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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

MULTİPL SKLEROZ HASTALARINDA PLATELET LENFOSİT ORANI, MONOSİT LENFOSİT ORANI, NÖTROFİL LENFOSİT ORANI, ERİTROSİT DAĞILIM GENİŞLİĞİ VE SİSTEMİK İMMÜN İNFLAMASYON İNDEKSİ DUYARLILIĞI: HASTALIK ALT TİPLERİ VE ENGELLİLİK İLE İLİŞKİSİ

SENSITIVITY OF PLATELET-LYMPHOCYTE RATIO, MONOCYTE-LYMPHOCYTE RATIO, NEUTROPHIL-LYMPHOCYTE RATIO, RED BLOOD CELL DISTRIBUTION WIDTH AND SYSTEMIC IMMUNE INFLAMMATORY INDEX IN MULTIPLE SCLEROSIS PATIENTS: RELATIONSHIP WITH DISEASE SUBTYPES AND DISABILITY

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ÖZET

AMAÇ: Multipl skleroz (MS) merkezi sinir sisteminin (MSS) süreğen, inflamatuar otoimmün bir hastalığıdır. Otoimmün yanıtların nasıl oluştuğu netlik kazanmasa da periferik kan hücrelerinin MS'te inflamatuar yanıtın başlamasına ve şiddetlenmesine katkıda bulunabileceği bilinmektedir. Bu çalışmanın amacı MS'de nötrofil-lenfosit oranı (NLR), monosit-lenfosit oranı (MLR), platelet-lenfosit oranı (PLR), eritrosit dağılım genişliği (RDW) ve sistemik immün inflamasyon indeksi (SIII) duyarlılığını ve özgüllüğünü değerlendirmek ve engellilik ile arasındaki ilişkiyi belirlemektir.

GEREÇ VE YÖNTEM: Bu tek merkezli, retrospektif vaka kontrol çalışmasına toplam 104 MS hastası ile yaş ve cinsiyet uyumlu 65 sağlıklı birey alındı. Engellilik, Genişletilmiş Engellilik Durumu Ölçeği (EDSS) ile değerlendirildi ve buna göre hastalar, hafif (EDSS<3), orta (3,5 ≤ EDSS ≥4,5) ve şiddetli (EDSS≥5) engelliler olarak sınıflandırıldı. Hastaların ve kontrol grubunun tam kan sayımlarına göre NLR, MLR, PLR, RDW ve SIII değerleri hesaplandı. Kontrol grubu ile MS hastaları, MS alt tipleri ve relapsing-remitting MS (RRMS) atak ve remisyon dönemi arasındaki inflamasyon belirteçleri karşılaştırıldı. Bu belirteçler ile hastalık süresi, atak sayısı ve özürlülük arasındaki ilişkiye bakıldı.

BULGULAR: MLR ve RDW, MS'de kontrol grubuna göre daha yüksekti. MS alt tiplerin arasında bu değerlerde anlamlı farklılık yoktu. Hastalık süresi, atak sayısı ve EDSS arttıkça RDW'nin de arttığı görüldü.

SONUÇ: Çalışmamızda MLR ve RDW'nin PLR, NLR ve SIII'ye göre inflamasyonu değerlendirmede daha belirleyici olduğu görülmüştür. RDW'nin MS hastalarında daha yüksek olması ve hastalık disabilitesinden etkilenmesi, MS hastalarının takibinde ve özürlülük derecesinin değerlendirilmesinde RDW'nin önemli bir rolü olabileceğini göstermektedir.

ANAHTAR KELİMELER: Multipl skleroz, İnflamatuar yanıt, İnflamasyon, Lenfosit, Eritrosit dağılım hacmi.

ABSTRACT

OBJECTIVE: Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system (CNS). Although it is not clear how autoimmune responses occur, it is known that peripheral blood cells may promote the initiation and exacerbation of the inflammatory response in MS. The aim of this study was to evaluate the sensitivity and specificity of neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), erythrocyte distribution width (RDW) and systemic immune inflammation index (SIII) in MS and to determine their relationship with disability.

