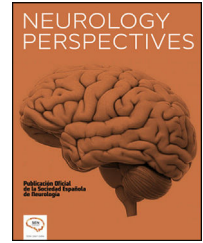




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## ORIGINAL ARTICLE

# Red cell distribution width as a predictor of disability in relapsing-remitting multiple sclerosis



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### KEYWORDS

Multiple sclerosis;  
Relapsing-remitting multiple sclerosis;  
Red blood cell distribution width

### Abstract

#### Background

Red blood cell distribution width (RDW) reflects the variability of circulating red blood cells. The relationship between multiple sclerosis (MS) and RDW is not well studied. The main objective of this work was to compare baseline RDW to EDSS at 5 years of diagnosis and verify if RDW predicts worse disability.

#### Methods

We conduct a retrospective observational study of relapsing-remitting MS (RRMS) patients followed in the Neuroimmunology Clinic that had at least one measuring of RDW at baseline.

#### Results

We included 82 patients with RRMS meeting inclusion criteria, 73,2% female with a mean age of 33,56 years old. Median EDSS score at baseline was 1.5.

9,8% patients had new T2 lesions in MRI at 5 years and 4,9% showed lesions capturing contrast at 5 years. Regarding DMT, 75,6% were treated with interferon, glatiramer acetate, teriflunomide, or dimethyl fumarate, and 21,9% were under fingolimod, natalizumab, rituximab, and cladribine, and the remaining 2,4% were without treatment at 5 years.

A multiple linear regression model confirmed increased disability (EDSS at 5 years) for patients undergoing second-line treatment ( $\beta=0,86;p=,003$ ) and higher RDW at baseline ( $\beta=0,47;p=,007$ ). Presenting RDW results for quartiles, it was statistically significant for quartile 4 [13,5;16,4]( $\beta=0,74;p=,039$ ), suggesting that a very increased RDW at baseline is strongly associated with higher EDSS at 5 years.

#### Conclusion

Higher RDW at baseline was correlated with a worse disability at 5 years in RRMS patients. Furthermore, RDW equal to or higher than 13,5% may be useful in identifying patients that will have a worse disability at 5 years.

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**PALABRAS CLAVE**

Esclerosis múltiple;  
Esclerosis múltiple  
recurrente-remitente;  
Ancho de distribución  
de glóbulos rojos.

## El ancho de distribución de los glóbulos rojos como predictor de discapacidad en la esclerosis múltiple remitente-recidivante

**Resumen****Introducción**

Ancho de distribución de glóbulos rojos (RDW) la combinación de los glóbulos rojos circulantes. La relación entre MS y RDW no está bien estudiada. El objetivo principal de este trabajo fue comparar el RDW basal con el EDSS a los 5 años del diagnóstico y verificar si el RDW predice una peor discapacidad.

**Métodos**

Realizamos un estudio observacional retrospectivo de EM remitente-recurrente (EMRR) de pacientes en la Clínica de Neuroinmunología que tenían al menos una medición de RDW al inicio del estudio.

**Resultados**

Se incluyeron 82 pacientes con EMRR que cumplieron los criterios de inclusión, el 73,2% mujeres con una edad media de 33,56 años. La puntuación media de la EDSS al inicio del estudio fue de 1,5. El 9,8% de los pacientes presentaron nuevas lesiones T2 en la RM a los 5 años y el 4,9% mostró captación de contraste a los 5 años. En cuanto a DMT, el 75,6% se trató con interferón, acetato de glatiramer, teriflunomida o dimetilfumarato, y el 21,9% con fingolimod, natalizumab, rituximab y cladribina, y el 2,4% restante sin tratamiento a los 5 años.

