

## ORIGINAL ARTICLE

# Radiomic phenotype of epicardial adipose tissue in the prognosis of atrial fibrillation recurrence after catheter ablation in patients with lone atrial fibrillation

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**Abstract**

**Background:** Epicardial adipose tissue (EAT) has been considered as one of the probable triggers of atrial fibrillation (AF). CT-radiomics is a perspective noninvasive method of assessment of EAT. We evaluate the radiomic phenotype of EAT in patients with lone AF in the prognosis of AF recurrence after catheter ablation.

**Methods:** A total of 43 patients with lone AF referred for CA and 20 out-hospital patients without arrhythmia underwent multidetector computed tomography coronary angiography. Segmentation of EAT and extraction radiomic features were performed on calcium scoring series using by 3D-Slicer. Clinical follow-up was performed for 12 months period after the CA.

**Results:** EAT in patients with lone AF had a distinct radiomic phenotype. Thus, 45 of 93 calculated radiomic features, volume and attenuation of EAT were significantly different between patients with lone AF and persons without any arrhythmia. In addition, 17 radiomic features were significantly different in subgroups with and without AF recurrence. Multivariate regression analysis demonstrated that only gray level nonuniformity normalized (GLSZM) was an independent predictor of AF recurrence (OR 1.0027, 95%CI 1.0009–1.0044,  $p = 0.002$ ). ROC analysis data showed that  $GLSZM > 1227.4$  indicates high probability of AF recurrence during 12 months (sensitivity 89.4%, specificity 70.8%, AUC: 0.809;  $p = 0.001$ ).

**Conclusion:** The radiomic parameter GLSZM is associated with late AF recurrence after CA in patients with lone AF. In current study GLSZM was a stronger predictor of lone AF recurrence in multivariate analysis comparing with other established risk factors and EAT volume and attenuation.

**KEYWORDS**

atrial fibrillation, CT, epicardial adipose tissue, radiomics

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## 1 | INTRODUCTION

Catheter ablation (CA) is one of the most effective and safest treatment for atrial fibrillation (AF) based on evidence illustrating its efficacy compared with antiarrhythmic drug therapy.<sup>1</sup> At the same time, success rate of the CA is 60–80% for paroxysmal AF and 50–60% for persistent AF,<sup>1,2</sup> and depends on multiple factors, including left atrium (LA) diameter, AF duration, heart rate, and others.<sup>1,3</sup> In recent years, several predictive scores for CA outcome have been developed and tested, but they need improvement and still have limited validation.<sup>3–6</sup> This is especially true to a small cohort of patients with lone AF, for which none of the existing predictive scores for rhythm outcome after CA can be applied. Therefore, new predictors are needed.<sup>3</sup>

Recently, an epicardial adipose tissue (EAT) has been considered as one of the probable triggers of AF. It is assumed that metabolic abnormalities of EAT, including increased secretion of pro-inflammatory cytokines, pro-fibrotic factors and oxidative stress molecules, have proarrhythmic effect through adipocytes infiltrating heart muscle.<sup>7</sup> Ultimately, such adverse metabolic influence leads to structural changes in the myocardium, atria remodeling and to the development and maintenance of AF.<sup>7</sup> Numerous studies in which noninvasive imaging of EAT (echocardiography, computed tomography [CT] and magnetic resonance imaging [MRI]) have been applied, demonstrated the relationship of morphometric EAT characteristics with the risk of AF onset, its severity and likelihood of arrhythmia recurrence after CA.<sup>8–10</sup> However, this knowledge is currently not fully proven, has no clinical application and the search for new imaging prognostic markers for AF recurrence is continues.

Today, a new approach to image analysis called radiomics has been proposed for clinical use.<sup>11</sup> The radiomics allows the extraction of new quantitative characteristics such as geometric structure, texture and intensity distribution in the region of interest from standard medical imaging<sup>11</sup> and opens up new perspectives for personalized medicine.<sup>12</sup> Nowadays the approach mentioned above has shown its clinical significance in oncology,<sup>13</sup> but in cardiology is under active studying.<sup>14–17</sup> Particularly, some investigators have successfully used radiomics of CT and MRI images for assessing the structure of atherosclerotic plaques in coronary arteries,<sup>15</sup> for prediction of acute myocardial infarction complications, for differential diagnosis of myocardial pathology.<sup>18,19</sup> In turn, we hypothesized that radiomic analysis of CT images of EAT may have a prognostic value in patients with lone AF and will allow to find out new predictors of AF recurrence after CA.

Because, according to our knowledge, such studies have not yet been performed, we set the goal to estimate the utility of pre-procedural CT-radiomic analysis of EAT to identify patients at risk for lone AF recurrence after CA.

## 2 | METHODS

### 2.1 | Patients

The study population (63 patients) consisted of study group (Group 1) and comparative group (Group 2).

### 2.1.1 | Group 1

From January 2019 to November 2020 43 (35 males, median age 42 [35;47]) patients with lone AF referred for CA at the Department of Surgical Treatment of Complicated Cardiac Arrhythmias and Pacing, Cardiology Research Institute Tomsk NRMC were considered for inclusion in the study. Before CA all of them underwent multidetector computed tomography coronary angiography (MDCT-CA) to exclude coronary artery pathology<sup>20</sup> and for preoperative assessment of pulmonary veins and LA anatomy.<sup>21</sup>

The inclusion criteria were as follows: age 18–60 years, paroxysmal, persistent or long-term persistent lone AF,<sup>3</sup> informed consent of patients to participate in the study. Paroxysmal AF is defined as AF that terminates spontaneously or with intervention within 7 days of onset, persistent AF—continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after >7 days, and long-term persistent AF was implied as continuous AF of >12 months' duration when decided to adopt a rhythm control strategy.<sup>3</sup>

Exclusion criteria were the following: any structural heart disease, CAD, arterial hypertension,<sup>22</sup> hypercholesterolemia, a history of stroke, left ventricular ejection fraction (LVEF) <50%, peripheral vascular disease, the presence LA thrombus, LA volume >150 ml (according to CT data), diabetes mellitus, and thyroid and urinary tract disorders. Patients with long-term AF. The presence of significant artifacts on CT images, mismatch of the X-ray tube parameters set forth in the MDCT-CA subsection during scanning were also exclusion criteria.

