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Evaluation of hematological markers and disease activity in relapsing-remitting multiple sclerosis

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ABSTRACT

Aims: Multiple sclerosis (MS) is an immune-mediated chronic disease of the central nervous system that causes demyelination and neuroaxonal damage. Systemic inflammation is thought to cause chronic neurodegeneration. It plays an essential role in the pathogenesis of MS. This study aims to compare the inflammatory parameters such as neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio, platelet-lymphocyte ratio (PLR), systemic immune-inflammatory index (SII) and systemic inflammatory response index (SIRI) in relapsing-remitting multiple sclerosis (RRMS) patients during relapse and remission periods with the healthy control group and to investigate the relationship between these parameters and disease activity in MS patients.

Methods: This study involved one hundred four patients between the ages of 18 and 47 who applied to Kastamonu Training and Research Hospital with an MS attack and were diagnosed with RRMS according to the 2017 McDonald criteria were included in the study. The patients' hemogram results were compared in the relapse and remission periods. In addition, the hemogram results in the relapse and remission periods were compared with the hemogram results of the healthy control group.

Results: A total of 104 MS patients and 64 healthy controls were included in the study. 70 (67%) of MS patients were female, and 24 (33%) were male. The average disease duration of the patients was calculated as 4.7±3.7, and the average Expanded Disability Status Scale score was 2.17. NLR, PLR, SIRI, and SII were significantly higher during the attack period compared to the healthy group. Also, NLR, PLR, SII, and SIRI were significantly higher in the remission period compared to the healthy control group. However, there was no significant difference in NLR, PLR, SII, and SIRI levels in MS patients between the attack and remission phases.

Conclusion: Elevated inflammatory markers in MS patients compared to healthy controls suggest inflammation's role in the disease. Notably, similar levels during relapse and remission periods may indicate possible chronic inflammation. Larger prospective studies are needed to confirm these findings.

Keywords: Multiple sclerosis, inflammation, NLR, SII, SIRI

INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated chronic disease of the central nervous system that causes demyelination and neuroaxonal damage.[1] MS is the leading cause of disability among young adults following trauma. Genetic and environmental risk factors are included in the multifactorial etiology. The most frequent type is relapsing-remitting multiple sclerosis (RRMS). It accounts for about 85 percent of the cases. RRMS is defined by recurring neurological symptoms that persist from a few days to weeks.[2]

MS pathology still needs to be fully understood. Systemic inflammation is thought to cause chronic neurodegeneration. It plays an important role in the pathogenesis of MS by triggering the activation of innate and adaptive immune cells and the production of pro-inflammatory cytokines. Thus, an inflammatory response occurs within the central nervous system (CNS), which causes demyelination by causing myelin damage in the white and gray matter in the CNS.[3] The variety and severity of clinical symptoms vary depending on the location and degree of this demyelination. Therefore, biomarkers that will help evaluate the disease process and treatment effectiveness are becoming essential. Markers such as light chain neurofilaments are gaining importance here, but

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since these markers are expensive and a significant portion of them are studied in cerebrospinal fluid (CSF), it is not always possible to reach them, so there is a need for easily accessible, reliable and cost-effective markers that will allow routine use.[4]

In various neurological diseases, neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR), which can be easily obtained from complete blood count, are increasingly coming to the fore as biomarkers of pathological inflammation.[5] For example, they have been used primarily to predict prognosis in cerebrovascular diseases, cancers, and autoimmune and inflammatory diseases.[6,7] In addition, platelet-leukocyte ratios are used in the diagnosis and prognosis prediction of many neurodegenerative diseases, including MS.[8]

The systemic immune-inflammatory index (SII) is calculated using the formula number of neutrophils x (number of platelets)/ number of lymphocytes. Its role in MS pathophysiology and prognosis has been investigated in various studies. In one study, it was higher in MS patients than in healthy controls, while in another study, it was higher in patients with active contrast retention.[9,10] Systemic inflammatory response index (SIRI) is calculated by the formula neutrophil count×monocyte count)/ lymphocyte count and its function has been investigated in neurological diseases such as cerebrovascular diseases and restless legs syndrome.[11,12] To our knowledge, very few studies examine the relationship between SII and MS. Moreover, there are no studies investigating the relationship between SIRI and MS.

This study compares the NLR, MLR, SII, and SIRI values of RRMS patients during relapse and remission periods with the healthy control group. We also aimed to investigate the relationship between these parameters and disease activity in MS patients.

