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Higher neutrophil to lymphocyte ratio is related to a lower ejection fraction in bicuspid aortic valve patients

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Background/aim: Inflammation plays an important role in the pathophysiology of vascular disease. In this study, we aimed to evaluate the associations of neutrophil to lymphocyte ratio (NLR; an indicator of inflammation) with left ventricular ejection fraction and ascending aorta diameter in patients with a bicuspid aortic valve (BAV).

Materials and methods: One hundred and thirty-nine consecutive patients with the diagnosis of BAV were enrolled in the study. Complete blood counts were analyzed for neutrophil and lymphocyte levels and NLR. The subjects were separated into two groups based on their ascending aorta diameter. The patients with ascending aorta diameter equal to or above 3.9 cm were included in group 1 whereas those with ascending aorta diameter below 3.9 cm were included in group 2.

Results: When the results were compared, it was demonstrated that there was a positive correlation between NLR and ascending aorta diameter (r: 0.485, P = 0.026), whereas there was a negative correlation between NLR and left ventricular end-diastolic diameter (r: 0.475, P = 0.030), left ventricular end-systolic diameter (r: 0.482, P = 0.027), and left ventricular ejection fraction (r: –0.467, P = 0.033) in BAV patients with ascending aorta dilatation (group 1).

Conclusion: NLR is associated with ascending aorta diameter and left ventricular ejection fraction in BAV patients with ascending aorta dilatation.

Key words: Bicuspid aortic valve, ascending aorta dilatation, left ventricular ejection fraction, neutrophil to lymphocyte ratio

1. Introduction

Bicuspid aortic valve (BAV) is the most commonly encountered congenital cardiac malformation in clinical practice. Aortic valve dysfunction, aortic dissection, infective endocarditis, and ascending aorta dilatation (AAD) are clinically important complications that are usually related to BAV (1). AAD is particularly troubling because it is included in the mechanism of aortic regurgitation in BAV (2) and it increases aortic stiffness (3) and the risk of aortic dissection (4), which often leads to the need for prophylactic aortic surgery (5). The mechanisms responsible for aortic dilatation have been discussed for years; probable reasons include anomalous blood flow in the ascending aorta produced by the anomalous dynamics of BAV (6,7) and genetic causes responsible for the anomalous structure of the aortic media (8,9). However, to date, the physiopathology of AAD in BAV patients is not completely understood, which suggests that other mechanisms could be involved.

Aortic valve dysfunction is the most common complication observed in BAV patients. If not treated it can cause progressive left ventricular (LV) dysfunction and influence the prognosis of BAV patients. However, LV systolic and diastolic functions were shown to be impaired in BAV patients without significant aortic valve dysfunction. The mechanism of this could not be elicited to date as well.

The neutrophil to lymphocyte ratio (NLR) is a novel marker of inflammation and its presence at high levels has been implicated in the pathogenesis of various clinical conditions. Thus, the aim of the present study was to analyze the potential role of NLR on the left ventricular ejection fraction (LVEF) and ascending aorta diameter in patients with BAV.

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2. Materials and methods

2.1. Selection of patients

We enrolled 139 consecutive patients who underwent transthoracic echocardiography and who were diagnosed with BAV between January 2014 and December 2014 in this study. Demographic data and clinical history including age, sex, body mass index, hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, and smoking were obtained. Subjects with a history of coronary artery disease, anemia, chronic systemic inflammatory disease, active infection, and hepatic, renal, and thyroid dysfunction were excluded from the study. The study protocol was approved by the Clinical Ethics Committee of Atatürk Education and Research Hospital and written informed consent was obtained from each patient.

2.2. Echocardiographic measurements

The echocardiographic examinations were carried out using a 2.5- to 3.5-MHz transducer with the Vingmed System 7 (Vivid 7, GE, Horten, Norway) by an experienced cardiologist. The absolute diagnosis of BAV was reached when fusion of two aortic leaflets, with or without raphe, was clearly visualized on the parasternal short-axis view of a transthoracic echocardiogram (10). In the case of suspicion, a transesophageal echocardiogram was performed according to the clinical criteria (10). After the diagnosis of BAV was definite, a blood sample was obtained from all of the patients and analyzed. Dilatation of the ascending aorta was diagnosed when the corresponding diameter was ≥39 mm with M-mode echocardiography. M-mode echocardiography was conducted using parasternal long-axis images according to data provided by the American Society of Echocardiography (11). The LV end-diastolic diameter (LVEDD) and LV end-systolic diameter (LVESD), left atrium (LA) and ascending aorta diameters, interventricular septum (IVS), and posterior wall (PoW) thicknesses were obtained using the M-mode echocardiographic tracings under the guide of 2D imaging. The LVEF was calculated according to the biplane modified Simpson method. Patients were separated into two groups based on their ascending aorta diameter. Group 1 included the patients with ascending aorta diameter of ≥3.9 cm whereas group 2 included the patients with ascending aorta diameter of <3.9 cm.

