The predictive value of the systemic immune-inflammatory index for left atrial appendage thrombus in non-valvular atrial fibrillation

Fatih Koca, Fatih Levent, Baris Sensoy, Erhan Tenekecioglu

Objective. The systemic immune inflammatory index (SII) has prognostic value in cardiovascular diseases. The aim of current study was to investigate whether or not left atrial appendage (LAA) thrombus could be predicted by SII in patients with non-valvular atrial fibrillation.

Method. The study included 525 patients newly diagnosed with non-valvular atrial fibrillation, who had not previously had anticoagulant treatment (50.7% male, mean age 62.94±10.79 years). All patients underwent transoesophageal echocardiography.

Results. LAA thrombus was observed in 86 patients (16.4%). In the ROC curve SII had a good diagnostic power in predicting LAA thrombus (AUC: 0.760, 95% CI: 0.703–0.818, *P*<0.001). In the multivariate regression analysis, diabetes (Hazard ratio: 2.264, 95% CI: 1.169–4.389, *P*=0.015), LAA emptying rate of <20 cm/s (Hazard ratio: 59.347, 95% CI: 25.397–138.680, *P*<0.001), and SII value of >750 (Hazard ratio: 4.291, 95% CI: 2.144–8.586 *P*<0.001) were determined as independent predictors for LAA thrombus. A poor correlation was found between SII and the CHADS2 VASc score (r=0.239, *P*<0.001)

Conclusion. The SII, a practical and easily obtained test, can be used as a predictor of LAA thrombus in patients with non-valvular atrial fibrillation, and to decide on the anticoagulant treatment.

Key words: systemic immune-inflammatory index, left atrial appendage thrombus, atrial fibrillation, diabetes

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INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, with a prevalence rate of 0.4% in the general population, and 9% in octogenarians[1]. AF may cause cardioembolic stroke and systemic emboli as a result of thrombus formation particularly in the left atrial appendix (LAA) following left atrial stasis. Management of the predisposing factors for LAA thrombus in AF patients is crucial in terms of reducing the risk of cardio-embolic events. Previous studies have revealed that factors related to the anatomic structure of the LAA (left atrial diameter, multilobular appendix) and functions (spontaneous echo contrast, LAA emptying velocity) could be associated with LAA thrombus formation[2-5].

The risk of LAA thrombus increases with higher CHA_2DS_2-VASc scores[6]. In addition, increasing platelet activation and inflammation could be related to thrombogenesis in AF (ref.[7]). A high level of C-reactive protein (CRP) and high neutrophil/lymphocyte ratio (NLR) are known to be associated with increased thrombogenesis in LAA (ref.[8,9]).

The systemic immune inflammatory index (SII) is another inflammation marker, which is obtained by multiplying the NLR by the platelet count, and this has prognostic value in many diseases such as cancer and cardiovascular diseases[10-14]. In addition, SII was shown to be independently associated with the presence of AF in patients with ischemic stroke or myocardial infarction and to be an independent predictor for AF recurrence after successful cardioversion[15-17].

The SII has been determined to be superior to the NLR in predicting prognosis in various malignancies[18,19]. The aim of this study was to investigate whether or not the SII is superior to the NLR in predicting LAA thrombosis in AF.

MATERIAL AND METHOD

This cross-sectional study was conducted in a regional high-volume training and research hospital. The study included patients who were planned to undergo medical or electrical cardioversion due to newly diagnosed AF between June 2017 and June 2022. From a total of 926 patients evaluated, 401 subjects were excluded from the study due to the following criteria: previous diagnosis of AF and/or use of anticoagulants, at least moderate valvular heart disease, a bioprosthesis or metal prosthesis valve, a history of hematological malignancy, the diagnosis of sepsis, history of surgery, trauma, or steroid use within last 3 months, and those with white blood cell (WBC)

count >12,000/uL or <4,000/uL. The remaining 525 patients were informed about the study and each patient provided written informed consent.

