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ORIGINAL ARTICLE

The Relationship between Inflammatory Markers and Activity of Multiple Sclerosis

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ABSTRACT

Background: The primary characteristics of multiple sclerosis (MS), a chronic autoimmune illness affecting the central nervous system (CNS), are inflammatory demyelination, widespread damage, and brain volume loss. These factors contribute to neurodegeneration and physical impairment. This study aimed to determine the relationship between Systemic immune inflammatory indices and Multiple sclerosis activity. **Methods:** This case-control study was conducted on 132 subjects; 62 clinically definite MS patients during relapse and 70 age and gender matched healthy control participants. The inflammatory markers NLR (neutrophil-to-lymphocyte ratio), PLR (platelet-to-lymphocyte ratio) and C- Reactive protein (CRP) were measured for all participants and Magnetic resonance imaging (MRI) of brain and spinal cord was done for MS patients during relapse. Assessment of patients' physical disability was based on Expanded Disability Status Score (EDSS) and 9-hole Peg test (9-HPT). **Results:** We found that PLR and NLR were higher among MS patients than healthy control group ($p \leq 0.001$, $p = 0.031$). The best cutoff point of serum NLR to detect radiological activity in MS patients was ≥3.18 at sensitivity 70.6% and specificity 61.5% and the best cutoff point of PLR to detect radiological activity in MS patients was ≥128.155 with area under curve 0.746 (95% CI; 0.598 to 0.894) at sensitivity 76.9% and specificity 60.2%. CRP correlated significantly with 9 HPT scores ($p=0.01$) **Conclusions:** A high PLR and NLR may be promising predictive markers that detect activity of Multiple sclerosis.

Keywords: Multiple sclerosis; inflammation**;** PLR; NLR

INTRODUCTION

Multiple sclerosis (MS) is the most prevalent demyelinating neurological disorder. Classically MS is considered one of the prime causes of physical disability worldwide, especially in young adults. In the last years, there is no doubt that MS possess numerous detrimental symptoms that could disturb quality of patients' life. It is well apparent in the recent years that main focus of recent MS researches in the therapeutic field is to prevent or reduce the numbers of MS attacks, aiming to prevent disease deterioration [1-2].

According to data from Egypt's Ministry of Health and Population, 1.4% of all neurological illnesses are cases of MS. This means that 1 in 1,500 persons may develop MS [3].

The underlying pathogenesis of MS involves the activation of innate and acquired immune cells brought on by autoimmunity, resulting in inflammation and neurodegeneration of the central nervous system (CNS) [4].

White blood cell differential counts are often used indicators to identify systemic inflammation. Numerous ratios, including platelet/lymphocyte

(PLR) and neutrophil/lymphocyte (NLR) ratios, are routinely used in practice and are believed to be more effective at displaying inflammation than using white blood cell subtypes alone [5]. In addition Hemond et al. [6] found that High NLR and PLR ratios were substantially linked to MS deterioration, even after controlling for all other clinical, psychosocial, treatment-related, and demographic factors.

In MS, it has been demonstrated that the neutrophil-to-lymphocyte ratio (NLR) is a predictive inflammatory biomarker [7]. Higher NLR and PLR levels have been linked to a considerable increase in relapse rates, according to earlier research [8]. A recent study from Yetkin and Mirza [9] found that in MS patients, an increased NLR has prognostic significance for therapy escalation.

Aim of the work:

This study aimed to determine the relationship between Systemic immune inflammatory indices and activity of Multiple sclerosis.

METHODS

This case-control study was conducted at neurology department and out-patient MS clinic of Zagazig University Hospitals, during the period from April 2023 to January 2024. This study was conducted on 132 subjects; 62 clinically definite Multiple Sclerosis patients during relapse and clinically isolated syndrome patients. The patients' age ranged from 18-49 years, they were 15 males and 47 females and were fulfilling the MacDonald`s criteria (2017) the revision of the diagnostic panel criteria for MS) [10]. The healthy control subjects were 70 (age and gender matched) that did not have any complaints or systemic disease. The Approval of institutional review board, faculty of medicine Zagazig University for this research had been issued in April, 2023 (ZU-IRB #10637/28-3-2023). All participants in this research signed a consent stating their agreement to participate in the research. This work was carried out according to the ethical guidelines of the Declaration of Helsinki (1975) for studies involving humans.

