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Original Article

Can red cell distribution width be a marker of disease activity in ulcerative colitis?

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Abstract: Aim: The current study aimed to investigate the association between disease activity and red cell distribution width (RDW) levels in ulcerative colitis and to determine whether RDW can be used as a marker of disease activity in non-anemic ulcerative colitis. Methods: The RDW levels of 310 ulcerative colitis patients who underwent colonoscopy were analyzed retrospectively. The patients were divided into two groups (active disease and remission) according to the endoscopic activity index. In addition, the accuracy of RDW in determining disease activity in non-anemic patients was assessed. The efficacy of RDW in determining disease activity was compared to that of white blood cell count, platelet count, C-reactive protein, and erythrocyte sedimentation rate. Results: Two hundred and six (66.5%) patients had active disease, and 104 (33.5%) were in remission. The mean RDW levels in patients with active ulcerative colitis and in those in remission were 16.8±2.9 and 15.5±1.4, respectively (P<0.001). Ninety-six (46.6%) patients in the active disease group and 89 (85.6%) in the remission group were non-anemic, and their respective RDW levels were 15.4±1.2 and 15.3±1.1 (P=0.267). The sensitivity and specificity of RDW in determining inflammation were 41% and 91%, respectively (AUC 0.65, P<0.001). Conclusions: This study demonstrated that RDW can be used as a marker for disease activity in ulcerative colitis, but it did not have the same efficacy in the non-anemic group.

Keywords: Red cell distribution width, ulcerative colitis, activity

Introduction

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is a chronic condition characterized by recurrent episodes of gastrointestinal tract inflammation. This inflammation is the underlying cause of many of the symptoms and findings of IBD. Therefore, the diagnosis and follow-up of the inflammation are critically important to the clinical management of the disease [1].

Over the past decade, several laboratory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), and platelet count (PLT) have been evaluated for their efficacy in determining disease activity. However, none of these has been identified as an ideal marker. An ideal marker must be fast, easy, and inexpensive to test, and should be able to identify individuals prone to a specific disease. The marker should be able to identify disease activity and should indicate the efficacy of the treatment. Unfortunately, such a marker is not yet available [2].

RDW reflects the variability in the dimensions of red blood cells, and because it is routinely measured by automatic laboratory equipment that is used for complete blood cell count, its measurement requires no additional cost [3]. RDW is frequently used in the differential diagnosis of anemia. In addition, recent studies have provided evidence for a relationship between high RDW levels and some diseases, such as cardiovascular diseases and celiac disease [4, 5]. Furthermore, some studies have indicated that RDW may also be used as a marker of inflammation in IBD [6-10].

Table 1. Demographic characteristics of the study group

	Active (n=206)	Remission (n=104)	P
Age	45.6 ± 15.8	46.68 ± 13.9	0.555
Sex/Male, *n (%)*	132 (64.1)	59 (56.7)	0.209
Non-Anemic, *n (%)*	96 (46.6)	89 (85.6)	<0.001
Activity Index	7.8 ± 2.2	-	-

Table 2. Comparison of the laboratory parameters in the active and remission groups with ulcerative colitis

	Active (n=206)	Remission (n=104)	P
WBC (/mm^3)	9736.7 ± 3460.3	7766.6 ± 1756.9	<0.001
PLT (/mm^3)	385.53 ± 137.9	281.4 ± 57.6	<0.001
Hb (g/dl)	12.1 ± 2.1	13.7 ± 1.4	<0.001
CRP (mg/dl)	7.1 ± 15.7	0.3 ± 0.4	<0.001
ESR (/hour)	38.5 ± 28.8	12.6 ± 11.5	<0.001
RDW (%)	16.8 ± 2.9	15.5 ± 1.4	<0.001

Table 3. Comparison of the laboratory parameters in non-anemic groups

	Active (n=96)	Remission (n=89)	P
WBC (/mm^3)	9140.8 ± 2971	7818 ± 1725.7	<0.001
PLT (/mm^3)	324.4 ± 85.8	277.5 ± 54.7	<0.001
Hb (g/dl)	13.9 ± 1.1	14.1 ± 1.1	0.477
CRP (mg/dl)	2.58 ± 5.6	0.37 ± 0.4	<0.001
ESR (/hour)	23 ± 19.5	11.4 ± 9.7	<0.001
RDW (%)	15.4 ± 1.2	15.3 ± 1.1	0.267

The current study aimed to evaluate the association between disease activity and RDW levels in UC and to evaluate whether RDW, which is a well-established marker of iron deficiency anemia, can be used as a marker of disease activity in patients with non-anemic UC.

