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ORIGINAL ARTICLE

Added Predictive Ability of Mean Platelet Volume and Red Cell Distribution Width to Inflammatory Parameters in Disease Activity of Ulcerative Colitis

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ABSTRACT

Background: Recently some noninvasive tests have been studied for determining the activity of disease in ulcerative colitis.

Aim: The aim of this study is to determine the added predictive ability of mean platelet volume (MPV) and red cell distribution width (RDW) in regard to inflammatory markers in disease activity of ulcerative colitis patients.

Materials and methods: Sixty-eight patients with ulcerative colitis were enrolled in this cross-sectional study. For all subjects white blood cell (WBC) count, platelet (PLT) count, RDW and MPV tests were performed. Serum high sensitivity C-reactive protein (hs-CRP) and proinflammatory cytokine; interleukin-12 (IL-12) levels were also measured. Disease activity was determined by endoscopic and clinical activity index (Powell-Tuck).

Results: There was an inverse significant association between MPV and clinical and endoscopic activity scores ($p < 0.01$). The levels of hs-CRP well correlated with disease activity ($p = 0.01$), while serum levels of IL-12 demonstrated no correlation with disease activity. Group markers including RDW, MPV, PLT counts added the predictive ability of disease activity about 20.6%. From these markers, RDW considered as an independent predictor of disease activity.

Conclusion: Our results suggest that easily available and inexpensive markers such as RDW, MPV and PLT may improve the predictive ability of inflammatory markers in disease activity of patients with ulcerative colitis.

Keywords: Ulcerative colitis, Mean platelet volume, Red cell distribution width, High sensitivity C-reactive protein.

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INTRODUCTION

Ulcerative colitis (UC) is a form of chronic inflammatory bowel disease (IBD) with unknown etiology.[1] Recent studies suggest that the number of UC patients visiting gastrointestinal clinics has been increasing gradually in Iran.[2] Dysregulated immune responses[1,3] and also active participation of cellular systems such as platelets[4,5] play the main roles in the pathogenesis of UC. Phagocytes produce large amounts of proinflammatory molecules such as interleukin-12 (IL-12) that promote differentiation and activation of effector T cells, which drive mucosal damage and inflammation.[6-8] Several findings indicate that platelets are potentially activated even during the inactive phase in IBD patients. Platelets initiate and exacerbate inflammatory responses in UC by releasing inflammatory mediators, so increased platelet count has been associated with disease activity.[5,9] Platelet (PLT) volume has also been found to be influenced in these patients. Mean platelet volume (MPV) was recently reported to be reduced and may be a more sensitive index of platelet function.[9-12] High sensitivity C-reactive protein (hs-CRP) has been shown to be a useful inflammation sensitive biomarker in patients with UC especially in remission and it correlates with clinical disease activity score.[13,14] Red cell distribution width (RDW) is a quantitative measure of anisocytosis, the variability in size of the circulating erythrocytes. It is typically elevated in condition of nutritional deficiencies, chronic inflammation, and also a strong predictor of cardiovascular death. Recently, several reports have pointed to a possible role of RDW in IBD as an additional inflammatory marker.[15-18] Endoscopic examination is costly and invasive method that is used for assessing disease activity in UC, besides clinical indices and noninvasive laboratory tests may help to investigate the activity of disease in these patients. RDW and MPV are components of the complete blood count (CBC) and may be easily available measure of inflammation. However, the significance of the new markers (RDW and MPV) in assessment of diseases activity in patients with UC is still uncertain. We took up this study to assess correlation of RDW and MPV with proinflammatory cytokine; IL-12, hs-CRP levels and clinical disease activity and also to determine the added predictive value of these markers in disease activity.