Un modelo de regresión lineal múltiple garantiza un aumento de la discapacidad (EDSS a los 5 años) para los pacientes sin tratamiento de segunda línea ( $\beta = 0,86$ ;  $p = 0,003$ ) y una mayor RDW al inicio del estudio ( $\beta = 0,47$ ;  $p = 0,007$ ). Al presentar los resultados de RDW para los cuartiles, fue estadísticamente significativo para el cuartil 4 [13.5; 16.4] ( $\beta = 0.74$ ;  $p = .039$ ), lo que sugiere que un RDW muy elevado al inicio del estudio está fuertemente asociado con una mayor EDSS a los 5 años.

**Conclusiones**

Un mayor RDW al inicio del estudio se correlacionó con una peor discapacidad a los 5 años en los pacientes con EMRR. Además, una RDW igual o superior al 13,5% puede ser útil para identificar a los pacientes que tendrán una discapacidad peor a los 5 años.

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**Background**

The advent of new and more effective disease-modifying therapies (DMT) is rapidly changing the management of multiple sclerosis (MS).<sup>1</sup> Therefore, the risk stratification of MS is becoming increasingly important to individually predict the probability of disease progression.<sup>1</sup>

The therapeutic approach of MS is based on several factors, including disease activity, risk of progression, individual patient preferences, and personal expertise.<sup>2</sup> However more biomarkers are needed to determine prognosis.

Red blood cell distribution width (RDW) is an objective measured value, which reflects the variability of circulating red blood cells. This measure is easily, inexpensively and rapidly calculated as ratio of standard deviation (SD) of red blood cell (RBC) volume and mean corpuscular volume (MCV) [i.e.,  $(RDW-SD)/(MCV) \times 100$ ], with final result expressed as percentage. The reference range typically spans between 12 and 15%, however the so-called normal values are largely dependent on instrumentation and population.<sup>3</sup>

The first and most clinically significant use of RDW is for evaluating different types of anemias. Several forms of anemia may manifest with high RDW, for example, RDW is

useful in the differential diagnosis between iron deficiency anemia and heterozygous thalassemia, whereby RDW is higher in the former condition and almost normal in the latter.<sup>3</sup> RDW can also increase in other conditions such as blood transfusion, chronic liver disease, autoimmune disorders, and cancer.<sup>3</sup>

In the past years, RDW has received attention in the field of inflammation as it was associated with the outcomes in patients with autoimmune and cardiovascular diseases.<sup>3,4</sup>

Multiple sclerosis (MS) is a progressive inflammatory disease of the central nervous system that results in neurological dysfunction and disability.<sup>5</sup>

Accumulating data have shown that immune and inflammatory factors are involved in the pathogenesis of MS, and loss of polyunsaturated fatty acids from plasma and blood cell membranes has also been reported in patients with MS, contributing to the variation of erythrocyte deformability.<sup>6</sup>

Peng et al (2015), made a retrospective study that suggested that elevated RDW values are associated with EDSS score in patients with MS when compared to controls.<sup>6</sup>

This study aimed to assess the association between red blood cell distribution width and RRMS. We hypothesized

that RDW at baseline can be an objective measure of predicting disability in RRMS patients at 5 years.

Our primary goal was to compare baseline RDW to EDSS at 5 years of diagnosis and verify if it predicts worse disability.

## Methods

A retrospective observational study was performed. We studied patients with RRMS followed in the Neuroimmunology Clinic of Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos that had at least one measuring of RDW at baseline. The Expanded Disability Status Scale (EDSS) score was used to evaluate disease progression of RRMS. We included patients diagnosed with RRMS (between 2005 and 2015) according to the McDonald 2017 criteria. Exclusion criteria were patients with hematologic, oncology, infections, and thyroid disease, renal or hepatic dysfunction, or other autoimmune diseases.

