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**Original Article**

# Inflammatory biomarkers as predictors of calcific aortic stenosis severity: examining platelet to lymphocyte and neutrophil to lymphocyte ratios

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## Abstract

**Objectives:** Platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) are novel inflammatory markers known for inflammatory and cardiovascular diseases. This study aimed to examine PLR and NLR as predictors of calcification aortic stenosis (CAS) severity.

**Methods:** This study investigated a total of 155 individuals who were referred to Chamran Heart Center in Esfahan, Iran between 2018 and 2019. The participants included 53 patients with severe AS, 50 patients with mild to moderate AS, and 52 individuals as a control group. The severity of aortic stenosis was evaluated in all participants using echocardiography. The study also calculated the PLR and NLR from CBC.

**Results:** The results of this study indicate that there was no significant difference in PLR among those with severe AS (108±66), mild to moderate AS (103±43), and the control group (110±50) (p=0.813). However, the NLR was significantly higher in those with severe AS (3.13±2.3) compared to mild to moderate AS (2.08±0.7) and the control group (2.1±1.3) ($p$=0.019). Age and diabetes mellitus were found to be significant and independent factors correlated with PLR, while the severity of AS was not. Additionally, severe AS was found to be an independent predictor of NLR, along with age and sex.

**Conclusions:** This study elucidated the intricate relationship between inflammatory markers and CAS, emphasizing the significance of NLR as an indicator of pro-inflammatory and anti-inflammatory contrast. Surprisingly, PLR exhibited no relationship with CAS severity. we suggest that future studies examine the effect of ethnic variation on the relationship between inflammatory markers and CAS. Also, explore the potential impact of additional inflammatory markers on new indices that may provide stronger predictive value for CAS severity.

**Keywords:** Calcific aortic stenosis, Platelet to lymphocyte ratio, Neutrophil to lymphocyte ratio, echocardiography

## Introduction

Calcific aortic stenosis (CAS) is a prevalent cardiovascular disease in high-income countries that is caused by lipid accumulation, mechanical stress, immune cell activation, and myofibroblast differentiation. This leads to left ventricle hypertrophy and can ultimately result in heart failure (HF) and death. Aortic valve stenosis, along with shear stress and turbulent flow patterns, can trigger platelet activation (1). In recent years, there has been a significant focus on the pathogenesis of aortic stenosis (AS), further reinforced by studies demonstrating that limiting exposure to inflammatory factors can reduce the progression of stenosis in AS (2). Platelets play a critical role in thrombosis, inflammation, and atherogenesis (3). The close interaction between immune cells and inflammation, coupled with an increase in the infiltration of macrophages, monocytes, and T cells in valvular interstitial cells, is known to exacerbate aortic valve calcification (4).Assessing the progression and severity of as can be aided by identifying inflammatory biomarkers. In one study, it was found that the lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were related to cardiovascular conditions (1, 5). Inflammatory conditions can cause an increase in lymphocyte apoptosis and megakaryocytic proliferation, leading to thrombosis (6). Elevated PLR is associated with cardiovascular mortality and morbidity, as well as adverse outcomes of malignant situations (7). Recent studies have also shown that PLR levels in patients with Systemic lupus erythematosus (SLE) tend to be higher. PLR levels are negatively associated with progression in individuals with advanced metastatic cancer and rheumatoid arthritis (RA) (8-10) Numerous studies rely on the clinical pathology of CAS, but there is a dearth of information regarding the inflammatory responses in patients (11-13). Consequently, more studies are urgently required to assess the potential clinical application of these biomarkers. The goal of this current study was to assess the predictive value of NLR and PLR in determining the severity of CAS.

## Materials and Methods

### Study population

This retrospective cross-sectional study included 155 participants referred to Chamran Heart Center (Esfahan, Iran) from February 2018 to October 2019, all with severe to mild AS and underwent echocardiography without AS. The study protocols were confirmed by the local ethics committee of Kashan University of Medical Sciences (IR.KAUMS.REC.1395.131). All the participants received the informed consent. The AS was confirmed by one cardiologist using transthoracic echocardiography (TTE) and current guidelines (14). The participants were divided into three groups: the group with severe AS (53 patients), mild to moderate AS (50 patients), and the control group (52 patients). The controls were chosen from outpatients with similar demographic and clinical features without AS history. The exclusion criteria were a history of renal failure (GFR< 90ml/min/1.73m2), rheumatic or congenital AS, coronary artery disease (CAD), HF, systemic autoimmune or allergic disease (like SLE, RA, asthma), chronic hepatic failure. Participants who were pregnant, had an active infection, were undergoing chemotherapy, or were using corticosteroids were excluded from the study.

