ORIGINAL RESEARCH

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Diagnostic accuracy of neutrophil-to-albumin ratio in predicting aortic valve sclerosis: A retrospective study

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Abstract

Objectives: Aortic valve sclerosis (AVS) is the thickening or calcification of the aortic valve without significant obstruction, primarily affecting the elderly and potentially progressing to calcific aortic valve disease with high morbidity and mortality. This study evaluates the diagnostic potential of the neutrophil-to-albumin ratio (NAR) in predicting AVS.

Methods: In this retrospective study, 494 patients aged 18-75 who underwent transthoracic echocardiography between December 2022 and March 2024 were analyzed. Patients were divided into two groups: 401 with AVS and 93 without. NAR was calculated from laboratory data.

Results: The AVS group had higher rates of diabetes mellitus, hypertension, and coronary artery disease compared to the control group ($p<0.001$ for all). Laboratory findings showed elevated fasting blood glucose, creatinine, cholesterol, HDL-C, LDL-C, WBC, and neutrophil counts in the AVS group. Multivariate analysis identified hypertension, diabetes mellitus, reduced left ventricular ejection fraction, and elevated NAR as independent predictors of AVS. Sensitivity of NAR in diagnosis of AVS was 56% and specificity 58%.

Conclusion: Elevated NAR is significantly associated with AVS and is an independent predictor. These findings suggest NAR could be a valuable marker for early diagnosis and management of AVS. Further research is needed to explore the mechanisms and potential therapeutic interventions targeting inflammation in AVS

Key words: Aortic valve sclerosis, neutrophil-to-albumin ratio, inflammation, predictive value, accuracy

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Introduction

Aortic valve sclerosis (AVS) is a condition characterized by thickening and/or calcification of the aortic valve without significant flow reduction or stenosis. It is predominantly observed in the elderly male and female population. In some patients with AVS, the condition progresses and develops into hemodynamically significant calcific aortic valve disease (CAVD). This condition is known as aortic stenosis (AS) (1).

Calcific aortic valve disease is estimated to cause approximately 15,000 deaths annually in the United States (2). Additionally, once it progresses to severe AS, it requires surgical and/or interventional procedures (3). In untreated cases, there is a significant increase in hospital admissions, posing a substantial financial burden on countries. As populations age, the prevalence of aortic sclerosis, and consequently AS, continues to rise, becoming a serious public health issue.

Aortic valve sclerosis and CAVD were previously considered passive degenerative processes associated with aging (4). However, recent studies and accumulating data have revealed that AVS is now understood to be a complex pathological process involving lipoprotein accumulation, chronic inflammation, and a calcification cascade similar to atherosclerosis (5, 6).

