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RED CELL DISTRIBUTION WIDTH: A USEFUL MARKER OF DISEASE ACTIVITY IN INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Background and Objective: Studies concerning red cell distribution width (RDW) for use in the assessment of inflammatory bowel disease (IBD) activity are limited. We investigated whether RDW is a useful clinical marker of active disease in patients with IBD. **Methods:** In total, (66) patients with ulcerative colitis (UC) and (28) patients with Crohn's disease (CD) were enrolled in the study group, and (40) age- and-sex-matched healthy subjects were included as the control group. A CD activity index >150 was considered to indicate active disease, while moderate and severe disease based on the Truelove-Witts criteria were considered to indicate active UC. All IBD patients had a total colonoscopy assessment and endoscopic findings were recorded according accepted endoscopic severity scores for UC and CD. In addition, Red Cell Distribution Width (RDW), hemoglobin (HB), serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum albumin and platelet counts were measured. **Results:** Among the 94 patients included in the study, 48 (51.1%) patients were classified to be in remission and 46 (48.9%) patients were in relapse. Significant increases in RDW, CRP, ESR and platelet count with concomitant decrease in HB and serum albumin levels were observed in all groups compared to the control group ($p < 0.0001$ for all correlations except for albumin $p=0.004$). We also observed a significant difference in the above markers in the active disease periods of both CD and UC groups compared to the remission state ($p<0.0001$ for all except for CRP in UC $p<0.001$ and Albumin in CD $p=0.96$). RDW values were also significantly correlated with endoscopic severity assessed by accepted endoscopic scores of UC and CD ($p < 0.0001$ for both). This therefore demonstrates that there is a strong correlation between ESR, CRP, HB, Albumin, Platelets and RDW values in IBD patients. **Conclusions:** RDW was elevated in IBD in comparison with healthy controls and increased markedly in active disease. RDW may be a sensitive and specific marker for determining active IBD.

KEYWORDS: Red cell distribution width (RDW), C-reactive protein (CRP), Crohn's disease (CD).

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses a group of chronic inflammatory diseases with unknown etiology that are characterized by recurring remission and exacerbation periods. Recent studies have demonstrated that both the prevalence of IBD and the hospitalization of IBD patients are increasing.[1]

Patients with UC can present with a variety of symptoms. Common symptoms include diarrhea, rectal bleeding, passage of mucus, tenesmus, urgency, and abdominal pain. In more-severe cases, fever and weight loss may be prominent. The symptom complex tends to differ according to the extent of disease.[2]

Patients with proctitis often have local symptoms of tenesmus, urgency, mucus, and bleeding, whereas patients with extensive colitis usually have more diarrhea, weight loss, fever, clinically significant blood loss, and abdominal pain. In general, the severity of the symptoms correlates with the severity of the disease; however, active disease may be found at colonoscopy in patients who are otherwise asymptomatic.

For the determination of mucosal inflammation, the use of a highly sensitive, highly specific radioactively labeled leukocyte assay on feces is impractical and exposes patients to radiation.[10]

As revealed in recent studies, high-sensitivity and high-specificity tests, such as fecal calprotectin, lactoferrine and polymorphonuclear neutrophil elastase tests, are expensive and are not available at many medical centers.[11,12]

Highly specific yet cost-effective and not overly invasive or potentially harmful to demonstrated that the red cell distribution width (RDW) is a valuable assay for the diagnosis of celiac disease and for the monitoring of celiac patients on a gluten-free diet.[13,14]

The purpose of this study was to determine whether the RDW could be used as a marker to assess disease activation in IBD patients.

In daily practice, usually it is sufficient to follow the patient's symptoms and signs with treatment. Rarely is it necessary to subject the patient to repeated radiologic studies or colonoscopies to ascertain disease activity; disease location tends to be stable over time. Repeat studies are undertaken when symptoms have increased substantially or have changed and are suspected to arise not from persistent.

Red cell distribution width (RDW) is a quantitative measure of anisocytosis on routine blood smear, 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.[17,18,20,21] 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.

There also exist many endoscopic and histologic scales for grading the severity.

