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Significance of novel hematologic inflammatory parameters in predicting aortic valve sclerosis

Aort kapak sklerozunun öngörülmesinde yeni hematolojik inflamatuar parametrelerin önemi

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Abstract

Aim: Inflammatory process plays a critical role in the progression of aortic valve sclerosis (AVS). This study aims to evaluate the haematological and biochemical inflammatory markers in AVS patients.

Methods: A retrospective observational study was included consecutive 557 patients who underwent an echocardiogram between June 2021 and September 2021. The study population was divided into two groups according to the presence of AVS. The groups were compared in terms of C-reactive protein (CRP), Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-HDL cholesterol ratio (MHR).

Results: The mean age was 63 ± 10 years. C-reactive protein (CRP), NLR, PLR and MHR were significantly higher in patients with AVS. The best cut-off values of the NLR were 1.4 (a sensitivity of 84%, a specificity of 74%), PLR was 116 (a sensitivity of 75%, a specificity of 54%), and MHR was 9.5 (a sensitivity of 78%, a specificity of 75%). CRP (OR: 1.246, 95% CI: 1.117 – 1.389; p < 0.001), NLR (OR: 2.10, 95% CI: 1.456 – 3.032; p < 0.001), and MHR (OR: 1.227, 95% CI: 1.125 – 1.339; p < 0.001) were independent predictors of the AVS when NLR and MHR analysed as a continuous variable. Using a cut off level of NLR > 1.4 (OR: 4.825, 95% CI: 2.430 – 9.583; p < 0.001) and MHR > 9.5 (OR: 13.937, 95% CI: 7.464 – 26.023; p < 0.001) were independent predictors of the AVS.

Conclusion: Increased CRP levels, NLR and MHR were found to be independent predictors for AVS. Hematological inflammatory biomarkers are cost effective and helpful approach for prediction of AVS presence.

Keywords: aortic valve sclerosis, C-reactive protein, monocyte count to high-density lipoprotein cholesterol ratio, neutrophil-to-lymphocyte ratio, platelet-to lymphocyte ratio

Öz

Giriş: İnflamatuvar süreç, aort kapak sklerozunun (AKS) ilerlemesinde kritik rol oynar. Bu çalışma, AKS hastalarında hematolojik ve biyokimyasal inflamatuar belirteçleri değerlendirmeyi amaçlamaktadır.

Yöntemler: Bu çalışma retrospektif, tek merkezli olup, Haziran 2021 ile Eylül 2021 arasında ekokardiyogram yapılan ardışık 557 hasta dahil edildi. Çalışma popülasyonu AKS varlığına göre iki gruba ayrıldı. Gruplar C-reaktif protein, Nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve monosit-HDL kolesterol oranı (MHR), değerleri açısından karşılaştırıldı.

Bulgular: Çalışmaya alınan hastaların ortalama yaşı 63 ± 10 yıl olarak bulundu. AKS izlenen hastalarda C-reaktif protein (CRP), NLR, PLR ve MHR anlamlı olarak daha yüksekti. NLR için en iyi kesme değerleri 1.4 (duyarlılık %84, özgüllük %74), PLR için 116 (duyarlılık %75, özgüllük %54) ve MHR için 9,5 (duyarlılık %78, özgüllük %75) olarak tespit edildi. CRP (OR: 1.246, %95 CI: 1.117 – 1.389; p < 0,001), NLR (OR: 2.10, %95 GA: 1.456 – 3,032; p < 0.001) ve MHR (OR: 1,227, %95 CI: 1,125 – 1,339; p < 0.001) AKS nun bağımsız öngördücüleri olarak bulundu. İlaveten veriler kategorik değişken olarak analiz edildiğinde, NLR > 1,4 değeri (OR: 4,825, %95 GA: 2,430 – 9,583; p < 0.001) ve MHR > 9,5 değeri (OR: 13,937, %95 GA: 7,464 – 26,023; p < 0,001) AKS için bağımsız öngördürücü olarak bulundu.

Sonuç: Artan CRP seviyeleri, NLR ve MHR, AKS için bağımsız öngördücüler olarak tespit edildi. Hematolojik inflamatuar biyobelirteçler, AKS varlığının öngörülmesi için uygun maliyetli ve faydalı parametreler olarak önemlidir.

