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Platelet-to-Lymphocyte Ratio May Predict the Severity of Calcific Aortic Stenosis

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Platelet-to-lymphocyte ratio (PLR) is an emerging inflammatory indicator which is closely associated with adverse cardiovascular events. Therefore, we aimed to investigate the relationship between PLR and the severity of calcific aortic stenosis (AS).

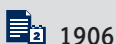
Material/Methods: The study was designed as a retrospective study. A total of 86 consecutive patients with calcific AS were divided into two groups as mild-to-moderate AS and severe AS according to the transaortic mean pressure gradient. PLR levels were calculated from the complete blood count (CBC).

Results: Platelet to lymphocyte ratio was significantly higher in severe and mild-to-moderate AS groups when compared to the control subjects (151 ± 31.2 , $p < 0.001$, 138 ± 28.8 vs. 126 ± 26.5 , $p = 0.008$, respectively). In the subgroup analysis of AS patients, PLR was found to be higher in the severe AS group compared to mild-to-moderate group ($p < 0.001$). A significant correlation was found between PLR and transaortic mean pressure gradient in patients with AS ($r = 0.421$, $p < 0.001$).

Conclusions: Our study results demonstrated that increased PLR correlates with the severity of calcific AS.

MeSH Keywords: **Aortic Valve Stenosis • Cardiology • Platelet Count**

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Background

The prevalence of calcific aortic stenosis (AS) increases with age, and the prevalence in individuals over 75 years of age is 5% [1,2]. Calcific AS is the most common form of valve disease and the most common indication for surgical valve replacement in developed nations. Therefore, detecting a biomarker to predict the prognosis of calcific AS may be beneficial.

Previous studies have demonstrated that platelet activation occurs in patients with AS [3]. Additionally, platelet count decrease has been reported after percutaneous coronary intervention and surgical aortic valve replacement [4]. However, it has also been demonstrated that even though polycythemia vera is reported as a possible cause of aortic valve stenosis, platelet count does not significantly differ between polycythemic stenotic patients compared to non-stenotic ones, but it does not distinguish between patients with mild-to-moderate and severe AS [5].

Increased platelet and decreased lymphocyte counts in the circulation have been associated with increased cardiovascular morbidity and mortality [6,7]. Recent reports have demonstrated that there is a relationship between PLR and the severity and complexity of coronary artery disease in patients with acute coronary syndromes and have also shown that increased PLR is an independent predictor of higher SX-score in patients with acute coronary syndromes [8].

Therefore, we aimed to investigate the relationship between PLR and the severity of calcific AS.

Material and Methods

Study population

The retrospective study included 86 patients diagnosed with calcific AS between May 2012 and January 2015. Patients with calcific AS were divided into two groups as mild-to-moderate AS and severe AS according to the transaortic mean pressure gradient.

Exclusion criteria included indications of atherosclerosis diagnosed by coronary angiography or scintigraphy, AS of congenital or rheumatic origin, severe mitral valve regurgitation, other forms of stenotic valve diseases, active and chronic infection, left ventricular systolic dysfunction, hemodynamically significant cardiac arrhythmias, renal or hepatic impairment, and comorbidities. An age- and gender-matched control group was formed including 42 healthy volunteers (24 females and 18 males with a mean age of 64.6 ± 11.7 years). All the participants in the study and control groups were evaluated using echocardiography. No cardiac abnormalities were observed in

the control group. Age, gender, hypertension, status of smoking, hyperlipidemia, diabetes mellitus, and family history were recorded. In addition, blood glucose, heart rate, blood pressure, hematological parameters, lipid profile, and serum creatinine were evaluated for each patient. The trial protocol was approved by the local ethics committee and the study conforms to the ethical principles contained in the Declaration of Helsinki.

