

ORIGINAL ARTICLE

The predictive value of galectin-3 levels on left atrial low voltage areas assessed by high-density mapping in patients with paroxysmal atrial fibrillation

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Abstract

Aims: Galectin-3 is an inflammation biomarker that is associated with atrial fibrosis and plays a role in the development of atrial fibrillation (AF). Low voltage areas (LVAs) identified using an electroanatomical mapping system represent the presence of fibrotic tissue. The present study aimed to determine the relationship between coronary sinus (CS) serum sampling of galectin-3 levels and the presence and extent of LVA in patients with paroxysmal AF.

Methods: A total of 115 consecutive paroxysmal AF patients underwent pulmonary vein isolation (PVI) included prospectively in the study. Voltage mapping was performed before PVI during sinus rhythm guided by multipolar high-density mapping catheter and LVAs were defined as regions where bipolar peak to peak voltage was <0.5 mV. Galectin-3 levels were measured via enzyme-linked immunosorbent assay.

Results: CS serum sampling of galectin-3 levels was significantly higher in paroxysmal AF patients with LVA than those without LVA (16.5 ± 3.7 ng/ml vs. 10.2 ± 2.7 ng/ml, respectively, $p < .001$). CS serum sampling of galectin-3 levels was significantly higher in paroxysmal AF patients with moderate and severe LVA than in paroxysmal AF patients with mild LVA (17 ± 3.5 ng/ml and 20.1 ± 1.3 ng/ml vs. 13.3 ± 2.3 ng/ml, respectively, $p = .002$). In the multivariate analysis female gender (odds ratio [OR] = 7.537, 95% confidence interval [CI]: 1.011–56.195; $p = .049$), left atrium volume (OR = 1.326, 95% CI: 1.052–1.67; $p = .017$), and CS serum sampling of galectin-3 levels (OR = 1.704, 95% CI: 1.169–2.483; $p = .006$) were significant and independent predictors for LVAs.

Conclusion: In this study, we found that the CS serum sampling of galectin-3 levels increased with the extent of LVA and was an independent predictor for the presence of LVA.

KEYWORDS

atrial fibrillation, galectin-3, low voltage areas, pulmonary vein isolation

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1 | INTRODUCTION

Galectin-3 is a member of the β -galactoside-binding lectin family and is released by macrophages and plays a role in inflammation and fibrosis. It acts as a mediator in the transformation of fibroblasts into activated myofibroblasts, collagen I production and increases the release of matrix proteins that play a role in fibrogenesis.¹ Studies found that high galectin-3 levels are associated with atrial fibrosis and play a role in the development of atrial fibrillation (AF).^{2,3} It has been reported that high galectin-3 level increase the risk of post-ablation AF recurrence undergoing catheter ablation and is a poor prognosis indicator in these patients.^{4,5}

Atrial fibrosis plays a role in the initiation and continuation of AF with intracellular distance with consequent reduced electrical coupling, non-uniform anisotropic impulse propagation, dispersion of atrial refractory periods, slow electrical conduction mechanisms. Delay-enhanced magnetic resonance imaging (MRI) studies showed that low voltage areas (LVAs) detected by MRI are correlated with LVA detected by bipolar three-dimensional electro-anatomical mapping system and also emphasized that LVA may be a predictor for AF recurrence after pulmonary vein isolation (PVI) in paroxysmal AF patients.^{6,7} The positive effects of LVA substrate modification in addition to the PVI procedure in AF patients on long-term outcomes have also been reported in the literature.⁸ However, the LVA ablation in addition to the posterior left atrial box isolation for persistent AF did not improve the outcomes much.⁹

In this study, we aimed to reveal the relationship between coronary sinus (CS) serum sampling of galectin-3 levels and the presence and extent of LVA in patients with paroxysmal AF who underwent PVI with a three-dimensional electroanatomical mapping system.

2 | MATERIAL AND METHODS

2.1 | Study population

Patients with symptomatic paroxysmal AF undergoing catheter ablation in our center were enrolled consecutively from January 2018 to March 2021. Standard 12-lead electrocardiography (ECG) or a single-lead ECG tracing of ≥ 30 s showing heart rhythm with no discernible repeating P waves and irregular RR intervals are diagnostic of clinical AF. Paroxysmal AF was defined as recurrent AF episodes which could terminate spontaneously or with interventional within 7 days of onset. At baseline, patients' demographic characteristics and medical conditions including comorbidities and medications were collected. The CHA₂DS₂-VASc were calculated using the baseline patient profile as follows; heart failure (HF), hypertension, age ≥ 75 (2 point), diabetes mellitus, previous stroke/TIA (2 point), vascular disease, age 65–75, female sex.¹⁰ Exclusion criteria were patients with a prior catheter or surgical ablation of AF, left atrial thrombus detected by transesophageal echocardiography (TEE), persistent and permanent AF, mechanical prosthetic heart valve(s), and moderate/

severe mitral stenosis. This study was approved by the ethics committee and informed consent was obtained from all participants.

