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Value of Serum Galectin-3 Levels as A Predictor of Thromboembolism in Nonvalvular AF

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ABSTRACT

Background: Galactin is involved in process of cardiac fibrosis. It is not clear if there is an association between serum galactin level and thromboembolism events in atrial fibrillation (AF).

Objective: To investigate whether serum galactin levels can be used as a predictor for thromboembolism in patients with non-valvular AF or not.

Patients and Methods: We conducted a case-control study on 200 participants (100 individuals as a control, 50 patients with AF and thromboembolism and 50 patients with AF but without thromboembolism). We recruited patients from Cardiology Department, Aswan University Hospital who had non valvular AF. Participants were subjected to detailed medical history, clinical examination, electrocardiography, and ELISA test to evaluate serum galactin level. **Results:** Serum galactin was only predictor for thromboembolic event (OR=2.4, 95% CI = {1.3: 4.3}, P value=0.005) with a sensitivity of 73% and specificity of 65% for the thrombus detection (AUC= 0.80, 95%CI= {0.69-0.89}). Serum galactin has a sensitivity of 81% and specificity of 77% to detect AF incidence (AUC= 0.84, 95%CI= {0.73-0.99}). Serum galactin was correlated to CHADS-VASc score (r= 0.75, p value < 0.001) and LVEF (r= - 0.586, p value <0.001).

Conclusion: Galactin-3 level is a possible predictor for thromboembolism in patients with non-valvular AF. Nevertheless, further studies are still needed to confirm our findings.

Keywords: Non-valvular AF, Thromboembolism, Galactin-3.

INTRODUCTION

Despite good progress in the management of patients with atrial fibrillation (AF), this arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. Furthermore, the number of patients with AF is predicted to rise steeply in the coming years [(1)].

Traditionally, patients with AF have been dichotomized into valvular and non-valvular AF. Although slightly different definitions have been used, valvular AF generally refers to AF patients with moderate to severe mitral stenosis or prosthetic heart valves (and valve repair in North American guidelines) [(2)].

In AF patients, reduced LAA flow velocity (LAAFV) and the presence of spontaneous echo contrast (SEC), an echogenic swirling pattern of blood flow, which indicates a low-flow state in the left atrium (LA). These have been shown to be markers of thromboembolic risk [(3)]**.** Studies have suggested a possible association between inflammation, AF, and thrombosis. Levels of inflammatory makers, such as C-reactive protein (CRP) have been found to be related to LA/LAA-located SEC and thrombus observed on trans-esophageal echocardiography (TEE) [(4, 5)]**.**

Galectin-3 is α-galactoside-binding lectin that has been shown to mediate cell-to- cell and cell-to-extracellular matrix interactions and act as a novel chemo-attractant for monocytes and macrophages [(6)]. Studies have supported an association between serum galectin-3 levels and atrial fibrosis demonstrated with delayed-enhancement of magnetic resonance imaging in AF patients [(7, 8)]**.** In this study, we investigated the possibility of using galactine-3 as a predictor of thromboembolism in non-valvular AF patients.

PATIENTS AND METHODS

Our study is a case-control study that was conducted from January 2018 to October 2019 at Cardiology Department, Aswan University Hospital and included 100 patients with non-valvular AF and 100 healthy control group. Then patients were divided into two subgroups: subgroup (A) 50 patients with nonvalvular AF with thromboembolic events and subgroup (B) 50 patients with non-valvular AF without thromboembolic events. Patients with Moderate to severe mitral stenosis and prosthetic valve, pregnant women, abnormal thyroid function, recent infection, Alcohol consumption, renal failure, and all patients with non-valvular AF on oral anticoagulant (warfarin and NOAC) were excluded from the study.

Ethical approval:

An approval of the study was obtained from Aswan University academic and ethical committee. All patients were informed about the purpose of the research, and written consent was obtained from each patient.

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All patients were subjected to:

1-History taking: A thorough history was taken from all members of the study group with special emphasis on age, sex, history of hypertension, history of diabetes mellitus, history of smoking, history of ischemic heart disease and calculation of CHA2DS2VASC score

2- Clinical evaluation: All patients were assessed clinically, including the evaluation of cardiovascular risk factors and general and local examination.

3- Electrocardiographic (ECG) evaluation: Twelve leads resting ECG was done for all patients to exclude any ischemic changes and to detect rate and rhythm.