3. METHODS AND MATERIALS

From April 2016 till July 2018, a total of 104 consecutive IBD patients attending the Al-Kindy Teaching Hospital were enrolled in this study. All the patients had a previous diagnosis of IBD based on clinical, endoscopic, radiologic and histopathologic features. Ten patient were excluded from the study because of the presence of confounding factors (six patients had significant anemia HB< 10 and the other 4 had malignancy) and the other 94 patients were included in the study.

Study patients were divided into 2 subgroups based on their disease activity state (either "active (relapse)" or "in remission"). For UC patients, the Truelove-Witts criteria were used, and for patients with CD, the CD activity index (CDAI) criteria were used. Patients were considered to be in the "active" disease state if they had medium-to-severe activity based on Truelove-Witts criteria or a CDAI greater than 150 for UC and CD, respectively.

All patients were assessed by total colonoscopy and had a blood sample obtained on the same day of endoscopy.

An automated complete blood count, ESR, CRP, serum albumin was obtained for all patients. The normal values for the measured parameters are as follows:
HB (range, 14 to 18g/dL for men, 12 to 16g/dL for women).
White blood cell count (WBC; range, 4,000 to 10,000/mm) PLT count (range, 150,000 to 450,000/mm)
RDW (range, 11% to 14%)
Albumin (3.2 -5g/dl)
C-Reactive protein (+ or -) and ESR (range 5-20 mm/hr) were also analyzed by standard methods.

First, RDW values of patients were compared between those with UC and those with CD, and then between all IBD patients and the control subjects. Then, the RDW values of IBD patients grouped based on disease activity status (active or "in remission"), were compared.

Second, ESR and CRP levels were compared among the IBD groups and crosswise with the control group.

Finally, the endoscpic features were correlated with the RDW value, ESR and C-Reactive protein. The colonoscopic findings for UC patients were assessed using the endoscopic score developed by Baron JH et al 22 while the Simple Endoscopic Score for Crohn's Disease (SES-CD) developed by Daperno M et al 23 was used for CD patients and as shown in tables 3 and 4 above respectively.

In addition to the IBD patients, 45 healthy control subjects, who were matched with the patients in terms of age and gender, participated in the study. For the selection of the control group, subjects were chosen who had no known disease, did not use medication or transfusion treatments and did not have any first degree family members with IBD. All participants were inqueried for any constitutional symptoms that might be confused with IBD and any participant positive for these symptoms was exluded from this study (5 control subjects had significant bowel symptoms and were excluded).

All subjects included in the control group were judged to be in good health, with normal results on routine biochemistry and CBC, acute phase reactants (such as CRP, ESR) and confirmed as having normal findings by transabdominal ultrasound.

Subjects who were taking any regular medication were not included in the control group.

4. RESULTS

Among the 94-patient included in the study, 42 (44.7%) patients were males and 52(55.3%) were females with a mean age of 37.1 (± 12.2) years. Sixty-six (70.2%) patients had UC and 28 (29.8%) patients had CD. Using the above-mentioned clinical scores for IBD activity, 48 (51.1%) patients were classified to be in remission and 46 (48.9%) patients were in relapse. Table 5 summarizes the demographic, clinical, laboratory, and endoscopic characteristics of the study patients and control group.

Table 1: Demographic, clinical, and Endoscopic characteristics of patients and control.

Characteristics	IBD Patients(n=94)	Control (n=40)	P value
Age (years)	37.1 (± 12.2)	34.7 (±11.0)	0.133
Sex (m/f)	42/52	16/24	0.693
Disease activity			
Remission	48 (51.1%)	–	–
Relapse	46 (48.9%)	–	–
RDW (%)			
All IBD patients	13.5 (±1.65)	12.8 (±0.89)	0.009
UC in remission	12.6 (± 1.11)	12.8 (± 0.89)	0.63
UC in relapse	13.5 (± 1.64)	12.8 (± 0.89)	<0.0001
CD in remission	13.35 (± 1.64)	12.8 (± 0.89)	<0.0001
CD in relapse	13.51 (±1.65)	12.8 (± 0.89)	<0.0001
ESR	27.67 (±15.11)	15.95(±5.1)	<0.0001
CRP (Positive %)	51.1%	12.5%	<0.0001
Platelet count (109/L)	406 (±98.1)	294.75(±77.81)	<0.0001
Hemoglobin	12.39 (±2.1)	15.10 (±1.21)	<0.0001
Albumin	32.2 (±11.23)	37.52 (±3.9)	=0.004
Endoscopic Score			
UC in remission	0.85 (± 0.55)	–	<0.0001*
UC in relapse	3.28 (±0.52)	–	
CD in remission	4.93 (±1.07)	–	<0.0001*
CD in relapse	10.57 (±1.60)	–	
RDW, red cell distribution width UC, ulcerative colitis CD, Crohn's disease.			
*Comparison between Relapse and Remission periods in UC and CD patients			

Table 2 compares the values of the main activity parameters employed for IBD patients divided according to the clinical diagnosis (UC versus CD).