MATERIAL AND METHODS: In this single-center, retrospective case-control study, 104 patients with MS and 65 healthy individuals were included. Disability was assessed with the Expanded Disability Status Scale (EDSS) score, and patients were classified as mild (EDSS<3), moderate (3.5 ≤ EDSS ≥4.5), and severe (EDSS≥5) disabilities. NLR, MLR, PLR, RDW and SIII values were calculated according to the complete blood counts of the patients and the control group. Inflammation markers between the control group and MS patients, MS subtypes, and relapsing-remitting MS (RRMS) attack and remission periods were compared. the relationship between these markers and duration of illness, number of attacks and disability was examined.

RESULTS: MLR and RDW were higher in MS than the controls. There was no significant difference in these values between MS subtypes. It was observed that RDW increased as the disease duration, number of attacks and EDSS increased.

CONCLUSIONS: In our study, in evaluating inflammation it was seen that MLR and RDW were more determinative than PLR, NLR and SIII. The fact that RDW is higher in MS patients and is affected by disease disability indicates that RDW may have an important role in the follow-up of MS patients and in evaluating the degree of disability.

KEYWORDS: Multiple sclerosis, Inflammatory response, Inflammation, Lymphocyte, Erythrocyte distribution volume.

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INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune demyelinating disease of the central nervous system (CNS) affecting mostly young adults. The etiology of MS is still obscure; however, a complex interaction of genetic and environmental factors have been suggested to underlie the immune dysregulation observed in MS. The principal mediators of MS are activated myelin-reactive T cells crossing the blood brain barrier (BBB) and recruiting a diverse set of myeloid cells including neutrophils and monocytes/macrophages. These cells along with CNS-resident microglia and astrocytes promote and execute an inflammatory cascade that ultimately results in myelin, oligodendrocyte and axonal damage in the CNS through direct cell contact-dependent mechanisms and action of wide range of inflammatory, anti-inflammatory cytokines, autoantibodies, oxidative species and enzymes secreted by these cells (1 - 3).

T cells are presumed to be activated in the periphery. Though it is still an enigma how the autoimmune responses are generated, it is recently well recognized and documented that peripheral blood cells including neutrophils, monocytes, and platelets may contribute to the initiation and aggravation of inflammatory response in MS. Even more, some hematological indices are reported to be independent predictors of the neurological disability and brain atrophy (4 - 6).

It has been stated that the inflammatory response in the body can be assessed by changes in the composition of inflammatory proteins and inflammatory cells in peripheral blood. In relation to this, serum hematological indices including the systemic immune inflammatory index (SIII), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), monocyte-lymhocyte ratio (MLR), red blood cell distribution width (RDW) and others have emerged as useful biomarkers of pathogenic inflammation and prognostication in many inflammatory diseases because of their availability and affordability (5 - 11). Even more, SIII is reported to be superior to NLR and PLR in reflecting the balance of one's inflammatory and immune status (12). The aim of this study was to evaluate the sensitivity and specifity of SIII, NLR, MLR, PLR and RDW and further to determine the prognostic accuracy of each in MS patients and relationship with acute exacerbation.

