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Is there any Correlation between Red Cell Distribution Width, Mean Platelet Volume Neutrophil Count, Lymphocyte Count, and Psoriasis Area Severity Index in Patients Under Treatment for Psoriasis?

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ABSTRACT Psoriasis vulgaris is a well-known systemic inflammatory disease accompanied by many cardiac, renal, and metabolic manifestations. In recent years, hematological parameters have been studied in different systemic diseases as markers for inflammation. In this study, we investigated the possible association between the hematological parameters, namely neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), red cell distribution width (RDW), and Psoriasis Area Severity Index (PASI) scores, in patients under treatment for psoriasis.

Forty-five patients with moderate to severe psoriasis and PASI values of 7 or greater were included in the study. Patients with other inflammatory diseases were excluded. All the patients were treated according to the severity of the disease. Hematological parameters and PASI were examined at baseline and at month 3, 6, 9, and 12.

Twenty-seven patients (60%) were women, and the mean age was 42.2 years. No statistically significant association was found between PASI values and NLR, PLR, or RDW at months 0 and 12. The mean platelet volumes increased only at month 3, and lymphocyte counts increased significantly at all months. However, platelet counts decreased significantly only at month 6, 9, and 12, while RDW decreased significantly only at month 3. All the remaining parameters such as: neutrophils count, lymphocyte count, and erythrocyte sedimentation rate decreased significantly.

The decrease in RDW and the increase in the mean platelet volume accompanied by a decrease in PASI values may represent contributing prognostic hematologic parameters to predict clinical progress and treatment response of patients with moderate-severe psoriasis during the first 3 months of treatment.

KEY WORDS: lymphocyte count, mean platelet volume, neutrophils, psoriasis

INTRODUCTION

Psoriasis vulgaris is a systemic multifactorial disease caused by both genetic factors and environmental interactions (1). Hematological parameters such as neutrophil-to-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and red cell distribution width (RDW) have been widely investigated as new inflam-

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mation markers for systemic inflammatory internal diseases (1-5). Since chronic dermatological diseases including psoriasis vulgaris are known to involve an inflammatory process, it is necessary to examine the possible role of these parameters and their statistical correlations in patients with different severities of psoriasis. Furthermore, evaluating the role of these markers in determining severity is also important.

The Psoriasis Area and Severity Index (PASI) scores of patients decrease over the course of treatment. We investigated whether NLR, PLR, RDW, or cell counts can be used as a prognostic factor for patients with moderate-to-severe psoriasis. The correlation between these parameters and the severity of psoriasis was also evaluated.

PATIENTS AND METHODS

This prospective, single-blinded study included 45 patients with moderate-to-severe psoriasis vulgaris that were referred to the Dermatology Department of Istanbul Medipol University in Istanbul, Turkey from March 2016 to January 2017. The study was approved by the local ethics committee of the same university (Approval number: 66291034-604.01.01-E2043). All the patients were diagnosed by clinical and histopathological examination. Written informed consent was obtained prior to the study. Sixty percent of the patients (27) were women. Eligibility requirements were being 16 years or older, having a clinical diagnosis of psoriasis for at least 6 months, having any form of moderate-to-severe psoriasis defined as 10% or more of body surface area affected, a PASI score of 7 or greater, and a Physician's Global Assessment of at least moderate severity at the baseline visit. The patients with PASI of 7-12 were considered to have moderate psoriasis vulgaris, while those with PASI greater than 12 were classified as having severe psoriasis vulgaris. Pregnant or lactating women, smokers, and patients with immunocompromised diseases, anemia, vitamin B12 or folate deficiencies, any infection or any other inflammatory disease including diabetes mellitus, peripheral arterial disease, Crohn's disease, ulcerative colitis, Behçet's disease, vasculitis, myocarditis, coronary arterial disease, hyperlipidemia, hypertension, pulmonary embolism, malignancy, hepatic or renal diseases, and malnutrition were excluded. Other exclusion criteria were being under treatment of anti-psoriatic, anti-inflammatory, or anti-coagulant medication such as topical steroids, calcipotriol, systemic corticosteroids, colchicum-Dispert, cyclosporine, acitretin, methotrexate, or oral contraceptive pills for the last 6 months, undergoing phototherapy, or having bleeding diathesis. All the patients were treated according to the current intensity of their disease using topical or systemic drugs such as cyclosporine, acitretin, methotrexate, or phototherapy. Of the all patients, 10 had used acitretin, 4 had used cyclosporine, 3 had used methotrexate, and 3 patients had undergone narrow-band UV-B treatment before the study. Additionally, 20 of the patients had already been treated with topical agents, either calcipotriol or corticosteroids. The PASI scores were recorded before treatment and at month 0, 3, 6, 9, and 12. Routine hematological parameters, namely white blood cell (WBC) count, neutrophil count (NC), lymphocyte count (LC), platelet count (PC), mean platelet volume (MPV), and erythrocyte sedimentation rate (ESR), were investigated at each visit. Non-selective inflammatory markers, NLR, PLR, and RDW, were examined before treatment and at month 0, 3, 6, 9, and 12. The statistical correlation between these inflammation markers and PASI was examined at months 0 and 12. Paired comparisons were performed between baseline values and those measured at each visit. None of the patients withdrew from the study.