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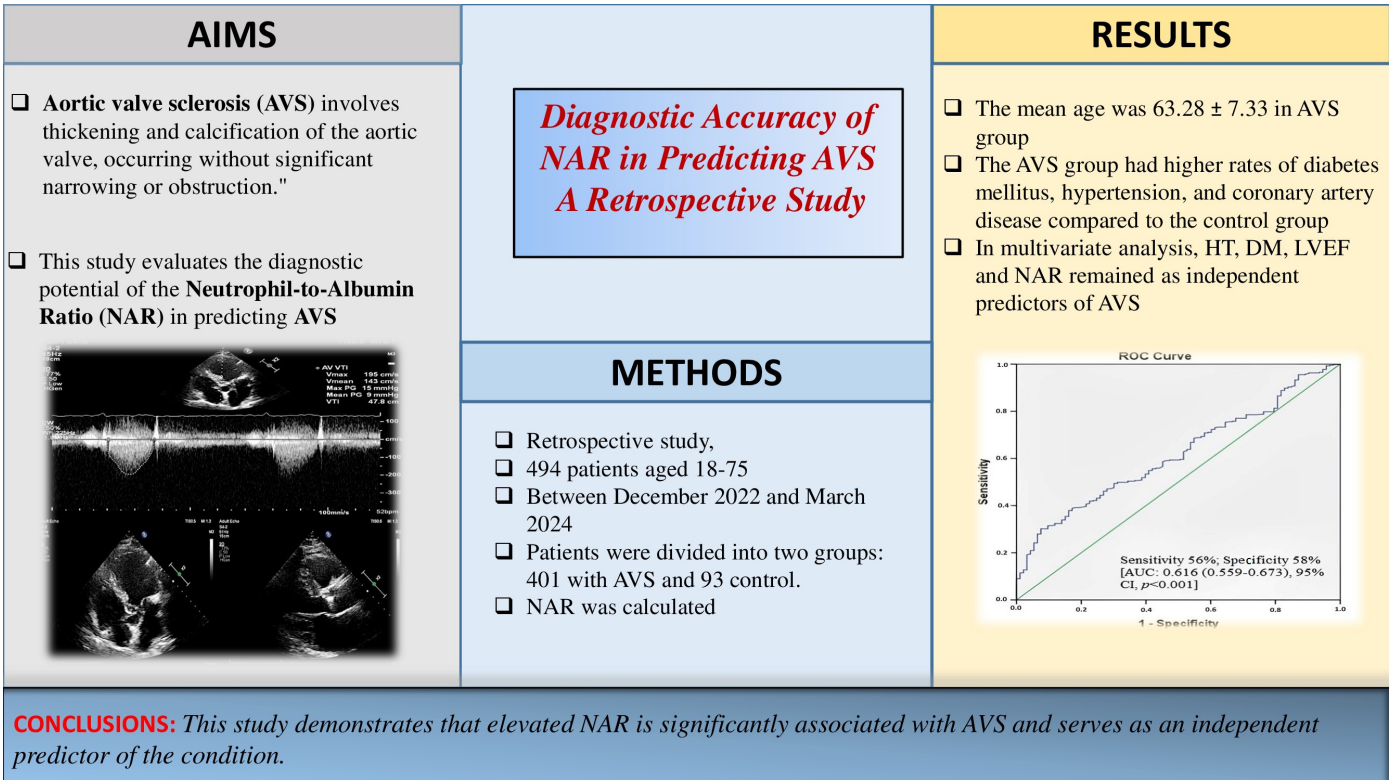
Graphical abstract



Despite this understanding, the underlying pathophysiology of AVS remains incompletely elucidated. Recent studies have shown that inflammatory markers play a significant role in cardiovascular diseases such as atherosclerosis and AVS, (7, 8). One such marker is the neutrophil-to-albumin ratio (NAR), which combines neutrophil counts and albumin levels to indicate both inflammation and nutritional status. The NAR has been identified as a significant prognostic marker in various cardiovascular conditions, including atherosclerosis and myocardial infarction (9, 10). Elevated NAR levels are associated with increased inflammatory activity and poor outcomes, suggesting its potential utility in predicting the severity and progression of cardiovascular diseases. However, few is known on predicting value of NAR of AVS and its diagnostic value.

The aim of this study is to evaluate the diagnostic accuracy of the NAR in predicting AVS. By analyzing NAR levels in patients with and without AVS, we seek to determine its potential as a non-invasive marker for early diagnosis and management of this condition. This research could lead to improved diagnostic and prognostic strategies in cardiovascular medicine, particularly for those at risk of developing AVS.

Methods

Study design and population

This study is a retrospective observational study focusing on the diagnostic accuracy of the NAR in predicting AVS. The study population consisted of 494 patients who underwent transthoracic echocardiography (TTE) between December 2022 and March 2024. Among them, 401 patients diagnosed with AVS formed the AVS group, while 93 patients without AVS served as the control group.

Exclusion criteria included patients with acute coronary syndrome, those outside the 18-75 age range, patients with atrial fibrillation (AF) or a history of AF, those with known rheumatic valve disease, and patients with a history of acute rheumatic fever in childhood. Additionally, patients with chronic inflammatory diseases known to facilitate AVS and influence inflammation, those diagnosed with cancer, patients with end-stage chronic kidney disease (glomerular filtration rate <15 ml/min), and those with severe valvular heart disease or an aortic velocity >2 m/s were excluded from the study.

