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ORIGINAL ARTICLE

Is neutrophyl to lymphocyte ratio really a useful marker for all grades of degenerative aortic stenosis?

Dejeneratif aort darlığının tüm evrelerinde nötrofil-lenfosit oranı gerçekten yararlı bir belirteç mi?

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ABSTRACT

Objective: Inflammatory processes play an important role in cardiac valve calcification and ossification. The aim of this study was to investigate the relationship between the neutrophil-lymphocyte ratio (NLR) and degenerative aortic stenosis (AS).

Methods: A total of 220 patients with AS and 158 healthy individuals who were a control group were included in the study. The NLR was calculated by dividing the number of neutrophils by number of lymphocytes in peripheral blood samples.

Results: The study group consisted of 220 AS patients (mild/moderate group: n=110; severe group: n=110) and 157 healthy controls. Both the mild/moderate AS group (p<0.001) and the severe AS group (p<0.001) had a significantly higher NLR compared with the control group. The NLR in the severe AS group was significantly higher than that of the mild/moderate AS group (p<0.001). The groups were similar with respect to other baseline characteristics. A receiver operating characteristic curve analysis yielded a strong predictive ability of NLR for the presence of AS (Area under the curve=0.930; 95% CI [confidence interval], 0.898–0.963; p<0.001). A cut-off value of 2.310 for NLR had a sensitivity and specificity of 80.4% and 92.4%, respectively, for the presence of AS. In multivariate logistic regression analysis, NLR (Odds ratio: 43.8; 95% CI, 14.7–130.7) was the only independent predictor of AS.

Conclusion: The discriminative performance of NLR for AS is high. NLR is strongly and independently associated with AS.

ÖZET

Amaç: Enflamatuvar proçes kalp kapak kalsifikasyonunda ve osifikasyonunda önemli rol oynamaktadır. Biz de çalışmamızda nötrofil lenfosit oranı (NLO) ile dejeneratif aort darlığı (AD) arasındaki ilişkiyi araştırdık.

Yöntemler: İki yüz yirmi AD hastası ve 158 sağlıklı kontrol grubu birey çalışmaya dahil edildi. Nötrofil lenfosit oranı, periferik kan örneğindeki nötrofil sayısının lenfosit sayısına bölünmesiyle elde edildi.

Bulgular: Çalışma grubu 220 AD hastası (110 hasta hafif/orta AD grubunda, 110 hasta ciddi AD grubunda) ve 157 sağlıklı birey kontrol grubu olarak çalışmaya dahil edildi. Kontrol grubuyla kıyaslandığında hafif/orta AD grubunda (p<0.001) ve ciddi AD grubunda (p<0.001) önemli derecede NLO yüksekliği saptandı. Ayrıca ciddi AD grubunda hafif/orta AD grubuna göre de NLO değerleri yüksek idi (p<0.001). Hasta demografik bulguları her grupta istatistiksel yönden benzerdi. ROC eğrisi analizinde AD olanlarda NLO için ciddi derecede güçlü prediktivite izlendi (AUC=0.930, %95 GA 0.898–0.963, p<0.001). NLR için 2.310 kesim değeri, AD varlığı için sırasıyla %80.4 ve %92.4'lük duyarlılık ve özgüllüğe sahipti. Çok değişkenli lojistik regresyon analizinde, AD'nin tek bağımsız öngördürücüsü NLO (OR: 43.8, %95 GA 14.7–130.7) idi.

Sonuç: Aort darlığı için NLO'nun ayrımcı performansı yüksektir. Nötrofil lenfosit oranı güçlü ve bağımsız olarak AD ile ilişkilidir.

The number of cases of degenerative aortic stenosis (AS), the most common valvular heart disease, is increasing in developed countries with the growing elderly population.[1] Aortic valve stenosis signs and symptoms generally develop when narrowing of the valve is severe, and can include angina, fainting with exertion, and shortness of breath, especially with exertion fatigue.[2] The patient's history and physical

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examination are essential in diagnosing AS; however, definitive diagnosis is made with echocardiography. AS jet, mean and peak valvular gradients, and aortic valve area (AVA) are used to evaluate the severity of AS.

