

Relationship between the presence of left atrial thrombus in patients with mitral stenosis and platelet-to-lymphocyte ratio

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ABSTRACT

Objective: Rheumatic carditis-induced mitral valve disease is associated with a chronic inflammatory process. The close relationship between inflammation and prothrombotic processes is known. Our goal was to examine the relationship between the presence of left atrial (LA) thrombus in patients with rheumatic mitral valve stenosis (RMVS) and platelet-to-lymphocyte ratio (PLR), which is an inflammatory marker.

Methods: This cross-sectional study included 351 consecutive patients diagnosed with RMVS upon presentation to the cardiology polyclinic. All patients were evaluated using transthoracic and transesophageal echocardiography and were divided into 2 groups: those with and without LA thrombus. In addition to echocardiographic and biochemical parameters, PLR was compared between the groups. Student's t-test, Mann-Whitney U test, logistic regression analysis, and receiver operating characteristic (ROC) curve analysis were used for statistical analysis.

Results: No significant differences in terms of age, gender, body mass index, and comorbidities were found between the groups with and without LA thrombus. In the group with LA thrombus, higher red cell distribution width, mean platelet volume, and platelet count and lower lymphocyte count were detected. In addition, C-reactive protein levels were significantly higher in the LA thrombus group (4.7 vs. 2.7 mg/L, $p < 0.001$). PLR was significantly higher in patients with thrombus than in those without (133 ± 38 vs. 119 ± 31 , $p = 0.001$). Higher PLR was identified as independently associated with the presence of LA thrombus (odds ratio: 1.03, 95% confidence interval: 1–1.06, $p = 0.016$).

Conclusion: Higher PLR was detected in the LA thrombus group of patients with RMVS. (*Anatol J Cardiol* 2016; 16: 673-7)

Keywords: C-reactive protein, inflammation, platelet-to-lymphocyte ratio, rheumatic mitral valve stenosis, thrombosis

Introduction

Rheumatic valve diseases are an important cause of morbidity and mortality, particularly in developing and undeveloped countries (1). The slowdown of blood flow and stasis in the left atrium associated with rheumatic mitral valve stenosis (RMVS) causes the formation of thrombus (2). The resulting thrombus joins the systemic circulation from the left atrium and causes embolic complications, the most serious being in the cerebrovascular system. However, it is not possible to explain the development of left atrial (LA) thrombus in patients with MS, and the major embolic events seen in around 20% of these (2) with only valvular obstruction. Rheumatic valve disease is an autoimmune inflammatory process triggered by group A streptococcal infection. The inflammatory reaction continues subclinically and can lead to the progression of valvular damage (3, 4). In addition to LA stasis, inflammation, oxidative stress, platelet size, and an increase in activation have been found to be associated with thrombus formation

(5–7). recently, the platelet-to-lymphocyte ratio (PLR), known to be an inflammatory marker, has been found to be associated with various cardiovascular diseases (8–10). PLR is a cheap and easily reproducible parameter that is obtained by complete blood count analysis and is analyzed in nearly every patient. There is a need for tools that can be used in every day practice for the determination of individuals with a high risk of thrombus among patients with RMVS, thus aiding the prevention of thromboembolic complications. Our study aimed to examine the relationship between the presence of LA thrombus in patients with RMVS and PLR and understand the importance of PLR in identifying at-risk patients.

Methods

Study group

In this cross-sectional study, data were collected prospectively. The study included consecutive patients determined to have RMVS as a result of transthoracic echocardiography (TTE)

