Red cell distribution width is increased in patients with ascending aortic dilatation

Çıkan aort genişlemesi olan hastalarda artmış kırmızı kan hücre dağılım aralığı

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ABSTRACT

Objectives: The prognostic importance of red cell distribution width (RDW) and neutrophil/lymphocyte ratio (NLR) in cardiovascular diseases has been shown. Ascending aortic dilatation (AAD) is a common cardiovascular disease and is associated with aortic wall inflammation and cystic degeneration. In this study, we aimed to investigate the relationship between serum levels of RDW, NLR and the presence of AAD.

Study design: Two-hundred consecutive patients with AAD diagnosed by transthoracic echocardiography were prospectively recruited and were compared to 170 age-gender-matched subjects with normal aortic diameters. Complete blood counts (CBCs) were analyzed for hemoglobin, RDW and NLR counts, as well as mean corpuscular volume (MCV). If possible, results of CBC tests within the previous two years were also included and the averages were used.

Results: RDW [median 13.9, interquartile range (IQR) 1.40 *vs.* median 13.3, IQR 1.05%, p=0.01], NLR (median 2.04, IQR 1.09 *vs.* median 1.78, IQR 0.90, p=0.01) and high-sensitive C-reactive protein (hs-CRP) (median 0.60, IQR 0.80 *vs.* median 0.44, IQR 0.68 mg/L, p=0.01) levels were significantly higher in the AAD group compared to the control group. In univariate correlation analysis, ascending aortic diameters were correlated with RDW levels (r=0.31, p=0.01), NLR levels (r=0.15, p=0.01) and hs-CRP levels (r=0.12, p=0.03). In multivariate logistic regression analysis, increased levels of RDW and hs-CRP remained as the independent correlates of AAD in the study population. Receiver operating characteristic (ROC) curve analysis revealed that a RDW measurement higher than >13.8% predicted AAD with a sensitivity of 49.5% and a specificity of 82.8% (area under the curve [AUC] 0.681, p=0.01).

Conclusion: In patients with AAD, RDW and hs-CRP levels are increased, which may indicate the role of inflammation in the pathogenesis of AAD.

ÖZET

Amaç: Kırmızı hücre dağılım genişliği (KHDG) ve nötrofil lenfosit oranı (NLO) ölçümlerinin kardiyovasküler hastalıklarda prognostik önemi olduğu gösterilmiştir. Çıkan aort genişlemesi (ÇAG) aort duvarında enflamasyon ve kistik dejenerasyonla seyreden ve sık görülen kardiyovasküler bir hastalıktır. Bu çalışmada, ÇAG olan hastalarda KHDC ve NLO değerlerini araştırmayı hedefledik.

Çalışma planı: Transtrorasik ekokardiyografide ÇAG saptanan 200 hasta ileriye dönük olarak çalışmaya alındı ve çıkan aort çapı normal olan, yaş ve cinsiyet dağılımı benzer 170 bireyle karşılaştırıldı. KHDG, NLO ve ortalama eritrosit hacmi ölçümü için tam kan sayımı (TKS) yapıldı. Geçmiş iki yıl içindeki TKS sonuçları da toplanarak analizlerde ortalama değerler kullanıldı.

Bulgular: Çıkan aort genişlemesi olan grupta, KHDG (ortanca 13.9, çeyreklerarası aralık [IQR] 1.40 ve ortanca 13.3, IQR %1.05; p=0.01), NLO (ortanca 2.04, IQR 1.09 ve ortanca 1.78, IQR 0.90; p=0.01) ve yüksek duyarlıklı C-reaktif protein (hs-CRP) ölçümleri (ortanca 0.60, IQR 0.80 ve ortanca 0.44, IQR 0.68 mg/L; p=0.01) kontrol grubuna göre istatistiksel olarak anlamlı şekilde daha yüksekti. Tekli korelasyon analizinde, çıkan aort çapı ile KHDG (r=0.31, p=0.01), NLO (r=0.15, p=0.01) ve hs-CRP (r=0.12, p=0.03) seviyeleri arasında korelasyon saptandı. Çoklu regresyon analizinde ise KHDG ve hs-CRP yüksekliği, ÇAG varlığının bağımsız bir belirteci olarak saptandı. Receiver operating characteristic (ROC) analizinde KHDG için >%13.8 sınır değerinin, ÇAG tanısı için %49.5 duyarlılık ve %82.8 özgüllüğe sahip olduğu bulundu (EAA 0.681, p=0.01).

Sonuç: Çıkan aort genişlemesi olan hastalarda, KHDG ve hs-CRP yükselmiştir. Bu değerler, AAD patogenezinde enflamasyonun rolü olabileceğini göstermektedir.

