



Manuscript ID ZUMJ-2403-3224 (R2)
DOI 10.21608/ZUMJ.2024.274151.3224

ORIGINAL ARTICLE

Prediction of Embolic Stroke in Non-Valvular Atrial Fibrillation Patients with Low CHADS-VASc Score

Moataz A.Elkot^{1*}, Elsayed M.Farag¹, Mostafa Mahmoud Mohamed Shams Eldeen², Hala Gouda Abomandour¹

¹ Cardiology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt

² Cardiovascular Department, Nasser institute for Research and Treatment, Cairo, Egypt

*** Corresponding author:**

Moataz A. Elkot, Cardiology

E-mail:

Mo3taz.elkot@gmail.com

Submit Date 2024-03-03

Revise Date 2024-03-17

Accept Date 2024-03-12



ABSTRACT

Background: Clinical research revealed that thromboembolic events are still a possibility for AF patients with low CHA2DS2-VASc scores.

Aim: To assess the ability of certain echocardiographic parameters and laboratory biomarkers to predict thromboembolic events in AF patients with low CHA2DS2-VASc score

Methods: This is a case-control study at the Cardiology Department, Zagazig University Hospitals and Nasser Institute for Research. and Treatment was conducted on 159 patients: group 1 included 53 nonvalvular AF patients having low CHA2DS2-VASc score with Acute Ischemic Stroke (AIS), group 2 included 53 non-valvular AF patients having low CHA2DS2-VASc score but without AIS and group 3 included 53 controls without AF or AIS. All groups were investigated by certain echocardiography parameters including left atrial emptying fraction (LAEF), left atrial volume index (LAVI) left atrial appendage flow velocity(LAA FV), mitral annular velocity (E') and E/e' ratio, also they were investigated by some laboratory markers including platelet count, red cell distribution width (RDW), platelet distribution width(PDW), creatinine level, D-dimer level, and troponin I.

Results: The Receiver Operating Characteristic (ROC) curve analysis showed that several echocardiographic parameters had significant predictive value for stroke, these parameters were LAVI, LAeF, E/e' ratios, and LAAFV. Also, the ROC curve analysis showed that PDW, D-dimer, and troponin had significant predictive value. A novel stroke risk scoring model was developed

Conclusions: The novel stroke risk score model may enhance the prediction of LAA thrombus in non-valvular AF patients with low CHADS-VASc score (0 in males, 1 in females)

Keywords: Left atrial appendage; Thrombus; Novel risk score; Acute ischemic stroke

INTRODUCTION

In clinical practice, atrial fibrillation (AF) is the most common heart arrhythmia. According to reports, AF accounts for roughly 15–20% of all stroke cases.. Consequently, the primary tenet of AF management is AIS prevention [1]. Oral anticoagulants help people with AF achieve better results and effectively prevent IS. To optimize the advantages of anticoagulant medications, stroke risk assessment is the first and most important step to take before starting anticoagulation [2]. The most authoritative

guidelines currently in use in clinical practice advise using the CHA2DS2-VASc score as the main tool for classifying patients with non-valvular AF (NVAf). Since the CHA2DS2-VASc score is based on clinical risk factors, its main advantages are its perspicuity and ease of use. Nevertheless, it also has some disadvantages, including a restricted capacity to predict the occurrence of stroke events and substantially varying stroke rates of non-anticoagulated AF patients in various groups [3]. Previous research has shown that the CHADS2-

VASc score has a limited predictive value for identifying the existence of LAAT.

Transesophageal echocardiography (TEE) is considered the gold standard for detecting left atrial appendage thrombus (LAAT). However, in some circumstances, the study's implementation was limited. The search for echocardiographic parameters that predict the risk of LAAT has been the subject of numerous studies thus far. [4]. Additionally, numerous research has looked at biomarkers that are differentially expressed in NVAF patients with and without IS. These biomarkers have also been summarized in a few earlier articles [5].

Our study aims to assess the ability of certain echocardiographic parameters and biomarkers to enhance the predictability of thromboembolic events and to provide guidance for anticoagulation therapy in non-valvular AF patients with low CHA2DS2-VASc score (0 in male, 1 in female)

METHODS

In our case-control study, our patients were divided into 3 groups, group 1 included 53 patients with nonvalvular AF and low CHA2DS2-VASc score (0 in male, 1 in female) who were admitted to Zagazig university hospital or Nasser Institute for Research and treatment with acute ischemic stroke (AIS), group 2 included 53 patients with nonvalvular AF patients and low CHA2DS2-VASc score (0 in male, 1 in female) but with no AIS and the control group with 53 control subjects. Patients with incomplete data, mitral valve stenosis, prosthetic valve, post mitral valve surgical or percutaneous intervention, and stroke due to non-embolic causes such as complex aortic plaque, significant carotid stenosis, or intracranial arterial stenosis were excluded from the current study.