Within 24 h before the medical/electrical cardioversion procedure, all patients underwent 2D transthoracic (TTE) and transesophageal echocardiography (TEE), performed by two experienced echocardiographers blinded to the clinical characteristics of the study subjects. An Epiq 7c Ultrasound System (Philips Medical System, Andover, MA, USA) device with a 1–5 MHz transthoracic probe and a 2–7 MHz transesophageal probe was used for the echocardiographic assessment. The measurements were performed according to the recommendations by the American Society of Echocardiography Committee guidelines[20,21]. The left ventricle ejection fraction (LVEF) was measured with the modified Simpson's method. Patients with LVEF <40% were determined as systolic heart failure. Left atrial diameter was measured from the posterior aortic wall towards the posterior atrial wall at the time just before mitral valve closure in the parasternal long axis.

On TEE, images were obtained in the long and short axis views of the LAA while the probe was at the mid-oesophageal level. The LAA peak emptying velocity was measured with pulsed Doppler at 1 cm below the LAA ostium on the long axis view of LAA. Patients with peak velocity <20 cm/s were evaluated as reduced emptying rate. LAA thrombus was defined as a homogenous dense mass with different echogenity from that of the left atrial endocardial wall[22] (Fig. 1). In order to distinguish LAA thrombus from dense spontaneous echocardiographic contrast (SEC), LAA was evaluated in multiple views. Spontaneous echocardiographic contrast (SEC) was defined as mobile "smoke-like" echoes with a characteristic rotating motion that did not disappear despite optimized gain settings[23]. Based on the presence of thrombus, the patients were divided into two main groups: patients with LAA thrombus (LAA thrombus+) and those without thrombus (LAA thrombus−).

Fasting blood samples were taken from all patients between 09:00 and 12:00 on the morning before the TEE procedure The clinical and demographic characteristics were recorded. Patients taking anti-diabetic drugs or with a fasting blood sugar level >126 mg/dL during hospitalization, were diagnosed with diabetes. Patients who were taking antihypertensive treatment or had a brachial blood pressure of >140/90 mmhg measured on at least two separate occasions, were accepted as hypertensive. The SII was calculated as the NLR multiplied by the platelet count.

The C_2HEST score was calculated for each patient as coronary artery disease (CAD) or chronic obstructive pulmonary disease (COPD) [C2, 1 point for each]; hypertension [H, 1 point]; elderly [E, age ≥75 years, 2 points]; systolic heart failure [S, 2 points]; thyroid disease [T, hyperthyroidism, 1 point]), and the CHA_2DS_2-VASc score [(Congestive heart failure, Hypertension, Age (>65=1 point, >75=2 points), Diabetes, previous Stroke/transient ischemic attack (2 points), vascular disease, age 65 to 74 years, sex category)].

Statistical Analysis

All the statistical analyses were performed using MedCalc 20.0.4 software (MedCalc Software Ltd, Ostend, Belgium). Continuous variables showing normal distribution according to the Kolmogorov-Smirnov test are summarised as means ± standard deviation, and those not showing normal distribution as median (25th-75th interquartile range) values. Categorical variables are stated as number (n) and percentage (%). The variables were compared between the two main groups (LAA thrombus+/LAA thrombus-) using the Paired Samples t-test for variables with normal distribution, the Mann Whitney U-test for variables not showing normal distribution, and the Chi-square test for categorical variables. For the assessment and comparison of the diagnostic power of the measured parameters (SII, NLR, PLR,) in predicting LAA thrombus, Receiver Operating Characteristic (ROC) curve analysis, and the Hanley and McNeil tests were used. Univariate analysis and multivariate logistic regression analysis were performed to determine independent predictors of LAA thrombus. Parameters with a significant *P*-value in the above-mentioned tests were used in univariate analysis, and then in the multivariate analysis, the parameters with a significant p-value in the univariate analysis were used. In all the statistical tests, a value of $P<0.05$ was accepted as statistically significant.

RESULTS

Of the 525 patients included in the study (50.7% male, mean age: 62.9 ± 10.8 years), LAA thrombus was detected in 86 patients (16.4%). Of the 439 patients without thrombus, 38 (8.6%) underwent medical cardioversion and the remaining 401 cases (91.3%) underwent electrical cardioversion. Return to sinus rhythm was obtained at the rate of 55.2% in medical cardioversion and 71.2% in electrical cardioversion. Following the cardioversion, no ischaemic cerebrovascular event was observed. The comparisons of the demographic and clinical characteristics of the groups are presented in Table 1.