Recent guidelines suggest the use of an AVA index to account for differences in body size in patients with AS.[3] Some mechanisms of AS are quite notable. These include chronic inflammation, lipid accumulation, remodeling of the extracellular matrix, fibrosis, and calcium deposition.[4–6] Of these, inflammation is the most commonly investigated mechanism.[7–9] Studies indicate that calcification and fibrosis of the aortic valve may be related to the inflammatory process.[10] The inflammatory process induces oxidative stress and reduces cellular antioxidant capacity.[11] The neutrophil-lymphocyte ratio (NLR) is closely linked to inflammatory status and oxidative stress. This study is an investigation of the relationship between NLR and degenerative AS.

Abbreviations:

AS	*Aortic stenosis*
ANOVA	*Analysis of variance*
AVA	*Aortic valve area*
BSA	*Body surface area*
CAD	*Coronary artery disease*
CI	*Confidence interval*
hsCRP	*High-sensitivity C-reactive protein*
HT	*Hypertension*
IL 6	*Interleukin 6*
LVEF	*Left ventricular ejection fraction*
MPV	*Mean platelet value*
NLR	*Neutrophil-lymphocyte ratio*
OR	*Odds ratio*
ROC	*Receiver operating characteristic*
TNF α	*Tumor necrosis factor alpha*

METHODS

Patient population

The study population was chosen from consecutive patients who were transferred to the catheter laboratory for coronary angiography between 2013 and 2015. Exclusion criteria were as follows: 1) significant valve disease other than AS; 2) an abnormal coronary angiogram; 3) uncontrolled hypertension (HT); 4) a history of diabetes or a glycated hemoglobin level of <6.5, 5) a history of hyperlipidemia; 6) the presence of any inflammatory process as evaluated using tumor necrosis factor alpha (TNF α), Interleukin 6 (IL 6), high sensitive C-reactive protein (hsCRP), blood glucose, and fibrinogen levels; 7) abnormal kidney function; or 8) echocardiographic findings of reduced left ventricular ejection fraction (LVEF <50%).

The institutional ethics committee approved the study protocol.

Clinical and biochemical data

Demographic and clinical characteristics of all of the patients were recorded. Height, weight, and arterial blood pressure of all of the patients were measured. Body surface area (BSA) was calculated using Mosteller's formula.[12]

Venous blood samples were drawn from patients after a 12-hour fasting period. After placing the samples into the proper collection tube, they were centrifuged for 5 minutes and the serum was separated. A complete blood count test, creatinine and lipid parameters, and fasting blood glucose levels were measured in the separated serum in the central biochemistry laboratory of the hospital. The NLR was calculated by dividing the number of neutrophils by the number of lymphocytes in the peripheral blood sample.

Echocardiographic evaluation

Echocardiographic examination was performed using a Philips EPIQ 7 3-dimensional echocardiography device (Philips Healthcare, Inc., Andover, MA, USA) and a 2.5-MHz probe. All images were recorded including 3 consecutive heartbeats and evaluated later. The echocardiographic assessment was performed in the left lateral decubitus position accompanied by electrocardiogram monitorization according to the recommendations of the American Echocardiography Society.[13] LVEF was calculated using the modified Simpson method. The mean and peak aortic valve gradient, aortic flow velocity, and velocity time interval were measured by placing the continuous-wave Doppler sample volume into the aortic valve opening and pulsed-wave sample volume into the sinotubular junction and left ventricular outflow tract in apical 5-chamber view. AVA was calculated using the continuity equation formula. The AVA index was calculated by dividing the AVA by the BSA2. Patients with AS were stratified into normal, mild-to-moderate (valve area more than 1.0 cm^2, jet velocity less than 4.0 m/second, mean gradient less than 40 mmHg, and AVA index more than 0.6 cm^2/m^2), and severe aortic stenosis (AVA less than 1.0 cm^2, jet velocity more than 4.0 m/second, mean gradient more than 40 mmHg, and AVA index less than 0.6 cm^2/m^2) groups. All of the echocardiographic examinations were completed before coronary angiography was performed.

Statistical analysis

Continuous variables were expressed as mean (±SD) or median (minimum-maximum), as appropriate. Categorical variables were presented as number and percentage. The distribution of continuous variables across the study groups was tested with the Kolmogorov-Smirnov test. Continuous data were analyzed using one-way analysis of variance (ANOVA) or the Kruskal-Wallis test, and categorical data were compared using the chi-square test. Post-hoc analysis for the one-way ANOVA was performed with Tukey's test. In the Kruskal-Wallis test, comparisons between paired groups were performed using the Mann-Whitney U test with a Bonferroni correction ($p<0.0167$). Receiver operating characteristic (ROC) curve analysis was conducted to assess the discriminative performance of NLR for AS. The area under curve (AUC) with the corresponding 95% confidence interval (CI) was presented. The sensitivity and specificity of the test were calculated.