Anahtar Kelimeler: aort kapak sklerozu, C-reaktif protein, monosit sayısı ile yüksek yoğunluklu lipoprotein kolesterol oranı, nötrofil-lenfosit oranı, trombosit-lenfosit oranı

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Introduction

Aortic valve sclerosis (AVS) is defined as the thickening of the aortic valve without a hemodynamically significant obstruction of the left ventricular outflow [1]. Several studies have shown that age, diabetes mellitus (DM), hypertension (HT) and hyperlipidaemia (HPL) are risk factors for AVS [2]. AVS includes multiple pathological similarities to the atherosclerotic process and the prognostic value of AVS is explained by its strong relationship to atherosclerotic risk factors [3, 4]. Numerous studies have confirmed that inflammatory process plays an important role in the beginning and progression of both coronary atherosclerotic disease and AVS [5].

It has been shown that small elevations of systemic inflammatory markers are associated with atherosclerotic arterial plaques in general populations [6]. Additionally, it has known that inflammation markers have elevated in AVS, and valve degeneration has associated with the severity of inflammation [7]. There has been strong attention to inflammatory biomarkers in atherosclerotic cardiovascular diseases since they give information about diagnostic assessment, risk stratification, and straightforward evaluation in practice clinical routine. The most common utilized inflammatory parameters involve C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to lymphocyte ratio (PLR) and monocyte count to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) [6, 8]. In this study, we aimed to evaluate haematological and biochemical inflammatory markers in patients with AVS.

Material and methods

Participants

The retrospective observational study was included consecutive 557 patients who underwent an echocardiogram between June 2021 and September 2021 admitted to our hospital cardiology outpatient clinics. AVS was defined as calcification and thickening of a trileaflet aortic valve with an aortic velocity of <2 m/sec. Patients with AF, aortic velocity ≥2 m/sec, severe valvular heart disease, bicuspid aortic valve, heart failure with reduced ejection fraction (Left ventricular ejection fractions ≤ 40%), glomerular filtration rate (GFR) ≤ 15 ml/min, history of acute rheumatic fever, connective tissue disease, cancer and missing clinical data were excluded. The study patients were divided into two groups based on the presence of AVS.

The Human Ethics Committee of our medical institution has been approved of this retrospective observational study protocol (Date: 20.04.2022, Number: E1-22-2559).

The baseline clinical and demographic characteristics for patients were obtained from the medical record. Transtoracic echocardiogram (TTE) (Philips Affiniti 50) was performed on all patients by two experienced cardiologists who had no knowledge of the clinical status of the patients. The interventricular septal thickness (IVST), left ventricular posterior wall thickness (PWT), left ventricular end-diastolic diameter (LVEDD) and ascending aorta diameter were calculated on the parasternal long-axis. Left ventricular ejection fractions (LVEF) were measured by applying biplane Simpson's method. We evaluated left ventricular diastolic dysfunction (LVDD) according to the update published by the current guidelines [9]. We assessed AVS from parasternal long, parasternal short views, and apical five chamber view. The presence of AVS was confirmed without using tissue harmonic imaging to avoid high gain settings [10]. We defined AVS as central regions of increased echogenicity and thickening of aortic valve leaflets without the restriction of motility and peak velocity of lower than 2.0 m/sec.

Peripheral blood samples were drawn to evaluate complete blood cell count, fasting blood glucose (FBG), triglyceride, low-density lipoprotein cholesterol (LDL-C), HDL-C, total cholesterol, urea, creatinine, albumin levels, total protein and CRP. Complete blood cell count was analyzed by an auto analyzer (Coulter LH 780 Haematology Analyzer, Beckman Coulter Corp., Hileh, FL) within 10-30 minutes after blood sampling and blood chemistry parameters were performed at the biochemistry laboratory of the health center. FBG, creatinine, urea, total cholesterol, HDL-C, LDL-C, triglyceride, and CRP were measured by conventional methods.

The NLR was calculated by dividing the number of neutrophils by the number of lymphocytes, the PLR was calculated by dividing the platelet count to the lymphocyte count and MHR was calculated by dividing the monocyte count to the HDL-C.