The demographic characteristics of all patients in the three groups, including age and sex, were recorded. Additionally, the medical history of diabetes mellitus (DM), hyperlipidemia (HLP), hypertension (HTN), non-cardiac diseases, CAD, and the use of medications such as corticosteroids, statins, and antihypertensive drugs were recorded.Hypertension (HTN) is identified as having a systolic blood pressure consistently above 140 mmHg or a diastolic blood pressure consistently above 90 mmHg in three consecutive measurements or currently being treated with antihypertensive medication. Diabetes mellitus (DM) is diagnosed if an individual's fasting blood sugar (FBS) levels have been consistently measured above 126 mg/dL on at least two occasions or if they are currently receiving treatment with anti-diabetes medication.

### Laboratory examination

The venous blood samples were taken before the surgery and were analyzed by an auto-analyzer (BT 1500, Biotecnica Instruments, Italy). PLR was the ratio of the platelets to absolute lymphocytes. The ratio of the absolute number of platelets to the absolute number of lymphocytes was defined as PLR, and the ratio of the absolute number of neutrophils to the absolute number of lymphocytes was defined as NLR.

### Echocardiographic measurement

An echocardiogram was performed using a Philips

iE33 ultrasound system (Andover, MA, USA) and a 2.5-5 MHz transducer. The evaluation involved obtaining parasternal short and long-axis views as well as apical views. To define mild to moderate AS, the criteria were an aortic jet velocity ranging from 2.0 m/s to 4.0 m/s or a mean transaortic pressure gradient below 40 mmHg. A severe AS was defined as an aortic jet velocity of more than 4.0 m/s or a mean transaortic pressure gradient above 40 mmHg (15, 16).

**Statistical analysis**

The data collected in the study were analyzed using the statistical software SPSS Version 19.0 (SPSS Inc., Chicago, IL, USA). Mean and standard deviation were used to represent quantitative variables, while frequency and percentages were used for qualitative variables. For comparing numerical variables, a one-way analysis of variance (ANOVA) test was conducted. The association between categorical variables was assessed using the chi-square test. Statistical significance was set at a two-sided P value of $\leq 0.05$.

**Results**

There was a significant difference in age, diabetes HLP, and taking statin between the groups ($P<0.05$). Among the laboratory parameters, platelet count and lymphocyte count were significantly higher in the study group compared with the severe AS ($P=0.008$). The NLR in the severe AS group was significantly higher than in the control group ($P<0.001$). Demographic, clinical, and laboratory characteristics have been shown in Table 1.

**Table 1:** Demographic, Clinical and Laboratory Characteristics of the Study Groups

| Parameters | Severe AS N=53 | Mild to moderate AS N=50 | Control N=52 | p-value |
|---|---|---|---|---|
| Demographics | | | | |
| Age, years | 54.7±15 | 52.4±14.8 | 45.2±15.6 | 0.004 |
| Sex, male, n (%) | 30(56.60) | 25(50) | 25(48.10) | 0.66 |
| Comorbidities | | | | |
| Diabetes mellitus, n (%) | 24(45.30) | 16(32) | 10(19.20) | 0.02 |
| Hypertension, n (%) | 14(26.4) | 19(38) | 15(28.80) | 0.41 |
| Hyperlipidemia, n (%) | 9(17) | 21(42) | 12(23.10) | 0.01 |
| Medications | | | | |
| Statin, n (%) | 6(11.3) | 18(36) | 7(13.5) | 0.03 |
| Calcium Channel Blocker, n (%) | 2(3.8) | 1(2) | 3(5.8) | 0.61 |
| β- Blocker, n (%) | 6(11.3) | 5(10) | 4(7.7) | 0.82 |
| ACEI, n (%) | 1(1.9) | 4(8) | 1(1.9) | 0.19 |
| ARB, n (%) | 7(13.2) | 8(16) | 7(13.5) | 0.91 |
| Laboratory parameters | | | | |
| WBC $10^3/mm^3$ | 7.3±1.6 | 7.1±1.5 | 8.4±9.3 | 0.44 |
| Platelet $10^3/mm^3$ | 183.1±75.9 | 214.6±68.8 | 222.6±59.6 | 0.009 |
| Neutrophil $10^3/mm^3$ | 4.7±1.5 | 4.4±1.2 | 4.1±1.3 | 0.14 |
| Lymphocyte $10^3/mm^3$ | 1.9±0.6 | 2.2±0.6 | 2.2±0.7 | 0.008 |
| PLR | 108±66 | 103±43 | 110±50 | 0.81 |
| NLR | 3.13±2.3 | 2.08±0.7 | 2.1±1.3 | <0.001 |