2 mL of venous blood samples was taken into tubes containing ethylenediaminetetraacetic acid (EDTA). At month 0, 3, 6, 9, and 12, all the blood materials were analyzed using a hemogram analysis machines for an hour (Sysmex xt-2000i osaka, Japan) to record NLR (%), PLR (%), RDW (%), WBC (10E3/uL), NC (10E3/uL), LC (10E3/uL), PC (10E3/uL), MPV (fL), and ESR (mm/hr). The normal ranges were 4.4-11.3 10E3/uL for WBC, 1.8-7.7 10E3/uL for NC, 154-386 10E3/uL for PC, 7.8-11 fL for MPV, 0.375-7.7% for NLR, 32.08-386% for PLR, 11.5-15% for RDW, and 0-15 mm/hr (men) and 0-20 mm/hr (women) for ESR.

Statistical analysis

The Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) was used for the statistical analysis. For evaluation of the data, in addition to descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum), a Friedman test was performed to analyze 3 or more follow-up datasets of the parameters showing an abnormal distribution, and a Wilcoxon signed-ranks test was used for dichotomous comparisons. $P<0.05$ was accepted as statistically significant.

RESULTS

Twenty-seven patients (60%) were women. The patients' age-range was 25-67 (mean ± Standard Deviation: 42.2±13.3). The baseline PASI values ranged from 10.4 to 46 (mean: 23.40±10.00). The results of the blood sample analysis at month 0 were as follows: WBC count 5.2-11.6 10E3/uL (mean: 8.3), NC 2.65-6.25 10E3/uL (mean: 5), LC 1.57-3.9 10E3/uL (mean: 2.2),

ESR 1-50 mm/hr (mean: 12 mm/hr), MPV 6.21-11.4 fL (mean: 9.2), NLR 1.22-2.95% (mean: 2.1%), PLR 59.1-160.5% (mean: 99.5%), RDW 11.6-17.3% (mean: 13.8%) (Table 1, Table 2). Hemoglobin levels, vitamin B12, and folate were within the normal range in all patients.

Paired comparisons showed a statistically significant decrease in the PASI values (P<0.01) at each visit compared with the baseline values (P=0.001). However, the assessment of the correlation between the PASI values and NLR, PLR, and RDW at months 0 and 12 showed no significant statistical association (P>0.05) (Table 3).

The changes in WBC at month 3, 6, 9, and 12 compared with the baseline values at month 0 were not significant (P>0.05) (Table 2). MPV significantly increased only at month 3 (p=0.033; P<0.05). LC significantly increased (P<0.01) at month 3, 6, 9, and 12 (P=0.001, P=0.001, P=0.003, and P=0.001, respectively). PC was noted to have significantly decreased at month 6, 9, and 12 (P<0.05) (Table 2). RDW significantly decreased only at month 3 (P=0.007; P<0.01) (Figure 1). All the remaining parameters (NC, PLR, and NLR) significantly decreased at each visit compared with month 0 (P<0.01) (Figure 2 and Figure 3). Furthermore, the changes in the ESR values measured at month 0, 3, 6, 9, and 12 were statistically significant (P=0.001; P<0.01). The results of paired comparisons showed a statistically significant decrease in the ESR values (P<0.05) at all visits (P=0.001, P=0.029, P=0.001, and P=0.005 for months 3, 6, 9, and 12, respectively).