MATERIALS AND METHODS

Sixty-eight patients were randomly recruited in this cross-sectional study during routine follow-up in the advanced clinic of University of Medical Sciences, Tabriz, Iran. The sampling method was simple random sampling whose random numbers were generated using Random Allocation Software. All patients were diagnosed UC based on clinical and pathological criteria. They gave their written informed

consent according to the Ethical Committee of the University of Medical Sciences (local ethical code: 8915). The activity of disease was determined by numerical Powell-Tuck and endoscopy (Mayo score) indices.[19] Study group included UC patients of 19 to 51 years old with mild to moderate disease activity and without any experience of relapse during last 6 months. All patients were steroid free. Individuals with any autoimmune disease such as diabetes, cardiovascular disease, pregnancy or obesity, recent (<3 months) episode of infection, those with a history of malignancy and/or recent trauma or surgery were excluded.

Laboratory Methods

Complete blood count: Blood was obtained from an antecubital vein puncture with minimal stasis and was collected into tubes containing dipotassium edetic acid (EDTA; 1.3 mg/ml) for the determination of a CBC. All measurements were performed within 2 hours of collection of blood because of the known effect of EDTA on platelet volume.[20] Hematological parameters, including white blood cell (WBC) count, platelet count, MPV and RDW were determined using the Sysmex XT 1800i counter (Sysmex Corporation, Kobe, Japan), which was subject to daily quality control. Serum samples were obtained and were drawn into 10 ml serum separator tubes and allowed to clot for 30 minutes before centrifugation at 2,000 rpm for 10 minutes. The serum was removed, and stored at −80°C until further use.

High sensitivity C-reactive protein (hs-CRP): Hs-CRP was determined using a latex-enhanced immunonephelometric method on a BN II Analyzer (Dade Behring, Marburg, Germany).

Serum levels of IL-12p40: Concentrations of cytokines were assayed in serum samples using commercially available enzyme-linked immunosorbent assay (ELISA) kits. IL-12p40 test kits were purchased from Diaclone (Besançon, France). The results are expressed as picograms per milliliter.

STATISTICAL ANALYSIS

All analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, IL). Data were presented by mean ± SE or median (p25-p75). The assumption of normality was evaluated using one-sample K-S test. For hs-CRP and IL-12, data were non-normal and hence a logarithmic transform was applied. To assess the added predictive ability of [RDW, MPV, platelet distribution width (PDW), WBC, PLT, lymphocyte] set of variables to hs-CRP and IL-12, two-step hierarchical regression was used. R^2 of change showed the added predictive ability. In addition, regression coefficients were presented as the effect size of interest. For this analysis the assumption of residual independence and homoscedasticity were evaluated and confirmed by Durbin-Watson statistics. Also there was no colinearity based on variance inflation factor (<5). Correlation test was performed to determine the correlation between the disease activity score and other parameters. p-value <0.05 was considered as statistically significant.

RESULTS

Study population characteristics: Demographic features, clinical characteristics and clinical and endoscopic activity scores of patients were shown in Table 1. Among patients 22.06% (n = 15) were treated by 5-aminosalicylic acid (ASA) and azathioprine, the rest 77.94% (n = 53) were treated with only 5-ASA. Large number of patients had mild to moderate disease activity according to endoscopic and clinical disease activity.

Table 1: Demographic and clinical characteristic of patients with ulcerative colitis

Parameters	*Ulcerative colitis (n = 68)*
Age (years)	32.9 ± 1.31 (19-51)†
Sex (female/male)	32/36 (47.06/52.94)‡
Duration of disease (years)	5 (3-8)§
Disease start age (years)	27.2 ± 1.33 (14-45) †
BMI (kg/m^2)	24.4 ± 0.74 (16.3-37.5) †
Smoking (+/−)	5/63 (7.35/92.65)‡
Disease activity	6.4 ± 0.48 (1-16) †
Extent of involvement Proctitis Left colitis Extensive colitis	 23 (33.82)‡ 32 (47.06)‡ 13 (19.12)‡
Endoscopic activity Mayo score (%) Normal or inactive (score 0) Mild (score 1) Moderate (score 2) Severe (score 3)	 6 (8.82) 36 (52.94) 25 (36.76) 1 (1.47)

BMI: body mass index, †: mean ± SE (min-max), ‡: N (%), §: median (P_{25}-P_{75})

Table 2 shows laboratory and inflammatory parameters in the studied patients. The association analyses showed, there was an inverse meaningful association between MPV and clinical disease activity score (r = −0.353, p = 0.02) and endoscopic scores (r = −0.345, p = 0.02). Also, hs-CRP levels (r = 0.325, p = 0.01) and PLT count (r = 0.259, p = 0.04) were well correlated with disease activity, while serum levels of IL-12 demonstrated no correlation with disease activity.

