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ORIGINAL PAPER

New inflammatory predictors for non-valvular atrial fibrillation: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio

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Abstract The objective of this study was to investigate the relationship of echocardiographic epicardial fat thickness (EFT) and neutrophil to lymphocyte ratio (NLR) with different types of non-valvular atrial fibrillation (AF) in a clinical setting. A total of 197 consecutive patients were enrolled in the study. Seventy-one patients had paroxysmal non-valvular AF, 63 patients had persistent/permanent non-valvular AF, and 63 patients had sinus rhythm (control group). EFT was measured with echocardiography, while NLR was measured by dividing neutrophil count by lymphocyte count. EFT was significantly higher in patients with paroxysmal non-valvular AF compared with those in the sinus rhythm group (6.6 ± 0.7 vs. 5.0 ± 0.9 mm, $p < 0.001$). Persistent/permanent non-valvular AF patients had a significantly larger EFT compared with those with paroxysmal AF (8.3 ± 1.1 vs. 6.6 ± 0.7 mm, $p < 0.001$). EFT had a significant relationship with paroxysmal non-valvular AF (odds ratio 4.672, 95 % CI 2.329–9.371, $p < 0.001$) and persistent/permanent non-valvular AF (OR 24.276, 95 % CI 9.285–63.474, $p < 0.001$). NLR was significantly higher in those with paroxysmal non-valvular AF compared with those in the sinus rhythm group (2.5 ± 0.6 vs. 1.8 ± 0.4, $p < 0.001$). Persistent/permanent non-valvular AF patients had a significantly larger NLR when compared with paroxysmal non-valvular AF patients (3.4 ± 0.6, vs. 2.5 ± 0.6, $p < 0.001$). NLR (>2.1) had a significant relationship with non-valvular AF (OR 11.313, 95 % CI 3.025–42.306, b 2.426, $p < 0.001$). EFT and NLR are highly associated with types of non-valvular AF independent of traditional risk factors. EFT measured by echocardiography and NLR appears to be related to the duration and severity of AF.

Keywords Epicardial fat thickness · Echocardiography · Neutrophil to lymphocyte ratio · Non-valvular atrial fibrillation · Left atrial enlargement

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice [1]. There are many pathophysiological mechanisms responsible for the formation of AF. However, among the most important mechanisms responsible for AF are inflammatory changes occurring in the atrium [2]. Neutrophil/lymphocyte ratio (NLR), which can be derived from the white blood cell (WBC) count, is a novel marker of prognosis in patients with cardiovascular disease [3, 4].

Epicardial adipose tissue is a source for several endocrine and inflammatory mediators [5]. Epicardial fat may play a central role in the pathogenesis of cardiovascular disease, which is mediated by its inflammatory properties [6–8]. An association between inflammatory markers (e.g., C-reactive protein (CRP), interleukin 6 (IL-6), and high-sensitive CRP (hs-CRP)) and AF development and continuity has been proposed [9–11].

To our knowledge, the relationship between echocardiographic epicardial fat thickness (EFT) and the concomitant evaluation of EFT and NLR in patients with non-

valvular AF has not been investigated. Therefore, in this study, we evaluated the relationship between echocardiographic EFT and the concomitant evaluation of echocardiographic EFT–NLR with different types of AF.

Methods

Study population

A total of 197 consecutive patients were enrolled in the study. One hundred thirty four of them were patients who were diagnosed non-valvular AF and had applied to the cardiology outpatient clinic (the paroxysmal and persistent/permanent groups). The remaining 63 individuals had no known AF (the control group).

All patients underwent a complete physical examination and their medical histories and clinical features were recorded. Body mass index (BMI) was defined as weight (kg) divided by the square of height (m). The different types of AF were defined according to European Society of Cardiology (ESC) guidelines [2] Paroxysmal AF is defined as self-terminating, usually within 48 h or 7 days. Persistent AF is considered to bean AF episode that either lasts longer than 7 days or requires termination by cardio version. Permanent AF exists when the presence of the arrhythmia is accepted by the patient and physician.

The inclusion criteria were determined as patients over 18 years of age who applied to the cardiology clinic with at least one attack of AF identified by electrocardiographic examination and assessed by a cardiologist.

Exclusion criteria were clinically significant valvular heart disease, significant congestive heart failure, hematological disease, cancer, severe renal or liver disease, ongoing infection or systemic inflammatory conditions, autoimmune disease, obesity (BMI > 30 kg/m^2) and patients with poor echocardiographic windows.