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Ascending aortic dilatation (AAD) is a common problem in clinical practice. The etiology is usually multi-factorial with both genetic and environmental factors playing a role in disease progression.[1] In patients with AAD, the aortic wall is weakened by cystic media degeneration, which is associated with degradation of elastic fibers and smooth muscle cell apoptosis.[2] Inflammatory markers such as C-reactive protein (CRP) and interleukin (IL)-6 are increased in patients with thoracic aortic aneurysms, and increased activity of matrix metalloproteinases (MMPs) has been described in the media of thoracic aortic aneurysm, which result in aortic wall weakening.[3-5]

Red cell distribution width (RDW) and neutrophil/lymphocyte ratio (NLR) are readily available laboratory parameters that are routinely reported in complete blood count (CBC) tests. The prognostic importance of these parameters has been shown in cardiovascular diseases such as heart failure, coronary artery disease, stroke, and nonvalvular atrial fibrillation.[6-14] The correlation of RDW and NLR with inflammatory markers has revealed these parameters to be indicators of chronic inflammation in disease progression, with increased levels resulting in worse outcome.[7]

The association of plasma levels of RDW and NLR with AAD has not been established yet. In this study, we aimed to investigate the relationship between these parameters and presence of AAD in the Turkish population.

PATIENTS AND METHODS

Patient selection

We prospectively recruited consecutive patients who underwent transthoracic echocardiographic examination and were diagnosed to have AAD between January 2012 and June 2013. During this period, a total of 12,250 patients were examined in our laboratory. Demographic data and clinical history concerning age, sex, hypertension, diabetes mellitus, coronary artery disease, hyperlipidemia, and smoking were obtained from patients with AAD. Hypertension was defined as a systolic pressure >140 mmHg and/or a diastolic pressure >90 mmHg, or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as a fasting glucose level >126 mg/dl and/or if the patient was taking anti-diabetic medication. Individuals who reported smoking at least one cigarette per day during the year before examination were classified as smokers. Body mass index (BMI) was calculated as weight (kg) / height (m^2), and body surface area (BSA) was calculated as ([height(cm) x weight (kg)]/3600)½. Exclusion criteria were presence of connective tissue disease associated with dilatation of the ascending aorta, congenital heart disease (including bicuspid aortic valve), renal insufficiency, chronic inflammatory disease, or unavailable medical records. The control group included subjects with demographic characteristics similar to those of the study group but with normal ascending aortic diameters. The study was approved by the local ethics committee, and all patients signed an informed consent form to participate in the study.

Abbreviations:

AAD	*Ascending aortic dilatation*
BMI	*Body mass index*
CBC	*Complete blood count*
CI	*Confidence interval*
CRP	*C-reactive protein*
IL	*Interleukin*
IQR	*Interquartile range*
MCV	*Mean corpuscular volume*
MMPs	*Matrix metalloproteinases*
MPV	*Mean platelet volume*
NLR	*Neutrophil/lymphocyte*
RDW	*Red cell distribution width*
ROC	*Receiver operating characteristic*
WBC	*White blood cell count*

Echocardiography

Subjects with AAD were re-examined with transthoracic echocardiography by an independent investigator who was blinded to the clinical and laboratory data of the study participants. A Vivid 7 echocardiography device (General Electric, Waukesha, WI, USA) equipped with a middle range frequency (3-8 MHz) broadband transducer was used. Two-dimensional measurements were performed in the parasternal long-axis view with the patient in the left lateral position. The left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's rule in two- and four-chamber apical views. Two-dimensional measurements of the aortic root were made at end-diastole in the parasternal long-axis views using the leading edge to leading edge technique in the views showing the largest aortic diameters at three levels as: (1) annulus, (2) sinus of Valsalva and (3) proximal ascending aorta.

Ascending aortic dilatation was determined on demonstration of aortic enlargement relative to the expected aortic diameter based on age- and body size-adjusted nomograms as recommended by the American Heart Association (AHA) guidelines.[15] Subjects

whose ascending aortic diameters were within the normal limits according to the age- and body size- adjusted nomograms served as the control group.

Collection of blood samples

Fasting blood samples were drawn by antecubital vein puncture into EDTA-treated or plain tubes according to hospital protocol. CBC testing utilized clinical laboratory methods (Coulter LH 780 Hematology Analyzer, Beckman Coulter Ireland Inc; Mervue, Galway, Ireland) for hemoglobin, RDW, total white blood cell count (WBC), mean corpuscular volume (MCV), platelet count, and mean platelet volume (MPV). High-sensitive (hs)-CRP measurements were conducted by a Cobas Integra analyzer (Roche Diagnostics, Turkey) using the turbidimetric method. The reference range for RDW was between 11.6-14.8% and for hs-CRP was <0.5 mg/L. Baseline NLR was measured by dividing neutrophil count by lymphocyte count. Laboratory results including hemoglobin <13 g/dL for men and <12 g/dL for women, WBC count >12,000 cells per µL or <4,000 cells per µL, and hs-CRP >10 mg/L were ignored, and the laboratory tests were repeated within a month. In addition, we obtained the laboratory results from the previous years and used the average measurements for hemoglobin, RDW, WBC, platelet count, MPV, and NLR (maximum 2 measurements on different occasions were collected). In 70 patients, the average of three measurements, and in 122 patients, the average of two measurements was collected. In 178 patients, only one CBC measurement could be analyzed. To examine the consistency of measurements for RDW and NLR, intraclass correlation coefficients were calculated, which were 0.85 [95% confidence interval (CI) 0.81-0.89] for RDW and 0.38 (95% CI 0.15-0.55) for NLR.