Platelet/lymphocyte ratio (PLR), NLR, and SII were significantly higher in the group with LAA thrombus ($P<0.001$ for each). LVEF was significantly lower in the LAA thrombus (+) group (46.21±14.35% vs. 51.66±12.74%, $P=0.001$). The comparisons of the laboratory and echocardiography characteristics of patients are shown in Table 2.

In the ROC analysis, SII was found to be superior to PLR in predicting LAA thrombus (AUC: 0.760 vs.0.696, $P=0.001$), whereas no significant difference was found between SII and NLR (AUC: 0.760 vs.0.763, $P=0.86$). When a cutoff value of 750 was determined, SII had 67.4% sensitivity and 71.3% specificity for the prediction of LAA thrombus. The ROC curve graph of the inflammation markers is shown in Fig. 2.

In the univariate logistic regression analysis, age, diabetes, hypertension, systolic heart failure (LVEF <40%), erythrocyte distribution width (RDW), creatinine clear-

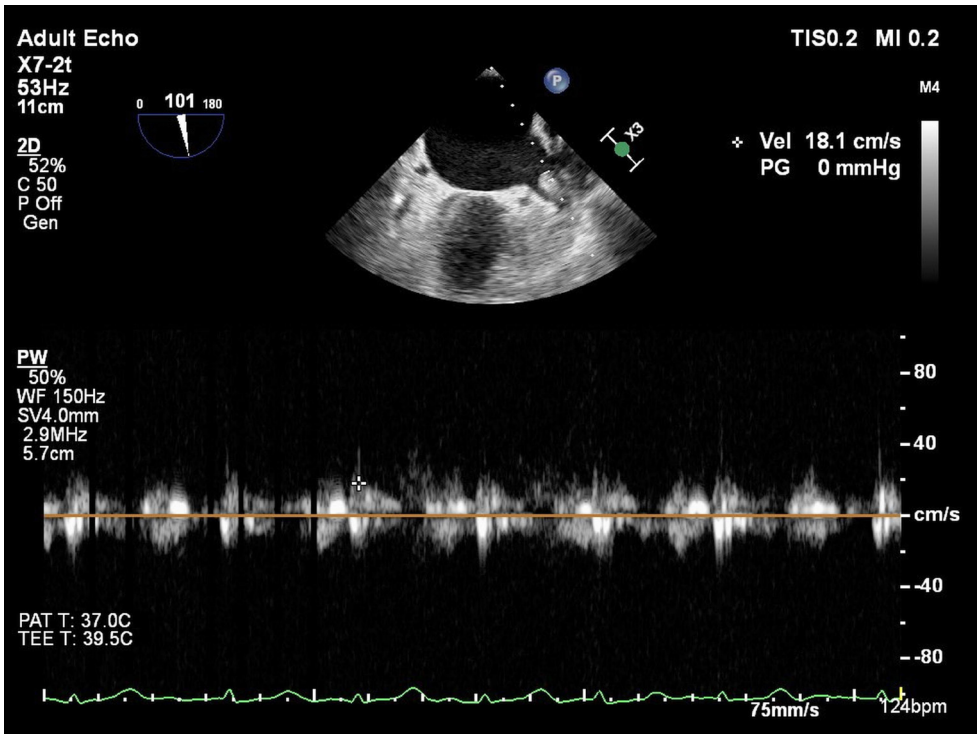

Fig. 1. LAA thrombus formation and measurement of the LAA emptying velocity from the orifice on two-dimensional transoesophageal echocardiography.