Echocardiography and epicardial fat measurement

All participants underwent transthoracic echocardiography using an echocardiograph equipped with a broadband transducer (Vivid S6, GE Medical Systems, USA). Measurements were obtained from the long axis and apical four-chamber view according to standard criteria. The echocardiographic images were entered in a computerized database (EchoPac system).

The offline measurements of the EFT were performed by two cardiologists blinded to the patient information in order to avoid inter-reader variability. The echocardiograms of 30 patients were randomly selected and a second measurement of the EFT was performed 2 weeks later in order to evaluate the inter-observer and intra-observer variability.

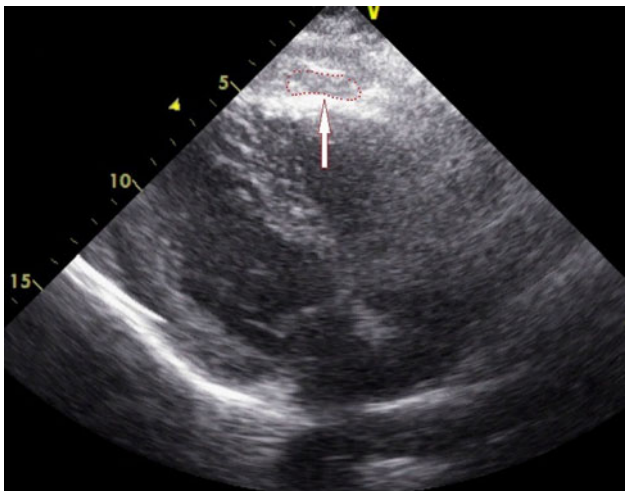

Fig. 1 Epicardial fat thickness. Echocardiographic parasternal long-axis views of epicardial fat thickness (the echo free space within the red dotted line)

Echocardiographic assessments of the EFT were measured according to previously published methods [12]. The epicardial fat was identified as an echo-free space in the pericardial layers on the two-dimensional echocardiography (Fig. 1). The maximum EFT was measured at the point on the free wall of the right ventricle along the midline of the ultrasound beam, perpendicular to the aortic annulus as the anatomic landmark at end-systole in three cardiac cycles. The inter-observer and intra-observer variabilities of the EFT were 2.4 and 1.8 %, respectively.

Left atrial diameter was measured at end systole in the parasternal long-axis view according to standard criteria. Left ventricular ejection fraction (LVEF) was calculated using the Simpson method [13].

Biochemical and hematological parameters

Total and differential leukocyte counts were measured by an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois). Absolute cell counts were used in the analyses. Baseline NLR was measured by dividing neutrophil count by lymphocyte count. Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and fasting glucose creatinine levels were measured using the Abbott Architect C16000 auto analyzer (Abbott Laboratory). HbA1c was measured using the Agilent HPLC methods.

Statistical analysis

The statistical analysis was carried out using the SPSS for windows version 18.0 (SPSS Inc. Chicago, IL, USA). All normally distributed variables were tested using the

Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as number and percentage. The Mann–Whitney U test was used for the continuous variables and the χ^2 test was used for the categorical changes. The Kruskal–Wallis test was used for continuous variables in more than two groups. Post hoc analysis was performed with the Mann–Whitney U-test with Bonferroni correction ($p < 0.017$ was considered significant for Bonferroni). Relationships between the variables were examined with Spearman's correlation coefficients. The cut-off values for the echocardiographic EFT and the NLR for predicting non-valvular AF with corresponding sensitivity and specificity was estimated by receiving operator characteristic (ROC) curve analysis. The determinants of the dependent echocardiographic EFT thickness variables were assessed with linear regression analyses using independent variables described below. Multivariate logistic regression analysis was performed to assess the independent predictors of non-valvular AF. All variables that were found to be significant in univariate analysis were included in the logistic regression model, and results are shown as an odds ratio (OR) with 95 % confidence intervals (CI).The multivariate multinomial logistic regression method was used to set the independent predictors of both paroxysmal non-valvular AF and persistent/permanent non-valvular AF. Variables that were statistically significant among the groups in the univariate analysis were accepted as covariates in the multinomial logistic regression analysis. Statistical significance was based on a value of $p < 0.05$.

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. All patients and controls gave informed consent prior to entry into this study.