Univariate and multivariate logistic regression analyses were conducted to assess the association of NLR and AS. In multivariate regression analysis (enter method), the effect size was adjusted for all variables with a univariate significance level of <0.25. Adjusted odds ratios (OR), along with their 95% CIs were presented. A 2-tailed p value of <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) and MedCalc Software for Windows, Version 15.4 (MedCalc Software, Ostend, Belgium) software.

RESULTS

The study group consisted of 220 AS patients (mild/moderate group: n=110; severe group: n=110) and 157 healthy controls (Table 1). The healthy control, mild/moderate AS, and severe AS groups were similar with respect to age (72.5±7.1 years vs. 73.6±7.8 years vs. 73.8±6.7 years; p=0.238), gender (female: 55.7% vs. 58.1% vs. 47.2%; p=0.865), prevalence of HT, LVEF, systolic blood pressure, diastolic blood pressure, and creatinine, glomerular filtration rate, hsCRP, TNF-α, IL-6, and fibrinogen levels. There was a statistically significant difference in terms of NLR between the 3 groups ($p<0.001$) (Table 1). Both the mild/moderate AS ($p<0.001$) and severe AS groups ($p<0.001$) had a significantly higher NLR than the control group (Figure 1). The NLR was significantly higher in the severe AS group than in the mild/moderate AS group ($p<0.001$).

ROC curve analysis yielded a strong predictive ability of NLR for the presence of AS (AUC: 0.930; 95% CI, 0.898–0.963; $p<0.001$) (Figure 2). A cut-off value of 2.310 for NLR had a sensitivity and specificity of 80.4% and 92.4%, respectively, for the presence of AS (Figure 2).

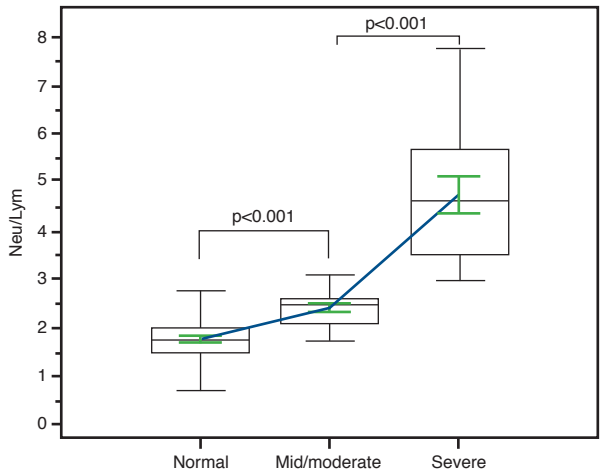

Figure 1. Distribution of the neutrophil-lymphocyte ratio in the study groups.

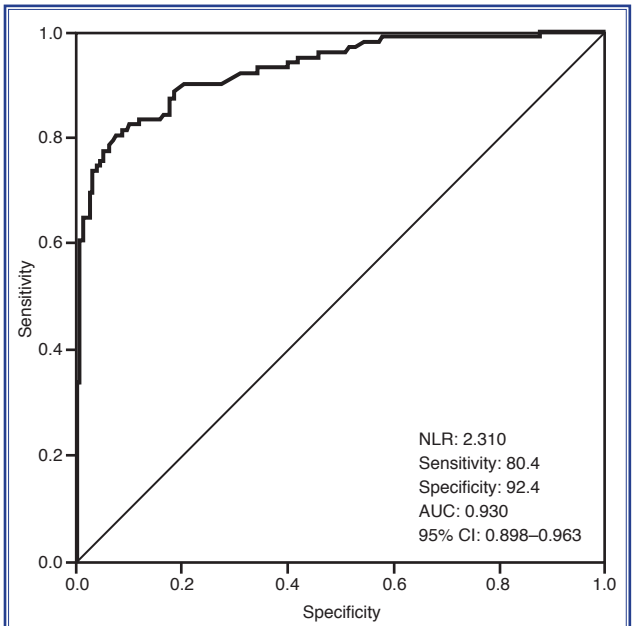

Figure 2. Receiver operating characteristic curve for neutrophil-lymphocyte ratio and aortic stenosis. AUC: Area under curve; CI: Confidence interval.