2.2 | Standard echocardiography

All patients underwent conventional two-dimensional transthoracic echocardiography evaluations before the PVI procedure. Echocardiographic examinations were performed by an experienced cardiologist with GE Vingmed Vivid 7 (GE Vingmed Ultrasound) echocardiography device in the left lateral decubitus position. Parasternal long axis, short axis, apical four-chamber, and two-chamber images were taken and the evaluation was made according to the criteria of the American Society of Echocardiography using M-mode, 2-D, continuous wave doppler, pulse wave doppler method.¹¹ The ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity (E/e') was calculated and used as an index of LV diastolic function. Left atrium (LA) volume was measured from standard apical 2 and 4 chamber views at end-systole. LA volumetric analyses were performed using the biplane Simpson's method and subsequently indexed to body surface area for left atrial volume index (LAVI) measurements.

2.3 | Biochemical measurements

Biochemical and hematological parameters were measured from peripheral venous blood samples. Biochemical parameters were measured using Abbott ARCHITECT c8000 (Abbott Laboratories) autoanalyzer using commercial kits. Hematological parameters were studied with Abbott Cell Dyn 3700 (Abbott Laboratories) device by laser and impedance method. Galectin-3 levels were measured from CS blood samples. Galectin-3 in EDTA-serum samples was stored at -80°C until enzyme-linked immunosorbent assay (ELISA) analysis was made. CS serum sampling of galectin-3 levels was determined using Multiwash (TriContinent Scientific) and Synergy 4 Microplate Reader (Biotek) devices and Human Galectin-3 Platinum ELISA kit (eBioscience, Inc.) by working according to the manufacturer's instructions with ELISA method. The standard curve was created by applying the five-parameter curve fit method and the results were calculated as ng/ml according to this curve. High sensitive C-reactive protein (CardioPhase) was measured quantitatively in BN II System Nephelometer (Dade Behring) by immunonephelometric method from patients' serum and the results were reported in ng/ml.

2.4 | Electroanatomical voltage mapping and radiofrequency ablation

We performed a catheter ablation procedure under intravenous sedation with midazolam and fentanyl with two experienced operators. TEE preceded the ablation procedure in order to exclude the LA thrombus. All antiarrhythmic drugs were suspended for at least five

half-lives (amiodarone was withdrawn for at least 6 weeks), however, oral anticoagulation was discontinued 12 h before the ablation procedure. A 6-Fr decapolar electrode was inserted into the CS via by long sheath (Preface; Biosense Webster), and after baseline, CS blood samples were drawn from the long sheath to perform galectin-3 measurements before the ablation procedure during sinus rhythm. Following two transeptal punctures, two long sheaths were introduced into the LA. After transeptal punctures, intravenous heparin was administered to maintain activated clotting time at 300–350. Preablation, LA electroanatomical voltage mapping was performed in stable sinus rhythm to all the patients using the CARTO three-dimensional mapping system (Biosense Webster, Inc.) with multipolar high-density mapping catheter (Pentaray; Biosense Webster, Inc.). Mapping with the ablation catheter was performed only when the location was difficult to access with the high-density mapping catheter. The peak-to-peak bipolar electrogram amplitudes were defined as follows: electrogram amplitudes ≥ 0.5 mV were deemed as normal voltage (encoded with purple), electrogram amplitudes ≤ 0.2 mV as dense scar (encoded with red), and those between 0.2 and 0.5 mV as borderline voltage (encoded with multi-color).⁹ The total LVA was calculated as the percentage of LA surface area excluding the pulmonary vein (PV) antral region, left atrial appendage orifice, and mitral valve. LVAs were defined as regions where bipolar peak to peak voltage was < 0.5 mV. In addition qualitative assessment of the extent of LVA as mild $< 10\%$, 10% \leq moderate $< 30\%$, extensive $\geq 30\%$ was completed (Figure 1).¹²

In all patients, PVI was done using an open-irrigated ablation catheter with a 3.5 mm tip (Thermocool SmartTouch; Biosense Webster) via a long sheath (Preface; Biosense Webster). Radiofrequency was delivered in a power-controlled mode aiming 35 W (irrigation flow up to 30 cc/min) irrespective of posterior or anterior ablation. Radiofrequency was delivered until an ablation index ≥ 400 at the posterior wall/roof and ≥ 550 at the anterior wall (the 'CLOSE' protocol).¹³ We considered PVI as complete when entrance and exit block was confirmed with the multipolar high-density mapping catheter (Pentaray; Biosense Webster, Inc.) (defined by both loss of PV potentials and failure to conduct to the LA by pacing at 10 mA from bipolar pairs of electrodes on multipolar high-density mapping catheter, positioned at the entrance of the PV). At the end of the procedure, isoproterenol was infused 20–30 mcg/min for 15–20 min to induce AF from non-PV foci and to look for acute pulmonary vein reconnection. When a non-PV focus was identified (both sustained triggers [> 30 s], as well as non-sustained drivers including repetitive short-lasting bursts of arrhythmia [30 s] or premature atrial contractions [10 bpm]), focal ablation was performed at the focus. Cavotricuspid isthmus linear ablation was also performed when a previous atrial flutter was documented or emerged during the procedure.