Radio frequency pulmonary vein isolation was a method of choice for AF ablation for all patients. Antiarrhythmic and antithrombotic therapy was used at the time of patient's inclusion in the study and administered in according to ABC pathway,<sup>2</sup> and was not changed throughout first 3 months of the follow-up period. Medication consisted of beta-blockers (30% of patients), amiodarone/sotalol/propafenone (93% of patients), and anticoagulants (100% of patients).

Clinical follow-up with 12-lead electrocardiogram (ECG) and 24-h Holter monitoring was performed for 12 months period after the CA (control visits at 3, 6 and 12 months).

### 2.1.2 | Group 2

The comparative group consisted of 20 out-hospital patients (15 males, median age 39 [34;44]) without any arrhythmias, who agreed to participate in the study and matched by age, gender, and body mass index (BMI) with patients from Group 1. All participants underwent MDCT-CA in order to exclude CAD. The inclusion criteria for Group 2 were pretest probability of CAD <15%,<sup>20</sup> absence coronary calcium (Agatston score = 0), the absence of signs of positive remodeling of the coronary artery wall. The exclusion criteria were rhythms and conductivity disorders, any cardiovascular pathology.

### 2.1.3 | MDCT-CA protocol

During MDCT-CA, all patients had sinus rhythm with a heart rate of 50–65 beats per minute. Heart rate and blood pressure were evaluated before each scan. Patients with a heart rate higher than 60 bpm were treated with intravenous infusion of 1 mg metoprolol before CT scan and all patients received 0.5 mg of sublingual nitroglycerin. In patients with long-term AF an electrical cardioversion with intravenous sedation was performed before the MDCT-CA.<sup>3</sup>

MDCT-CA was performed on a 64-detector CT scanner (GE Discovery NM/CT 570c, GE Healthcare, Milwaukee, WI, USA).

An unenhanced coronary artery calcium scoring scan was obtained according to the following protocol: prospective triggering at 75% of R-R interval; tube voltage of 120 kV; tube current of 400 mA and 1.25 mm slice thickness.

For the contrast-enhanced scans, 70–90 ml of nonionic contrast agent (Iopamidol 370 mg iodine/mL, Bracco Diagnostics, Italy) was injected intravenously through an 18-gauge antecubital catheter at a flow rate of 5–5.5 ml/s followed by 40 ml of saline. Obtained data were reconstructed in the diastole phase (mostly, 75% of RR interval duration) and analyzed using Advantage Workstation 4.6, GE Healthcare.<sup>23</sup>

The total radiation exposure ranged from 4 to 5.5 mSv.

### 2.1.4 | Adipose tissue segmentation and radiomics features extraction

The feature extraction and definition in this study were consistent with the Imaging Biomarker Standardization Initiative.<sup>24</sup>

Segmentation and subsequent radiomic analysis of EAT were performed on an unenhanced coronary artery calcium scoring series of 3D DICOM images that were exported to the 3D-Slicer software (Boston, MA).<sup>25</sup> The volume of interest of EAT was obtained by semiautomatic segmentation using the Segment Editor package. Segmentation of EAT was performed manually, using a hand-held instrument of various sizes, from the level of the pulmonary trunk bifurcation to the apex of the heart in Segmentations module. The range of adipose tissue attenuation valued from –190 to –30 HU (Figure 1).

Feature extraction such as average attenuation of the EAT, the volume, as well as the radiomic features of the EAT including 18 parameters of the first-order statistics, 24 parameters of the gray level co-occurrence matrix (GLCM), 16 parameters gray level run length matrix (GLRLM), 14 parameters gray level dependence matrix (GLDM), 16 parameters gray level size zone matrix (GLSZM), and five parameters neighboring gray-tone difference matrix (NGTDM) was based on the 3D slicer platform and used the PyRadiomics package (version 3.0.1).

Segmentation and extraction of radiomic parameters were re-performed by two experienced radiologists who were not aware of the patient's clinical history and of the results of prior conventional imaging.

## 2.2 | Follow-up and endpoint

All patients were followed up prospectively for 12 months after the CA in the outpatient clinic. Holter ECG monitoring was performed at 3, 6, and 12 months. If patient had symptoms suggestive of AF, additional ECGs and Holter ECG recordings were obtained. The criteria of AF recurrence were AF episodes of more than 30 s duration. A blanking period of 3 months was applied and AF recurrence within the first month was considered transient. The primary endpoint of the study was AF recurrence between 3 and 12 months after ablation. Secondary endpoint was major adverse cardiovascular event (MACE) such as sudden cardiac death, AMI, stroke, hospitalization because of HF, revascularization, including percutaneous coronary intervention, and coronary artery bypass graft.