2.3. Laboratory analysis

After a 12-h overnight fast, blood samples were drawn into plain Vacutainer tubes from the antecubital veins of the subjects. All biochemical analysis, including glucose, creatinine, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) concentrations, were performed with an oxidase-based technique in the central biochemistry laboratory of the Atatürk Education and Research Hospital. Complete blood counts with automated differential counts, which included total white blood cells (WBCs), neutrophils, lymphocytes and platelets, hemoglobin (Hb), red cell distribution width (RDW), and mean platelet volume (MPV), were obtained at the time of admission. The NLRs were calculated as the ratio of the neutrophil and lymphocyte counts.

2.4. Statistical analysis

All statistical analyses were performed using SPSS 17 (SPSS, Chicago, IL, USA). We reported continuous data as means and standard deviations or medians. We compared continuous variables using the Student t-test or Mann–Whitney U test between groups. Categorical variables were summarized as percentages and compared with the chi-square test. Pearson correlation coefficients were used to examine the degree of association between examined variables. $P < 0.05$ was considered statistically significant.

3. Results

A total of 21 BAV patients with AAD (group 1) (90% male, mean age: 47.8 ± 12.4 years) and 118 BAV patients without AAD (group 2) (66% male, mean age: 39.3 ± 12.4 years) were included in our study. The baseline demographic and clinical characteristics of the patients are presented in Table 1. In group 1, most of the patients were men and their mean age was significantly higher compared with group 2 (47.8 ± 12.4 vs. 39.3 ± 12.4 years, respectively, $P = 0.05$). There were significant differences in sex between group 1 and group 2 ($P = 0.025$). Demographic characteristics including body mass index, incidence of hypertension, diabetes mellitus, hyperlipidemia, and smoking status were similar between the groups. When we compared the lipid profile of the subjects, LDL-C levels were significantly higher in patients with AAD than in patients without it (126.6 ± 45.5 vs. 106.3 ± 35.3 mg/dL, respectively, $P = 0.033$). On the other hand, the levels of TC, HDL-C, and TG were similar between the groups.

The comparison of hematological parameters is summarized in Table 2. According to these results, WBC, neutrophil, lymphocyte, and platelet counts and MPV, RDW, and Hb levels were similar between groups. In addition, NLR was similar in patients with and without AAD (2.16 ± 0.8 vs. 2.34 ± 1.47, respectively, $P = 0.599$).

Echocardiographic parameters of the study subjects are demonstrated in Table 3. There was no significant difference between group 1 and 2 in terms of LVEDD, LVESD, IVS, PoW thicknesses, and LA diameter. The mean ascending aorta diameter was 4.13 ± 0.28 cm (range: 3.9–5.0 cm) in group 1, whereas it was 3.30 ± 0.32 cm (range: 2.4–3.8 cm) in group 2 and this difference was statistically significant ($P < 0.001$). In group 1, only 6 (28.6%) patients had moderate to severe aortic regurgitation (AR), whereas in group 2, the number of patients with moderate to severe AR was 27 (22.8%). Moreover, the number of occurrences

Table 1. Demographic and clinical features of the subjects.

Variables	Group 1 (n = 21)	Group 2 (n = 118)	P-value
Age (years)	47.8 ± 12.4	39.3 ± 12.4	0.050
Sex (M/F)	19/2	78/40	0.025
BMI (kg/m^2)	22.3 ±5.4	21.7 ± 4.4	0.646
Smoking rate (%)	23	26	0.493
Hypertension (%)	12	13	0.975
Diabetes mellitus (%)	14	15	0.871
Hyperlipidemia (%)	48	54	0.576
TC (mg/dL)	198.4 ± 35.4	185.7 ± 45.2	0.251
LDL Cholesterol (mg/dL)	126.6 ± 45.5	106.3 ± 35.9	0.033
HDL Cholesterol (mg/dL)	51.05 ± 11.1	49.7 ± 16.07	0.731
TG (mg/dL)	122.8 ± 57.5	139.7 ± 98.2	0.451

M/F: Male/female; BMI: body mass index; TC: total cholesterol; LDL: low-density lipoprotein; HDL: high-density lipoprotein; TG: triglyceride.

