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Research Article

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THE ASSOCIATION BETWEEN PLATELET TO LYMPHOCYTE RATIO AND LEFT ATRIAL APPENDAGE THROMBOGENIC MILIEU IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

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Abstract

Objectives: To assess the diagnostic value of platelet to lymphocyte ratio (PLR) with respect to the risk of left atrial appendage thrombogenic milieu (LAA TM) in patients with nonvalvular atrial fibrillation (AF), which has not been studied before.

Materials and Methods: This is a retrospective study that included consecutive patients with non-valvular AF who underwent transesophageal echocardiography (TEE) prior to electrical cardioversion or prior to AF catheter ablation. The potential association between PLR and LAA TM, which was defined as the presence of a thrombus, sludge and spontaneous echo contrast in LAA, was analyzed using multivariate logistic regression analysis.

Results: A total of 120 patients (59 females, mean age: 66.15 ± 10.2 years) with nonvalvular AF were included in the study. The thrombogenic milieu was determined in 37 (30.83%) patients on TEE examination. Patients with LAA TM were found to have a higher mean CHA2DS2-VASc score (3.00 vs. 2.00, p=0.009), decreased LAA velocity (23.60 vs. 36.20 m/s, p=0.002) and left ventricular ejection fraction (49.70 vs. 56.90 %, p=0.010), greater left atrial diameter (4.70 vs. 4.30 cm, p= 0.001) and higher PLR value (157.91 vs. 126.13, p=0.023) compared to those without thrombogenic milieu. Only LAA velocity (OR=0.854; p=0.001) and PLR (OR=1.024; p=0.012) were found to be independently associated with LAA TM.

Conclusion: PLR may be an independent risk factor for LAA TM in nonvalvular AF patients; however, beyond research purposes, the rather low sensitivity and specificity values must be interpreted with caution in the routine clinical setting.

Keywords: Atrial fibrillation, platelet to lymphocyte ratio, left atrial appendage thrombogenic milieu.

Introduction

Atrial fibrillation (AF) is the most common arrhythmic disorder with an important association with cardio-embolic stroke.[1] Formation of thrombus, sludge and spontaneous echo contrast (SEC) in the left atrium or its appendix is the precursor mechanism of cardiac thromboembolism, and these formations are firmly related to the presence of AF. Current literature adopted the novel terminology of left atrial appendage thrombogenic milieu (LAA TM), an umbrella term consisting of thrombus, sludge and SEC.[2] Although the mechanisms behind thrombogenesis in patients with non-valvular AF are multifactorial, including left atrial stasis, inflammation and oxidative stress, identifying predictors of LAA TM is crucial because early treatment can help prevent thromboembolic complications. Several studies have sought to determine predictors of LAA TM.[3-5] These studies showed that predictors for LAA TM in patients with AF include higher natriuretic peptide levels, increased left atrium diameter, decreased left ventricular ejection fraction, longer AF duration, and persistent or permanent AF.[3-5] Recently, Fu and colleagues revealed that blood group A is an independent risk factor for left atrial and/or left atrial appendage thrombogenic milieu in patients with non-valvular AF.[6] Platelets have a pivotal role in thrombogenesis and inflammation, and platelet to lymphocyte ratio (PLR) has emerged as a new inflammatory marker.[7]

Although the association between inflammatory status and thrombosis risk in patients with non-valvular AF has been shown in previous studies, the relationship between the presence of LAA TM and PLR has not been studied yet. Therefore, we aimed to investigate the predictive value of PLR for LAA TM in patients with non-valvular AF.

Materials and Methods

We retrospectively analyzed the data of patients with non-valvular AF who had undergone TEE examination prior to electrical cardioversion (2) or prior to AF catheter ablation between January 2016 and June 2018 at our hospital. All patients included in the study had provided written informed consent for the scheduled procedure(s) and the possible use of their data for scientific purposes. Ethical approval was obtained prior to the study.

Study group and variables

Patients with mitral stenosis or a mechanical prosthetic heart valve, patients with concomitant infection and incomplete medical records on blood count were excluded. Patients with signs of infection that may affect PLR levels were not included in our study. The patients did not have a history of antibiotic use. Apart from infection and valvular disease, there were also several other clinical conditions that were excluded because they might

have affected PLR values. Thus, patients with systemic diseases, hematological disorders, metabolic diseases, congenital abnormalities, malignancies, those receiving chemotherapy treatment, individuals with a history of previous percutaneous coronary intervention or coronary artery bypass grafting, and patients with chronic renal, respiratory or hepatic disease were excluded. The CHA2DS2–VASc score (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 or 65–74 years, diabetes, thromboembolism or a history of stroke, vascular disease, and sex) was obtained for assessing stroke risk in AF.

