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Can red blood cell distribution width (RDW) predict clinical and endoscopic activity in ulcerative colitis patients?

Kırmızı kan hücresi dağılım genişliği (RDW) ülseratif kolit hastalarında klinik ve endoskopik aktiviteyi tahmin edebilir mi?

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Abstract

Aim: Classification of ulcerative colitis (UC) according to disease activity and severity is important in clinical practice for it determines the management of the patient. In this study, we aimed to investigate the relationship between red blood cell distribution width (RDW) and clinical activity index (CAI) in UC patients as well as endoscopic activity indexes (EIA) that determine disease severity relative to mucosal disease.

Methods: This research was planned as a case-control study. Ninety-nine patients diagnosed with UC were divided an active disease group and a remission group according to their clinical and endoscopic findings. Age and gender-matched control groups were formed from 56 individuals with normal colonoscopic findings.

Results: Serum RDW levels were significantly higher in the UC group (P<0.001). In post-hoc comparisons, a statistically significant difference was observed between the control group and active disease groups (P<0.001). However, RDW values did not significantly predict clinical and endoscopic activity in either the active disease or the remission groups (P=0.05 and P=0.09, respectively). In predicting clinical and endoscopic activity indices, the cut-off values of RDW were 14.25 (66% sensitivity and 72% specificity) and 13.75 (64% sensitivity and 62% specificity), respectively.

Conclusion: This study showed that RDW can be used as a marker for disease activity in ulcerative colitis, but it did not show the same efficacy in remission and active disease distinction.

Keywords: Ulcerative colitis, RDW, Endoscopic activity index, Clinical activity index

Öz

Amaç: Ülseratif kolitin (ÜK) hastalık aktivitesi ve şiddetine göre sınıflandırılması klinik uygulamada önemlidir, çünkü hastanın yönetimini belirler. Bu çalışmada, ÜK hastalarında kırmızı kan hücresi dağılım genişliği (RDW) ile klinik aktivite indeksi (KAİ) ve mukozal hastalığa göre hastalık şiddetini belirleyen endoskopik aktivite indeksleri (EAİ) arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Araştırma bir vaka kontrol çalışması olarak planlandı. ÜK tanısı alan 99 hasta klinik ve endoskopik aktivitelerine göre aktif hastalık grubu ve remisyon grubu olmak üzere iki gruba ayrıldı. Kolonoskopi yapılan ve normal bulunan 56 kişiden yaş ve cinsiyet uyumlu kontrol grupları oluşturuldu.

Bulgular: Serum RDW düzeyleri ÜK grubunda anlamlı olarak yüksekti (P<0,001). RDW ile yapılan post-hoc karşılaştırmalarda, kontrol grubu ile aktif hastalık grupları arasında istatistiksel olarak anlamlı farklılıklar gözlenmiştir (P<0,001). Bununla birlikte, RDW değerleri klinik ve endoskopik aktivitenin belirlenmesinde, aktif hastalık ve remisyon grupları arasında anlamlı değildi (sırasıyla P=0,05 ve P=0,09). Klinik ve endoskopik aktivite indekslerini tahmin ederken, RDW'nin cut-off değerleri sırasıyla 14,25 (%66 duyarlılık ve %72 özgüllük) ve 13,75 (%64 duyarlılık ve %62 özgüllük) idi.

Sonuç: Bu çalışma, RDW'nin ülseratif kolitte hastalık aktivitesi için bir belirteç olarak kullanılabileceğini gösterdi, ancak remisyon ve aktif hastalık ayrımında aynı etkinliği göstermedi.

Anahtar kelimeler: Ülseratif kolit, RDW, Endoskopik aktivite indeksi, Klinik aktivite indeksi

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic, and recurring and remitting inflammatory bowel disease characterized by a limited, diffuse, nonspecific inflammation of the colon's mucosa, often beginning from the rectum, and extending continuously to the end of the ileum. One or more relapses may develop after the first attack in up to 90%, and early relapse or active disease occurring in the first 2 years is associated with a worse disease course [1].

