Increased level of red cell distribution width is associated with poor coronary collateral circulation in patients with stable coronary artery disease

Artmış eritrosit dağılım genişliği kararlı koroner arter hastalarında yetersiz koroner kollateral dolaşımı ile ilişkilidir

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ABSTRACT

Objectives: Previous studies have shown the association between various hematological parameters and cardiovascular diseases, and their prognostic value. In this study, we compared red cell distribution width (RDW), neutrophil lymphocyte ratio (NLR) and mean platelet volume (MPV) measurements among patients with poor coronary collateral circulation (CCC) and well-developed CCC.

Study design: 326 patients with stable coronary artery disease (CAD) were evaluated retrospectively. CCC was graded by using the Rentrop classification. The poor CCC group included patients with Rentrop 0-1 CCC, and the good CCC group included Rentrop 2-3 CCC.

Results: There were 171 subjects (84% male; mean age 56.6±10.4 years) in the poor CCC group, and 155 subjects (89% male; mean age 57.6±9.7 years) in the good CCC group. The total number of vessels with >95% stenosis (1.1±0.5 *vs.* 1.0±0.4; p=0.64) and Gensini scores (84.4±38.8 *vs.* 83.3±37.4; p=0.83) was not higher in the poor CCC group compared to the good CCC group. RDW was significantly higher in the poor CCC group compared to the good CCC group (14.19±1.36% *vs.* 13.89±1.19%; p=0.04). In multivariate logistic regression analysis, elevated levels of RDW and LDL were found to be independent predictors of poor CCC (OR 1.73, 95% CI: 1.30-2.29, p=0.01 and OR 1.01 95% CI 1.002-1.02; p=0.02, respectively).

Conclusion: In the present study, poor CCC was found to be independently correlated with RDW, but not with any other hematological parameters in patients with stable CAD.

ÖZET

Amaç: Hematolojik parametrelerin kardiyovasküler hastalıklarla ilişkisi ve prognostik önemleri gösterilmiştir. Bu çalışmada eritrosit dağılım genişliği (EDG), nötrofil lenfosit oranı (NLO) ve ortalama trombosit hacmi (OTH), yetersiz koroner kollateral dolaşımı (KKD) ve iyi gelişmiş KKD olan hastalarda karşılaştırılmıştır.

Çalışma planı: Kararlı koroner arter hastalığı (KAH) olan 326 kişi geriye dönük olarak incelendi. KKD değerlendirilmesi Rentrop sınıflandırılması kullanılarak yapıldı. Yetersiz KKD grubuna Rentrop 0-1 kollateral dolaşımı olan, iyi gelişmiş KKD grubuna Rentrop 2-3 kollateral dolaşımı olan hastalar alındı.

Bulgular: Yetersiz KKD grubunda 171 olgu (%84 erkek, ortalama yaş 56.6±10.4 yıl), iyi gelişmiş KKD grubunda 155 olgu (%89 erkek, ortalama yaş 57.6±9.7) bulunmaktaydı. Yetersiz KKD grubunda >%95'den fazla darlık bulunan toplam damar sayısı (1.1±0.5 ve 1.0±0.4, p=0.64) ve Gensini skoru (84.4±38.8 ve 83.3±37.4; p=0.83) iyi gelişmiş KKD grubundan yüksek değildi. Hematolojik parametrelere bakıldığında, sadece EDG düzeyinin, yetersiz KKD grubunda anlamlı olarak daha yüksek olduğu bulundu (14.19±1.36 ve %13.89±%1.19, p=0.04). Çoklu değişkenli lojistik regresyon analizinde artmış EDG ve LDL-kolesterol düzeylerinin yetersiz KKD'nin bağımsız belirleyicisi olduğu saptandı (sırasıyla, OR 1.73, %95 CI: 1.30-2.29, p=0.01 ve OR 1.01 %95 CI 1.002-1.02; p=0.02).

