was a significant predictor of AF in the present study. A study agreed with us that reported a significant association with AF in the prediction of AF among stroke patients [13]. LAD and LAVI are the other significant components of our model. In agreement with us, a study conducted on 215 found that patients who developed new-onset AF had significant higher LAD value [9]. Additionally, another study found a larger LAVI was associated with post stroke AF among 174 patients without AF history [17].

4. Conclusions

To early predict and manage paroxysmal AF among acute ischemic stroke patients, we recommend the AF prediction scale of present study (PAAS) based on baseline laboratory, echocardiographic, and electrocardiographic data including parameters.

5. List of abbreviations

AF	atrial fibrillation
BMI	body mass index
BNP	brain natriuretic peptide
CT	Computed tomography
DM	Diabetes mellitus
ECG	Electrocardiogram
HbA1c	hemoglobin A1c
HF	heart failure
HTN	hypertension
ICM	implantable cardiac monitors
ICU	intensive care units
IHD	Ischemic heart disease
LAD	left atrial diameter
LAVI	Left atrial Volume Index
MRI	Magnetic resonance imaging
PAF	paroxysmal atrial fibrillation
PTF	P wave terminal force
SD	standard deviation
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography
VHD	Valvular heart disease

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