Informed Consent and Ethics Committee/IRB Approval

The study was approved by the research ethics council of the faculty of medicine at Zagazig University under "ZU-IRB #9088" and all participants supplied written informed permission. This study adhered to the Declaration of Helsinki, a guideline of ethics for medical research involving human subjects.

All patients were subjected to full history taking with special emphasis on demographic criteria including age, sex, hypertension, diabetes, dyslipidemia, smoking status, family history of cerebrovascular disease, previous hospital or ICU admission, and detailed medical and cardiac history. Then the

calculation of the CHA2DS2-VASc score for all participants was done [6].

Comprehensive general and local examination, with particular focus on baseline vital signs, heart rate, blood pressure, and body mass index (BMI; weight [kg]/height squared [m²]).

Twelve lead surface ECG confirming atrial fibrillation was done on admission. All patients were examined by trans-thoracic echocardiography using a 1.5-3.6 MHz phased array probe with Philips affiniti 50 W echocardiography machine, under the supervision of experienced cardiologists. Echocardiographic parameters were assessed in agreement with the American Society of Echocardiography's guidelines [7].

The following echocardiographic and laboratory parameters were assessed as predictors for thromboembolic stroke: i) Left atrial emptying fraction (LAEF), LA emptying fraction was calculated as $(LAV_{Imax} - LAV_{Imin}) / LAV_{Imax} \times 100$. LAEF is considered impaired if the value less than 35% [8]. ii) Left atrial volume index (LAVI) measurement utilizing the uniplane Simpson's method at the end of the systole in the apical four-chamber view, then dividing the volume by body surface area [9]. iii) Left atrial appendage flow velocity, in the study of Carranza et al, there was no difference in the LAA FV determination by TTE and TEE in the subgroup with AF [10], so Pulsed Doppler was used to measure the velocity of left atrial appendage in apical two-chamber view. iv) Mitral annular velocity (E') by tissue Doppler and E/e' ratio. v) laboratory biomarkers were collected from all patients including platelet count, platelet distribution width (PDW), red cell distribution width (RDW), creatinine level, D-dimer level, and troponin I level, analyzed as markers of platelet reactivity, general patient performance, renal function, thromboembolism, and myocyte injury, respectively [11].

STATISTICAL ANALYSIS

SPSS 20 (Statistical Package for the Social Services) was used to analyze the data. Two formats were used to present the results: tabular and graphical. The results were presented using common statistical metrics including means, medians, standard confidence intervals, and standard deviations. Statistics were utilized to illustrate the data's accuracy. When assessing data involving quantitative independent variables, the student's t-test (T) is utilized. Pearson Chi-Square test was used to analyze the qualitative data (X²). The receiver-

operating characteristics (ROC) curve was performed to assess the cut-off point of PA-TDI duration. A p-value of 0.05 or less was judged statistically significant.

RESULTS

Demographic data and risk factors of the studied group are presented in Table 1. The Echocardiographic data of the studied groups (Table 2) showed that the LAVI value was highest in the AF with AIS group, in comparison to the AF group or control group with $p < 0.001$. LAeF presented a notable decrease in the AF with the AIS group in comparison to the AF group or the control group with $p < 0.001$. The E/e' ratio showed a significant increase in both medial and lateral measurements in AF with AIS in comparison to the AF group and the control group. Lastly, the LAAFV significantly decreased in the AF with the AIS group in comparison to the AF group or the control group with a $p < 0.001$.

Laboratory data of the studied groups (Table 3) showed that PDW levels exhibited a significant increase in the AF with the AIS group, compared to the AF groups or the Control group with a $p < 0.001$. D-Dimer levels also showed a significant upward trend, especially notable in the AF with AIS group compared to the AF group or Control group with a $p < 0.001$. Troponin I and serum creatinine were significantly higher in the AF with AIS group than the AF group and control group. (ROC) curve analysis showed that left atrial volume index (LAVI), left atrial emptying fraction (LAeF), E/e' ratios and left atrial appendage flow velocity (LAAFV) had significant predictive value for stroke, with area under the curve (AUC) values of 0.864 ($P < 0.001$), 0.752 ($P < 0.001$), 0.67 ($P < 0.05$), and 0.807 ($P < 0.001$) respectively. At the identified optimal cut-off points, LAVI ≥ 32.25 mL/m² had a

sensitivity of 90.6% and specificity of 60.4%; LAeF ≤ 26.75 % had a sensitivity of 86.8% and specificity of 50.9%; E/e' ratios ≥ 10.05 had a sensitivity of 73.6% and specificity of 50.9%, and LAAFV less than ≤ 39.95 cm/s had a sensitivity of 79.2% and specificity of 81.1% for predicting stroke (Table 4 and figure 1).