This retrospective observational study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of our hospital (Approval Date: 22.05.2024, Approval number: AEŞH-BADEK-2024-475). All patients provided their informed consent for procedures.

Baseline Variables

The baseline variables included demographic data, risk factors, and therapy variables. These were age, gender, diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), fasting blood glucose (FBG), creatinine levels, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), white blood cell (WBC) count, hemoglobin (Hb), and medication use (beta-blockers, renin-angiotensin-aldosterone system (RAAS) blockers, acetylsalicylic acid (ASA), and statins). These variables are detailed in Table 1.

Echocardiographic examination

Transthoracic echocardiography (TTE) was performed on patients using our hospital's TTE devices (General Electric Vivid E80, GE Healthcare, Milwaukee, Wisconsin, USA) by two experienced cardiologists who were blinded to the clinical status of the patients. The TTE data were obtained retrospectively. Measurements included left ventricular posterior wall thickness (PWT), left ventricular end-diastolic diameter (LVEDD), ascending aorta, and left atrium (LA) diameter, which were recorded from the parasternal long-axis view. The ejection fraction (LVEF) was calculated using the biplane Simpson method (11).

AVS assessments were conducted from the parasternal long-axis, parasternal short-axis, and apical five-chamber views. AVS was defined as increased echogenicity at the midpoint of the aortic leaflets, leaflet thickening those results in restricted movement, and a peak velocity ≤2.0 m/sec, in accordance with certain clinical guidelines on valvular heart diseases (12). However, there are inconsistencies in the literature regarding the definition of AVS. For instance, some echocardiographic guidelines consider a peak velocity of ≤2.5 m/sec as a criterion for aortic sclerosis (2, 13). We chose the ≤2.0 m/sec criterion based on its usage in several key clinical guidelines (12). Tissue harmonic imaging was avoided to prevent overestimation of echogenicity; therefore, AVS presence was identified without using high-gain settings (14) (Fig. 1).

