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ORIGINAL ARTICLE

Red Blood Cell Distribution width: A Reliable Marker in Patients with Multiple Sclerosis?

Kırmızı Kan Hücresi Dağılım Genişliği: Multipl Sklerozlu Hastalarda Güvenilir Bir Belirteç mi?

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ABSTRACT

Objective: The red blood cell distribution width (RDW) is a prognostic marker in patients with active or chronic inflammation, cardiovascular, and other autoimmune diseases. Therefore, this study aimed to evaluate levels of RDW in patients with multiple sclerosis (MS), disease subtypes, and attacked groups.
Material and Methods: MS patients and healthy controls were included in the study. Demographic characteristics of MS and controls, types of MS, MS attacks or no attacks, and laboratory parameters analysis were evaluated. RDW was calculated according to the following formula: RDW = (Coefficie t of Variability of RBC ÷ mean MCV) × 100. All groups and subgroups were compared according to the RDW value.
Results: The study was conducted on 105 MS patients, 74 (70.5%) females, and 31 (29.5%) males, with a mean of 38 (20-64) years of age. RDW values in the MS group were 13.8 (12.1-27.1), whereas in the control group, the values were 13.4 (12.1-17.4) (p=0.007). Receiver operating characteristic (ROC) analysis revealed that using a cut-off point of 13.55, RDW predicts MS with a sensitivity of 59% and specificity of 54.2%. There was no statistically significant difference among the MS subgroups and attacked groups according to RDW value (p=0.41, p=0.92).
Conclusion: RDW would be a novel, low-cost-effective, widely and immediately available biomarker for patients with MS.

Keywords: Red blood cell distribution width, Multiple sclerosis, Biomarker,Inflammatio

ÖZ

Amaç: Eritrosit dağılım genişliği (RDW), aktif veya kronik inflamasyonu olan, kardiyovasküler ve diğer otoimmun hastalıkları olan hastalarda prognostik bir belirteçtir. Bu çalışmanın amacı multiple skleroz hastalarında, hastalık alt tiplerinde ve atak gruplarında RDW düzeylerini değerlendirmektir.
Gereç ve Yöntem: Çalışmaya multiple skleroz (MS) hastaları ve sağlıklı bireyler dahil edildi. MS ve kontrol grubunun demografik özellikleri, MS tipleri, MS atağı olup olmadığı ve laboratuvar parametrelerinin analizi değerlendirildi. RDW şu formüle göre hesaplandı: RDW = (RBC Değişkenlik Katsayısı ÷ ortalama MCV) × 100. Tüm gruplar ve alt gruplar RDW değerine göre karşılaştırıldı.
Bulgular: Çalışma, yaş ortalaması 38 (20-64) yıl olan, 74'ü (%70,5) kadın ve 31'i (%29,5) erkek olmak üzere 105 MS hastası üzerinde gerçekleştirildi. MS grubunda RDW değerleri 13,8 (12,1-27,1), kontrol grubunda ise 13,4 (12,1-17,4) idi (p=0,007). Alıcı işlem karakteristikleri (ROC) analizi, RDW'nin 13,55 kesme noktası kullanıldığında hastalığı %59 duyarlılık ve %54,2 özgüllükle tahmin ettiğini ortaya çıkardı. MS alt grupları ve atak grupları arasında RDW değerine göre istatistiksel olarak anlamlı fark yoktu (p=0,41, p=0,92).
Sonuç: RDW, MS hastalarına yönelik yeni, düşük maliyetli, yaygın olarak ve hemen bulunabilen bir biyobelirteç olabilecektir.

Anahtar kelimeler: Eritrosit dağılım genişliği, Multiple skleroz, Biyobelirteç, İnflamasyo

Introduction

Red blood cell distribution width (RDW) is a routinely reported parameter in the complete blood cell count test and refle ts variation in red blood cell size or red blood cell volume (1). Recent studies have shown that RDW is an inflammatory biomarker. Furthermore, the complete blood cell count test reported a positive correlation between RDW and the severity of inflammation (2). RDW is a prognostic biomarker in patients with cardiovascular diseases, COVID-19, brain injury, active or chronic inflammation, and other autoimmune diseases (3-8).

It is well-known that autoimmune diseases develop because of chronic inflammation. Multiple Sclerosis (MS) is an autoimmune disease associated with the activation of the immune system, leading to demyelination of the central nervous system (9).

MS is divided into 4 main groups according to the clinical course of the disease. The most common MS subtype is the relapsing-remitting MS variant (RRMS), in which the disease presents with relapses. In this disease group, separate attacks that can last from days to weeks are observed. Clinical stability is observed between attacks. Complete recovery is expected after the first attacks. However, the attacks start to leave disability after a while. In the following periods, some patients with RRMS have fewer attacks, but clinically significant progression

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is observed. This group is called secondary progressive MS (SPMS). There is also a type of MS in which clinical progression is observed from the beginning of the disease with no attacks. This group is called primary progressive MS. The least common MS variant is progressive relapsing MS (PRMS), in which progression continues, with occasional attacks. Although this variant has similarities with primary progressive MS, it is distinguished by occasional attacks (10).