MATERIALS AND METHODS

Participants

The study was a single-center retrospective case-control study. A total of 104 patients with MS and 65 age- and gender-matched healthy individuals were enrolled into the study. Sample size was estimated in the G* Power program, with t tests and two-way method, the total minimum sample size required for the patient and healthy group was accepted as 5% type 1 error, 95% confidence interval, and the medium effect size suggested by Cohen as 0.50 and 80% power. It was calculated with 144. The patient group was planned as a minimum of 96, and the control group as 48. MS patients were selected consecutively among outpatient clinic of Süleyman Demirel University Medical Faculty Neurology Department between January 2019 and October 2021. Patients older than 18 years of age with a definite diagnosis of MS according to McDonald criteria were included (13). Presence of any hematological and autoimmune comorbidities (including rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, Behçet's disease and others), diabetes and hyperlipidemia, hypertension, cardiovascular diseases, liver and kidney dysfunction, malignancies, anti-coagulant or anti-platelet use, history of infection within the previous month were determined as exclusion criterias for both groups. Furthermore, MS patients who received corticosteroid within the last 3 months, who used any herbal medicine, or who were pregnant were excluded. Volunteers constituting the control group were recruited from individuals who applied to the outpatient clinic for routine controls, did not have any chronic diseases, and met the inclusion and exclusion criteria. All participants were assessed by a trained neurologist. Among a total sample of 183 patients, 79 were excluded **(Figure1)**. The remaining 104 MS patients were re-evaluated for clinical and demographic data prior to blood sampling. MS subtype, disease duration, disability status and current

disease modifying drugs the patients are on was recorded. Disability was estimated by the Expanded Disability Status Scale (EDSS) score, and accordingly MS patients were grouped as those with mild (EDSS<3), moderate (3.5 ≤ EDSS ≥4.5) and severe (EDSS≥5) disability (14, 15).

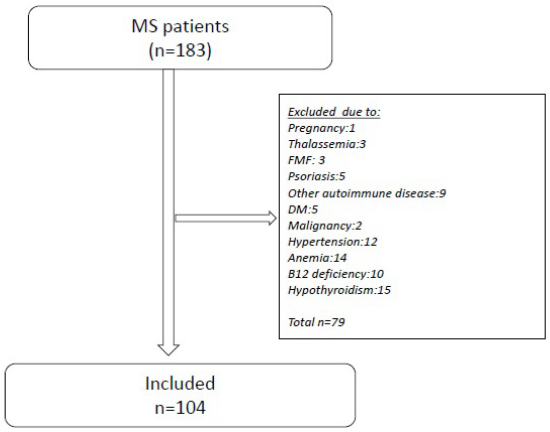

Figure 1: Flowchart of sample selection

Complete Blood Counts

Blood samples of the participants were drawn from the antecubital vein after 12 hours of fasting and flow cytometry method (Beckman Coulter LH 780 Analyzer; Beckman Coulter Inc., Miami, FL) was used for the analysis. The analyzer was calibrated twice a day by determining low and high parameters with the control blood samples. Results were determined and recorded. To evaluate the temporal change of hematological indices during remission and relapse, blood samples of RRMS patients during the acute attack, before receiving intravenous methylprednisolone therapy, were achieved retrospectively from hospital records. Total white and red blood cell and platelet counts were collected for both groups. In addition, red cell distribution volume, differential numbers of monocytes, lymphocytes and neutrophils were determined and NLR, PLR, MLR values were calculated from each component. SIII was calculated according to formula SIII: (plateletXneutrophil)/lymphocyte.

Ethical Committee

The study was carried out according to the tenets of the Helsinki Declaration and has been approved by the institutional review board of Süleyman Demirel University Medical Faculty (01.07.2021/75783). Written informed consent form was obtained from all individuals participating to the study.

Statistical Analysis

SPSS 23.0 software was used to analyze data (SPSS Inc., Chicago, IL). Normality of variables was evaluated by the Kolmogorov-Smirnov and the Shapiro-Wilk normality tests. Continuous variables were given as mean±standard deviation, and categorical variables as number and percentage. The Chi-square test was used to compare the ratios in the groups. The Student's t-test or Mann-Whitney U-test was used to compare the two independent groups according to their distribution state. Comparisons of more than two independent groups were assessed with one-way ANOVA and Kruskal–Wallis tests according to their Gaussian distribution. Post-hoc analysis was conducted using Duncan's and Dunn's multiple comparison test, when appropriate. The correlation between variables were evaluated with Pearson's and Spearman's correlation tests. Further, receiver operating characteristics (ROC) curve analysis was used to determine the cut-off values of the hematological indices. For all the analyses, the significance level was established as $p < 0.05$.