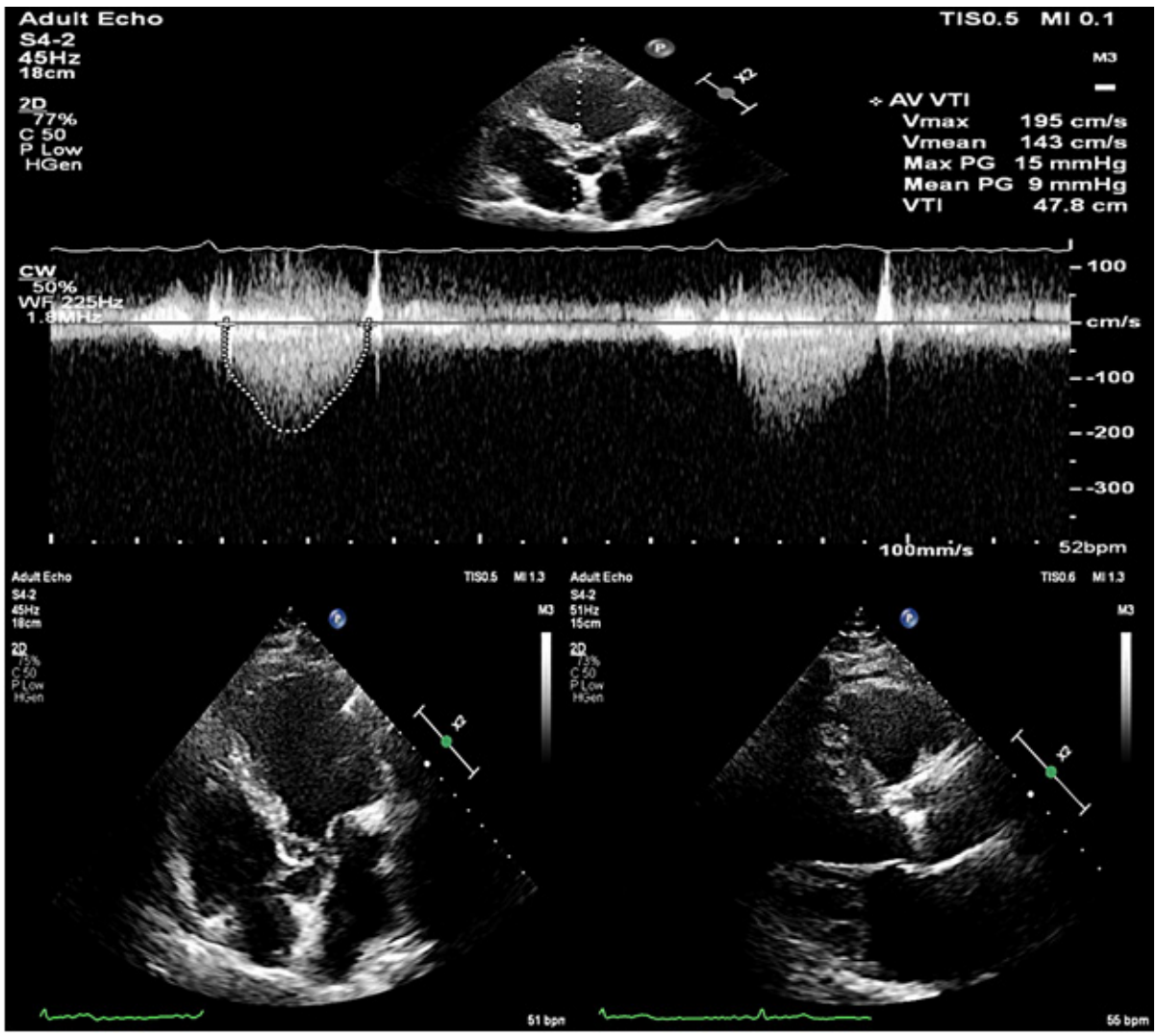


Figure 1. Echocardiographic image demonstrating aortic valve sclerosis and its determination in a patient

Laboratory evaluation

Blood samples were collected after overnight fasting and analyzed within 10-30 minutes following collection. Complete blood cell counts, including WBC, Hb, and neutrophil counts, were analyzed using an automated hematology analyzer (Coulter LH 780 Hematology Analyzer, Beckman Coulter Corp., Hialeah, FL). Serum biochemistry parameters, including FBG, creatinine, urea, TC, HDL-C, LDL-C, and albumin were measured using standard automated methods in the hospital's biochemistry laboratory. The NAR was calculated by dividing the absolute neutrophil count by the serum albumin level.

Statistical Analysis

All data were analyzed using the SPSS 22.0 statistical software package for Windows (IBM, Armonk, New York, USA). The normality of distribution was evaluated using the Kolmogorov–Smirnov test. Continuous variables were presented as mean (standard deviation) for normally distributed data, or as median (interquartile range) for non-normally distributed data. Categorical variables were reported as counts and percentages. Comparisons among groups were performed using the Student's t-test for normally distributed continuous variables, and the Mann–Whitney U test for non-normally distributed continuous variables. Categorical variables were analyzed using the χ^2 test or Fisher's exact test, as appropriate. Multiple logistic regression analysis was conducted to assess the association between hematological and biochemical inflammatory markers and AVS. The diagnostic ability of the NAR for predicting AVS was evaluated using receiver operating characteristic (ROC) curve analysis and the area under the curve (AUC). The optimal cut-off value for NAR was determined using the Youden index. A p-value of less than 0.05 (two-sided test) was considered statistically significant.

Results

In this study, a total of 494 patients were analyzed, including 401 patients with AVS and 93 control patients. The clinical characteristics of the two groups are summarized in Table 1.

Clinical characteristics

The mean age of the AVS group was 63.28 (7.33) years, while the control group had a mean age of 62.17 (5.16) years. The combined mean age across both groups was calculated to be 63.07 years with an SD of 6.98 years. Gender distribution was similar between the groups, with 61.6% males in the AVS group and 61.3% males in the control group (p=0.956).

