ORIGINAL ARTICLE

Predictive value of platelet-to-lymphocyte ratio in severe degenerative aortic valve stenosis

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Background: Aortic valve stenosis (AVS) is the most common cause of left ventricular outflow obstruction, and its prevalence among elderly patients causes a major public health burden. Recently, platelet-to-lymphocyte ratio (PLR) has been recognized as a novel prognostic biomarker that offers information about both aggregation and inflammation pathways. Since PLR indicates inflammation, we hypothesized that PLR may be associated with the severity of AVS due to chronic inflammation pathways that cause stiffness and calcification of the aortic valve. **Materials and Methods:** We retrospectively enrolled 117 patients with severe degenerative AVS, who underwent aortic valve replacement and 117 control patients in our clinic. PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. Severe AVS was defined as calcification and sclerosis of the valve with a mean pressure gradient of >40 mmHg. **Results:** PLR was 197.03 ± 49.61 in the AVS group and 144.9 ± 40.35 in the control group, which indicated a statistically significant difference ($P < 0.001$). A receiver operating characteristic (ROC) curve analysis demonstrated that PLR values over 188 predicted the severity of aortic stenosis with a sensitivity of 87% and a specificity of 70% (95% confidence interval = 0.734–0.882; $P < 0.001$; area under ROC curve: 0.808). **Conclusion:** We suggest that the level of PLR elevation is related to the severity of degenerative AVS, and PLR should be used to monitor patients' inflammatory responses and the efficacy of treatment, which will lead us to more closely monitor this high-risk population to detect severe degenerative AVS at an early stage.

Key words: Aortic valve stenosis, biomarkers, platelets

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INTRODUCTION

Aortic valve stenosis (AVS) is the most common cause of left ventricular outflow obstruction in adults, and its prevalence is increased among older patients. Aortic valve sclerosis is defined as aortic valve thickening and calcification without a significant gradient (defined as an aortic jet velocity of <2 m/s). Inflammation plays an important role in fibrosis formation and leaflet thickening, which results in severe stenosis of the aortic valve. Some treatments are available to decrease inflammation and reduce the acceleration of degenerative AVS. It is, therefore crucial to use a biomarker to foresee the progression of AVS.

During sustained inflammation, lymphocyte counts decrease as a result of increased lymphocyte apoptosis. The resulting inflammatory conditions lead to increased proliferation in megakaryocytic series and relative thrombocytosis. Platelet-to-lymphocyte ratio (PLR), a novel prognostic biomarker, offers information about both aggregation and inflammation pathways, and it may be more valuable than either platelet or lymphocyte counts alone for predicting inflammatory burden, and thus for predicting the progression of AVS. In this study, we

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investigated the value of PLR for predicting the severity of degenerative AVS.

MATERIALS AND METHODS

Study population and study protocol

The current study is a single-center retrospective study. The study protocol was approved by a local noninvasive Ethics Committee. Between March 2012 and August 2015, we enrolled 117 patients, who underwent prosthetic aortic valve replacement and 117 control patients with normal echocardiographic findings who visited cardiology polyclinic. There were not any specific characteristics of control patients, and they were consecutive 117 patients among subjects who had normal echocardiographic findings. Patients with a history of chronic kidney failure (glomerular filtration rate <90 mL/min/1.73 m^2), atherosclerosis documented by coronary angiography, increased leukocyte count (>11.0 × 10^9 L), bicuspid or rheumatic aortic stenosis, or concomitant severe valve disease were excluded from the study.

The demographic and clinical variables of the patients (including age, gender, and a history of diabetes mellitus, hyperlipidemia, or hypertension) were recorded. A detailed physical examination was performed for all patients included in the study, and they were asked whether they had a history of diabetes mellitus, hypertension, noncardiac diseases, or coronary artery disease (CAD). Patients were considered to have arterial hypertension when they had at least three repeated measurements of blood pressure above 140 mmHg systolic and 90 mmHg diastolic or were actively using antihypertensive drugs. Patients were considered to have diabetes mellitus when they had at least two measurements of fasting plasma glucose levels above 126 mg/dL or were currently using antidiabetic drugs. Patients were considered to have a history of CAD if they had experienced CAD or sudden cardiac death due to atherosclerosis documented via coronary angiography.