## 2.3 | Statistical analyses

Statistical processing of data was performed with Statistica 11.0 (StatSoft, USA) and R. The distribution of continuous variables was checked by using the Shapiro–Wilk *W*-test. Statistical comparisons between two subgroups were performed by the Mann–Whitney *U*-test, between three subgroups were performed by the Kruskal–Wallis test. Categorical variables were compared using the Fisher's exact test. Cox regression analysis was also used to determine the

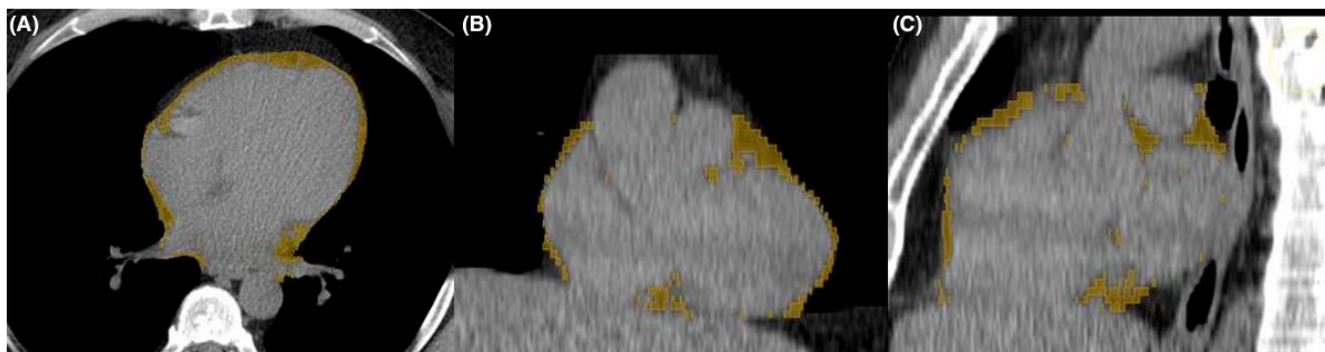


FIGURE 1 Segmentation of epicardial adipose tissue on noncontrast CT scans: (A) axial slice; (B) frontal slice; (C) sagittal slice.

significant radiomics predictors of AF recurrences. The values of sensitivity, specificity, and diagnostic accuracy, as well as the positive and negative predictive values of the models were calculated based on generally accepted formulas and ROC curves.

Reliability of radiomic features were calculated using two-way random model (absolute agreement type) intraclass correlation coefficients (ICCs) and their 95% confidence intervals (CI) for each feature. The ICC estimates and CI were stratified to indicate poor (ICC CI < 0.5), moderate (0.5 < ICC CI < 0.75), good (0.75 < ICC CI < 0.9) and excellent (ICC CI > 0.9) reliability.<sup>26</sup>

### 3 | RESULTS

#### 3.1 | Patients characteristics

The baseline characteristics of patients of Group 1 and Group 2 are shown in Table 1.

In Group 1, paroxysmal form of AF was in 20 (46.5%) patients, persistent in 12 (27.9%) patients, long-term persistent in 11 (25.5%).<sup>3</sup> All patients denied alcohol consumption; eight (18.6%) of them were smokers or smoked before.

TABLE 1 Baseline characteristics of Group 1 and Group 2

Characteristic	Group 1 AF patients (n = 43)	Group 2 comparative group (n = 20)	p-value
Gender n, (%)			
Men	35 (81.3%)	15 (75%)	p = .1731
Women	8 (18.7%)	5 (25%)	p = .8117
Age, years <sup>a</sup>	42 (35–47)	39 (34–44)	p = 0.0867
Duration of AF history, years <sup>a</sup>	4 (2–7)		
AF type, n, (%)			
Paroxysmal	20 (46.5%)		
Persistent	12 (27.9%)		
Long-standing persistent	11 (25.5%)		
BMI, kg/m <sup>2a</sup> Me	28.3 (24.8–30.8)	27.7 (23.5–30)	p = .3088
Overweight (BMI 25–29.9), n, (%)	18 (58%)	11 (55%)	p = .5164
Obesity			
1 degree (BMI 30–34.9), n, (%)	10 (32%)	0	
2 degree (BMI 35–39.9), n, (%)	3 (9.6%)	0	
3 degree (BMI 40 and more), n, (%)	0	0	
Glucose (mmol/L)	4.4 (3.4–4.9)	Not defined	
Glucose tolerance test (mmol/L)	6 (5.1–6.5)		
Total cholesterol (g/ml)	3.9 (3.5–4.8)	4.4 (3.8–4.9)	p = .1637
High-density lipoprotein (mmol/L)	1.6 (1.4–1.9)	1.8 (1.6–2.2)	p = .0977
Low-density lipoprotein (mmol/L)	2.4 (2.1–2.6)	2.2 (1.8–2.5)	p = .1285
Smoker, current, or past, n, (%)	8 (18.6%)	5 (25%)	p = .2778
Alcohol consumption, n, (%)	0	0	
Obstructive sleep apnea syndrome, n, (%)	0	0	
Office blood pressure, mmHg			
Normal	30 (70%)	13 (65%)	p = .2932
High normal	13 (30%)	7 (35%)	p = .1976
Echocardiography			
EF, % <sup>a</sup>	66 (62–70)	65 (61–70)	p = .8032
EDV, ml <sup>a</sup>	112 (101–127)	105 (98–111)	p = .1029
ESV, ml <sup>a</sup>	37 (34–44)	33 (26–40)	p = .3251
LA diameter, mm <sup>a</sup>	40 (35–44)	34 (31–38)	p = .0035
MDCT-CA			
LA max volume, sm <sup>3a</sup>	100.5 (80–127)	79 (72–85)	p = .0019
CAD, n, (%)	0	0	

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CA, catheter ablation; CAD, coronary artery disease; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LA, left atrium.

<sup>a</sup>Data are presented as Me (lower quartile – upper quartile).

The Me of BMI was 28.3 kg/m<sup>2</sup> (24.8; 30.8). Overweight (BMI 25–29.9 kg/m<sup>2</sup>) was in 18 (58%) patients, grade 1 of obesity - in 10 (32%) patients, grade 2 of obesity - in 3 (9.6%) patients.<sup>27</sup> High normal office blood pressure<sup>22</sup> was diagnosed in 13 (30%) patients. The medians of total cholesterol, high-density lipoprotein, and low-density lipoprotein were 3.9 (3.5–4.8), 1.6 (1.4–1.9), and 2.4 (2.1–2.6), respectively.