DISCUSSION

Psoriasis vulgaris is a chronic systemic inflammatory disease accompanied by abnormal proliferation of keratinocytes and circulating inflammatory cytokines (1-6). The role of inflammatory cytokines in psoriasis vulgaris, e.g. C reactive protein (CRP), e-selectin, intra-cellular adhesion molecule-1, haptoglobin, interleukin (IL) 1-β, IL-6, IL-8, IL-12, and IL-18, and tumor

Table 1. The evaluation of the hematological parameters at month 0, 3, 6, 9, and 12

		Min-Max (Median)	Mean ± SD (Standard Deviation)	[a]P	[b]P
MPV	**Month 0**	6.21-11.4 (9.2)	9.22±1.59	***0.042****	$P_{months\ 0\text{-}3=}$ ***0.033****
	Month 3	6.85-11.8 (9.7)	9.41±1.67		
	Month 6	6.13-11.8 (10.0)	9.54±1.64		$P_{months\ 0\text{-}6=}$ ***0.053***
	Month 9	6.02-11.8 (9.4)	9.25±1.69		$P_{months\ 0\text{-}9=}$ ***0.131***
	Month 12	6.13-11.9 (9.7)	9.16±1.66		$P_{months\ 0\text{-}12=}$ ***0.852***
PLR	**Month 0**	59.1-160.5 (99.5)	103.66±29.18	***0.001****	$P_{months\ 0\text{-}3}$ ***0.001****
	Month 3	51.1-132.9 (78.5)	87.88±25.34		$P_{months\ 0\text{-}6}$ ***0.001****
	Month 6	43.9-140.5 (87.7)	85.59±26.73		$P_{months\ 0\text{-}9}$ ***0.001****
	Month 9	43.5-134.4 (83.3)	82.28±22.57		$P_{months\ 0\text{-}12}$ ***0.001****
	Month 12	43.5-110.9 (82.2)	82.21±21.87		
RDW	**Month 0**	11.6-17.3 (13.8)	14.21±1.50	***0.001****	$P_{months\ 0\text{-}3}$ ***0.007****
	Month 3	11.57-16.3 (12.9)	13.56±1.59		$P_{months\ 0\text{-}6}$ ***0.548***
	Month 6	11.7-16.9 (13.5)	14.15±1.70		$P_{months\ 0\text{-}9}$ ***1.000***
	Month 9	12.2-19.6 (14)	14.49±1.94		$P_{months\ 0\text{-}12}$ ***0.959***
	Month 12	10.5-17.2 (13.9)	14.15±2.04		
ESR	**Month 0**	1-50 (12)	13.38±12.31	***0.001****	$P_{months\ 0\text{-}3}$ ***0.001****
	Month 3	2-40 (6)	9.80±9.99		$P_{months\ 0\text{-}6}$ ***0.029****
	Month 6	2-33 (6)	9.93±9.77		$P_{months\ 0\text{-}9}$ ***0.001****
	Month 9	2-33 (6)	8.33±8.53		$P_{months\ 0\text{-}12}$ ***0.005****
	Month 12	2-33 (6)	9.33±9.04		
PASI	**Month 0**	10.4-46 (20.8)	23.40±10.00	***0.001****	$P_{months\ 0\text{-}3}$ ***0.001****
	Month 3	1.2-18 (5.4)	5.52±4.36		$P_{months\ 0\text{-}6}$ ***0.001****
	Month 6	0-15.6 (2.0)	3.57±4.29		$P_{months\ 0\text{-}9}$ ***0.001****
	Month 9	0-14.8 (1.2)	2.17±3.58		$P_{months\ 0\text{-}12}$ ***0.001****
	Month 12	0-17.6 (1.2)	2.64±4.51		

[a]Friedman Test; [b]Wilcoxon Signed Ranks Test; *P<0.05; **P<0.01; MVP: mean platelet volume; PLR: platelet-lymphocyte ratio; RDW: red cell distribution width; ESR: erythrocyte sedimentation rate; PASI: Psoriasis Area Severity Index

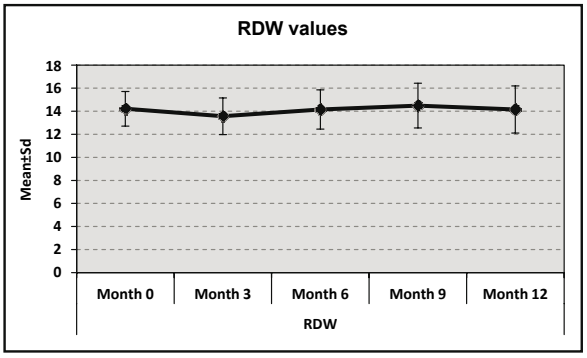

Figure 1. The distribution of the red cell distribution width (RDW) values during the study.

