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Original Article *Özgün Araştırma*

THE RELATIONSHIPS BETWEEN THE NEUTROPHIL/LYMPHOCYTE, PLATELET/LYMPHOCYTE, EOSINOPHIL/LYMPHOCYTE, AND MONOCYTE/LYMPHOCYTE RATIOS AND DISEASE ACTIVITY IN PATIENTS WITH MULTIPLE SCLEROSIS

Multipl Sklerozlu Hastalarda Nötrofil/Lenfosit, Trombosit/Lenfosit, Eozinofil/Lenfosit ve Monosit/Lenfosit Oranları ile Hastalık Aktivitesi Arasındaki İlişkiler

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ABSTRACT

Objective: Multiple sclerosis primarily affects young adults. The prevalence is increasing worldwide, although the reason for this rise is not fully understood. The disease usually progresses with attacks. The diagnosis of disease activation is made clinically and by magnetic resonance imaging. Magnetic resonance imaging is an expensive and time-consuming examination. It is obvious that there is a need for an inexpensive and fast-resulting test that will aid in the diagnosis of active patients. Data from a complete blood count may be one of them.This study aimed to examine the association between disease activity in multiple sclerosis patients and the ratios of neutrophils to lymphocytes, platelets to lymphocytes, eosinophils to lymphocytes, and monocytes to lymphocytes.

Material and Methods: One hundred and twenty patients diagnosed with multiple sclerosis and 110 healthy controls were enrolled. Demographic characteristics such as age, sex, and duration of disease, magnetic resonance lesion characteristics, and Expanded Disability Symptom Scale results were recorded.

Results: The mean neutrophil-to-lymphocyte ratio in active patients was significantly higher compared to both the inactive disease group and the control group ($p<0.001$). Similarly, the mean monocyte-to-lymphocyte ratio in active patients was significantly also higher compared to the control group ($p=0.002$). The active and inactive patients' platelet/lymphocyte ratio values were both significantly higher than those of the control group ($p<0.001$).

Conclusion: This study suggests that the neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios are associated with the activation of multiple sclerosis. More extensive studies with larger patient populations and healthy controls are now needed to clarify the association between serum neutrophil/lymphocyte, platelet/lymphocyte and monocyte/lymphocyte ratios and disease activity in multiple sclerosis.

Keywords: *Multiple sclerosis, neutrophil/lymphocyte ratio, monocyte/lymphocyte ratio, platelet/lymphocyte ratio, eosinophil/lymphocyte ratio*

ÖZ

Amaç: Multipl skleroz çoğunlukla genç yetişkinleri etkileyen bir hastalıktır. Yaygınlığı dünya çapında artmaktadır, ancak bu artışın nedeni tam olarak anlaşılmamıştır. Hastalık genellikle ataklarla ilerler. Hastalığın aktivasyonunun tanısı klinik olarak ve manyetik rezonans görüntüleme ile yapılır. Manyetik rezonans görüntüleme pahalı ve zaman alıcı bir incelemedir. Aktif hastaların tanısında yardımcı olacak ucuz ve hızlı sonuç veren bir teste ihtiyaç olduğu açıktır. Tam kan sayımından elde edilen veriler bunlardan biri olabilir.
Bu çalışmanın amacı, multipl sklerozlu hastalarda nötrofil/lenfosit, trombosit/lenfosit, eozinofil/lenfosit ve monosit/lenfosit oranları ile hastalık aktivitesi arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler: Multipl skleroz tanısı almış 120 hasta ve 110 sağlıklı kontrol çalışmaya dahil edildi. Yaş, cinsiyet ve hastalık süresi gibi demografik özellikler, manyetik rezonans lezyon özellikleri ve Genişletilmiş Engellilik Belirti Ölçeği sonuçları kaydedildi.

Bulgular: Aktif hastaların ortalama nötrofil/lenfosit oranı değerleri, inaktif hastalık ve kontrol gruplarındakilerden anlamlı derecede yüksekti ($p<0,001$). Aktif hastaların ortalama monosit/lenfosit oranı değeri, kontrol grubundakilerden anlamlı derecede yüksekti ($p=0,002$). Aktif ve inaktif hastaların trombosit/lenfosit oranı değerleri, kontrol grubundakilerden anlamlı derecede yüksekti ($p<0,001$).