(ROC) curve analysis showed that platelet distribution width (PDW), D-dimer, and troponin had significant predictive value for stroke, with area under the curve (AUC) values of 0.782 ($P < 0.001$), 0.804 ($P < 0.001$), and 0.648 ($P = 0.008$), respectively. At the identified optimal cut-off points, PDW ≥ 14.1 had a sensitivity of 79.2% and specificity of 64.2%; D-dimer ≥ 0.33 had a sensitivity of 81.1% and specificity of 66.0%; and troponin ≥ 0.150 had a high sensitivity of 88.7% but low specificity of 37.7% for predicting stroke (Table 5 and figure 2). The univariate binary logistic regression analysis identified several risk factors that were significantly associated with stroke prediction including advanced age, family history, high BMI, high PDW, elevated D-dimer, elevated troponin, increased LAVI, reduced LAeF, high E/e' ratios, decreased LAAFV. (Table 6).

We developed a novel score model to predict LAAT and risk of ischemic stroke in nonvalvular AF patients with low CHADS-VASc scores consisting of PDW, D.dimer, Troponin, E/e' ratios, LAVI, LAeF, and LAAFV. The maximum possible score in this stroke risk scoring system is 18 and we categorized the total scores into three risk categories: Low Risk with a Total score up to 6, Moderate Risk with a Total score between 6 and 12, and High Risk with a total score above 12 (table7). The ROC curve of this score indicates an excellent predictive accuracy for the stroke risk scoring system, with an AUC of 0.991 and a statistically significant P value of less than 0.001 (Figure 3).

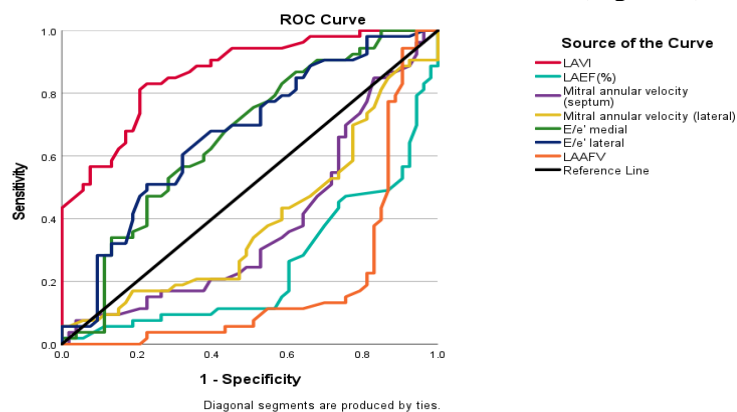


Figure (1): ROC curves of echocardiographic parameters for the prediction of stroke

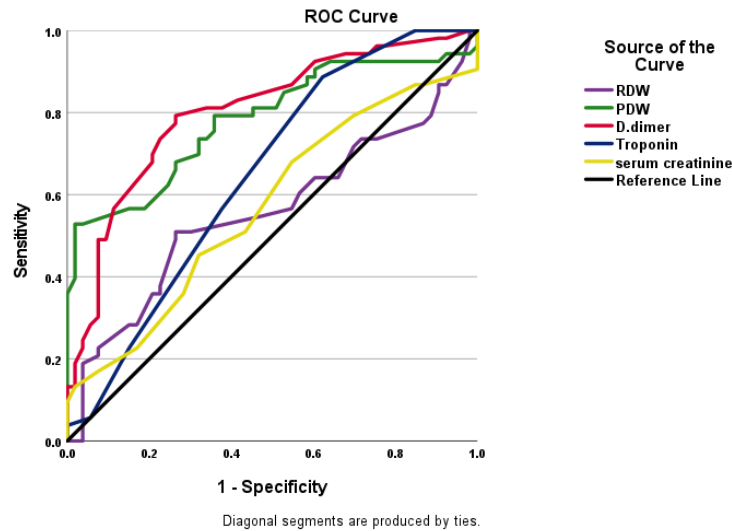


Figure (2): ROC curves of laboratory parameters for the prediction of stroke

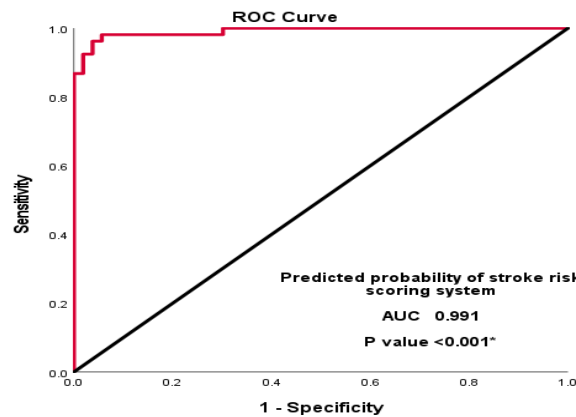


Figure (3): Roc curve of the developed score model

Table 1: Demographic and clinical characteristics of the studied groups.

