

■ Original Article

The relationship between red cell distribution width and resistant hypertension

Kırmızı hücre dağılım genişliği ile dirençli hipertansiyon arasındaki ilişki

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Abstract

Aim: Erythrocyte distribution width (RDW) is known to be associated with cardiovascular diseases. Patients with resistant hypertension (RHT) have a higher risk of cardiovascular events. In this study, we aimed to evaluate the relationship between RDW and resistant hypertension.

Material and Methods: A total of 157 patients, 69 (43%) of them being resistant hypertension, who had 24-hour ambulatory blood pressure measurement (ABPM) were included in this study. RDW and other laboratory parameters were measured after ABPM.

Results: The average age in the study population was 57 ± 11 , and 77% (121) of the patients were female. Patients were divided into two groups as controlled and RHT. The RDW was significantly higher in the RHT group (14.8 ± 1.4) compared to the CHT group (14.1 ± 1.2); ($p=0,02$). RDW by multivariable logistic regression analysis (odds ratio [OR]: 1.684, 95% confidence interval [CI]: 1.250-2.201 $p < 0.001$), diabetes mellitus (OR: 3.459, 95% CI: 1.095-10.930 $p = 0.035$) and Body Mass Index (BMI) (OR: 1.085, 95% CI: 1.013-1.163 $p = 0.02$) was found to be an independent predictor of RHT. In the ROC analysis performed of RDW in predicting RHT, the optimal predictive value for RDW was % 14.65 with 62.5% sensitivity and 65.2% specificity. RDW's Area Under Curve (AUC) value was 0.63 (95%CI: 0.551-0.726).

Conclusion: RDW, which was found to be associated with high mortality in cardiovascular diseases, was significantly higher in the RHT patient group compared to the CHT patient group, and RDW was found to be an independent predictor of resistant hypertension.

Keywords: Red blood cell width; hypertension; resistant hypertension; controlled hypertension; ambulatory blood pressure measurement

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Öz

Amaç: Eritrosit dağılım genişliğinin (RDW) kardiyovasküler hastalıklarla ilişkili olduğu bilinmektedir. Dirençli hipertansiyonu (DHT) olan hastalarda kardiyovasküler olay riski daha yüksektir. Bu çalışmada RDW ile dirençli hipertansiyon arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu çalışmaya 24 saatlik ambulator kan basıncı ölçümü (AKBÖ) yapılan 69 (%43) dirençli hipertansiyon olmak üzere toplam 157 hasta dahil edildi. AK-BÖ'den sonra RDW ve diğer laboratuvar parametreleri ölçüldü.

Bulgular: Çalışma popülasyonundaki ortalama yaş 57 ± 11 idi ve hastaların %77'si (121) kadındı. Hastalar kontrollü HT (KHT) ve DHT olarak iki gruba ayrıldı. RDW, KHT grubuna (14.1 ± 1.2) kıyasla DHT grubunda (14.8 ± 1.4) anlamlı olarak daha yüksekti; ($p=0,002$). Çok değişkenli lojistik regresyon analizi ile RDW (olasılık oranı [OR]: 1.684, %95 Güven Aralığı [GA]: 1.250-2.201 $p < 0.001$), diabetes mellitus (OR: 3.459, %95 GA: 1.095-10.930 $p = 0.035$) ve Vücut Kitle İndeksi (VKI) (OR: 1.085, %95 GA: 1.013-1.163 $p = 0.02$), RHT'nin bağımsız bir belirleyicisi olarak bulundu. RDW'nin RHT'yi öngörmede yaptığımız ROC ana-lizinde, RDW için optimal prediktif değer %62,5 duyarlılık ve %65,2 özgüllük ile %14.65 idi. RDW'nin Eğri Altındaki Alan (AUC) değeri 0,63 (%95CI: 0,551-0,726) idi.

Sonuç: Kardiyovasküler hastalıklarda yüksek mortalite ile ilişkili bulunan RDW, DHT hasta grubunda KHT hasta grubuna göre anlamlı olarak daha yüksek bulundu ve RDW dirençli hipertansiyonun bağımsız bir öngördürücüsü olarak bulundu.