METHODS

Ethics

The study was approved by the Kastamonu University Clinical Researches Ethics Committee (Date: 01.11.2023, Decision No: 2023-KAEK-132) by the Declaration of Helsinki.

Study Design and Population

This study, conducted at Kastamonu Training and Research Hospital, has a retrospective character. The hospital HIS (hospital information management system) was used to obtain the data and was scanned between January 2012 and June 2023. One hundred four patients between the ages of 18 and 47 who applied to Kastamonu Training and Research Hospital with an MS attack and were diagnosed with RRMS according to the 2017 McDonald criteria were included in the study[2]. The hemogram results of these patients, taken both during the attack period and later during the inter-attack periods, were compared. In addition, a healthy group with no statistically significant age and gender differences was created, and their hemogram results were obtained from white blood cell count (WBC), red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT), mean corpuscular volume (MCV), platelet count (PLT), neutrophil count (NEUT), lymphocyte count (LYMPH), monocyte count (MONO), NLR, PLR, SII, and SIRI were also compared. The NLR, MLR, PLR, SII, and SIRI were calculated as follows: NLR = Neutrophil count (x10³/µL) / Lymphocyte count (x10³/µL), MLR = Monocyte count (x10³/µL) / Lymphocyte count (x10³/µL), LMR = Lymphocyte count (x10³/µL) / Monocyte count (x10³/µL), PLR = Platelet count (x10³/µL) / Lymphocyte count (x10³/µL), SII = Platelet count (x10³/µL) x NLR, and SIRI = Neutrophil count (x10³/µL) x MLR. Patients with hematological and autoimmune comorbidities, patients with kidney and liver dysfunction, patients with cardiac and cerebrovascular diseases, patients receiving anticoagulant treatment, patients who had an infection in the last month, and patients who received steroid treatment in the previous month were excluded from the study. Hemogram parameters were routinely measured on the Sysmex XN 1000 hematology analyzer (Sysmex Corporation, Kobe, Japan) and were compared statistically between groups.

Statistical Analysis

The "Statistical Package for Social Sciences 18.0 for Windows" (SPSS Inc., Chicago, USA) program was used to analyze the data. Descriptive statistics of the data obtained were given as numbers and percentages for categorical variables and medians (25 Percentiles, 75 Percentiles) for numerical variables. Mann Whitney U test was used to compare the data between the group with an MS attack and the healthy groups and the data between the group in the MS attack period and the healthy groups, as the data did not comply with normal distribution. The Wilcoxon Test was used to compare the attack and inter-attack periods in MS patients since the groups were dependent. Receiver operating characteristic (ROC) analysis was performed and Youden's index was used to determine area under curve (AUC), cut-off, sensitivity and specificity values. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 104 MS patients and 64 healthy controls who met the inclusion criteria were included in the study. 70 (67%) of MS patients were female, and 24 (33%) were male. In the healthy group, 44 (69%) were women, and 20 (31%) were men. The median age of the patients was 30(26, 35); In the healthy group, the median age was 30 (25, 40). There was no statistically significant difference between the healthy group and the MS group in terms of both age and gender (Table 1). The average disease duration of the patients was calculated as 4.7±3.7, and the average Expanded Disability Status Scale score was 2.17.

Table 1. Demographic data of MS patients and healthy control groups

	Attack group (104)	Healthy group (64)	p
Age, (year)	30 (26, 35)	30 (25, 40)	0.567
Male gender, n (%)	24 (33)	20 (31)	0.948
Disease duration (year)	4.7±3.7	-	
Expanded Disability Status Scale	2.17±1.41	-	
Disease-modifying therapy (DMT) n (%)			
Interferon beta-1a	31 (30)		
Interferon beta-1b	4 (4)		
Glatiramer acetate	21 (20)		
Fingolimod	10 (10)		
Teriflunomide	19 (18)		
Dimethyl fumarate	15 (14)		
Natalizumab	1 (1)		

MS: Multiple sclerosis, DMT: Dimetiltriptamin

When MS patients experiencing attacks were compared with the healthy control group, NLR (p=0.004), PLR (p=0.009), SIRI (p=0.015), and SII (p=0.001) values were significantly higher

during the attack period compared to the healthy group. The lymphocyte count was found to be significantly low (p=0.024) (Table 2).