Table 1. Clinical and demographic characteristics of patients with ascending aortic dilatation and controls

	AAD (n=200)	Control (n=170)	*p*
Age (years)	57.1±9.6	55.7±12.1	0.21
Male gender (%)	125 (62.5)	100 (58.8)	0.49
Body-mass index (kg/m^2)	29.3±3.5	28.7±3.1	0.16
Body surface area (m^2)	1.93±0.14	1.92±0.17	0.25
Hypertension (%)	132 (66)	104 (61.1)	0.38
Hypertension duration (years)	6.6±3.5	6.1±3.2	0.22
Diabetes mellitus (%)	32 (16)	28 (16.4)	0.65
Hyperlipidemi (%)	85 (42.5)	60 (35.3)	0.18
Coronary artery disease (%)	51 (25.5)	35 (20.6)	0.28
Current smoker (%)	45 (22.5)	30 (17.6)	0.21
Aortic operation (%)	27 (13.5)	–	
Echocardiography			
Left ventricular end-diastolic diameter (mm)	51.4±2.8	48.9±2.9	0.42
Left ventricular end-systolic diameter (mm)	31.3±5.6	29.2±5.8	0.22
IVS (mm)	10.1±1.3	9.5±1.2	0.09
Left ventricular ejection fraction (%)	59.1±5.9	61.2±7.5	0.90
Annulus diameter (cm)	2.26±0.31	2.11±0.26	0.01
Sinus of Valsalva diameter (cm)	3.72±0.49	3.19±0.41	0.01
Ascending aortic diameter (cm)	4.45±0.55	3.29±0.37	0.01
Ascending aortic diameter/BSA (cm/m^2)	2.31±0.34	1.72±0.21	0.01
Moderate-severe AR (%)	6 (3)	–	

Parametric variables with normal distribution were reported as mean±standard deviation. Parametric variables without normal distribution were reported as median (interquartile range). AAD: Ascending aortic dilatation; AR: Aortic regurgitation; IVS: Interventricular septum.

Table 2. Comparison of laboratory parameters in the study and control groups

	AAD (n=200)	Control (n=170)	*p*
Hemoglobin (g/dL)	13.7±1.9	13.9±1.4	0.21
Platelet (10^3 /μL)	250.4±71.1	233.4±63.4	0.25
Mean platelet volume (fL)	8.87±0.98	8.89±0.85	0.19
White blood cell count (10^3 /μL)	7.55±1.73	7.50±2.08	0.56
Neutrophil (10^3 /μL)	4.30 (1.89)	4.29 (1.82)	0.76
Lymphocyte (10^3 /μL)	2.11 (0.78)	2.22 (0.47)	0.46
Neutrophil/lymphocyte ratio	2.04 (1.09)	1.78 (0.90)	0.01
Red cell distribution width (%)	13.9 (1.40)	13.3 (1.05)	0.01
Mean corpuscular volume (fL)	87.9 (6.65)	88.9 (5.7)	0.07
Fasting glucose (mg/dL)	105.3±31.7	110.4±37.4	0.06
Creatinine (mg/dL)	0.82±0.15	0.83±0.15	0.59
AST (U/L)	22 (8)	23 (9)	0.32
ALT (U/L)	21 (12)	22 (14)	0.41
Total cholesterol (mg/dL)	195±39	185±36	0.79
LDL cholesterol (mg/dL)	117±36	115±33	0.71
HDL cholesterol (mg/dL)	45 (14)	47 (15)	0.08
Triglycerides (mg/dL)	140 (81)	129 (79)	0.06
Hs-CRP (mg/L)	0.60 (0.80)	0.44 (0.68)	0.01

Parametric variables without normal distribution were reported as median (interquantile range). AAD: Ascending aortic dilatation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HDL: High-density lipoprotein; hs-CRP: High-sensitive C-reactive protein; LDL: Low-density lipoprotein; MCV: Mean corpuscular volume; MPV: Mean platelet volume; NLR: Neutrophil/lymphocyte ratio; RDW: Red cell distribution width; WBC: White blood cell count.