The pathologic mechanisms in MS types are not fully understood. However, inflammation is always present with active demyelination and neurodegeneration occurs in all forms of MS (11). The pathological mechanism of MS types has yet to be sufficiently clarified. However, inflammation always coexists with active demyelination and neurodegeneration occurs in all forms of MS. In some cases, MS can be complicated to diagnose.

A hemogram is a straightforward and widely available test. Our first aim in this study was to evaluate the RDW level and its correlation in patients with MS. With correlation, it is thought to be a helpful and simple biomarker for the diagnosis of MS. Our second aim is to examine the RDW levels between attacks and also MS subtypes.

Methods

In our retrospective study, we included patients admitted to the Department of Neurology, Selcuk University Faculty of Medicine Hospital, who were diagnosed with MS according to the 2017 McDonald criteria, and who had been followed up in our department for at least 1 year (12-15). The study was approved by the Selcuk University Local Ethics Committee (Reg. number: 2018/24, Decision number: 2018/437). Between November 2017 and December 2018, 105 MS patients (patient group) and 59 healthy individuals (control group) were included in the study. MS and control groups were matched in terms of age and gender. The medical records of the patients were obtained retrospectively through the hospital automation system. Demographic characteristics, MS subtypes, attack positive/non-attack positive groups, and laboratory parameters were recorded. Patient records were reviewed and the diagnosis of the disease and the specified MS subtype were recorded. Patients were not retrospectively diagnosed with MS subtype. MS patients were analyzed in 3 subtypes: relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS). Progressive relapsing MS patients were also included in the PPMS group. Patients with clinically isolated syndrome or radiologic isolated syndrome were not included in the study.

RDW level was analyzed in the study. Since we aimed to examine the correlation that can only be understood with a simple test, such as a hemogram, other parameters were not included in the study. The RDW level in the first hemogram test performed on the hospital automation system when the patient came for follow-up or was admitted to the hospital was recorded.

Patients with comorbidities that might affect RDW levels were not included in the study. Therefore, patients with a history of rheumatologic diseases, active or chronic infections, hematologic diseases, hypertension, diabetes, cardiovascular diseases, malignancies, and renal or hepatic insufficiency were excluded. RDW was calculated according to the formula RDW = (RBC Coefficient of Variation ÷ mean MCV) × 100. The RDW reference range in our laboratory is between 1 and 15.0%.

This study was conducted under the national regulations and the Declaration of Helsinki. Ethics committee approval was obtained from the Ethics Committee of the Faculty of Medicine at Selcuk University.

Statistical analysis

The data in this study were analyzed with Statistical Package for the Social Sciences (SPSS), version 20.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The Shapiro-Wilk test was used for data distribution analysis. Categorical variables were summarized as numbers and percentages; continuous variables were presented as standard deviation if normally distributed, otherwise as median (minimum-maximum). The groups were compared using an independent sample t-test or Mann-Whitney U test for continuous variables and chi-square tests for categorical variables according to the distribution of the data. Kruskal-Wallis analysis was used to compare the three groups. An additional evaluation was performed to determine cut-off points for RDW in MS using receiver operating characteristic (ROC) curve analysis. A p-value of <0.05 was considered statistically significant

Results

The study was conducted patients with 105 MS patients, 74 (70.5%) females, and 31 (29.5%) males,

with a mean age of 38 (20-64) years. Fifty-nine patients were included in the control group, 35 (59.3%) were female and 24 (40.7%) were male, with a mean age of 34 (26-55) years. There was no statistically significant difference between the groups according to age or gender (p=0.2, p=0.2). The RDW values were higher in the MS group. As shown in Table 1, the RDW values were 13.8 (12.1-27.1) in the MS group and 13.4 (12.1-17.4) in the control group (p=0.007). Using a cut-off point of 13.55, ROC analysis revealed that RDW predicted MS with 59% sensitivity and 54.2% specificity (Figure 1). The area under the curve for this association was 0.627 and the 95% CI was 0.541-0.713 (p=0.007).

Table 1. The red blood cell distribution width (RDW) in patients with multiple sclerosis and control group

	MS (n=105)	Control (n=59)	*P* value
Age (median, mean-maximum)	38 (20-64)	34 (26-55)	0.2
Gender (n, %) Male Female	 31 (29.5%) 74 (70.5%)	 24 (40.7%) 35 (59.3%)	0.2
RDW (%) (median, mean-maximum)	13.8 (12.1-27.1)	13.4 (12.1-17.4)	0.007*

*Statistically significant value, MS: Multiple sclerosis, n: number, RDW: Red blood cell distribution width

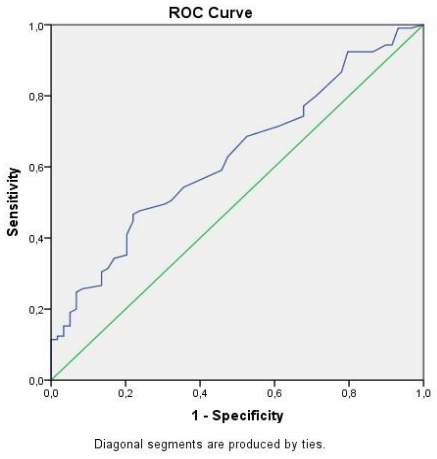

Figure 1. The red blood cell distribution width (RDW) in MS with receiver operating characteristic (ROC) curve analysis