RESULTS

Of the 104 patients included in the study, 77 were relapsing-remitting MS (RRMS) and 27 were secondary progressive MS (SPMS). Characteristics of all patients and healthy participants and blood test data are summarized in **Table 1.** Lymphocyte values were lower in MS patients (p=0.017). MLR, RDW and MPV were higher in MS than in controls (p<0.001, p=0.002 and p=0.027 respectively). Although PLR, NLR and SIII were higher in MS patients compared to controls, this difference was not statistically significant (Table 1). Although MLR, PLR, NLR, RDW, SIII values were higher in RRMS compared to SPMS, no statistically significant difference was found **(Table 2)**. When the RRMS attack and remission periods were evaluated, MLR and PLR were found to be higher in the remission period than in the attack period (p<0.001 and p=0.003).

Although NLR, RDW and SIII were found to be higher in the remission period, these differences were not statistically significant **(Table 3)**. When evaluated according to disability groups, NLR was statistically significantly higher in moderate disability (p=0.008). Although MLR, PLR,

SIII were higher in moderate disability, it was not statistically significant **(Table 4)**. When the correlation of parameters with EDSS, duration of disease, number of attacks is examined,it was observed that NLR, RDW and SIII values were higher as the EDSS value increased. It was observed that NLR, PLR, SIII and RDW increased as the disease duration increased **(Table 5)**. Relative to the ROC analysis results, when the cut-off value for MLR was taken as 0.28, the area under the curve (AUC) was obtained as 0.673. This value obtained is statistically significant (p<0.001). Sensitivity was 64.36% and specificity was 67.69%. When the cut-off value for RDW is taken as 14.2, the area under the curve (AUC) is obtained as 0.641. This value obtained is statistically significant (p=0.002). Sensitivity was 43% and specificity was 81.54% **(Table 6)**.

Table 1: Demographic data of MS patients and comparison of inflammation parameters with the control group

	MS	Control	Test statistic	P
Gender (K)	68 (65,4)	43 (66,2)	χ^2=0,011	0,918
Age	36,5 ± 9,9	34,8 ± 10,2	U=3747,5	0,235
Disease duration (year)	7,6 ± 5,9			
number of attacks	3,2 ± 2,1			
EDSS	2,7 ± 2,1			
EDSS groups				
mild disability	67			
moderate disability	13			
severe disability	24			
Treatment				
No drugs	12			
Interferon beta	21			
Glatiramer asetat	19			
Dimetil fumarat	17			
Ocrelizumab	13			
Fingolimod	12			
Teriflunomid	9			
Natalizumab	1			
Lymphocyte	1,84 ± 0,76	2,10 ± 0,61	t=2,416	**0,017**
Neutrophil	4,08 ± 1,40	4,08 ± 1,10	t=0,003	0,998
Monocyte	0,57 ± 0,17	0,52 ± 0,15	U=2792	0,080
Platelet	232,05 ± 60,18	245,75 ± 47,74	t=1,631	0,105
NLR	2,78 ± 2,18	2,11 ± 0,85	U=2834	0,114
MLR	0,39 ± 0,30	0,27 ± 0,11	U=2149,5	**<0,001**
PLR	157,72 ± 106,85	124,91 ± 41,14	U=2920	0,195
RDW	15,40 ± 10,00	13,67 ± 1,22	U=2331	**0,002**
MPV	9,08 ± 1,07	8,76 ± 0,80	t=-2,228	**0,027**
SIII	640,15 ± 569,19	508,95 ± 206,56	U=3036	0,360

EDSS: Expanded Disability Status Scale, NLR: Neutrophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, RDW: Erythrocyte distribution width, MPV: Mean platelet volume, SIII: Systemic immune inflammation index χ^2: Chi-square test statistic, U: Mann-Whitney U test statistic, t: Two independent samples t-test statistics *Display: Mean ± s. deviation, frequency (percent)