Statistical analysis

All data are presented as a mean ± SD or a median (interquartile range [IQR]) for parametric variables and as percentages for categorical variables. Continuous variables were checked for the normal distribution assumption using Kolmogorov-Smirnov statistics. Categorical variables were tested by Pearson's χ^2 test and Fisher's exact test. Differences between patients and control subjects were evaluated using the Kolmogorov-Smirnov test or the Student t-test when appropriate. Correlations between two continuous variables were assessed with Pearson's test. Binary logistic regression analysis was used to find the possible independent association between dilation of the ascending aorta and clinical parameters. Hosmer-Lemeshow test was used to check goodness-of-fit of the logistic regression. Receiver operating characteristic (ROC) curves were analyzed to assess the best cut-off values of RDW to discriminate AAD. P-values are two-sided and values <0.05 were considered statistically significant. All statistical studies were carried out using the Statistical Package for the Social Sciences software (SPSS 16.0 for Windows, SPSS Inc.; Chicago, IL, USA).

RESULTS

A total number of 200 patients with AAD (60.6% male; mean age 57.1±9.6) and 170 control subjects (58.8% male; mean age 55.7±12.1) were included in the study. The demographic and clinical characteristics of the subjects are summarized in Table 1. Patients with AAD were similar to control subjects in regards to demographic characteristics including age, gender, frequencies of hypertension, diabetes mellitus, and coronary artery disease, and smoking status. Twenty-seven of the subjects in the AAD group (13.5%) required aortic root replacement operation. Echocardiographic parameters were comparable except for aortic annulus, sinus of Valsalva and ascending aortic diameters. Mean ascending aortic di-

ameter was 4.45±0.55 cm (range 3.8-8.3 cm) in the AAD group and 3.29±0.37 cm (range 2.6-3.8 cm) in the control group. Only 6 subjects in the AAD group (3%) had moderate-severe aortic regurgitation.

The comparison of laboratory parameters is shown in Table 2. RDW (median 13.9, IQR 1.40 *vs.* median 13.3, IQR 1.05%; p=0.01), NLR (median 2.04, IQR 1.09 *vs.* median 1.78, IQR 0.90; p=0.01) and hs-CRP (median 0.60, IQR 0.80 *vs.* median 0.44, IQR 0.68 mg/L; p=0.01) levels were significantly higher in the AAD group compared to the controls. However, hemoglobin, WBC, MCV, MPV, and other biochemical parameters were not significantly different between the groups. ROC analysis revealed that a RDW measurement higher than >13.8% predicted AAD with a sensitivity of 49.5% and a specificity of 82.8% (AUC 0.681, p=0.01) in the study population (Figure 1). Cut-off values of NLR and hs-CRP for diagnosis of AAD in the study population were 2.01 and 0.65 mg/L, respectively (Figure 1).

In addition, we compared the study parameters in subgroups formed using the tertiles of ascending aortic diameters. Tertile 1 included 125 subjects with ascending aortic diameters of <3.6 cm; tertile 2 included 134 subjects with ascending aortic diameters of 3.6-4.3 cm; and tertile 3 included 110 subjects with ascending aortic diameters of ≥4.3 cm. RDW levels were significantly higher in tertile 3 compared to tertiles 2 and 1 (median 14.1%, IQR 1.35% *vs.* median 13.5%, IQR 1.20% *vs.* median 13.2%, IQR 1.0%, respectively; p=0.01). In addition, NLR was significantly higher in tertile 3 compared to tertiles 2 and 1 (median 2.12, IQR 1.20 *vs.* median 1.88, IQR 1.05 *vs.* median 1.72, IQR 0.90, respectively; p=0.01). Hemoglobin, MCV and hs-CRP levels were not different between the tertiles (p=0.12, p=0.09 and p=0.08, respectively).

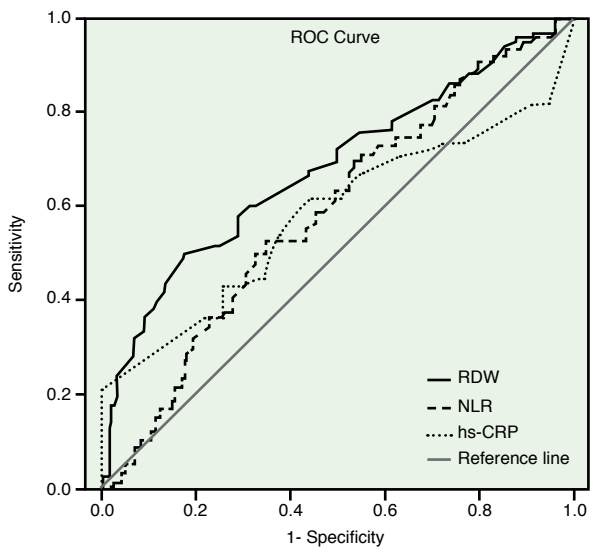

Figure 1. Receiver operating characteristic curve of red cell distribution width (RDW), neutrophil lymphocyte ratio (NLR) and hs-CRP levels for predicting ascending aortic dilatation in the study population.

