

# Association of epicardial adipose tissue thickness and inflammation parameters with CHA<sub>2</sub>DS<sub>2</sub>-VASc score in patients with nonvalvular atrial fibrillation

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**Background:** Epicardial adipose tissue (EAT), mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) have been shown to be helpful in predicting adverse cardiovascular events. However, to date, in the literature, there have been no studies demonstrating the relationship between EAT, MPV, PLR, NLR, and thromboembolism risk in atrial fibrillation (AF). Therefore, we examined the relationship between EAT, MPV, PLR, NLR, and CHA<sub>2</sub>DS<sub>2</sub>-VASc score used for the evaluation of thromboembolism risk in patients with AF.

**Methods:** The study included 96 consecutive patients with AF and 52 age- and sex-matched control subjects. We calculated CHA<sub>2</sub>DS<sub>2</sub>-VASc risk score for each patient and measured baseline EAT thickness, MPV, PLR, NLR, left atrial volume index, and left ventricular ejection fraction.

**Results:** The group with high CHA<sub>2</sub>DS<sub>2</sub>-VASc score had higher EAT (7.2±1.5 vs 5.9±1.2 mm,  $P<0.001$ ), MPV (9.1±1.1 vs 8.4±1.0 fL,  $P=0.004$ ), PLR (152.3±28.4 vs 126.7±25.4,  $P=0.001$ ), and NLR (4.0±1.6 vs 3.2±1.3,  $P<0.001$ ) compared to group with low-intermediate CHA<sub>2</sub>DS<sub>2</sub>-VASc score. Moreover, CHA<sub>2</sub>DS<sub>2</sub>-VASc score was found to be positively correlated with EAT ( $r=0.623$ ,  $P<0.001$ ), MPV ( $r=0.350$ ,  $P=0.004$ ), PLR ( $r=0.398$ ,  $P=0.001$ ), and NLR ( $r=0.518$ ,  $P<0.001$ ).

**Conclusion:** Our study results demonstrated that EAT thickness, MPV, PLR, and NLR were associated with the thromboembolic risk exhibited by CHA<sub>2</sub>DS<sub>2</sub>-VASc score in patients with nonvalvular AF.

**Keywords:** atrial fibrillation, epicardial adipose tissue, platelet, neutrophil, mean platelet volume

## Introduction

Nonvalvular atrial fibrillation (AF) is the most frequently sustained arrhythmia in clinical practice and presents a high risk of thromboembolism.<sup>1</sup> Numerous scoring systems have been used in the stratification of thromboembolism risk in AF patients.<sup>2</sup> Of these, CHA<sub>2</sub>DS<sub>2</sub>-VASc is the most commonly suggested system. All the components of this system have been demonstrated to be associated with increased incidence of thromboembolism in patients with AF.<sup>3</sup> The genesis of AF is of a multifactorial nature, but the study has shown that inflammation plays a key role in the initiation and progression of AF.<sup>4</sup>

Epicardial adipose tissue (EAT) functions as an active endocrine organ and has been demonstrated to be a significant source of inflammatory mediators and to play a major role in the pathophysiology of AF since it is located close to the heart.<sup>5</sup> Mean platelet volume (MPV), a measure of platelet activation and function, is a potential mediator of the relationship between inflammation and thrombosis.<sup>6</sup> MPV is higher in patients

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with AF compared to that in patients with sinus rhythm.<sup>7</sup> Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have recently been used as systemic inflammatory markers and prognostic indicators of adverse cardiovascular events.<sup>8,9</sup> NLR is also used for predicting the left atrial (LA) thrombus in patients with nonvalvular AF.<sup>10</sup>

The aim of this study was to investigate the association between EAT thickness, MPV, NLR, PLR, and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score used for the stratification of thromboembolism risk in patients with nonvalvular AF.