The obstructive sleep apnea syndrome was excluded in all patients, based on history and complains.

Impaired glucose tolerance and diabetes mellitus were excluded in 100% of patients. Thus, the Me of fasting glucose level was 4.4 (3.4; 4.9) mmol/L, Me of glucose level on 75-g oral glucose tolerance test was 6 (5.1; 6.5) mmol/L.

According to echocardiography data, the values of ejection fraction (EF), end-diastolic volume (EDV), and end-systolic volume (ESV) in all patients were normal: the median of LVEF was 66% (62; 70), EDV 112 (101; 127) ml, and ESV 37 (34; 44) ml. The median of LA diameter was 40 (35; 44) mm, wherein this parameter was increased (25–38 mm)<sup>28</sup> in 23 patients. The maximum LA volume exceeded 90 cm<sup>3</sup><sup>29</sup> in 23 patients and averaged 100.5 (80; 127) cm<sup>3</sup>.

In Group 2, the median age of patients was 39 (34; 44) years. Echocardiographic EF, EDV, and ESV were within the normal range: 65 (61; 70) %, 105 (98; 111) ml, 33 (26; 40) ml, respectively. All patients denied diabetes mellitus, 5 (25%) of them were smokers or smoked earlier. Hypertension of the first stage (medically corrected) was reported by seven (35%) patients. The median BMI in this group was 27.7 (23.5; 30) kg/m<sup>2</sup>, whereas 11 (55%) patients had overweight (25–30 kg/m<sup>2</sup>). According to MDCT-CA data, CAD was excluded in all patients enrolled to the study.

Statistical comparison of Group 1 and Group 2 indicators was performed using the Fisher's exact test and the Mann-Whitney U-test and showed the absence of significant differences between groups.

### 3.2 | Interobserver reliability

The interobserver reliability was excellent for all radiomics features.

For EAT volume ICC – 0.806 (95% CI 0.759–0.882,  $p < .001$ ), EAT attenuation – 0.991 (95% CI 0.977–0.996,  $p < .001$ ).

A comprehensive ICC analysis for each radiomics feature and figure illustrating ICC (Mean, 95%CI) for each radiomic feature grouped by matrices are provided in Supplement S1.

### 3.3 | CT and radiomic characteristics of epicardial adipose tissue in Groups 1 and 2

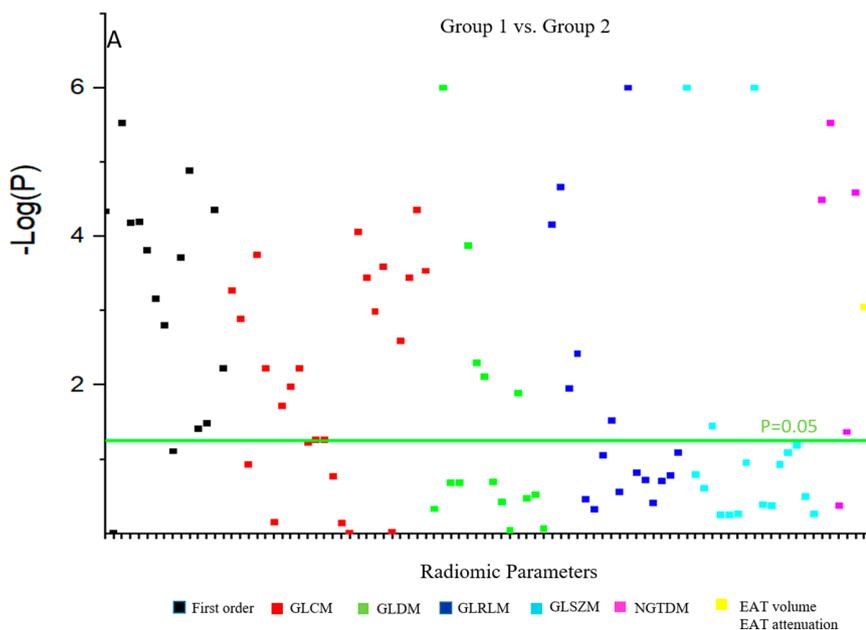
The median volume of EAT in Group 1 was 175.2 cm<sup>3</sup> (129; 226) and the median attenuation was –77 (–79; –76) HU. We found a moderate correlation between the EAT volume and BMI ( $r = 0.426$ ,  $p = .006$ ), as well as a good correlation between the EAT volume and LA diameter ( $r = 0.631$ ,  $p = .001$ ). Other clinical parameters, including duration of AF and type of AF, had no significant correlation with EAT volume and attenuation.

In Group 2 (comparative), the EAT volume and attenuation were significantly lower than in Group 1: 107.4 (86; 126) cm<sup>3</sup> vs. 175.2 cm<sup>3</sup> (129; 226) ( $p = .0009$ ), and –81.6 (–83; –79) vs –77 (–79; –76) HU ( $p = .001$ ), respectively.

Among 93 extracted radiomic characteristics of EAT, 45 (48.4%) parameters (12 – first-order statistics, 15 – GLCM, 5 – GLDM, 6 – GLRLM, 3 – GLSZM, and 4 – NGTDM) had significant differences between Groups 1 and 2 (Figure 2).

### 3.4 | Follow-up result

The follow-up for 12 months (interquartile range 5.2–12.2) was complete in all 43 patients. According to the ECG Holter monitoring, AF



**FIGURE 2** Manhattan plots of  $p$ -values for Mann-Whitney  $U$ -test of basic EAT characteristics and all radiomic parameters among Group 1 and Group 2. Negative logarithm of  $p$ -values is plotted on the y-axis for each of the 93 radiomic parameters lined up on the x-axis. The green horizontal line  $p$ -value of .05. Parameters above the line are considered statistically significant. EAT, epicardial adipose tissue.

recurrence was registered in 19 (44%) patients. During the follow-up period, neither atrial tachycardia nor MACE and other potential complications were registered in the study population.