Methods

Patients with a diagnosis of UC who were followed-up with between January 2009-December 2011 at the Gastroenterology Department of Ataturk Education and Research Hospital, Izmir Katip Celebi University, were retrospectively examined. Patients were included in this study if they underwent colonoscopy within three days after their ESR and CRP levels and complete blood cell count were determined. Three hundred and ten patients were included in this study, and a complete blood cell count was used to determine their WBC, PLT, RDW, and hemoglobin (Hb) levels. Lower than normal levels of Hb were defined as 12 g/dl and 13 g/dl for female and male patients, respectively.

The endoscopic activities of the patients were calculated using the Rachmilewitz activity index. Patients with an activity index lower than 4 were considered to be in remission, while patients with an activity index higher than 4 were identified as actively diseased. The WBC, PLT, CRP, ESR, Hb, and RDW levels of the actively diseased patients and those in remission were compared. We also compared these parameters between the non-anemic actively diseased patients and those in remission by excluding anemic patients. The accuracy of RDW in identifying disease activity was determined.

The local hospital ethics committee approved the study.

All statistical analyses were performed using SPSS version 16 for Windows. Descriptive statistics were represented as means ± standard deviations (SD) and frequencies (%). A students-t test was used to compare the actively diseased and remission groups with respect to age and the serum levels of WBC, PLT, Hb, CRP, ESR, and RDW. A chi-square test was used to compare gender and anemia. The Youden Index method was used to identify the cut-off vales for each selected marker. ROC curves were constructed, and the areas under the curves were calculated to determine the sensitivity and specificity. Additionally, a logistic regression analysis was performed to determine the multivariate interaction of the markers. Significance was accepted as $P<0.05$.

Results

Of the 310 patients included in the study, 206 (66.5%) were actively diseased and 104 (33.5%) were in remission. There were no significant differences between the ages (P=0.555) and genders (P=0.209) of the active and remission groups. However, there was a significantly higher number of non-anemic patients in the remission group (85.6% vs 46.6%, P<0.001) (**Table 1**). In addition, the

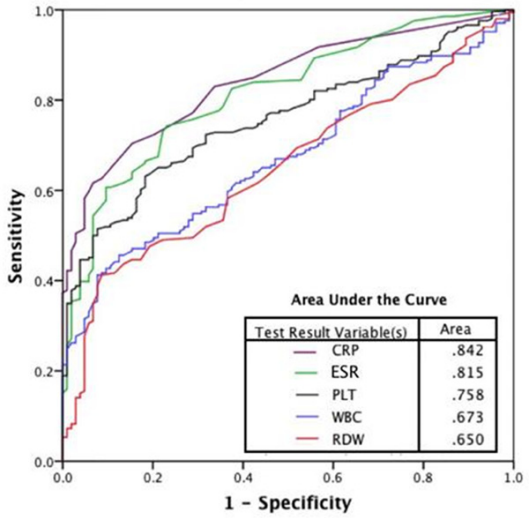

Figure 1. ROC curve and AUC analyses of laboratory parameters.

mean WBC, PLT, CRP, ESR, and RDW levels were significantly higher in patients with active UC compared to those in remission, but their Hb levels were significantly lower (P<0.001) (**Table 2**).

Ninety-six (46.6%) of the patients with active UC and 89 (85.6%) patients in remission were non-anemic. Among these non-anemic patients, the mean WBC, PLT, CRP, and ESR levels in patients with active disease were significantly higher than those of the patients in remission (P<0.001). However, the RDW levels of the non-anemic patients were similar in both groups (P=0.267) (**Table 3**).