## Materials and methods

### Study population

The study was performed in compliance with the Declaration of Helsinki, and the study protocol was approved by the Yuzuncu Yil University, Faculty of Medicine Ethics Committee. The participants' written informed consent was also obtained. The cross-sectional observational study included a total of 96 consecutive patients who presented to the outpatient clinics of our university hospital with nonvalvular AF and 52 age- and sex-matched control subjects. The inclusion criteria were patients over 18 years of age who presented to the cardiology clinic with at least one attack of AF diagnosed by electrocardiographic examination and assessed by a cardiologist. Exclusion criteria included autoimmune disease, significant congestive heart failure, renal or hepatic disease, clinically significant valvular heart disease, cancer, ongoing infection or systemic inflammatory conditions, comorbidities, and patients with poor echocardiographic windows.

A complete physical examination was performed in all the patients. Also, the medical histories and clinical features of the patients were recorded. AF was defined as the absence of P waves on electrocardiography and irregular R-R interval. The types of AF were defined in accordance with the European Society of Cardiology guidelines. According to these guidelines, a patient detected with AF for the first time is considered a patient with first diagnosed AF, regardless of the duration of arrhythmia or the presence and severity of AF-related symptoms. Paroxysmal AF is generally self-terminating and continues for up to 7 days. In persistent AF, the episode either lasts for >7 days or requires termination by cardioversion, either by medication or direct current cardioversion. In long-standing persistent AF, the episode lasts for ≥1 year, and a rhythm control strategy is adopted. On the other hand, if the patient presents with long-standing AF, in whom cardioversion has failed or has not been tried, the patient is considered to have permanent AF. In this study, we used the CHA<sub>2</sub>DS<sub>2</sub>-VASc scoring system, which is used to stratify the risk of long-term thromboembolic events

**Table 1** CHA<sub>2</sub>DS<sub>2</sub>-VASc score

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age >75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1
Age 65–74 years	1
Sex category (ie, female sex)	1

**Abbreviations:** LV, left ventricle; TIA, transient ischemic attack.

related to AF (Table 1). Depending on this system, the AF patients were divided into two groups: 1) low-intermediate risk group and 2) high-risk group. Accordingly, a score of “0” was regarded as low risk, “1” as intermediate risk, and “≥2” as high risk.

### Echocardiography

Each patient underwent transthoracic two-dimensional echocardiography at rest under standard procedures. The patient was placed in the left lateral decubitus position, and a commercial echocardiographic device (Vivid 3, General Electric, Chicago, IL, USA) with a 3.0 MHz transducer was used for the examination. The examinations were performed by two experienced cardiologists blinded to the study. In order to avoid interreader variability, the offline assessments of the EAT thickness were performed by two cardiologists blinded to the patient data. In order to assess the inter- and intraobserver variability, the echocardiograms of 30 patients were randomly selected and a second measurement of the EAT thickness was performed 2 weeks later. The inter- and intraobserver variability of the EAT thickness were 3.2% and 2.6%, respectively. The diameter of the left atrium was measured at end-systole in the parasternal long-axis view using the standard criteria. Left ventricular ejection fraction (LVEF) was also calculated. The epicardial fat was identified as an echo-free space in the pericardial layers on the two-dimensional echocardiography. By using the Simpson's method, the maximum EAT thickness 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, which is used as the anatomic landmark at end-systole in three cardiac cycles.

### Biochemical and hematological measurements

Blood sample was collected from the antecubital vein using a 21-gauge sterile syringe without stasis between 8 and 10 am, following a 12-hour fasting period. To assess complete blood

count, a Coulter LH 780 Hematology Analyzer (Architect plus ci16200, Abbott, Lake Forest, IL, USA) was used for measuring the hematological parameters including platelet counts, neutrophil counts, lymphocyte counts, and MPV. Baseline NLR was measured by dividing neutrophil count by lymphocyte count. Baseline PLR was measured by dividing platelet count by lymphocyte count.

## Statistical analysis

All the statistical data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as mean  $\pm$  standard deviation, and the categorical data were expressed as percentage. When necessary, the Pearson's or the Spearman's correlation coefficient was performed to analyze the correlation between the variables. Statistical comparisons were performed using one-way analysis of variance, followed by Scheffé's test. A *P*-value of  $<0.05$  was considered significant.