Statistical analysis

All data were examined with the SPSS 22.0 statistical software package for Windows (SPSS; IBM, Armonk, New York, USA). A Kolmogorov–Smirnov test was used for the evaluation of the normality of distribution. Continuous variables were submitted as mean ± standard deviation ıf a normal distribution or median ± interquartile ranges ıf a skewed Distribution without and categorical variables as the numeral and percentages of subject. The comparisons among the subjects were performed with a Student t test for normally distributed variables and a Mann–Whitney U test for variables without a normal distribution. Categorical variables from study population were analyzed utilization the $\chi 2$ or Fisher's exact test. Multivariate logistic regression analysis were used to evaluate the association between hematological and biochemical inflammatory markers and AVS. The ability of the NLR, PLR, MHR and CRP values to estimation the AVS were separately evaluated by a receiver operating characteristic curve and area under curve (AUC) values. The optimum cut-off values for NLR, PLR, and MHR were evaluated using the Youden index. A p-value lower 0.05 (using a two-sided test) was accepted as significant.

Results

A total of 557 patients who underwent echocardiogram constituted the study population. Baseline clinical, demographic characteristics and echocardiographic finding of the study population were presented in Table 1. The mean age was 63 ± 10 years, and male gender ratio was 48.8% in the study group patients. We divided the patients into two groups according to detection of AVS (AVS +, n= 119) or not (AVS -, n= 438). Patients with AVS had a higher prevalence of prior myocardial infarction (MI) ($p < 0.001$), previous cerebrovascular accident (CVA) ($p < 0.001$), DM ($p < .001$), HT ($p < 0.001$), HPL ($p < 0.001$), known diagnosis of heart failure ($p < 0.001$), history of peripheral arterial disease ($p < 0.001$), and known coronary artery disease ($p < 0.001$) compared to the patients without AVS. In echocardiographic findings, mean LVEF was 60% ± 2% in the patient without AVS and 55% ± 11% in the patients with AVS. Compared to the patients without AVS, LVEDD ($p = 0.001$), IVST ($p < 0.001$), PWT ($p < 0.001$), ascending aortic diameter ($p < 0.001$) were higher in the patients with AVS. There were no differences between the groups regarding aortic valve jet velocity. On the other hand, compared to the patients without AVS, patients with AVS were higher LVDD rates (Table 1).

White blood cell (WBC) counts ($p = 0.001$), monocyte counts ($p < 0.001$), neutrophil counts ($p < 0.001$), FBG ($p = 0.042$), LDL-C ($p = 0.010$), HDL-C ($p < 0.001$), total cholesterol ($p <$

0.001), urea (p < 0.001), creatinine (p < 0.001), CRP (p < 0.001), NLR (p < 0.001), PLR (p< 0.001) and MHR (p < 0.001) were significantly higher in patients with AVS as shown in Table 2.

Table 1. Baseline clinical, demographic characteristics and echocardiographic finding of the study population.

	All Group (n=557)	AVS – (n =438)	AVS + (n =119)	p-value
Age (year)	63 ± 10	62 ± 9	66 ± 11	0.002
Male, n (%)	272 (48.8)	191 (43.6)	81 (68.1)	<0.001
Prior MI, n (%)	94 (16.9)	54 (12.3)	40 (33.6)	< 0.001
Previous CVA, n (%)	36 (6.5)	16 (3.7)	20 (16.8)	< 0.001
Diabetes mellitus, n (%)	137 (24.6)	87 (19.9)	50 (42)	<0.001
Hypertension, n (%)	406 (72.9)	292 (66.7)	114 (95.8)	<0.001
Hyperlipidemia, n (%)	268 (48.2)	187 (43.1)	76 (67.9)	<0.001
Known diagnosis of heart failure, n (%)	54 (9.7)	23 (5.3)	31 (26.1)	<0.001
History of PAD, n (%)	65 (11.7)	30 (6.8)	35 (24.9)	<0.001
Known CAD, n (%)	159 (28.5)	94 (21.5)	65 (54.6)	<0.001
	Echocardiographic findings			
LVEF, %	60 ± 5	60 ± 2	55 ± 11	< 0.001
LVEDD, cm	4.6 ± 0.3	4.6 ± 0.3	4.7 ± 0.5	0.001
IVST, cm	1.2 ± 0.2	1.1 ± 0.2	1.3 ± 0.2	<0.001
PWT, cm	1.0 ± 0.1	1.0 ± 0.1	1.1 ± 0.2	<0.001
Aortic velocity, m/sec	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.4	0.245
Asc. aorta diameter	3.5 ± 0.4	3.4 ± 0.3	3.6 ± 0.4	<0.001
LVDD, n (%)	321 (57.6)	226 (51.6)	95 (79.8)	<0.001

Continuous data are expressed as percentage, mean± standard deviation, or median± interquartile ranges. Categorical data are expressed as number (percentage)
MI: Myocardial infarction; CVA: Cerebrovascular accident; PAD: Peripheral arterial disease; CAD: Coronary artery disease; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; IVST: Interventricular septal thickness; PWT: Posterior wall thickness; LVDD: Left ventricular diastolic dysfunction.