The ROC curve analysis for CRP, ESR, PLT, WBC, and RDW indicated that CRP is the most significant marker of active UC (area under curve [AUC] for CRP was 0.84) (**Figure 1**). For a CRP cutoff of 0.85, the sensitivity for detecting active UC was 61% and the specificity was 93% (P<0.001) (**Table 4**). The same analysis indicated that RDW is the weakest marker of disease activity. At an RDW cut-off of 16.66, the sensitivity was 41% and the specificity was 91% (AUC 0.65, P<0.001) (**Table 4**).

A logistic regression analysis revealed that, when used in combination, RDW, CRP, WBC, and PLT can determine disease activity (P<0.05). The odds ratios calculated by the multivariate analysis for RDW, CRP, WBC, and PLT are shown in **Table 5**. In addition, RDW was highly correlated with CRP (P=0.001), WBC (P=0.001), and PLT (P<0.001) levels, but not with ESR (P=0.756) (**Table 6**).

Discussion

RDW is a quantitative measurement of anisocytosis. RDW is routinely reported by the automated hematology analyzers that are used to perform complete blood cell counts. RDW may increase as a result of ineffective red blood cell production, increased red blood cell destruction, or following blood transfusion [11]. Pro-inflammatory cytokines have been reported to inhibit the maturation of erythrocytes, which is caused by erythropoietin. Thus, inflammation causes immature red blood cells to be released into the peripheral circulation, which may result in anisocytosis [11-13].

Several previously published studies indicate that RDW increases during inflammation. In their extensive cohort study with 3845 patients, Lippi et al. reported that RDW increased during inflammation [14]. Other recent studies have reported that RDW is correlated with increased mortality due to any medical cause from any clinical condition. This correlation is most likely caused by chronic inflammation and oxidative stress, which can result in an increased RDW [15]. Perlstein et al. reported that high RDW levels are highly and independently associated with mortality due to cardiovascular disease, cancer, and chronic lower respiratory disease [16]. Some other recent studies have indicated that RDW is a predictor of prognosis in patients with cardiovascular diseases [17-21]. In addition, Patel et al. reported that RDW is a powerful predictor of mortality in middle aged and elderly individuals in the general population [22].

Some studies have been published regarding the relationship between RDW and IBD, in addition to many other diseases. In a study by Song et al., which included 221 patients with IBD, 120 patients with UC, and 101 patients with CD, RDW levels were found to increase in parallel with the severity of disease activity. In addition, they reported a correlation between RDW levels with ESR and PLT levels, but not CRP levels, in patients with UC. They concluded that RDW was a good independent predictor of disease activity in patients with UC, in addition to being the best indicator for disease activity in a non-anemic subpopulation [6]. Cakal et al. reported high RDW levels in 88.4% of the

Table 4. Cut-off values of laboratory parameters and sensitivity and specificity values of cut-off points

		Active n (%)	Remission n (%)	Total n	P	Sensitivity	Specificity	Accuracy
WBC	≥10050	85 (91.4)	8 (8.6)	93	<0.001	0.413	0.923	0.584
	<10050	121 (55.8)	96 (44.2)	217				
PLT	≥321.5	130 (87.2)	19 (12.8)	149	<0.001	0.631	0.817	0.694
	<321.5	76 (47.2)	85 (52.8)	161				
CRP	≥0.85	127 (94.8)	7 (5.2)	134	<0.001	0.617	0.933	0.723
	<0.85	79 (44.9)	97 (55.1)	176				
ESR	≥15.5	21 (100)	0 (0)	21	0,001	0.743	0.769	0.403
	<15.5	185 (64)	104 (36)	289				
RDW	≥16.65	85 (90.4)	9 (9.6)	94	<0.001	0.413	0.913	0.581
	<16.65	121 (56)	95 (44)	216				

Table 5. Logistic regression analysis results (95% confidence intervals for OR)

	B	S.E.	P	OR	Lower	Upper
RDW	1.723	0.425	<0.001	5.6	2.434	12.885
CRP	2.609	0.441	<0.001	13.589	5.722	32.269
WBC	1.034	0.47	0.028	2.812	1.12	7.059
PLT	1.08	0.351	0.002	2.945	1.479	5.863

B: Coefficient, S.E.: Standart Error, OR: Odds Ratio.