Table 2. Hematological parameters of the subjects.

Parameters	Group 1 (n = 21)	Group 2 (n = 118)	P-value
WBCs	6912 ± 1670	8155 ± 2572	0.346
Neutrophils	4190 ± 1330	5001 ± 2155	0.098
Lymphocytes	2040 ± 592	2373 ± 796	0.070
NLR	2.16 ± 0.8	2.34 ± 1.47	0.599
Hemoglobin (g/dL)	14.1 ± 1.8	14.3 ± 1.9	0.622
MPV	10.9 ± 1.0	11.2 ± 7.7	0.857
Platelets	248.340	260.788	0.513
RDW	15.2 ± 6.4	15.7 ± 8.3	0.796

WBC: White blood cell; NLR: neutrophil to lymphocyte ratio; Hb: hemoglobin, MPV: mean platelet volume; RDW: red cell distribution width.

of moderate to severe aortic stenosis (AS) in the AAD group was 1 (4.8%), whereas it was 22 (18.6%) in group 2. When we compared the LVEF between the groups, it was found that in patients with AAD, LVEF was significantly lower than in patients without AAD (55.0 ± 16.9% vs. 63.7 ± 3.2%, respectively, P < 0.001).

The correlation of NLR with demographic and clinical characteristics and the echocardiographic parameters of both groups are shown in Table 4. According to these results, there was a positive correlation between NLR and age (r: 0.478, P = 0.028), LVEDD (r: 0.475, P = 0.030), LVESD (r: 0.482, P = 0.027), and ascending aorta diameter (r: 0.485, P = 0.026), whereas there was a negative correlation between NLR and LVEF (r: –0.467, P = 0.033) in patients with AAD. However, there were no significant correlations between the given variables and NLR in group 2.

4. Discussion

The main finding of the present study was that higher NLR is independently correlated with lower LVEF in BAV patients with AAD. In addition, NLR was correlated with the diameter of ascending aorta and LVEDD and LVESD in

Table 3. Echocardiographic parameters of the patients.

Variables	Group 1 (n = 21)	Group 2 (n = 118)	P-value
LVEDD (mm)	51.6 ± 6.3	46.5 ± 4.1	0.154
LVESD (mm)	34.6 ± 8.4	28.4 ± 4.7	0.214
IVS (mm)	1.11 ± 0.22	1.0 ± 0.16	0.127
PoW (mm)	1.09 ± 0.18	1.0 ± 0.13	0.136
LA (mm)	3.5 ± 0.45	3.4 ± 0.43	0.457
LVEF (%)	55.0 ± 16.9	63.7 ± 3.2	<0.001
AAD (cm)	4.13 ± 0.28	3.30 ± 0.32	<0.001
Degree of aortic stenosis (%)			NS
Absent	76.2	49.2	
Mild	19.0	32.2	
Moderate	4.8	11.0	
Severe	0	7.6	
Degree of aortic regurgitation (%)			NS
Absent	23.8	28.0	
Mild	47.6	49.2	
Moderate	28.6	21.2	
Severe	0	1.7	

LVEDD: Left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; IVS: interventricular septum thickness; PoW: posterior wall thickness; LA: left atrium diameter; LVEF: left ventricular ejection fraction, AAD: ascending aorta diameter; NS: nonsignificant.

Table 4. Correlation of NLR with echocardiographic and other parameters of patients.

Variables	Group 1 (n = 21) Coefficient (P-value)	Group 2 (n = 118) Coefficient (P-value)
Age	0.478 (0.028)	–0.073 (0.430)
Sex	0.061 (0.793)	0.079 (0.396)
BMI	0.106 (0.672)	0.201 (0.542)
Total cholesterol	–0.354 (0.137)	–0.111 (0.281)
LDL cholesterol	–0.335(0.161)	–0.021 (0.837)
HDL cholesterol	0.112 (0.648)	–0.180 (0.078)
Triglyceride	–0.083 (0.737)	–0.022 (0.828)
LVEDD	0.475 (0.030)	–0.092 (0.320)
LVESD	0.482 (0.027)	–0.080 (0.390)
IVS	0.292 (0.200)	0.105 (0.257)
PW	0.302 (0.183)	0.048 (0.604)
LA	0.220 (0.338)	0.059 (0.525)
LVEF	–0.467 (0.033)	–0.029 (0.759)
AAD	0.485 (0.026)	–0.010 (0.912)

BMI: Body mass index; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; IVS: interventricular septum thickness; PW: posterior wall thickness; LA: left atrium diameter; LVEF: left ventricular ejection fraction; AAD: ascending aorta diameter.

this patient group. To the best of our knowledge, this study is the first to evaluate the association between NLR and LVEF and diameter of ascending aorta in patients with BAV.