Table 2: Comparison of parameters between RRMS and SPMS groups

	RRMS	SPMS	Test statistic	P
	Mean ± s. deviation	Mean ± s. deviation		
NLR	2,84 ± 2,47	2,62 ± 1,06	U=883,5	0,328
PLR	163,30 ± 119,93	142,20 ± 55,43	U=996	0,900
MLR	0,42 ± 0,33	0,32 ± 0,13	U=858,5	0,365
RDW	15,61 ± 11,66	14,83 ± 2,00	U=821	0,201
MPV	9,12 ± 1,11	8,96 ± 0,96	t=0,679	0,498
SIII	653,29 ± 645,07	603,65 ± 268,96	U=898	0,385

RRMS: Relapsing-remitting multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, NLR: Neutrophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, RDW: Erythrocyte distribution width, MPV: Mean platelet volume, SIII: Systemic immune inflammation index, t: Two independent samples t-test statistics *Display: Mean ± s. deviation, frequency (percent)t: Independent two-sample t-test statistic, U: Mann-Whitney U test statistic

Table 3: Comparison of the attack period and remission period parameters in the relapsing remitting MS (RRMS) group

	Attack	Remission	Test statistic	P
	Mean ± s. deviation	Mean ± s. deviation		
NLR	2,75 ± 2,35	2,85 ± 2,48	Z=-0,859	0,390
MLR	0,28 ± 0,13	0,42 ± 0,34	Z=-4,231	**<0,001**
PLR	131,19 ± 101,64	163,28 ± 120,75	Z=-3,006	**0,003**
RDW	14,14 ± 2,83	15,64 ± 11,73	Z=-1,698	0,090
MPV	9,16 ± 1,12	9,13 ± 1,12	t=0,448	0,656
SIII	637,21 ± 565,02	656,77 ± 648,77	Z=-0,617	0,537

NLR: Neutrophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, RDW: Erythrocyte distribution width, MPV: Mean platelet volume, SIII: Systemic immune inflammation index, t: Paired two sample t-test statistic, Z: Wilcxon test statistic

Table 4: Comparison of parameters according to EDSS groups

	mild disability	moderate disability	severe disability	Test statistic	P
	Mean ± s. Deviation	Mean ± s. deviation	Mean ± s. deviation		
NLR	2,66 ± 2,46	3,90 ± 1,99	2,50 ± 1,06	χ^2=9,76	**0,008**
MLR	0,38 ± 0,29	0,58 ± 0,45	0,32 ± 0,13	χ^2=1,09	0,580
PLR	159,53 ± 120,27	182,79 ± 107,37	139,23 ± 56,13	χ^2=5,56	0,062
RDW	15,81 ± 12,55	14,11 ± 0,91	15,04 ± 2,01	χ^2=4,322	0,115
MPV	9,13 ± 1,11	9,05 ± 1,28	8,95 ± 0,85	F=0,247	0,782
SIII	633,07 ± 665,34	803,88 ± 441,59	570,65 ± 262,34	χ^2=4,776	0,092

EDSS: Expanded Disability Status Scale, NLR: Neutrophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, RDW: Erythrocyte distribution width, MPV: Mean platelet volume, SIII: Systemic immune inflammation index, χ^2: Kruskal Wallis test statistic, F: One-way analysis of variance test statistics

Table 5: Correlation of parameters with EDSS, disease duration and number of attacks

	EDSS		Disease duration		Number of attacks	
	r	p	r	p	P	R
NLR	0,252	**0,011**	0,245	**0,013**	0,221	**0,026**
PLR	0,136	0,173	0,211	**0,033**	0,134	0,180
MLR	0,085	0,396	0,118	0,242	0,010	0,918
RDW	0,291	**0,003**	0,198	**0,049**	0,283	**0,004**
MPV	-0,078	0,436	-0,038	0,706	-0,026	0,793
SIII	0,198	**0,046**	0,215	**0,030**	0,176	0,077