Variables		Groups						p-value
		Control (n = 53)		AF (n = 53)		AF with AIS (n = 53)		
Demographic								
Age (years)		41.53 ± 12.16 38.00 (31.00 - 53.00)		41.60 ± 8.70 41.00 (35.00 - 46.00)		53.49 ± 7.90 52.00 (47.00 - 61.00)		<0.001* A-B:0.656 A-C:<0.001* B-C: <0.001*
BMI		26.81 ± 3.26 27.00 (24.00 - 29.00)		26.68 ± 2.80 26.00 (25.00 - 28.00)		29.13 ± 2.29 29.00 (28.00 - 30.00)		<0.001* A-B:0.689 A-C:<0.001* B-C: <0.001*
Sex	Male	43	81.1%	41	77.4%	45	84.9%	0.611
	Female	10	18.9%	12	22.6%	8	15.1%	
Co-morbidity								
Smoker		17	32.1%	28	52.8%	32	60.4%	0.010* A-B: 0.031*

							A-C: 0.006* B-C: 0.433
HTN	0	0.0%	0	0.0%	0	0.0%	
DM	0	0.0%	0	0.0%	0	0.0%	
Dyslipidemia	22	41.5%	36	67.9%	38	71.7%	0.002* A-B: 0.006* A-C: 0.082 B-C: 0.833
Family history	5	9.4%	32	60.4%	43	81.1%	<0.001* A-B: <0.001* A-C:<0.001* B-C: 0.019*

Data represent as Mean ± SD, Median (IQR) or number (percentage).

A-B: Comparison between Control and AF groups

A-C: Comparison between Control and AF with AIS groups

B-C: Comparison between AF and AF with AIS groups

p: p value for comparing between the two studied groups. *: Statistically significant at p ≤ 0.05

Table (2): Echocardiographic data in the studied groups.

Variables	Groups			p-value
	Control (n = 53)	AF (n = 53)	AF with AIS (n = 53)	
Demographic				
LAVI	21.04 ± 5.10 20.80 (16.60 - 24.90)	31.06 ± 6.84 30.60 (27.00 - 35.30)	43.43 ± 8.72 43.20 (37.60 - 49.60)	<0.001* A-B:<0.001* A-C:<0.001* B-C:<0.001*
LAEF (%)	40.77 ± 5.65 41.00 (39.00 - 45.00)	32.86 ± 6.35 32.50 (27.50 - 38.00)	26.53 ± 6.99 26.50 (23.00 - 29.60)	<0.001* A-B:<0.001* A-C:<0.001* B-C:<0.001*
Mitral annular velocity (septum)	8.40 ± 3.02 8.00 (6.70 - 9.60)	8.88 ± 2.28 9.00 (7.10 - 10.40)	8.15 ± 2.15 7.60 (6.60 - 8.60)	0.109 A-B: 0.134 A-C:0.677 B-C: 0.004*
Mitral annular velocity (lateral)	9.97 ± 3.28 9.60 (8.20 - 11.70)	10.98 ± 2.21 10.60 (9.40 - 12.90)	10.23 ± 2.53 9.60 (8.60 - 11.40)	0.060 A-B: 0.033* A-C:0.578 B-C:0.056
E/e' medial	9.18 ± 2.91 8.70 (7.50 - 10.40)	10.40 ± 3.48 10.00 (8.50 - 11.40)	11.89 ± 2.99 10.90 (10.00 - 14.00)	<0.001* A-B: 0.029* A-C:<0.001* B-C: 0.004*
E/e' lateral	7.70 ± 2.54 7.10 (6.00 - 8.80)	8.14 ± 2.29 8.10 (6.40 - 9.01)	9.42 ± 2.29 9.10 (7.90 - 10.80)	<0.001* A-B:0.147 A-C:<0.001* B-C: 0.003*
LAAFV	48.38 ± 6.87 47.50 (43.30 - 52.00)	44.29 ± 8.48 44.80 (40.60 - 48.00)	36.07 ± 4.99 35.50 (33.00 - 38.80)	<0.001* A-B: 0.031* A-C:<0.001* B-C:<0.001*