Inclusion criteria included MS patients during relapse, patients were considered in a relapse when they showed an episode of new neurological symptom or exacerbation of previous symptom lasting at least 24h in absence of infection or metabolic derangement [11], or on brain/spinal cord MRI, active lesions were classified as new T2 lesions or at least one T1 gadolinium-enhancing lesion. [12]. Patients' age between 18 and 65 years. Exclusion criteria were; diseases that could elevate systemic immune inflammatory indices such as; Viral or bacterial infection, burns, coronary heart diseases, cerebrovascular strokes, malignancy and pregnant females.

All patients underwent history taking, clinical assessment for MS patients included; Complete general and neurological examination. Using EDSS-plus scale, MS patients' physical disabilities were clinically assessed. The patients were given the Expanded Disability Status Score (EDSS), a scale measures patients' disability regarding signs of pyramidal, cerebellar, brain stem, sensory, visual, and bladder dysfunctions. Individuals with MS who score up to 4.5 do not require any assistance with their daily activities, while those who score 5.0 or more have a disability that is severe enough to interfere with their ability to engage in their daily activities completely [13].

The 9-hole Peg test (9-HPT), a quantitative assessment of the function of the upper extremities (hand and arm) requires the participant to use only one hand to move each of the nine pegs into one of the nine holes on a peg-board, picking up one peg at a time, and then removing all of the pegs. The 9-HPT was given twice, one to each hand, and the average time needed to finish the job was noted. [14].

All participants underwent

Laboratory investigations including;

Complete blood count (CBC) by Sysmex (XN1000), liver and kidney function tests

Each patient had five milliliters of blood extracted, and the serum was separated via centrifugation and kept at -20°C until needed. As part of the hemogram, the counts of white blood cells (WBC), platelets, neutrophils (N), and lymphocytes (L) were calculated, as well as the NLR and PLR. The Xn550 differential haematology analyzer measures both PLR and NLR.

Serum Platelet to Lymphocyte Ratio; (Normal range of PLR in males: 36.63 to 149.13, in females: 43.36 to 172.68) [15].

Serum Neutrophil to Lymphocyte Ratio; (Normal range of NLR in males: 0.43 to 8.61 and in females: 0.23 to 7.63) [15].

C-Reactive Protein (normal range: <5 mg/L). A blood specimen is taken from a peripheral venous draw from MS patients during relapse, through centrifugation; the plasma is extracted from the erythrocytes in the capillary or venous blood sample. Subsequently, the plasma sample is combined with CRP antibody latex reagent in a reaction chamber after being diluted with buffer. The CRP antibody on the latex particle binds to the CRP in the diluted plasma. The Auto Analyzer Cobas 6000 is used to measure the quantity of agglutination, and the altered absorbance at 525 nm and 625 nm is used to compute the CRP content.

Radiological Investigation:

When each patient was recruited, their brain and

spinal cord were imaged using magnetic resonance imaging (MRI). Pre- and post-gadolinium (Gd) augmenting T1 pictures, T2 images, and fluid-attenuated inversion recovery (FLAIR) images were acquired from MS patients during relapse.