Classification of UC according to disease activity and severity is especially important in clinical practice as it will determine the management of the patient. Early detection of disease activity reduces the rate of surgery and mortality in serious UC cases [2]. In clinical practice, various combinations of endoscopic parameters, including clinical and laboratory studies, imaging tests and histopathology are used to determine the activity of the disease. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells (WBC), fecal calprotectin are widely used to reflect disease activity in UC [3,4]. However, none of them have been identified as an ideal marker. An ideal marker should be fast, easy, inexpensive, be able to identify individuals prone to a disease along with disease activity and indicate the effectiveness of treatment. Unfortunately, such an ideal marker is not yet available [5].

Red blood cell distribution width (RDW), which reflects the variation in the size of circulating red blood cells, is routinely reported by automated lab equipment used to perform complete blood counts [6,7]. The value of RDW in evaluating the severity and clinical outcome of the disease in various diseases has been proven (e.g. sepsis, renal dysfunction, cardiovascular and lung diseases, and malignancies) [7-10]. In addition, some studies suggest that RDW may be an inflammatory marker for UC [11,12]. However, the sensitivity of these and similar inflammatory markers in the identification of endoscopic active disease and their correlation with mucosal sores are low. In this study, we aimed to investigate the relationship between RDW, which is a marker of inflammation, and clinical activity index (CAI) in patients with UC, as well as endoscopic activity indices (EAI), which determine disease severity according to mucosal disease.

Materials and methods

Patient selection

Adult patients with newly diagnosed UC who presented to the territorial hospital's Gastroenterology outpatient clinics between October 2017 and March 2020 were included in this case-control study. The diagnosis of UC was made by gastroenterology specialists based on clinical, laboratory, colonoscopic and pathological examinations. 99 patients diagnosed with UC were divided into two groups as an active disease group and remission group according to their clinical and endoscopic findings.

Within the same age and gender range, 56 healthy individuals from the healthy population who had colonoscopy due to various indications and whose colonoscopy reports were normal were included as the control group. Those with a history of malignancy, those who had undergone surgery in the last 6 months, patients and / or healthy individuals with active infections, which were detected by chest x-ray, urine sample analysis and stool test, were excluded from the study.

Endoscopic procedure

Endoscopic procedures were performed in the endoscopy unit of our Gastroenterology Department with experienced gastroenterology specialists. Following optimal bowel preparation with sodium phosphate solution, accompanied by the appropriate diet, one colonoscope (EVIS LUCERA ELITE CLV-290SL; Olympus Medical Systems, Tokyo, Japan) was used for each colonoscopic procedure. Colonoscopy reports of each patient at the time of admission were taken as a basis.

Montreal classification was used to determine the anatomical prevalence of UC patients who were evaluated [13]. In this classification, disease prevalence was categorized as E1: proctitis, E2: left colon involvement, E3: extensive colitis.

According to the endoscopic findings of patients with UC, activity indices were routinely evaluated with Modified Baron EAI in our unit [14]. There are four classes in this endoscopy-based scoring system: normal mucosa (0), abnormal vascular pattern granular mucosa (1), brittle mucosa (2), microulceration with spontaneous bleeding (3), and gross ulceration (4). Class 0 and 1 were evaluated as remission, and 2, 3 and 4 were evaluated as active diseases.

Clinic and laboratory

Disease activity in UC patients was evaluated with the criteria of Truelove and Witts [15]. These criteria enable the patients with UC to be classified simply and quickly. Using this classification, patients with UC were classified as mild, moderate, or severe depending on their daily bloody stool count, heart rate, hemoglobin, ESR, and body temperature. Moderate and severe disease classes were evaluated as active disease.

Laboratory findings, including complete blood count, obtained on the day of the colonoscopic examination were gathered from the medical records of the patients.