Sonuç: Bu çalışma, nötrofil/lenfosit, trombosit/lenfosit ve monosit/lenfosit oranlarının multipl sklerozun aktivasyonu ile ilişkili olduğunu göstermektedir. Multipl sklerozda serum nötrofil/lenfosit, trombosit/lenfosit ve monosit/lenfosit oranları ile hastalık aktivitesi arasındaki ilişkiyi açıklığa kavuşturmak için artık daha geniş hasta popülasyonları ve sağlıklı kontrollerle daha kapsamlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: *Multipl skleroz, nötrofil/lenfosit oranı, monosit/lenfosit oranı, trombosit/lenfosit oranı, eozinofil/lenfosit oranı*

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INTRODUCTION

Multiple sclerosis (MS) is the leading cause of disability in young people after trauma. Its prevalence is rising globally in both developed and developing countries, though the reasons behind this trend remain unclear.

Inflammation and new white matter lesions are seen in relapsing remitting multiple sclerosis (RRMS) at magnetic resonance imaging (MRI), while inflammation is less observed in more progressive cases. Widespread atrophy is also seen in white and gray matter. The severity and frequency of new attacks in the early period of MS affect the process of transition to the progressive stage. Studies have shown that inflammation is greater in the early stages of MS, while a marked neurodegenerative process independent of inflammation occurs in the progressive stage.

Inflammatory demyelinating lesions are seen in acute MS attacks, and more frequently in RRMS. Acute MS plaque formation begins with the accumulation of inflammatory mononuclear cells in white matter and the perivascular area. Abundant T and B cells, macrophages, and activated microglia are present in inflammatory lesions.

In addition to demyelination, axonal and oligodendrocyte damage also occur in demyelinating plaques. Free radicals, myelin phagocytosis, protease release, natural killer-mediated cytotoxicity, antibody complement activation, oligodendrocyte apoptosis and especially autoreactive CD4+T lymphocytes, all play a role in the development of plaques.

Acute demyelinating plaques can be seen in manifestations ranging from mild destruction with myelin loss in which the axons are relatively preserved to advanced destruction in which axons are degenerated. As demyelination continues, acute axonal damage and losses occur, while remyelination halts this degeneration to some extent.

Chronic plaques, classified as active and inactive, are paler lesions with greater myelin loss and gliosis. Inflammation, active microglia, macrophages, and reactive astrocytes are seen in chronic active plaques. Inflammation in MS attacks lasts for days or weeks. Oligodendrocyte precursors are activated in the central nervous system (CNS) and initiate the remyelination of axons with myelin damage. The newly formed myelin sheath cannot be restored entirely to its previous form - the myelin components are different, and it is functionally imperfect. Nerve conduction is therefore slower. Intensive remyelination is seen in active plaques in the early stages of MS. However, remyelination is rare in subsequent stages, particularly in progressive MS. While some patients experience better remyelination, it is seen less in others, although the reasons for this are unclear.

A number of studies have investigated the effect of disease activation in MS on the blood neutrophil/lymphocyte ratio (NLR). These parameters investigated in blood may increase in case of infection or inflammation.

Studies have indicated that the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) may hold prognostic value in conditions such as cardiovascular diseases, malignancies, diabetes mellitus, hypertension, familial Mediterranean fever, and hepatic cirrhosis. [1] The eosinophil/lymphocyte ratio (ELR) is also related to diseases associated with allergic reactions.[2] The monocyte/lymphocyte ratio (MLR) can increase in cases of cancer, tuberculosis and autoimmune disease.[3] These values may also vary and provide important prognostic information in MS. While some studies have reported a correlation between MS activity and the NLR, others have observed weak or no correlation.[4,5] The possibility of a relationship between the MLR and disability in MS has also been proposed.[6] Interestingly, our scan of the literature revealed no studies examining the PLR and ELR and MS disease activation. No easily applied, rapid, and low-cost method of assessing disease activation is as yet available. The activation of the disease is currently assessed and the course of treatment is determined based on the patient's clinical attack status and MRI results. However, MRI is costly, not easily accessible, and does not provide immediate results. An easily applied and inexpensive test is therefore needed.