The RDW ratio was not statistically different in patients with and without MS attacks (14.7±2.5% vs. 14.7±2.8%, *P*=0.92) (see Table 2). Eighty-five patients (80.9%) were diagnosed with RRMS, seven patients (6.7%) with PPMS, and 13 patients (12.4%) with SPMS. There was no statistically significant difference in RDW values between the groups (p=0.41) (see Table 3). RDW at diagnosis was found to be an independent predictor for the diagnosis of the disease in patients with MS.

Table 2. The red blood cell distribution width (RDW) according to attacks groups in patients with multiple sclerosis

	Attack (n=68)	No Attack (n=37)	*P* value
Age (mean SD)	38.8±12.1	38.6±9.6	0.95
Gender (n, %) Male Female	 19 (%27.9) 49 (%72.1)	 12 (%32.4) 25 (%67.6)	0.8
RDW (%) (mean SD)	14.7±2.5	14.7±2.8	0.92

RDW: Red blood cell distribution width, n: Number, SD: Standard deviation

Table 3. The red blood cell distribution width (RDW) according to disease subgroups in patients with multiple sclerosis

	RRMS (n=85)	PPMS (n=7)	SPMS (n=13)	*P* Value
Age (mean SD)	37.9±11.5	34.6±8.2	46.1±8.2	0.02*
Gender (n, %) Male Female	 21 (%24.7) 64 (%75.3)	 5 (%71.4) 2 (%28.6)	 5 (%38.5) 8 (%61.5)	0.02
RDW (%) (mean SD)	14.8±2.7	13.8±1.2	14.7±2.7	0.41

Discussion

It has been shown that inflammation can cause changes in red blood cell maturation. RDW is a parameter refl cting the greater degree of red blood cell volume distribution and can also be used as an indicator of inflammation. Studies on atherosclerosis have revealed that a high RDW level is a marker for atherosclerotic diseases and also indicates an increased risk of the progression of atherosclerosis. Furthermore, many diseases have shown that an increased RDW level can predict severe morbidity and mortality. In addition, RDW may reflect subclinical inflammation and is associated with poor functional status among the elderly (16-19). It is known that RDW increases with age. In our study, the groups and subgroups were middle-aged. RDW values were not at very high levels. High RDW levels can be detected in numerous diseases, including hematologic diseases, hypertension, diabetes mellitus, cardiovascular diseases, malignancies, renal or hepatic disorders, and other inflammatory diseases. Therefore, we excluded these diseases from our study.

The pathogenesis of MS is multifactorial, but it is considered an autoimmune disease. Most MS research has focused on the pathologic involvement of B and T lymphocytes. However, there is also some research on erythrocytes, which may play an important role in MS pathology. Erythrocytes have antioxidant enzymes and

structural proteins. The impaired antioxidant capacity of erythrocytes can lead to oxidative stress. Oxidative stress may be associated with inflammation. In one study, advanced oxidation protein products (AOPP), malondialdehyde (MDA), and superoxide dismutase (SOD) activity in erythrocytes were significantly correlated with clinical severity, radiological findings (gadolinium uptake lesion volume) and disease duration in RRMS. Neuroinflammation in MS is associated with altered oxidative status and this may have effects on erythrocytes. We examined this inflammatory effect not at the enzyme level but as a more gross change in RDW (20).

RRMS patients have been shown to have increased RDW levels compared to healthy controls. They also revealed that increased RDW levels were positively correlated with EDSS scores (20). In our study, it is surprising that no change was found in RDW values in patients with and without attacks. This may be related to immunosuppressive or immunomodulatory treatments. However, we did not evaluate the relationship between disease, RDW, and treatment options in this study.

Many studies have shown that increased RDW level is associated with poor prognosis and morbidity (20-23). In our study, we did not evaluate in terms of prognosis or clinical severity, but it is obvious that there is a certain disease progression and morbidity in patients with MS, since a comparison was made with the control group. Our study showed that despite increased RDW levels in all patients with MS, there was no significant difference between MS subtypes. This may also be related to immunosuppressive or immunomodulatory therapies. Therefore, RDW is not a parameter to be used to determine prognosis and subtypes in patients with MS.

Conclusion

RDW will be a new, suitable, low-cost-effective, widespread, and available biomarker for MS patients. Although the exact mechanism is unknown, it may reflect the inflammatory status of MS. However, RDW is not a parameter to be used for determining prognosis and relapse in MS. Our study has some limitations. The MS patients were relatively small, and the study was conducted in a single center. In addition, immunosuppressive or immunomodulatory treatment options were not evaluated.

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Conflicts of interest

Authors have no conflicts of interest to disclose

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Presentation in congress

This study was presented as an oral presentation at the International Turkish World Multiple Sclerosis Congress on 14-17 February 2019.

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