The complete blood counts, which were obtained immediately before TEE, included total white blood cell, neutrophil, lymphocyte and platelet count analyses which were measured via automated blood counters, the Sysmex XS1000i and XE2100 devices (Sysmex Corporation, Kobe, Japan). Platelet-to-lymphocyte ratio was calculated as the ratio of the platelets to lymphocytes obtained from the blood samples.

The TEE Procedure

Echocardiographic examinations were performed with System V and a Vivid T8 from GE Ultrasound (G E Medical Systems, Wisconsin, USA) with a 1.7/3.4 MHz harmonic transducer and a multiplane 6.7 MHz transoesophageal probe. Subcutaneous heparin was administered prior to TEE. Assessment of the LAA function was done by the recording of LAA velocity by placing a pulsed wave Doppler sample volume just inside the base of the appendage. TEE images were reviewed for the presence of LAA thrombus/sludge and spontaneous echo contrast by experienced observers. The patients were classified as having an LAA TM if any of the following were present: dense spontaneous echo contrast, sludge or thrombus in LAA, and LAA flow velocity ≤20 m/s.

Statistical analysis

All statistical analyses were performed using the SPSS 20 (SPSS INC, Chicago, Illinois, USA). For the normality check, the Shapiro-Wilk test was used. Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to the normality of distribution and frequency (percentage) for categorical variables. Normally distributed variables were analyzed with the independent samples t-test, and non-normally distributed variables were analyzed with the Mann-Whitney U test. Chi-square tests were used to compare the distribution of categorical variables between the groups. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal PLR cut-off value for predicting LAA TM. A calculated difference of $p<0.05$ was considered to be statistically significant.

Results

A total of 120 patients (59 female, mean age: 66.15±10.2 years) with nonvalvular AF were included in the study. The comparison of baseline characteristics of the study population according to the presence of LAA TM is summarized in Table 1.

Table 1: Baseline Characteristics of the Groups

	LAA TM+ (n=37)	**LAA TM - (n=83)**	**p**
Age, y	67.39±10.32	64.89±10.01	0.528
Female / Male (n)	20(54.05%) / 17(45.94%)	39(46.98%) /44(53.01%)	0.555
Persistan AF(n, %)	22 (59.00%)	37 (44.50%)	0.054
AF duration, month	7.50 (2.00-24.00)	10.00(2.50-36.00)	0.480
Coronary artery disease (n%)	18 (48.60%)	32 (38.60%)	0.322
Hypertension (n, %)	28 (75.70%)	49 (59.00%)	0.100
Diabetes mellitus (n, %)	11 (29.70%)	17 (20.50%)	0.350
Hyperlipidemia (n, %)	10 (27.00%)	15 (18.10%)	0.331
Stroke (n, %)	3 (8.10%)	2 (2.40%)	0.170
CHA_2DS_2-VASc score	3.00 (2.00-5.00)	2.00 (1.00-4.00)	0.008
Left atrium, cm	4.70±0.45	4.30±0.62	0.001
Left ventricular ejection fraction, %	49.70(38.00-60.00)	56.90 (55.00-60.00)	0.010
Left atrial appendage velocity	23.60±15.92	36.20±16.44	0.002
Hemoglobin, g/dL	13.41±1.74	13.54±1.77	0.804
Platelet	254.83±74.26	241.21±77.7	0.037
Lymphocyte	2.09±0.77	2.20±0.84	0.194
Platelet to lymphocyte ratio	157.91±73.41	126.13±57.20	0.023
Glucose, mg/dL	115.12 (103.06-131.03)	114.01 (100.06-121.64)	0.285
Glomerular filtration rate	71.54 (61.02-85.04)	72.04 (65.04-89.03)	0.200
Antiplatelets (n, %)	12 (32.40%)	22 (26.50%)	0.518
Oral anticoagulants (n, %)	31 (83.80%)	70 (84.30%)	0.939
NOAC (n, %)	15 (40.50%)	58 (69.90%)	0.002
VKA (n, %)	16 (43.21%)	12 (14.54%)	0.001

Abbreviations: LAA TM: Left atrial appendage thrombogenic milieu; AF: atrial fibrillation; CHA_2DS_2-VASc: congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 or 65–74 years, diabetes, thromboembolism or a history of stroke, vascular disease, and sex, NOAC: non–vitamin K antagonist oral anticoagulant; VKA: vitamin K antagonist.
Data are given as mean ± standard deviation or median (1st quartile – 3rd quartile) for continuous variables according to the normality of distribution and as frequency (percentage) for categorical variables