Sonuç: Çalışmamızda hematolojik parametrelerden sadece EDG ile yetersiz KKD arasında bağımsız bir korelasyon olduğu saptanmıştır.

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Coronary collateral circulation (CCC) is an alternative source of blood supply to the myocardium, and has a vital function in case of inadequate oxygenation of the myocardium secondary to critical stenosis or occlusion of the coronary arteries.[1] The development of collateral circulation varies much among patients, even those with the same degree of stenosis. The main determinants of angiogenesis is the severity and duration of myocardial ischemia, diabetes mellitus (DM), hypertension (HT), dyslipidemia, cigarette smoking, exercise, drugs, chronic inflammation, and especially oxidative stress.[2]

Previous studies have shown the correlation between hematological parameters and various cardiovascular diseases (CVD) including heart failure, coronary artery disease (CAD), and acute coronary syndromes and atrial fibrillation.[3-10] Elevated red cell distribution width (RDW) and neutrophil lymphocyte ratio (NLR) are correlated with the severity of chronic inflammation, which has been shown to be a poor prognostic indicator in patients with CVD.[11-13]

Several reports have shown the correlation between RDW levels and CVDs and presence of the aforementioned co-morbid conditions.[14,15] In stable CAD patients, mean platelet volume (MPV), NLR, gama-glutamyltransferase (GGT), HDL cholesterol, white blood cell count (WBC), have been shown to be correlated with the degree of CCC development.[16,17] However, consistent correlations of these parameters with CCC development and a biologically plausible mechanism explaining the role of these parameters in angiogenesis has not been established.

In this study, we aimed to investigate the correlation of hematological parameters with degree of CCC development in a well-defined group of stable CAD patients with established critical coronary artery stenosis.

PATIENTS AND METHODS

Study population

This study is a retrospective cross-sectional study conducted between May 2009 and December 2012. A total number of 4.552 coronary angiographies were screened and patients with a diagnosis of stable CAD and who had one or more epicardial vessels' stenosis over 95% were further evaluated. Hospital records of subjects were evaluated for the presence of exclusion criteria. Patients with coronary artery stenosis <%95 (n=2604), with acute coronary syndromes (n=1077), older than 75 years (n=318), with a history of coronary artery bypass grafting (CABG) (n=245), and anemia (a hemoglobin level <13 g/dL in men and <12 g/dL in women) (n=194) were excluded. In addition, 88 subjects were excluded from the study due to the presence of any of the following conditions: acute infection, chronic inflammatory disease, renal/hepatic failure, history of blood transfusion within the last three months. Finally, 326 consecutive patients were included in the study.

Abbreviations:

CAD	*Coronary artery disease*
CBC	*C omplete blood count*
CCC	*Coronary collateral circulation*
CVD	*Cardiovascular diseases*
DM	*Diabetes mellitus*
GGT	*Gama-glutamyltransferase*
HDL	*High density lipoprotein*
HT	*Hypertension*
LDL	*Low density lipoprotein*
MPV	*Mean platelet volume*
NLR	*Neutrophil lymphocyte ratio*
RDW	*Red cell distribution width*
TC	*Total cholesterol*
TG	*Triglyceride*
WBC	*White blood cell count*

Demographic, clinical, laboratory and angiography patient data were recorded. Obesity was defined as a body mass index (BMI) over 30 m^2/kg, HT was defined as using antihypertensive drugs or a baseline blood pressure over 140/90 mmHg, DM was defined as using antidiabetic drugs or fasting plasma glucose levels of >126 mg/dL, and hyperlipidemia was defined as total serum cholesterol levels >240 mg/dL. Smoking status was defined as current tobacco use.