Results

Baseline characteristics

A total of 197 patients were studied. One hundred thirty four of these were patients with non-valvular AF, and 63 were controls with sinus rhythm. The baseline characteristics of the non-valvular AF and sinus rhythm (control) groups are shown in Table 1. Within the non-valvular AF group, there were 71 patients with paroxysmal non-valvular AF and 63 patients with persistent/permanent non-valvular AF (Table 2). Patients with non-valvular AF had significantly more EFT compared with those in the control group (7.4 ± 1.3 vs. 5.0 ± 0.9 mm, $p < 0.001$). The mean EFT value of the paroxysmal non-valvular AF group was significantly higher than that of the control group (6.6 ± 0.7 vs. 5.0 ± 0.9 mm, $p < 0.001$) (Fig. 2a), and persistent/permanent non-valvular AF patients had a larger EFT compared with patients who had paroxysmal non-valvular AF (8.3 ± 1.1 vs. 6.6 ± 0.7 mm, $p < 0.001$) (Fig. 2a). The mean NLR value of the paroxysmal non-valvular AF group was significantly higher than that of the control group (2.5 ± 0.6 vs. 1.8. ± 0.4, $p < 0.001$) (Fig. 1b) and the mean NLR value of the persistent/permanent non-valvular AF group was significantly higher than that of the paroxysmal non-valvular AF group (3.4 ± 0.6 vs. 2.5 ± 0.6, $p < 0.001$) (Fig. 2b). Spearman's correlation analysis revealed significant correlations between EFT and NLR (r = 0.660, $p < 0.001$), left atrium (LA) (r = 0.724 $p < 0.001$), age (r = 0.156, $p = 0.029$) and LVEF (r = −0.257, $p < 0.001$) values. Similarly,

Table 1 Baseline characteristics of patients with sinus rhythm (control) and all patients with non-valvular atrial fibrillation

	Sinus rhythm (n = 63)	Atrial fibrillation (n = 154)	*p* value[a]
Age (years)	61.1 ± 11.2	64.0 ± 10.0	0.075
Sex, female, n (%)	34 (54)	71 (53)	0.897
Hypertension n (%)	11(18)	32 (24)	0.309
Diabetes mellitus n (%)	12 (19)	25 (19)	0.948
Smoking n (%)	12 (19)	41 (31)	0.088
BMI (kg/m^2)	25.1 ± 1.3	25.1 ± 1.7	0.719
LA (mm)	34.3 ± 3.5	42.1 ± 5.0	<0.001
LVEF (%)	59.8 ± 1.2	57.8 ± 5.0	<0.001
EFT (mm)	5.0 ± 0.9	7.4 ± 1.3	<0.001
WBC (K/L)	9.8 ± 2.0	11.2 ± 2.2	0.001
Neutrophil count (K/UL)	5.9 ± 1.4	7.3 ± 1.5	<0.001
Lymphocyte count (K/UL)	3.3 ± 0.8	2.6 ± 0.7	<0.001
NLR	1.8 ± 0.4	2.9 ± 0.7	<0.001
Monocyte count (K/UL)	0.8 ± 0.4	0.9 ± 0.9	0.666
Hemoglobin (g/dl)	13.3 ± 1.6	13.9 ± 1.7	0.040
Platelet count (K/UL)	259.8 ± 95.9	258.1 ± 80.1	0.898
Total cholesterol (mg/dl)	195.1 ± 39.9	184.2 ± 42.7	0.090
LDL (mg/dl)	12.8 ± 35.5	117.0 ± 37.3	0.035
HDL (mg/dl)	43.1 ± 10.4	40.0 ± 9.2	0.016
Triglycerides (mg/dl)	148.3 ± 93.5	167.1 ± 106.0	0.230
Creatinin (mg/dl)	0.9 ± 0.3	1.0 ± 0.7	0.226
Glucose (mg/dl)	104.0 ± 22.0	97.5 ± 30.0	0.148
HbA1c	7.2 ± 0.8	7.4 ± 0.5	0.678

Values are mean ± SD or n (%)

BMI body mass index, *LVEF* left ventricular ejection fraction, *LDL* low-density lipoprotein *HDL* high-density lipoprotein. *LA* left atrial diameter, *WBC* white blood cell count, *NLR* neutrophil/lymphocyte ratio, *EFT* epicardial fat thickness

[a] Student's *t* test; Mann–Whitney *U* test; χ^2 test

Table 2 Baseline characteristics of patients with sinus rhythm (controls), paroxysmal non-valvular AF, and persistent/permanent non-valvular AF