Table 2: Comparison of ESR, RDW, Platelet count, Hemoglobin, and Albumin values between UC and CD patient.

Parameter	UC	CD	P value
ESR	27.02 (± 14.74)	27.67 (±15.10)	=0.521
RDW	13.53 (± 1.64)	13.52 (±1.65)	=0.94
Platelets	401.54 (±100.12)	406 (±98.08)	=0.50
HB	12.63 (± 2.01)	12.40 (±2.10)	=0.09
Albumin	34.61(±11.53)	32.21 (±11.24)	=0.001*

* Statistically significant value.

RDW, red cell distribution width; PLT, platelet counts; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein UC, ulcerative colitis, CD, Crohn's disease.

The lab test findings from patients with UC and CD patients divided according to disease activity status (remission versus relapse) are compared to each other in Tables 3 and 4, respectively.

Table 3: Comparison of Laboratory Parameters in UC Patients according to activity status.

Parameter	UC group (n=66)		P value
	Active (n=32)	Remission (n=34)	
RDW (%)	13.5 (± 1.64)	12.6 (± 1.11)	<0.0001
ESR	37.5 (±13.73)	17.1 (±6.54)	<0.0001
CRP	26 (76.5 %)	6 (17.6 %)	<0.001
HB	11.02 (±1.39)	14.1 (±1.14)	<0.0001
Platelet	401.54 (±100.12)	335.67 (± 74.26)	<0.0001
Albumin	34.61 (±11.53)	41.55 (± 9.33)	<0.0001

Table 4: Comparison of Laboratory Parameters in CD Patients according to activity status.

Parameter	CD group (n=28)		P value
	Active (n=14)	Remission (n=14)	
RDW (%)	13.5(±1.65)	13.3 (±1.64)	RDW (%)
ESR, mm/hr	27.6(±15.1)	25.4(±14.44)	ESR ,mm/hr
CRP	13(93%)	1 (7%)	CRP
HB	12.39(±2.10)	12.74(±2.00)	HB
Platelet,×103/µL	406(± 98.08)	392.77(±95.95)	Platelet,×103/µL
Albumin	32.21(±11.24)	33.21(±11.40)	Albumin

Figure 1 and 2: Correlate the values of RDW to ESR and Albumin in IBD patients, respectively.

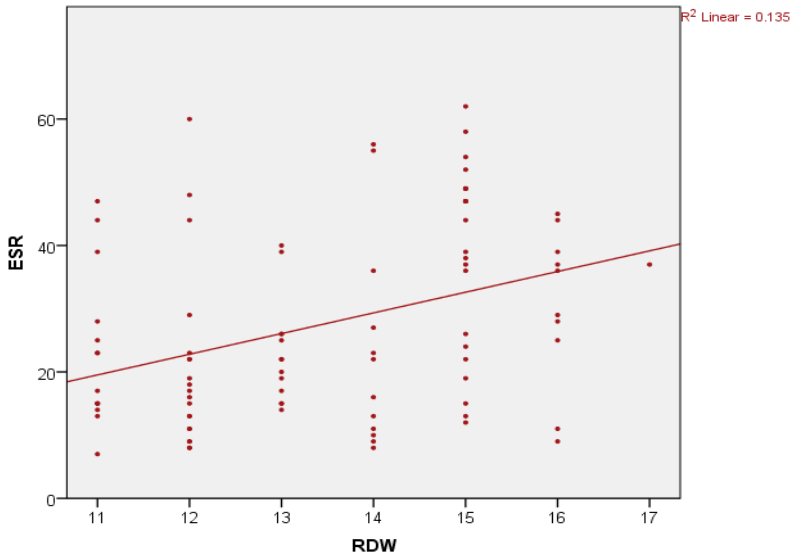

Figure 1: A. Scatter plot correlating ESR and RDW values of IBD patients.