Statistical analysis

Version 26 of the SPSS (Statistical Package for the Social Sciences) program was used to analyze the data. When comparing categorical variables, the chi square test and, when necessary, the Monte Carlo tests were used to characterize the data using their absolute frequencies. P<0.05 was chosen as the level of statistical significance

RESULTS

The mean age of MS patients was 31.77± 8.29 and that of control subjects was 30.92 ± 8.79. Forty five (72.6%) were female patients and 17(27.4%) males. There was statistically non-significant difference between the studied groups regarding age (P=0.578) or gender (P=0.556). Table [1]

The mean PLR elevated in MS patients when compared with the control subjects (159.83±58.17 vs. 125.5±50.78, p< 0.001). The mean NLR was higher in MS patients than control subjects (6.91±1.82 vs. 5.1±2.98,P=0.031). Regarding CRP level, there was no significant difference between MS patients and control subjects (4.99 ±1.91 vs. 4.56 ±2.54, P=0.079). Table [2]

The best cutoff point of serum NLR to detect radiological activity in MS patients was ≥3.18 with area under curve 0.736 (95% CI; 0.563 to 0.909) at sensitivity 70.6% and specificity 61.5% .Table [3] and Figure (1). The best cutoff point of PLR to detect radiological activity in MS patients was ≥128.155 with area under curve 0.746 (95% CI; 0.598 to 0.894) at sensitivity 76.9% and specificity 60.2. Figure [2]

The MS patients with high PLR had more active lesions on MRI than those with normal PLR, with significant difference value (P=0.002). We did not find any significant differences between two groups regarding age (P=0.428) , sex (P=0.265), disease duration (P=0.959), number of relapses (P=0.817), EDSS score (P=0.898), 9HPT (P=0.311, 0.09), black holes (P=0.148) on MRI. Table [4]

By comparing MS patients with normal NLR and those with high NLR we did not find any significant differences between two groups regarding age (P=0.905), sex (P=0.683), disease duration (P=0.562), number of relapse (P=0.495), EDSS during relapse (P=0.979), 9HPT (P=0.141, 0.075) or number of patients with active lesions or black holes (P=0.338, 0.85). Table [5]

The performance of MS patients with elevated CRP level on 9HPT scale was worse than that of patients with normal CRP level (right hand: P=0.01, left hand: p=0.02) respectively. No obvious differences were detected between two groups regarding age (P=0.99), sex (P=0.44), disease duration (P=0.562), number of relapses (P=0.495), EDSS score (P=0.979) or black holes on MRI (P=0.75). Table [6]

CRP level correlated significantly with MS patients' scores of 9HPT scales of right hand (P=0.01) and left hand (P=0.026). The PLR of MS patients correlated significantly with number of radiological active lesions (P=0.049). However, PLR, NLR, CRP did not show any significant correlations with age,(p=0.76, p= 0.61, p=0.07, respectively) disease duration (p=0.53,p= 0.87, p=0.54, respectively) , EDSS (p=0.41, p= 0.22, p=0.90, respectively), or number of relapses (p=0.44, p=0.45, p= 0.45, respectively).Table [7].

Table (1): Demographic data in MS patients and control subjects:

	Case group N=62 (%)	Control group N=70 (%)		
Sex:				
Female	45(72.6%)	43(61.4%)	1.84	0.175
Male	17(27.4%)	27(38.6%)		
	Mean ± SD	**Mean ± SD**	**T**	**p**
Age (year)	31.77 ± 8.29	30.92 ± 8.79	0.557	0.578

χ^2 Chi square test t independent sample t test

Table(2): Comparison between MS patients and control subjects regarding inflammatory markers:

	Case group Mean ± SD	Control group Mean ± SD		
PLR	159.83 ± 58.17	125.5 ± 50.78	3.501	<0.001**
NLR	6.91 ± 1.82	5.1 ± 2.98	4.078	0.031*
CRP(mg/dl)	4.99 ± 1.91	4.56 ± 2.54	1.088	0.079

PLR=platelets to lymphocytes, NLR=neutrophils to lymphocytes, CRP=c-reactive protein.t independent sample t test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant ¥p for Wilcoxon signed rank test

Table (3): Performance of inflammatory markers in prediction of radiological activity of Multiple Sclerosis:

	Cutoff	AUC	95% CI	Sensitivity	Specificity	p
NLR	**≥3.18**	0.736	0.563 – 0.909	79.6%	61.5%	0.009*
PLR	**≥128.155**	0.746	0.598 – 0.894	79.6%	60.2%	0.007*

AUC: area under curve CI: Confidence interval *p<0.05 is statistically significant **p≤0.001 is statistically highly significant. NLR: neutrophils to lymphocytes ratio, PLR : platelets to lymphocytes ratio.