2.5 | Statistical analysis

IBM SPSS version 21.0 was used for the evaluation of the data. Categorical data were presented as numbers and percentages. The

chi-square test was used for the comparison of categorical data. The distribution of continuous data was evaluated with the Shapiro-Wilk test of normality. Continuous data were presented as mean and standard deviation. Independent samples *t*-test and analysis of variance were used in the comparison of continuous data. Tukey test was used for post hoc comparison. Univariate and multivariate logistic regression analyses were used in the evaluation of independent factors determining the presence of LVA. Regression analysis results were analyzed with odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristics (ROC) analysis was performed to determine the cut-off level of galectin-3 level in estimating the presence of LVA. The area under the curve (AUC) was calculated as a measure of the accuracy of the test. Youden Index was used to calculate the optimal cut-off sensitivity and specificity. *p*-value of $< .05$ was considered to be statistically significant in the study.

3 | RESULTS

3.1 | Baseline patient characteristics

We included 115 consecutive paroxysmal AF patients who underwent PVI. Baseline characteristics of patients are shown in Table 1. LVA was observed in 21 (18.3%) paroxysmal AF patients, and not observed in 94 (81.7%) paroxysmal AF patients. Age ($p = .003$), female ($p = .029$), body mass index ($p = .045$), coronary artery disease ($p < .001$), duration of AF ($p = .029$), and CHA₂DS₂VAS_c score ($p < .001$) were significantly higher in paroxysmal AF patients with LVA than those without LVA. LA diameter, LA volume, and LAVI were significantly higher in paroxysmal AF patients with LVA than those without LVA. Also, LVEF was significantly lower in paroxysmal AF patients with LVA than those without LVA. Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, statin, and amiodarone treatment usage were significantly higher in paroxysmal AF patients with LVA than those without LVA. There was no significant difference in the ablation procedure.

3.2 | Electroanatomical properties of the LA and LVA

Endocardial high-density voltage mapping data are shown in Table 2. The total left atrial area was significantly higher in paroxysmal AF patients with LVA than those without LVA (136.2 ± 22.5 cm² vs. 117.6 ± 16.9 cm², respectively, $p < .001$). Mapping points/total left atrial area was significantly higher in paroxysmal AF patients with LVA compared with paroxysmal AF patients without LVA (mean values of 26.3 ± 7.5 vs. 18 ± 5.7 , respectively, $p < .001$). Among the 21 paroxysmal AF patients with LVA, left atrial LVA was 28.3 ± 18.9 cm² and the percentage of left atrial LVA was 21.6 ± 13.3 . The extent of left atrial LVA in relation to left atrial area was $< 10\%$ (mild) in seven patients (33.3%), 10%–30% (moderate) in nine (42.9%) and $\geq 30\%$ (severe) in five (23.8%) patients.