The ability of the NLR, PLR, MHR and CRP to predict AVS were evaluated by ROC curve analysis. The AUC value of this analysis is presented in Figure 1.The AUC for the NLR was 0.773 (95% confidence Interval [CI]: 0.712 – 0.834, p < 0.001), the AUC for the PLR was 0.728 (95% CI: 0.668 – 0.787, p < 0.001), the AUC for the MHR was 0.789 (95% CI: 0.747 –0.830, p < 0.001) and the AUC for the CRP was 0.640 (95% CI: 0.580 – 0.699, p < 0.001). According to the Youden index for predicting of AVS, the best cut-off values of the NLR was 1.4 (with a sensitivity of 84%, a specificity of 74%), PLR was 116 (with a sensitivity of 75%, a specificity of 54%), and MHR was 9.5 (with a sensitivity of 78%, a specificity of 75%) (Figure 1).

The presence of DM (odds ratio [OR]: 2.142, 95% CI: 1.117 – 4.108; p = 0.022), HT (OR: 8.365, 95% CI: 2.353 – 29.736; p = 0.001), HPL (OR: 3.114, 95% CI: 1.612 – 6.016; p = 0.001) and CRP (OR: 1.246, 95% CI: 1.117 – 1.389; p < 0.001), NLR (OR: 2.10, 95% CI: 1.456 – 3.032; p < 0.001), and MHR (OR: 1.227, 95% CI: 1.125 – 1.339; p < 0.001) were independent predictors of the AVS when NLR and MHR analysed as a continuous variable (Model 1). Using a cut off level of NLR > 1.4 (OR: 4.825, 95% CI: 2.430 – 9.583; p < 0.001) and MHR > 9.5 (OR: 13.937, 95% CI: 7.464 – 26.023; p < 0.001) were independent predictors of the AVS (Model 2) (Table 3).

Table 2. Laboratory findings of the patients with aortic value sclerosis (AVS) and the patients without AVS.

	All Group (n=557)	AVS – (n =438)	AVS + (n =119)	p-value
WBC (x10³/ µL)	7.0 ± 2.2	6.8 ± 1.8	7.3 ± 2.7	0.001
Monocyte (x10³/ µL)	0.4 ± 0.1	0.3 ± 0.1	0.4 ± 0.2	<0.001
Neutrophil (x10³/ µL)	4.1 ± 1.5	3.9 ± 1.3	5.1 ± 2.9	<0.001
Lymphocyte (x10³/ µL)	2.1 ± 1.0	2.1 ± 0.8	1.5 ± 1.0	<0.001
Platelet (x10³/ µL)	259 ± 78	260 ± 80	249 ± 66	0.578
Hemoglobin (mg/dL)	13.8 ± 1.5	13.8 ± 1.4	14.1 ± 2.4	0.401
FBG (mg/dL)	98 ± 20	98 ± 20	97 ± 28	0.042
Triglycerides (mg/dL)	143 ± 105	151 ± 106	132 ± 105	0.631
LDL-C (mg/dL)	124 ± 47	125 ± 49	107 ± 41	0.010
HDL-C (mg/dL)	46 ± 15	48 ± 15	38 ± 11	<0.001
Total cholesterol (mg/dL)	201 ± 45	204 ± 45	189 ± 43	<0.001
Urea (mg/dL)	33 ± 12	32 ± 11	37 ± 13	<0.001
Creatinine (mg/dL)	0.8 ± 0.3	0.8 ± 0.2	0.9 ± 0.3	<0.001
Albumin (g/dL)	44 ± 3	44 ± 3	44 ± 5	0.011
Total Protein (g/dL)	69 ± 4	69 ± 5	68 ± 7	0.002
C-reactive protein (mg/L)	6 ± 4	5 ± 4	7 ± 4	<0.001
NLR	1.8 ± 1.0	1.75 ± 0.7	3.25 ± 4.1	<0.001
PLR	120 ± 64	114 ± 54	164 ± 120	<0.001
MHR	7.9 ± 3.7	7.3 ± 3.4	10.9 ± 3.7	<0.001

WBC: White blood cell; FBG: Fasting Blood Glucose; LDL-C: low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to lymphocyte ratio; MHR: Monocyte count to high-density lipoprotein cholesterol ratio.
Continuous data are expressed as percentage, mean ± standard deviation, or median ± interquartile ranges.