Table 1. The demographic distribution of the study population

	Normal (n=158)	Mild/moderate AS (n=110)	Severe AS (n=110)	*p*
Age (years)*	72.47±7.1	73.58±7.8	73.80±6.7	0.238
Female, n (%)**	88 (55.7%)	64 (58.1%)	52 (47.2%)	0.865
HT, n (%)**	14 (8.8%)	8 (7.2%)	10 (9%)	0.161
Creatinin (mg/dL)*	1.13±0.6	1.08±0.7	1.05±0.1	0.095
GFR (mL/min/1.73 m^2)*	95.8±5.9	93.4±8.2	96.6±5.6	0.072
AVA (cm^2)***	2.46 (2.09–2.87)	1.22 (1.15–1.37) [a]p<0.001	0.93 (0.83–1.02) [b]p<0.001 [c]p<0.001	<0.001
AVA index (cm^2/m^2)***	1.35 (1.19–1.55)	0.70 (0.63–0.75) [a]p<0.001	0.51 (0.45–0.55) [b]p<0.001 [c]p<0.001	<0.001
P grad (mmHg)*	14.04±9.5	53.48±8.8 [a]p<0.001	79.75±15.0 [b]p<0.001 [c]p<0.001	<0.001
M grad (mmHg)*	6.91±7.2	33.05±5.2 [a]p<0.001	61.96±13.3 [b]p<0.001 [c]p<0.001	<0.001
J vel, (m/sec)*	1.78±0.5	3.64±0.3 [a]p<0.001	4.447±0.4 [b]p<0.001 [c]p<0.001	<0.001
LVEF (%)*	60.27±4.2	60.00±4.0	60.53±4.3	0.796
SBP (mmHg)*	126.48±10.0	126.17±9.6	124.50±8.2	0.964
DBP (mmHg)*	74.50±8.4	75.54±7.6	71.33±7.8	0.522
hsCRP (mg/L)*	0.79±0.24	0.76±0.19	0.83±0.16	0.212
TNF α*	16.8±2.5	15.7±1.8	16.2±2.1	0.586
IL 6*	13.51±10.15	11.48±12.34	12.38±11.08	0.188
Fibrinogen (mg/dL)*	185±24.8	172±21.7	169±30.4	0.851
WBC (×10^3 per μL)*	7.6±1.5	7.5±1.2	7.9±1.1	0.124
RBC (million/mcL)*	4.8±0.4	5.1±0.9	4.8±0.6	0.625
Hemoglobin (g/dL)*	12.9±2.0	13.5±1.6	12.3±1.0	0.514
Hematocrit (%)*	0.42±5.8	0.45±6.4	0.44±4.5	0.451
Platelets (×10^3 per μL)*	248.2±45.8	304±.54.2	301±39.7	0.098
L count (×10^3 per μL)***	3.10 (2.40–3.80)	2.30 (1.90–2.60)	1.40 (1.20–1.70)	0.215
N count (×10^3 per μL)***	5.45 (4.20–6.27)	5.50 (4.70–6.10)	6.70 (5.10–8.00)	0.182
NLR***	1.77 (1.48–2.03)	2.68 (2.13–2.68) [a]p<0.001	4.62 (3.50–5.76) [b]p<0.001 [c]p<0.001	<0.001

AS: Aortic stenosis; AVA: Aortic valve area; DBP: Diastolic blood pressure; HL: Hyperlipidemia; hsCRP: High sensitivity C-reactive protein; HT: Hypertension; IL 6: Interleukin 6; J vel: Jet velocity; L: Lymphocyte; LVEF: Left ventricular ejection fraction; M grad: Mean gradient; N: Neutrophil; NLR: Neutrophil-lymphocyte ratio; P grad: Peak gradient; RBC: Red blood cell; SBP: Systolic blood pressure; TNF α: Tumor necrosis factor alpha; WBC: White blood cell. *One-way analysis of variance; **Chi-square test; and ***Kruskal-Wallis tests were used for comparisons. Post-hoc Tukey's test was performed for the variables that had a p value of <0.05 in the analysis of variance test. Mann-Whitney U test was performed for variables with Bonferroni correction in which the p value was <0.0167. [a]Comparison between the control group and the mild/moderate group; [b]Comparison between the control group and the severe group. [c]Comparison between the mild/moderate group and the severe group.