Statistical analysis

Statistical analysis was performed using the SPSS 22.0 statistics package (SPSS, Inc., Chicago, IL, USA). The data were expressed as mean (SD). Mann Whitney U test was used to evaluate the differences in demographic parameters, and Kruskal Wallis test was used to compare laboratory parameters between groups. Statistical difference was analyzed with the Dunnett's T3 test. Spearman correlation was used to analyze the correlation between parameters. All P values were two-way, and $P<0.05$ was considered statistically significant. Sensitivity, specificity, and cut-off points were evaluated using a receiver operating characteristic curve analysis (ROC).

Ethical approval

Written informed consent was obtained from each subject before endoscopic examination. This study was approved by the Mersin City Training and Research Hospital Ethical Committee and conducted in accordance with the Helsinki Declaration.

Results

A study group was established with 99 patients with UC, and a control group was formed with 56 individuals. The general features of the groups are presented in Table 1. The mean

age of the study and control groups was 42.52 (15.82) years and 46.25 (14.50) years, respectively. There were 60 males (60.6%) and 39 females (39.6%) in the study group, and 32 males (57.1%) and 24 females (42.9%) in the control group. There was no statistically significant difference between the groups in terms of age and gender distribution (P=0.09 and P=0.67, respectively).

Considering the anatomical distribution of patients with UC, E1: 34 cases (33.66%), E2: 28 cases (27.72%), E3: 37 cases (36.63%) were identified. According to their EAI, 27 cases (27.3%) were in remission and 72 patients (72.7%) had active disease. The distribution of patients according to their CAI was as follows: 36 patients (36.4%) were in remission, 63 cases (63.6%) had active disease.

Comparison of inflammatory markers between groups of disease clinical activity is presented in Table 2. The mean WBC, CRP and ESR values of the active disease group were significantly higher than that of the remission and control groups (P<0.001). The mean RDW values of the control, UC remission and active UC patient groups were 13.70 (1.00), 14.36 (1.56), and 15.25 (2.07), respectively. The mean RDW value of active patients was significantly higher than that of the inactive UC and control groups (P<0.001). In post-hoc multiple comparisons of WBC, CRP, ESR and RDW (Table 3), statistically significant differences were observed between the control and active disease groups (P<0.001). Only the CRP and ESR variables were significantly different between the remission and control groups (P=0.03 and P<0.001, respectively). Only CRP displayed a significant difference in remission and active disease groups (P<0.001).

Positive correlations were found between CAI and RDW (r_s=0.37; P<0.001), WBC count (r_s=0.39; P<0.001), CRP (r_s=0.62; P<0.001), and ESR (r_s=0.65; P<0.001), as yielded by correlation analyses.

ROC analysis was applied to WBC, ESR, CRP and RDW values to predict the CAI (Figure 1). Variables with the highest AUC values were ESR 0.84 (0.05) (P<0.001), CRP 0.82 (0.06) (P<0.001), WBC 0.74 (0.06) (P=0.01) and RDW 0.71 (0.06) (P=0.01), respectively. The cut-off value of 14.25 for RDW had 66% sensitivity and 72% specificity.

Comparison of inflammatory markers between patient groups according to their EAIs is given in Table 4. The mean WBC, CRP and ESR values of the active disease group were significantly higher than that of the remission and the control groups (P<0.001). The mean RDW values of control, remission and active UC patients were 13.70 (1.00), 14.14 (1.33) and 15.22 (2.05) respectively. The mean serum RDW value of active disease patients was significantly higher than that of inactive UC and control groups (P<0.001). Post-hoc multiple comparisons were made with WBC, CRP, ESR and RDW (Table 5): Statistically significant differences were observed between the control and active disease groups and the remission and active disease groups in terms of CRP (P<0.001, P=0.04, respectively), but no statistically significant difference was observed between the control group and the remission group (P=0.16). In terms of WBC, statistically significant differences were observed between the control and active disease groups (P<0.001), while there was no statistically significant difference between the control and the remission groups (P=0.29) or the remission and active disease groups (P=0.08). In terms of ESR, there was a significant difference between the control group and both the remission and active disease groups (P<0.001). There was no statistically significant difference between remission and active disease groups (P=0.20). In terms of RDW, a statistically significant difference was determined between the control and active disease groups (P<0.001), while no statistically significant difference was observed between the control and the remission group (P=0.35) or the remission and active disease groups (P=0.09).