Table (4): Comparison between MS patients with normal PLR and MS patients with high PLR regarding demographic and clinical data:

	Normal PLR	High PLR	χ^2	p
	N=33 (%)	N=29 (%)		
	Mean ± SD	Mean ± SD		
Age(year)	31 ± 9.42	32.66 ± 6.83	-0.798	0.428
Sex: **Female** **Male**	 11 (33.3%) 22 (66.7%)	 6 (20.7%) 23 (79.3%)	1.24	0.265
Disease duration(year)	2.3 ± 1.74	2.5 ± 1.79	0.051	0.959
Number of relapses	2.36 ± 1.56	2.54 ± 1.27	-0.232	0.817
	Mean ± SD	**Mean ± SD**	**T**	**p**
EDSS during relapse	3.06 ± 1.41	3.18 ± 1.18	-0.129	0.898
9HPT right hand/sec.	20.27 ± 3.49	21.34 ± 4.75	-1.021	0.311
9HPT left hand/sec.	19.84 ± 3.69	21.37 ± 3.24	-1.723	0.09
	Median (IQR)	**Median (IQR)**	**Z**	**P**
Radiology: **Active lesions on MRI** **Black holes on MRI**	 21 (63.6%) 10 (30.3%)	 28 (96.6%) 16 (55.2%)	 Fisher 3.921	 0.002* 0.148
Treatment **None** **Symptomatic** **DMT**	 21 (63.6%) 3 (9.1%) 9 (27.3%)	 11 (37.9%) 4 (13.8%) 14 (48.3%)	 MC	 0.129

χ^2 Chi square test MC Monte Carlo test t independent sample t test *p<0.05 is statistically significant, Z Mann Whitney test, EDSS: expanded disability state scale, 9HPT :9hole peg test, MRI :magnetic resonance imaging, DMTs: disease modifying therapies

Table (5): Comparison between MS patients with normal NLR and MS patients with high NLR regarding demographic and clinical data:

	Normal NLR N=39 (%) Mean ± SD	High NLR N=23 (%) Mean ± SD	χ^2	p
Age(year)	31.87 ± 8.46	31.61 ± 8.17	0.12	0.905
Sex: Female Male	10 (25.6%) 29 (74.4%)	7 (30.4%) 16 (69.6%)	0.167	0.683
Disease duration(year)	2.17 ± 1.72	2.41 ± 1.79	-0.583	0.562
Number of relapses	2.31 ± 1.3	2.57 ± 1.62	-0.687	0.495
	Mean ± SD	**Mean ± SD**	**t**	**p**
EDSS during relapse	3.24 ± 1.29	3.91 ± 1.35	-0.029	0.979
9HPT right hand/sec.	20.18 ± 3.51	21.78 ± 4.93	-1.492	0.141
9HPT left hand/sec.	19.95 ± 2.5	21.61 ± 4.72	-1.813	0.075
	Median (IQR)	**Median (IQR)**	**Z**	**P**
Radiology: Active lesions on MRI	29 (74.4%)	20 (87%)	Fisher	0.338
Black holes on MRI	16 (41%)	10 (43.5%)	0.038	0.85
Treatment None Symptomatic DMT	21 (63.6%) 3 (9.1%) 9 (27.3%)	11 (37.9%) 4 (13.8%) 14 (48.3%)	MC	0.129

χ^2 :Chi square test MC: Monte Carlo test t independent sample t test *p<0.05; statistically significant, Z Mann Whitney test, EDSS: expanded disability state scale, 9HPT: 9hole peg test, MRI: magnetic resonance imaging, DMTs: disease modifying therapies