4- Laboratory assessment: Blood sampling procedures and assay of serum galectin-3 level from peripheral vein samples of serum plasma were gotten. The blood samples were collected and immediately centrifuged at 2000-3000 rpm for 20 minutes and stored at −80°C. Plasma concentrations of Gal-3 were detected by an enzyme-linked immunosorbent assay kit (SinoGeneClon Biotech Co. Ltd). Procedure and calibration of assay was performed according to the manufacturer's protocol [9]**.** Briefly, plasma Gal-3 was bound to the anti-Gal-3 antibody, that was adsorbed onto micro-well plates and was captured with a secondary antibody anti-Gal-3 bio-tenanted (Sandwich method), that was revealed through the HRP-streptavidin exposed to TMB substrate. The colorimetric reaction was measured at 450 nm using an enzyme-linked immunosorbent assay (ELISA) plate reader. The standard curve ranged between 0.47ng/ml to 30.00ng/ml. The limit of detection was 0.99 ng/ml and the reproducibility coefficient of variation of intra-assay and inter-assay were 3.3% and 6.8% respectively. In addition, routine biochemical work-up was performed including**:**

- Kidney function tests (urea, creatinine): Blood urea by colorimetric or automated chemical analyzer, serum creatinine by Jaffe reaction.
- Electrolytes (sodium, potassium, calcium): Sodium and potassium by atomic absorption spectrometer, ionized calcium by Ion Selective Electrodes.
- Measurement of thyroid function tests (TSH, free T3, and free T4): Enzyme Linked Fluorescent Assay (ELFA).

5-Echocardiography:

ECG trace transthoracic and transesophageal echocardiography examination were performed using Philips IE 33 machine with X5-1 MHz transducer. Images were obtained by a single operator blinded to clinical and biochemical information.

1) Transthoracic echocardiography was done in the left lateral position, while the patient holding breath after expiration and m-mode and 2 D was acquired to evaluate regional wall motion abnormalities and left ventricular ejection fraction [10]**.**
2) Transesophageal echocardiography parameters: All patients were fasted for at least 4h and, then underwent TEE study. Sedation with 2-5mg I.V. Diazepam was used in all patients. The pharynx was anesthetized with topical 10% lidocaine spray, and the probe was introduced into the esophagus with the patient lying on the left side. The LAA was viewed from the basal short axis, with the tip of the probe slightly flexed to observe the whole length and breadth of the LAA. The procedure was performed with continuous monitoring of heart rate, blood pressure, and a 12-lead electrocardiogram [11]**.** Transesophageal echocardiography was tolerated well by all patients, and no complications occurred.

Statistical analysis

An independent t test was conducted to compare continuous variables and the chi-square and Fisher's exact tests were performed to compare categorical variables. Continuous variables are expressed as mean and standard deviation, while categorical variables as frequency and percentage. A multivariate linear regression analysis was conducted to determine the independent correlation between average aortic valve sclerosis score index. P values equal or less than 0.05 was considered significant. We performed all statistical analyses using the Statistical Package for the Social Sciences/ Predictive Analytics Software version 18 (SPSS, Inc., Chicago, IL, USA).

RESULT

The mean age of the nonvalvular AF patients was 60.05 ± 4.8 years old and most of the patients were males. The patient's group was divided into two groups: Group (A) included 50 patients with AF and thromboembolic event. The mean age of these patients was 60.7 ± 4.02 years old and the majority of them were males (60%). Group (B) included 50 patients with AF without thromboembolic event. The mean age of these patients was 59.4 ± 5.44 years old and the majority of them were males (64%). There was no statistically significant difference between patient's groups and control group as regards age (p = 0.148), gender (p = 0.315, BMI (p = 0.367) and smoking (p = 0.188). Also, there was no statistically significant differences between the two patient's groups as regards age (p = 0.177), gender (p = 0.68), smoking (p = 0.102), and BMI (p =0.348) as shown in table (1).

