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Original Article

The role of red cell distribution width as a marker in inflammatory bowel disease

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Aim: To determine whether red cell distribution width could be used for the assessment of disease activity in patients with inflammatory bowel disease.

Materials and methods: A total of 165 patients with inflammatory bowel disease (105 ulcerative colitis; 60 Crohn's disease) and 43 healthy blood donors were included in this retrospective study in a tertiary care setting. The medical records of the patients were reviewed to note clinical activity indices, red cell distribution width, serum C reactive protein, erythrocyte sedimentation rates, leukocyte, and platelet counts.

Results: Red cell distribution width, serum C reactive protein, erythrocyte sedimentation rate, platelet count, and the proportion of individuals with increased red cell distribution width were all significantly elevated in the patients compared to the controls ($P < 0.05$). Red cell distribution width and the proportion of patients having elevated red cell distribution width were higher in patients with Crohn's disease compared with ulcerative colitis ($P < 0.05$). Red cell distribution width was significantly correlated with erythrocyte sedimentation rate, endoscopic activity index (in ulcerative colitis), and platelet count ($P < 0.05$). For a red cell distribution width cut-off of 14.45 sensitivity for differentiation of Crohn's disease from ulcerative colitis was 70% and specificity was 56%.

Conclusion: Red cell distribution width, as a cost-effective tool, could be an additional parameter to assess disease activity in inflammatory bowel disease and an adjunctive marker in the differentiation between ulcerative colitis and Crohn's disease.

Key words: Inflammatory bowel disease, red cell distribution width

Kırmızı hücre dağılım hacminin inflamatuar barsak hastalığında belirteç olarak rolü

Amaç: Bu çalışma, kırmızı hücre dağılım hacminin, inflamatuar barsak hastalığı olan hastalarda, hastalık aktivitesinin değerlendirilmesinde kullanılabilirliğini belirlemek amacıyla yapılmıştır.

Yöntem ve gereç: İnflamatuar barsak hastalığı olan toplam 165 hasta (105 ülseratif kolit; 60 Crohn hastalığı) ve 43 sağlıklı kan donörü, tersiyer bir merkezde bu retrospektif çalışmaya dahil edildi. Hastaların tıbbi kayıtları klinik aktivite endeksi, kırmızı hücre dağılım hacmi, serum C reaktif protein, eritrosit sedimentasyon hızı, lökosit ve trombosit sayısı kaydedilmek için gözden geçirildi.

Bulgular: Kırmızı hücre dağılım hacmi, serum C reaktif protein, eritrosit sedimantasyon hızı, trombosit sayısı ve artmış kırmızı hücre dağılım hacimli bireylerin oranı, kontrollerle karşılaştırıldığında hastalarda anlamlı bir biçimde yüksekti ($P < 0,05$). Kırmızı hücre dağılım hacmi ve artmış kırmızı hücre dağılım hacimli bireylerin oranı ülseratif kolit ile karşılaştırıldığında, Crohn hastalığı olan hastalarda daha yüksekti ($P < 0,05$). Kırmızı hücre dağılım hacmi, eritrosit sedimentasyon hızı, endoskopik aktivite indeksi (ülseratif kolitde) ve trombosit sayısı ile anlamlı bir biçimde ilişkiliydi

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(P < 0,05). Crohn hastalığının ülseratif kolitden ayrımında, kırmızı hücre dağılım hacmi kestirim değeri 14,45 için duyarlılık % 70, özgüllük % 56 idi.

Sonuç: Kırmızı hücre dağılım hacmi, maliyet etkin bir araç olarak, inflamatuar barsak hastalığında hastalık aktivitesinin değerlendirilmesi için ek bir parametre ve Crohn hastalığının ülseratif kolitden ayrımında bir ek belirteç olabilir.