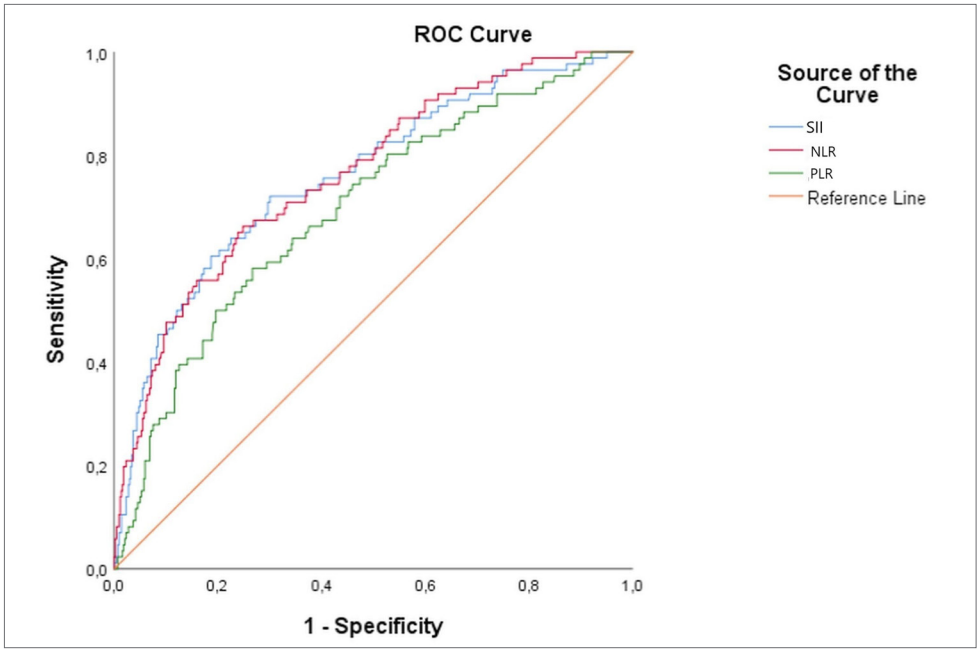

Fig. 2. ROC curve analysis of the systemic immune inflammatory index (SII), Neutrophil/lymphocyte ratio (NLR), and Platelet/lymphocyte ratio (PLR) for the prediction of LAA thrombus.

ance, LAA emptying rate <20 cm/sec, and SII >750 were found to be associated with LAA thrombus. In the multivariate regression analysis, diabetes (HR: 2.264, 95% CI: 1.169–4.389, *P*=0.015), LAA emptying rate of <20 cm/s (HR: 59.347, 95% CI: 25.397–138.680, *P*< 0.001), and SII values >750 (HR:4.291, 95% CI: 2.144–8.586 *P*<0.001) remained as independent predictors for LAA thrombus (Table 3).

In the Spearman correlation analysis, a moderate correlation was found between SII and the CHADS2 VASc score (r=0.239, *P*<0.001). In the subgroup of 105 patients with $CHADS_2$ VASc score of 0 or 1, in which LAA thrombus was observed in only 9 (8.5%) patients, the median SII value in the group with LAA thrombus was determined to be significantly higher than those with-

Table 1. Demographic and clinic characteristics of the patients.

Variable	LAA thrombus (+) (n:86)	LAA thrombus (–) (n:439)	*P*
Age years, mean ± SD	65.79 ± 9.88	62.39 ± 10.88	**0.007**
Male, n (%)	49 (57.0)	217 (49.4)	0.201
BMI kg/m^2, mean ± SD	28.85 ± 4.37	28.36 ± 4.43	0.353
Diabetes, n (%)	41 (47.7)	110 (25.1)	**0.002**
Hypertension, n (%)	79 (91.9)	361 (82.2)	**0.027**
Active smoking, n (%)	32 (33.1)	170 (38.7)	0.792
Stroke, n (%)	6 (7.0)	9 (2.1)	**0.012**
CAD, n (%)	31 (36.0)	121 (27.6)	0.113
COPD, n (%)	3 (3.5)	21 (4.8)	0.781
SHF, n (%)	26 (30.2)	80 (18.2)	**0.011**
Hyperthyroidism, n (%)	2 (2.3)	10 (2.3)	0.978
AF-related semptoms day (25th–75th)	20 (8–52)	10 (5–30)	**0.004**
CHA_2DS_2-VASc, median (25th–75th)	3.5 (3–5)	3 (2–4)	**<0.001**
C2 HEST, median (25th–75th)	3 (1–4)	2 (1–3)	**<0.001**
Antiplatelet drug, n (%)	11 (12.8)	39 (8.9)	0.259

AF, Atrial fibrillation; BMI, Body mass index; CAD, Coronary artery disease; COPD, Chronic obstructive pulmonary disease; LAA,Left atrial appendage; SHF, Systolic heart failure.