## Results

A total of 148 patients (96 patients with nonvalvular AF and 52 control subjects) were included in the present study. Baseline demographic, clinical, and laboratory characteristics of the nonvalvular AF and the control groups are presented in Table 2. The median CHA<sub>2</sub>DS<sub>2</sub>-VAsC score was 2, and 53.1% of the patients were in the high CHA<sub>2</sub>DS<sub>2</sub>-VAsC group. Within the nonvalvular AF group, there were 51 patients with high CHA<sub>2</sub>DS<sub>2</sub>-VAsC score and 45 patients with low-intermediate CHA<sub>2</sub>DS<sub>2</sub>-VAsC score. Of all the patients, 22.9% of the cases had paroxysmal, 16.7% had persistent, and 60.4% had permanent AF. Other baseline characteristics and previous medications are shown in Table 3. Patients with nonvalvular AF had significantly higher EAT (6.6 $\pm$ 1.3 vs 4.9 $\pm$ 1.0 mm, *P* $<$ 0.001), MPV (8.9 $\pm$ 1.1 vs 7.8 $\pm$ 1.0 fL, *P* $<$ 0.001), PLR (140.3 $\pm$ 24.2 vs 119.3 $\pm$ 21.9, *P*=0.002), and NLR (3.6 $\pm$ 1.5 vs 2.9 $\pm$ 1.3, *P* $<$ 0.001) compared to the control subjects. LA volume index (*P* $<$ 0.001) was significantly higher in the nonvalvular AF group compared to the controls. However, LVEF (*P* $<$ 0.001) was significantly lower in the nonvalvular AF group compared to the controls (Table 2). High CHA<sub>2</sub>DS<sub>2</sub>-VAsC group had higher EAT (7.2 $\pm$ 1.5 vs 5.9 $\pm$ 1.2 mm, *P* $<$ 0.001), MPV (9.1 $\pm$ 1.1 vs 8.4 $\pm$ 1.0 fL, *P*=0.004), PLR (152.3 $\pm$ 28.4 vs 126.7 $\pm$ 25.4, *P*=0.001), and NLR (4.0 $\pm$ 1.6 vs 3.2 $\pm$ 1.3, *P* $<$ 0.001) compared to the low-intermediate CHA<sub>2</sub>DS<sub>2</sub>-VAsC group. Moreover, age (*P* $<$ 0.001), LA volume index (*P* $<$ 0.001), hypertension (*P* $<$ 0.001), and diabetes (*P*=0.006) were significantly higher in the high CHA<sub>2</sub>DS<sub>2</sub>-VAsC group

**Table 2** Baseline characteristics of all patients with nonvalvular atrial fibrillation and control group

	Atrial fibrillation (n=96)	Sinus rhythm (n=52)	P-value
Age, years	63.6 $\pm$ 11.6	64.5 $\pm$ 11.8	0.696
Sex, female, %	36	44	0.364
Smoking, %	26	21	0.503
BMI, kg/m <sup>2</sup>	25.6 $\pm$ 3.2	25.3 $\pm$ 2.9	0.698
Hypertension, %	25	19	0.429
Diabetes, %	18	15	0.721
Glucose, mg/dL	106.4 $\pm$ 19.3	103.1 $\pm$ 17.0	0.038
Creatinine, mg/dL	0.9 $\pm$ 0.4	0.8 $\pm$ 0.3	0.402
Triglycerides, mg/dL	170.4 $\pm$ 102.6	165.8 $\pm$ 96.3	0.387
Cholesterol, mg/dL	188.7 $\pm$ 87.4	182.2 $\pm$ 78.7	0.188
HDL, mg/dL	42.6 $\pm$ 6.1	44.3 $\pm$ 6.4	0.114
LDL, mg/dL	112.1 $\pm$ 28.4	104.8 $\pm$ 26.6	0.128
LVEF, %	53.4 $\pm$ 7.1	61.4 $\pm$ 2.5	$<$ 0.001
LA volume index, mL/m <sup>2</sup>	37.1 $\pm$ 8.1	33.1 $\pm$ 4.4	$<$ 0.001
EAT thickness, mm	6.6 $\pm$ 1.3	4.9 $\pm$ 1.0	$<$ 0.001
Hemoglobin, g/dL	14.3 $\pm$ 1.1	14.5 $\pm$ 1.0	0.240
White blood cell count, K/L	7.3 $\pm$ 1.9	6.9 $\pm$ 1.8	0.223
Platelet count, K/UL	265.5 $\pm$ 73.4	248.2 $\pm$ 67.2	0.016
Neutrophil count, K/UL	6.8 $\pm$ 1.6	6.1 $\pm$ 1.5	0.003
Lymphocyte count, K/UL	1.9 $\pm$ 0.8	2.1 $\pm$ 0.9	0.008
Mean platelet volume, fL	8.9 $\pm$ 1.1	7.8 $\pm$ 1.0	$<$ 0.001
PLR	140.3 $\pm$ 24.2	119.3 $\pm$ 21.9	0.002
NLR	3.6 $\pm$ 1.5	2.9 $\pm$ 1.3	$<$ 0.001