Table 3. The independent predictors of aortic value sclerosis (AVS) in multivariate analysis.

	OR (95% CI)	p value
MODEL 1		
Diabetes	2.142 (1.117 – 4.108)	0.022
Hypertension	8.365 (2.353 – 29.736)	0.001
Hyperlipidemia	3.114 (1.612 – 6.016)	0.001
CRP	1.246 (1.117 – 1.389)	<0.001
NLR	2.101 (1.456 – 3.032)	<0.001
PLR	1.004 (0.996 – 1.012)	0.309
MHR	1.227 (1.125 – 1.339)	<0.001
MODEL 2		
Diabetes	1.865 (0.999 – 3.480)	0.050
Hypertension	8.054 (2.900 – 22.367)	<0.001
Hyperlipidemia	3.678 (2.001 – 6.761)	<0.001
CRP	1.233 (1.113 – 1.365)	<0.001
NLR >1,4	4.825 (2.430 – 9.583)	<0.001
PLR >116	0.782 (0.342 – 1.788)	0.560
MHR >9,5	13.937 (7.464 – 26.023)	<0.001

CRP: C-Reactive Protein; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to lymphocyte ratio; MHR: Monocyte count to high-density lipoprotein cholesterol ratio.

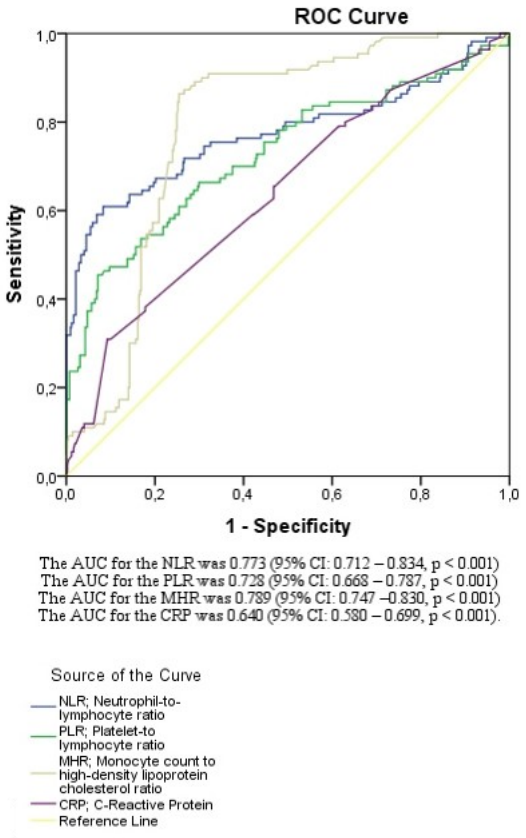

Figure 1. The receiver-operating characteristic curve analysis of the neutrophil-to-lymphocyte ratio (NLR), platelet-to lymphocyte ratio (PLR), monocyte count to high-density lipoprotein cholesterol ratio (MHR) and C-reactive protein (CRP) for predicting AVS.

Discussion

The major results of our report involve that (1) there are higher inflammatory markers in patients with AVS and (2) CRP, NLR and MHR are significant and independent predictors of AVS. This is the first study evaluation the inflammatory condition and haematological and biochemical paramarkers in patients with AVS.

AVS is closely connected with atherosclerosis. AVS has prognostic significance due to its close relationship with atherosclerotic heart diseases. In this study, patients with AVS were higher atherosclerosis risk factors such as CVA, DM, HT, HPL, and peripheral arterial disease compared to in patients without AVS. Previous studies have been suggested that AVS may be a "window" on coronary arteries, which could aid identifying patients in the pre-clinical stage of the disease [11]. It was not surprising that patients with AVS had a higher ratio of prior MI, previous CVA, and known coronary artery disease in this study.