	Sinus rhythm (n = 63)	Paroxysmal AF (n = 71)	Persistent/permanent AF (n = 63)	*p* value[a]
Age (years)	61.1 ± 11.2	63 ± 8.7	64.6 ± 11.3	0.014
Sex, female, n (%)	34 (54)	34 (58)	37 (59)	0.451
Hypertension n (%)	11(18)	13 (18)	19 (30)	0.150
Diabetes mellitus n (%)	12 (19)	10 (14)	15 (24)	0.360
Smoking n (%)	12 (19)	17 (24)	24 (38)	0.043
BMI (kg/m^2)	25.1 ± 1.3	25.0 ± 1.7	25.2 ± 1.7	0.829
LA (mm)	34.3 ± 3.5	39.8 ± 4.0	44.9 ± 4.7	<0.001
LVEF (%)	59.8 ± 1.2	58.4 ± 4.8	57.1 ± 5.0	<0.001
EFT (mm)	5.0 ± 0.9	6.6 ± 0.7	8.3 ± 1.1	<0.001
WBC (K/UL)	9.8 ± 2.0	11.5 ± 2.5	10.9 ± 2.0	0.002
Neutrophil count (K/UL)	5.9 ± 1.4	7.4 ± 1.8	7.2 ± 1.3	<0.001
Lymphocyte count (K/UL)	3.3 ± 0.8	3.1 ± 0.7	2.2 ± 0.5	<0.001
NLR	1.8 ± 0.4	2.5 ± 0.6	3.4 ± 0.6	<0.001
Monocyte count (K/UL)	0.8 ± 0.4	1.0 ± 1.1	0.8 ± 0.4	0.953
Hemoglobin (g/dl)	13.3 ± 1.6	13.8 ± 1.7	13.9 ± 1.7	0.080
Platelet count (K/UL)	259.8 ± 95.9	248.9 ± 59.0	268.6 ± 98.0	0.739
Total cholesterol (mg/dl)	195.1 ± 39.9	186.4 ± 47.3	181.7 ± 36.8	0.222
LDL (mg/dl)	12.8 ± 35.5	115.8 ± 39.2	118.3 ± 35.5	0.108
HDL (mg/dl)	43.1 ± 10.4	39.4 ± 8.3	39.8 ± 10.4	0.040
Triglycerides (mg/dl)	148.3 ± 93.5	177.6 ± 109.5	155.3 ± 101.4	0.145
Creatinin (mg/dl)	0.9 ± 0.3	1.0 ± 0.3	1.1. ± 1.0	0.326
Glucose (mg/dl)	104.0 ± 22.0	90.2 ± 26.3	105.7 ± 31.4	0.002
HbA1c	7.2 ± 0.8	7.1 ± 0.3	7.5 ± 0.6	0.076

Values are mean ± SD or n (%)

[a] Kruskal–Wallis tests; Mann–Whitney *U* test; χ^2 test. *AF* atrial fibrillation; other abbreviations as in Table 1

significant correlations were observed between NLR and LA (r = 0.556, $p < 0.001$), age (r = 0.145, $p = 0.043$) and LVEF (r = 0.276, $p < 0.001$) values. Figure 3 shows the correlation between EFT, NLR and LA enlargement. An EFT of 6.05 mm predicted AF with a sensitivity of 88.8 % and a specificity of 92.1 % (ROC area AUC 0.847, 95 % CI 0.910–0.984; $p < 0.001$) (Fig. 4). A cut-off level of 2.13 for NLR predicted AF with a sensitivity of 86.5 % and a specificity of 81.0 % (ROC AUC 0.897, 95 % CI 0.854–0.939, $p < 0.001$(Fig. 4). Table 3 shows the ROC analysis of EFT and NLR for the non-valvular AF group. LA size ≥37.5 mm predicted non-valvular AF with a sensitivity of 81.3 % and a specificity of 82.5 % specificity (ROC AUC 0.897, 95 % CI 0.853–0.941; $p < 0.001$).

Epicardial fat, neutrophil to lymphocyte ratio, and non-valvular AF

A multivariate linear regression analysis for the relationship between EFT and other variables is shown in Table 4. There was a relationship between EFT and both LA size (b = 0.13, 95 % CI 0.107–0.170, $p < 0.001$) and NLR (b = 0.726, 95 % CI 0.516–0.936, $p < 0.001$). Multivariate binary logistic regression analysis revealed that high levels of EFT and NLR were independent predictors of non-valvular AF. EFT was associated with non-valvular AF (OR 4.453 95 % CI 1.941–10.219, b = 1.494, $p < 0.001$), LA size (OR 1.388, 95 % CI 1.101–1.749, b = 0.328, $p = 0.005$), and NLR (>2.13, NLR cut off level 2.13) (OR 11.313, 95 % CI 3.025–42.306, $p < 0.001$ b = 2.426) (Table 5). Multivariate multinomial logistic regression analysis revealed a relationship between EFT and both paroxysmal non-valvular AF (OR 4.672, 95 % CI 2.329–9.371, $p < 0.001$) and persistent/permanent non-valvular AF (OR 24.276, 95 % CI 9.285–63.474, $p < 0.001$).These relationships were completely independent of every risk factor (Table 6). LA diameter (mm) was associated with both paroxysmal non-valvular AF (OR 1.251, 95 % CI 1.059–1.478, $p = 0.009$) and persistent/permanent non-valvular AF (OR 1.510, 95 % CI 1.226–1.859, $p < 0.001$).