**Note:** Data are presented as mean  $\pm$  standard deviation.

**Abbreviations:** BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LA, left atrial; EAT, epicardial adipose tissue; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

compared to the low-intermediate CHA<sub>2</sub>DS<sub>2</sub>-VAsC group. However, LVEF (*P* $<$ 0.001) was significantly lower in the high CHA<sub>2</sub>DS<sub>2</sub>-VAsC group compared to the low-intermediate CHA<sub>2</sub>DS<sub>2</sub>-VAsC group (Table 3). Moreover, CHA<sub>2</sub>DS<sub>2</sub>-VAsC score was found to be positively correlated with EAT (*r*=0.623, *P* $<$ 0.001) (Figure 1), MPV (*r*=0.350, *P*=0.004) (Figure 2), PLR (*r*=0.398, *P*=0.001) (Figure 3), and NLR (*r*=0.518, *P* $<$ 0.001) (Figure 4).

## Discussion

There were three main findings of the present study. First, EAT thickness was found to be higher in the nonvalvular AF group compared to the control group. Second, inflammation markers including MPV, PLR, and NLR were significantly elevated in the nonvalvular AF group. Third, EAT thickness, MPV, PLR, and NLR were correlated with the CHA<sub>2</sub>DS<sub>2</sub>-VAsC score in patients with nonvalvular AF, which were also independent predictors of high CHA<sub>2</sub>DS<sub>2</sub>-VAsC score.

Nonvalvular AF is the most frequently sustained arrhythmia in clinical practice and presents a high risk of stroke and thromboembolism.<sup>1</sup> The incidence of thromboembolism may

**Table 3** Baseline clinical and laboratory characteristics according to CHA<sub>2</sub>DS<sub>2</sub>-VAsC score in patients with nonvalvular AF