Table 1: General characteristics of the groups

Variables	Control group	Study group	*P*-value
Age	46.25 (14.50)	42.52 (15.82)	0.09
Gender (%)	32 male (57.1%)	60 male (60.6%)	0.67
	24 female (42.9%)	39 female (39.6%)	
Anatomical distribution (%)		E1:34 (33.66%)	
		E2:28 (27.72%)	
		E3:37 (36.63%)	
EAI n, (%)	Normal	Active disease 72 (72.7%)	
		Remission 27 (27.3%)	
CAI n, (%)	Normal	Active disease 63 (63.6%)	
		Remission 36 (36.4%)	
n	56	99	

EAI: Endoscopic activity index, CAI: Clinical activity index

Table 2: Comparison of inflammatory markers between groups according to CAI

Variables	Control group	Remission group	Active disease group	*P*-value
WBC	7277.86 (1717.22)	8320 (2267.13)	9664.76 (3544.65)	<0.001
ESR	4.89 (2.27)	20.20 (14.88)	27.89 (18.21)	<0.001
CRP	4.47 (2.48)	9.91 (8.12)	42.93 (42.77)	<0.001
RDW	13.70 (1)	14.36 (1.56)	15.25 (2.07)	<0.001

WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width

Table 3: Post-hoc test results after one-way analysis of variance (ANOVA) to determine between which groups the variables differ

Dependent variable	(I) CAI group	(J) CAI group	*P*-value*	95% Confidence Interval	
				Lower Bound	Upper Bound
CRP	Control	Remission	0.03	-10.58	-0.30
		Active	<0.001	-57.53	-19.39
	Remission	Control	0.04	0.30	10.58
		Active	<0.001	-52.53	-13.49
WBC	Control	Remission	0.06	-2126.65	42.36
		Active	<0.001	-3607.20	-1166.61
	Remission	Control	0.06	-42.36	2126.65
		Active	0.07	-2765.52	76.00
ESR	Control	Remission	<0.001	-21.65	-8.97
		Active	<0.001	-28.71	-17.28
	Remission	Control	<0.001	8.97	21.65
		Active	0.09	-16.01	0.64
RDW	Control	Remission	0.08	-1.31	0.06
		Active	<0.001	-2.26	-0.83
	Remission	Control	0.08	-0.06	1.38
		Active	0.05	-1.78	0.01

* Dunnett T3, CAI: Clinical activity index, WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width

Table 4: Comparison of inflammatory markers between groups according to EAI

Variabels	Control group	Remission group	Active disease group	*P*-value
WBC	7277.86 (1717.22)	8164.44 (2553.33)	9555 (3341.69)	<0.001
ESR	4.89 (2.27)	20.62 (13.08)	26.76 (18.56)	<0.001
CRP	4.47 (2.48)	15.21 (19.47)	37.20 (41.60)	<0.001
RDW	13.70 (1.00)	14.14 (1.33)	15.22 (2.05)	<0.001

WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width

Table 5: Post-hoc test results after one-way analysis of variance (ANOVA) to determine between which groups the variables differ

Dependent variable	(I) EAİ group	(J) EAI group	*P*-value*	95% Confidence Interval	
				Lower Bound	Upper Bound
CRP	Control	Remission	0.16	-24.90	3.42
		Active	<0.001	-50.12	-15.34
	Remission	Control	0.16	-3.42	24.90
		Active	0.04	-43.43	-0.54
WBC	Control	Remission	0.29	-2239.06	465.89
		Active	<0.001	-3381.55	-1172.73
	Remission	Control	0.29	-465.89	2239.06
		Active	0.08	-2935.01	153.90
ESR	Control	Remission	<0.001	-22.30	-9.14
		Active	<0.001	-27.30	-16.44
	Remission	Control	<0.001	9.14	22.30
		Active	0.20	-14.43	2.14
RDW	Control	Remission	0.35	-1.15	0.28
		Active	<0.001	-2.19	-0.84
	Remission	Control	0.35	-0.28	1.15
		Active	0.09	-1.94	-0.22