Anahtar Kelimeler: Kırmızı kan hücresi genişliği; hipertansiyon; dirençli hipertansiyon; kontrollü hipertansiyon; ayaktan kan basıncı ölçümü

Introduction

Resistant hypertension is defined as inability to control blood pressure with 3 or more drugs despite appropriate lifestyle changes and optimal medical treatment or reaching the target blood pressure with 4 or more drugs [1,2]. Although the exact prevalence of resistant hyper-tension (RHT) is not known, it is estimated that this rate is <10% in treated hypertensive patients [3]. Risk factors for resistant hypertension include advanced age, obesity, chronic kidney disease, black race, and diabetes mellitus [4]. Adverse cardiovascular events are more common in patients with resistant hypertension than patients with controlled hypertension [5].

The red cell distribution width (RDW) is an index that is examined in the complete blood count showing the distribution of the size of the circulating erythrocytes. The erythrocyte distribution width is used in the diagnosis of anemia, and its increase is observed in hemolysis and production disorders of erythrocytes [6]. Erythrocyte distribution height is observed not only in hematological diseases, but also as a result of chronic inflammation and ineffective erythropoiesis due to activation of the neurohumoral system [7-9].

Studies have reported that high RDW is associated with cardiovascular diseases, and the RDW level is also high in hypertensive and prehypertensive patients [10]. Although the RDW level has been evaluated in different hypertensive patient groups, there are no studies evaluating the RDW

level in patients with resistant hypertension. So, we aimed to examine the relationship between resistant hypertension and RDW in patients with essential hypertension in this study.

Material and Methods

Study population

Patients who applied to the cardiology outpatient clinic and had 24-hour ambulatory blood pressure measurement (ABP) were included in the study. Those with secondary HT, heart failure, coronary artery disease, moderate and severe valvular heart disease, peripheral artery disease, stroke, chronic renal failure, liver disease, hematological diseases, clinical evidence of infection and thyroid function tests were not included in the study group. After the above-mentioned exclusion criteria, a total of 157 patients were included in the study, 69 (44%) of them being resistant HT and 88 (56%) being controlled HT according to ABPM. The study was approved by the local institutional ethics committee. Our study protocol complies with the Helsinki Declaration.

Ambulatory Blood Pressure Measurement

For 24-hour ABP, with a commercially approved, non-invasive device (Schiller BR-102 plus, Germany), 15-minute intervals during the day (from 6:00 to 22:00) and at night, (from 22:00 to 06:00) measurements were made at 30-minute intervals. The cuff was attached to the patient's passive arm. All patients were instructed to continue their daily activities during ABS, avoid excessive exercise, and remain still during the

measurement. The sleeping and waking times of the patients were recorded according to their own reports. Computer software was used during the analysis of the records. Patients whose blood pressure (BP) measurement failed 20% or more were excluded from the study. For each patient, the 24-hour ABP mean value was calculated according to the hourly averages of daytime and nighttime SBP and DBP.

Including appropriate lifestyle changes, at least one of which is a diuretic, an angiotensin converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB) and a long-acting calcium channel blocker are also given to target blood pressure with 3 or more drugs at the maximum tolerable dose. Failure to reach (systolic blood pressure <140 mmHg and / or diastolic blood pressure <90 mmHg) or reaching the target blood pressure value with at least 4 drugs was defined as Resistant Hypertension [1,2].

Laboratory Evaluation

Blood samples were taken from an antecubital vein by atraumatic venipuncture after 12 hours of fasting. Biochemical parameters such as serum total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, triglycerides, glucose, and creatinine were measured in abbot ARCHITECT c8000 device. Hemoglobin (Hb), RDW and white blood cell (WBC) counts were performed on the MINDRAY BC-6800 automatic blood count device.

Statistical Analysis

Continuous variables were given as mean±standard deviations (SD or as median (interquartile range (IQR)). The Kolmogorov-Smirnov test was used to determine the distribution of the data. Category variables were expressed as percentages. Continuous variables were compared to the student-t test if they were distributed normally, otherwise compared to the Mann Whitney U test. Categorical variables were compared to the chi-square test or the Fisher exact test. In order to determine the effect of RDW on resistant hypertension, multivariate logistic regression analysis was performed by adjusting with age, gender, DM, BMI, total cholesterol, and creatinine. A p value of < 0.05 was considered statistically

significant for all statistical analyses. Receiver operating characteristic (ROC) curve analysis was performed to obtain area under curve (AUC) of the RDW for predicting RH. Analysis of the data was done using SPSS-24(Statistical Package for Social Science for Windows).