Echocardiography

Each patient was evaluated using transthoracic two-dimensional echocardiography at rest under standard procedures. With the patient in the left lateral decubitus position, the examination was performed using a commercial echocardiographic device (Vivid 3, General Electric, Chicago, IL, USA) with a 3.0-MHz transducer. The examinations were conducted by two experienced cardiologists who were blinded to study. The measurement of left atrial and ventricular dimensions and left ventricular ejection fraction was achieved by M-mode echocardiography in the parasternal long-axis view. Aortic valve peak velocity, peak gradient, and mean gradient were measured by Doppler. Aortic and valve regurgitation were assessed using color flow Doppler.

Biochemical measurements

Blood sampling was achieved through the antecubital vein using a 21-g sterile syringe without stasis between 08.00 and 10.00 AM, following a 12-hour fasting period. To assess complete blood count (CBC), a Coulter LH 780 Hematology Analyzer (Architect plus ci16200 Abbott Illinois, USA) was used for measuring the hematological parameters including white blood cells, hemoglobin level, lymphocyte counts, mean platelet volume (MPV), and platelet counts. Platelet count, lymphocyte count and MPV were measured in a blood sample collected in dipotassium EDTA tubes and measured within 30 minutes after sampling to prevent EDTA-induced platelet swelling.

Statistical analysis

Data analysis was achieved using SPSS 17.0 for Windows (SPSS Inc., USA). Continuous data were presented as mean \pm standard deviation and the categorical data were presented as percentage. The Pearson or the Spearman correlation coefficient was used for the analysis of the correlation between the variables, as needed. One-Way ANOVA was used for statistical comparisons, followed by Scheffé's test. The *p* values less than 0.05 were accepted as statistically significant.

Results

A total of 128 patients (86 patients with AS and 42 control subjects) were included in the present study. Baseline

Table 1. Clinical characteristics of the patients with AS and the control subjects.

	Mild-to-moderate AS (n=47)	Severe AS (n=39)	Control (n=42)	P
Age	66.8±12.7	67.5±11.6	64.6±11.9	0.364
Sex, male,%	45%	42%	44%	0.486
Smoking,%	29%	32%	27%	0.382
Total cholesterol, mg/dl	191±87.6	193±91.4	188±94.2	0.254
Triglyceride, mg/dl	174±108.5	173±98.7	169±85.3	0.421
HDL-cholesterol, mg/dl	42±6.9	41±6.3	44±7.1	0.198
LDL-Cholesterol, mg/dl	115±49.8	112±52.1	111±45.3	0.227
Creatinine, mg/dl	0.91±0.24	0.88±0.28	0.89±0.27	0.688
Fasting glucose, mg/dl	105±24.7	103±28.6	97±18.3	0.184
Heart rate (beats/min)	74±12.3	77±13.4	73±11.9	0.366
SBP, mm Hg	127±22.4	124±18.8	129±16.2	0.258
DBP, mmHg	78±13.4	81±14.7	79±12.1	0.221
Platelet count, ×10 ³ μ/L	249±48.3	261±56.6	237±40.6	<.001
Lymphocyte, ×10 ³ μ/L	1.85±0.6	1.78±0.5	2.01±0.7	0.018
Platelet/lymphocyte ratio	138±28.8	151±31.2	126±26.5	<.001
MPV, fL	8.3±1.2	8.8±1.3	7.9±0.9	<.001

AS – aortic stenosis; HDL – high-density lipoprotein; LDL – low-density lipoprotein; SBP – systolic blood pressure; DBP – diastolic blood pressure; MPV – mean platelet volume.

Table 2. Echocardiographic findings between aortic stenosis patients and the control subjects.

	Mild-to-moderate AS (n=47)	Severe AS (n=39)	Control (n=42)	P
AV Vmax, m/sec	3.1±0.6	4.6±0.5	1.3±0.3	<.001
AV max gradient, mmHg	40.4±18.5	83.6±20.3	7.8±3.8	<.001
AV mean gradient, mmHg	27.5 ±8.5	53.8±12.5	3.7±0.9	<.001
LVEF,%	63.3±4.4	61.6±5.7	64.5±2.8	0.118
LVEDD, mm	4.9±0.5	5.2±0.6	4.8±0.3	<.005
LVESD, mm	3.1±0.4	3.7±0.5	3.2±0.2	0.008
IVS, mm	1.24±0.1	1.32±0.2	1.12±0.1	0.011
PW, mm	1.16±0.1	1.24±0.2	1.08±0.1	0.023