### 3.5 | Relationship between CT characteristics of epicardial adipose tissue, radiomic features of epicardial adipose tissue, and atrial fibrillation recurrence in Group 1

After the end of the follow-up, we divided patients of Group 1 into two subgroups, which included those with (Group 1a) and without (Group 1b) AF recurrence. Then we have compared some of their clinical characteristics, which are considered as risk factors for AF recurrence after CA,<sup>3</sup> CT characteristics of EAT

(volume and attenuation) (Table 2.) and radiomic characteristics of EAT.

According to our results there were no significant differences between Group 1a and Group 1b for the main clinical risk factors for the development and recurrence of AF, as well as for EAT volume and density estimated by CT (Table 2).

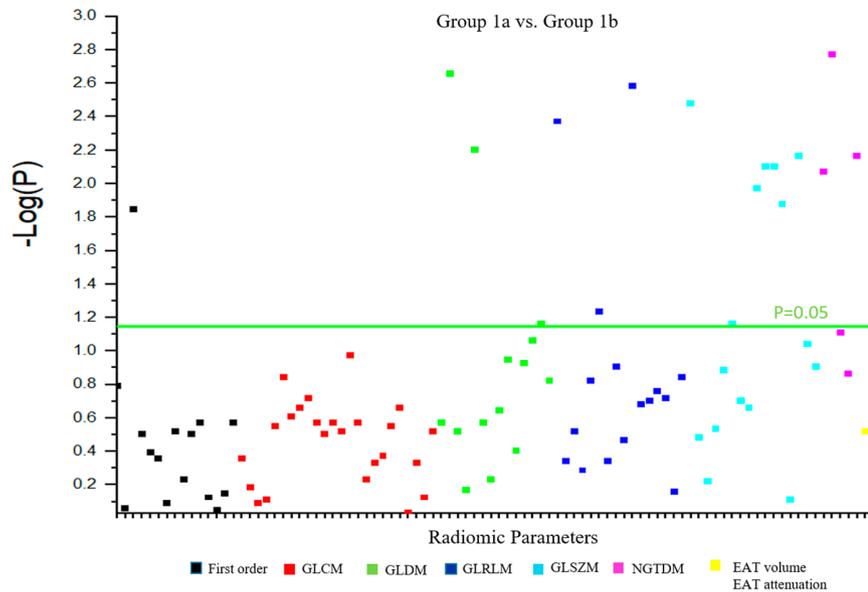
Of 93 radiomic parameters of EAT, 17 parameters (16.1%) were significantly different between these subgroups (Figure 3). All the same radiomic parameters of EAT were independent predictors for AF recurrence according to univariable logistic analyses (Table 3), whereas clinical risk factors such as AF type and duration, smoking, hypertension, BMI, LA volume, and diameter were not significant (Table 3).

Subsequently, multivariable analysis demonstrated that only gray level nonuniformity parameter (GLSZM) was an independent

TABLE 2 Clinical characteristics of patients with and without AF recurrence after CA

Characteristic	Group 1a (with AF recurrence) n = 19	Group 1b (without AF recurrence) n = 24	Mann-Whitney U-test p-value/ *Kruskal-Wallis test
Gender n, (%)			
Men	17 (89.4%)	18 (75%)	p = .1104
Women	2 (10.6%)	6 (25%)	p = .0892
Age, years	43.8 ± 12.17	40.6 ± 7.19	p = .1029
Duration of AF history, years	5.47 ± 4.14	4.75 ± 3.33	p = .6536
AF type, n, (%)			
Paroxysmal	6 (31.5%)	14 (58.3%)	*p = .1354
Persistent	8 (42.1%)	4 (16.6%)	*p = .6607
Long-standing persistent	5 (26.3%)	6 (25%)	*p = .2097
BMI, kg/m <sup>2</sup>	27.9 ± 2.67	28.3 ± 3.42	p = .1749
Overweight (BMI 25–29.9), n, (%)	13 (68.4%)	5 (20.8%)	p = .092
Obesity			
1 degree (BMI 30–34.9), n, (%)	3 (15.7%)	8 (33.3%)	p = .1104
2 degree (BMI 35–39.9), n, (%)	0	2 (8.3%)	p = .066
3 degree (BMI 40 and more), n, (%)	0	0	
Glucose (mmol/L)	4.31 ± 0.8	4.11 ± 0.9	p = .2631
Glucose tolerance test (mmol/L)	6.04 ± 0.8	5.9 ± 0.7	p = .1282
Smoker, current, or past, n, (%)	4 (21%)	4 (16.6%)	p = .8032
Office blood pressure, mmHg			
Normal	14 (73.7%)	16 (67%)	p = .1421
High normal	5 (26.3%)	8 (33%)	p = .0904
EF, %*	61.7 ± 12.25	64.5 ± 7.36	p = .6082
EDV, ml*	120.1 ± 37.16	112.5 ± 17.7	p = .0959
ESV, ml *	50 ± 37.44	40.4 ± 10.22	p = .6105
LA diameter, mm*	39.8 ± 7.14	39.4 ± 5.89	p = .5832
LA max volume, sm <sup>3</sup> *	117.2 ± 38.7	100 ± 35.24	p = .2011
EAT volume, sm <sup>3</sup>	174 ± 56.9	176.6 ± 73.3	p = .2354
EAT density, Hu	-78.4 ± 2.2	-77.4 ± 3.33	p = .1681

Abbreviations: AF, atrial fibrillation; BMI, bodymass index; CA, catheter ablation; CAD, coronary artery disease; EAT, epicardial adipose tissue; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; Hu, Hounsfield units; LA, left atrium.