* Dunnett T3, EAI: Endoscopic activity index, WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width

Correlation analysis revealed that CAI positively correlated with RDW (r_s=0.37; *P*<0.001), WBC count (r_s=0.41; *P*<0.001), CRP (r_s=0.55; *P*<0.001), and ESR (r_s=0.65; *P*<0.001).

ROC analysis was applied to WBC, ESR, CRP and RDW values to predict the EAI (Figure 2). Valuables with the highest AUC values were ESR 0.82 (0.05) (*P*<0.001), WBC 0.81 (0.05) (*P*<0.001), CRP 0.74 (0.06) (*P*<0.001), and RDW 0.69 (0.06) (*P*=0.01). The cut-off value for RDW was 13.75 with 64% sensitivity and 62% specificity.

Inflammatory markers were not associated with anatomical distribution in UC patients. P values for WBC, CRP, ESR and RDW were *P*=0.32, *P*=0.22, *P*=0.26, and *P*=0.10, respectively.

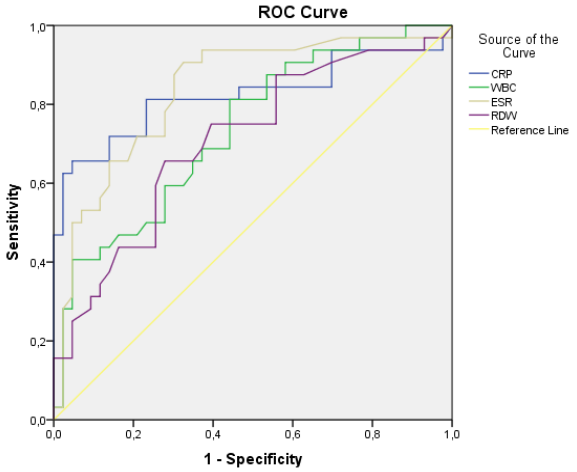

Figure 1: Comparison of inflammatory markers in terms of predicting disease clinical activity (WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width)

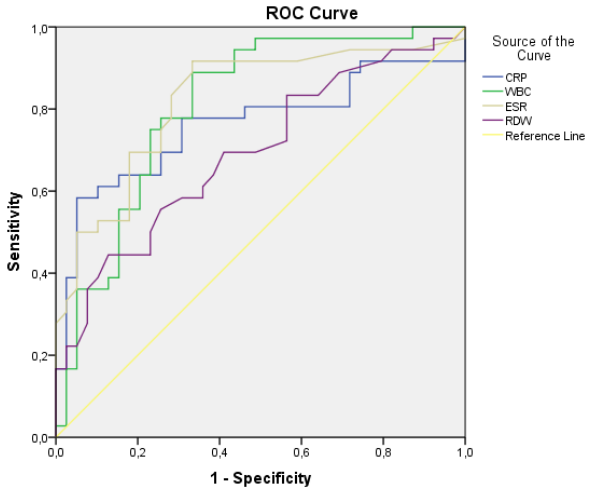

Figure 2: Comparison of inflammatory markers in terms of predicting disease endoscopic activity (WBC: Leukocyte count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RDW: Red cell distribution width)

Discussion

UC is a chronic inflammatory disease that progresses with periods of remission and exacerbation. Classification of UC according to disease activity and severity is important in clinical practice because the patient's management is determined accordingly. For this purpose, a large number of clinical and endoscopic activity indices have been developed [16-18]. Our study revealed that RDW values were associated with both clinical activation and endoscopic activation indices in UC patients, but could not distinguish between remission and active patient groups.