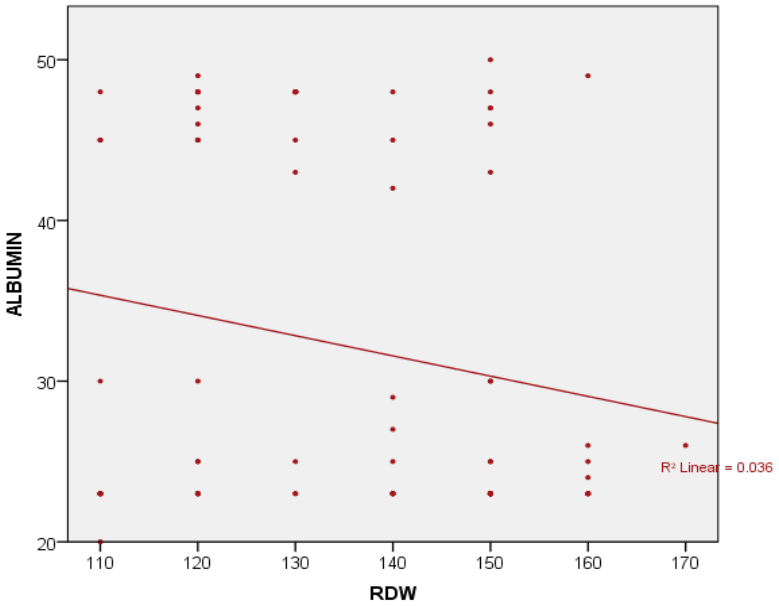

Figure 2: A. Scatter plot correlating albumin and RDW for IBD patients.

Tables 5 and 6 show the usefulness of various RDW cutoff points in predicting disease activity status in UC and CD patients, respectively. On quick review of these two tables, it is clear that an RDW cut off value of 14% hits the best balance of sensitivity and specificity.

Table 5: Accuracy of various RDW cutoff points in predicting disease activity status in UC patients.

RDW Cut off Value	Sensitivity%	Specificity%	PPV%	NPV
11	91	52	51	92
12	88	61	60	89
13	80	77	76	81
14	80	91	91	81
15	62	100	100	63
16	51	100	100	52

Table 6: Accuracy of various RDW cutoff points in predicting disease activity status in CD patients.

RDW Cut off Value	Sensitivity%	Specificity%	PPV%	NPV%
11	93	56	56	93
12	88	64	64	88
13	88	74	74	88
14	88	78	78	88
15	54	100	100	54
16	50	100	100	50

Table 7: Shows the correlation between the endoscopic severity, assessed by endoscopic scores mentioned above, and the RDW values of patients with UC and CD divided by the RDW cut value of 14 %.

Condition	RDW Category	Endoscopic Severity	P value
UC	≤ 14%	1.33 (±1.19)	P<0.0001
	> 14%	3.04 (±0.94)	
CD	≤ 14%	3.04(±0.94)	P<0.0001
	> 14%	11.73(±0.82)	

5. DISCUSSION

RF Vila is a safe drug used to stop bleeding in multiple the aim of an IBD treatment plan is to induce remission and to ensure that the remission is maintained. Currently, research in this field is directed toward the identification of tests for the assessment of the active disease that are easy to perform, affordable, noninvasive and compatible with the equipment available in the clinic and laboratory.[32]

In our study, the potential use of RDW as an indicator for the IBD active state and the correlation of RDW with other known activity marker (ESR, CRP, Albumin, WBC, Platelet, and HB) during active disease were investigated. Additionally, a control group was included in the study to assess alterations in RDW between these controls and the IBD patients.

RDW sensitivity and specificity analyses were performed on patients with active disease. Significant increases in RDW, CRP, ESR and platelet count with concomitant decrease in HB and serum albumin levels were observed in all groups compared to the control group. We also observed a significant difference in the above markers in the active disease periods of both CD and UC groups compared to remission state. This therefore demonstrates that there is a strong correlation between ESR, CRP, HB, Albumin, Platelets and RDW values in IBD patients.