**FIGURE 3** Manhattan plots of  $p$ -values for Mann–Whitney  $U$ -test of basic EAT characteristics and all radiomic parameters among Group 1a and 1b. Negative logarithm of  $p$ -values are plotted on the y-axis for each of the 93 radiomic parameters lined up on the x-axis. The green horizontal line  $p$ -value of .05. Parameters above the line are considered statistically significant. EAT, epicardial adipose tissue.

**TABLE 3** Univariate and multivariate regression analysis of radiomic features of EAT

Matrix	Futures	Univariable analysis		Multivariate regression model	
		OR (95% CI)	$p$ -value	OR (95% CI)	$p$ -value
First order	Energy	1.0210 (1.0037–1.0386)	.0174		NS
GLCM	lmc1	0.6932 (0.4868–0.9872)	.0311		NS
GLDM	Gray level nonuniformity	1.0858 (1.0178–1.1583)	.0015		NS
	Large dependence high Gray level emphasis	1.2409 (1.0024–1.5361)	.035		NS
	Small dependence high Gray level emphasis	0.4432 (0.1897–1.0356)	.0602		NS
GLRLM	Gray level nonuniformity	1.1217 (1.0262–1.2260)	.0014		NS
	Long-run emphasis	8.2179 (1.0211–66.1364)	.033		NS
	Run variance	9.3349 (1.009–8450.04)	.034		NS
	Run length nonuniformity	1.0390 (1.0089–1.0701)	.0016		NS
GLSZM	Gray level nonuniformity	1.2498 (1.0687–1.4616)	.0011	0.10027 (1.0009–1.0044)	.002
	Size zone nonuniformity	1.1087 (0.6972–1.9639)	.0053		NS
	Size zone nonuniformity normalized	0.8198 (0.0210–1.49)	.0153		NS
	Small area emphasis	0.8076 (0.6766–0.9639)	.006		NS
	Zone entropy	95.87 (2.47–3709.53)	.0144		NS
NGTDM	Busyness	1.0434 (1.0084–1.0796)	.0147		NS
	Coarseness	0.9746 (0.9548–0.9948)	.0140		NS
	Strength	0.9161 (0.8484–0.9891)	.0251		NS

Abbreviations: CI, confidence interval; EAT, epicardial adipose tissue; GLCM, gray level co-occurrence matrix; GLDM, parameters gray level dependence matrix; GLRLM, gray level run length matrix; GLSZM, gray level size zone matrix; NGTDM, neighboring gray-tone difference matrix; OR, odds ratio.

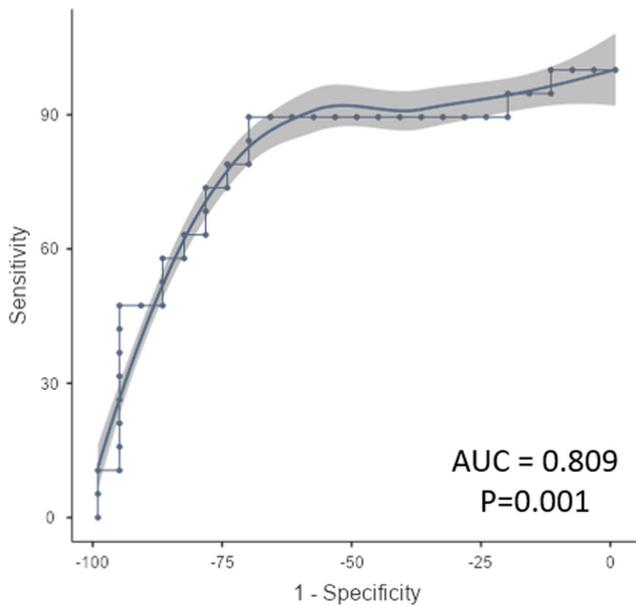
radiomic predictor of AF recurrence within 12 months after CA (OR 1.0027, 95% CI 1.0009–1.0044,  $p = .002$ ) (Table 3).

ROC analysis data (Figure 4) showed that  $GLSZM > 1227.4$  (cut-off point) indicates high probability of lone AF recurrence during 12 months after CA (specificity 70.8%, sensitivity 89.4%, AUC 0.809,  $p < .001$ ).

Kaplan–Meier analysis also showed that the  $GLSZM > 1227.4$  significantly increases the risk of AF recurrence after CA ( $p < .003$ ) (Figure 5).

It should be noted that GLSZM characterizes the variability of gray level intensity, which increased with decreasing of gray levels uniformity.<sup>30</sup> In fact, GLSZM characterizes the morphological heterogeneity of EAT.

In addition, we have revealed that GLSZM had a positive correlation with maximum LA volume and diameter (Spearman's  $r = 0.346$ ,  $r = 0.441$ ,  $p < .05$ , respectively). No correlations were found for other clinical, laboratory, and instrumental parameters.



**FIGURE 4** Receiver operating curves for gray level nonuniformity GLSZM in predicting late AF recurrence after CA. AF, atrial fibrillation; CA, catheter ablation.

## 4 | DISCUSSION

The major finding of the present study is that pre-procedural radiomic CT parameters of EAT, particularly  $GLSZM > 1227.4$ , can identify patients at risk for lone AF recurrence after pulmonary vein ablation, in the absence of other predictors.

We have also found that patients with lone AF have larger volume and higher attenuation of EAT, comparing with population without cardiac arrhythmias. These data are consistent with other studies, which have been showed that EAT can have a proarrhythmic effect through the action on the atria.<sup>7,31–33</sup> This can be explained by one of the mechanisms previously described in literature. The first is the direct infiltration of the myocardium by adipocytes, which leads to the formation of tissue and electrical heterogeneity, following by LA structural remodeling.<sup>34</sup> The second mechanism is induction of inflammation and fibrosis in the myocardium due to the secretion of proinflammatory cytokines by adipose tissue itself.<sup>7,35</sup> The third mechanism is associated with the increase of adrenergic activation of ganglionic plexuses, located in EAT, presumably as a result of increased catecholamine content in adipose tissue or as a result of  $Ca^{2+}$  current changing.<sup>36–38</sup> The presence of one or several of the processes described above is possible in the EAT; however, the reasons for their initiation in patients with lone AF remain unclear.