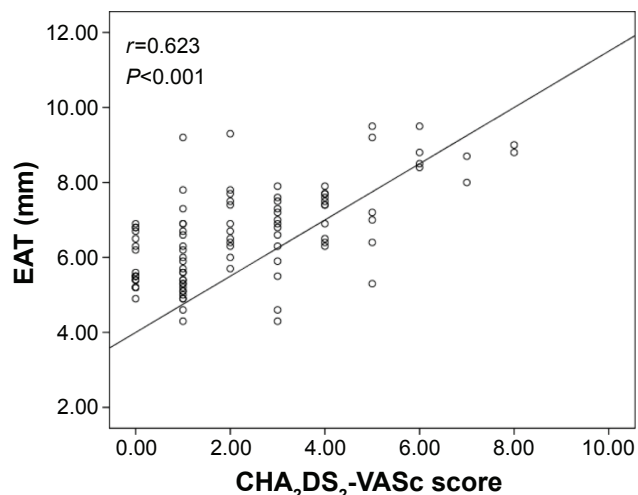
	Low-intermediate risk (n=45)	High risk (n=51)	P-value
Age, years	58.4±10.1	68.2±11.6	<0.001
Sex, female, %	33	39	0.554
Smoking, %	24	27	0.741
BMI, kg/m <sup>2</sup>	25.3±3.1	25.8±3.3	0.443
Hypertension, %	9	39	<0.001
Diabetes, %	7	27	0.006
Glucose, mg/dL	105.2±18.9	107.5±19.7	0.235
Creatinine, mg/dL	0.9±0.3	0.9±0.4	0.993
Triglycerides, mg/dL	167.7±97.4	172.7±106.7	0.454
Cholesterol, mg/dL	186.9±89.7	190.3±91.2	0.586
HDL, mg/dL	43.3±6.5	41.9±5.8	0.287
LDL, mg/dL	110.1±27.5	113.9±28.6	0.523
LVEF, %	59.3±3.4	48.2±8.5	<0.001
LA volume index, mL/m <sup>2</sup>	35.1±6.6	38.8±7.9	<0.001
EAT thickness, mm	5.9±1.2	7.2±1.5	<0.001
Hemoglobin, g/dL	14.3±1.7	14.4±1.5	0.905
White blood cell count, K/L	7.1±1.7	7.4±1.6	0.376
Platelet count, K/UL	258.3±55.8	271.8±60.6	0.037
Neutrophil count, K/UL	6.5±1.5	7.1±1.7	0.002
Lymphocyte count, K/UL	2.0±0.8	1.8±0.8	0.008
Mean platelet volume, fL	8.4±1.0	9.1±1.1	0.004
PLR	126.7±25.4	152.3±28.4	0.001
NLR	3.2±1.3	4.0±1.6	<0.001
Previous medication			
Antiplatelet, %	49	80	<0.001
Anticoagulant, %	9	43	<0.001
β-blocker, %	46	57	0.324
ACEI/ARB, %	39	42	0.908
CCB, %	27	31	0.616
Statin, %	11	14	0.701

**Note:** Data are presented as mean ± standard deviation.

**Abbreviations:** AF, atrial fibrillation; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction; LA, left atrial; EAT, epicardial adipose tissue; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

vary according to the coexisting clinical, echocardiographic, and biochemical factors in AF patients. Therefore, numerous scoring systems have been developed for the stratification of thromboembolism risk in AF patients.<sup>2</sup> Of these systems, the CHA<sub>2</sub>DS<sub>2</sub>-VAsC score is the most commonly suggested system.<sup>11</sup> This system categories the thromboembolism risk in AF patients into two levels: low risk and high risk. Accordingly, patients with high risk have a higher incidence of thromboembolic events.

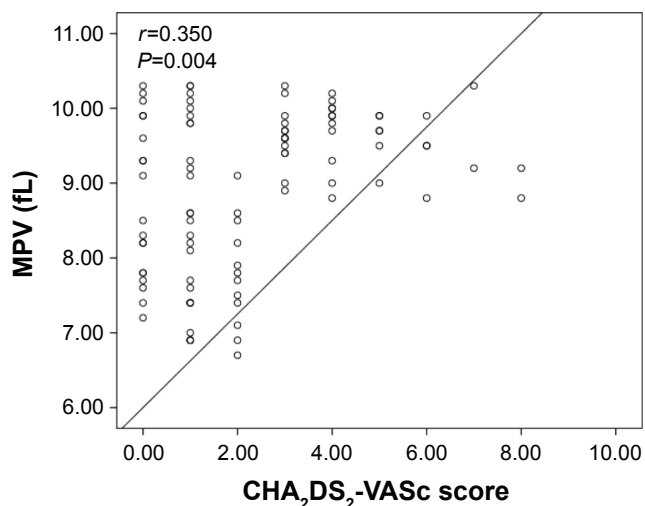
In addition to the effects of well-known cardiovascular risk factors on the initiation and progression of AF,