A-B: Comparison between Control and AF groups

A-C: Comparison between Control and AF + STROKE groups

B-C: Comparison between AF and AF + STROKE groups

p: p value for comparing between the two studied groups. *: Statistically significant at $p \leq 0.05$

Table (3): Laboratory data in the studied groups

Variables	Groups			p-value
	Control (n = 53)	AF (n = 53)	AF with AIS (n = 53)	
Demographic				
RDW	12.61 ± .87 12.60 (11.90 - 13.40)	12.91 ± 1.02 12.90 (12.20 - 13.40)	13.12 ± 1.14 13.30 (12.00 - 14.00)	0.069
PDW	13.04 ± 1.37 13.00 (12.00 - 14.10)	13.44 ± 1.93 13.50 (11.60 - 15.40)	15.85 ± 2.47 16.50 (14.40 - 17.60)	<0.001* A-B:0.393 A-C:<0.001* B-C: 0.001*
D. Dimer	.28 ± .12 .30 (.20 - .38)	.31 ± .10 .30 (.22 - .36)	.45 ± .15 .42 (.36 - .53)	<0.001* A-B:0.271 A-C:<0.001* B-C:<0.001*
Troponin	.02 ± .03 .02 (.02 - .02)	.02 ± .01 .02 (.01 - .03)	.03 ± .01 .03 (.02 - .03)	0.021* A-B:0.235 A-C:0.960 B-C: 0.007*
Serum creatinine	.81 ± .33 .70 (.60 - 1.00)	.94 ± .26 .90 (.70 - 1.20)	1.03 ± .34 1.00 (.80 - 1.20)	0.002* A-B: 0.015* A-C:<0.001* B-C:0.215

A-B: Comparison between Control and AF groups

A-C: Comparison between Control and AF + STROKE groups

B-C: Comparison between AF and AF + STROKE groups

p: p value for comparing between the two studied groups. *: Statistically significant at $p \leq 0.05$

Table (4): ROC curves of Echocardiography parameters for the prediction of stroke

Test Result Variable(s)	AUC	P value	Asymptotic 95% Confidence Interval		Cut off point	Sensitivity	Specificity
			Lower Bound	Upper Bound			
LAVI	0.864	<0.001*	0.797	0.932	≥ 32.25	90.6%	60.4%
LAEF (%)	0.752	<0.001*	0.659	0.845	≤ 26.75	86.8%	50.9%
Mitral annular velocity (septum)	0.616	0.040*	0.506	0.725	≤ 7.77	67.9%	52.8%
Mitral annular velocity (lateral)	0.608	0.045*	0.499	0.716	≤ 9.70	66.0%	52.4%
E/e' medial	0.661	0.004*	0.556	0.765	≥ 10.05	73.6%	50.9%
E/e' lateral	0.670	0.003*	0.567	0.773	≥ 8.50	67.9%	60.4%
LAAFV	0.807	<0.001*	0.716	0.899	≤ 39.95	79.2%	81.1%

Table (5): ROC curves of Laboratory parameters for the prediction of stroke

Test Result Variable(s)	AUC	P value	Asymptotic 95% Confidence Interval		Cut off point	sensitivity	specificity
			Lower Bound	Upper Bound			
RDW	0.559	0.296	0.447	0.671			
PDW	0.782	<0.001*	0.693	0.872	≥14.1	79.2%	64.2%
D.dimer	0.804	<0.001*	0.719	0.888	≥0.33	81.1%	66.0%
Troponin	0.648	0.008*	0.543	0.754	≥0.150	88.7%	37.7%
serum creatinine	0.569	0.218	0.460	0.679			

Table (6): Univariate binary logistic regression analysis of the studied groups' data to predict stroke.

Test Result Variable(s)	Odds ratio	Asymptotic 95% Confidence Interval		P value
		Lower Bound	Upper Bound	
Age (years)	1.176	1.104	1.253	<0.001*
Gender (male)	1.646	0.612	4.429	0.323
Smoker	1.735	0.940	1.988	0.434
Dyslipidemia	1.836	0.364	1.918	0.672
Family history	2.822	1.169	6.811	0.002*
BMI (Kg/m2)	1.461	1.218	1.752	<0.001*
RDW	1.201	.838	1.720	0.318
PDW	1.585	1.298	1.936	<0.001*
D. Dimer	7.095	2.930	17.179	<0.001*
Troponin	4.245	1.866	9.658	<0.001*
serum creatinine	2.562	0.717	9.154	0.148
LAVI	1.236	1.139	1.342	<0.001*
LAEF (%)	0.865	0.806	0.928	<0.001*
Mitral annular velocity (septum)	0.860	0.720	1.027	0.069
Mitral annular velocity (lateral)	0.872	0.739	1.030	0.107
E/e' medial	1.159	1.020	1.317	0.024*
E/e' lateral	1.286	1.069	1.546	0.008*
LAAFV	0.840	0.779	0.904	<0.001*