Assessment of aortic valve stenosis

Echocardiography examinations were performed by two different echocardiographers using a GE Vivid 3 ultrasound machine (General Electric, Fairfield, Connecticut, USA). Severe AVS with normal systolic function was defined as calcification and sclerosis of the valve with a mean pressure gradient of >40 mmHg, measured by continuous wave Doppler, and the left ventricular ejection fraction of ≥50%.[1]

Platelet-to-lymphocyte ratio analysis

Blood samples for PLR analysis were drawn the day before operation and analyzed by a Beckman Coulter LH 780 Analyzer (Pasadena, California, USA). The samples were stored in EDTA-containing tubes. PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. Neutrophil-to-lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count. In a population-based study, reference mean value of PLR and NLR was calculated as 137 ± 102 and 2.8 ± 1.6 consecutively.[2]

Statistical analysis

SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous variables were described as means and standard deviation. Categorical variables were presented as percentages. The normality of distribution for continuous variables was confirmed with the Kolmogorov–Smirnov test. The independent sample *t*-test or the Mann–Whitney U test was used for continuous variables according to the distribution pattern of the continuous variables. Chi-square test was used for categorical variables. A receiver operating characteristic (ROC) curve analysis was performed to determine the optimum cutoff PLR value to predict the existence of severe degenerative AVS. A two-tailed $P < 0.05$ indicated a statistically significant difference between the groups.

RESULTS

The mean age of the study population was 55.7 ± 14.3 in the AVS group and 57.1 ± 12.4 in the control group ($P = 0.57$). The mean count of white blood cells was 8153.7 ± 2855.2/mcL in the AVS group and 5967.1 ± 1097/mcL in the control group, which indicated a statistically significant difference ($P < 0.001$). There were no statistically significant differences between the two groups in terms of age, gender, hypertension, diabetes mellitus, or hyperlipidemia. Table 1 shows the demographic characteristics of the study population.

As can be seen in Table 2, PLR was 197.03 ± 49.61 in the AVS group and 144.9 ± 40.35 in the control group, which indicated a statistically significant difference ($P < 0.001$) [Figure 1]. PLR values over 188 predicted the severity of aortic stenosis with a sensitivity of 87% and a specificity of 70% (95% confidence interval [CI] = 0.734–0.882; $P < 0.001$; area under ROC

Table 1: Demographic characteristics of the study population

	Aortic valve stenosis group (*n*=117)	Control group (*n*=117)	*P*
Age (years)	55.7±14.3	57.1±12.4	0.57
Gender (%)			
Male	68 (58.1)	66 (56.4)	
Female	49 (41.8)	51 (43.5)	
Diabetes mellitus (%)	21 (17.9)	16 (13.6)	0.64
Hypertension (%)	24 (20.5)	13 (11.1)	0.45
Hyperlipidemia (%)	15 (12.8)	9 (7.6)	0.32
White blood cell (/mcL)	8153.7±2855.2	5967.1±1097.1	<0.001

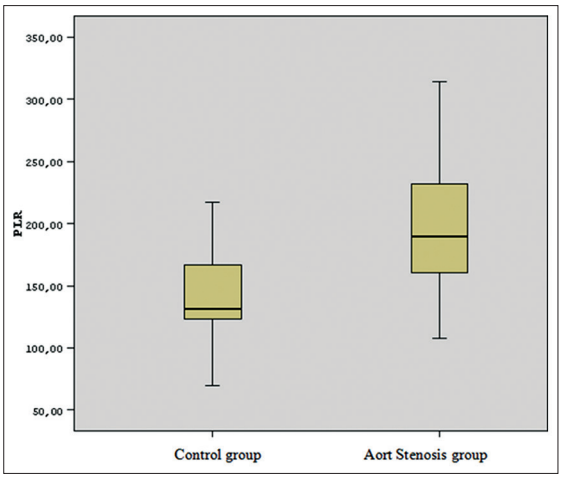

Figure 1: Comparison of the values of PLR between severe aortic valve stenosis and control groups. PLR: Platelet-to-lymphocyte ratio

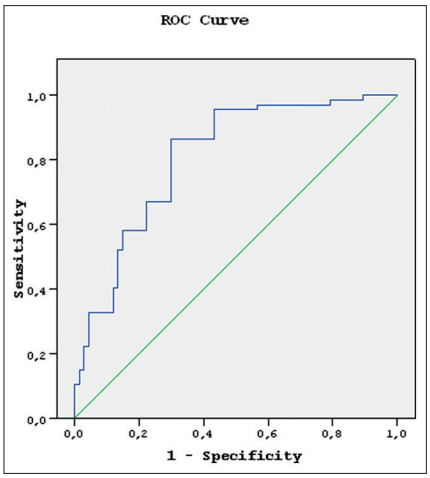

Figure 2: The ROC curve analysis demonstrating platelet-to-lymphocyte ratio for predicting severe aortic valve stenosis. ROC: Receiver operating characteristic

Table 2: Mean platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio levels in both groups

	Aortic valve stenosis group (*n*=67)	Control group (*n*=67)	*P*
Platelet-to-lymphocyte ratio	197.03±49.61	144.9±40.35	<0.001
Neutrophil-to-lymphocyte ratio	3.13±1.22	2.64±0.59	0.004

curve (AUC): 0.808; positive predictive value: 91%; negative predictive value: 56%) [Figure 2]. NLR was 3.13 ± 1.22 in the AVS group and 2.64 ± 0.59 in the control group, which indicated a statistically significant difference (P = 0.004).