Coronary angiography evaluation and CCC grading

All coronary angiographies were performed through the femoral artery using the Seldinger technique. Coronary angiographies with epicardial coronary stenosis of 95% or more were included, and the CCC was graded according to the Rentrop classification.[18] According to this classification; Grade 0 refers to lack of filling in collateral vessels, Grade 1 refers to filling in side branches via collateral channels without visualization of the epicardial artery, Grade 2 refers to partial filling in the epicardial major coronary artery via collateral channels, and Grade 3 refers to complete filling in the epicardial major coronary artery. The severity of CAD was also evaluated by calculation of Gensini scores for each patient.[19]

The coronary angiographies were evaluated by three interventional cardiologists who were blinded

to the clinical, laboratory and demographic data of the patients. When more than one vessel met the predefined criteria, the CCC with the highest Rentrop grade was used for analysis. The patients were classified into two different groups according to their CCC, namely the poor CCC group (Rentrop grades 0-1) and the good CCC group (Rentrop grades 2-3).

Hematologic and other laboratory parameters

All blood samples were drawn before the procedure after an overnight fasting. Hematological parameters such as hemoglobin (Hgb), WBC, platelet count, neutrophil and lymphocyte counts, RDW, MPV were measured as part of the automated complete blood count (CBC) using a Sysmex XT-1800i (Roche Diagnostic, Istanbul, Turkey). The reference range was between 11.5-14.5% for RDW; 7.2-11.1 fl for MPV; and 80-99 fl for MCV. Baseline NLR was measured by dividing neutrophil count by lymphocyte count. In addition, fasting glucose, creatinine, total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride (TG) levels were studied.

Statistical analysis and approval of the study

All data is presented as mean±SD or median [interquartile range] for parametric variables, and as percentage 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's t-test as appropriate. Binary logistic regression analysis was used to find the possible predictors of poor CCC in the study population. For multivariate regression analysis, parameters with a $p<0.10$ in univariate analysis and parameters with established correlation with poor CCC (MPV, NLR, RDW, GGT, fasting glucose, uric acid, LDL cholesterol) were included in the model. P-values were two-sided, and values <0.05 were considered statistically significant. All statistical studies were carried out using Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, Illinois). The study was approved by the Local Ethics Committee of the hospital.

RESULTS

A total of 326 patients with stable CAD were recruited. Demographic and clinical properties of the subjects are summarized in Table 1. There were 171 subjects (84% male; mean age 56.6±10.4 years) in the poor CCC group, and 155 subjects (89% male; mean age 57.6±9.7 years) in the good CCC group. The other demographic parameters were similar across the two groups. The total number of vessels with >95% stenosis (1.1±0.5 *vs.* 1.0±0.4; p=0.64) and Gensini scores was not higher in the poor CCC group compared to the good CCC group (84.4±38.8 *vs.* 83.3±37.4; p=0.83).

Table 1. Clinical and demographic properties of patients with poor and good coronary collateral circulation

	Poor CCC (n=171)			Good CCC (n=155)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age, years			56.6±10.4			57.6±9.7	0.41
Male gender	145	84		139	89		0.19
Hypertension	130	76		107	69		0.16
Diabetes mellitus	51	29		47	30		0.92
Hyperlipidemia,	81	47		83	53		0.27
Current smoker	66	38		64	41		0.62
Prior myocardial infarction	121	70		107	69		0.68
Left ventricular ejection fraction			49.1±9.5			48.7±10.8	0.77
Angiographic findings							
Total number of vessels with >95% stenosis			1.1±0.5			1.0±0.4	0.64
Gensini scores			84.4±38.8			83.3±37.4	0.83

CCC: Coronary collateral circulation.