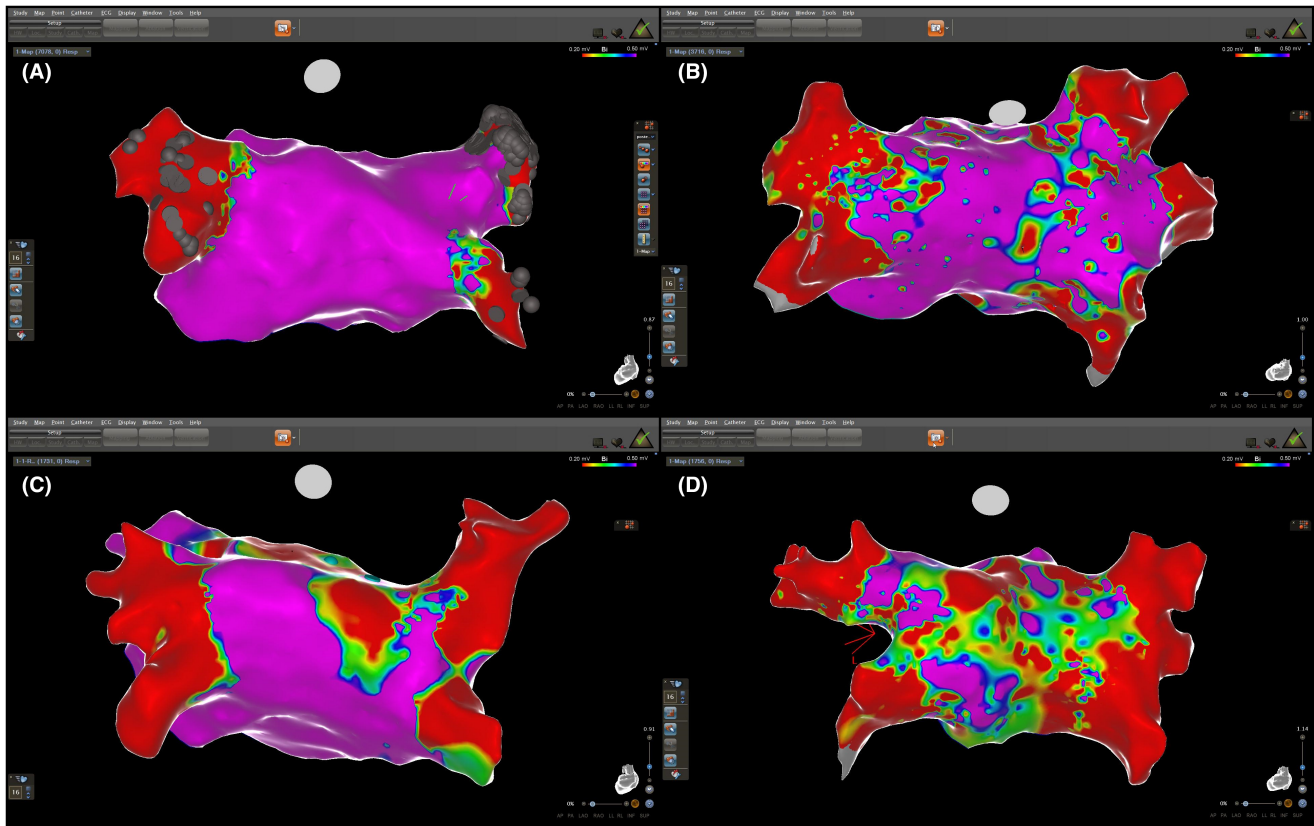


FIGURE 1 Posterior–anterior view of a high-density electroanatomical voltage mapping of the left atrium in a patient with paroxysmal AF. The peak-to-peak bipolar electrogram amplitudes were defined as follows: Electrogram amplitudes ≥ 0.5 mV were deemed as normal voltage (encoded with purple), electrogram amplitudes ≤ 0.2 mV as dens scar (encoded with red), and those between 0.2 and 0.5 mV as borderline voltage (encoded with multi-color). (A) Non-LVA. (B) Mild LVA ($<10\%$). (C) Moderate LVA ($10\% \leq \text{moderate} < 30\%$). (D) Extensive LVA ($\geq 30\%$). AF, atrial fibrillation; LVA, low voltage area

3.3 | CS serum sampling of galectin-3 levels and left atrial LVA

Coronary sinus serum sampling of galectin-3 levels was significantly higher in paroxysmal AF patients with LVA than those without LVA (16.5 ± 3.7 ng/ml vs. 10.2 ± 2.7 ng/ml, respectively, $p < .001$) (Table 1).

3.4 | CS serum sampling of galectin-3 levels and extent of left atrial LVA

Coronary sinus serum sampling of galectin-3 levels was significantly higher in paroxysmal AF patients with moderate and severe LVA than in paroxysmal AF patients with mild LVA (17 ± 3.5 ng/ml and 20.1 ± 1.3 ng/ml vs. 13.3 ± 2.3 ng/ml, respectively, $p = .002$) (Table 3). Also, CS serum sampling of galectin-3 levels was significantly higher in paroxysmal AF patients with mild LVA than in non-LVA (13.3 ± 2.3 ng/ml vs. 10.2 ± 2.7 ng/ml, respectively, $p = .025$). There was no significant difference in CS serum sampling of galectin-3 levels between paroxysmal AF patients with moderate and severe LVA ($p = .141$) (Figure 2). There was a significant correlation between galectin-3 levels and LVA (%) ($r = .761$, $p < .001$) (Figure 3).

3.5 | Predictors of left atrial LVA

Univariate logistic regression analysis revealed that $\text{CHA}_2\text{DS}_2\text{VAS}_\text{c}$ score ≥ 2 (OR = 5.139, 95% CI: 1.127–23.436; $p = .034$), age (OR = 1.093, 95% CI: 1.027–1.163; $p = .005$), female gender (OR = 3.795, 95% CI: 1.285–11.21; $p = .016$), LVEF (OR = 0.941, 95% CI: 0.891–0.993; $p = .028$), LA volume (OR = 1.437, 95% CI: 1.207–1.709; $p < .001$), CS serum sampling of galectin-3 levels (OR = 1.977, 95% CI: 1.476–2.649; $p < .001$), and CAD (OR = 4.982, 95% CI: 1.824–13.606; $p = .002$) showed an association with the presence of LVA. In the multivariate analysis, female gender (OR = 7.537, 95% CI: 1.011–56.195; $p = .049$), LA volume (OR = 1.326, 95% CI: 1.052–1.67; $p = .017$), and CS serum sampling of galectin-3 levels (OR = 1.704, 95% CI: 1.169–2.483; $p = .006$) remained statistically significant (Table 4).

The ability of CS serum sampling of galectin-3 levels to differentiate paroxysmal AF patients with LVA from those without LVA was assessed by ROC curve analysis. ROC curves for the occurrence of LVA had an AUC of 0.909. The optimal cut-off value of CS serum sampling of galectin-3 levels for the prediction of LVA was 12.75 ng/ml. CS serum sampling of galectin-3 cut-off value of 12.75 ng/ml had a sensitivity of 81% and specificity of 81% for the presence of LVA (Figure 4).