EDSS: Expanded Disability Status Scale, NLR: Neutrophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, RDW: Erythrocyte distribution width, MPV: Mean platelet volume, SIII: Systemic immune inflammation index, r: Spearman's rho correlation coefficient

Table 6: ROC analysis results

Parametre	Cut-off	AUC (%95 CI)	p	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR	---	0,573 (0,486 – 0,659)	0,114	---	---	---	---
PLR	---	0,56 (0,473 – 0,646)	0,195	---	---	---	---
MLR	≥0,28	0,673 (0,59 – 0,756)	**0,000**	64,36%	67,69%	75,58%	55%
RDW	≥14,2	0,641 (0,557 – 0,726)	**0,002**	43%	81,54%	78,18%	48,18%
MPV	---	0,587 (0,5 – 0,673)	0,059	---	---	---	---
SIII	---	0,542 (0,455 – 0,629)	0,360	---	---	---	---

ROC: Receiver operating characteristics, AUC: Area under the curve, PPV: Positive predictive value, NPV: Negative predictive value, NLR: Neutrophil-lymphocyte ratio, MLR: Monocyte-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, RDW: Erythrocyte distribution width, MPV: Mean platelet volume, SIII: Systemic immune inflammation index,

DISCUSSION

The BBB is a critical physiological barrier to protect the CNS from inflammatory cells found in peripheral blood. Disruption of the BBB in MS is one of the early signs of the disease. In the early stage of immune-inflammatory diseases, neutrophils can infiltrate the CNS, triggering and exacerbating the inflammatory response. Cytokines, including interleukin-1 beta (IL-1β), IL-6 and tumor necrosis factor-alpha (TNF-α), can be released from neutrophils in the acute phase of inflammation and impair BBB function and increase BBB permeability (16, 17). Moreover, platelets also play a vital role in inflammation by communicating with many types of cells, including white blood cells found in peripheral blood (18). Activated platelets pro-

mote the activation of neutrophils, monocytes and dendritic cells with selectin and CD40L (19). Proinflammatory stimulation in microglial cells contributes to the increase of inflammatory cells (lymphocytes, neutrophils, monocytes, and macrophages), destruction of the myelin sheath, and formation of demyelinating lesions (11).

The inflammatory response in the body is manifested by changes in inflammatory proteins and the number of inflammatory cells in the blood. The most common markers for assessing inflammation in the body include NLR, MLR, PLR, RDW, and SIII.

In recent studies have focused on NLR, which is the ratio of neutrophils to lymphocytes (20). In response to conditions such as systemic inflammation, an increase in the number of neutrophils and a decrease in the number of lymphocytes is observed. NLR increases due to this change (21). NLR has also been investigated in central and systemic neurological diseases such as ischemic and hemorrhagic cerebrovascular diseases, myasthenia gravis, and MS, and its relationship with prognosis has been demonstrated (22 - 25). In some studies, NLR level was higher in MS than in the control group (4, 25, 26). Although NLR levels were higher in MS patients in our study, this difference was not statistically significant. No statistically significant difference was found between RRMS attack-remission periods and between MS subtypes in terms of NLR. Güzel et al. determined NLR higher in patients with an EDSS score of 5 and above and reported that NLR could be a distinctive inflammatory marker in terms of disease progression (27). In our study, NLR was significantly higher in moderate disabilities. It was observed that the NLR value was as higher as the EDSS value and the number of attacks increased and the duration of the disease increased.

PLR was first defined in the literature in 2008 by Smith RA et al. The authors reported that thrombocytosis and lymphocytopenia indicate the degree of systemic inflammation of individuals and that PLR may be a critical marker (28). Our study demonstrated no significant difference in PLR between the MS patients and the control group. In RRMS, PLR was higher in the remission than in the attack period. No correlation was observed between PLR and disease disability.