Results

The average age in the study population was 57 ± 11 , and 121 (77%) of the patients were followed by female gender. The patients were divided into two groups as controlled (n = 88) and resistant hypertension (n = 69). The clinical, laboratory and demographic characteristics of the patients were compared in Table 1. The average 24-hour systolic blood pressure was 141 mmHg (140-146) in the RHT group, 122 mmHg (118-125) in the CHT group, the average 24-hour diastolic blood pressure was 89 mmHg (84-93) in the RHT group and 78 mmHg (74-81) in the CHT group. The ratio of patients with RDW level, BMI value and DM was significantly higher in the RHT group compared to the CHT group (p = 0.02, p = 0.005, p = 0.001, respectively). RDW by multivariable logistic regression analysis (odds ratio [OR]: 1.684, 95% confidence Interval [CI]: 1.250-2.201 p <0.001), diabetes mellitus (OR: 3.459, 95% CI: 1.095-10.930 p = 0.035) and Body Mass Index (BMI) (OR: 1.085, 95% CI: 1.013-1.163 p = 0.02) was found to be an independent predictor of resistant hypertension (Table 2). In the ROC analysis performed of RDW in predicting RHT, the optimal predictive value for RDW was % 14.65 with 62.5% sensitivity and 65.2% specificity. RDW's Area Under Curve (AUC) value was 0.63 (95%CI: 0.551-0.726) (Figure 1 and Table 3).

Figure 1: ROC curve analysis for RDW level to predict resistant hypertension with 65,2% sensitivity and 62,5% specificity.

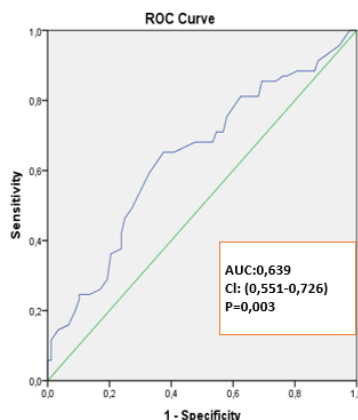


Table 1: Comparison of the clinical, laboratory and demographic data of the Controlled and Resistant Hypertension groups

	Controlled Hypertension (n = 88)	Resistant Hypertension (n = 69)	p value
Age (years)	56±10	59±12	0.122
Gender (female%)	71 (%80)	50 (%72)	0.224
DM (%)	5 (%5)	14 (%20)	0.01
Smoking (%)	12 (%13)	10 (%14)	0.878
ACEI/ARB (%)	82 (%93)	69 (%100)	<0.001
Diuretic (%)	61 (%70)	69 (%100)	<0.001
Ca Channel Blocker (%)	55 (%62)	56 (%81)	<0.001
Beta Blockers (%)	15 (%17)	39 (56)	<0.001
Hemoglobin (gr/dl)	13.7±1.3	13.8±1.5	0.965
Leukocyte (103)	7.9±1.4	8.3±1.3	0.114
Creatinine (mg / dl)	0.78 (0.6-0.9)	0.80 (0.64-0.98)	0.170
Total Cholesterol (mg / dl)	195±35	201±31	0.281
Triglyceride (mg / dl)	189±93	178±75	0.857
LDL (mg/dl)	107±32	114±32	0.180
HDL (mg/dl)	49±10	50±11	0.481
RDW (%)	14.1±1.2	14.8±1.4	0.02
BMI (kg/m2)	29.6±4.8	31.3±5.7	0.05
SBP 24 hours average (mmHg)	122 (118-125)	141 (140-146)	<0.001
DBP 24 hours average (mmHg)	78 (74-81)	89 (84-93)	<0.001

Note: Normally distributed numerical parameters were given as average ± standard deviation, numerical parameters not showing normal distribution were given as median value and 25-75%. Categorical variables were expressed as numbers (percentages). ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, LDL: Low density lipoprotein, HDL: High density lipoprotein, RDW: erythrocyte distribution width, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2. Multivariable logistic regression analysis to determine predictors of resistant hyper-tension