Table (1): Comparison between the two patient's groups regarding demographic data (n= 100)

		Groups			Test of sig.		
			Non-Valvular AF (N=100)				
		Controls (N=100)	AF without TE (N= 50)	AF with TE (N=50)	P-Value (1)	P-Value (2)	P-Value (3)
		Mean ± SD N (%)	Mean ± SD N (%)	Mean ± SD N (%)			
Age		61.43 ± 8.2	59.4 ± 5.44	60.7 ± 4.02	$0.073^{(T)}$	$0.465^{(T)}$	$0.177^{(T)}$
Sex	Male	55 (55%)	32 (64%)	30 (60%)	$0.292^{(C)}$	$0.56^{(C)}$	$0.68^{(C)}$
	Female	45 (45%)	18 (36%)	20 (40%)			
BMI		27.21 ± 2.26	27.74 ± 3.04	27.28 ± 1.62	$0.231^{(T)}$	$0.828^{(T)}$	$0.348^{(T)}$
Smoking	No	54 (54%)	26 (52%)	34 (68%)	$0.817^{(C)}$	$0.101^{(C)}$	$0.102^{(C)}$
	Yes	46 (46%)	24 (48%)	16 (32%)			

(T) Student t-test of significance. (C) Chi-Square test of significance. *Data are presented as mean ± SD, median (Range), or number (%). P value ≤ 0.05, BMI = body mass index. *P- Value (1): Between controls and (AF without TE) group. *P-Value (2): Between controls and (AF with TE) group. *P-Value (3): Between (AF without TE) group and (AF with TE) group.

Regarding comparison between controls and patient's groups, there was a statistically significant difference between patient's groups and controls as regards history of CAD, history of DM and history of hypertension. Patients' groups was more likely to have CAD ($p < 0.001$), hypertension ($p < 0.001$) or diabetes ($p < 0.001$), but there was no statistically significant differences between the two patient's groups as regards history of hypertension ($p = 0.383$), diabetes ($p = 0.334$), CAD ($p = 0.817$), and HF ($P = 0.26$) (Table 2).

Table (2): Comparison between the two patient's groups as regards medical comorbidities

		Groups			Test of sig.		
			Non-Valvular AF (N=100)				
		Controls (N=100)	AF without TE (N= 50)	AF with TE (N=50)	P-Value (1)	P-Value (2)	P-Value (3)
		N (%)	N (%)	N (%)			
Hypertension	No	41 (41%)	37 (74%)	33 (66%)	< 0.001	0.004	0.383
	Yes	59 (59%)	13 (26%)	17 (34%)			
Diabetes	No	40 (40%)	41 (82%)	37 (74%)	< 0.001	< 0.001	0.334
	Yes	60 (60%)	9 (18%)	13 (26%)			
CAD	No	40 (40%)	38 (76%)	37 (74%)	< 0.001	< 0.001	0.817
	Yes	60 (60%)	12 (24%)	13 (26%)			
Heart failure	Negative	100 (100%)	39 (78%)	34 (68%)	< 0.001	< 0.001	0.26
	Positive	0 (0%)	11 (22%)	16 (32%)			
	Positive	0 (0%)	0 (0%)	50 (100%)			

P value ≤ 0.05, CAD = coronary artery disease. *P-Value (1): Between Controls and (AF without TE) group. *P-Value (2): Between Controls and (AF with TE) group. *P-Value (3): Between (AF without TE) group and (AF with TE) group.

There was statistically significant difference between patient's groups and controls as regards galectin-3 level ($p < 0.001$), LVEF ($p < 0.001$) and CHA_2DS_2-VASc scoring ($p < 0.001$). Patients with AF had significantly higher galectin-3 level than controls. There was statistically significant difference between patient's groups as regards galectin-3 level ($P = 0.001$). Group (A) had significantly higher galectin-3 level than group (B). Also, there was statistically significant difference between patient's groups as regards CHA_2DS_2-VASc scoring ($P < 0.001$), group (A) had significantly higher CHA_2DS_2-VASc scoring than group (B) s shown in table (3).

Table (3): Comparison between patient's groups as regards galectin-3 level and CHA_2DS_2-VASc scoring

	Groups	Test of sig.

	Controls (N=100)	Non-Valvular AF (N=100)		P-Value (1)	P-Value (2)	P-Value (3)
		AF without TE (N= 50)	AF with TE (N=50)			
	Mean ± SD Median	Mean ± SD Median	Mean ± SD Median			
Serum Galectin	5.8 ± 1.21	13.87 ± 3.78	17.14 ± 4.32	<0.001	<0.001	<0.001
CHA2DS2-VASc scoring	0 (0 - 0)	1 (0 - 2)	4 (3 - 4)	<0.001	<0.001	<0.001

P value ≤ 0.05, *P-Value (1): Between Controls and (AF without TE) group. *P-Value (2): Between Controls and (AF with TE) group. *P-Value (3): Between (AF without TE) group and (AF with TE) group.