Table (6): Comparison between MS patients with normal CRP and MS patients with high CRP regarding demographic and clinical data**:**

	Normal CRP level N=27 (%) Mean ± SD	High CRP level N=35 (%) Mean ± SD	χ^2	P
Age(year)	26.7 ± 5.2	31.61 ± 8.17	-3.7	0.99
Sex: Female Male	10 (37.04%) 17 (62.96%)	17 (48.57%) 18 (51.43%)	0.57	0.44

Disease duration(year)	2.5 ± 1.1	3.4 ± 1.4	-0.583	0.562
Number of relapses	1.9 ± 1.07	2.57 ± 1.62	-0.687	0.495
	Mean ± SD	**Mean ± SD**	**t**	**P**
EDSS during relapse	3.1 ± 0.36	2.72 ± 1.35	-0.029	0.979
9HPT right hand/sec.	20.1 ± 1.9	26.7 ± 14.4	-2.4	0.01*
9HPT left hand/sec.	22.3 ± 2.5	28.6 ± 13.3	-2.5	0.02*
	Median (IQR)	**Median (IQR)**	**Z**	**P**
Radiology: **Active lesions on MRI** **Black holes on MRI**	 17 (62.96%) 10 (37.04%)	 20 (57.14%) 15 (42.86%)	 Fisher 0.038	 0.308 0.75
Treatment **None** **Symptomatic** **DMT**	 14 (51.85%) 3 (11.1%) 10 (37.04%)	 18 (51.43%) 12 (34.29%) 5 (14.29%)	 MC	 0.229

χ^2 Chi square test MC Monte Carlo test t independent sample t test *p<0.05 is statistically significant,. Z Mann Whitney test, EDSS: expanded disability state scale, 9HPT: 9hole peg test, MRI: magnetic resonance imaging, DMTs :disease modifying therapies

Table (7): Correlation between PLR, NLR, CRP and studied parameters:

	PLR		**NLR**		**CRP**	
	R	**p**	**R**	**p**	**R**	**p**
Age(year)	-0.039	0.763	-0.065	0.618	-0.231	0.071
Disease duration(year)	0.079	0.539	0.021	0.871	-0.097	0.543
Number of relapses	0.099	0.443	0.098	0.451	0.098	0.451
EDSS during relapse	0.106	0.411	0.155	0.228	-0.015	0.907
Radiology: Number of active lesions on MRI Number of black holes on MRI	 0.25 0.039	 0.049* 0.866	 0.032 0.021	 0.671 0.87	 0.086 -0.017	 0.555 0.894
9HPT of rt hand/sec.	0.142	0.27	0.137	0.288	0.39	0.01*
9HPT of lt hand/sec.	0.204	0.111	0.219	0.087	-0.283	0.026*

r: Spearman rank correlation coefficient, *p<0.05 is statistically significant, EDSS: expanded disability status scale, 9HPT:9 hole peg test, MRI:magnetic resonance imaging.