AV – aortic valve; LVEF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic diameter; LVESD – left ventricular end-systolic diameter; IVS – interventricular septum; PW – posterior wall.

demographic, clinical, echocardiographic, and laboratory characteristics of the study groups were presented in Tables 1 and 2. PLR, platelet count, and MPV were highest in severe AS group (151±31.2, $p<0.001$, 261±56.6 μ/L, $p<0.001$, 8.8±1.3 fL, $p<0.001$,

respectively). In addition, PLR (138±28.8 vs. 126±26.5, $p=0.008$), platelet count (249±48.3 vs. 237±40.6 μ/L, $p=0.046$) and MPV (8.3±1.2 vs. 7.9±0.9 fL $p=0.062$) were higher in mild-to-moderate AS group compared to the control group. However, absolute

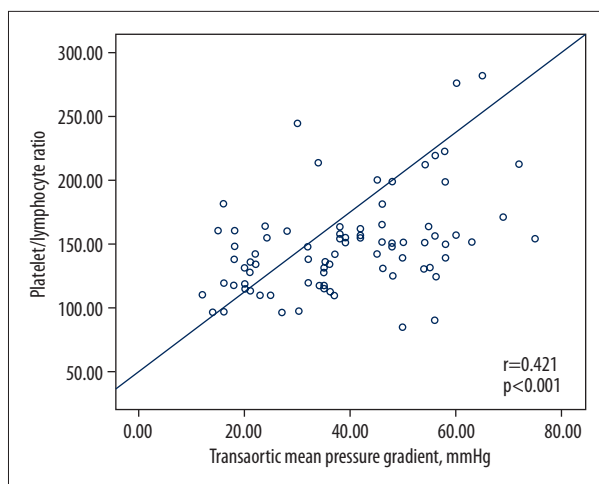


Figure 1. Correlation between platelet/lymphocyte ratio and transaortic mean pressure gradient in patients with AS.

lymphocyte count was lowest in the severe AS group ($1.78 \pm 0.5 \mu\text{L}$, $p < 0.001$) and lower in mild-to-moderate AS group ($1.85 \pm 0.6 \mu\text{L}$, $p = 0.046$) than in the control group.

Expectedly, transaortic mean pressure gradient, peak pressure gradient and aortic peak velocity were found to be significantly higher in the AS group compared to the control group ($p < 0.001$ for all the parameters). Moreover, left ventricular end-diastolic diameter ($p < 0.005$), left ventricular end-systolic diameter ($p = 0.008$), interventricular septum ($p = 0.011$), and posterior wall thickness ($p = 0.023$) were significantly higher in the severe AS group compared to the control group. No difference was found between the two groups in terms of other baseline characteristics.

In patients with AS, PLR established a significant positive correlation with transaortic mean pressure gradient (odds ratio [OR] 1.021, 95% confidence interval [CI] 1.016 to 1.026, $r = 0.421$, $p < 0.001$) (Figure 1). In the subgroup analysis of AS patients, PLR, platelet count, and MPV were found to be higher in the severe AS group compared to mild-to-moderate group ($p < 0.001$, $p = 0.032$, and $p = 0.027$, respectively), whereas the absolute lymphocyte count was found to be decreased in the severe AS group compared to the mild-to-moderate group ($p = 0.048$).

Discussion

Our results support the view that elevated PLR is associated with the severity of calcific AS, and PLR seems to be a simple method for the prediction of the severity of calcific AS. To the best of our knowledge, the present study is the first to evaluate the correlation between PLR and the severity of calcific AS.