Table 2. Demographic and hemogram data of MS patients in the attack group and the healthy control group

	Attack group (104)	Healthy group (64)	p
Age	30 (26, 35)	30 (25, 40)	0.567
Male gender n (%)	24 (33)	20 (31)	0.948
WBC (10^3/μL)	6.94 (5.89, 8.80)	6.80 (5.43, 8.33)	0.477
RBC (10^6/μL)	4.91 (4.56, 5.38)	4.79 (4.50, 5.19)	0.199
HGB (g/dL)	13.6 (12.8, 15.3)	13.9 (12.8, 15.0)	0.839
HCT (%)	41.5 (38.4, 45.4)	40.8 (39.2, 44.6)	0.860
MCV (fL)	85 (82.2, 87.6)	85.5 (83.3, 88.5)	0.156
PLT (10^3/μL)	252 (219, 302)	260 (214, 287)	0.714
NEUT (10^3/μL)	4.21 (3.39, 5.65)	4.00 (2.84, 5.15)	0.171
LYMPH (10^3/μL)	1.91 (1.43, 2.49)	2.15 (1.80, 2.60)	0.024
MONO (10^3/μL)	0.51 (0.40, 0.70)	0.49 (0.41, 0.61)	0.751
NLR	2.14 (1.59, 3.52)	1.83 (1.42, 2.36)	0.004
PLR	138 (100, 187)	118 (94, 138)	0.009
SIRI	1.14 (0.76, 1.94)	0.84 (0.65, 1.43)	0.015
SII	604 (415, 950)	441 (339, 589)	0.001

MS: Multiple sclerosis, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet, NEUT: Neutrophil, LYMP: Lymphocyte, MONO: Monocyte, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SIRI: Systemic inflammation response index, SII: Systemic immune-inflammation index

When MS patients in the inter-attack period were compared with the healthy control group, monocyte (p=0.018), NLR (p=0.006), PLR (p=0.007), SII (p=0.011), and SIRI (p<0.001) values were significantly higher in the inter-attack period compared to the healthy control group. The lymphocyte count was found to be significantly low (p=0.004) (Table 3).

Table 3. Demographic and hemogram data of MS patients in the inter-attack period and the healthy control group

	Inter-attack group (104)	Healthy group (64)	p
Age	30 (26, 35)	30 (25, 40)	0.567
Male gender n (%)	24 (33)	20 (31)	0.948
WBC (10^3/μL)	6.68 (5.44, 7.93)	6.80 (5.43, 8.33)	0.371
RBC (10^6/μL)	4.81 (4.47, 5.22)	4.79 (4.50, 5.19)	1.000
HGB (g/dL)	13.6 (12.7, 15.0)	13.9 (12.8, 15.0)	0.769
HCT (%)	40.7 (38.3, 44.4)	40.8 (39.2, 44.6)	0.528
MCV (fL)	85.6 (83.5, 87.7)	85.5 (83.3, 88.5)	0.392
PLT (10^3/μL)	245 (212, 286)	260 (214, 287)	0.542
NEUT (10^3/μL)	4.00 (3.26, 5.06)	4.00 (2.84, 5.15)	0.684
LYMPH (10^3/μL)	1.84 (1.44, 2.42)	2.15 (1.80, 2.60)	0.004
MONO (10^3/μL)	0.57 (0.46, 0.78)	0.49 (0.41, 0.61)	0.018
NLR	2.28 (1.62, 3.10)	1.83 (1.42, 2.36)	0.006
PLR	135 (105, 176)	118 (94, 138)	0.007
SIRI	1.38 (0.82, 2.24)	0.84 (0.65, 1.43)	<0.001
SII	565 (356, 817)	441 (339, 589)	0.011

MS: Multiple sclerosis, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet, NEUT: Neutrophil, LYMP: Lymphocyte, MONO: Monocyte, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SIRI: Systemic inflammation response index, SII: Systemic immune-inflammation index

No significant difference was observed in NLR, PLR, SII, and SIRI values between attack and remission periods in MS patients. RBC values were significantly higher in the attack group compared to the inter-attack period (p=0.027). Monocyte values were significantly low (p=0.001) (Table 4).