The first model as the base model consisted of hs-CRP and IL-12 as the independent variables, predicting about 13% of disease activity variation. In this model, hs-CRP was significantly related to endoscopic disease activity score.

Table 2: Laboratory and inflammatory parameters in the study patients

Parameters	*Mean ± SE*
WBC (×10^3/µl)	7.56 ± 0.31
RBC (×10^6/µl)	4.82 ± 0.09
Hemoglobin (gm/dl)	14.01 ± 0.28
HCT (%)	43.43 ± 0.72
MCV (fL)	90.38 ± 0.93
RDW (%)	13.73 ± 0.22
PLT (×10^3/µl)	303.72 ± 18.20
MPV (fL)	6.74 ± 0.14
PDW (%)	57.00 ± 0.87
Lymphocyte (×10^3/µl)	1.85 ± 0.09
IL-12 (pg/ml)	50.5 (37.2-83.5)¶
hs-CRP	1.30 (0.52-3.40) ¶

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, HCT: hematocrit, MCV: mean corpuscular volume, RDW: red blood cell distribution width, PLT: platelet, MPV: mean platelet volume, PDW: platelet distribution width, Lymp: lymphocyte, IL-12: Interleukin-12, hs-CRP: high sensitivity C-reactive protein. ¶: median (P_{25}-P_{75})

By adding second set of variables (lymphocyte, PLT, PDW, WBC, RDW, MPV) to the first set the model predicted the disease activity about 33.6%, with a change R^2 about 20.6% was observed. In the other words, second set of variables improved the predictive ability of disease activity about 20.6% (Table 3). In the second step, by adding new markers, RDW and lymphocyte showed significant relationship with disease activity ($p < 0.05$) (Table 4).

Table 3: Results of values and change value of R^2 to investigate added predictive ability

Model	*R*	*R^2*	*R^2 change*
1[a]	0.360	0.130	0.206
2[b]	0.580	0.336	

Predictors: Log.IL-12, Log.hs-CRP; b.Predictors: Log.IL-12, Log. hs-CRP, Lymp, PLT, PDW, WBC, RDW, MPV

Table 4: Results of two-step hierarchical regression for predicting clinical disease activity

		B (SE)	*Beta*	*p-value*
Model 1	Log hs-CRP	2.628 (1.168)	0.357	0.03*
	Log IL-12	1.631 (1.699)	0.137	0.34
Model 2				
	RDW	−0.788 (0.384)	−0.372	0.03*
	MPV	−0.231 (0.762)	−0.070	0.76
	PDW	−0.017 (0.112)	−0.031	0.88
	WBC	−0.087 (0.244)	−0.058	0.72
	PLT	0.009 (0.005)	0.331	0.08
	Lymp	−2.227 (0.837)	−0.441	0.01*

Model 1: predictors: Log.IL-12, Log.hs-CRP; Model 2: predictors: log.IL-12, Log.hs-CRP, Lymp, PLT, PDW, WBC, RDW, MPV;*: statistically significant

DISCUSSION

This study examined whether inflammatory markers (RDW and MPV) would improve the predictive ability of disease activity in UC patients. Additive logistic models showed that group variables, including RDW, MPV, PDW, WBC, PLT and lymphocyte count improve the predictive ability of disease activity about 20.6%. Other variables such as patient's age, sex and medication, which were included in predictive group variables of second model, did not have any effect on predictive ability.

CRP has been shown to be a useful inflammation-sensitive biomarker in patients with IBD. It is currently used in addition to the clinical score to monitor IBD activity. Low CRP (0.3 mg/l) concentration might be detected in IBD patients in remission and all patients with undetectable standard CRP had measurable hs-CRP levels.[13,21,22] Only a few groups have studied the hs-CRP levels in IBD and their findings indicated that, hs-CRP correlates with clinical disease activity in both UC and Crohn's disease.[14] Similarly, we found a strong correlation between hs-CRP and clinical disease activity score in current study.