Table (7): Stroke risk scoring model based on the significant variables

Variable	Odds Ratio	Score
PDW ≥14.1	1.585	2
D. Dimer ≥0.33	7.095	7
Troponin ≥0.150	4.245	4
LAVI ≥32.25	1.236	1
LAEF (%) ≤26.75	0.865	1
E/e' medial ≥10.05	1.159	1
E/e' lateral ≥8.50	1.286	1
LAAFV ≤39.95	0.840	1
Total	18	

The maximum possible score in this stroke risk scoring system is 18. Based on this, we can categorize the total scores into three risk categories:

Low Risk: Total score up to 6 (approximately one-third of the maximum score)

Moderate Risk: Total score between 6 and 12 (approximately between one-third and two-thirds of the maximum score)

High Risk: Total score above 12 (more than two-thirds of the maximum score)

DISCUSSION

The most authoritative guidelines currently in use in clinical practice advise using the CHA2DS2-VASc score as the main tool for classifying patients with non-valvular AF (NVAf). Since the CHA2DS2-VASc score is based on clinical risk factors, its main advantages are its perspicuity and ease of use. Nevertheless, it also has some disadvantages, including a restricted capacity to predict the occurrence of stroke events and substantially varying stroke rates of non-anticoagulated AF patients in various groups [3]. We aimed in our study to assess whether certain echocardiographic and laboratory parameters could predict the presence of LAAT in non-valvular AF patients with low CHA2DS2-VASc scores (0 in male, 1 in female) or not, and thus prevent unpredicted thromboembolic events in those non-anticoagulated populations. In our study by using the univariate binary logistic regression analysis, we identified several echocardiographic and laboratory parameters that were significantly associated with stroke prediction. Accordingly, we developed a novel risk-scoring model using these predictors, this score could risk stratify patients with low CHADS-VASc (0 in male, 1 in female) into low, moderate, or high risk for left atrial appendage thrombus and thromboembolic stroke with an AUC of 0.991 and a statistically significant P value of less than 0.001.

Echocardiographic parameters: In our study, LAVI value was highest in the AF with AIS group (43.43 mL/m² ± 8.72) in comparison to the AF group and control group, LAVI ≥ 32.25 mL/m² had a sensitivity of 90.6% and specificity of 60.4% to predict LAAT in our population with P value < 0.001. This was in line with the Segan et al study, they found cut off point of LAVI more than (34 mL/m²) was associated with LAAT in consecutive patients with atrial fibrillation (AF)/atrial flutter undergoing transesophageal echocardiography before cardioversion [12]. A higher cut-off value of LAVI (40 mL/m²) was revealed in Kim et al study as a predictor for spontaneous echo contrast (SEC) and thrombus in a prospective follow-up, this may be related to the difference in the selection of the study population as he included patients with high CHADS-VASc score in his study [13].

In our study, LAeF presented a notable decrease in the AF with the AIS group (26.53% ± 6.99), in comparison to the AF group and control group, LAeF ≤ 26.75% had a sensitivity of 86.8% and specificity of 50.9% predict LAAT in our population with P

value < 0.001. This was in line with Kim et al study who found that the cut-off value of LAeF less than 30% was a predictor for SEC and thrombus in a prospective follow-up and had a sensitivity of 92% and specificity of 81% with P value < 0.001 [13].

Of course, standard assessment of LAAfV is done by TEE but in the study of Carranza et al there was no difference in the LAAfV determination by TTE and TEE in the subgroup with AF and TTE was able to detect flow velocity < 30 cm/sec [10]. Accordingly, we assess LAAfV in our population by TTE. Our study revealed that LAAfV by TTE significantly decreased in the AF with AIS group (36.07 cm/s ± 4.99) in comparison to the AF group and control group, and LAAfV less than ≤ 39.95 cm/s had a sensitivity of 79.2% and specificity of 81.1% for predicting stroke with P value < 0.001. Lesser values were obtained in the study of Zabalgoitia et al, he found that one of the TEE features independently associated with increased thromboembolic risk was left atrial appendage peak flow velocities ≤ 20 cm/s (p = 0.008). This difference in LAAfV values may be related to his population selection as they had larger LA dimensions which may be associated with more impairment of LAAfV [14].