In subgroup analysis, RDW, NLR and hs-CRP levels were not statistically different between males and females (p=0.67, p=0.59 and p=0.83, respectively). In hypertensive subjects, levels of RDW (median 13.6%, IQR 1.30% *vs.* median 13.3%, IQR 1.20%; p=0.16), NLR (median 2.01, IQR 1.10 *vs.* median 1.81, IQR 1.19; p=0.19) and hs-CRP (median 0.50, IQR 0.80 *vs.* median 0.45, IQR 0.80 mg/L; p=0.78) were not different from normotensive subjects. In 27 patients who underwent surgery, RDW levels were significantly higher compared to the remainder of the AAD group (median 14.2%, IQR 1.50% *vs.* median 13.7%, IQR 1.57%; p=0.02), whereas NLR (median 2.36, IQR 1.49 *vs.* median 2.0, IQR 1.1; p=0.06) and hs-CRP (median 0.60, IQR 0.80 *vs.* median 0.60, IQR 0.75 mg/L; p=0.78) measurements were not different between AAD subjects who did or did not undergo surgery.

In univariate correlation analysis, RDW levels were positively correlated with age (r=0.19, p=0.02), WBC counts (r=0.12, p=0.03) and hs-CRP levels (r=0.18, p=0.01) and were negatively correlated with hemoglobin levels (r= -0.22, p=0.01) and MCV levels (r=-0.26, p=0.01). The NLR levels were positively correlated with hs-CRP levels (r=0.15, p=0.01). Ascending aortic diameters were positively correlated with age (r=0.18, p=0.01), BMI (r=0.15, p=0.01), duration of hypertension (r=0.20, p=0.01), RDW levels (r=0.31, p=0.01), NLR levels (r=0.15, p=0.01), and hs-CRP levels (r=0.12, p=0.03) (Figure 2).

In univariate binary logistic regression analysis, increased age, RDW and hs-CRP levels and presence of hypertension were associated with AAD. In multivariate binary logistic regression analysis, only increased levels of RDW and hs-CRP remained as the independent markers of AAD in the study population (Table 3). The Hosmer-Lemeshow test statistic was 7.32 (df=8, p=0.51), which indicates good model fit.