BAV is the most common congenital heart defect (12), affecting 1.3% of the population (13). Patients with a BAV constitute a heterogeneous population with variable clinical presentation and complications. They may be completely asymptomatic, but about 30% of individuals with a BAV develop complications (14). The most common complication of BAV is valve dysfunction (15,16). However, BAV has also been suggested to cause aortopathy (17–19). Proximal thoracic aorta dilatation is not an unusual finding in BAV patients and is thought to be associated with aortic dissection and rupture. Aortic size is an important factor for the future risk of dissection, rupture, and death (20). Earlier intervention for asymptomatic aortic dilatation has been recommended because of the increased risk of aortic complications in patients with BAV (20). However, although AAD is responsible for the most critical complications, not all patients with BAV are at high risk for rupture and dissection. To identify the patients at high risk of these aforementioned complications as early as possible, additional criteria are required. In some studies (21–23) it was determined that there is an association between advancing age and aortic dimensions. Age, by itself, is not an independent factor for increased aortic size because children with BAV constitute a significant number of cases with dilatation of proximal thoracic aorta (23–25). However, significant correlation of age with the extension and grade of aortic dilatation was demonstrated in another study (23). This is consistent with the fact that hemodynamic tension on the aortic wall, together with medial abnormalities observed in BAV patients, may play an important role in determining aortic dilatation.

Left coronary artery dominance is more common in subjects with BAV (29% to 56.8%) and in 90% of cases, the left main coronary artery is <5 mm in length (26,27). These abnormalities may contribute to an inadequate myocardial blood supply and an increased risk of myocardial infarction (28,29). Demir (30) reported the association of BAV with impaired LV systolic function even in patients without significant valvular dysfunction. In addition, Santarpia et al. (31) demonstrated that the LV longitudinal circumferential and radial strain were lower in subjects with BAV. However, the impact of inflammation on LV systolic functions has not been reviewed in BAV patients until now.

In the past, the role of inflammatory markers was comprehensively studied in cardiovascular diseases and a sustained association between diverse inflammatory markers and cardiovascular diseases was established. NLR has newly emerged and participates in a vast number of these inflammatory markers. NLR is calculated from complete blood count and it is a cheap, easily obtainable, and widely available marker of inflammation. It can be used in the risk stratification of patients with various cardiovascular diseases together with the traditionally used markers. In this study, our main aim was to investigate whether NLR provides any prognostic value in patients with BAV. Inflammation plays a key role in all phases of the atherosclerotic process. With the incremental understanding of the role of inflammation in the atherosclerotic process, studies have focused on inflammatory markers in the assessment of cardiovascular risk (32). NLR is a measure of the balance between neutrophil and lymphocyte levels in the body and is an indicator of systemic inflammation (33,34). Activated neutrophils release various proteolytic enzymes such as myeloperoxidase, which are responsible for tissue injury (35). Therefore, we speculated that higher NLR may be associated with ascending aorta diameter in patients with BAV. Our main finding, which we have demonstrated, to our knowledge, for the first time here, is that higher NLR is associated with LVEF and ascending aorta diameter evaluated with the help of transthoracic echocardiography in BAV patients with AAD. This association might also be related to impaired epicardial and microvascular perfusion due to rheological changes related to absolute and relative neutrophilia (36,37), which might be linked to proinflammatory cytokine release and lack of cytoskeletal flexibility (38).

The major limitation of the present study is the relatively small number of BAV patients with AAD. However, our study patients included homogeneous, unselected patients who were recruited consecutively. Therefore, our results can reflect real world data but larger-scale studies are required to confirm these results.

In conclusion, the NLR is related to LVEF and ascending aorta diameter in BAV patients with AAD. NLR is an inexpensive and immediately available novel biomarker of inflammation that can help in identifying BAV patients at risk for lower ejection fraction and AAD.

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