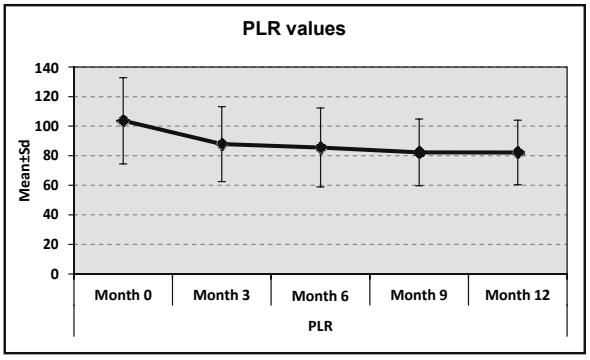

Figure 2. The distribution of the platelet-lymphocyte ratio (PLR) values throughout the study.

necrosis factor (TNF)-α has been demonstrated (6). Recently, it has been suggested that psoriasis is not just a skin condition but a multi-system disease affecting the bone and articular system, kidneys, myocardium, and peripheral blood (1). Thus, there is still an ongoing search for a biomarker for psoriasis vulgaris. Inflammatory markers such as highly sensitive-CRP, RDW, NLR, and PLR have been shown to increase in many chronic inflammatory diseases, indicating the presence and severity of disease activities (1-5). However, to date only one retrospective study has been undertaken to assess the possible role of RDW as a biomarker for the severity of psoriasis vulgaris (7,8).

RDW is a measure of variability in the size of circulating erythrocytes (anisocytosis) (9). It is calculated by dividing the standard deviation of red blood cell (RBC) volume by the mean corpuscular volume (MCV). RDW has also been used to differen-

Table 2. The evaluation of the hematological parameters at month 0, 3, 6, 9, and 12

		Min-Max (Median)	Mean±Sd	[a]p	[b]p
Neutrophil	**Month 0**	2.65-6.25 (5)	4.94±1.05	***0.002***	$P_{months\ 0\text{-}3}$=***0.020****
	Month 3	1.51-6.79 (4.5)	4.60±1.41		$P_{months\ 0\text{-}6}$=***0.003****
	Month 6	2.38-6.45 (4.5)	4.56±1.20		$P_{months\ 0\text{-}9}$=***0.020****
	Month 9	1.93-7.9 (4.8)	4.66±1.39		$P_{months\ 0\text{-}12}$=***0.001****
	Month 12	1.74-6.55 (4.1)	4.28±1.29		
Lymphocyte	**Month 0**	1.57-3.9 (2.2)	2.48±0.68	***0.006****	$P_{months\ 0\text{-}3}$=***0.001****
	Month 3	1.64-4.93 (2.6)	2.84±0.88		$P_{months\ 0\text{-}6}$=***0.001****
	Month 6	1.43-5.36 (2.6)	2.84±0.93		$P_{months\ 0\text{-}9}$=***0.003****
	Month 9	1.54-5.81 (2.6)	2.94±1.02		$P_{months\ 0\text{-}12}$=***0.001****
	Month 12	1.8-5.81 (2.8)	2.92±0.93		
NLR	**Month 0**	1.22-2.95 (2.1)	2.08±0.57	***0.001****	$P_{months\ 0\text{-}3}$=***0.001****
	Month 3	0.66-2.86 (1.6)	1.68±0.63		$P_{months\ 0\text{-}6}$=***0.001****
	Month 6	0.65-3.04 (1.7)	1.72±0.58		$P_{months\ 0\text{-}9}$=***0.001****
	Month 9	0.65-3.1 (1.7)	1.72±0.66		$P_{months\ 0\text{-}12}$=***0.001****
	Month 12	0.74-2.27 (1.6)	1.51±0.42		
PLR	**Month 0**	162-307 (252)	241.33±46.80	***0.001****	$P_{months\ 0\text{-}3}$=***0.070***
	Month 3	150-314 (232)	234.33±42.69		$P_{months\ 0\text{-}6}$=***-0.001****
	Month 6	150-298 (233)	225.00±46.64		$P_{months\ 0\text{-}9}$=***0.011****
	Month 9	148-293 (251)	230.73±48.66		$P_{months\ 0\text{-}12}$=***0.001****
	Month 12	139-298 (220)	227.07±46.88		
WBC	**Month 0**	5.2-11.6 (8.3)	8.50±1.65	***0.165***	$P_{months\ 0\text{-}3}$=***0.216***
	Month 3	4.04-12.41 (8.2)	8.601±2.14		$P_{months\ 0\text{-}6}$=***0.879***
	Month 6	5.82-13.23 (8.3)	8.50±2.01		$P_{months\ 0\text{-}9}$=***0.369***
	Month 9	5.13-12.6 (8.4)	8.69±2.10		$P_{months\ 0\text{-}12}$=***0.369***
	Month 12	4.55-12.28 (8.1)	8.25±2.15		