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[mitral valve area (MVA): $<2 \text{ cm}^2$] following presentation at the cardiology outpatient clinic with various complaints between January 2011 and March 2015. TTE and transesophageal echocardiography (TEE) were performed and patients with RMVS were divided into 2 groups: those with and without LA thrombus. Venous blood samples were collected within 12 h of echocardiography. As the patients included in the study were either diagnosed with RMVS for the first time and/or were pre-diagnosed but untreated, they were not using anticoagulants, antiplatelets, or other cardiac medications. The exclusion criteria consisted of significant valvular heart disease except mitral valve disease (moderate and severe aortic valve disease, severe mitral regurgitation); heart failure; presence of acute coronary syndrome; previous cardiac surgery and/or percutaneous balloon valvuloplasty; hematologic disorders; anemia (defined according to the World Health Organization as hemoglobin levels of $<12 \text{ g/dL}$ in women or $<13 \text{ g/dL}$ in men); active infectious or inflammatory diseases; rheumatologic diseases; current therapy with corticosteroids, non-steroidal antiinflammatory drugs, cytotoxic drugs, thrombolytic therapy, and glycoprotein IIb/IIIa inhibitors; thyroid disease; smoking; chronic kidney disease [estimated glomerular filtration rate (eGFR) of $<60 \text{ mL/min/1.73 m}^2$] or abnormal liver function (elevation of transaminases levels to >3 times the upper limit of normal); and malignancy. Medical history, physical examination, routine biochemical tests, and electrocardiogram were obtained from all patients. Height and body weight were measured to calculate the body mass index (BMI). Hypertension (HT) was defined as systolic blood pressure of $\geq 140 \text{ mm Hg}$ and/or diastolic blood pressure of $\geq 90 \text{ mm Hg}$ or medication use. Diabetes mellitus (DM) was defined as fasting blood glucose levels of $\geq 126 \text{ mg/dl}$ or use of insulin or an oral hypoglycemic medication. Coronary artery disease (CAD) was assessed from the patients' medical reports. Presence of atrial fibrillation (AF) was identified by 12-lead electrocardiography.

Informed consent was obtained from all patients. The study was approved by the institutional ethics committee and the investigation conformed to the principles of the Declaration of Helsinki.

Echocardiographic evaluation

TTE (2.5–3.5-MHz transducer) and TEE (5-MHz transducer) (Vivid 7 system, GE-Vingmed Horten, Norway) were performed by the standard methods. Following local pharyngeal anesthesia, the TEE probe was advanced 25–35 cm in the esophagus, and TEE was performed at the position with the clearest image. All images were recorded and analyzed by 2 separate cardiologists. The modified Simpson's method in 2-dimensional echocardiographic apical 4-chamber view was used to calculate the left ventricular ejection fraction. The LA anteroposterior diameter was measured by M-mode echocardiography. The transmitral gradient and left atrial appendage peak flow velocity (LAV) were measured by Doppler echocardiography. MVA was measured using the planimetric method. Thrombus was recognized as a

homogeneous mobile or fixed mass with similar echodensity to the myocardium located at the left atrium and LA appendix. With 50 randomly selected patient images, the intra- and interobserver variabilities in terms of LA thrombus were evaluated and determined to be 2.8% and 3.9% respectively.

Laboratory evaluation

In all patients, venous blood samples were drawn within 12 h of echocardiographic examination, and routine biochemical analyzes were performed. Blood samples for complete blood count were drawn into the anticoagulated collection tube containing EDTA. The mean platelet volume (MPV), red cell distribution width (RDW), platelet count, and other blood cell indices were measured using a Beckman Coulter method of counting and sizing, automatic diluting, and mixing (Beckman Coulter, Inc., Hialeah, Florida). PLR was calculated as the ratio of the platelet count to the lymphocyte count. C-reactive protein (CRP) levels were measured using the nephelometric method (Beckman Coulter IMMAGE 800). The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR for each patient.

Statistical analysis

SPSS 17.0 for Windows (SPSS 17.0, Chicago, Illinois) software package was used for all analyses. Continuous variables were expressed as mean \pm standard deviation (SD) (for parameters with normal distribution) and median (interquartile range, IQR) (for parameters with non-normal distribution), and categorical variables were expressed as percentages. The chi-square test was used to compare categorical variables between the groups. Analysis of normality was performed using the Kolmogorov–Smirnov test. The independent samples t test was used to compare continuous variables with normal distribution and the Mann–Whitney U test was used to compare continuous variables with non-normal distribution. Power analysis (GPower program by Erdfelder, Faul, & Buchner, 1996) was conducted with an effect size set to 0.25 (medium effect size) and alpha level set to $p < 0.05$. It was considered that a total number of 88 subjects who have LA thrombus should be recruited to the study to reach an acceptable statistical power of 0.80. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal PLR cut-off value for predicting LA thrombus. Binary logistic regression analysis was performed to identify independent factors associated with the presence of LA thrombus. A 2-sided p value of <0.05 was considered significant within a 95% confidence interval (CI).

Results

The total number of patients was 351, with LA thrombus determined in 92 (26.2%) patients and not determined in 259 (73.8%) patients. The mean age of the group with LA thrombus was 56 ± 9.9 years, and the group consisted of 61 (66.3%) women. No significant differences in terms of age, gender, BMI, and comorbidities (DM, HT, and CAD) were found between the groups. A higher in-

cidence of AF was determined in the LA thrombus group (Table 1).