Although an ideal serum marker to predict the severity of the disease is not available, WBC, CRP and ESR are often used in clinical applications to determine UC activity. These markers do not adequately reflect disease activity due to their low sensitivity and specificity for intestinal inflammation [18,19]. Previous studies have shown that CRP and ESR are more significant parameters than WBC in determining disease activity [18-20]. Osada et al. [18] reported that CRP, ESR and WBC counts correlated with the sum of endoscopic and histological scores, and that CRP and ESR were not compatible with distal colon involvement but correlated well with the activity of proximal colon involvement. In our study, it was revealed that the three above-mentioned markers strongly correlated with both CAI and EAI index in accordance with the literature, and this was independent of localization. In terms of predicting EAI, variables with the highest AUC values were ESR (82%), followed by WBC (81%) and CRP (74%). The use of these markers in conjunction with clinical observation, other laboratory parameters and colonoscopy will increase their importance in determining UC activity.

Under normal conditions, the erythrocyte cycle in the body is under strict control. It is observed that there is a change in erythrocyte cycle in pathological conditions. As a result, both the increase in the permanence of old cells in the circulation and the increase due to inflammation may disrupt erythrocyte maturation due to secretion of cytokines and cause early release of larger cells from the bone marrow. Thus, RDW can increase in many diseases [7,21,22].

Several studies have been published in the literature investigating the relationship between RDW and inflammatory bowel diseases. In the study conducted by Song et al. [12], which included 120 UC patients and 101 patients with Crohn's disease, it was found that RDW levels increased in parallel with the severity of the disease activity. They concluded that RDW is a good independent factor in predicting disease activity in patients with UC. Cakal et al. [11], reported high RDW levels in 88.4% of patients with active UC, 29% of patients with UC in remission, and 10% of the control group, and these differences were statistically significant. When fibrinogen, ESR, CRP, PLT and RDW were evaluated together, the most significant indicator for active UC was determined as RDW. The sensitivity and specificity of RDW for the detection of active UC were determined to be 86% and 75%, respectively.

In another study conducted by Yeşil et al. [23], the specificity and sensitivity of RDW in demonstrating active disease in UC were 84% and 17%, respectively, so they concluded that RDW could not be a significant indicator of active disease. Oustamanolakis et al. [24] reported that RDW levels were significantly higher in patients with UC than healthy control group patients. However, the study did not find a significant difference in RDW levels between patients with active disease and those in remission. In addition, they could not find a correlation between RDW and CRP levels. İpek et al. [25] determined that WBC, PLT, CRP, ESR and RDW levels increased significantly in patients with active UC compared to patients in remission. In the non-anemic subgroup, WBC, PLT, CRP and ESR levels increased significantly in patients with active UC compared to patients in remission; however, there was

no significant difference between RDW levels. They concluded that RDW increase developed due to anemia among patients with active disease and in remission.

In this study, it was shown that RDW levels were significantly higher in patients with active UC than healthy controls, but this difference was not significant between remission and active disease groups. Among the variables studied, ESR was the strongest variable in predicting disease CAI, while RDW was the weakest variable (84% and 71%, respectively). The strongest variable in predicting EAI was ESR, while the weakest variable was RDW (82% and 69%, respectively). The cut-off value of 14.25 for RDW had a sensitivity of 66% and a specificity of 72% in predicting CAI. The cut-off value of 13.75 for RDW estimated EAI with 64% sensitivity and 62% specificity.

Limitations

Our study contains several limitations, one being its retrospective nature and the other, including results from a single center. It should also be remembered that the parameters studied are not specific to the disease, and that the results may vary depending on many factors (infection, medication, anemia, inflammation, etc.).

Conclusions

Although no significant difference was found between active disease and disease in remission, our study showed that RDW levels in active UC patients increased significantly, which correlated with clinical, endoscopic and laboratory indices. These inflammatory markers can predict disease activity alone or in combination. The data obtained need to be supported by larger and multi-centered studies. As a result of all this, we believe that these non-invasive, inexpensive markers can be a valuable tool for the rapid assessment of disease activity in UC.

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