Epicardial fat and left atrial size

Consistent with previous studies, LA size was larger in AF patients compared with the control group (sinus rhythm)

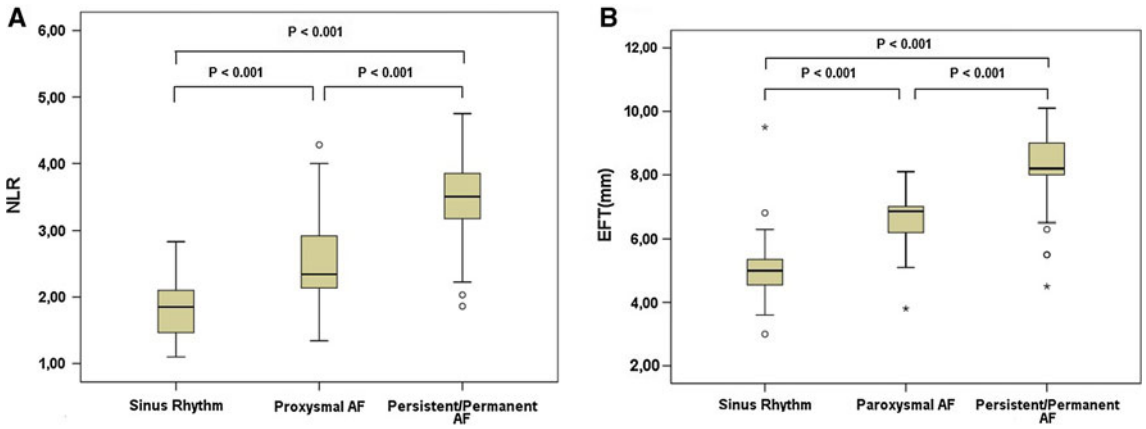

Fig. 2 **a** Box plot presentation of the comparison of neutrophil to lymphocyte ratio with sinus rhythm (control), paroxysmal AF, and persistent/permanent non-valvular AF. **b** Box plot presentation of the comparison of echocardiographic epicardial fat thickness among patients with sinus rhythm (control), paroxysmal, and persistent/permanent non-valvular AF

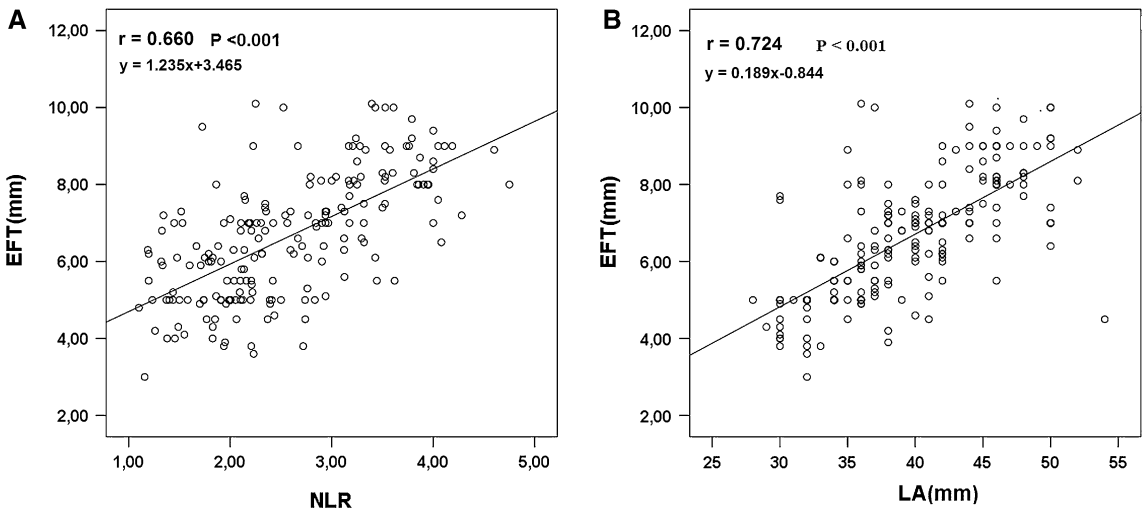

Fig. 3 **a** Correlation between echocardiographic epicardial fat thickness andneutrophil to lymphocyte ratio. **b** Correlation between echocardiographic epicardial fat thickness and *left* atrial diameter on echocardiography