Table 2. The laboratory and echocardiographic characteristics of the patients.

Variable	LAA thrombus (+) (n:86)	LAA thrombus (-) (n:439)	*P*
Hemoglobin g/dL; mean ± SD	13.47 ± 2.23	13.32 ± 2.04	0.564
White blood cell, ×10^9/L , mean + SD	8.87 ±2.02	8.09 ± 1.91	**0.001**
Neutrophils ×10^9/L , mean ± SD	6.42 ± 1.74	5.17 ±1.46	**<0.001**
Lymphocytes ×10^9/L , mean ± SD	1.68 ± 0.65	2.20 ± 0.85	**<0.001**
Platelet, ×10^3/L mean ± SD	249.94 ± 75.65	244.09 ± 69.03	0.480
MPV fL mean ± SD	10.84 ± 1.39	10.93 ± 4.41	0.840
RDW %, median (25th–75th)	14.60 (13.70–16.37)	13.90 (13.20–15.00)	**<0.001**
CrCl* mL/min , median (25th–75th)	70.95 (55.35–86.26)	79.70 (61.10–92.60)	**0.007**
Total cholesterol mg/dL, mean ± SD	178.60 ± 49.49	176.62 ± 44.62	0.710
Triglyceride mg/dL mean ± SD	142.38 ± 80.76	149.34 ± 97.25	0.534
TSH mIU/L, median (25th–75th)	1.38 (0.80–2.79)	1.30 (0.80–2.20)	0.412
D-Dimer mg/L, median (25th–75th)	1.02 (0.30–2.30)	0.20 (0.20–0.30)	**<0.001**
Neutrophil/Lymphocyte ratio mean ± SD	4.53 ± 2.54	2.69 ± 1.34	**<0.001**
Platelet/Lymphocyte ratio mean ± SD	168.13 ± 74.96	126.42 ± 63.52	**<0.001**
SII mean ± SD	1096.34 ± 598.69	648.26 ± 371.63	**<0.001**
LVEF % mean ± SD	46.21 ± 14.35	51.66 ± 12.74	**0.001**
Left atrial diameter, mm, mean ± SD	46.93 ± 5.58	46.14 ± 3.84	0.109
LAA emptying velocity cm/s, mean ± SD	15.71 ± 7.37	40.67 ± 8.31	**<0.001**

CrCI, Creatinine Clearance; LAA, Left atrial appendage; LVEF, Left ventricular ejection fraction; MPV, Mean platelet volume; RDW, Red cell distribution width; SII, Systemic immune-inflammation index; TSH, Thyroid-stimulating hormone; *Calculated according to the Cockcroft-Gault equation.

out LAA thrombus (median [25–75 IQR] :791.05 [513.86 –1354.59] vs. 471.00 [359.66–670.35] *P*=0.004).

DISCUSSION

The results of this study demonstrated that high SII values, reduced LAA emptying velocity, and the presence of diabetes were independent predictors for LAA thrombus in non-valvular AF. It has been previously proven that NLR is a predictor of LAA thrombus in patients with non-valvular AF (ref.[8]). The current study is the first to have investigated the relationship between LAA thrombus and SII, a new inflammatory marker obtained by multiplying the NLR by the platelet count.

LAA thrombus was observed at the rate of 16.4% in the current study while it was observed at 10.3% in a study by Yalçın et al., which similarly investigated non-valvular AF patients[8]. The fact that patients who had previously used anticoagulants were excluded from the current study, whereas 29.1% of the patients in the study by Yalçın et al. had previously received anticoagulant treatment, could explain the higher rate of thrombus in the current study. Similarly, Habara et al reported LAA thrombus at the rate

Table 3. Logistic regression analysis for identifying predictors of left atrial appendage (LAA) thrombus.