Anahtar sözcükler: İnflamatuar barsak hastalığı, kırmızı hücre dağılım hacmi

Introduction

The inflammatory bowel diseases (IBD) comprise 2 major phenotypes: Crohn's disease (CD) and ulcerative colitis (UC). Although research in recent years has led to great advances in understanding the inflammatory bowel, the diagnosis is still based on a combination of clinical, histologic, endoscopic, and radiologic data and the distinction between UC and CD can be difficult because of the lack of a differentiating single gold standard (1). Regarding laboratory work-up, combined testing for perinuclear antineutrophil cytoplasmic antibody (pANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) can be helpful in categorising IBD, with specificity and positive predictive value increasing to more than 95% (2). However, they are not yet widely used because of some variability in the results between laboratories and absence of international standards.

Red cell distribution width (RDW) is a quantitative measure of anisocytosis, the variability in size of the circulating erythrocytes. It is routinely measured by automated haematology analysers and is reported as a component of the complete blood count (CBC). RDW is typically elevated in conditions of ineffective red cell production (such as iron deficiency, B12 or folate deficiency), haemolysis and after blood transfusion. As a possible integrative measure of multiple pathologic factors (nutritional deficiencies, inflammatory stress, and renal dysfunction), RDW has been hypothesised to be associated with several disease processes including occult colon cancer, neoplastic metastases to marrow, liver disease, and heart failure (3-6). Recently one report has pointed to a possible role of RDW in inflammatory bowel disease as an additional inflammatory marker (7). Two other studies have shown that RDW can be potentially used as a marker for differentiating CD from ulcerative colitis UC (8,9). The results were promising because RDW can be routinely obtained from blood count, which is a simple, inexpensive, and readily available tool that provides potential for high rates of patient acceptance and compliance.

We designed the present study to determine whether RDW could be used for the assessment of disease activity in our patients with IBD. We also try to find out whether RDW could serve to differentiate CD from UC.

Materials and methods

A total of 165 IBD patients, 105 with UC and 60 with CD were included in the study. Forty-three healthy blood donors were chosen at random as the control group. The medical records of the patients were retrospectively reviewed to note haemoglobin (Hb) (range 14-18 g/dL for men, 12-16 g/dL for women), white blood cell count (WBC) (range 4000-10,000/mm^3), platelet count (range 150,000-450,000/mm^3), red cell distribution width (RDW, range 11%-14.2%), erythrocyte sedimentation rate (ESR) (range, 0-20 mm/h), and C-reactive protein (CRP) (0-0.8 mg/dL). The patients with CD who have a Crohn's Disease Activity Index (CDAI) higher than 150 were accepted as having active CD. Patients having moderate or severe disease according to the Truelove-Witts scale were accepted as having active UC. Endoscopic activity index (EAI) was also noted in the patients with UC. The tubes with EDTA were used for automatic blood count. The blood counts were determined on a Coulter STKS (Beckman Coulter, England).

All data are expressed as the mean ± standard deviation (SD). Statistical analyses were performed using SPSS release 10.0 for Windows. For comparisons of group results, P < 0.05 was considered statistically significant. Comparisons of parametric data between

the study subjects and controls were performed by using independent t test and one-way ANOVA. Nonparametric data were compared by using Mann-Whitney U-test and Kruskal-Wallis variance analysis. Pearson correlation analysis was used to analyse the relations between RDW and ESR, CRP, WBC, PLT, MPV, and EAI. Receiver operating characteristic (ROC) curves were obtained for RDW to explore the sensitivity and specificity for the diagnosis of CD and UC separately.