The main roles in the pathogenesis of UC are played by immunological disorders, which are the result of an imbalance between pro- and anti-inflammatory cytokines.[1,3] IL-12 is a proinflammatory cytokine, which promotes the differentiation of Th1 cells and induces gamma interferon, has been strongly implicated in IBD and that generally, is produced by monocytes, macrophages, dendritic cells, neutrophils and to a lesser extent to B cells.[7,8,23] Previous studies have reported increased expression of IL-12 and IL-17 in Caucasian patients with active IBD.[7] Recently, Pang et al[8] have observed an elevated level of IL-12 mRNA expression in the mucosal tissues of UC patients. However, peripheral blood IL-12 is not found to be increased in UC patients, suggesting that increased IL-12 may be a localized event in UC. Therefore, in our study, we assessed the serum value of IL-12 in UC patients for determination of its correlation with clinical disease activity and hs-CRP levels. Our study demonstrated that serum IL-12 levels had no correlation with clinical disease activity and hs-CRP levels.

The monitoring of disease activity is important issue, because remitting and relapsing conditions often changes in chronic UC, but till now there is not a single parameter or laboratory value for diagnosing UC available; diagnosis is confirmed by clinical evaluation and a combination of biochemical, radiological, endoscopic and histological analyses.[24,25] Although endoscopy with biopsy is still considered the gold standard for the evaluation of mucosal inflammation, it is invasive, costly, and uncomfortable for patients especially for those who did not experience any relapse episode during last long time.[24,25]

In recent years, growing interest in substitution of easy available, cost-effective with less discomfort methods for disease monitoring has led to a number of studies investigating several biomarkers correlation with the degree

of IBD activity such as WBC count, platelet count or ESR. Because these parameters have low sensitivity and specificity for intestinal inflammation, recently new markers such as MPV, RDW and fecal calprotectin have replaced the general parameters.[12,17,26]

Chronic inflammatory process in patients with UC causes an increase in the number of blood PLT and changes in their morphological parameters. MPV is a simple marker showing platelet function and activation that can be determined by clinical hematologic tests and is influenced by inflammation, so a decrease in MPV may has a clinical importance in UC especially in active phase.[4,5,9,27]

According to several studies, there was a negative correlation between MPV and endoscopic activity score, CRP and ESR.[10,12] A significant inverse correlation was observed in this study between the MPV with colonoscopic, clinical disease activity and hs-CRP levels. Shen et al[28] have shown that PLT and PDW were higher in CD and UC patients than in healthy controls. However, they determined significant associations of PLT and PDW with disease activity only in patients with active UC. In our study, there was a strong correlation between MPV and PDW with hs-CRP levels. Similarly, we found significant association between PLT and MPV with clinical disease activity score, while there was not similar relation between PDW and disease activity maybe because of inactive condition of patients in this study.

RDW is an index of the variation in cell volume with the red cell population that is influenced by inflammation. Several studies indicated that RDW could be used as an indicator of disease activity in patients with IBD. According to their results, RDW elevation correlated with inflammatory biomarkers including CRP, ESR, fibrinogen and platelet count. RDW at a cutoff of 14 was found to be more sensitive and specific for activity assessment of UC.[15-18] Our study demonstrated strong correlation between hs-CRP levels and RDW ($p = 0.001$). In this study, we can consider RDW as an independent predictor of clinical disease activity while the result is not similar about MPV. It needs to be mention that increase in RDW may be influenced by other conditions like nutritional deficiencies and oxidative stresses. So for future studies, it should better consider all mentioned factors.

Comparison of findings between severely active patients and nonactive ones can lead to more definite conclusion. Absence of severely active group and limited number of patients consider as limitation of present study.

CONCLUSION

The outcomes of this study showed that group markers including RDW, MPV, and PLT count can relatively improve the predictive ability of disease activity in regard to inflammatory markers in UC without imposing any extra charge for patients.

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