A significant difference was observed in the prevalence of comorbidities between the two groups. DM was present in 44.4% of the AVS group compared to 15.1% in the control group (p<0.001). HT was notably higher in the AVS group (92.8%) compared to the control group (54.8%) (p<0.001). Similarly, CAD was more prevalent in the AVS group (54.1%) than in the control group (12.9%) (p<0.001).

Medication use varied significantly between the two groups. The use of beta-blockers, renin-angiotensin-aldosterone system (RAAS) blockers, acetylsalicylic acid (ASA), and statins was markedly higher in the AVS group compared to the control group (all p<0.001).

Laboratory data

Several laboratory parameters showed significant differences between the groups. FBG levels were slightly higher in the AVS group compared to the control group (p=0.032). Creatinine levels were also elevated in the AVS group relative to the control group (p<0.001). TC, HDL-C, and LDL-C levels were significantly different between the groups, with p values of 0.035, 0.023, and 0.038, respectively. WBC count was higher in the AVS group (p = 0.024,), while Hb levels were lower in the AVS group compared to the control group (=0.013). Neutrophil count was significantly higher in AVS group as compared to controls (4.35 (1.91) vs3.96 (1.30), p<0.001) and albumin level did differ between groups (p=0.098).

Echocardiographic findings

The echocardiographic assessment revealed significant differences between the AVS and control groups in several parameters. The NAR was significantly higher in the AVS group (1.06 (0.37) vs (0.90 (0.23) p<0.001) compared to the control group, indicating a strong association between elevated NAR levels and the presence of AVS. Similarly, several echocardiographic parameters showed significant differences between the groups (Table 2). LVEF was lower (p<0.001), LA size and ascending aorta diameter (p<0.001, p<0.001) were larger and aortic valve velocity was higher in AVS (p=0.039) group as compared to control one.

Table 1. Clinical characteristics

Variables	AVS (n=401)	Control (n=93)	p
Age, years	63.28 (7.33)	62.17 (5.16)	0.89
Sex, male, n (%)	247 (61.6)	57 (61.3)	0.956
Comorbidities, n (%)			
DM	178 (44.4)	14 (15.1)	**<0.001**

Table 1. Clinical characteristics (continued from page 457)			
Variables	**AVS (n=401)**	**Control (n=93)**	**p**
Comorbidities, n (%)			
HT	372 (92.8)	51 (54.8)	**<0.001**
CAD	217 (54.1)	12 (12.9)	**<0.001**
Laboratory findings			
FBG, mg/dL	99.00 (38.00)	94.00 (20.50)	**0.032**
Creatinine, mg/dL	0.94 (0.31)	0.82 (0.15)	**<0.001**
Total Protein, g/dL	6.87 (0.39)	6.95 (0.36)	0.095
Albumin, g/dL	4.37 (0.29)	4.42 (0.30)	0.098
TC, mg/L	185.23 (43.61)	195.77 (42.71)	**0.035**
HDL-C mg/L	44.00 (13.00)	44.29 (14.50)	**0.023**
LDL-C mg/L	109.00 (44.00)	113.00 (48.00)	**0.038**
WBC,x10^3/uL	7.26 (2.50)	7.00 (1.99)	**0.024**
Neutrophil, x10^3/uL	4.35 (1.91)	3.96 (1.30)	**<0.001**
Hb, g/dL	13.90 (2.50)	14.40 (1.70)	**0.013**
Platelet x10^3/uL	259.00 (85.50)	249.00 (93.00)	0.130
Medications, n (%)			
Beta-blocker	262 (65.3)	25 (26.9)	**<0.001**
RAAS blocker	275 (68.6)	44 (47.3)	**<0.001**
ASA	244 (60.8)	33 (35.5)	**<0.001**
Statin	199 (49.6)	19 (20.4)	**<0.001**

Data are shown as mean (standard deviation, SD), median (min-max) and count (percentage)
ASA- acetylsalicylic acid, AVS- aortic valve sclerosis, CAD- coronary artery disease, DM- diabetes mellitus, FBG- fasting blood glucose, Hb- hemoglobin, HDL-C- high density lipoprotein cholesterol, HT- hypertension, LDL-C- low density lipoprotein cholesterol, RAAS- renin-angiotensin-aldosterone system, TC- total cholesterol, TG- triglyceride, WBC- white blood cell