Table 4. Comparison of hemogram data of MS patients during the attack period and the inter-attack period

	Attack group (104)	Inter-attack group (104)	p
WBC (10^3/μL)	6.94 (5.89, 8.80)	6.68 (5.44, 7.93)	0.066
RBC (10^6/μL)	4.91 (4.56, 5.38)	4.81 (4.47, 5.22)	0.027
HGB (g/dL)	13.6 (12.8, 15.3)	13.6 (12.7, 15.0)	0.349
HCT (%)	41.5 (38.4, 45.4)	40.7 (38.3, 44.4)	0.071
MCV (fL)	85 (82.2, 87.6)	85.6 (83.5, 87.7)	0.161
PLT (10^3/μL)	252 (219, 302)	245 (212, 286)	0.195
NEUT (10^3/μL)	4.21 (3.39, 5.65)	4.00 (3.26, 5.06)	0.141
LYMPH (10^3/μL)	1.91 (1.43, 2.49)	1.84 (1.44, 2.42)	0.254
MONO (10^3/μL)	0.51 (0.40, 0.70)	0.57 (0.46, 0.78)	0.001
NLR	2.14 (1.59, 3.52)	2.28 (1.62, 3.10)	0.475
PLR	138 (100, 187)	135 (105, 176)	0.858
SIRI	1.14 (0.76, 1.94)	1.38 (0.82, 2.24)	0.653
SII	604 (415, 950)	565 (356, 817)	0.316

MS: Multiple sclerosis, WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin, HCT: Hematocrit, MCV: Mean corpuscular volume, PLT: Platelet, NEUT: Neutrophil, LYMP: Lymphocyte, MONO: Monocyte, NLR: Neutrophil-to-lymphocyte ratio, MLR: Monocyte-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SIRI: Systemic inflammation response index, SII: Systemic immune-inflammation index

In the ROC analysis (comparing the attack group with the healthy group), SIRI (cut off: 1.22, AUC: 0.612), SII (cut off: 592, AUC: 0.649), PLR (cut off: 137, AUC: 0.622) and NLR. (cut off: 2.67, AUC: 0.633) tests showed moderate predictive properties (Figure, Table 4).

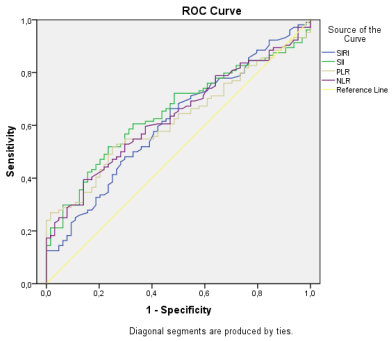

Figure. ROC curve analysis of some hematological data in MS patients

ROC: Receiver operating characteristic, SIRI: Systemic inflammation response index, SII: Systemic immune-inflammation index, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, MS: Multiple sclerosis

DISCUSSION

The most important results of this study are that NLR, PLR, SII, and SIRI biomarkers of inflammation were significantly higher in MS patients compared to healthy controls during relapse and remission periods (Tables 2, 3). In addition, monocyte values were significantly lower, and red blood cell values were significantly higher in MS patients compared to remission periods (Table 5).

Neutrophils play an essential role in neuroinflammation in MS. They are thought to play an important role in the damage and inflammation of the blood-brain barrier (BBB). However, markers such as NLR can be biomarkers of systemic

Table 5. ROC analysis values of inflammation biomarkers in MS patients

	Cut-off	AUC	95%CI	p	Sensitivity%	Specificity%
SIRI	1.22	0.612	0.53-0.70	0.015	48	70
SII	592	0.649	0.57-0.73	0.001	52	77
PLR	137	0.622	0.65-0.80	0.009	52	75
NLR	2.67	0.633	0.55-0.72	0.004	40	86

SIRI: Systemic inflammation response index, SII: Systemic immune-inflammation index, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio

inflammation in many inflammatory and autoimmune diseases, better than neutrophils or lymphocytes alone.[13] In particular, it has recently gained increasing importance as a marker of systemic inflammation, as it is an easily accessible and inexpensive parameter.[14]

Since diagnosis and treatment follow-up are important in MS, cheap and practical biomarkers such as NLR have been widely studied. Many studies in the literature investigate the relationship between NLR and MS. Demirci et al.[15] first made the relationship between MS and NLR, and in this study, they found the NLR value to be higher in RRMS patients compared to healthy controls and showed a correlation between clinical symptom severity and NLR value. In another study, many cases showed a significant increase in NLR values between MS and healthy controls. In their case-control study on patients who had not yet received any disease-modifying therapy, Hasselbalch et al.[16] found the NLR value in MS patients to be significantly higher than in healthy controls, but a weak relationship was found between MS severity and NLR. Disease activity of MS is evaluated by the frequency of relapses, new T2 lesions and contrast-enhancing lesions, and the Expanded Disability Status Scale (EDSS). There are several studies investigating the relationship between NLR and disease activity. Damico and colleagues found that the risk of disease activity was higher in MS patients with high NLR who presented for the first time and had not received any treatment.[17] Hemond et al.[5] found that NLR was closely associated with high EDSS and discriminated between patients with poor prognosis. In a study conducted in Turkiye, NLR levels were higher in MS patients with EDSS ≥5 than in patients with EDSS <5.[5] Yetkin et al.[19] showed that baseline NLR in RRMS patients who have just started treatment can predict high-risk patients and guide the selection of disease-modifying treatment. In a recent study, they found a significantly higher NLR value in MS patients compared to healthy controls, but they did not find a relationship between disease activity and disability.[20] In our study, similar to the literature, NLR values were significantly higher than those of the healthy control group, supporting the inflammatory pathogenesis in MS. Moreover, NLR (cut off: 2.67, AUC: 0.633) showed moderate predictive properties. However, no significant difference was found between relapse and remission periods in MS patients by chronic inflammation, which probably continues during the remission period in MS patients.[21]