In our study, The E/e' ratio, indicative of diastolic function, showed a significant increase in both medial and lateral measurements in the AF group with AIS in comparison AF group and control group, cut off value of medial E/e' ≥ 10.05 had a sensitivity of 73.6% and specificity of 50.9% for predicting stroke with P value < 0.05. This is in agreement with the Yang et al study which aimed to examine the prognostic value of echocardiographic predictors against CHA2DS2-VASc score in permanent nonvalvular AF (NVAf), demonstrated that for the prediction of ischemic stroke, the addition of E/e ratio to CHA2DS2-VASc score provides extra prognostic value besides that it offers incremental value over CHA2DS2-VASc score for prediction of future cardiac events [15].

Laboratory parameters: The prevalence of LAA thrombi is linked to rising levels of cardiac strain markers and inflammatory parameters, as well as abnormal platelet function, diminishing renal function, and abnormal coagulation cascade, all of which indicate a dynamic process of organ function deterioration. So, we examined certain laboratory markers for the prediction of LAAT. In our study, (ROC) curve analysis of our laboratory

markers showed that platelet distribution width (PDW), D-dimer, and troponin had significant predictive value for stroke, with area under the curve (AUC) values of 0.782 ($P<0.001$), 0.804 ($P<0.001$), and 0.648 ($P=0.008$), respectively. At the identified optimal cut-off points, $PDW \geq 14.1$ had a sensitivity of 79.2% and specificity of 64.2%; $D\text{-dimer} \geq 0.33$ had a sensitivity of 81.1% and specificity of 66.0%; and $troponin \geq 0.150$ had a high sensitivity of 88.7% but low specificity of 37.7% for predicting stroke (Table 5 and figure 2). In concordance with our results was the Yang et al study, which aimed to predict ischemic stroke in non-valvular atrial fibrillation by using a routine blood test, he found that the risk of ischemic stroke was higher in patients with $PDW \geq 13.2\%$ [16]. In the study of Bedier et al, the ROC analysis revealed the accuracy of D-dimer to predict the presence of LA thrombus (AUC = 0.711), corresponds to a Sensitivity of 50 % and a Specificity of 90.6% for the prediction of LA thrombus [17]. In line with our study was Tanaka et al study which aimed to find the relation between patients with abnormal LAA by TEE and cardiac Troponin I (cTnI), he found that elevated cTnI was associated with LA abnormality and subsequent ischemic stroke in patients with NVAf [18].

Our novel score model could enhance LAAT risk prediction and help to identify patients with CHA₂DS₂-VASc score (0 in male, 1 in female) who are at higher risk for thromboembolic stroke, and thus we could recommend that these patients to be on oral anticoagulation, and even if they had normal TEE before they could be still at risk, our score had an excellent predictive accuracy for the stroke prediction with an AUC of 0.991 and a statistically significant P-value of less than 0.001. Different scoring models were investigated as an alternative to the CHADS-Vasc score e.g. Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) score, other scoring models tried to add new parameters to increase the predictive value of the CHADS-VASc score as mentioned in Yang et al study [15]. However, only a few limited studies selected populations with low CHADS-VASc scores who were the scope of our study. In a study by Shin et al, they concluded that a new score model including both echocardiographic and laboratory markers could help to refine stroke risk differentiation among AF patients who were initially defined as low risk [19].

CONCLUSIONS

The novel stroke risk score model may enhance the prediction of LAA thrombus in non-valvular AF

patients with low CHADS-VASc score (0 in male, 1 in female) with an AUC of 0.991 and a statistically significant P-value of less than 0.001. The score could risk stratifying these patients into low, moderate, or high risk for left atrial appendage thrombus and thromboembolic stroke.

REFERENCES

- 1- Pistoia F, Sacco S, Tiseo C, Degan D, Ornello R and Carolei A. The epidemiology of atrial fibrillation and stroke. *Cardiol Clin* 2016; 34:255–68. doi:10.1016/j.ccl.2015.12.002.
- 2- López-López JA, Sterne JAC, Thom HHZ, Higgins J P T, Hingorani A D, Okoli G N, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost-effectiveness analysis. *BMJ* 2017; 359:j5058. doi:10.1136/bmj.j5058.
- 3- Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. *Thromb Haemost* 2018; 118:2171–87. doi:10.1055/s-0038-1675400Jaakkola,
- 4- Willens HJ, Gómez Marín O, Nelson K, DeNicco A, Moscucci M. Correlation of CHADS₂ and CHA₂DS₂-VASc scores with transesophageal echocardiography risk factors for thromboembolism in a multiethnic United States population with nonvalvular atrial fibrillation. *J Am Soc Echo cardiogr.* 2013; 26:175–84. doi:10.1016/j.echo.2012.11.002CrossrefMedlineGoogle Scholar.
- 5- Ellis K, Ziada KM, Vivekananthan D, Latif AA, Shaaraoui M, Martin D, et al. Transthoracic echocardiographic predictors of left atrial appendage thrombus. *Am J Cardiol* 2006; 97:421–5. doi:10.1016/j.amjcard.2005.08.065
- 6- Kim TH, Yang PS, Uhm JS, Kim JY, Pak HN, Lee MH, et al. CHA₂DS₂-VASc Score (Congestive Heart Failure, Hypertension, Age ≥ 75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65-74, Female) for Stroke in Asian Patients With Atrial Fibrillation: A Korean Nationwide Sample Cohort Study. *Stroke.* 2017;48(6):1524-30. doi:10.1161/STROKEAHA.117.016926. Epub 2017 Apr 28. PMID: 28455320.
- 7- Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the