(42.1 ± 5.0 vs. 34.3 ± 3.5 mm, $p < 0.001$) (Table 1) and was independently associated with non-valvular AF. Echocardiographic EFT correlated with LA enlargement as measured by LA diameter with 2-dimensional echocardiography (b = 0.138; 95 % CI 0.107–0.170, $p < 0.001$) (Table 4) and(r = 0.724, $p < 0.001$) (Fig. 3**).**

Discussion

The present study demonstrated that increased levels of echocardiographic EFT and NLR are independent predictors for non-valvular AF. Also, there was a significant correlation between the echocardiographic EFT and NLR. Moreover, our study showed that EFT ≥ 6 mm and NLR ≥ 2 predicted the presence of non-valvular AF with sensitivities of 89 and 87 % and specificities of 92 and 81 %, respectively. To our knowledge, this is the first study to report the concomitant relationship between the echocardiographic EFT and NLR and the type of non-valvular AF.

The pathophysiology of AF is complex, with structural, molecular and genetic changes. Although the exact pathophysiology of AF is unknown, one of the responsible mechanisms is thought to be inflammation [14–16].

It has been shown that patients with AF have elevated levels of inflammatory cytokines, which have been shown to be indicators of AF [17].

Epicardial fat, inflammation and non-valvular AF

The epicardial adipose tissue reflects visceral adiposity, which has been proposed as a new cardiometabolic risk factor [18].

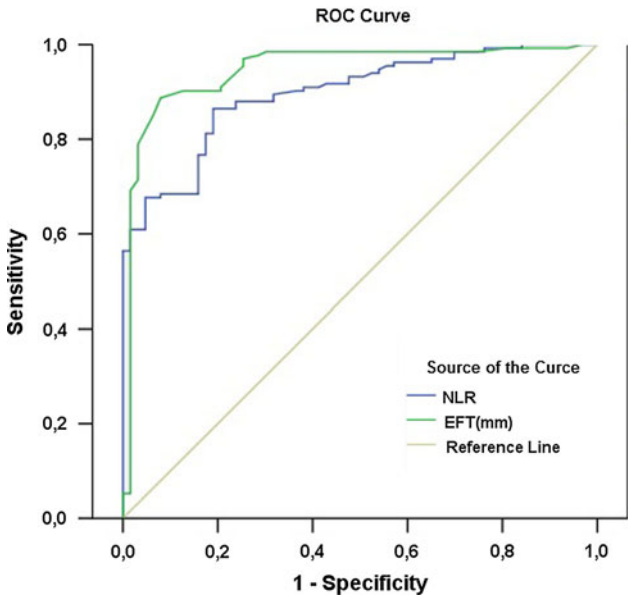

Fig. 4 Receiver operator characteristic curve analysis of neutrophil to lymphocyte ratio and the epicardial fat thickness level predicting the non-valvular AF

Table 3 Receiver operator characteristic curve analysis of the echocardiographic EFT and NLR predicting the non-valvular AF

	Sensitivity	Specificity	AUC	*p* value
EFT (mm)				
5.95	0.903	0.873	0.947 (0.910–0.984)	<0.001
6.05	0.888	0.921		
6.15	0.851	0.937		
NLR				
2.1293	0.865	0.794	0.897 (0.854–0.939)	<0.001
2.1365	0.865	0.810		
2.1425	0.850	0.810		

EFT epicardial fat thickness, *NLR* neutrophil/lymphocyte ratio, *AUC* area under curve

Epicardial fat may play a central role in the pathogenesis of cardiovascular disease mediated by its inflammatory properties [6–8].

In a study conducted by Venteclef et al. [19]. adipo-fibrokine levels secreted by EFT was found to be correlated with atrial and ventricular myocardial fibrosis level in AF patients who had undergone coronary bypass surgery and especially patients with low LVEF had a high level of Activin-A which was released from epicardial adipose tissue.