[a]Friedman Test; [b]Wilcoxon Signed Ranks Test; *P<0.05; **P<0.01; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-lymphocyte ratio; WCB: white blood cell count

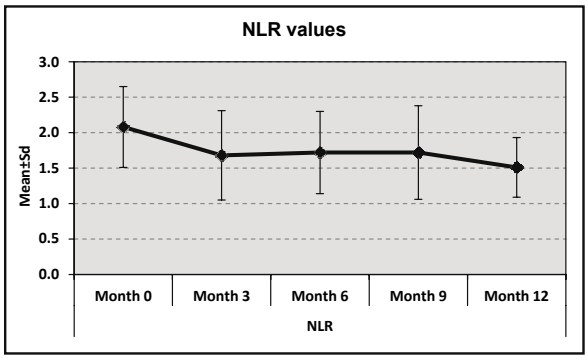

Figure 3. The distribution of the neutrophil-to-lymphocyte ratio (NLR) values throughout the study.

tiate causes of anemia. RDW is known to increase in several conditions including pregnancy, inflammatory diseases e.g. thrombocytopenic purpura, inflammatory bowel diseases, anemia, blood hemolysis, blood transfusion, and ineffective red cell production in cases of iron, vitamin B12, or folate deficiencies (5,10). Elevated RDW values have been reported in myocardial infarctions, stroke, cardiac failure, pulmonary hypertension, and peripheral arterial diseases (2,4,5) as well as Alzheimer's, diabetes mellitus, and rheumatoid arthritis (11-13). A higher RDW is considered a strong and independent negative predictive mortality marker indicating an adverse outcome. Decreased kidney function has been implicated for the negative effect of RDW. Furthermore, increased RDW often accompanies elevated levels of highly sensitive CRP and neurohumoral markers (β-type natriuretic peptide) and lower levels of anti-oxidative elements e.g. selenium (14). In inflammatory diseases, circulating cytokines are responsible for the lower antioxidant status, which shows the damaging oxidative effects predominant on all body systems including the hematological system. Thus, immature erythropoiesis causes low cell survival and juvenile circulating erythrocytes, resulting in higher RDW. Increased inflammation means greater oxidative stress and a further increase in RDW (15). Based on this evidence, we believe that RDW is not only a routine diagnostic parameter but may also act as a prognostic marker in moderate-to-severe psoriasis in the first three months of treatment. However, it is not certain why RDW showed a positive correlation with PASI scores only during the early treatment period (month 3) and not in the later phases. The release of cytokines after the initiation of treatment may have caused an onset of an anti-inflammatory, anti-oxidant effect, triggering a regular hematopoiesis and mature erythrocytes (low RDW) that may have diminished over time. On the other hand, Coimbra *et al.* found that enhanced RBC damage, aging and clearance caused erythroid

Table 3. The association between Psoriasis Area Severity Index (PASI) and hematological parameters

	Month 0		Month 12	
	r	*P*	r	*P*
PASI & NLR	0.243	***0.108***	-0.048	***0.752***
PASI & PLR	0.189	***0.213***	-0.091	***0.551***
PASI & RDW	-0.279	***0.064***	-0.073	***0.635***
PASI & MPV	0.173	***0.204***	-0.064	***0.642***

r: Spearman's correlation coefficient; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-lymphocyte ratio; RDW: red cell distribution width; MPV: mean platelet volume

disturbance in Portuguese patients with psoriasis (16). The authors also reported that RBC was lower in patients with psoriasis and several changes indicating an enhanced damage and/or ageing process were present, which seemed to be strongly connected with neutrophil activation, oxidative stress, and disease deterioration (16). Since erythroid disturbance was not completely resolved after a successful treatment, it has been suggested that RDW does not correlate with PASI.