- European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39.e14.
- 8- Blume GG, Mcleod CJ, Barnes ME, Seward JB, Pellikka PA, Bastiansen PM, et al. Left atrial function: physiology, assessment, and clinical implications. *Eur J Echocardiogr* 2011;12:421-30.
 - 9- Barnes ME, Miyasaka Y, Seward JB, Gersh BJ, Rosales AG, Bailey KR, et al.. Left atrial volume in the prediction of first ischemic stroke in an elderly cohort without atrial fibrillation. *Mayo Clin Proc.* 2004; 79:1008–14. doi: 10.4065/79.8.1008.
 - 10- Carranza C, Abufhele A, Cartes F and Forero A. Transthoracic Versus Transesophageal Two-Dimensional Echo Doppler Determination of Flow Velocity in the Left Atrial Appendage. *Echocardiography.* 1997 Jul;14(4):357-362. doi: 10.1111/j.1540-8175.1997.tb00735.x. PMID: 11174967.
 - 11- Hijazi, Z., Oldgren, J., Siegbahn, A. and Wallentin, L. Application of biomarkers for risk stratification in patients with atrial fibrillation. *Clin Chem* 2017; 63(1), 152-64.
 - 12- Segan L., Nanayakkara S., Spear E., Shirwaiker A , Cheing D , Prabhu S et al. Identifying Patients at High Risk of Left Atrial Appendage Thrombus Before Cardioversion: The CLOTS-AF Score. *Am Heart J Assoc* 2023; e029259.
 - 13- Kim MN , Kim SA , Choi J, Park SM , Park SW and Kim YH. Improvement of Predictive Value for Thromboembolic Risk by Incorporating Left Atrial Functional Parameters in the CHADS2 and CHA2DS2-VASc Scores. *Int Heart J Assoc* 2015.
 - 14- Zabalgaitia M, Halperin J., Pearce L.A, Blackshear J.L, Asinger R.W. and Hart R.G. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke prevention in atrial fibrillation III investigators. *J. Am. Coll. Cardiol* 1998;11:1622–26.
 - 15- Yang T, Tsai W C and Su H. M. Echocardiographic parameters versus CHA2DS2-VASc score in prediction of overall cardiac events, heart failure, and stroke in non-valvular atrial fibrillation. *Cardiol J* 2018; 25(1): 60-71.
 - 16- Yang S, Cha M. J, Kwak S, Kwon S , Lee S , Park J et al. Prognostic value of routine blood tests along with clinical risk factors in predicting ischemic stroke in non-valvular atrial fibrillation: a prospective cohort study. *Int J arrhythm* 2020.
 - 17- Bedier A, Sally T, and elshal A. "The Value of D-Dimer Blood Concentrations in Prediction of Presence of Left Atrial Thrombus in Patients with non-valvular Atrial Fibrillation," *Mansoura Med J* 2022; 51: (3) Article 3.
 - 18- Tanaka S ,Hirai T , Inao K , Fukuda N, Nakagawa K, Inoue H, et al. High Cardiac Troponin I Is Associated With Transesophageal Echocardiographic Risk of Thromboembolism and Ischemic Stroke Events in Non-Valvular Atrial Fibrillation Patients . *Circ J* 2018; 82: 1699–1704 doi:10.1253/circj.CJ-17-1238.
 - 19- Shin SY, Han SJ, Kim JS, Im SI, Shim J, Ahn J, et al.. Identification of Markers Associated With Development of Stroke in "Clinically Low-Risk" Atrial Fibrillation Patients. *J Am Heart Assoc* 2019; 8 :(21):e012697.

To Cite:

Elkot, M., Farag, E., Shams Eldeen, M., Abomandour, H. Prediction Of Thromboembolic Stroke in Non-Valvular Atrial Fibrillation Patients With Low CHA2DS2-VASc Score. *Zagazig University Medical Journal*, 2024; (139-148): -. doi: 10.21608/zumj.2024.274151.3224