Platelets are closely associated with the development of thrombosis, inflammation, and atherogenesis. Platelets lead to the

production of cytokines and chemokines which function as mediators for vascular inflammation and these mediators are activated by the particles produced by the cells on the vascular wall [9]. Moreover, platelets have a significant role in the transportation of progenitor cells and leukocytes into the sites of inflammation and vascular injury and in the mobilization of anti-inflammatory, proinflammatory, angiogenic factors, and microparticles into the circulation [10]. Increased platelet count has been shown to have a relation with the severity of atherosclerosis and coronary artery disease [11]. A number of recent studies have reported that PLR is significantly associated with the severity and complexity of coronary atherosclerosis in patients with acute coronary syndrome [8]. Previous studies have also demonstrated that platelet activation occurs in patients with AS. Chirkov et al. [12] demonstrated that there is an association between AS and platelet hyperaggregability, regardless of the presence and/or absence of coronary artery disease. Platelet activation in the patients with AS is likely to change the hemodynamic characteristics of the circulatory system when severe stenosis of aortic valve is present [13,14]. Moreover, a number of studies have revealed that platelet activation is triggered by the shear stresses in turbulent flow caused by stenotic valves [15]. Furthermore, stenosis has also been shown to be related to platelet activation in patients with other heart valve diseases [16]. Varol et al. [17] reported that the MPV in patients with mitral stenosis with sinus rhythm was significantly increased compared to the MPV in the control group. In our study, the PLR levels of the participants established a positive correlation with the MVP levels.

Prior studies have shown that decreased lymphocyte count is a useful diagnostic and prognostic tool in patients with acute coronary syndrome and it is associated with bad prognosis in these patients. Ommen et al. [18] reported that decreased lymphocyte count was significantly associated with survival in patients with stable coronary artery disease and it had a potential independent prognostic value for these patients. In the present study, we found that lymphocyte count was lower in patients with calcific AS when compared to the control group.

Increased platelet and decreased peripheral blood lymphocyte counts have been found to have an association with the development of atherosclerosis and acute coronary syndromes [6,11]. Elevated PLR, which has been recently developed as a novel prognostic marker, combines the predictive risk of these 2 parameters into 1. Kurtul et al. [19] reported the platelet-to-lymphocyte ratio is useful in predicting angiographic reflow after primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. Akboğa et al. [20] found that PLR was positively correlated with serum CRP level as an indicator of systemic inflammation and higher PLR levels were significantly and independently related to the presence of slow coronary flow. Yayla et al. [21] reported that there was a

significant relationship between the PLR on admission and the degree of myocardial perfusion in patients with ST-segment elevation myocardial infarction who underwent pre-primary percutaneous coronary intervention and PLR was an independent predictor of an occluded infarct-related artery in patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention. Azab et al. [22] reported that elevated PLR leads to an elevation in long-term all-cause mortality in patients with non-ST-segment elevation myocardial infarction. Similarly, Acar et al. [23] demonstrated that PLR is an independent factor for the development of coronary collateral circulation in patients with chronic total occlusion. In our study, the highest PLR levels were found in the severe AS group, and the PLR levels were higher in mild-to-moderate AS group compared to the control group.

We hypothesized that PLR, in association with systemic inflammation, might play a role in calcific AS. Our study findings confirmed that PLR was significantly higher in patients with calcific AS compared to the control group. In addition, we found a correlation between increased PLR and the severity of calcific AS. This correlation revealed that the presence of high inflammatory status assessed by PLR is effective on the severity of calcific AS. Thus, PLR may be used as a predictor marker in evaluating the severity of calcific AS.

Limitation

The main limitations of this study include the relatively small sample size due to numerous exclusion criteria. Moreover, we

did not evaluate other cytokines or inflammatory markers such as, fibrinogen, nitric oxide, myeloperoxidase, and interleukin-6 and did not compare them with PLR. However, such inflammatory biomarkers are expensive and are not immediately available in everyday practice. Despite these limitations, we present the first study that focused on the predictive value of PLR in patients with calcific AS.

Conclusions

Our study results demonstrated that a high PLR was independently associated with the severity of calcific AS. These findings suggest that besides its already known effect on prothrombotic status, a higher PLR level may exhibit proinflammatory effect on calcific AS. Thus, PLR may be used in clinic practice for the prediction of calcific AS. Further studies are needed to explain the mechanisms and effects of the relationship between PLR and calcific AS.

Conflicting of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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