Data were presented using mean± SD and frequency (percentage). Statistical analysis was conducted using the chi-square test and ANOVA.

Multivariate linear regression analysis showed that PLR correlated significantly and independently with age, and DM, while severity of AS did not. It was found that in addition to age and sex, severe AS were independent factors for predicting an NLR. These data are shown in Tables 2 & 3.

 

**Table 2:** Independent predictors of PLR by Multivariate Linear Regression Analysis

| | | Coefficient | S.E. | Standardized Coefficient | p value | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Constant | | 87.887 | 19.843 | - | 0.001 | 48.671 | 127.102 |
| Age | | 0.772 | 0.312 | 0.222 | 0.015 | 0.154 | 1.389 |
| Sex | | -1.918 | 8.435 | -0.018 | 0.82 | -18.587 | 14.751 |
| Diabetes mellitus | | -22.262 | 10.361 | -0.192 | 0.033 | -42.738 | -1.786 |
| Hyperlipidemia | | -2.159 | 16.78 | -0.018 | 0.898 | -35.319 | 31.002 |
| Statin | | -34.857 | 18.947 | -0.258 | 0.068 | -72.301 | 2.587 |
| Group | Control | | - | | - | - | - |
| | Mild to moderate AS | -1.386 | 10.693 | -0.012 | 0.897 | -22.518 | 19.746 |
| | Severe AS | -4.948 | 10.823 | -0.043 | 0.648 | -26.336 | 16.441 |

**Table 3:** Independent Predictors of NLR by Multivariate Linear Regression Analysis

| | | Coefficient | S.E. | Standardized Coefficient | p value | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Constant | | 1.889 | 0.605 | - | 0.002 | 0.694 | 3.085 |
| Age | | 0.021 | 0.01 | 0.197 | 0.029 | 0.002 | 0.04 |
| Sex | | -0.439 | 0.257 | -0.132 | 0.09 | -0.947 | 0.069 |
| Diabetes mellitus | | -0.05 | 0.316 | -0.014 | 0.875 | -0.674 | 0.574 |
| Hyperlipidemia | | -0.011 | 0.511 | -0.003 | 0.982 | -1.022 | 0.999 |
| Statin | | -.257 | 0.578 | -0.062 | 0.657 | -1.398 | 0.884 |
| Group | Control | | - | | - | - | - |
| | Mild to moderate | -0.137 | 0.326 | -0.038 | 0.676 | -0.781 | 0.508 |
| | Severe | 0.782 | 0.33 | 0.223 | 0.019 | 0.13 | 1.434 |

## Discussion

This study aimed to explore the relationship between PLR and NLR and the CAS, a topic that has been rarely investigated worldwide. The study included three groups: severe AS, mild AS, and healthy individuals. The PLR levels in severe AS, mild AS, and healthy individuals were found to be 108±66, 103±43, and 110±50, respectively. However, there was no significant difference in PLR levels among these groups which contradicts the findings of other studies. Interestingly, these levels were similar to those found in healthy individuals in a previous study conducted by Yayla et al. (17). As all previous studies were conducted in Turkey, the non-correspondence could be attributed to ethnic differences. The study revealed that there were some confounding variables in each group which had significant differences. To reduce the confounding effects, regression analysis was conducted. Even after this, there appeared to be no meaningful relationship among the three groups regarding PLR. However, the t-test analysis showed that there was a significant difference in PLR between healthy individuals and those with DM and HLP. The individuals with DM had a significantly lower PLR(91.4±42.1) than the healthy ones(114.9±57.8), while those with HLP had a lower PLR(89.1±36.5) compared to healthy individuals(114.17±58.2).