The primary aim of this research was to explore the relationship between MS disease activity and data derived from complete blood counts, a cost-effective, simple, and widely accessible test that provides quick results.

MATERIALS AND METHODS

This study included 230 participants aged between 18 and 65 who presented to the Kırıkkale University Medical Faculty Neurology Clinic between 2014 and 2021. Among them, 120 patients were diagnosed with MS based on the 2017 revision of the McDonald criteria, while 110 served as healthy controls. The study received approval from the Kırıkkale University Medical Faculty Clinical Research Ethics Committee (Date: 25.03.2021, Decision No: 2021.03.27).

Individuals with active infection, active or chronic inflammatory disease, or autoimmune disease, pregnant women, and individuals with malignancy of histories of surgery in the previous twelve weeks were excluded from the patient and control groups.

The MS patients' complete blood counts were scanned from the hospital information system. NLR, MLR, PLR, and ELR values were calculated from the data yielded by complete blood count parameters. T2 lesion numbers

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and T1 gadolinium contrast involvement were investigated from cranial and spinal MR images obtained on the same date as the blood tests. MS activity was determined according to the patient experiencing clinical attacks or T1 gadolinium involvement at MRI. MRI, EDSS values, and drugs used were compared between the active and inactive MS patients. Blood parameters were compared between the active MS patients, inactive MS patients and the control group.

The data were entered and analyzed using IBM SPSS Statistics version 23 software. Numerical variables were reported as descriptive statistics (mean and standard deviation). Differences between more than two groups were assessed using One-Way Analysis of Variance (ANOVA). After ANOVA, Levene's test was applied to check for homogeneity of variances, and a "multiple comparison test" (Bonferroni or Tamhane's T2) was used to identify the group or groups where differences occurred. The Bonferroni test was applied for variables with homogeneity of variance between groups, and Tamhane's T2 test was used for variables without homogeneity of variance. The Chi-square test was used to assess the relationship between categorical variables. Additionally, multinomial logistic regression analysis was performed to evaluate the effect of blood parameters on the groups.

RESULTS

Table 1 presents the characteristics of the study participants. No statistically significant differences were observed between the groups regarding age, sex, EDSS, disease duration, or platelet, monocyte, eosinophil, and ELR values. However, lesion count, contrast involvement, and spinal involvement rates on MRI were notably higher in patients with active disease (p=0.017, p<0.001, and p=0.006, respectively). Mean neutrophil levels were considerably higher in active MS patients compared to both the inactive patient and control groups (p=0.002). Mean lymphocyte levels were considerably higher in the control group than in the active and inactive patient groups (p<0.001). Mean NLR values were markedly elevated in active patients compared to the inactive patient and control groups (p<0.001). Mean MLR values were considerably higher in the active patients compared to the control group (p=0.002). PLR values were notably higher in both the active and inactive patient groups than in the control group (p<0.001) (Table 1).

Table 1: Characteristics of participants and study results

		Active patients		Inactive patients		Control		P
		N	%	N	%	N	%	
Age		40.04±9.49		41.37±9.93		37.63±9.98		0.070
Sex	Female	56	70.9	31	75.6	79	71.8	0.855
	Male	23	29.1	10	24.4	31	28.2	
Contrast	No	4	5.1	41	100.0	0	0.0	**<0.001***
	Yes	75	94.9	0	0.0	0	0.0	
Spinal	No	25	32.5	24	58.5	0	0.0	**0.006***
	Yes	52	67.5	17	41.5	0	0.0	
EDSS		1.54±2.22		1.92±2.35		-		0.409
Duration		8.91±5.78		10.95±6.87		-		0.089
Medication used	Injectable	40	51.9	25	65.8	0	0.0	-
	TER	7	9.1	4	10.5	0	0.0	
	DMF	15	19.5	6	15.8	0	0.0	
	FIN	12	15.6	1	2.6	0	0.0	
	NAT	0	0.0	0	0.0	0	0.0	
	OCR	1	1.3	0	0.0	0	0.0	
	IMMUNE	2	2.6	2	5.3	0	0.0	
Platelet		262.75±63.09		254.29±69.66		264.28±60.14		0.681
Neutrophil		5.51±2.71a		4.39±1.48b		4.64±1.33b		**0.002***
Lymphocyte		1.96±1.05b		1.91±0.72b		2.38±0.60a		**<0.001***
Monocyte		0.51±0.18		0.52±0.31		0.46±0.13		0.079
Eosinophil		0.16±0.25		0.18±0.17		0.16±0.10		0.796
NLR		3.55±2.74a		2.60±1.29b		2.07±0.82c		**<0.001***
MLR		0.35±0.30a		0.36±0.60		0.20±0.09b		**0.002***
ELR		0.10±0.20		0.12±0.27		0.07±0.04		0.111
PLR		185.52±160.01a		150.78±79.54a		117.77±39.02b		**<0.001***
Lesion		43.44±31.33		31.63±21.08		-		**0.017***