Results

There were no differences among CD and UC patients and the controls with respect to age and sex. The proportion of male patients among the ones with elevated RDW was 61.7% and 56.9% in the CD and UC groups, respectively. Moreover, there was no significant difference compared to the patients with normal RDW in each group (P > 0.05). The disease duration was also similar in patients with UC and CD (Table 1). It was median 84 (6-312) and 52 (1-300) months in CD patients with normal and high RDW, respectively (P = 0.265). It was median 60 (9-250) and 48 (1-240) months in UC patients with normal and elevated RDW, respectively (P = 0.185). Anaemia was significantly more common and RDW and inflammatory markers were significantly higher (except for MPV) in patients compared to the controls (Tables 2 and 3). The proportion of individuals having elevated RDW was significantly higher in the patient group as well. RDW and the proportion of patients having elevated RDW were higher in CD patients compared to UC patients (Table 4). RDW was significantly correlated with inflammatory markers as well as EAI (Table 5). Active disease was not correlated with an elevated RDW in both CD and UC patients (Table 6) and no significant correlation was observed between the extent of involvement and elevated RDW (Table 7). For a RDW cut-off of 14.45 sensitivity for differentiation of CD from UC was 70% and specificity was 56% [Area under curve: 0.668 (0.581-0.754), P < 0.001)] (Table 8 and Figure).

Table 1. Clinical and demographic characteristics of the patients with inflammatory bowel disease and the control subjects.

	CD (n = 60)	UC (n = 105)	Control (n = 43)	P
Age	37.7 ± 13.2	39.7 ± 10.7	35.3 ± 10.2	0.105
Sex (F/M)	21/39	45/59	12/31	0.191
Duration of disease (months)	86.3 ± 69.3	76.7 ± 65.1		0.377
Disease activity				
Active disease	11 (18.3%)	42 (40%)		
In remission	49 (81.7%)	63 (60%)		
Extent of involvement				
Ileitis	17 (28.3%)			
Colitis	15 (25.0%)			
Ileocolitis	28 (46.7%)			
Pancolitis		29 (27.6%)		
Extensive colitis		23 (21.9%)		
Left colitis		45 (42.9%)		
Proctitis		8 (7.6%)		

Crohn's disease: CD, Ulcerative colitis: UC, Female: F, Male: M

Table 2. Comparison of laboratory parameters between UC patients and the control group.

	UC (n = 105)	Control (n = 43)	P
Hb (g/dL)	13.4 ± 2	14.7 ± 1.3	< 0.001*
Htc	41.1 ± 5.2	44.2 ± 4.4	< 0.005*
MCV (fL)	79.7 ± 10.8	87.9 ± 3.9	< 0.001*
MPV (fL)	8.5 ± 1	8.9 ± 0.6	< 0.005*
PLT (/mm^3)	311,660 ± 97,350	269,210 ± 87,188	0.014*
WBC (/mm^3)	7763 ± 2761	6112 ± 1626	< 0.001*
ESR (mL/hour)	14.9 ± 14	-	-
CRP (mg/dL)	2 ± 4	-	-
RDW	15.3 ± 3.4	12.5 ± 1.4	<0.001*
RDW ≥14.2	51 (48.6%)	6 (14%)	<0.001*

Ulcerative colitis: UC, Haemoglobin: Hb, Haematocrit: Htc, Mean cellular volume: MCV, Mean platelet volume: MPV, Platelet: PLT, White blood cell: WBC, Erythrocyte sedimentation rate: ESR, C reactive protein: CRP, Red cell distribution width: RDW
*Statistically significant

Table 3. Comparison of laboratory parameters between CD patients and the control group.

	CD (n = 60)	Control (n = 43)	P
Hb (g/dL)	13.3 ± 2.1	14.7 ± 1.3	< 0.001*
Htc	40.2 ± 5.9	44.2 ± 4.4	< 0.001*
MCV (fL)	83.8 ± 8.4	87.9 ± 3.9	0.011*
MPV (fL)	8 ± 1	8.9 ± 0.6	< 0.001*
PLT (/mm^3)	349,100 ± 111,711	269,210 ± 87,188	< 0.001*
WBC (/mm^3)	7837 ± 2541	6112 ± 1626	< 0.001*
ESR (mL/h)	17 ± 12.4	-	-
CRP (mg/dL)	2.8 ± 4.9	-	-
RDW	16.5 ± 3.0	12.5 ± 1.4	< 0.001*
RDW ≥14.2	47 (78.3%)	6 (14%)	< 0.001*

Crohn's disease: CD, Haemoglobin: Hb, Haematocrit: Htc, Mean cellular volume: MCV, Mean platelet volume: MPV, Platelet: PLT, White blood cell: WBC, Erythrocyte sedimentation rate: ESR, C reactive protein: CRP, Red cell distribution width: RDW
*Statistically significant

Table 4. Comparative analysis of RDW in UC and CD patients.