There were statistically significant differences between patient's groups and controls concerning LA/LAA thrombus ($p < 0.001$), LA/LAA dense SEC ($p < 0.001$), and LAA flow velocity ($p < 0.001$). Also, there were statistically significant differences between patient's groups as regards LAA flow velocity ($p < 0.001$), LA/LAA dense SEC ($p = 0.037$) and LA/LAA thrombus ($p = 0.037$). Patients of group A had lower LAA flow velocity and higher incidence of LA/LAA thrombus and dense SEC than patients of group B (Table 4).

Table (4): Comparison between patients and control regarding echocardiographic parameters

		Groups			Test of sig.		
		Controls (N=100)	Non-Valvular AF (N=100)				
			AF without TE (N= 50)	AF with TE (N=50)	P-Value (1)	P-Value (2)	P-Value (3)
		N (%)	N (%)	N (%)			
LAA flow velocity M/S	<0.25	0 (0%)	12 (24%)	35 (70%)	<0.001	<0.001	<0.001
	>0.25	100 (100%)	38 (76%)	15 (30%)			
LA/LAA dense SEC	Negative	100 (100%)	42 (84%)	25 (50%)	<0.001	<0.001	<0.001
	Positive	0 (0%)	8 (16%)	25 (50%)			
LA/LAA thrombus	Negative	100 (100%)	47 (94%)	40 (80%)	0.013	<0.001	0.037
	Positive	0 (0%)	3 (6%)	10 (20%)			

P value ≤ 0.05, LA = left atrium. LAA = left atrial appendage. SEC = spontaneous echo contrast *P-Value (1): Between Controls and (AF without TE) group. *P-Value (2): Between Controls and (AF with TE) group. *P-Value (3): Between (AF without TE) group and (AF with TE) group.

There were statistically positive correlations between serum galectin-3 and LA/LAA dense SEC ($r = 0.645$, $p < 0.001$). Also, there were statistically positive correlations between serum Gelactin-3 and LA/LAA thrombus ($r = 0.529$, $p < 0.001$). In contrary, there were statistically negative correlations between serum galectin-3 and LAA flow velocity ($r = - 0.783$, $p < 0.001$) (Table 5).

Table (5): Correlation analysis between serum galectin-3 and echocardiographic parameters

Non-Valvular AF (N=100)		LA/LAA thrombus	LA/LAA dense SEC	LAA flow velocity (ms)
Serum Galectin	Correlation Coefficient (r)	0.529	0.645	-0.783
	P-Value	<0.001	<0.001	<0.001
	Sig.	S	S	S

*Data are presented as odds ratio and 95% confidence interval. P value ≤ 0.05, LA/LAA= left atrium and left atrial appendage, SEC= spontaneous echo contrast

The ROC curve results of galectin-3 for study groups showed that galectin-3 was a significant discriminator between AF and normal population. At cutoff value of ≥ 7.25 ng/mL. The galectin-3 yielded a sensitivity of 81% and specificity of 77% for the detection of AF (Table 6). Also, the galectin-3 was a significant discriminator of the presence of LAA flow velocity of less than 25 m/s at cut-off value of 8.25 ng/mL with a sensitivity of 82% and specificity of 70%. In addition, galectin-3 was a significant discriminator of the presence of LA/LAA dense SEC at cut-off value of 8.25 ng/mL with a sensitivity of 91% and specificity of 70%. The galectin-3 was a significant discriminator of the presence of LA/LAA thrombus at cut-off value of 13.8 ng/mL with a sensitivity of 73% and specificity of 68% (Table 7).