AVS has been shown to resemble atherosclerosis in many ways: AVS has been associated with well-known traditional atherosclerosis risk factors; it shares similar inflammatory pathways with atherosclerosis [3]. As in atherosclerosis, the pathophysiology of AVS includes inflammation, blood pressure, fluid shear stress, high blood lipid and cholesterol levels, fibrosis, and calcification [12]. Increased mechanical stress and decreased shear stress cause valve endothelial dysfunction, lipid penetration and inflammation [13]. Inflammatory cells including neutrophils, monocytes and lymphocytes accumulate in the damaged tissue, produce numerous pro-inflammatory cytokines and cause degenerative processes resulting in fibrosis and calcification [14, 15]. NLR, PLR, and MHR have been indicated as possible markers to identify inflammation in cardiac and non-cardiac disorders [16, 17]. In additional, it has been reported CRP has been stored and localized together with LDL-C and macrophages in atherosclerotic plaque [18]. Our finding has shown that hematologic inflammatory markers such as NLR, PLR, MHR, and CRP were significantly higher in the patients with AVS compared to the patients without AVS. On the other hand, multivariate analysis showed that aortic valve sclerosis was independently associated with CRP, NLR and MHR levels whereas PLR was not independent predictors of aortic valve sclerosis.

Hematologic parameters can be used to predict progression and establish the clinical significance in AVS patients. In addition, hematologic parameters are low-cost and practically measurable laboratory factors in clinical practice.

NLR is simply measured by dividing neutrophil to lymphocyte in a complete blood count. It has been known that it is one of the best evaluated haematological biomarkers, which provides prognostic information in atherosclerotic events. Therefore, its importance in cardiovascular diseases has been investigated widely in recent years [19]. The combination of neutrophil and lymphocyte counts has a stronger prognostic significance than each theirs separately [20]. Recently, it has been shown that both patients with severe aortic stenosis and patients with severe mitral stenosis had an elevated NLR compared to patients with moderate and mild aortic or mitral stenosis [21]. In this study, NLR was significantly higher in patients with AVS and NLR was an independent predictor of aortic valve sclerosis.

PLR is calculated by dividing the platelet count to the lymphocyte count. PLR is a significant marker of two diverse inflammatory pathways simply calculated from a complete blood count [19]. PLR has been shown as an important marker in various cardiovascular diseases such as stable coronary artery disease, acute coronary syndrome, heart failure and valvular heart diseases [22]. Platelets and lymphocytes trigger the secretion of acute phase proteins that task as inflammation mediators [23]. It has been reported that PLR was strongly correlated with a transaortic mean pressure gradient in patients with aortic stenosis, and higher PLR was closely related to the severity of calcific aortic stenosis [24]. In our finding, PLR was a higher in patients with AVS. However, PLR was not reached statistical significance in multivariate regression analysis.

In recent studies, it has shown that the MHR is a significant indicator in cardiovascular diseases [25]. It has been reported that MHR with its strong correlation with CRP, also a predictor of atherosclerotic progress and worse outcomes in cardiovascular disease associated with inflammatory condition [17]. However, to our knowledge, no information is available on the relationship between MHR and AVS. In this study, MHR was significantly higher in patients with AVS and MHR was reached statistical significance in multivariate regression analysis. MHR, both continuous variable and categorical variable, was established to be a significant predictor of AVS.

Jeevanantham et al. [26] shown that CRP levels were significantly associated with the early stage of aortic valve disease. It was reported that the patients with rapid aortic stenosis progression were elevated CRP levels compared to patients with slow aortic stenosis progression [15]. On the contrary, some studies also have shown a weak relationship between CRP and aortic sclerosis [27]. In this study, CRP was significantly higher in patients with AVS, and CRP was a significant predictor of aortic valve sclerosis.

Our findings are similar to other studies showing that other significant predictors, such as DM, HT and HPL in particular, is also associated with AVS [2, 10].

This study has several limitations. The small number of patients limited the power of the study. All the data were based on a single measurement. We did not grade aortic valve calcification based on echocardiography. AVS was not evaluated quantitatively.

In conclusion, it is important that recent studies confirmed AVS as a marker for increased cardiovascular risk and increased cardiac adverse events [28]. Our study showed that haematological inflammatory biomarkers were elevated in patients with AVS. In addition, increased NLR, MHR and CRP levels were found to be independent predictors for AVS in our study. We believe that our findings are valuable like novel researchs' about AVS. Because using haematological inflammatory biomarkers is cost effective and helpful approach for prediction of AVS presence. Further studies with prospective design including larger patient populations are needed to substantiate these findings.

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