Table 2. Comparison of NAR and echocardiographic findings between AVS and control groups			
Variables	**AVS (n=401)**	**Control (n=93)**	**p**
NAR	1.06 (0.37)	0.90 (0.23)	**<0.001**
LVEDD, cm	4.60 (0.30)	4.60 (0.40)	**0.074**
LVEF, %	56.50 (10.00)	60.00 (5.00)	**<0.001**
PWT, cm	1.08 (0.15)	1.02 (0.11)	**<0.001**
LA size, cm	3.86 (0.43)	3.63 (0.29)	<0.001
Ascending aorta diameter, cm	3.50 (0.40)	3.40 (0.35)	<0.001
Aortic valve velocity, m/sec	1.35 (0.27)	1.30 (0.18)	0.039

Data are shown as mean (standard deviation, SD), median (min-max) and count (percentage)
LA- left atrium, LVEDD- left ventricular end-diastolic diameter, LVEF- left ventricular ejection fraction, NAR- neutrophil-albumin ratio, PWT- posterior wall thickness

Predictors of AVS development

In univariate analysis, HT (OR: 10.564, 95% CI: 6.056-18.427, p<0.001), DM (OR: 4.504, 95% CI: 2.468-8.220, p<0.001), LVEF (OR: 0.847, 95% CI: 0.800-0.896, p<0.001), HDL-C (OR: 0.977, 95% CI: 0.960-0.995, p=0.012), FBG (OR: 1.011, 95% CI: 1.003-1.018, p=0.005), creatinine (OR: 9.852, 95% CI: 2.880-33.696, p<0.001), and NAR (OR: 5.247, 95% CI: 2.254-12.216, p=0.001) were significant predictors of AVS. In multivariate analysis, HT (OR: 6.131, 95% CI: 3.361-11.184, p < 0.001), DM (OR: 4.125, 95% CI: 1.765-9.640, p=0.001), LVEF (OR: 0.883, 95% CI: 0.831-0.938, p<0.001), and NAR (OR: 3.401, 95% CI: 1.300-8.902, p=0.013) remained as independent predictors of AVS (Table 3).

Table 3. Univariate and multivariate logistic regression analysis showing the independent predictors of aortic valve sclerosis

Variables	Univariate		Multivariate	
	Odds ratio 95% CI	p	Odds ratio 95% CI	p
HT	10.564 (6.056-18.427)	**<0.001**	6.131 (3.361-11.184)	**<0.001**
DM	4.504 (2.468-8.220)	**<0.001**	4.125 (1.765-9.640)	**0.001**
LVEF	0.847 (0.800-0.896)	**<0.001**	0.883 (0.831-0.938)	**<0.001**
HDL-C	0.977 (0.960-0.995)	**0.012**	1.016 (0.992-1.040)	0.196
FBG	1.011 (1.003-1.018)	**0.005**	0.996 (0.988-1.004)	0.279
Creatinine	9.852 (2.880-33.696)	**<0.001**	4.097 (0.945-17.758)	0.059
NAR	5.247 (2.254-12.216)	**0.001**	3.401 (1.300-8.902)	**0.013**

Data shown as odds ratio (95% confidence interval) and p value.
DM- diabetes mellitus, FBG- fasting blood glucose, HDL-C- high density lipoprotein cholesterol, HT- hypertension LVEF- left ventricular ejection fraction, NAR- neutrophil-albumin ratio

Diagnostic accuracy of NAR in prediction of AVS

The ROC curve analysis (Fig. 2) indicated a sensitivity of 56% and a specificity of 58% for the model. The AUC was 0.616 (95% CI: 0.559-0.673, p<0.001), demonstrating a moderate ability to discriminate between AVS and control patients.