When the laboratory results were analyzed, no difference was observed between the 2 groups in terms of glucose levels, low-density lipoprotein cholesterol levels, eGFR, hemoglobin levels, hematocrit, neutrophil count, and leukocyte count. In the LA thrombus group, while CRP levels, PLR, RDW, MPV, and platelet count were higher, lymphocyte count was determined to be lower (Table 1) (Fig. 1). In terms of echocardiographic parameters, while a difference could not be determined between the groups in terms of left ventricular ejection fraction, the LA anteroposterior diameter and mitral valve gradient values were higher and MVA and LAV were lower in the LA thrombus group (Table 1).

ROC curve analysis showed that the optimal PLR cut-off value for predicting LA thrombus was 115, with a sensitivity of 79.0% and specificity of 71.5% (AUC = 0.83, 95% CI: 0.78–0.87) (Fig. 2).

In multiple logistic regression analysis, LAV, RDW, MPV, PLR, CRP levels, mean gradient, and presence of AF were found to be independently associated with the presence of LA thrombus (Table 2).

Discussion

In our study, we detected higher PLR in RMVS patients with LA thrombus than in those without LA thrombus. This relationship was independent of the severity of MS and presence of AF. In addition, we determined lower lymphocyte and higher platelet counts in patients with thrombus, along with increased MPV and RDW values.

Rheumatic valve diseases are the most serious form of rheumatic fever, and RMVS has the most devastating complications. Although the underlying mechanisms are not fully understood, it has inflammatory and autoimmune pathophysiological features. It has been determined that inflammation continues subclinically (3, 4). Gölbaşı et al. (3) demonstrated increased high-sensitivity CRP (hs-CRP) levels in patients with rheumatic heart disease (RHD) who were still in the chronic phase as compared with a control group. A similar study reported increased hs-CRP levels as well as increased oxidative stress products in patients with chronic RHD when compared with healthy individuals (4). While intra-atrial stasis plays the major role in the formation of thrombus in RMVS, it alone cannot explain all the mechanisms. Important data on the relationship between inflammation and prothrombotic state is available (11, 12). PLR is an easy-to-obtain parameter that can be used as a marker for inflammation at the clinical level (13). In addition, more consistent values are obtained with PLR than blood parameters, which are affected by some factors such as dehydration, overhydration, or blood collection technique. Platelets, which are acute phase reactants, increase in number with stimulus such as systemic infection and inflammation and lead to overproduction of inflammatory cytokines (14, 15). The increase in platelets due to the proliferation of megakaryocytes through the stimulation of inflammatory mediators may reflect the underlying inflammatory state. The cause

Table 1. Comparison of clinical and laboratory findings

Variables	LAT (+) (n=92)	LAT (-) (n=259)	P
Age, years	56±9.9	53.7±13	0.118
Female, n, %	61 (66.3%)	185 (71.4%)	0.241*
BMI, kg/m ²	25±1.3	25.2±1.6	0.281
AF, n, %	38 (41.3%)	31 (12%)	<0.001*
CAD, n, %	10 (10.9%)	29 (11.2%)	0.552*
DM, n, %	9 (9.8%)	27 (10.4 %)	0.520*
HT, n, %	15 (16.3%)	40 (15.4%)	0.481*
Hyperlipidemia, n,%	11 (12%)	28 (10.8%)	0.764*
Mean gradient, mm Hg	12.2 (10.9)	10.4 (13.5)	<0.001**
MVA, cm ²	0.9±0.1	1.1±0.2	<0.001
Mitral regurgitation (mild), n, %	30 (32.6%)	77 (29.7%)	0.302*
Mitral regurgitation (moderate), n, %	26 (28.3%)	58 (22.4%)	
LVEF, %	58.9±3.7	59.8±4.2	0.1
LAV, cm/s	25.2±5	35.4±10.4	<0.001
LAAPD, mm	47±7.6	40.8±6.6	<0.001
Glucose, mg/dL	82.2±11.6	80.3±11.5	0.170
LDL, mg/dL	128 (45)	121 (31)	0.254**
CRP, mg/L	4.7 (2.7)	2.7 (1.5)	<0.001**
eGFR, ml/min/1.73 m ²	84.5±8.8	85.2±7.7	0.532
Hemoglobin, g/dL	13.5±1.4	13.4±1.5	0.898
Hematocrit, %	40.7±6	39.8±4	0.125
RDW, %	14.8±1.4	12.9±1.1	<0.001
Leukocytes, mm ⁻³	6819±169	6496±132	0.06
Neutrophil, mm ⁻³	4705±825	4570±961	0.232
Lymphocytes, mm ⁻³	1916±176	1985±175	0.001
Platelets, × 10 ⁹ /L	251±61	236±50	0.03
MPV, fL	8.8 (1.1)	7.9 (1)	<0.001**
PLR	133±38	119±31	0.001