TABLE 1 Baseline characteristics of PAF patients with and without low voltage area

	PAF with LVA (n = 21)	PAF without LVA (n = 94)	p
Age, years	63.8 ± 8.3	57.2 ± 9.1	.003
Female, n, %	14 (66.7)	38 (40.4)	.029
BMI, kg/m ²	26.7 ± 4.5	24.4 ± 3.4	.045
Diabetes mellitus, n, %	8 (38.1)	18 (19.1)	.061
Hypertension, n, %	18 (85.7)	65 (69.1)	.126
Coronary artery disease, n, %	11 (52.4)	17 (18.1)	<.001
COPD, n, %	2 (9.5)	14 (14.9)	.520
Previous stroke, n, %	3 (14.3)	5 (5.3)	.144
Duration of AF, years	5 ± 2.6	3.7 ± 0.7	.029
EHRA score	3 ± 0.6	2.7 ± 0.5	.070
CHA ₂ DS ₂ VAS _C score	3.8 ± 1.7	2.1 ± 1.4	<.001
Hemoglobin, g/dl	12.5 ± 2	12.7 ± 1.9	.582
White blood cell, 10 ³ /mm ³	7.8 ± 2.2	8 ± 2.3	.748
Creatinine, mg/dl	1 ± 0.4	1 ± 0.6	.638
hs-CRP, ng/ml	0.7 ± 0.4	0.6 ± 0.4	.161
GFR, ml/min/1.73 m ²	82 ± 25.5	90.3 ± 25.3	.176
Galectin-3, ng/ml	16.5 ± 3.7	10.2 ± 2.7	<.001
LA diameter, mm	46.9 ± 3.8	42.2 ± 5.5	<.001
LA volume, ml	71.1 ± 4.8	55.2 ± 9.9	<.001
LAVI	36.9 ± 4.3	31.1 ± 6.6	<.001
LVEF, %	51.1 ± 8.4	55.5 ± 7.7	.022
E/e ratio	9.3 ± 1.9	8.5 ± 2.2	0.119
ACEi/ARB, n, %	17 (81)	50 (53.2)	.020
Diuretics, n, %	7 (33.3)	22 (23.4)	.343
Statin, n, %	12 (57.1)	20 (21.3)	.001
Beta blocker, n, %	12 (57.1)	51 (54.3)	.810
Calcium channel blocker, n, %	3 (14.3)	14 (14.9)	.943
Amiodarone, n, %	13 (61.9)	24 (25.5)	.001
Propafenon, n, %	3 (14.3)	28 (29.8)	.148
Sotalol, n, %	1 (4.8)	9 (9.6)	.479
Antiplatelets, n, %	4 (19)	18 (19.1)	.991
Warfarin, n, %	2 (9.5)	13 (13.8)	.596
NOACs, n, %	16 (76.2)	59 (62.8)	.243
Pulmonary vein isolation, n, %	21 (100)	94 (100)	-
CTI ablation, n, %	2 (9.5)	5 (5.3)	.466
Others ablation, n, %	3 (14.3)	4 (4.3)	.082

Bold value indicates the statistically significant of $p < .05$. Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CTI, cavotricuspid isthmus; hs-CRP, high sensitive C-reactive protein; GFR, glomerular filtration rate; LA, left atrium; LAVI, left atrium volume index; NOAC, novel oral anticoagulants; PAF, paroxysmal atrial fibrillation.

4 | DISCUSSION

In our study, we found that CS serum sampling of galectin-3 levels was significantly higher in paroxysmal AF patients with LVA than in those without LVA. Furthermore, we also found that CS serum sampling of galectin-3 levels was an independent predictor for the presence of LVA.

Galectin-3 is a biomarker that is upregulated and mediates fibrosis in several fibrotic conditions. It activates and promotes profibrotic factors, fibroblast proliferation, transformation, proapoptotic effects, collagen deposition, and subsequent cardiac fibrosis and myocyte dysfunction.¹⁴ Galectin-3 levels was shown to play a role in the development of AF by contributing to atrial remodeling and high galectin-3 levels have also been reported in the literature to be a predictor of recurrence after AF ablation.^{4,5} In the study by Takemoto et al., galectin-3 inhibition was found to reduce atrial fibroblast proliferation, atrial dilatation and fibrosis, and galectin-3 has been shown to be a potential mediator for atrial substrate in the development of AF.¹⁵

Low voltage areas identified using an electroanatomical mapping system represent the presence of fibrotic tissue.¹⁶ Similarly, in the study by Oakes et al., LVAs detected with bipolar electroanatomically guided voltage map correlated with present LVAs with delayed enhancement on MRI.⁷ LVA caused by atrial remodeling is known to be associated with a variety of electrical disturbances, such as heterogeneities in atrial action potential duration, effective refractory period, and conduction velocity.¹⁷ In light of these mechanisms, it was shown that the presence of LVA plays a role as an arrhythmogenic substrate and contributes to the development and persistence of AF.¹⁸ As a matter of fact, studies showed that LVA is more common in persistent AF patients than in paroxysmal AF patients. Although the presence of LVA in paroxysmal AF patients varies between 10% and 34%, this rate was found to be 18.3% in our study.^{19–21} In furtherance, it was reported that the presence of LVA in paroxysmal AF patients is a predictor of AF recurrence after catheter ablation.^{6,22}

In the few studies that have assessed the relationship between the presence and extent of LVA and various biomarkers. In the study by Zhou et al., MicroRNA-21 levels, which is a cardiac fibrosis marker and released by fibroblasts, were found to be significantly correlated with the extent of left atrial LVA. In addition, MicroRNA-21 serum levels were associated with procedure outcomes in patients with persistent AF undergoing ablation.²³ In the study by Kornej et al., troponin T levels were found to be significantly higher in paroxysmal AF and persistent AF patients with LVA than in those without LVA, and persistent AF, LA size, and troponin T levels were found to be a significant predictor for the presence of LVA.²⁴ In another study, the novel ANP score (one point for age ≥ 65 years, NT-proANP over 75th percentile in peripheral circulation [17 ng/ml] and persistent AF type) ≥ 2 demonstrated good sensitivity and specificity for the LVAs presence (72% and 70%, respectively).²⁵ The study by Yalcin et al., in which LA fibrosis areas were evaluated with delayed-enhancement cardiac MRI, showed a significant correlation between serum galectin-3 levels and the extent of left atrial fibrosis.²⁶ Similarly, in our