In a retrospective study investigating the association of RDW with psoriasis severity, RDW was reported to have a significant correlation with ESR, but not CRP (7). However, ESR was significantly correlated with CRP. In contrast, Yeşil *et al.*reported a significant correlation of RDW with both ESR and CRP in patients with inflammatory bowel disease (17). In another clinical study investigating inflammatory biomarkers in patients with rheumatoid arthritis, RDW was found to be significantly correlated with only CRP (13). Moreover, RDW was not correlated with PASI (7). RDW was reported to be significantly increased in patients with a PASI of greater than 12 (severe) compared with patients with a PASI less than 7 (mild) (7). However, no significant difference was reported between patients with moderate and severe psoriasis vulgaris. Additionally, Doğan *et al.* reported that patients with psoriasis who do not have any major cardiovascular risk factors still have high levels of CRP and RDW, supporting the hypothesis that psoriatic inflammation itself can simultaneously cause CRP and RDW elevation (8). A previous case-control study carried out on 50 patients with psoriasis and 50 healthy control subjects examined the correlation between platelet count, MPV, and RDW with PASI values (18). The mean values for MPV and RDW were found to be higher and the platelet count lower compared with controls in patients of both sexes . The MPV values in male patients and platelet counts in female patients were reported to show strong positive and negative

correlation with the PASI score, respectively (18). As a result of this study, it was similarly concluded that rising MPV and decreasing PLR could be good indicators of disease severity and progression that help in assessing the treatment course of the disease (18).

The present study had certain limitations such as the lack of a control group. However, we excluded the presence of all probable factors that may have affected the evaluated biomarkers. For example, systemic methotrexate intake which triggers folate or vitamin B12 deficiency may also cause higher values of MCV and RDW in patients with psoriasis (7). Since hemoglobin levels were within the normal range and none of the patients were under methotrexate treatment, we easily excluded the probability of iron, folate, or vitamin B12 deficiencies. We believe that the comparison of the change in the PASI values and biomarkers during the treatment period compared with the baseline and the examination of their possible affiliation improved the value of the study.

Coimbra *et al.* did not consider RDW to be a prognostic marker to estimate the severity of psoriasis vulgaris, but associated higher RDW with psoriasis vulgaris (16). In another study that examined MPV and RDW in patients with pityriasis rosea, no significant difference was reported between the patient and control groups (3). The lower RDW values seen in acute pityriasis rosea were attributed to a viral infection that could have suppressed the bone marrow and resulted in a temporary loss in erythropoietic activity (3). Moreover, in systemic sclerosis, RDW was reported as a valuable measure of multiple pathological processes including extensive vasculopathy, fibrosis, and ongoing inflammation (19). Based on the results, we conclude that RDW is only correlated with early PASI measurements since RBC distribution and erythropoiesis may not really change after long-term anti-psoriasis treatment.

MPV is another determinant of inflammation easily measurable using an automated hematology analyzer in a routine complete blood cell analysis (20). As a sign of platelet function and activation, MPV is elevated during the increased peripheral destruction of platelets and reduced during impaired platelet production (20). MPV has been studied as an inflammatory marker of cutaneous vasculitis, psoriasis, and cardiovascular and rheumatologic diseases. Furthermore, Topal *et al.* reported that the MPV value was higher in preschool children with atopic eczema, whereas RDW was not statistically different (21). In recent studies, elevated MPV levels have been observed in diseases such as psoriasis, psoriatic arthritis, Behçet's, diabetes mellitus, acute coronary syndrome, stroke, preeclampsia, renal artery stenosis, and hypercholesterolemia (20,22-25). In a study that examined the effects of colchicine in patients with recurrent aphthous stomatitis, NLR, WBC, and RDW significantly decreased; however, no changes were seen in MPV, PLR, and hemoglobin levels in patients under colchicine treatment (26). In the current study, similar to the RDW results, the MPV values significantly increased only at month 3, indicating a significant change only in the early treatment period. This may be attributed to the acute temporary destructive or suppressive effects of a systemic anti-psoriatic drug. Furthermore, following the rise in MPV at month 3, PC significantly decreased at month 6, 9, and 12 due to the destruction of platelets.

CONCLUSION

RDW measurement is a simple, efficient, and cost-effective tool to include in routine whole-blood examinations to monitor patients with psoriasis vulgaris in everyday practice. It can be concluded that RDW may help predict the severity of psoriasis vulgaris faster than the measurement of PASI values during the early treatment period. Further multi-centered, controlled clinical studies are needed to confirm the prognostic importance of biomarkers such as RDW or MPV in patients with psoriasis vulgaris. Furthermore, cytogenetic and bone marrow evaluations would clearly reveal the exact mechanism of erythroid disturbance in these patients. Finally, the effect of specific drugs, e.g. colchicine, could be examined.

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