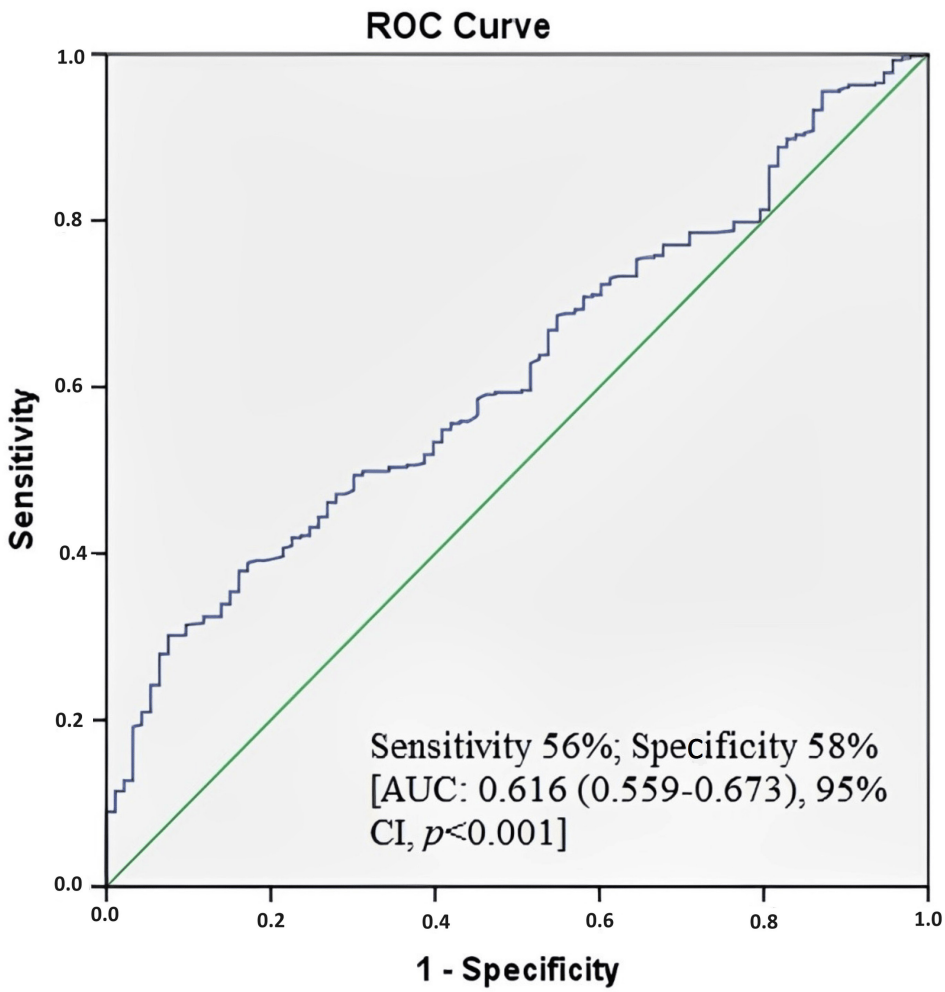


Figure 2. ROC curve for neutrophil-to-albumin ratio in predicting aortic valve sclerosis in predicting aortic valve sclerosis

Discussion

In this study, we evaluated the relationship between NAR and AVS, examining its potential role as a marker of inflammation and its association with the pathophysiology of AVS.

Our findings indicate that patients with AVS have higher incidences of comorbidities, altered laboratory parameters, and distinct echocardiographic findings compared to control patients. Univariate and multivariate analyses identified HT, DM, reduced LVEF, and elevated NAR as significant predictors of AVS. The ROC analysis further underscores the importance of these variables in predicting the presence of AVS.

The results of our research highlight several significant findings that contribute to the understanding of AVS and its underlying mechanisms.

Previous studies have established a link between inflammation and the progression of aortic valve diseases. AVS, once considered a passive degenerative process, is now recognized as an active condition involving chronic inflammation, lipoprotein deposition, and subsequent calcification (1, 15). In our study, we found that patients with AVS had significantly higher NAR levels compared to controls, suggesting that elevated NAR could be indicative of increased inflammatory activity in AVS. This aligns with existing literature that emphasizes the role of inflammatory markers in cardiovascular diseases, including AVS (16-19).