Table (6): Area under the curve and the diagnostic accuracy of Galectin-3 for study's groups (n= 200)

	AUC	95% CI	P-	Cut-off	Sensitivity	Specificity

			Value	point		
AF versus Control	0.84	0.73 to 0.99	<0.001	≥7.25ng/mL	81%	77%

*AUC: area under curve; CI: Confidence interval. P value ≤ 0.05

Table (7): Area under the curve and the diagnostic accuracy of galectin-3 in nonvalvular AF patients (n= 100)

	AUC	95% CI	P-Value	Cut-off point	Sensitivity	Specificity
LA/LAA thrombus	0.8	0.69 to 0.89	<0.001	≥ 13.8	73%	68%
LA/LAA dense SEC	0.94	0.87 to 0.99	<0.001	≥ 8.25	91%	70%
LAA flow velocity MS	0.84	0.73 to 0.99	<0.001	≥ 8.25	82%	70%

AUC: area under curve; CI: Confidence interval. P value ≤ 0.05

DISCUSSION

Atrial fibrillation is considered one of the most common cardiac arrhythmias as it affects nearly 30 million people worldwide [(12)]. This arrhythmia remains one of the major causes of stroke, heart failure, sudden death, and cardiovascular morbidity in the world. It is believed that this disease occurs as a result of fibrosis, which may affect left atrium [(1)]. Galectin-3 is an α-galactoside-binding lectin that has been shown to mediate cell-to- cell and cell-to-extracellular matrix interactions and act as a novel chemo-attractant for monocytes and macrophages [(6)]. It has an important role in a number of fibrotic conditions, including cardiac fibrosis [(13)]. Also, it has important roles in the cardiovascular inflammation and fibrosis that result in cardiac remodeling. Higher circulating galectin-3 concentrations were found to be related with increased risk of AF [(14)]. However, it is not clear whether galectin-3 is a possible predictor for thrombus formation in patients with AF. Hence, we conducted the current study to investigate whether serum galectin-3 levels can be used as a predictor of thromboembolism in non-valvular AF patients.

There were high serum galectin-3 level in AF group compared to control group with higher level in subgroup Ib compared to subgroup Ia, positive correlation between galectin-3 and CHADS-VASc scoring system in nonvalvular AF patient's and positive correlations between serum galectin-3 and LA/LAA dense SEC. Also, there was positive correlation between serum galectin-3 and LA/LAA thrombus in nonvalvular AF patients. In contrary, there was negative correlation between serum galectin-3 and LAA flow velocity in nonvalvular AF patient's.

Our study showed that a significant association between high serum galectin-3 and incidence of AF. In AF group, galectin-3 level was 5.8 ± 1.21 while in control group, it was 15.51 ± 4.36 (P value < 0.001). Also, serum galectin-3 has a sensitivity of 81% and specificity of 77% to detect AF incidence [AUC= 0.84, 95%CI= (0.73-0.99)]. Our results are consistent with several studies where **Szadkowska *et al.*** [(15)] conducted a study on 145 patients with first acute MI and underwent with primary percutaneous coronary intervention (PCI) with stent implantation.

They found that elevated serum galectin-3 level was associated with a higher rate of new-onset AF. **Sonmez *et al.*** [(16)] studied 52 non-valvular AF and 33 patients with sinus rhythm to detect markers that might predict AF and affect atrial remodeling. Galectin-3 was among markers that was higher in patients with AF (1204 versus 1166 pg/ml, p=0.001) and had a strong positive correlation with left atrium index volume (LAVI) (r = 640, p = 0.021). Our findings are also in agreement with another case-control study on 76 patients with AF who were above age of 75 years old. They showed the role of galectin-3 in the pathogenesis of AF. Results showed that serum galectin-3 (OR= 87.53, 95%Cl {6.1 to 1,265.03}, P value = 0.001) was independent predictor of AF. In correlation analysis, serum galectin-3 was only correlated with left atrium index volume [(16)]. Our findings are also in agreement with a recent meta-analysis on seven prospective cohort studies including 645 AF patients. They investigated the relationship between baseline serum galectin-3 levels and AF recurrence in patients undergoing catheter ablation. They concluded that high baseline serum galectin-3 levels may be associated with increased risk of AF recurrence after catheter ablation [(17)]. Similar to our findings also a systematic review and meta-analysis on 28 studies involving 10830 patients examined the association of galecti-3 and incidence of AF. They concluded that galectin-3 was a higher in patients with persistent AF than those with paroxysmal AF. Moreover it can predict AF incidence and recurrence after treatment [18].