Table 2. Comparison of laboratory parameters in the study groups

	Poor CCC (n=171)	Good CCC (n=155)	*p*
Hemoglobin (g/dL)	14.7±1.2	14.8±1.3	0.69
White blood cell count (10^3 /μL)	8.45±2.77	8.44±3.20	0.97
Platelets (10^3 /μL)	245±66	236±59	0.19
Neutrophils (10^3 /μL)	6.0±2.6	6.1±3.0	0.85
Lymphocytes (10^3 /μL)	2.45±1.18	2.38±1.1	0.56
Neutrophil/lymphocyte ratio	2.34 [1.91]	2.43 [2.03]	0.57
Mean platelet volume (fL)	9.46±1.28	9.45±1.33	0.98
Red cell distribution width (%)	14.19±1.36	13.89±1.19	0.04
Red cell distribution width >14.5%, n (%)	63 (37)	40 (26)	0.03
Mean corpuscular volume (fL)	87.7±7.4	87.9±8.4	0.71
Fasting glucose (mg/dL)	129 [79]	127 [69]	0.58
Creatinine (mg/dL)	1.02±0.33	1.0±0.29	0.97
Total cholesterol (mg/dL)	198 [67]	190 [69]	0.21
Low density lipoprotein cholesterol (mg/dL)	126±44	117±42	0.11
High density lipoprotein cholesterol (mg/dL)	42±10	41±10	0.43
Triglycerides (mg/dL)	160 [132]	168 [118]	0.56
Uric acid (mg/dL)	5.89±1.49	5.64±1.52	0.24
Gama glutamyl transferase (IU/L)	28 [18]	25 [17]	0.16

Parametric variables without normal distribution were reported as median [interquartile range]. CCC: Coronary collateral circulation.

The comparison of laboratory parameters is shown in Table 2. Fasting glucose, creatinine, TC, LDL cholesterol, HDL cholesterol, TG, GGT and uric acid levels were similar across the two groups. Regarding the CBC parameters; Hgb, WBC, platelets, neutrophil/lymphocyte counts, NLR, MPV, and MCV were not statistically different between the groups. Only RDW was significantly high in the poor CCC group compared to the good CCC group (14.19±1.36% *vs.* 13.89±1.19%; p=0.04). The frequency of subjects with RDW levels greater than the upper normal limit (reference range for RDW is 11.5-14.5%) was significantly higher in the poor CCC group (37% *vs.* 26%; p=0.03) (Figure 1).

In the univariate binary logistic regression analysis, increased RDW (OR: 1.20, 95% CI 1.01-1.43, p=0.03) or presence of RDW >14.5% (OR: 1.67, 95% CI 1.05-2.70, p=0.04) revealed a significant correlation with poor CCC in the study group. In multivariate logistic regression analysis using a model adjusted for RDW, NLR, MPV, fasting glucose, GGT, uric acid, and LDL cholesterol measurements, the elevated levels of RDW and LDL were found to be independent predictors of poor CCC in the study group (OR 1.73, 95% CI: 1.30-2.29, p=0.01 and OR 1.01 95% CI 1.002-1.02; p=0.02, respectively) (Table 3). The Hos-

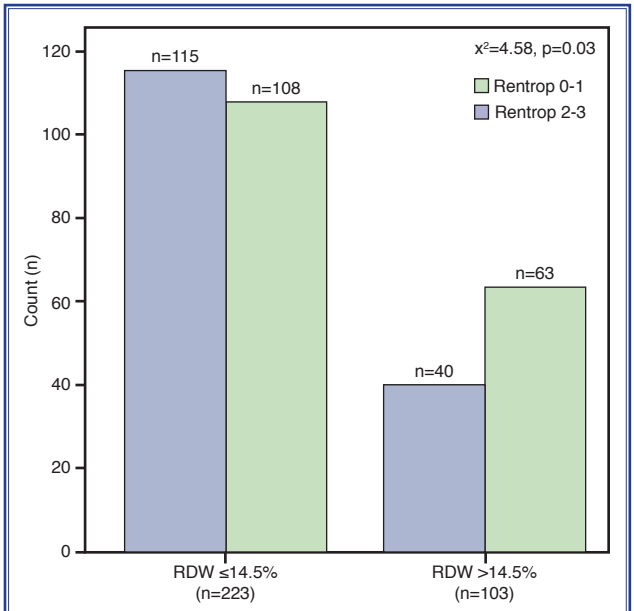

Figure 1. Distribution of patients according to RDW measurements and and Rentrop classifications.