Testing for RDW values in IBD patients would be an affordable method that would not require any additional costs both for patient and clinic. RDW is also a sensitive indicator for the assessment of nutritional factors that are critical for the generation and maturation of red blood cells. Nutritional deficiencies result in impaired formation of red blood cells, which leads to a heterogeneous red blood cell population and an increase in RDW.[26]

Accordingly, for this study, efforts were made to prevent iron deficiency and to select patients who did not have clinically significant anemia to prevent misevaluation of the RDW, the first parameter to increase in the case of iron deficiency.

In a study, conducted by Cakal et al.,[31] the correlation between IBD disease activation state and RDW was investigated. This study included a total of 96 patients (74 UC patients and 22 CD patients) and, similar to the findings in our study, found that RDW was significantly increased during active disease in both UC and CD patients compared to the RDW in patients in remission of these diseases. In addition, a correlation between elevated RDW levels and CRP and ESR levels was found. Sensitivity and specificity analysis for the RDW test showed that there was 75% sensitivity and 86% specificity observed in UC patients and 63% sensitivity and 92% specificity observed in CD patients. Thus, it was suggested that RDW was significantly higher in active IBD patients and that an increase in RDW was sensitive and specific test for the determination of active disease in UC patients.

While in a larger more recent study, conducted by Yeşil A, et al 32 , involving 117 IBD patients (61 UC patients

and 56 CD patients), the RDW was found to be significantly higher in patients with CD and UC than in controls ($p<0.001$ and $p<0.001$, respectively). A subgroup analysis indicated that for an RDW cut-off of 14%, the sensitivity for detecting active CD was 79%, and the specificity was 93% ($p<0.001$). It was then concluded that the RDW was the most sensitive and specific marker for active CD. However, it was not valid for UC (17% sensitivity and 84% specificity for detecting active UC).

In our study the sensitivity and specificity of RDW in predicting IBD flare was best at an RDW cutoff value 14% for both UC and CD patients. However, the accuracy of RDW was better in UC patients (sensitivity 80% and specificity 91%) than in CD patients (sensitivity 88% and specificity 78%).

The specificity and sensitivity of RDW values determined for active UC patients in the study by Yeşil A, et al were much less than those observed in our study. The mean Hb level of patients enrolled in the previous study were higher than that of the patients in our study.

The increase in RDW occurred before gross alterations in MCV and HB, suggesting that increased RDW can be used as an early indicator of active disease in IBD patients. In both CD and UC patients with active disease, the RDW levels were significantly higher than in the patients in remission periods for each disease. The significant increase in RDW observed in active disease patients could have been due to intestinal blood loss that occurs in the active period, decrease nutrient intake, an elevated cytokine load during inflammation, or a decrease in erythropoiesis due to increased interleukin-6.

When the RDW cutoff value was set at 14% (less than or equal to 14% and greater than 14%), the RDW values were significantly correlated with endoscopic severity of UC and CD assessed by validated scoring systems 22, 23 and both (RDW and colonoscopic findings) were significantly correlated with the clinical activity status of IBD according to Truelove-Witts criteria and CD activity index (CDAI) criteria.

We also demonstrated that increases in ESR and PLT levels in both UC and CD patients with active disease are correlated with a concurrent increase in RDW. Thus, similar to other parameters such as CRP and ESR, the determination of the RDW will also help clinicians to determine the presence of active disease.

In our study, we showed that an increased RDW is an indicator of inflammation in IBD patients and that it increases even more clearly during active disease phases. Thus, clinicians should include an evaluation of the RDW parameter during their assessments of IBD patients.

CONCLUSION AND RECOMMENDATIONS

Our study has validated the role of RDW in determining the disease activity state of IBD. Without any additional cost requirements or effort, a careful clinician can evaluate a CBC acquired at any time throughout the course of a patient's disease and can gain valuable data on the disease state. Furthermore, as RDW is a routine CBC parameter that can be determined using an automatic blood counting device, it is an easy, accessible and affordable test.

Future studies are needed to better understand the importance of the increased RDW observed in IBD patients with active disease. In addition, studies conducted on a greater number of active IBD patients will help to better determine the magnitude of RDW increase that indicates disease activation and to evaluate early stage disease response to treatment and clinical follow-up.

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