TABLE 2 Electroanatomical properties of the left atrium in the study patients

	PAF with LVA		PAF without LVA		p
	Mean \pm SD	Median (Min–Max)	Mean \pm SD	Median (Min–Max)	
Total left atrial area (cm ²)	136.2 \pm 22.5	135.2 (84–189.4)	117.6 \pm 16.9	115.7 (85.3–161.4)	<.001
Mapping points	3659.2 \pm 1377.9	3716 (1610–5960)	2182.7 \pm 987.7	1970 (990–5290)	<.001
Mapping points/total left atrial area	26.3 \pm 7.5	25.7 (15.6–43.5)	18 \pm 5.7	17 (9.49–34.81)	<.001
Left atrial LVA (cm ²)	28.3 \pm 18.9	25.2 (4.1–71.2)			
Percentage of left atrial LVA, %	21.6 \pm 13.3	19.7 (3.8–49.2)			
Mild LVA (<10%), n, %	7 (33.3)				
Moderate LVA (10%–30%), n, %	9 (42.9)				
Severe LVA (\geq 30%), n, %	5 (23.8)				

Abbreviations: LVA, low voltage area; PAF, paroxysmal atrial fibrillation; SD, standard deviation.

TABLE 3 Extent of left atrial low voltage area and galectin-3 levels

	n	Galectin-3	p
LVA <10% Mild LVA	7	13.3 \pm 2.3 ^a	.002
10%–30% Moderate LVA	9	17 \pm 3.5 ^b	
\geq 30% Severe LVA	5	20.1 \pm 1.3 ^b	
Total	21	16.5 \pm 3.7	

Abbreviation: LVA, low voltage area.

^{a,b}Means followed by the same letter in the same column do not differ statistically among themselves by Tukey test ($p < .05$).

study, we also found that CS serum sampling of galectin-3 levels was significantly higher in paroxysmal AF patients with LVA than those without LVA. Our study is the first in the literature to reveal the relationship between CS-serum sampling of galectin-3 levels and three-dimensional electroanatomical high-density mapping guidance for the presence and extent of LVA. Galectin-3 plays a role not only in cardiac fibrosis but also in lung, liver, kidney, and vascular fibrosis.^{27–30} Therefore, CS serum sampling of galectin-3 levels and peripheral blood levels may differ. It is common knowledge that galectin-3 is excreted in the urine but at the same time, it could be formed in the heart in cardiomyopathy and HF and act as a fibrosis trigger by stimulating fibroblasts proliferation and differentiation into myofibroblasts.³¹ In the study by Chumakova et al., it was concluded that in patients with ischemic cardiomyopathy (ICMP), galectin-3 concentration in the CS was higher than in peripheral blood. Also, CS serum sampling of the galectin-3 level was higher in ICMP patients than in CAD patients without ICMP with an equivalent state of renal function. Moreover, this study stated that the difference between the CS serum sampling of galectin-3 and peripheral blood levels is because of its overproduction, rather than decreased excretion.³² On account of this, CS sampling of galectin-3 levels may be more accurate and specific than peripheral venous strategies for the prediction of left atrial LVAs in paroxysmal AF patients.

Various mechanisms such as oxidative stress, atrial dilatation, calcium-overload, inflammation, transient receptor canonical potential channel-mediated myofibroblast activation provide a basis for “AF-induced atrial remodeling.” On the contrary, the AF episodes in paroxysmal AF patients result in electrical and structural remodeling.³³ All these mentioned incidents may contribute to the “atrial fibrillation begets atrial fibrillation” mechanism. In paroxysmal AF, atrial remodeling may not directly contribute to the impairing of atrial myocardial viability and the formation of LVAs, as in persistent AF. As a matter of fact, studies clearly showed the relationship between LVA and scoring systems that include risk factors that may cause atrial remodeling in paroxysmal AF patients.^{20,25,34} In our study, similar to these data, risk factors that may cause atrial remodeling such as age, female, duration of AF, CHA₂DS₂VAS_c score, LA diameter, LA volume, LAVI, and total left atrial area were observed to be higher in paroxysmal AF patients with LVA compared to those without LVA.