	UC (n = 105)	CD (n = 60)	P
RDW	15.3 ± 3.4	16.5 ± 3.0	0.017*
RDW ≥ 14.2	51 (48.6%)	47 (78.3%)	< 0.001*

Crohn's disease: CD, Ulcerative colitis: UC, Red cell distribution width: RDW
*Statistically significant

Table 5. Correlation of RDW with EAI, Hb, Htc, and inflammatory markers.

Parameter	Spearman Correlation	P
EAI	0.218	<0.05*
BK	0.122	>0.05
PLT	0.361	<0.05*
MPV	-0.324	<0.05*
ESR	0.316	<0.05*
CRP	0.135	>0.05
Hb	-0.551	<0.05*
Htc	-0.584	<0.05*

Haemoglobin: Hb, Haematocrit: Htc, Mean cellular volume: MCV, Mean platelet volume: MPV, Platelet: PLT, White blood cell: WBC, Erythrocyte sedimentation rate: ESR, C reactive protein: CRP, Red cell distribution width: RDW, EAI: Endoscopic activity index in ulcerative colitis. *Statistically significant

Table 6. RDW and disease activity in UC and CD.

		RDW < 14.2 n (%)	RDW ≥ 14.2 n (%)	P
CD (n: 60)	Active (n: 11)	2 (18.2)	9 (81.8)	0.756
	Remission (n: 49)	11 (22.4)	38 (77.6)	
UC (n: 105)	Active (n: 42)	21 (50.0)	21 (50.0)	0.811
	Remission (n: 63)	33 (52.4)	30 (47.6)	

Ulcerative colitis: UC, Crohn's disease: CD, Red cell distribution width: RDW

Table 7. RDW and the extent of involvement.

		RDW ≥ 14.2	P
CD	Ileitis (n = 17)	14 (82.4%)	0.825
	Colitis (n = 15)	11 (73.3%)	
	Ileocolitis (n = 28)	22 (78.6%)	
UC	Proctitis (n = 8)	1 (12.5%)	0.068
	Left-sided (n = 45)	20 (44.4%)	
	Extensive (n = 23)	15 (65.2%)	
	Pancolitis (n = 29)	15 (51.7%)	

Ulcerative colitis: UC, Crohn's disease: CD, Red cell distribution width: RDW.
*Statistically significant if $P < 0.05$.

Table 8. Validity data for RDW for the differential diagnosis of CD from UC.

	AUC	Cut-off	Sensitivity (%)	Specificity (%)	P
RDW	0.668	14.45	70	56	P < 0.001*
		14.95	63	69	
		15.05	62	71	

AUC: Area under curve, Crohn's disease: CD, Red cell distribution width: RDW.
*Statistically significant

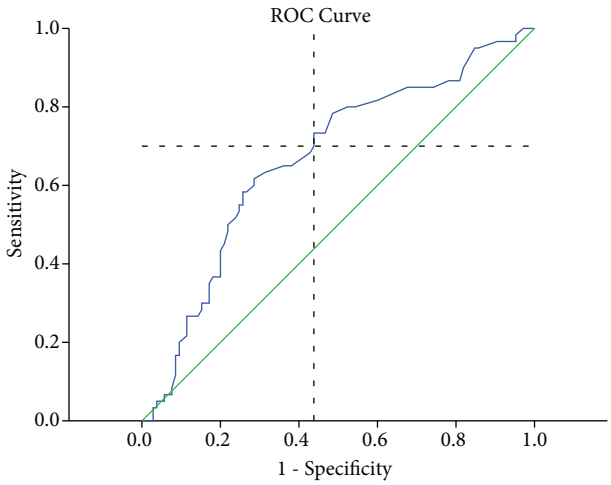

Figure. Differentiation of CD from UC. ROC curve for RDW for CD (Crohn's disease: CD, Red cell distribution width: RDW). Area under the curve is 0.668, P < 0.001.