Variables	OR	CI 95%	P value
Gender (female)	2.170	0.864-5.452	0.099
Age (years)	1.027	0.994-1.060	0.105
Diabetes mellitus	3.459	1.095-10.930	0.035
Total cholesterol (mg / dl)	1.005	0.995-1.016	0.308
Creatine (mg / dl)	1.825	0.297-11.228	0.516
BMI (kg/m2)	1.085	1.013-1.163	0.02
RDW	1.684	1.250-2.201	<0.001

Note: CI=confidence interval; OR=odds ratio; RDW=Red cell distribution width, BMI: Body mass index

Table 3. Receiver operating characteristic (ROC) curve comparison of RDW level in predict-ing resistans hypertension and controlled hypertension

RISK FACTOR	AUC (95%)	Cut off	p	Sensitivity (%)	Spesifty (%)
Resistant Hypertension	0.639 (0.551-0.726)	14.65	0.003	65.2	62.5

Area Under the ROC curve (AUC), sensitivity and specificity by the optimized Cutoff points for RDW level in predicting resistant hypertension



Discussion

According to the results of our study, RDW level was found to be significantly higher in the RHT group compared to the CHT group. In multivariable logistic regression analysis, RDW level was monitored as an independent predictor of RHT.

RHT is associated with an increased risk of major adverse cardiovascular events and death. Studies have reported that cardiovascular diseases such as myocardial infarction, congestive heart failure and stroke are more common in RHT patients [11]. In prospective studies comparing RHT and HRT, it was found that the frequency of cardiovascular events was nearly twice as high [12-15]. Risk factors for RHT include advanced age, obesity, chronic kidney disease, black race, and diabetes mellitus [4]. In previous studies, MPV values, which are among the hemogram parameters, have been shown to predict adverse cardiovascular events in RHT patients [16]. In our study, the rate of diabetic patients ($p = 0.01$) and BMI ($p = 0.05$) were higher in the RHT group. Again, in multivariable regression analysis, BMI and DM resistant hypertension were found to be independent predictors.

The erythrocyte distribution width is a parameter showing the distribution of the size of erythrocytes and is analysed in routine complete blood count. During inflammation, inflammatory cytokines suppress erythrocyte maturation and increase erythrocyte heterogeneity by causing juvenile erythrocyte entry into the circulation [7-9]. Lippi et al. showed that RDW is associated with inflammatory markers hs-CRP and erythrocyte sedimentation rate [17]. It has been suggested that the possible mechanism of the relationship between RDW, which is considered an inflammatory marker, and cardiovascular diseases, is chronic inflammation [18].

Studies have shown that RDW level increases like other inflammatory markers in acute myocardial infarction, coronary artery disease, and heart failure [19-23]. The erythrocyte distribution width is a strong and independent predictor of mortality in cardiovascular diseases [24]. Oxidative stress has been shown to play an important role in the increase of RDW in patients with cardiovascular disease. Oxidative stress increases the RDW level by causing endothelial dysfunction and changes in the skeletal structure of the cell [25]. Tonelli M et al. found that high RDW levels were independently associated with cardiovascular events and mortality in patients with HT [26]. Tanindi et al. found higher RDW levels in prehypertensive and hypertensive patients than healthy individuals. They mentioned 2 possible mechanisms for RDW height. The first

of these was the activation of the renin angiotensin system in which angiotensin II caused increased erythropoietin and early proliferation of erythroid progenitors. The second mechanism is that the activation of the adrenergic system increases the activation of the sympathetic nervous system, and this increases the RDW level by causing an increase in erythropoietin production [10]. In a different study, it was observed that RDW was higher in the patient group with non-dipper pattern in patients with hypertension compared to the patient group with dipper pattern [27]. In our study, it was found that the RDW level was higher in the RHT group and that the RDW level in the hypertensive patient population was an independent predictor of resistant hypertension.

The high RDW value in hypertension patients can be used as an early warning system in identifying RHT patients. Early detection and treatment of RHT can reduce the risk of cardiovascular events. In our study, we determined that patients with a RDW of less than % 14.65 would have RHT with 62,5% specificity and 65,2 % sensitivity

Conclusion: RDW, which was found to be associated with high mortality in cardiovascular diseases, was significantly higher in the RHT patient group compared to the CHT patient group, and RDW was found to be an independent predictor of resistant hypertension.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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