Table 2. Univariate and multivariate logistic regression analysis of non-AS group and AS patients

	Univariate		Multivariate	
Variables	OR (95% CI)	*p*	Adjusted OR (95% CI)	*p*
Age	1.028 (0.992–1.064)	0.126	1.022 (0.969–1.078)	0.420
Hypertension	1.005 (0.418–2.415)	0.992		
Systolic blood pressure	0.996 (0.971–1.022)	0.751		
Hemoglobin	1.306 (1.109–1.538)	<0.001	1.242 (0.962–1.604)	0.097
Neutrophil-lymphocyte ratio	41.684 (14.523–119.639)	<0.001	43.781 (14.666–130.692)	<0.001
Creatinin	0.876 (0.573–1.340)	0.542		
Left ventricular ejection fraction	0.996 (0.938–1.057)	0.900		
Platelets	0.998 (0.994–1.002)	0.407		

AS: Aortic stenosis; CI: Confidence interval; OR: Odds ratio.

Age (p=0.126), hemoglobin level (p<0.001), and NLR (p<0.001) were associated with AS with a p value of <0.25 in univariate logistic regression analysis (Table 2). In multivariate logistic regression analysis, NLR (OR: 43.8; 95% CI, 14.7–130.7) was the only independent predictor of AS.

DISCUSSION

Degenerative AS is an important cardiovascular disease that mostly affects the elderly population. It may progress for years without any symptoms. Even hemodynamically insignificant AS in the elderly increases cardiovascular morbidity and mortality by 5%.[14] Identification of degenerative AS in standard 2-dimensional echocardiography is a risk factor for myocardial infarction, angina pectoris, congestive heart failure, and stroke.[14–16]

Recent histopathological studies of degenerative AS have demonstrated that it is a chronic inflammatory process with findings of atherosclerotic plaque in the coronary arteries similar to those seen in atherosclerosis.[8–11] The identification of lipid particles, inflammation cells, and calcium crystals in both processes supports the idea that degenerative AS is a part of atherosclerosis.[8–11] Early in calcific aortic valve stenosis, there is lipid accumulation and fibrosis thickening with collagen and elastin in the lesions, and adjacent fibrosis with chronic inflammatory infiltrate (macrophages and T lymphocytes). The similar classic risk factors that contribute to both degenerative AS and atherosclerosis formation also support this view.[15–17]

Definitive treatment of AS is always valve repair or replacement of the aortic valve using newly emerging technology and techniques.[18] As both procedures are costly operations, pre- and post-treatment follow-up of these patients are equally important.[18] Two-dimensional standard echocardiography is used in follow-up, but these measurements are still not optimal and depend on the operator; thus, a considerable number of patients may remain untreated1. Many studies have shown that some cheap, easily accessible, routine tests done in patients who present at a cardiology policlinic or who were diagnosed as coronary artery disease (CAD) might be helpful in AS.[19–22] Some of these tests are mean thrombocyte volume, b-type natriuretic peptide, N-terminal pro b-type na-

triuretic peptide, hsCRP, high-sensitivity troponin, interleukins, uric acid level, platelet-lymphocyte ratio and NLR.[19–27] A study by Kurisu et al.[23] included 75 elderly patients who were diagnosed as AS according to peak pressure gradient. The correlation between AS severity and mean platelet value (MPV) value of these patients was evaluated and it was determined that the MPV value was higher in patients with AS compared with the control group.

The anti-inflammatory effect of statins has been proven in large-scale studies.[24,28,29] According to a study that aimed to observe the effect of anti-hyperlipidemic use in AS patients on major outcome endpoints,[24] events connected with ischemic heart disease were significantly low, especially in patients with high CRP; once again proving AS is an inflammatory progress. Chin et al. used high-sensitivity troponin as a marker in another cohort-type study[25] and observed progress from hypertrophy to heart failure. The cohort-type study of Chin et al. showed that patients with a high level of high-sensitivity troponin had a greater risk of progression to heart failure, which could serve to predict these patients.