Data are presented as mean±standard deviation, median (interquartile range), and frequency (percentages). *Chi-square test; **Mann-Whitney U test; for other statistics, independent samples t test
AF - atrial fibrillation; BMI - body mass index; CAD - coronary artery disease; CRP - C-reactive protein; DM - diabetes mellitus; eGFR - estimated glomerular filtration rate; fL - femtoliters; LAAPD - left atrial anteroposterior diameter; LAT - left atrial thrombus; LAV - left atrial appendage peak flow velocity; LDL - low density lipoprotein cholesterol; LVEF - left ventricular ejection fraction; MPV - mean platelet volume; MVA - mitral valve area; PLR - platelet-to-lymphocyte ratio; RDW - red cell distribution width

of lymphopenia is the decreased production of lymphocytes secondary to increased steroid production caused by stress and increased lymphocyte apoptosis secondary to increased inflammatory status in patients with RMVS (16, 17). In some malignancies such as ovarian and pancreatic ductal adenocarcinomas, there is an adverse outcome with high PLR (18, 19). In addition, a relationship with poor prognosis in various cardio-

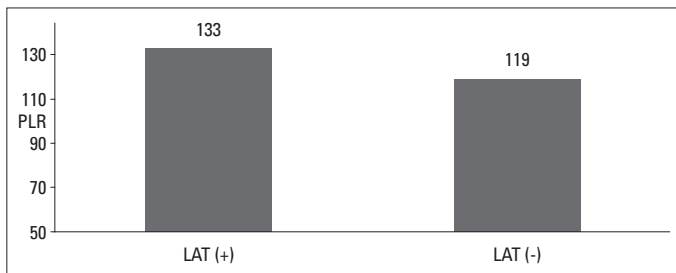


Figure 1. Platelet-to-lymphocyte ratio (PLR) in the left atrial thrombus negative [LAT (-)] and positive [LAT (+)] groups. ($p=0.001$; It was statistically significant)

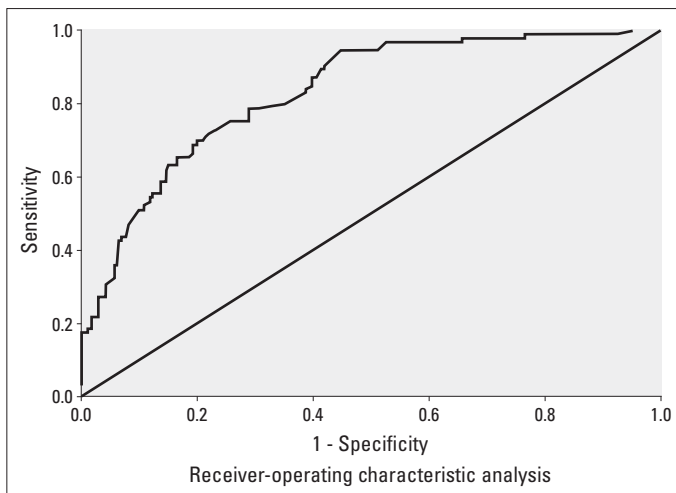


Figure 2. Receiver operating characteristic curve analysis of the platelet-to-lymphocyte ratio data for the presence of left atrial thrombus (sensitivity: 79%, specificity: 71.5%, AUC=0.83, 95% CI: 0.78–0.87)

vascular diseases has been found (9, 10). Azab et al. (20) have determined PLR as an indicator of long-term mortality in non-ST-segment elevation myocardial infarction. It has been reported that PLR is associated with a non-dipper blood pressure pattern, atherosclerotic peripheral artery disease, severity of coronary atherosclerosis, and insufficiency in the development of coronary collateral (8–10, 21). In a previous study, the neutrophil-to-lymphocyte ratio, an indicator of inflammation, was found to be higher in patients with RMVS when compared with the control group (22). In our study, we detected higher PLR in RMVS patients with LA thrombus than in those without for the first time. It has been reported that high platelet and low lymphocyte counts are closely related to poor clinical outcomes in patients with cardiovascular diseases (23–26).