## Statistical analysis

Statistical analysis was performed with IBM® SPSS® Statistics version 26. Descriptive statistics were presented as means (M) and standard deviations (SD) for continuous symmetrical variables. Frequencies (n) and percentages were presented for categorical variables. Univariate comparisons and associations with EDSS at 5 years were assessed with t-tests, ANOVAs, and Pearson correlations accordingly. Red cell distribution width was evaluated in two ways; i) RDW was included as a continuous variable ii) red cell distribution width quartiles using the lowest quartile as the reference category. Multiple linear regression was used to measure the effect size ( $\beta$ ) of the previously detected statistically significant predictors in EDSS at 5 years. Significance was based on a 95% confidence interval (95% CI). Residuals normality and homoscedasticity were assessed and confirmed, respectively with visual inspection of the histogram and the plot of standardized residuals vs fitted values. Multicollinearity was ruled out by confirming Tolerance >.10 and VIF <4. No residuals were found outside the [-3; 3] interval. The quality of regression was assessed with the F-test and  $R^2$ .

## Standard protocol approvals, registrations and patient consents

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Results

We identified 82 patients with RRMS meeting inclusion criteria, 60 (73,2%) female and 22 (26,8%) male. The patients had a mean age of 33,56 years old (SD=20,21), ranging from 14 to 55. Education was distributed by the levels of basic (n=28; 34,1%), secondary (n=23; 28,0%) and high education (n=28; 34,1%). Intention to get pregnant was explicit in clinical records in 18 patients, representing 30.0% of the women at childbearing age. The median EDSS score at baseline was 1.5.

At 5 years of diagnosis, eight (9,8%) patients had new T2 lesions in MRI and 4 (4,9%) showed lesions capturing contrast. Regarding DMT, 62 (75,6%) were treated with interferon, glatiramer acetate, teriflunomide, or dimethyl fumarate, and 18 (21,9%) were under fingolimod, natalizumab, rituximab, and cladribine, and the remaining 2 (2,4%) were without treatment at 5 years. Patient preferences regarding the treatment were mentioned in 6 (7,3%) cases. (Table 1)

RDW at baseline ( $r=,451$ ;  $p<,01$ ), EDSS at baseline ( $r=,596$ ;  $p<,01$ ), age at diagnosis ( $r=,339$ ;  $p<,01$ ), platelets at

**Table 1** Patient demographics and clinical data.

Variable	
Sex	
Male	22 (26.8%)
Female	60 (73.2%)
Age at diagnostic	33.56 (20.21) [14-55]
Education	
Basic education	28 (34.1%)
Secondary education	23 (28.0%)
High education	28 (34.1%)
NR	3 (3,7%)
EDSS at baseline	1.5 (1.5) [0-6.0]
Analytic assessment at baseline	
Hemoglobin (g/dL)	13.50 (1,21) [11.8-15.8]
Mean corpuscular volume (fL)	89.37 (4.47) [70.4-99.1]
RDW (%)	13.24 (0.76) [12.1-16.4]
White blood cells (exp3/uL)	7.18 (1.92) [2.6-11.9]
Platelets (Exp3/uL)	224.85 (52.17) [124.0-361.0]
C-reactive protein	1.05 (1.33) [0.01-5.80]
Sedimentation rate	11.34 (3.4) [1.0-18.0]
MRI at 5 years (n=42)	
New T2 lesions at 5 years	8 (9.8%)
Contrast enhancement lesions	4 (4.9%)
Pregnancy intention	18 (30.0%)
Treatment preference	6 (7.3%)
Treatment type at 5 years	
No treatment	2 (2.4%)
First-line (interferon, glatiramer acetate, teriflunomide, dimethyl fumarate)	62 (75.6%)
Second-line (fingolimod, natalizumab, rituximab, and cladribine)	18 (21.9%)
Results presented as n(%), mean (SD) [min-max] and median (IQR).	

baseline ( $r=,401$ ;  $p<,01$ ) and second-line treatment ( $p=,009$ ) were associated with a higher score of EDSS at 5 years. No significance was found for the association of EDSS at 5 years with sex, education, haemoglobin, mean corpuscular volume, white blood cells, C-reactive protein, and sedimentation rate at baseline.