Notes: a.b: Differences between group means (a=highest mean). *:p<0.05

Abbreviations: TER: Teriflunomide; DMF: Dimethyl fumarate; FIN: Fingolimod; NAT: Natalizumab; OCR: Ocrelizumab; IMMUN: Immunosuppressive; NLR: Neutrophil/lymphocyte ratio; MLR: Monocyte/lymphocyte ratio; ELR: Eosinophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio.

DISCUSSION

Multiple sclerosis (MS) is a neurodegenerative, demyelinating, long-term inflammatory disease that impacts the central nervous system (CNS) and typically affects individuals aged 20-40 years. The prevalence and incidence of MS have increased worldwide in recent

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years. MS lesions cause patients to exhibit various symptoms affecting sensorial-motor, autonomic or visual functions. Although genetic and environmental triggers, such as infectious diseases, HLA-DRB1, IL-7 receptor alleles, IL-2 receptors, and vitamin D deficiency have been implicated, the etiology of MS remains uncertain. Although B lymphocytes and humoral factors also play a role, T lymphocytes are the principal mediators in the pathogenesis of MS. Neutrophils are essential in innate immunity. Studies have investigated T cell and antibody responses in MS, although research into the role of neutrophils or other natural immunity cells in MS is limited.[7] Neutrophils can release reactive oxygen species and proinflammatory enzymes and produce proinflammatory mediators. They are also believed to potentially contribute to the pathogenesis of MS by amplifying inflammation and causing tissue damage.[8] Despite numerous studies investigating the etiology, pathogenesis, diagnosis, and treatment of MS, the amount of research into biomarkers showing the progression and activation of the disease is inadequate. In particular, there is a lack of a dependable predictor for patients with RRMS, the most common form of MS, as well as a simple and inexpensive test linked to disease activity.[9] MRI, Nfl, and CSF microvesicles are currently employed to determine disease activity in MS.[10] However, these tests are both costly and not easily performed, and there is therefore a clear need for a simpler, low-cost test for determining MS activity.

The peripheral immune compartment is also thought to be associated with MS, an inflammatory response of the CNS. Several studies have investigated the levels of inflammatory markers in patients with MS.

Martins et al. reported an increase in TNF-α, IFN gamma, IL-1, IL-2, IL-4, IL-10, and IL-13 levels in the sera of patients with MS and suggested that these cytokines may be associated with the disease progression and activation.[11]

Recent studies have proposed NLR values as an inexpensive, easily available, non-invasive, peripheral biomarker correlated with disease activation in MS. The NLR is thought to be of greater value than neutrophil or lymphocyte values by themselves.