A univariate logistic regression analysis identified persistant AF (odds ratio [OR] = 2.511; p=0.045), CHA_2DS_2-VASc score (OR= 1.416; p=0.006), left atrial diameter (OR= 3.358; p=0.003), left ventricular ejection fraction (OR= 0.952; p=0.006), LAA velocity (OR= 0.943; p=0.003) and PLR (OR= 1.008; p=0.018) as predictors of LAA TM. However, in multivariate logistic regression analysis, only LAA velocity (OR=0.854; p=0.001) and PLR

(OR=1.024; p=0.012) were found to be independently associated with LAA TM in patients with non-valvular AF (Table 2). ROC curve analysis showed that the optimal PLR cut-off value for predicting LAA was 124.50 with a sensitivity of 62.20% and specifity of 60.20% (AUC= 0.641, 95% CI: 0.534-0.748, p=0.014) (Figure 1).

Table 2. Univariate and Multivariate Regression Analysis for Predicting Left Atrial Appendage Thrombogenic Milieu

Variables	Univariate OR (95 % CI)	p	Multivariate OR (95 % CI)	p
Age, year	1.025 (0.985-1.067)	0.218		
Female	1.327 (0.610-2.887)	0.475		
Persistan AF	2.511 (1.023-6.162)	0.045	1.267 (0.170-9.462)	0.817
AF duration, month	0.987 (0.964-1.011)	0.285		
Coronary artery disease	1.510 (0.691-3.299)	0.302		
Hypertension	2.159 (0.905-5.148)	0.083		
Diabetes Mellitus	1.643 (0.679-3.975)	0.271		
Hyperlipidemia	1.679 (0.672-4.196)	0.268		
Stroke/TIA	3.574 (0.571-22.354)	0.173		
CHA_2DS_2-VASc score	1.416 (1.102-1.818)	0.006	1.156 (0.740-1.805)	0.524
Left atrium, cm	3.358 (1.528-7.381)	0.003	1.575 (0.368-6.745)	0.540
LV ejection fraction, %	0.952 (0.920-0.986)	0.006	1.004 (0.943-1.070)	0.899
LA appendage velocity, cm/sn	0.943 (0.907-0.981)	0.003	0.854 (0.778-0.938)	0.001
Hemoglobin, g/dL	0.972 (0.780-1.212)	0.803		
Platelet to lymphocyte ratio	1.008 (1.001-1.014)	0.018	1.024 (1.005-1.042)	0.012
Glucose, mg/dL	1.007 (0.996-1.018)	0.209		
Glomerular filtration rate	0.984 (0.960-1.008)	0.191		
Antiplatelets	1.331 (0.573-3.093)	0.507		
Oral anticoagulants	1.189 (0.391-3.617)	0.761		

Abbreviations: OR: odds ratio; CI: Confidence interval; TIA: transient ischemic attack; LV: left ventricle; LA; left atrium. Other abbreviations are as in Table 1.

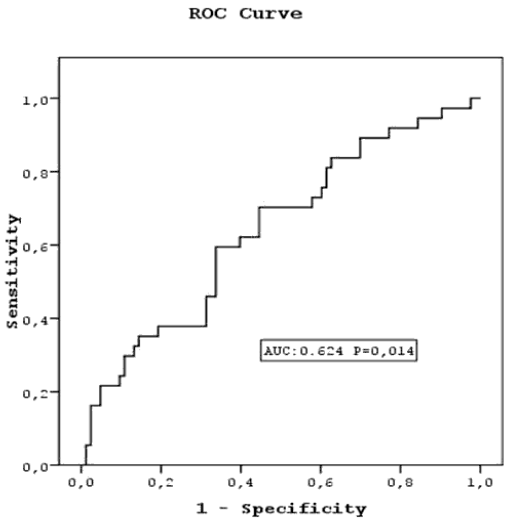

Figure 1: ROC Curve Analysis for PLR on Predicting LAA TM (AUC: 0,641, 95%ci:0.534-0.748, p=0.014).

Discussion

In the present study, we observed a significant association between PLR and increased risk of LAA TM in patients with nonvalvular AF. Although previous studies documented the potential use of TEE parameters as markers of LAA TM, to the best of our knowledge, this is the first study that reports an association between PLR and LAA TM in AF patients. However, taking into account the low sensitivity and specificity values, it is evident that PLR values cannot be used for diagnostic purposes in this context.