**Figure 1** Correlation plots between echocardiographic EAT thickness and CHA<sub>2</sub>DS<sub>2</sub>-VAsC score.

**Abbreviation:** EAT, epicardial adipose tissue.

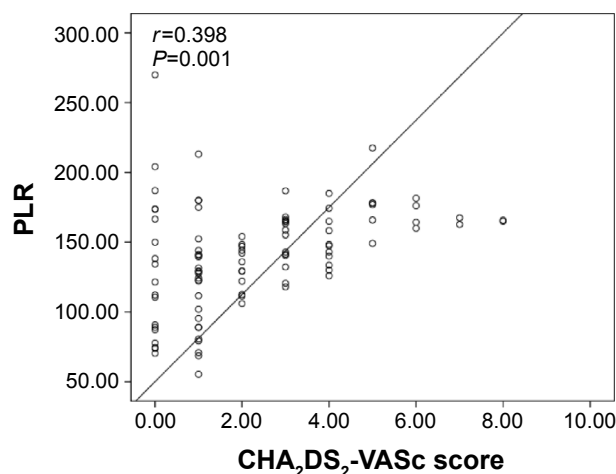
researchers have recently aimed at evaluating the role of inflammation on the progression of AF.<sup>12</sup> EAT has been shown to be effective on the progression of both coronary atherosclerosis and cardiac arrhythmia.<sup>13</sup> EAT is a true visceral fat deposited around the heart, particularly around the subepicardial coronary vessels. It has been demonstrated that EAT functions as an active endocrine organ, which generates several proinflammatory and proatherogenic cytokines and bioactive adipokines.<sup>14</sup> EAT thickness has recently emerged as a novel risk factor for cardiovascular disease in the general population.<sup>14</sup> A previous study has reported the autocrine and paracrine effects of EAT on cardiac physiology.<sup>15</sup> Moreover, a study also investigated the relationship between EAT thickness assessed by various methods and found a positive correlation between EAT thickness and AF.<sup>13</sup> Recently, Shin



**Figure 2** Correlation plots between MPV and CHA<sub>2</sub>DS<sub>2</sub>-VAsC score.

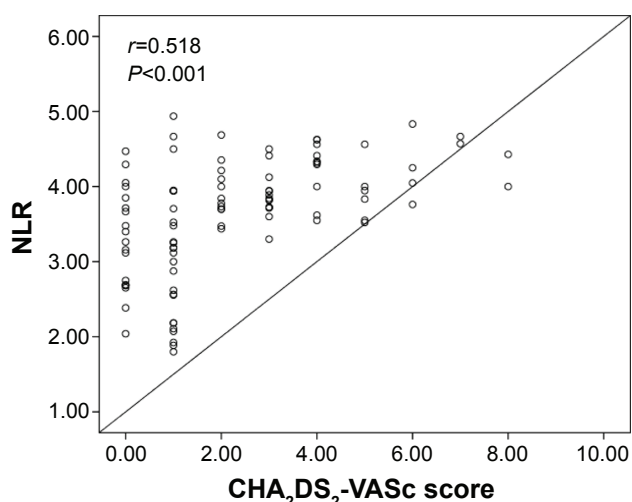
**Abbreviation:** MPV, mean platelet volume.





**Figure 3** Correlation plots between PLR and CHA<sub>2</sub>DS<sub>2</sub>-VASc score.  
**Abbreviation:** PLR, platelet-to-lymphocyte ratio.

et al<sup>16</sup> also reported that computed tomography-measured epicardial fat volumes established a significant correlation with the presence and progression of AF. In addition, a relationship between the epicardial fat and long-term clinical outcomes following AF ablation has also been reported. Similarly, Nagashima et al<sup>17</sup> also reported greater epicardial fat volumes in patients with AF recurrence after radiofrequency ablation. In another study, the same authors reported a correlation between the dominant frequency sites and the epicardial fat locations. They also reported higher epicardial fat volumes and higher levels of serum inflammatory markers in patients with persistent AF when compared to the patients with paroxysmal AF.<sup>18</sup> Recently, EAT thickness as assessed by echocardiography has emerged as a practical method for the evaluation of the cardiometabolic risk and the risk of visceral adiposity. In this study, EAT thickness was measured using echocardiography, and a positive correlation was found



**Figure 4** Correlation plots between NLR and CHA<sub>2</sub>DS<sub>2</sub>-VASc score.  
**Abbreviation:** NLR, neutrophil-to-lymphocyte ratio.

between the CHA<sub>2</sub>DS<sub>2</sub>-VASc score and epicardial fat in the nonvalvular AF group.