Discussion

Our study showed that RDW could reflect inflammatory activity in IBD although it is not strong enough as a single parameter to be directly related with disease activity. The significant negative correlation with EAI shows that it may be an early indicator of clinical activity as well. RDW tended to increase as the involvement became more extensive in UC, which suggests a possible role in predicting disease extension. Our results also revealed that RDW may aid differentiation between CD and UC.

Distribution of erythrocyte volume (RDW) is a measurement of anisocytosis, rendered easy by modern cell counters, and is calculated as the coefficient of variation, i.e. the standard deviation of the distribution of red blood cell volumes divided by the mean corpuscular volume (MCV). Since the number of microcytic blood cells increases before overt anaemia, an elevated RDW in an otherwise normal blood count is a sensitive and specific indicator of early iron deficiency (10,11). The blood loss from the gastrointestinal tract may account for the elevated RDW in IBD patients compared to the control group (Tables 1 and 2). Nutritional deficiencies (i.e. B12 and folate) and blood transfusions during active disease also contribute to increases in RDW in this group of patients (10).

What is the explanation for different RDW values between CD and UC? The ileum, the site of vitamin B12 absorption, is involved in approximately 80% of CD cases (12). Absorption of iron occurs mainly in the proximal part of the duodenum, which is affected in 12%-15% of CD patients (13,14). These 2 differences related to the metabolism of 2 important micronutrients may lead to elevated RDW in CD compared to UC. Currently definitive distinction between UC and CD cannot be made even with histological examination, leading to the diagnosis of indeterminate IBD in 20%-30% of patients (15). Except for RDW none of the routine laboratory tests including inflammatory markers has been shown to be useful in this aspect. Previously Clarke et al. published a study on the potential role of red blood cell distribution width (RDW) as a marker for differentiating CD from UC (9). The authors found a statistically significant difference in favour of CD. The results of another series suggested that the RDW value may differentiate between UC and CD in patients when these diseases are in remission or inactive, but not when they are active (8). In our series RDW was more elevated in CD in both active

disease and remission, and for a RDW cut-off of 14.45 sensitivity for differentiation of CD from UC was 70% and specificity was 56%. Although the specificity is low, RDW may be used as an adjunctive parameter to the combination of ANCA and ASCA, which has a specificity of 92.8% but a sensitivity of only 54.6% in the diagnosis of CD. In this regard the role of RDW should not be underestimated because it is an inexpensive tool already obtained routinely as a component of CBC.

In the present study RDW elevation strongly correlated with the inflammatory markers including ESR, CRP, PLT, and MPV (Table 5). Beside disturbances in micronutrient metabolism, inflammation may also influence RDW. Proinflammatory cytokines have been found to inhibit erythropoietin-induced erythrocyte maturation, which is reflected in part by an increase in RDW (**16**). One hypothesis is that enzymes produced by leukocytes may lead to changes in red blood cell membrane (e.g. decrease in sialic acid), which ends in variability in cell shapes (**17**). This may contribute to elevation in RDW. The absence of correlation of RDW with active disease status in our study is understandable because the disease activity was evaluated with only clinical index, and ESR, even CRP, is also not perfect in this regard (**18,19**). Another striking correlation was present between RDW and EAI. This suggests a possible role of RDW to predict relapse and to monitor therapy (**20**). In our series RDW was non-significantly elevated as the extent of involvement increased in UC. If this finding is proved to be significant in a large group of patients in the future, RDW would also have a role to predict the extent of disease in UC.

In conclusion, RDW, as a cost-effective tool, could be an additional parameter to assess disease activity in IBD. It could also be used in the differentiation between UC and CD as an adjunctive marker. Our retrospective data should be confirmed in a prospective manner with large samples.

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