Previous studies have established that the left atrium, particularly LAA, is the most frequent location of cardiac thromboembolism. Therefore, prediction of LAA TM is important.[8-11] Transesophageal echocardiography has been the recommended procedure for this purpose.[12, 13] Because of its semi-invasive nature, there has been an interest in the prediction of LAA TM by the routine, non-invasive parameters such as clinical, transthoracic echocardiographic and biochemical markers. However, current literature indicates inconclusive findings on this topic. Yarmohammadi et al. found a positive relationship between CHADS2 score and left atrial thrombosis in patients with low left ventricular ejection fraction (≤20%) (2). Contrary to this, Jaroch and colleagues' retrospective study consisting of 202 patients with persistent AF failed to demonstrate the predictive value of CHA_2DS_2-VASc score for LA TM.[3] They found that duration of AF (exceeding one year), left atrial diameter exceeding 51 mm, left ventricular end-diastolic dimension (exceeding 52 mm), and radiographic evidence of aortic plaques were independent predictors of LAA TM. In a recent study, Kizawa et al. found that patients with TM had a lower incidence of paroxysmal AF and higher CHA_2DS_2-VASc scores compared to those without TM.[14] Presence of TM was associated with greater left atrial volume index, lower left ventricular ejection fraction, lower glomerular filtration rate and higher prevalence of left ventricular hypertrophy. In addition to the controversy on these prediction rules, the inconclusive findings still persist in the laboratory parameters. In patients with nonvalvular AF, Habara et al. revealed that plasma D-dimer was the most powerful predictor of LAA thrombus.[15] Similarly, Ochiumi et al. showed that brain natriuretic peptide levels higher than 251.2 pg/mL may predict LAA thrombus.[16] In contrast, Pant and colleagues showed that brain natriuretic peptide predicts spontaneous echo contrast, but its predictive ability does not include LAA thrombus.[5] In addition to this, Bejinariu and colleagues revealed that neither D-dimer nor BNP values were predictors of LAA TM.[17] Cianfrocca et al. Showed that C-reactive protein had an additive effect on left atrial appendage velocity on the prediction of LAA TM. [18] Our study also showed that LAA velocity was independently associated with LAA TM in patients with nonvalvular AF.

High platelet counts may increase thrombocyte activation and aggravate the release of inflammatory mediators. PLR reflects both inflammation and thrombosis and is more valuable than either platelet or lymphocyte counts alone. Recent data have shown that PLR, a novel systemic inflammatory response marker, is an important prognostic factor in numerous diseases such as acute coronary syndromes.[19]

In addition, many studies have shown that PLR is an important parameter in predicting the occurrence and recurrence of AF. In a study examining patients after CABG surgery, Gungor et al. showed that in addition to age and PLR values higher than 119.3 predicted AF recurrence with a sensitivity of 64% and a specificity of 56%.[20] In another study, Dereli et al. showed that PLR values higher than 147 predicted AF recurrence with a sensitivity of 83.3% and a specificity of 84.5% in nonvalvular AF patients undergoing electrical cardioversion.[21] However, the predictive value of PLR in LAA TM has not been investigated up to date. In our study, patients with LAA TM had a higher mean CHA_2DS_2-VASc score, decreased LAA velocity and left ventricular ejection fraction, increased left atrial diameter and higher PLR than patients without LAA TM. Of these parameters, only LAA velocity and PLR were found to be independently associated with LAA TM in patients with non-valvular AF.

Limitations

As this was a retrospective, single-center study, which included relatively small sample size, the potential cause-effect relationship could not be determined. All subjects in the current study were scheduled to receive cardioversion or ablation treatment, and selection bias must be considered when applying the results to the entire population of AF patients. The absence of measurement of other established inflammatory markers such as CRP, interleukin-6, tumor necrosis factor or BNP may also be considered a potential limitation.

Although there was no difference between the groups, the use of antiplatelet may have affected the results. In addition, the statistically significant difference between NOAC and vitamin K usage rates between the groups is a limitation of our study that may affect the results.

Our data also showed that CHA_2DS_2-VASc score could not predict LAA TM. This finding may raise concerns about the statistical power of the study; however, similar results have been reported previously. Comprehensive studies examining more cases may yield different results in this regard.

Conclusion

To our knowledge, this is the first study that combines echocardiographic, clinical and laboratory parameters for the prediction of the LAA TM presence. Although TEE is the gold-standard technique for the detection of LAA TM, identifying these novel predictors, such as PLR, may provide clinical insight and also may guide clinicians to conduct further research. This study also showed that PLR predicts LAA TM regardless of clinical prediction rules in patients with nonvalvular AF; however, as mentioned, caution must be taken to implement these findings in bedside practice as the current cut-off value of 124.5 had rather low sensitivity and specificity values and therefore can not reliably useful in the routine clinical setting.

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Ethical Considerations: The study protocol was approved by the TOBB Economics and Technology University local ethic committee (No: 118028, Date: 16/01/2019).

Conflict of Interest: The authors declare no conflict of interest

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