PLR has previously been investigated as a marker for diagnosis and prognosis prediction in many neurological diseases. It has been shown that high PLR levels are associated with poor prognosis, especially in ischemic stroke patients.[22,23] There are a few studies on PLR levels in MS patients. In a recent study, PLR values were higher in patients with contrast-enhancing lesions on cranial and cervical magnetic resonance imaging (MRI) than in patients without contrast enhancement.[9] Fathy et al.[24] found high PLR values associated with 3-year deterioration and attributed this to the possible relationship of platelets with other inflammatory mediators. In their study, Saçmaci et al.[25] found the PLR values higher in MS patients than healthy controls. However, no significant relationship existed between PLR and EDSS values in MS patients. Moreover, a recent study showed that PLR values were not associated with MS prognosis.[24] In our study, while a significant difference was observed in PLR values between MS and the healthy control group, it was determined that PLR values were unrelated to MS severity and did not distinguish relapses and remissions in MS.

As an inflammatory index, SII's role in diagnosis and prognosis prediction in many neurological diseases has been investigated.[26-28] These studies have shown that SII is associated with poor prognosis. Several studies investigated the relationship between SII and MS. Vural et al.[29] found that SII in the emergency department could predict MS relapses. In a recent prospective study conducted in Turkiye, the SII value was significant in patients with NEDA-3.[30] Saçmacı et al.[10] In their study, they found the SII value of patients with EDSS >3 to be higher than those with EDSS <3 and stated that SII could indicate the prognosis in MS. Gokce et al.[9] found the SII value higher in MS patients than healthy controls. In addition, the SII value was significantly higher in patients with contrast-enhancing lesions than others. In our study, consistent with the literature, the SII value was significantly higher in MS patients compared to healthy controls during relapse and remission periods. Furthermore, SII (cut off: 592; AUC: 0.649) had moderate predictive properties. However, no significant difference was detected in SII values between relapse and remission periods in MS patients. This result may be due to chronic inflammation that continues, albeit at a low level, in MS patients during the remission period.[31]

The possible effect of SIRI on diagnosis and prognosis in neurological diseases has been investigated in a few studies. Moreover, to our knowledge, no study has examined the relationship between MS and SIRI. Our study is the first in this respect. Recent studies have shown that SIRI can predict neurological deterioration in ischemic stroke.[32] Li et al.[33] showed that intracerebral hemorrhage was an independent predictor of 3-month functional outcomes and 1-month mortality. In our study, the SIRI value was significantly higher in MS patients compared to the healthy control group. Furthermore, SIRI (cut-off: 1.22, AUC: 0.612) had mild predictive properties. However, no significant difference was observed between relapse and remission periods.

Limitations

There were some limitations in our study. It is a single-center retrospective study. Only RRMS patients were included in the study, and secondary progressive and primary progressive MS patients were excluded. In addition, since our study was retrospective, information such as smoking and body mass index, which may affect hematological parameters, could not be obtained. Additionally, due to the relatively small number of patients, the possible effects of disease-modifying agents on hematological parameters could not be evaluated. Therefore, prospective studies with a large sample size are needed.

CONCLUSION

As a result, inflammatory parameters such as NLR, PLR, SII, and SIRI were found to be higher in MS patients than in the

healthy control group, both during relapse and remission periods. However, no significant difference was found in these parameters between relapse and remission periods. These findings support inflammatory pathogenesis in MS patients. Additionally, the lack of a significant difference in these inflammatory parameters between relapse and remission periods may support ongoing chronic inflammation in MS patients. More comprehensive, prospectively designed studies with a large sample size are needed in the future on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kastamonu University Clinical Researches Ethics Committee (Date: 01.11.2023, Decision No: 2023-KAEK-132).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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