Table 3. Univariate and multivariate regression analysis of possible predictors of poor coronary collateral circulation in the study population

Variables	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)*	*p*
Age, 1-SD increase	0.99 (0.97-1.0)	0.41	–	–
Female gender	1.56 (0.80-3.03)	0.19	–	–
Hypertension	1.42 (0.88-2.32)	0.16	–	–
Hyperlipidemia	1.22 (0.83-1.78)	0.26	–	–
Smoking	0.89 (0.57-1.29)	0.62	–	–
Diabetes mellitus	0.98 (0.61-1.57)	0.92	–	–
Glucose, 1-SD increase	1.002 (0.99-1.004)	0.45	1.00 (0.99-1.004)	0.89
Creatinine, 1-SD increase	1.011 (0.53-1.93)	0.97	–	–
Total cholesterol, 1-SD increase	1.03 (0.99-1.06)	0.18	–	–
LDL cholesterol, 1-SD increase	1.005 (0.99-1.01)	0.10	1.01 (1.002-1.02)	0.02
HDL cholesterol, 1-SD decrease	1.009 (0.98-1.032)	0.42	–	–
Triglycerides, 1-SD increase	1.001 (0.99-1.003)	0.59	–	–
GGT, 1-SD increase	1.001 (0.98-1.02)	0.85	1.001 (0.98-1.02)	0.94
Uric acid, 1-SD increase	1.11 (0.93-1.32)	0.24	0.92 (0.75-1.16)	0.53
Hemoglobin, 1-SD increase	0.97 (0.81-1.15)	0.69	–	–
WBC, 1-SD increase	1.001 (0.93-1.07)	0.97	–	–
MCV, 1-SD increase	0.99 (0.97-1.02)	0.71	–	–
RDW, 1-SD increase†	1.20 (1.01 – 1.43)	0.03	1.72 (1.30-2.29)	0.01
RDW >14.5%	1.67 (1.05-2.70)	0.04	–	–
NLR, 1-SD increase	0.98 (0.90-1.06)	0.61	0.97 (0.87-1.08)	0.57
MPV, 1-SD increase	–	–	1.03 (0.79-1.35)	0.81
Platelets, 1-SD increase	1.002 (0.99-1.006)	0.19	–	–

*Adjusted for age, gender, glucose, LDL cholesterol and RDW levels. †These parameters were analyzed separately in multivariate regression model in order to prevent multicollinearity. HDL: High density lipoprotein; LDL: low density lipoprotein; GGT: Gama-glutamyltransferase; WBC: White blood cell count; MCV: Mean corpuscular volume; RDW: Red cell distribution width; NLR: Neutrophil/lymphocyte ratio; MPV: Mean platelet volume.

mer-Lemeshow test statistic was 6.72 (df=8; p=0.56), which indicated a good model fit.

DISCUSSION

The main finding of this study is that, when all hematological parameters are taken into account, only RDW levels are significantly higher in stable CAD patients with poor CCC development compared to patients with good CCC development.

Various studies have shown the correlation of hematological parameters such as RDW, MPV and NLR with prognosis in patients with CVD.[3-5,11,17] However, as hematological parameters are affected by several biological factors such as inflammation, blood loss, inadequate erythropoiesis and nutritional status, the pathophysiological mechanisms of these correlations have not been well established. Nevertheless, when circulating red blood cells are considered as a barometer of the vascular system, white blood cells as an indicator of inflammation, and thrombocytes as the major cells moderating thrombosis, correlation of hematological parameters with etiological factors of CVD is highly probable and warrants further investigation.