Various studies of LVA predictors in AF patients were reported. It is stated in the “management guidelines” that age constitutes the pathophysiological basis for the development of atrial fibrosis and is an etiological factor for the development of AF.¹⁰ It was shown that aging contributes to LA scar development by causing fibroblast activation and excessive accumulation of extracellular matrix fibrillar collagen.³⁵ The relationship between the presence of LA scar and gender was not clearly identified. In a study by Li et al., in which the relationship between low AF ablation success in female sex and the development of atrial fibrosis was examined, gender differences in atrial fibrosis remodeling of AF were mainly because of the inherent differential expression of fibrosis-related genes and proteins related to the TGF β /Smad3 pathway; upregulation of these biomarkers was detected in females promoting an aggravation of fibrosis remodeling was detected. In that study, Li et al., assessed pulmonary vein sleeves to identify gender-specific mechanistic differences in fibrosis remodeling of AF patients. Pulmonary vein sleeves further analysis using microarray, immunohistochemistry, and western blot displayed the aggravation of fibrosis remodeling in women because

FIGURE 2 The distribution of CS serum sampling of galectin-3 levels and extent of LVA in patients with paroxysmal AF. AF, atrial fibrillation; CS, coronary sinus; LVA, low voltage area

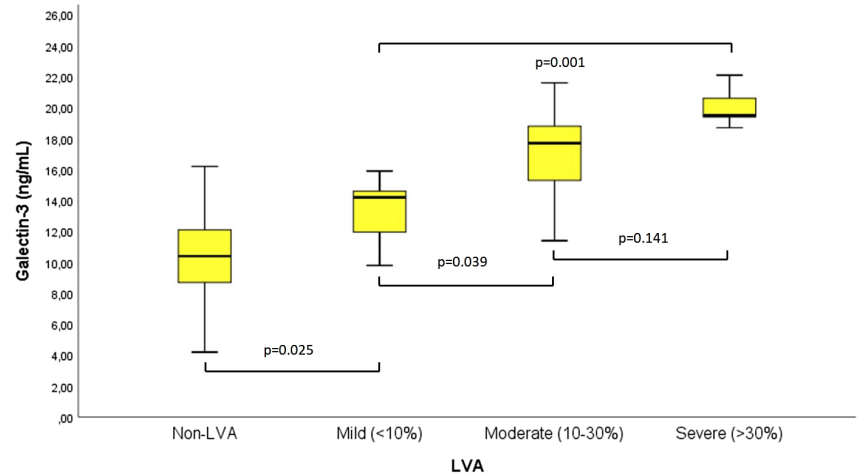


FIGURE 3 Correlation between CS serum sampling of galectin-3 levels and LVA. CS, coronary sinus; LVA, low voltage area

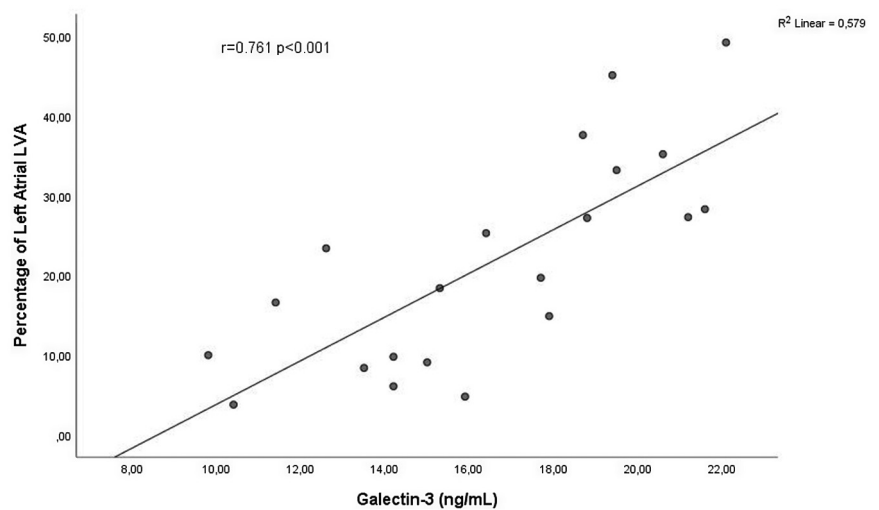


TABLE 4 Multivariate logistic regression analysis for the presence of left atrial low voltage area in patients with PAF

	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	p-value	OR	95% CI	p-value
CHA ₂ DS ₂ VAS _C score ≥2	5.139	1.127-23.436	0.034			
Age	1.093	1.027-1.163	0.005			
Female	3.795	1.285-11.21	0.016	7.537	1.011-56.195	.049
LVEF	0.941	0.891-0.993	0.028			
LA volume	1.437	1.207-1.709	<0.001	1.326	1.052-1.67	.017
Galectin-3	1.977	1.476-2.649	<0.001	1.704	1.169-2.483	.006
Diabetes mellitus	2.598	0.937-7.203	0.066			
Coronary artery disease	4.982	1.824-13.606	0.002			

Abbreviations: CI, confidence interval; LA, left atrium; LVEF, left ventricular ejection fraction; OR, odds ratio; PAF, paroxysmal atrial fibrillation.

of the inherent differential expression of fibrosis-related genes and proteins.³⁶ Our present study showed that age and female sex are associated with the presence of LVA, consistent with previous studies.^{19,20,34} Moreover, female sex was an independent predictor for the presence of LVA.