Some studies have evaluated the importance of inflammation in rheumatic valvular heart diseases. In these studies, both higher levels of CRP (4) in patients with rheumatic valvular heart diseases as well as rising CRP levels correlating with the severity of rheumatic valvular heart diseases have been identified (27). In our study, we observed a close relationship between the presence of LA thrombus and CRP levels.

As expected, higher mitral valve mean gradient and lower MVA were observed in the LA thrombus group. Presence of AF is an important risk factor for thrombus development in patients

Table 2. Factors related to LA thrombus according to univariate and multivariate logistic regression analysis

Variables	Univariate (OR, 95% CI)	P	Multivariate (OR, 95% CI)	P
AF	5.17 (2.95–9.05)	<0.001	5.07 (1.5–16.8)	0.014
LAAPD, mm	1.12 (1.08–1.16)	<0.001	1.1 (1.02–1.2)	0.06
LAV, cm/s	0.85 (0.82–0.89)	<0.001	0.82 (0.75–0.89)	<0.001
RDW, %	2.9 (2.3–3.7)	<0.001	2.8 (1.8–4.4)	<0.001
MPV, fL	2.73 (1.6–3.5)	<0.001	2.6 (1.7–4)	<0.001
MVA, cm ²	0.37 (0.3–1.4)	<0.001	0.26 (0.2–1.3)	0.08
Mean gradient, mm Hg	1.26 (1.15–1.38)	<0.001	1.2 (1.02–1.4)	0.02
CRP, mg/L	2.13 (1.5–2.9)	<0.001	1.9 (1.4–2.6)	<0.001
PLR	1.04 (1–1.08)	0.002	1.03 (1–1.06)	0.016

*Univariate and multivariate logistic regression analysis were performed to identify factors associated with the presence of LA thrombus
 AF - atrial fibrillation; CI - confidence interval; CRP - C-reactive protein; LAAPD - left atrial anteroposterior diameter; LAV - left atrial appendage peak flow velocity; MPV - mean platelet volume; MVA - mitral valve area; OR - odds ratio; PLR - platelet to lymphocyte ratio; RDW - red cell distribution width

with MS. A higher incidence of AF was determined in the LA thrombus group in our study. In addition, the relationship between PLR, an inflammatory marker, and presence of LA thrombus continued was observed in multivariate analysis, independent of other factors including AF.

While treatment indications are clearer in patients with AF, clinical scoring and laboratory results do not give such a clear answer in patients with MS. TEE is the most sensitive test for the detection of LA thrombus; however, it is semi-invasive, not tolerable by all patients, relatively expensive, and not appropriate for frequent repetitions. In addition, the primary aim should not be the detection of thrombus but the determination of patients who are at a high risk of developing thrombus and are candidates for anticoagulant therapy. When considering the relationship between cardiovascular risk and PLR, which is determined from a commonly used hemogram in daily practice, our results may demonstrate PLR to be a simple, cheap, and easily reproducible indicator for determining thrombus risk in patients with RMVS. Prospective studies with long-term follow-up of PLR in specific patients are required to determine the thrombus development risk.

Study limitations

One limitation of our study is that a definitive conclusion regarding the cause–effect relationship cannot be made with the cross-sectional design. In addition, other inflammatory markers such as interleukins and oxidative stress markers could not be measured. However, if we compare this study with other studies examining the relationship between inflammation and the formation of SEC or thrombus in mitral valve diseases, several differences can be noted. This study has a cross-sectional design that allowed many factors affecting the outcome to be excluded

when compared with other studies of retrospective design. In addition, a strength of our study is the ability to better understand the pathophysiology of thrombus formation in mitral stenosis because of the low number of patients with AF and those not using any antiplatelets and/or anticoagulants.

Conclusion

There is a relationship between the presence of LA thrombus and PLR, an inflammatory marker, independent of other important factors including AF. There is a need for cheaper indicators that are easy to obtain and replicate in daily practice, such as PLR, for the prediction of thrombus formation and thus the risk of embolization.

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