Most studies confirm the contribution of inflammation in the EAT to the progression of cardiovascular disease. Several studies have shown the relationship of immune cell infiltration of perivascular adipose tissue, progression of atherosclerotic process and EAT attenuation, using histological verification and circulating inflammatory markers.<sup>39–41</sup> Liu Z. et al.<sup>42</sup> suggest that decreased perivascular adipose tissue density is a sign of fibrotic changes and an increase is a sign of inflammation. Besides, Ishii et al.<sup>43</sup> showed that decreased

adipocyte size is closely associated with fibrous remodeling of EAT, and decreased EAT attenuation measured on CT images may represent a noninvasive marker of fibrous remodeling. Although we did not use methods to verify inflammation, therefore, we cannot exclude its contribution to the development, persistence, and recurrence of AF, as well as fibrosis's contribution.

Previous study has shown the relationship of AF duration, severity and the LA echocardiographic measures.<sup>44</sup> Another study showed an increase in epicardial fat mass of the posterior wall of the LA in patients with persistent AF. At the same time, LA volume was associated with the severity of arrhythmia.<sup>45</sup> In the present study, we found a relationship between EAT volume, LA diameter, and LA volume, but not with AF severity and its duration from first diagnosis. This inconsistency with the results of the current study may be explained by differences in studied populations.

According to the results of our study, patients with lone AF also had a pronounced radiomic EAT phenotype compared to patients without cardiac arrhythmias. Differences in radiomic characteristics were most often observed in the matrix of the first-order statistics, representing the physical characteristics of zone of interest (attenuation, volume, etc.) on the CT scan, and in the matrix of the gray level co-occurrence, reflecting the texture characteristics (graininess, uniformity, regularity, roughness). In turn, changes in textural (radiomic) characteristics can be signs of molecular peculiarities of adipose tissue, showing EAT dysfunction in patients with AF. Considering the absence of significant differences in clinical parameters between the comparison group and patients with lone AF, these results show prospects for the use of radiomic analysis of EAT images for individual AF risk assessment. This can be achieved by using artificial intelligence algorithms and methods of multivariate data analysis in larger patient cohort.<sup>15</sup>

At the same time, successful and widespread applying of radiomics in clinical practice is only possible under good reproducibility of radiomic parameters, which depends on the segmentation method (manual or automatic), X-ray tube parameters, image reconstruction algorithm, and the type of used software.<sup>46,47</sup> We chose to analyze noncontrast images because the Ca-scoring protocol is standardized. In addition, it was important for us to make a prognostic assessment using native radiomic features of the EAT, while maintaining high reproducibility of the results. In our study, we used the manual method of image segmentation and obtained excellent interobserver reproducibility (ICC range 0.9–1). We did not use contrast-enhanced images, as this could have distorted the native radiomic values. Considering that the EAT is just as well vascularized, the use of the contrast agent may affect the radiomic values. On the other hand, X-ray tube parameters for the contrast series of coronary artery scans are variable and are set individually depending on heart rate, patient weight and scan volume, which excludes the use of data in multicenter studies and requires standardization or introduction of correction coefficients.<sup>46</sup>

Current 12 months follow-up results mostly agree with previous studies. Particularly, late post-ablation AF recurrence occurred in 44% of enrolled patients, which is consistent with other data.<sup>3,48</sup>