MPV, PLR, and NLR, which are the parameters measured in routine blood samples, are inflammatory markers of cardiovascular disease.<sup>6–9</sup> MPV is a measure of platelet size and is regarded as a marker and determinant of platelet function since the platelets with larger sizes are hemostatically more reactive than the platelets with normal sizes, thus increasing the predisposition to thrombosis and resulting in acute coronary syndromes or ischemic stroke.<sup>19,20</sup> A study reported that the MPV level was higher in AF patients compared to subjects in sinus rhythm.<sup>21</sup> Additionally, Ha et al<sup>19</sup> reported that MPV functions as a predictive marker of stroke in AF patients. In the same study, MPV was found to add incremental predictive value to the clinical variables involved in the CHADS<sub>2</sub> score. Very recently, a case–control study reported that stroke patients with AF exhibited higher MPV levels than those exhibited by AF patients with no history of stroke.<sup>22</sup> In our study, the MPV levels were higher in the nonvalvular AF group and correlation was established between the MPV levels and CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

PLR and NLR have recently been used as significant inflammatory markers and novel predictors of major adverse outcomes in cardiovascular disease.<sup>8,9</sup> Recent studies have also shown that high platelet count and low lymphocyte count have a close relationship with the poor prognosis in patients with coronary artery disease.<sup>23–25</sup> Azab et al<sup>24</sup> reported that elevated PLR was an independent predictor for long-term mortality in patients with non-ST elevation myocardial infarction. Akkaya et al<sup>25</sup> found that PLR has a significant role in the increase in adverse clinical outcomes and mortality within the 6 months after percutaneous coronary intervention in patients with ST elevation myocardial infarction.

Increased PLR and NLR are associated with the severity of coronary atherosclerosis in patients with coronary artery disease and congestive heart failure.<sup>9,26</sup> A study reported that increased NLR was associated with higher inpatient mortality in patients with advanced heart failure.<sup>26</sup> Another study found that NLR levels were associated with the increased risk of ventricular arrhythmias during percutaneous coronary intervention.<sup>8</sup> Moreover, NLR has recently emerged as a risk marker for AF progression following coronary artery bypass grafting and as a predictor for early recurrence of AF following radiofrequency catheter ablation.<sup>27,28</sup> Also, elevated NLR has been shown to increase the risk of thromboembolic stroke in patients with nonvalvular AF.<sup>29</sup> In our study, PLR and NLR levels were higher in the nonvalvular AF group and a positive correlation was established between CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

Stratification of the thromboembolism risk is of prime importance for the prevention of adverse outcomes in patients with nonvalvular AF. We propose that EAT thickness, MPV, NLR, and PLR, which can be measured by an inexpensive and simple method, may be significant predictors of the thromboembolism risk in patients with nonvalvular AF.

## Limitations

Our study is limited since it had a relatively small number of patients. Echocardiographic EAT thickness is a linear measurement, and thus it may not assess the total epicardial fat volume that varies at various myocardial locations. Moreover, other cytokines or inflammatory markers were not evaluated and not compared with MPV, NLR, and PLR.

## Conclusion

To our knowledge, this is the first study to determine the association of EAT thickness, MPV, PLR, and NLR with CHA<sub>2</sub>DS<sub>2</sub>-VASc score in patients with nonvalvular AF. The study revealed that EAT thickness, MPV, PLR, and NLR were associated with the thromboembolic risk exhibited by CHA<sub>2</sub>DS<sub>2</sub>-VASc score in patients with nonvalvular AF. On the other hand, it is of interest that we can infer from this article that there is a certain correlation between inflammatory markers and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores, suggesting that anti-inflammatory therapy may be beneficial in reducing risk factors in AF patients. Moreover, these parameters may be beneficial in the stratification of the thromboembolic risk. However, further large-scale studies are needed in this regard.

## Disclosure

The authors report no conflicts of interest in this work.

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