Variables	HR	95% CI	*P*
Univariate Analysis			
Age	1.033	1.009–1.058	**0.008**
Diabetes	3.283	2.041–5.279	**<0.001**
Hypertension	2.438	1.084–5.485	**0.031**
SHF	1.945	1.156–3.271	**0.012**
AF-related semptoms	1.007	0.999–1.015	0.074
RDW	1.242	1.106–1.395	**<0.001**
CrCl	0.985	0.975–0.996	**0.006**
SII >750	5.089	3.099–8.356	**<0.001**
LAA velocity <20 cm/s	45.513	22.633–91.524	**<0.001**
Multivariate Analysis			
Age	1.037	0.997–1.078	0.068
Diabetes	2.264	1.169–4.386	**0.015**
Hypertension	1.722	0.452–6.564	0.426
SHF	1.265	0.610–2.626	0.528
RDW	1.099	0.935–1.290	0.251
CrCl	0.991	0.976–1.007	0.286
LAA velocity <20 cm/s	59.347	25.347–138.680	**<0.001**
SII >750	4.291	2.144–8.586	**<0.001**

AF, Atrial fibrillation; CrCI, Creatinine Clearance; LAA, Left atrial appendage; RDW, Red cell distribution width; SHF, Systolic heart failure; SII, Systemic immune-inflammation index.

of approximately 9% in patients with non-valvular AF. The rate of anticoagulant use was significantly lower in the group with LAA thrombus, supporting that previous anticoagulant use reduces LAA thrombus formation[24]. As anticoagulant use reducing the risk of LAA thrombus is a confounding factor, those patients were excluded from the current study.

Similar to the current study, Shi et al determined diabetes as a factor associated with LAA thrombus in non-valvular AF (ref.[24]). The fact that diabetes in AF causes reverse left atrial remodelling, characterized by increased orifice growth and decreased orifice velocity in the left atrial appendix, may explain the increased LAA thrombogenesis in such diabetic patients[25].

In the current study, LAA emptying rate <20cm/sec was an independent predictor of LAA thrombus and this finding has been reported by several previous studies[26-29]. Reduced LAA velocity causing stasis is associated with LAA mechanical dysfunction[30-32].

Previous studies have shown that both the PLR and NLR are independent predictors of LAA thrombus in non-valvular AF (ref.[8,33]). There is as yet no evidence that SII, which consists of PLR and NLR, predicts LAA thrombus although it has been found to be associated with thrombotic events in patients with acute coronary syndrome or malignancy[10-12]. In the current study, whereas SII was not found to be superior to NLR in predicting LAA thrombus, it was superior to PLR in predicting LAA thrombus In addition, a weak correlation was determined in the current study between SII and the CHA_2DS_2-VASc score. The determination of higher SII values in the patients with LAA thrombus and low CHA_2DS_2-VASc score (0 or 1) suggests that a high SII may be an indicator to initiate anticoagulant treatment in such patients.

There is evidence that the formation of LAA thrombus is facilitated in AF patients through several mechanisms such as systemic inflammation, left atrial endothelial cell dysfunction, and activation of the coagulation cascade[34-38]. The current analysis could explain the relationship between SII and LAA thrombus.

Limitations

This was a single-centre study and the number of patients included was limited. The duration and medication for diabetes were not assessed. Finally, other parameters such as LAA anatomy, which can be a predisposing factor for thrombus, were not investigated.

CONCLUSION

The results of this study demonstrated that SII and diabetes were significant predictors of LAA thrombus in non-valvular AF. SII, which is a practical and straightforward marker, can be used to identify high thrombus-related embolic risk in patients with non-valvular atrial fibrillation, even when there is a low CHA_2DS_2-VASc score.

ABBREVIATIONS

AF, Atrial fibrillation; CRP, C-reactive protein; LAA, Left atrial appendage; LVEF, Left ventricle ejection fraction; NLR, Neutrophil/lymphocyte ratio; PLR,

Platelet/lymphocyte ratio; ROC, Receiver Operating Characteristic; SII, Systemic immune inflammatory index; TTE, Transthoracic echocardiography; TEE, Transoesophageal echocardiography.

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