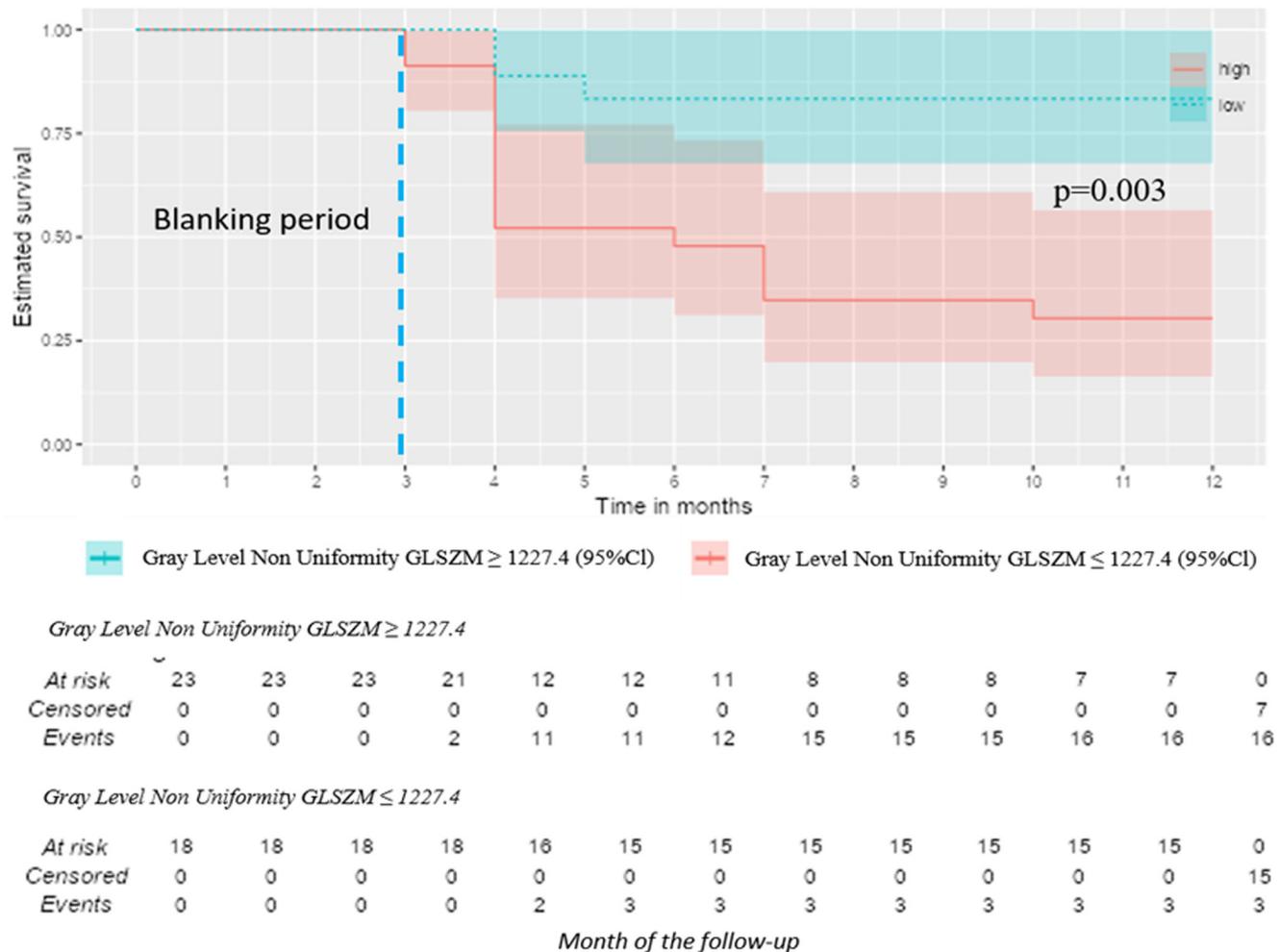


FIGURE 5 Kaplan-Meier AF recurrence-free rate curves (KMunicate-style plot). AF recurrence-free curves in patients with gray level nonuniformity GLSZM  $\geq$  1227.4 and with gray level nonuniformity GLSZM  $\leq$  1227.4. AF, atrial fibrillation.

Also, we did not find significant differences in clinical risk factors between subgroups of patients with and without AF recurrence. Accordingly, this shows the difficulty of the recurrence risk assessment in a cohort of patients with lone AF using the generally accepted clinical scores. In addition, we did not find significant differences in EAT volume and density, despite the fact that the effect of EAT on the development of AF has been proven earlier.<sup>49</sup> Wherein, 16.1% of radiomic parameters of EAT were significantly different between subgroups with and without AF recurrence, showing the presence of structural differences of adipose tissue in patients at risk.

In our study, the only independent predictor of post CA AF recurrence within 12 months follow-up was EAT radiomic parameter gray level nonuniformity (GLSZM), which shows the variability of gray level intensity values. This may indicate morphological heterogeneity of the tissue, but in the absence of histological analysis of EAT, it is impossible to prove and explain this assumption. However, considering the positive correlation between gray level nonuniformity and volumes of LA and EAT, we believe that the changes of this

parameter are associated with morphological heterogeneity of the EAT caused by hypertrophy and hyperplasia of adipocytes, as well as by fibrotic changes.

It should be noted, that for our knowledge the current study is the first, which assessed radiomic parameters of EAT on CT images of patients with lone AF. For this reason, we had no ability to compare our results with results of other studies.

## 5 | CONCLUSION

The radiomic characteristics of EAT in patients with lone AF significantly differ from those in a population without cardiac arrhythmias. In the present study, it was shown that the radiomic parameter GLSZM is associated with AF recurrence after CA in patients. Moreover, GLSZM was the stronger predictor of lone AF recurrence in multivariate analysis comparing with other established risk factors and EAT volume and attenuation. Thus, radiomic analysis of CT images of EAT has a potential to be used for prediction of the patient's outcome after CA.

## 6 | LIMITATIONS

The present study has several limitations, the most notable of which is relatively small sample size and short follow-up period. In addition, asymptomatic episodes of AF might have gone unrecognized. Due to the small sample size, we did not use advanced machine learning and artificial intelligence algorithms. The results of radiomic analysis in our study are not supported with data on the level of biochemical inflammation markers and data on histological studies of EAT.

### AUTHOR CONTRIBUTIONS

Study concept and design: Ilyushenkova J, Sazonova S, Batalov R.

Acquisition of data: Popov E, Archakov E, Moskovskikh T.

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Drafting of the manuscript: Ilyushenkova J.

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Statistical analysis: Ilyushenkova J.

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### CONFLICT OF INTEREST

Author J.N. Ilyushenkova declares that she has no conflict of interest; Author S.I. Sazonova declares that she has no conflict of interest; Author E.V. Popov declares that he has no conflict of interest; Author K.V. Zavadovsky declares that he has no conflict of interest; Author R.E. Batalov declares that he has no conflict of interest; Author S.V. Popov declares that he has no conflict of interest; Author E.A. Archakov declares that he has no conflict of interest; Author T.V. Moskovskikh declares that she has no conflict of interest; Author S.M. Minin declares that his work was supported by Russian Science Foundation, grant №17-75-20118; Author A.B. Romanov declares that his work was supported by Russian Science Foundation, grant №17-75-20118.

### DATA AVAILABILITY STATEMENT

All data are the property of Cardiology Research Institute and can be provided after a reasonable request.

### ETHICS APPROVAL

This prospective study was approved by the Ethics Committee of Federal State Budgetary Scientific Institution "Tomsk National Research Medical Center of the Russian Academy of Sciences." Written informed consent was obtained from all patients.

### INFORMED CONSENT

Written informed consent was obtained from all patients.

Registry and the Registration No: N/A.

Animal Studies: N/A.

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#### SUPPORTING INFORMATION

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