On the other hand, two previous studies reported that galectin-3 level was not associated with AF incidence. **Zakeri *et al.*** [19] study included 216 patients with heart failure and preserved ejection fraction. In AF group galectin-3 level was 14.3 (11.7-19.7) ng/ml while in sinus rhyme group, it was 13.6 (10.8-16.9) ng/mL with no significant difference between both groups (p = 0.15). These findings may be due to small number of patients who had AF (only 37%), which is not enough to observe significant difference in galectin-3 level between groups**.**

In our study, serum galectin-3 had a strong positive correlation with CHADS-VASc scoring system (r = 0.75, p value <0.001) and the total score was higher in AF patients with thromboembolic event than AF patients without thromboembolic event (range was 3 to 4 versus 0 to 2, p value < 0.001, respectively). Our findings are in agreement with previous studies where **Tang *et al.*** [20] study reported that galectin-3 was identified as an independent determinant for CHADS-VASc score (OR 0.091, 95%CI = {0.008–0.981}, p = 0.048). In another study higher serum galectin-3 levels were associated with higher both CHADS2 (p=0.008) and CHA2DS2-VASC (p = 0.016) score [21].

In our study, serum galectin-3 had a positive correlation with LA/LAA dense SEC (r =0.645, p <0.001) and the presence of left atrial/left atrial appendage-located spontaneous echo contrast was higher in AF patients with thromboembolic events than AF patients without thromboembolic events. Our findings are in agreement with previous studies where **Kocyigit *et al.*** [22] study found that patients with higher galectin-3 levels (P <.001) more frequently had dense SEC in LA/LAA (P < .001), while **Tang *et al.*** [20] study found that there were non-statistically significant results (p = 0.116). Also, there were positive correlations between serum galectin-3 and LA/LAA thrombus (r = 0.529, p < 0.001).

Similar to our findings, **Tang *et al.*** [20] study showed that high level of galectin-3 levels was associated with occurrence of LAA thrombus (p < 0.01). There were strong negative correlations between serum galectin-3 levels and LAA flow velocity (r = -0.783, p < 0.001). Our findings are in agreement with previous study, in **Kocyigit *et al.*** [22]. They found a negative correlation between LAA flow velocity and serum galectin-3 levels (r = -.440, P<.001). On other hand, **Tang *et al.*** [20] reported that the correlation wasn't statistically significant (p = 0.022).

Our result showed that serum galectin-3 was a significant predictor for thromboembolic event [OR=2.4, 95%CI = {1.3: 4.3}, P value=0.005] and with cut of value 8.25ng/mL, sensitivity of 73% and specificity of 68% for the thrombus detection [AUC= 0.80, 95%CI= {0.69-0.89}]. Similarly, a study on 153 patients with non-valvular AF showed that high levels of galectin-3 were also a predicator for LAA thrombus formation (OR= -12.925, 95%CI = {-16.2: -9.6}, P value<0.01) and it had a sensitivity of 90.9% and 96.9% specificity for the thrombus detection. But they set a cut off higher than the one we determined in our study (>18.95 ng/ml) [20]. Regarding the presence of left atrial/left atrial appendage-located spontaneous echo contrast, our result showed that galectin-3 had a sensitivity of 91% and 70% specificity [AUC= 0.94, 95%CI= {0.87-0.99}]. Our findings are in agreement with previous studies of **Kocyigit *et al.*** [22] who conducted a study on 65 persistent AF patients and showed that high levels of galectin-3 were also a predicator for the presence of left atrial/left atrial appendage-located spontaneous echo contrast (AUC: 0.909, 95% CI: 0.840-0.977, P<.001) and galectin-3 had a sensitivity of 91% and 79% specificity (AUC= 0.90, 95%CI= {0.84-0.97}). Additionally, regarding left atrial appendage flow velocity, our result showed that galectin-3 had a sensitivity of 82% and 70% specificity (AUC= 0.84, 95%CI= {0.73-0.99}). In line with these findings, **Kocyigit *et al.*** [22] reported similar results that high levels of galectin-3 predicted LAAFV < 0.25 m/s with a sensitivity and specificity of 86% and 76% respectively (AUC:0.851,95%CI: 0.732-0.971, P<.001).

CONCLUSION

Galectin-3 level is a possible predictor for thromboembolism in patients with non-valvular AF. Nevertheless, further studies are still needed to confirm our findings.

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