Much as there are studies about the inflammation process in AS, there are also many studies using NLR as a marker.[27,30–37] As a matter of fact, all branches of medicine have researched the correlations. NLR was found to be statistically significant in cardiology studies. A recent, large-scale, cohort-type study conducted by Verdoia et al.[32] demonstrated the relationship of NLR to CAD by distributing patients into 4 groups according to the severity of coronary artery lesions seen in angiography and reported that NLR was an independent predictor in all groups.

The relationship between atherosclerosis and NLR cannot be underestimated. A review of this subject pointed out that NLR, as with other inflammation markers, is increased in a chronic process like diabetes, hyperlipidemia, metabolic syndrome, or hypertension, and that examining NLR is more easily accessible and a cheaper method compared with other markers.[30–37] However, many of the studies didn't exclude other inflammation processes, and as a result, it couldn't be identified whether this valuable ratio is a finding of under-researched disease or chronic disease. Consequently, the results were controversial. For example, a study that examined the association between NLR and CAD in diabetic patients, found that NLR was significantly high in diabetic patients with CAD, but the pathophysiology of this condition was not explained in either chronic inflammatory process.[32]

Zhang et al.[33] also researched the relationship of NLR and CAD severity, and included patients with coronary atherosclerosis, stabile angina, and acute coronary syndrome. These patients were then grouped according to Gensini score using coronary angiography. This study also found a significant NLR and suggested that this value might indicate the severity of CAD. Because atherosclerosis plays the lead role in ectasia coronary pathophysiology, a study written by Balta et al.[34] compared NLR with coronary ectasia cases and included 181 suspected CAD patients stratified into 3 groups: normal, ectasia, and newly diagnosed CAD. The results demonstrated that coronary ectasia was positively correlated with NLR.

Recent studies have shown an NLR relationship not just with the aortic valve, but also other valves. Studies have suggested that NLR was statistically high in patients with mitral annular calcification.[35,36] A study by Avci et al.[37] that is similar to our study included 96 calcific AS patients and compared these patients according to demographic characteristics. Patients were stratified according to mean gradient, but severe AS patients with low LVEF, low flow, and low gradient were also included in the study. Patients were grouped as mild/middle AS, severe AS with normal LVEF, and severe AS with low LVEF. The inflammation process indicated by NLR increased as the severity of valvular stenosis increased. The authors suggested that degenerative AS is an inflammatory process just like atherosclerosis, and that increased markers can also be identified in AS. However, that study had the limitation of not definitely excluding CAD according to evidence and excluded only patients with coronary angiography. Thus, it might have included CAD patients because they weren't diagnosed with coronary angiography. Valvular area was not calculated; patients were separated into groups based just on gradient, and as a result, this might not exclude paradoxical AS defined as normal LVEF, low gradient, and severe AS, and didn't exclude other important inflammatory processes, such as diabetes.

Another paper similar to ours, published by Demir et al.[26] in 2012, found a positive correlation between

the severity of AS and serum uric acid, but this study didn't exclude patients with inflammatory events either and didn't explain uric acid as a marker of inflammation. It could be affected by other inflammatory processes. Yayla et al.[27] found a correlation between platelet-lymphocyte ratio and the severity of AS, but that study also did not exclude other inflammatory processes. None of these studies could explain whether the correlated inflammatory marker was increased due to AS or another inflammatory process. Only a few of these studies reported this limitation.

We also used NLR, as in many recent studies,[30–37] but unlike other studies, we researched the importance of this ratio in patients with mild-moderate and severe AS and without proven CAD. We were cautious not to include patients with diabetes mellitus, any other valvular disease, uncontrolled HT, any active inflammation, or CAD. Thus, this inflammation marker we researched in AS was not affected by a secondary inflammation processes.

Our results, as expected in line with other studies, proved the presence of inflammation, and we observed a statistically significant increase in NLR as the valvular stenosis ratio increased. Our study used an AVA index for AS classification, an evaluation specific to all patients. More importantly, we excluded any other inflammatory process or chronic disease that might affect this marker. We observed significant inflammation in the severe AS group compared with other groups, according to the most recent echocardiography guidelines.[13]

Conclusion

The discriminative performance of NLR for AS is high. NLR is strongly and independently associated with AS. As an inexpensive and readily available marker of chronic inflammation, NLR may be an alternative method of assessing the severity of the disease when combined with standardized clinical mortality risk estimation scores and other inflammatory markers. Further studies will be required to consider NLR a useful marker in clinical settings.

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