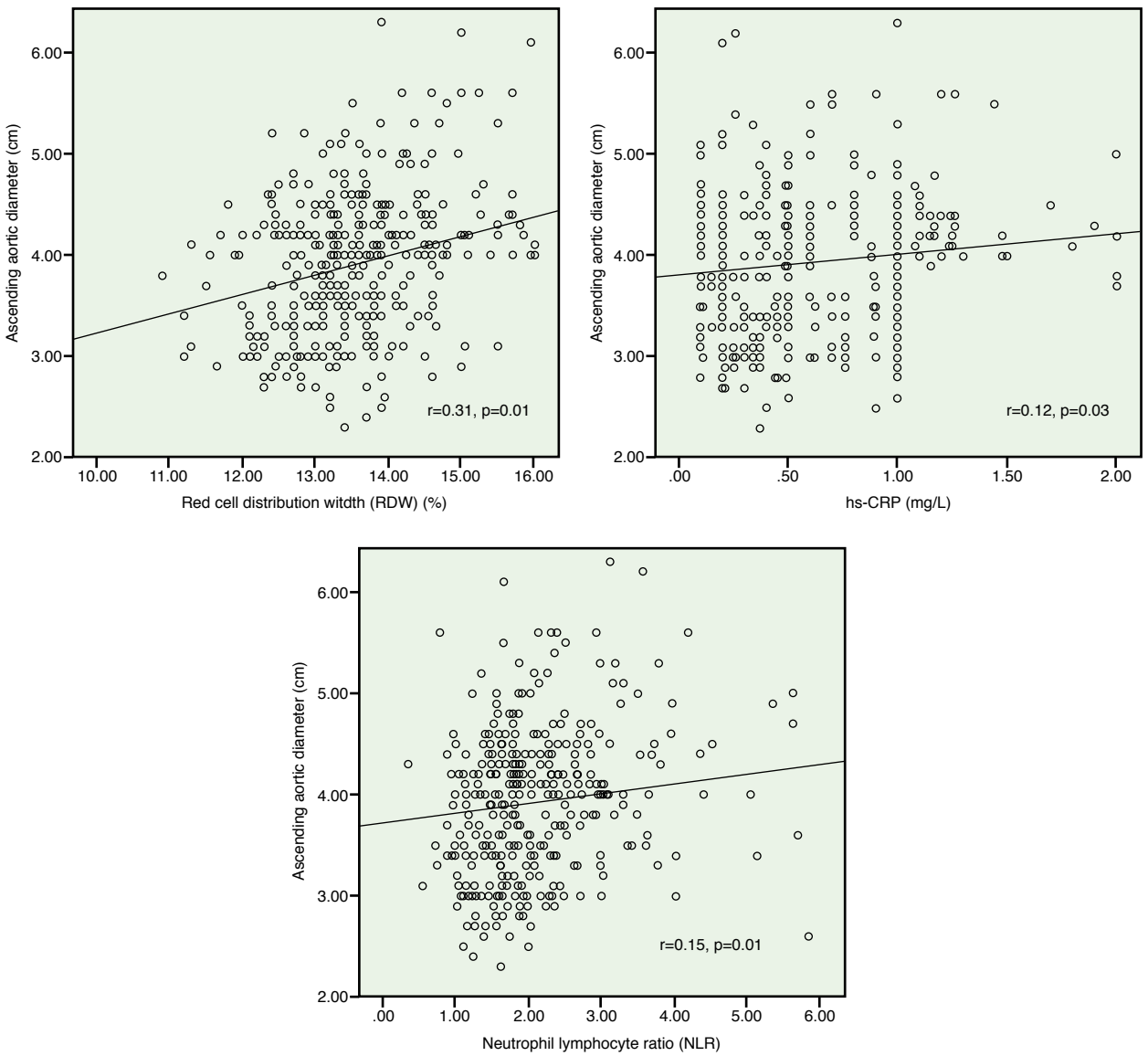

Figure 2. Scatter plot showing the correlation between red cell distribution width (RDW), hs-CRP and neutrophil lymphocyte ratio (NLR) with ascending aortic diameter.

DISCUSSION

The main finding of our study was that an increased level of RDW is independently correlated with the presence of AAD. In addition, RDW levels are correlated with hs-CRP levels, which are also increased in patients with AAD. To our knowledge, this is the first study to evaluate the relationship between increased RDW levels and AAD.

Aortic root dilatation is a commonly encountered clinical situation especially in elderly patients.[16] Bicuspid aortic valve and hypertension may accelerate this process and may result in early AAD. In addition, genetic polymorphisms such as Marfan syndrome, Ehlers-Danlos syndrome and Loeys-Dietz syndrome may result in aneurysm formation and aortic dissection at younger ages.[2,17] The aortic wall is weakened by cystic media degeneration. Aneurysm formation is associated with chronic aortic wall inflammation, which can be estimated by increased levels of CRP and IL-6.[5] The tissue environment of the aneurysm includes pro-inflammatory cytokines capable of stimulating macrophage expression of connective tissue

Table 3. Univariate and multivariate regression analysis of possible predictors of ascending aortic dilatation in the study population

Variables	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)*	*p*
Age	1.02 (1.01-1.03)	0.02	1.01 (0.98-1.03)	0.45
Male gender	1.17 (0.77-1.79)	0.45	–	–
Hypertension	1.21 (1.12-2.23)	0.01	1.13 (0.68-1.89)	0.65
Smoking	1.40 (0.84-2.35)	0.21	–	–
Glucose	1.002 (0.99-1.013)	0.29	–	–
Creatinine	1.86 (0.84-4.11)	0.13	–	–
Hemoglobin	0.92 (0.82-1.05)	0.21	–	–
Mean corpuscular volume	0.96 (0.92-1.05)	0.06	0.99 (0.97-1.02)	0.57
Red cell distribution width	1.32 (1.11 - 2.25)	0.01	1.82 (1.42-2.36)	0.01
Neutrophil/lymphocyte ratio	1.09 (0.91-1.28)	0.35	–	–
hs-CRP	2.51 (1.48-4.25)	0.01	2.02 (1.11-3.64)	0.02

*Adjusted for age, hypertension, RDW, MCV, and hs-CRP levels. CI: Confidence interval; Hs-CRP: High-sensitive C-reactive protein; MCV: Mean corpuscular volume; NLR: Neutrophil/lymphocyte ratio; OR: Odds ratio; RDW: Red cell distribution width.

proteinases, such as tumor necrosis factor-α, IL-1β, IL-6, and interferon-γ.[5,18] Increased expression of proteinases such as MMPs (type 2 and 9) results in tissue degradation and aneurysm formation.[4,19]

It has been demonstrated in previous trials that CRP is expressed and produced in atherosclerotic lesions and aneurysmal tissue, and is associated with aneurysmal size.[20-22] Domanovits et al.[23] observed that patients with symptomatic and ruptured aneurysms had elevated serum CRP compared with controls. Consistent with previous findings, in our study, hs-CRP levels were higher in the AAD group compared to the controls. Hs-CRP, RDW and NLR levels are also intercorrelated and increase in inflammation.[10,24-26]

Red cell distribution width (RDW) reflects variability in the size of red blood cells in the circulation and is used in the differential diagnosis of anemia. Recently, the relationship of RDW levels with adverse cardiovascular events independent of hemoglobin levels have raised RDW measurements as a prognostic indicator in the general population.[7,24,27-29] Especially in critically ill patients, nutritional deficiencies, chronic inflammation, impaired renal function, and inadequate production of erythropoietin may result in decreased life span of erythrocytes and cause appearance of immature erythrocytes in the circulation.[7] In our study, as all of the subjects were in good clinical condition and none had anemia, which may cause overt elevation of RDW levels, this explanation may not be valid for AAD cases.