A multiple linear regression model (table 2) confirmed increased disability (EDSS at 5 years) for patients undergoing second-line treatment ( $\beta=0,86$ ;  $p=,003$ ) and higher RDW at baseline ( $\beta=0,47$ ;  $p=,007$ ). Finally, EDSS at baseline also shows a positive association with the same measure, five years later ( $\beta=0,61$ ;  $p<,001$ ). Adjusted  $R^2$  was  $R^2=,520$ , suggesting that 52,0% of the EDSS at 5 years was explained by the considered predictors.

A secondary analysis was made and RDW was distributed into quartiles 12,1; 12,8[ ( $n=17$ ; 20,7%), [12,8; 13,1[ ( $n=20$ ; 24,4%), [13,1; 13,5[ ( $n=23$ ; 28,0%) and [13,5; 16,4[ ( $n=22$ ; 26,8%). When adjusting for predictors, RDW results for quartiles, considering the first quartile as reference, were statistically significant for quartile 4 ( $\beta=0,74$ ;  $p=,039$ ), suggesting that a very increased RDW at baseline is associated with higher EDSS at 5 years.

## Discussion

In this study, we analyzed factors that may predict progression on RRMS at 5 years.

The main determinants of RRMS progression at 5 years included higher RDW, high EDSS at baseline and patients under fingolimod, natalizumab, rituximab, and cladribine.

Higher RDW at baseline was correlated with a worse disability at 5 years in RRMS patients in this study. This correlation was found in both models, RDW as a continuous variable and comparing RDW to the lowest quartile.

From our study, RDW more than 13,5% may be useful in enabling differentiation between patients with worse disability at 5 years, despite the small number of patients in quartiles groups.

Treatment with fingolimod, natalizumab, rituximab, and cladribine was correlated with worse EDSS at 5 years which is expected due to the use of this kind of treatment for the more aggressive/active disease.

This study has potential limitations related to its retrospective design. The main limitation of this work

relates to the fact that this study only includes patients from one clinical site, which limits the generalizability of the study conclusions. The time we evaluate EDSS can be short, and an EDSS at 10 years could be more accurate in the sense that with the new treatments most of the patients have a mild disability at 5 years. Another limitation of this study is the RDW can be influenced by many factors and is very difficult to control. In this study the population is young and we excluded most of the diseases that can have an impact on RDW, however we didn't control for nutritional deficiency and genetic factors that can interfere with RDW.

## Conclusion

This is the first study about RDW as a disability biomarker in RRMS. We observed that higher RDW at baseline was correlated with a worse disability at 5 years in RRMS patients. Furthermore, RDW equal to or higher than 13,5% may be useful in identifying patients that will have a worse disability at 5 years. As a marker that can be used to estimate disability status in RRMS patients, RDW is an inexpensive and available test.

More studies should be held to confirm this association once biomarkers determining disability can have an impact on the therapeutic approach and in this sense, are imperious.

## Funding statement

The authors received no financial support for the research, authorship, and/or publication of this article.

## Ethical Considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

We followed the usual protocols on the patients publication, and we respected the privacy of the subjects, treating them anonymously.

This study was approved by the Ethics Committee from the "Unidade Local de Saúde de Matosinhos" with reference number 53/CE/JAS.

## Declaration of competing interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

## Acknowledgments

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**Table 2** Multiple linear regression predicting EDSS at 5 years

Variable	Odds ratio (Exp( $\beta$ ))	p-value	95% Confidence interval	
			Lower	Upper
Age of diagnosis	0,02	$p=,248$	-0,01	0,04
2 <sup>nd</sup> -line treatment	0,86	$p=,003^{**}$	0,30	1,43
RDW at baseline	0,47	$p=,007^{**}$	0,14	0,81
EDSS at baseline	0,61	$p<,001^{***}$	0,38	0,85
Platelets at baseline Exp <sup>3/uL</sup>	0,01	$p=,282$	-0,01	0,01

Tolerance  $>,10$ ; VIF  $<4$ ; \*  $p<,05$ ; \*\*  $p<,01$ ; \*\*\*  $p<,001$ ;  $R^2=,520$ ;  $F_{(5,72)}=15,63$  ( $p<,001$ )

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