It is thought that MLR may have a role in disability in MS by contributing to the proinflammatory process. Hemond et al. reported higher levels of MLR in the progressive MS subtype compared to the relapsing MS subtype. They found a strong correlation between high EDSS scores and increased MLR levels in MS patients. They reported that although increased MLR level did not affect T2 hyperintense lesion volume on MRI, it was strongly associated with brain atrophy (6). In our findings, MLR levels were significantly higher in MS patients than in controls and in RRMS in the remission period compared to the attack period. Contrary to the study by Hemond et al., MLR was higher in the form of MS with relapses in our study. There was no significant relationship between disease disability and MLR.

The relationship of various platelet markers, such as mean platelet volume (MPV), with inflammation and thrombosis, has been investigated. A relationship between thrombosis and many diseases with inflammation and platelet activation has been determined (29).While Uzar et al. reported no difference in MPV levels between MS patients and the control group (30). In our study, MPV level was statistically significantly higher in MS patients than in controls. There was no association between disease disability and MPV.

Oxidative stress is considered to shorten the effective erythrocyte lifespan and increase hemolysis susceptibility (31). It was suggested that neurohumoral activation might also cause an increase in RDW by increasing anisocytosis and that proinflammatory cytokines inhibit erythropoietin-induced erythrocyte maturation, resulting in increased RDW (32). Decreased erythrocyte deformability also increases RDW (33). Another hypothesis is that RDW may be increased, as enzymes produced by leukocytes cause changes in the red blood cell membrane (e.g., decrease in sialic acid), resulting in changes in cell shapes (34). In some studies, it was reported that RDW is increased in various inflammatory events (35 - 37).

Recent studies revealed that RDW is increased in stroke and MS (5, 38). RDW can be a useful marker for predicting disability status and treatment efficacy in patients with MS. Peng et al. found a higher RDW value in MS patients than

healthy controls and found a positive correlation between EDSS and RDW. They reported that the RDW values of 109 RRMS patients who received Rebiff treatment were lower than the RDW value measured after starting Rebiff treatment (5). In our study, RDW was higher in MS than the controls. It was seen that RDW increased as the duration of the disease increased, the number of attacks increased and EDSS progressed.

The SIII is highlighted as a new inflammatory marker calculated from platelet, lymphocyte, and neutrophil counts. SIII is associated with the severity and prognosis of acute stroke (39). Mei et al. found that the SIII value measured 30 days after the treatment in patients with a diagnosis of autoimmune encephalitis was higher in those who responded poorly to immunotherapy than in those who responded well. They emphasized that SIII is a potential biomarker that can be easily used to predict the prognosis of the disease and whether immunosuppressive therapy can be initiated (40). In Saçmacı et al.'s study, SIII was higher in MS patients. They found a significant relationship between EDSS and SIII and stated that a high SIII value could be an effective prognostic marker in demonstrating disease disability in MS (8). In our study, there was no difference between groups in SIII, and we did not find any correlation with disease disability.

In conclusion, MLR, PLR, RDW, MPV and SIII, which are included in routine whole blood analysis, can be considered as quickly accessible, practical and inexpensive markers for evaluating inflammation for MS patients. The fact that MLR and PLR are higher in the RRMS remission period compared to the attack period can be clarified by prospective studies in a large number of patients. It can be assumed that MLR and RDW are more predictive markers than PLR and NLR in evaluating inflammation. Due to the possibility of drugs used in MS treatment possibility of doing lymphopenia, just looking at the lymphocyte count may be misleading in assessing the degree of inflammation. The fact that RDW is higher in MS patients than in controls and is affected by disease disability indicates that RDW has an essential role in the follow-up of MS patients in evaluating treatment response and severity of the disability. Hence, further prospective studies with larger numbers of patients are needed.

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