DISCUSSION

PLR is a novel hematological parameter that indicates the inflammatory and prothrombotic state of the patient. High PLR values have often been associated with poor prognosis in patients with cardiovascular diseases. However, the literature that was reviewed included no data about the association between PLR and the severity of degenerative AVS in patients with normal systolic function.[2-9] Degenerative AVS and aortic annular calcification have a close relationship with atherosclerotic changes in various vascular systems of the human body such as CAD and carotid atherosclerosis.[10,11] Although the precise underlying pathophysiology of degenerative AVS still remains unclear, metabolic imbalances, particularly those including calcium and phosphorus accumulation, play a role as well. In 2006, Fox *et al*. suggested that inflammatory mediators such as interleukin-6, intercellular adhesion molecule-1, and C-reactive proteins are increased in patients with valvular calcification.[12] In addition, Avci *et al*. demonstrated a statistically significant correlation between NLR and calcific aortic stenosis.[13] In the current study, we revealed that a high PLR level was significantly associated with the severity of degenerative AVS in patients with normal systolic function. This study showed that PLR values over 188 predicted the severity of AVS with a sensitivity of 87% and a specificity of 70% (95% CI = 0.734–0.882; P < 0.001; AUC: 0.808). To the best of our knowledge, this study is the first to investigate the relationship between PLR and the severity of degenerative AVS.

The initiation and expansion of atherosclerosis in coronary arteries are influenced by many contributing factors. Inflammation plays a key role in all stages of atherosclerosis. Similar inflammatory, fibrotic, and calcific processes exist in both atherosclerosis and degenerative AVS.[14] Lymphocytopenia is an unusual finding during the course of chronic inflammatory clinical conditions due to increased lymphocyte apoptosis. Moreover, leukocyte formation in bone marrow tends to shift toward increasing neutrophils and decreasing lymphocytes as a response to a chronic inflammatory state. The diagnostic and prognostic practicality of a low lymphocyte count has been demonstrated in patients with acute coronary syndrome, and a low lymphocyte count has been found to be significantly associated with stable CAD.[15] In addition, it was suggested that a low lymphocyte count is a novel prognostic indicator in patients with stable CAD.[15] Therefore, it is reasonable to suppose that lymphocyte count is an early marker of systemic inflammation, which may lead to increased valve stiffness.[16]

Increased proliferation in megakaryocytic series and relative thrombocytosis is consequences of a continuing inflammatory state, and they cause a prothrombotic condition. It has been stated previously that healthy individuals with increased platelet counts have an augmented risk of experiencing cardiovascular events. In other studies, high platelet and low lymphocyte counts have been shown to be risk factors for worse cardiovascular

outcomes.[17] High PLR, as a novel prognostic marker, combines the predictive potential of these two parameters into one. The advantage of PLR is that it provides more reliable information than either lymphocyte or platelet counts alone for predicting inflammatory burden, and thus for predicting the severity of degenerative AVS.

In this study, we found a statistically significant correlation between increased PLR and the severity of degenerative AVS in patients with normal systolic function. This correlation indicated that an elevated inflammatory status measured by PLR is associated with the severity of degenerative AVS. These results are consistent with the hypothesis that inflammation plays a central role in the pathology of degenerative AVS. According to our results, PLR should be considered an early indicator of elevated risk of atherosclerotic and inflammatory burden. More intensive and aggressive control of cardiovascular risk factors should be taken into consideration for patients with higher PLR values. This indicator may also be used to monitor patients' inflammatory responses and the efficacy of treatment. Closer monitoring and visiting of this high-risk population can be arranged to detect severe degenerative AVS at an early stage.

CONCLUSION

PLR is a widely available and inexpensive biomarker of systemic inflammation. This study suggests that the level of PLR elevation is related to the severity of degenerative AVS. We believe that awareness of the relationship between PLR and degenerative AVS may better expose the pathophysiological process of AVS and may help researchers discover new treatment modalities for reducing inflammation.

Study limitations

The current study has few limitations. Due to the retrospective design of the study, we do not know whether the relationship between PLR and the severity of degenerative AVS influences mortality. In addition, further prospective studies are required to investigate whether PLR predicts outcomes in patients with severe degenerative AVS.

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Conflicts of interest

There are no conflicts of interest.

AUTHORS' CONTRIBUTIONS

- EE contributed to the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- HR contributed to the conception of the work, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- AHK contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- MK contributed to the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- AOK contributed in the revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- ÜİT contributed in the conception of the work, drafting and revising the draft, and agreed for all aspects of the work
- KÖ contributed in the conception of the work and agreed for all aspects of the work
- ME contributed to the conception of the work and agreed for all aspects of the work
- ÇŞ contributed in the approval of the final version of the manuscript and agreed for all aspects of the work
- BK contributed in the revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work
- HG contributed to the conception of the work and agreed for all aspects of the work
- İD contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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