Coronary collateral circulation is one of the main protective adaptations of the heart. It was found to diminish the extension of infarct zone in the acute onset of myocardial infarction and to reduce ventricular aneurysm formation, with subsequent improvement in global function and wall motion of the ventricle.[20-22] Degree of coronary stenosis, DM, HT, dyslipidemia,

cigarette smoking, exercise, drugs, chronic inflammation, myocardial ischemia and oxidative stress are the main factors attributed to CCC development.[2]

Red cell distribution width, in other words anisocytosis, is a numerical measure of the variability in the size of circulating erythrocytes, and is used in the differential diagnosis of anemia.[23] The documented association of this parameter with CVDs has increased its clinical use.[3-5,11] However, RDW levels may be influenced by various clinical conditions such as chronic disease, inflammation, iron deficiency, hemolysis, B12 and folate deficiency and chronic renal failure.[24] In our study, we included patients younger than 75 years of age in order to minimize the frequency of these confounding factors which may increase RDW values. In addition, we excluded patients with ACS, which also results in acute deterioration of several hematological parameters.

Neutrophils are the major protective cells of the immune system against the acute phase of inflammation and bacterial infection, while lymphocytes, which consist of T cells, B cells and natural killer cells, are members of the adaptive immune system, and react against viral infections. The NLR can also be determined easily from the reported CBC without any additional cost. The NLR level is associated with cardiovascular events and mortality.[11]

NLR values were found to be significantly higher in patients with poor CCC. However, our analyses do not support these findings.[25]

Mean platelet volume is another hematological parameter associated with cardiovascular mortality and morbidity. Larger platelets have greater prothrombotic potential than smaller platelets.[26] It has been reported that increased MPV is associated with atherosclerotic risk factors, including DM, HT and obesity.[27-29] Ege et al. investigated the correlation between MPV and CCC development in patients with coronary artery stenosis of more than 50%.[17] They reported that increased MPV levels and lower Gensini scores were independently associated with poor CCC development. Similarly to our study, healthy subjects were not included in their control group. In our study, we included patients with coronary artery stenosis of >95%, which is more convenient in studying CCC development, as the severity of stenosis directly influences the pressure gradient within the vessel and the driving force of neoangiogenesis. This major methodological difference between the two studies may have resulted in contradicting results.

The association between impaired CCC in coronary artery disease and hematologic parameters has been investigated by Tanboga et al.[30] and Ayhan et al.[31] Our findings confirm the correlation between increased RDW levels and poor CCC development in non-ST segment elevation myocardial infarction previously documented in a larger study population of patients with stable CAD.[30] However, Ayhan et al. did not find any significant correlation between poor CCC and RDW in their study, which was conducted on only 96 patients with stable CAD. As their study included only 1/3 of our study population, it may be considered relatively underpowered compared to ours.

Previous studies have clearly demonstrated the association between elevated inflammatory activity and poor CCC.[32,33] Although the exact mechanism of high RDW levels and their correlation with poor prognosis of CVD remains unclear, inflammation appears to be the most probable hypothesis.[34-36] Inflammation is mediated by inflammatory cytokines which inhibit maturation of red blood cells; and consequently, more immature red blood cells enter the circulation, leading to anisocytosis and increased RDW levels.

Limitation

There are some limitations to the present study. First, it is a retrospective, cross-sectional single-center study, in which the selected population may not reflect the whole cohort. Secondly, other causes that alter RDW values such as ferritin, vitamin B12, folate and iron levels were not measured. Thirdly, parameters with a possible role in the pathophysiology, such as VEGF, NO, erythropoietin, TNF-a, and BNP were not measured, and these measurements could have been useful in establishing the association between RDW and impaired CCC. Lack of CRP levels and interleukin levels as inflammatory markers is another limitation of our study.

In the present study, we found an independent correlation between RDW and impaired CCC in patients with stable CAD. Utilization of hematological parameters as prognostic indicators in CVD is eligible in clinical practice; however, further studies should be conducted to assure their impact and limitations across cardiovascular diseases.

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

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Key words: Collateral circulation; coronary artery disease; red cell distribution width.

Anahtar sözcükler: Koroner kollateral dolaşım; koroner arter hastalığı; eritrosit dağılım genişliği.