Two recent studies [20, 21]. indicate that periatrial epicardial fat, not periventricular fat, was associated with AF. Abed et al. [20] demonstrated that periatrial fat volume, but not periventricular fat or total fat, was associated with severity of AF in a multivariate-adjusted model including age, sex, body mass index, hypertension, obstructive sleep apnea, and left atrial area. Batal et al. [21] also showed that periatrial fat thickness between the left atrium and esophagus was an independent risk factor for AF after adjusting age, body mass index, and left atrial area. Furthermore, pericardial adipose tissue has both proinflammatory and anti-inflammatory characteristics. Epicardial fat is a source of several proinflammatory cytokines, including tumor necrosis factor-alpha, IL-1, and IL-6. However, it also secretes adiponectin with insulin-sensitizing and anti-inflammatory effects. Very recently [22] showed that an increased adiponectin release from epicardial fat was associated with freedom from AF after cardiac surgery [23] demonstrated that peri-atrial epicardial adipose tissue volume estimated by multidetector computed tomography predicted the development of new-onset AF in patients with coronary artery disease, independent of LA enlargement. Local inflammation caused by periatrial epicardial tissue.

In previous studies, EFT was typically measured with computed tomography (CT) and magnetic resonance imaging (MRI). EFT as assessed by echocardiography has recently been used as a practical method for evaluating the risk of visceral adiposity and cardiometabolic risk [12, 24]. Echocardiography is more readily available and less expensive than MRI or CT. Unlike CT, echocardiography does not expose patients to radiation or to contrast media. Therefore, echocardiography may be more practical for longitudinal studies of EFT and ultimately for clinical settings. However, echocardiography only samples a tomographic slice of the

Table 4 Independent predictors for Echocardiographic epicardial fat thickness by multivariate linear regression analysis

Model	Unstandardized coefficients		Standardized coefficients	t	*p* value	95.0 % confidence interval for B		Collinearity statistics	
	B	SE	Beta			Lower bound	Upper bound	Tolerance	VIF
Age	−0.005	0.007	−0.030	−0.630	0.530	−0.019	0.010	0.927	1.079
LA	0.138	0.016	0.509	8.646	<0.001	0.107	0.170	0.624	1.603
LVEF (%)	0.013	0.019	0.035	0.698	0.486	−0.024	0.050	0.873	1.146
NLR	0.726	0.106	0.379	6.819	<0.001	0.516	0.936	0.701	1.427

Dependent variable: epicardial fat thickness EFT (mm). R^2: 0. 587 ANOVA[b] $p < 0.001$

LA left atrial diameter (mm), *LVEF* (%) left ventricular ejection fraction, *NLR* neutrophil to lymphocyte ratio, *B* coefficient of regression

Table 5 Multiple logistic regression comparing non-valvular atrial fibrillation to sinus rhythm (control)

	B	*p* value	Exp (B)	95 % CI for Exp (B)	
				Lower	Upper
EFT	1.494	<0.001	4.453	1.941	10.219
LA	0.328	0.005	1.388	1.101	1.749
WBC	0.309	0.048	1.362	1.002	1.852
HDL	−0.043	0.213	0.958	0.895	1.025
NLR (>2.13)	2.426	<0.001	11.313	3.025	42.306
Smoking	1.073	0.183	2.924	0.603	14.178
Age	−0.033	0.271	0.967	0.912	1.026

CI confidence interval, *EFT* epicardial fat thickness (mm), *LA* left atrial diameter (mm), *WBC* white blood cell count, *HDL* high-density lipoprotein, *NLR* neutrophil to lymphocyte ratio

Table 6 Multivariate multinomial logistic regression analysis comparing paroxysmal and persistent/permanent non-valvular AF to sinus rhythm (control)

	B	*p* value	Exp (B)	95 % CI for Exp (B)	
				Lower	Upper
Paroxysmal non-valvular AF					
EFT	1.542	<0.001	4.672	2.329	9.371
LA	0.224	0.009	1.251	1.059	1.478
LVEF	−0.032	0.781	0.968	0.773	1.214
WBC	0.355	0.007	1.426	1.102	1.846
HDL	−0.028	0.360	0.972	0.915	1.033
Age	−0.011	0.689	0.989	0.939	1.042
HT	0.096	0.903	1.100	0.235	5.154
DM	−0.652	0.397	0.521	0.115	2.356
Persistent/permanent non-valvular AF					
EFT	3.189	<0.001	24.276	9.285	63.474
LA	0.412	<0.001	1.510	1.226	1.859
LVEF	−0.032	0.794	0.968	0.762	1.231
WBC	0.344	0.048	1.411	1.002	1.985
HDL	−0.028	0.496	0.972	0.896	1.055
Age	−0.018	0.624	0.982	0.913	1.056
HT	0.703	0.460	2.020	0.313	13.056
DM	0.138	0.886	1.148	0.172	7.686