Table 6. Correlation of RDW and other parameters in defining disease activity based on the cut-off values calculated using the Youden index

		RDW<16.65 (n=216)		RDW≥16.65 (n=94)		Total	p
		n	%	n	%	n	
CRP	<0.85	136	62.9	40	42.5	176	0.001
	≥0.85	80	37.1	54	57.5	134	
ESR	<15.5	202	93.5	87	92.5	289	0.756
	≥15.5	14	6.5	7	7.5	21	
WBC	<10050	164	75.9	53	56.4	217	0.001
	≥10050	52	24.1	41	43.6	93	
PLT	<321.5	132	61.1	29	30.9	161	<0.001
	≥321.5	84	38.9	65	69.1	149	

patients with active UC, 29% of the patients with UC in remission, and in 10% of the control group. The differences between these groups were significant. When fibrinogen, ESR, CRP, PLT, and RDW were evaluated, RDW was found to be the most meaningful indicator for active UC. The sensitivity and specificity of RDW for determining active UC were 86% and 75%, respectively [7].

In a study performed by Yesil et al., the specificity and sensitivity of RDW as an indicator of active disease in UC were 84% and 17%, respectively, and therefore, RDW was not determined to be a significant indicator of active disease [8]. Oustamanolakis et al. reported that RDW levels were significantly higher in patients with UC compared to healthy controls. However, the study found no significant difference in the RDW levels between actively diseased patients and those in remission. In addition, they found no correlations between RDW and CRP levels [9].

In the present study, CRP was the most powerful marker of UC activity, while RDW was the weakest. In addition, RDW was significantly correlated with CRP, WBC, and PLT, but not with ESR in determining disease activity.

The correlation between increased RDW and increased disease activity in UC is not fully understood. Since RDW is known as a sensitive indicator of iron deficiency anemia, we hypothesized that anemia may play a role in this correlation. Anemia is a frequent complication of IBD, and its prevalence in UC has been reported to vary between 8.8% and 66.6% [22]. Iron deficiency is the most frequent cause of anemia in IBD, and it is due to intestinal bleeding and iron malabsorption resulting from inflammation and ulceration [23, 24]. Increased RDW indicates a more heterogeneous distribution of red blood cell volumes. A marked increase in mean RDW levels can be used in the diagnosis of iron deficiency anemia, in which there is an inverse correlation between RDW and serum hemoglobin levels [25]. Inflammation may contribute to increased RDW levels not only by disrupting the

iron metabolism, but also by shortening the life of red blood cells, inhibiting the erythropoietin response, or by inhibiting erythropoietin production [12].

In this study, WBC, PLT, CRP, ESR, and RDW levels were significantly increased in patients with active UC compared to the patients in remission. In the non-anemic subgroup, WBC, PLT, CRP, and ESR levels were significantly increased in patients with active UC compared to the patients in remission; however, no significant difference was found in RDW levels. Among patients with active disease and those in remission, the percentage of non-anemic patients was 46.6% and 85.6%, respectively ($P<0.001$), indicating that the majority of the patients with active disease were anemic. This suggests that the increased RDW, which is a good predictor of iron deficiency anemia, might be a result of the anemia, which is frequently seen in patients with active disease. In the majority of previously published studies, patients with UC were not separated into groups as with or without anemia. However, Song et al. [6] evaluated RDW in a non-anemic group, and reported that RDW was also a good indicator of activity in non-anemic patients. Inflammation was reported to be the primary cause of increased RDW in previous studies. The results of the current study suggest that increased RDW may be due to both inflammation and anemia, which are both common in active disease.

In conclusion, this study is the most extensive study to evaluate RDW in patients with UC. RDW levels were significantly increased in patients with active UC; however, there was no significant difference between the non-anemic actively diseased patients and those in remission. Since there are a limited number of studies regarding the role of RDW in non-anemic patients with UC, we believe further studies with larger sample sizes are needed.

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Disclosure of conflict of interest

None.

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