No significant difference in PLR was observed between those with and without HTN. The reduction of PLR in individuals with DM corresponds with the study done by Mertoglu et al. (18). However, no study has been conducted on the relationship between PLR and contextual variables of HLP and HTN. About this finding, the non-correspondence of the relationship between PLR and AS can be partly justified, given that the percentage of individuals with DM in the severe AS group is higher.

According to this study, when it comes to other quantitative variables that can be referred to as WBC, there was no significant difference between the three groups in terms of the number of WBC. This finding is consistent with the studies conducted by Yayla et al. (17) and Küçükseymen (19), but it contradicts the findings of the study conducted by Edem et al (20).

In this study, the number of lymphocytes was investigated and it was found that there was a significant difference among the three groups. The healthy individuals had more lymphocytes than those with AS, and the number of lymphocytes was related to the severity of the disease. This result is consistent with previous studies by Yayla et al. (17) and

Serkan(21), but it does not match Küçükseymen et al.'s(19) study. Additionally, the number of neutrophils did not differ significantly among the three groups. This finding is consistent with Küçükseymen et al's (19) study, but Yayla et al's(17) study found that the number of neutrophils was higher in patients than in healthy individuals. However, there was no difference between the severe and mild cases of the disease.

The study examined the Neutrophil to Lymphocyte Ratio (NLR) among different groups and found a significant difference between them. The individuals with severe AS had a higher NLR (3.13 ± 2.3) compared to the mild (2.08 ± 0.7) and healthy individuals (2.1 ± 1.3). However, there was no significant difference between the mild and healthy individuals. Previous studies by Yayla et al. (17), Kyoung et al. (22), Küçükseymen et al. (19), Avci et al. (8), and Edem et al. (20) have shown a significant relationship between In this study, researchers investigated the relationship between NLR and contextual variables such as DM, HTN, and HLP. However, no meaningful relationship was found between them. On the other hand, a relationship between NLR and AS was observed. Additionally, while a relationship was found between PLR and contextual variables, no relationship was found with AS. This lack of relationship between PLR and AS may be attributed to genetic and ethnic differences, as well as confounding factors. Overall, the absence of a relationship between PLR and AS can be explained by these contextual variables.the NLR and the severity of AS. In contrast, our study found no such relationship. However, Kyoung et al.'s study (22) showed that the NLR in individuals with severe AS and better prognosis was less than 2, similar to the NLR of the mild AS group in our study.

In this study, researchers investigated the relationship between NLR and contextual variables such as DM, HTN, and HLP. However, no meaningful relationship was found between them. On the other hand, a relationship between NLR and AS was observed. Additionally, while a relationship was found between PLR and contextual variables, no relationship was found with AS. This lack of relationship between PLR and AS may be attributed to genetic and ethnic differences, as well as confounding factors. Overall, the absence of a relationship between PLR and AS can be explained by these contextual variables.

It should be noted that there are certain limitations present in this study. Firstly, the findings may not be easily generalized as the sample size used was relatively small and limited to a specific region. Secondly, the demographic characteristics of the participants might not be fully representative of the population's diversity. Additionally, the study was retrospective in nature, which could result in selection bias. Lastly, this article solely focused on a few inflammatory markers, thus more research is needed to gain a more comprehensive understanding of the severity of CAS.

## Conclusion

This study elucidated the intricate relationship between inflammatory markers and CAS, emphasizing the significance of NLR as an indicator of pro-inflammatory and anti-inflammatory contrast. Surprisingly, PLR exhibited no relationship with CAS severity. The study enhances our understanding of the intricate pathogenesis of CAS and provides critical insights into the limitations of particular inflammatory markers in predicting disease severity.To better understand the relationship between inflammatory markers and coronary artery stenosis (CAS), it is important to consider genetic influences and ethnic variations. We recommend that future studies take these factors into account and explore the impact of additional inflammatory markers beyond NLR and PLR. This could lead to the development of new indices that provide stronger predictive value for CAS severity. It would also be beneficial to conduct multicenter collaborations to collect larger and more diverse data sets, which could facilitate a more comprehensive analysis of inflammatory markers in CAS across different populations.

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**Conflicts of Interest**
The authors declare no conflict of interest.

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**Ethical statements**
Ethical approval for this study was obtained from the local ethics committee of Kashan University of Medical Sciences (IR.KAU MS.REC.1395.131). The informed consent was received from all of the attendees.

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