R^2: 0.804. *CI* confidence interval, *EFT* epicardial fat thickness (mm), *LA* left atrial diameter (mm); LVEF (%), left ventricular ejection fraction, *WBC* white blood cell count, *HDL* high-density lipoprotein, *HT* hypertension, *DM* diabetes mellitus

epicardial and pericardial fat and may not reflect the total volume. Nevertheless, EFT measured by echocardiography correlates highly with that determined by MRI [25]. While the use of echocardiographic measurements in AF has limitations, our study supports the fact that epicardial fat measurement with echocardiography correlates with the type of AF. This result is inconsistent with the study by Al Chekakie et al. [26]. In that study, pericardial fat volume was measured using computerized tomography, which revealed that pericardial fatis highly associated with paroxysmal and persistent/permanent non-valvular AF. That study also proposed that the volume of pericardial fat may play a role in the pathogenesis of AF. Our study demonstrated significant differences in echocardiographic EFT between patients with sinus rhythm (control) and paroxysmal non-valvular AF. The echocardiographic EFT of persistent/permanent non-valvular AF patients was significantly higher than those from paroxysmal non-valvular AF and sinus rhythm (control) patients. The present study, which uses an echocardiography-based quantification of epicardial fat, demonstrates a relationship between cardiac adiposity, as measured by epicardial fat, and non-valvular AF. Our findings, if confirmed, suggest that epicardial fat may represent a novel risk factor for AF. Also, these local inflammatory effects may provide a mechanism to explain the association between AF and epicardial fat. This hypothesis needs to be addressed in future studies.

Epicardial fat, NLR, and non-valvular AF

WBC count and its subtypes are markers of inflammation in cardiovascular disease [27]. Several recent studies have shown that NLR is an indicator of systemic inflammation [28–30]. NLR has emerged as new prognostic marker [31]. Several studies have shown a relationship between NLR and the presence of AF. Of note, Im et al. [32] demonstrated that NLR is an independent predictor for early recurrence after radiofrequency catheter ablation in patients with AF. Canpolat et al. [33] show that elevated preablation NLR was associated with an increased recurrence of AF after cryoballoon-based catheter ablation. Gibson et al. [31] showed that NLR isa predictor of new-onset AF after coronary artery bypass grafting. Ertaş et al. [34] show that NLR is an independent predictor of thromboembolic stroke in patients with non-valvular AF. However, there have been no reports on the association of types of non-valvular AF and NLR. In the present study, NLR was found to be an independent predictor of types of non-valvular AF. Moreover, we demonstrated that NLR and concomitant echocardiographic EFT are independent predictors of types of non-valvular AF.

Epicardial fat, LA size and non-valvular AF

Recent evidence has shown an association between epicardial fat and LA size [35]. However, ours is the first study to show a correlation between the concomitant evaluation of echocardiographic EFT with NLR and LA size in non-valvular AF in non-morbidly obese patients. In our study, significant correlations were observed between

the LA enlargement, echocardiographic EFT, and NLR value. In multivariate logistic regression analysis and multivariate multinomial logistic regression analysis, LA enlargement was an independent predictor of types of non-valvular AF. In the ROC analysis, LA size $\geq$37.5 mm predicted the presence of non-valvular AF patients with a sensitivity of 81 % and a specificity of 83 %. Since echocardiographic EFT and NLR are fully independent of LA size and other AF risk factors, they maybe additional parameters to consider when evaluating an individual's risk of having non-valvular AF.

Limitations

Echocardiographic EFT is a linear measurement, and therefore, it may not reflect the total epicardial fat volume that varies at different locations around the myocardium. Echocardiography is more accurate, easier, more readily available, and less expensive than magnetic resonance imaging and computed tomography, which are the gold standard diagnostic methods for assessing EFT and volumes. A limitation of the study is the exclusion of the patients with new-onset AF. Another limitation of this study is that we did not take note of leukocyte and lymphocyte subtypes. However NLR is a reliable marker of inflammation and is related to AF. Although we found significant associations, further studies are needed to investigate the clinical significance of echocardiographic EFT and NLR in non-valvular AF.

Conclusion

To our knowledge, our study is the first to determine the relationship between echocardiographic EFT and the types of non-valvular AF. Echocardiographic EFT was correlated with NLR value. Unlike many other inflammatory markers and bioassays, NLR and echocardiographic EFT are inexpensive and readily available markers that may be useful for risk stratification in patients with non-valvular AF.

Conflict of interest None.

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