The literature includes many clinical risk scoring studies predicting stroke, arrhythmia recurrences after catheter ablation, and

mortality in AF patients.³⁷ However, clinical risk scoring studies predicting the LA electroanatomical substrate are limited. In the study presented by Chao et al., it was shown that left atrial voltage decreased in increased CHADS₂ score and increased CHADS₂ score was associated with the recurrence rate of paroxysmal AF after catheter ablation.³⁸ In our study, the CHA₂DS₂VAS_C score was also found to be related to the presence of LVA. The components of the

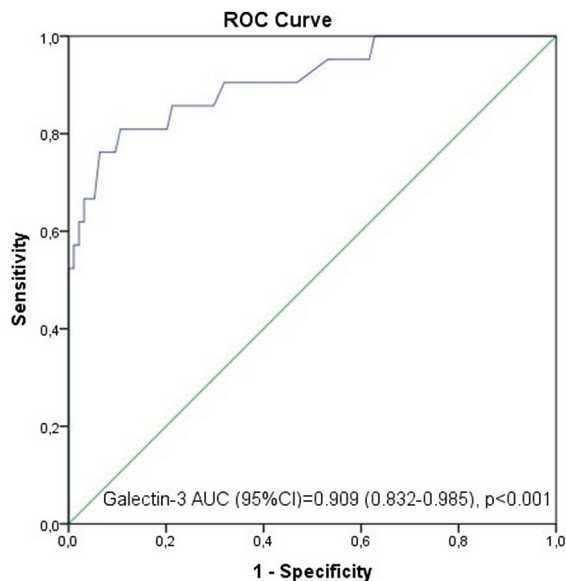


FIGURE 4 ROC analysis determining sensitivity and specificity of CS serum sampling of galectin-3 levels in the prediction of LVA in patients with paroxysmal AF. AF, atrial fibrillation; CS, coronary sinus; LVA, low voltage area; ROC, receiver operating characteristics

CHA₂DS₂-VAS_C score may contribute to the development of AF,³⁹ as well as to the development of LVA with pathophysiological conditions such as atrial shear stress and remodeling process in these patients.

Left atrium enlargement had been used as a marker of advanced electroanatomical remodeling because of its strong association with AF initiation and progression. In the study of Seewöster et al., LA dimensions parameters were evaluated with cardiac magnetic resonance and their relationship with LVA was revealed. This study found LA volume to be a stronger predictor for the presence of LVA than other various monoplane LA diameters.⁴⁰ Atrial enlargement was associated with atrial fibrosis was reported in an autopsy study.⁴¹ The study by Nery et al. found no relationship between the presence of LVA and AF classification, while age and LA volume were found to be predictors for the presence of LVA in multivariable analysis.⁴² In our study, similar to the studies mentioned, LA volume is an independent predictor for the presence of LVA.

Tissue injuries detected in atrial fibrosis cause galectin-3 synthesis and secretion, which causes atrial extracellular matrix production and provides a basis for the onset and progression of AF.⁴³ In the study by Berger et al., it was concluded that the changes in serum galectin-3 levels reflect alterations of the arrhythmogenic substrate following thoracoscopic AF surgery. Further, they found that patients in whom galectin-3 levels increases after ablation have a high recurrence rate reflecting ongoing profibrotic signaling, irrespective of arrhythmia continuation.⁴⁴ In our study, CS serum sampling of galectin-3 levels was significantly higher in paroxysmal AF patients with moderate and severe LVA than in paroxysmal AF patients with mild LVA. Furthermore, we also found that increased CS serum

sampling of galectin-3 levels was an independent predictor for the presence of LVA. In light of these results, we are of the opinion that galectin-3 is a potential mediator in the fibrotic and inflammatory atrial substrate, which forms the pathophysiological basis of the presence and extent of LVA.

There were some limitations in the present study. This was an observational study performed on a relatively small study population. We were not able to completely evaluate the prognostic value of CS serum sampling of galectin-3 levels on cardiovascular outcomes in paroxysmal AF patients with and without LVA. Moreover in this study, we do not report the association between the extent of LVAs and AF recurrence following ablation. We have not evaluated additional biomarkers related to fibrosis or extracellular matrix turnover. Also, we did not measure galectin-3 levels from peripheral venous blood samples simultaneously. Therefore, the difference between CS serum sampling of galectin-3 levels and peripheral blood galectin-3 levels was not present in our study.

5 | CONCLUSION

In this study, we found that the CS serum sampling of galectin-3 levels increased with the extent of LVA and was an independent predictor for the presence of LVA. Galectin-3 is a favorable parameter to estimate the presence of LVA and it may provide useful information for the treatment strategy for AF and the prediction of the outcome after ablation. In the light of the findings of our study, galectin-3 may be an important activator and indicator of the fibrotic and inflammatory process forming the pathophysiological basis of atrial remodeling development in patients with paroxysmal AF.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Samsun Education and Research Hospital ethics committee.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer reviewed.

CONSENT FOR PUBLICATION

The corresponding author had the written consent of the patients to use the data for publication.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Conception and design: Gökhan Aksan, Ahmet Yanık, Osman Can Yontar. *Data collection and processing:* Gökhan Aksan, Ahmet Yanık, Osman Can Yontar, Faruk Boyacı, Korhan Soylu. *Analysis and interpretation:* Gökhan Aksan, Ahmet Yanık, Melisa Uçar. *Literature review:* Gökhan Aksan, Ahmet Yanık, Mustafa Kürşat Şahin, Melisa

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DATA AVAILABILITY STATEMENT

The data are available for sharing.

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