Gümüş et al. determined higher NLR in active MS patients compared to inactive patients and a healthy group. They also evaluated whether any correlation existed between NLR values and EDSS, although no such correlation was found.[12] Hasselbalch et al. reported NLR elevation in patients with MS who had not yet received disease-modifying therapy and observed a mild correlation between NLR values and MS severity scores. This suggests that neutrophils may be associated with the pathogenesis of MS, and that when the relationship between neutrophils and MS is further clarified in the future, the measurement of blood neutrophil levels, a simple test, may play an important role in determining disease activation and progression. Bisgaard et al. found that NLR was higher in MS patients and those with optic neuritis compared to healthy individuals. Additionally, NLR levels were elevated in patients during the attack phase compared to those in remission.[4]

Demirci et al. found notably higher NLR in MS patients compared to a control group and observed higher NLR in active MS patients compared to those with inactive MS.[5]

The NLR has also been explored in various neurological conditions, including Parkinson's disease, and Alzheimer's disease.[13,14] Kuyumcu et al. found notably higher NLR values in patients with Alzheimer's disease and proposed that inflammation might contribute to the development of the disease.[13] Akıl et al. reported a link between elevated NLR and Parkinson's disease.[14] Multiple studies have examined the connection between NLR and the activation as well as the prognosis of various non-neurological diseases such as thyroid cancer, ovarian cancer, and prostate cancer, and breast cancer. Patients with any of these conditions were excluded from the current study.

Since the NLR is an inexpensive and simple test easily calculated from complete blood counts, it is a parameter that can be evaluated as a marker of response to treatment, activation, and prognosis in several diseases, and research into this parameter is still ongoing. The notable increase in NLR values observed in active patients in this study suggests that NLR could be used to monitor the course of MS.

Except for Christopher et al., no studies have directly explored the association between MLR and MS activity. Both MLR and NLR were evaluated in patients with MS in this study, and both exhibited an association with the severity of the disease.[6]

Some research has examined the relationship between the MLR and neurological diseases other than MS. Liu et al.'s retrospective study reported that monocyte/HDL and MLR values were separately associated with the risk of ischemic stroke. When the two parameters were taken together, the relationship between the MLR and ischemic stroke was more significant.[15]

The present research examines the MLR in the context of MS disease activity. MLR was significantly higher in the active patient group than in the control group, supporting the idea that, similarly to the NLR, the MLR may also be capable of use in assessing disease activity. Granulocyte-macrophage (GM)-CSF, which stimulates the production and growth of granulocytes and macrophages, is thought to play a role in the pathogenesis of MS. Produced from pathological T cells in patients with MS, GM-CSF has been shown to

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stimulate monocytes and cause them to migrate to the CNS, while monocytes in the CNS result in further inflammation by producing various cytokines, such as TNF-alpha.[16] Monocytes not stimulated by GM-CSF do not contribute to the pathogenesis. Another study also showed that interferon beta used in the treatment of MS suppresses GM-CSF production.[17] In light of the above, it is clear that GM-CSF, and therefore monocytes, are involved in the pathogenesis. The MLR results from the present study also refer to the peripheral compartment, they will contribute to future studies of the relationship between monocytes and MS.

Putman et al. showed that venous thrombosis plays a role in the demyelination of the CNS in the pathogenesis of MS.[18] Subsequent studies showed that some platelet-specific components increased in plasma in patients with MS and that this elevation was associated with the severity of the disease.[19]

Platelet microparticles are bioactive substances, the levels of which in blood rise in various physiological or pathological conditions and which play a role in intercellular communication. They are thought to play a role in inflammation since they increase in some autoimmune and inflammatory diseases. Studies on the subject have also been performed with MS patients. Marcos Ramiro et al. reported significant platelet microparticle level elevation in patients with MS.[20]

The fact that such studies of platelets suggest that these can be of use in evaluating disease activity, prognosis, and treatment also encouraged us to study platelets and the PLR. The significant elevation in PLR values in the present study shows that platelets are involved in the immunopathogenesis of MS and a relationship between the PLR and disease activation. No previous research has directly examined the relationship between MS activity and the PLR.

We conclude that the NLR and PLR are associated with MS disease activation. We also observed significantly higher MLR values in the active patient group compared to the control group. There was no difference in ELR values between the groups.

Since MS is a chronic inflammatory disease generally affecting the younger population and requires long-term treatment and follow-up, there is a need for easily applicable and accessible tests capable of showing disease progression and activation. The NLR, PLR, and MLR have the potential to represent one such test, a fact supported by the present study. However, more extensive, prospective studies involving the NLR, PLR, and MLR are now needed.

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