The NAR combines neutrophil count and serum albumin levels, providing a composite measure that reflects both inflammatory status and nutritional condition. Elevated NAR has been associated with various cardiovascular conditions, including atherosclerosis and myocardial infarction (9, 10). Our findings suggest that NAR is not only elevated in AVS patients but also serves as an independent predictor of AVS, as demonstrated by multivariate logistic regression analysis. This underscores the potential utility of NAR as a non-invasive, easily accessible marker for identifying patients at risk of AVS.

The significant association between NAR and AVS points to its possible role in clinical practice. By incorporating NAR into routine diagnostic workups, clinicians could better identify patients at higher risk for AVS, facilitating earlier intervention and potentially improving outcomes. Additionally, the moderate sensitivity and specificity of NAR, as indicated by the ROC curve analysis, suggest that while it is a valuable marker, it should be used in conjunction with other clinical assessments and diagnostic tools to enhance accuracy and reliability (20).

Our study also contributes to the understanding of the pathophysiological mechanisms underlying AVS. The association between higher NAR levels and AVS suggests that systemic inflammation plays a critical role in the progression of this condition. This is consistent with the hypothesis that AVS shares common pathophysiological pathways with atherosclerosis, including chronic inflammation and calcification processes (21, 22). These insights could pave the way for new therapeutic strategies targeting inflammatory pathways to slow down or halt the progression of AVS.

Study limitations

Despite the valuable insights gained from this study, there are several limitations that should be acknowledged. Firstly, the retrospective observational design may introduce biases related to patient selection and data collection. Secondly, the study population was limited to a single center, which may affect the generalizability of the findings. Additionally, the reliance on hospital records for data collection could lead to inaccuracies or incomplete information.

Another significant limitation is that the comorbidities were not evenly distributed between the groups. The differences in comorbidities such as DM, HT, and CAD between the AVS and control groups may have influenced the results, as these conditions are known to affect the progression and outcomes of AVS. This imbalance could potentially confound the observed associations between NAR and AVS, making it difficult to isolate the effect of NAR from other influencing factors. Future studies should aim to match groups more closely on comorbidities or adjust for these variables in the analysis to mitigate their impact on the results (7, 17).

Moreover, while our study highlights the association between NAR and AVS, it does not establish causality. Further research is needed to elucidate the biological mechanisms underlying this relationship. Prospective studies with larger, multi-center cohorts are necessary to validate these findings and explore whether interventions targeting inflammation could modify NAR levels and impact AVS progression (21-23).

Conclusions

In conclusion, our study demonstrates that elevated NAR is significantly associated with aortic valve sclerosis and serves as an independent predictor of the condition. The ROC analysis revealed that NAR has moderate sensitivity and specificity, making it a valuable tool in the early identification of patients at risk for AVS.

Given these findings, we recommend considering the use of NAR in patients with comorbid conditions such as DM, HT, and reduced LVEF as part of a comprehensive echocardiographic evaluation for AVS. This could enhance the early diagnosis and management of AVS, particularly in high-risk populations. Further research is warranted to validate these findings and explore the potential of NAR as a routine clinical marker in cardiovascular practice.

Ethics: Patient's informed consent for all procedures was obtained. The study was performed in accordance with the Declaration of Helsinki, and was approved by the, Ankara Etlik City Hospital Clinical Research Ethics Committee (Approval Date: 22.05.2024, Approval number: AEŞH-BADEK-2024-475).

Peer-review: Internal

Conflict of interest: None to declare

Authorship: Concept – A.K and F.B., Design- A.K. and M.A., Supervision – V.O.T and F.B., Data collection and/or processing – M.A. and K.K and CT., Analysis and/or interpretation – F.B. and K.K., Writing – A.K. and CT, Critical review- V.O.T and F.B. All authors read and approved the final version of the manuscript and fulfilled authorship criteria.

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Statement on A.I.-assisted technologies use: We declare that we did not use AI-assisted technologies in preparation of this manuscript

Availability of data and material: The data that support the findings of this study are available on request from the corresponding author, (A.K.)

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