The more plausible mechanism to explain the increased levels of RDW in AAD is the presence of a chronic inflammatory state that affects the aortic wall. Inflammatory cytokines, which are continuously secreted from the aneurysmal tissue, may decrease erythropoietin production and desensitize the erythroid progenitor cells to erythropoietin, leading to ineffective erythropoiesis.[7] These pathophysiological pathways result in increased levels of hs-CRP and RDW. It has been shown that RDW is correlated with inflammatory markers including hs-CRP, which is also accepted as a risk factor for adverse cardiovascular events.[10,24-26] RDW levels are increased in subjects with hypertension compared to normotensive subjects.[30] In our study group, as frequency of hypertension was similar between the two groups, we did not observe this difference in the subgroup analysis.

Neutrophil and lymphocyte counts respond to acute inflammation as an increase in neutrophil counts and NLR. Recently, NLR has been shown to be a predictor of adverse outcomes in patients with cardiovascular diseases.[31] In our study, neutrophil and lymphocyte counts were not statistically different between the AAD and control groups. Yet, NLR was significantly higher in the AAD group and NLR levels were correlated with hs-CRP levels, as expected.

However, in multivariate regression analysis, NLR levels did not remain as an independent correlate of AAD in the study population. An important issue to be underlined is that the interclass correlation coefficient of NLR measurements was very low compared to RDW, which indicates the necessity of using the average of two or more NLR measurements obtained on different occasions to draw better clinical conclusions for NLR. However, in most of the previous trials, only one measurement was included in the analysis. In our study, we used the averages of RDW, NLR, MCV, and other CBC parameters in all of the analyses to overcome this issue.

In conclusion, elevated levels of RDW are associated with the presence of AAD probably secondary to chronic inflammation in AAD and subsequent ineffective erythropoiesis. Further studies with a larger group of patients and longer follow-up are needed to confirm the results of the present study and to evaluate whether the levels of RDW can be used as a marker of the disease progression and prognosis in patients with AAD.

Limitations

This is a mid-sized cross-sectional study. Thus, we can only observe an association between study parameters and AAD but cannot establish a causal relationship. Prospective trials could yield valuable results on the correlation of RDW and hs-CRP levels with AAD and progression of the disease. Only hemoglobin levels were measured in this study; other factors associated with erythrocyte homeostasis such as levels of iron, ferritin, vitamin B12, and folate and other inflammatory mediators were not evaluated.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Ramanath VS, Oh JK, Sundt TM 3rd, Eagle KA. Acute aortic syndromes and thoracic aortic aneurysm. Mayo Clin Proc 2009;84:465-81. CrossRef
2. Albornoz G, Coady MA, Roberts M, Davies RR, Tranquilli M, Rizzo JA, et al. Familial thoracic aortic aneurysms and dissections--incidence, modes of inheritance, and phenotypic patterns. Ann Thorac Surg 2006;82:1400-5. CrossRef
3. Segura AM, Luna RE, Horiba K, Stetler-Stevenson WG, McAllister HA Jr, Willerson JT, et al. Immunohistochemistry of matrix metalloproteinases and their inhibitors in thoracic aortic aneurysms and aortic valves of patients with Marfan's syndrome. Circulation 1998;98(19 Suppl):II331-8.
4. LeMaire SA, Wang X, Wilks JA, Carter SA, Wen S, Won T, et al. Matrix metalloproteinases in ascending aortic aneurysms: bicuspid versus trileaflet aortic valves. J Surg Res 2005;123:40-8. CrossRef
5. Artemiou P, Charokopos N, Rouska E, Sabol F, Chrysogonidis I, Tsavdaridou V, et al. C-reactive protein/interleukin-6 ratio as marker of the size of the uncomplicated thoracic aortic aneurysms. Interact Cardiovasc Thorac Surg 2012;15:871-7.
6. Felker GM, Allen LA, Pocock SJ, Shaw LK, McMurray JJ, Pfeffer MA, et al. Red cell distribution width as a novel prognostic marker in heart failure: data from the CHARM Program and the Duke Databank. J Am Coll Cardiol 2007;50:40-7. CrossRef
7. Förhécz Z, Gombos T, Borgulya G, Pozsonyi Z, Prohászka Z, Jánoskuti L. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J 2009;158:659-66. CrossRef
8. van Kimmenade RR, Mohammed AA, Uthamalingam S, van der Meer P, Felker GM, Januzzi JL Jr. Red blood cell distribution width and 1-year mortality in acute heart failure. Eur J Heart Fail 2010;12:129-36. CrossRef
9. Allen LA, Felker GM, Mehra MR, Chiong JR, Dunlap SH, Ghali JK, et al. Validation and potential mechanisms of red cell distribution width as a prognostic marker in heart failure. J Card Fail 2010;16:230-8. CrossRef
10. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M; for the Cholesterol and Recurrent Events (CARE) Trial Investigators. Relation Between Red Blood Cell Distribution Width and Cardiovascular Event Rate in People With Coronary Disease. Circulation 2008;117:163-8. CrossRef
11. Ani C, Ovbiagele B. Elevated red blood cell distribution width predicts mortality in persons with known stroke. J Neurol Sci 2009;277:103-8. CrossRef
12. Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. Am J Cardiol 2010;105:312-7. CrossRef
13. Güngör B, Ozcan KS, Erdinler I, Ekmekçi A, Alper AT, Osmonov D, et al. Elevated levels of RDW is associated with non-valvular atrial fibrillation. J Thromb Thrombolysis 2013 Jul 3.
14. Uyarel H, Isik T, Ayhan E, Ergelen M. Red cell distrubition width (RDW): a novel risk factor for cardiovascular disease. Int J Cardiol 2012;154:351-2. CrossRef
15. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with Thoracic Aortic Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, Ameri-

can Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. Circulation 2010;121:266-369. CrossRef

16. Patel HJ, Deeb GM. Ascending and arch aorta: pathology, natural history, and treatment. Circulation 2008;118:188-95.
17. Loeys BL, Chen J, Neptune ER, Judge DP, Podowski M, Holm T, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in TGFBR1 or TGFBR2. Nat Genet 2005;37:275-81.
18. Golledge J, Norman PE. Pathophysiology of abdominal aortic aneurysm relevant to improvements in patients' management. Curr Opin Cardiol 2009;24:532-8. CrossRef
19. LeMaire SA, Pannu H, Tran-Fadulu V, Carter SA, Coselli JS, Milewicz DM. Severe aortic and arterial aneurysms associated with a TGFBR2 mutation. Nat Clin Pract Cardiovasc Med 2007;4:167-71. CrossRef
20. Sun H, Koike T, Ichikawa T, Hatakeyama K, Shiomi M, Zhang B, et al. C-reactive protein in atherosclerotic lesions: its origin and pathophysiological significance. Am J Pathol 2005;167:1139-48. CrossRef
21. Venugopal SK, Devaraj S, Jialal I. Macrophage conditioned medium induces the expression of C-reactive protein in human aortic endothelial cells: potential for paracrine/autocrine effects. Am J Pathol 2005;166:1265-71. CrossRef
22. Reynolds GD, Vance RP. C-reactive protein immunohistochemical localization in normal and atherosclerotic human aortas. Arch Pathol Lab Med 1987;111:265-9.
23. Domanovits H, Schillinger M, Müllner M, Hölzenbein T, Janata K, Bayegan K, et al. Acute phase reactants in patients with abdominal aortic aneurysm. Atherosclerosis 2002;163:297-302. CrossRef
24. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med 2009;169:588-94.
25. Lappé JM, Horne BD, Shah SH, May HT, Muhlestein JB, Lappé DL, et al. Red cell distribution width, C-reactive protein, the complete blood count, and mortality in patients with coronary disease and a normal comparison population. Clin Chim Acta 2011;412:2094-9. CrossRef
26. Kyne L, Hausdorff JM, Knight E, Dukas L, Azhar G, Wei JY. Neutrophilia and congestive heart failure after acute myocardial infarction. Am Heart J 2000;139:94-100. CrossRef
27. Pascual-Figal DA, Bonaque JC, Redondo B, Caro C, Manzano-Fernandez S, Sánchez-Mas J, et al. Red blood cell distribution width predicts long-term outcome regardless of anaemia status in acute heart failure patients. Eur J Heart Fail 2009;11:840-6. CrossRef
28. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009;133:628-32.
29. Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, et al. Red cell distribution width and mortality in older adults: a meta-analysis. J Gerontol A Biol Sci Med Sci 2010;65:258-65. CrossRef
30. Ozcan F, Turak O, Durak A, Işleyen A, Uçar F, Giniş Z, et al. Red cell distribution width and inflammation in patients with non-dipper hypertension. Blood Press 2013;22:80-5. CrossRef
31. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther 2013;11:55-9. CrossRef

Key words: Ascending aortic dilatation; C-reactive protein/metabolism; echocardiography; erythrocyte indices; red cell distribution width; ROC curve.

Anahtar sözcükler: Çıkan aort dilatasyonu; C-reaktif protein/metabolizma; ekokardiyografi; eritrosit indeksleri; kırmızı kan hücre dağılım aralığı; ROC eğrisi.