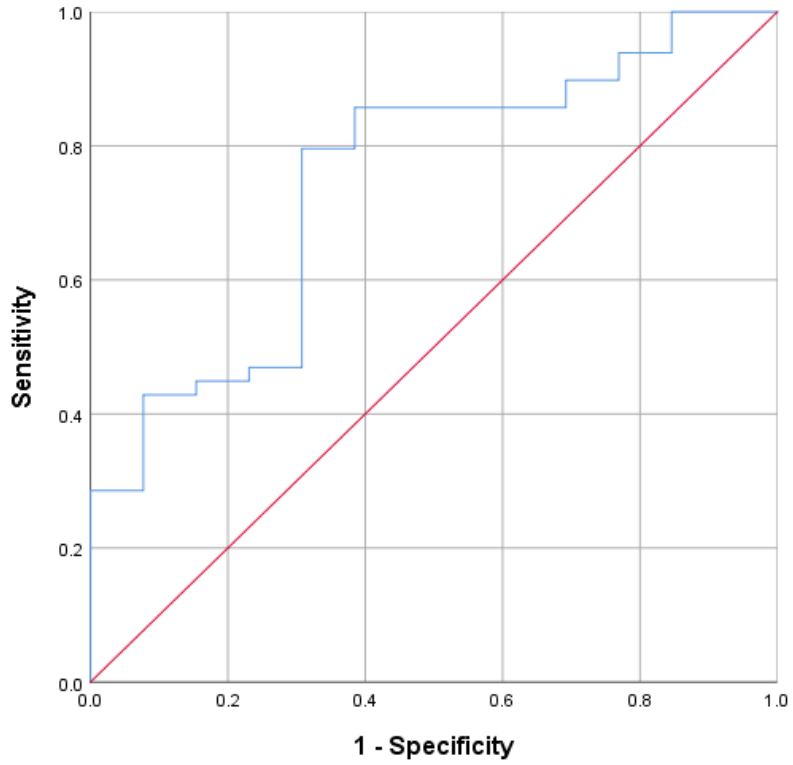

Figure (1): ROC curve showing performance of NLR to detect radiological activity of MS.

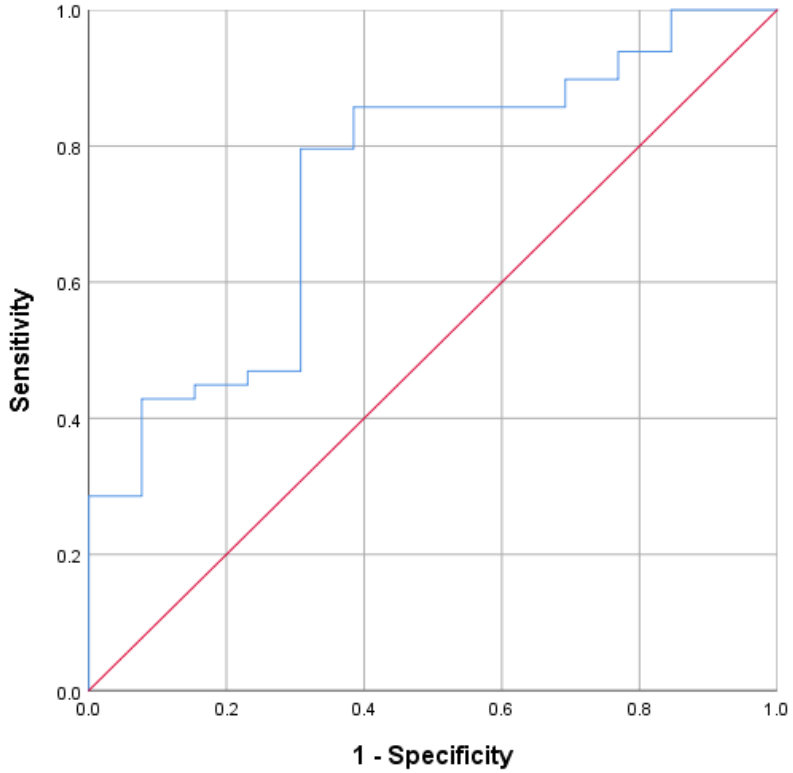

Figure (2): ROC curve showing performance of PLR to detect radiological activity of MS.

Discussion

This current study showed that female to male ratio was 2.65:1. This is in agreement with other studies that confirmed female dominance in MS patients with female: male ratio 2.5:1 Khedr et al. [16] and 2.8:1 Gerges et al. [17]

Angeloni et al. [18] found that women's higher risk of MS has been attributed to factors relating to hormones, particular physiology, and in addition to sex hormones, sex-biased genetic factors also influence disparities in immune response regulation between males and females. Sex-chromosome inactivation, or skewed X chromosome, in particular, has been found to be a factor in the female bias in MS disease prevalence [19].

The total leukocyte count, which is influenced by a variety of circumstances, is a trustworthy measure of inflammation. The relationship between inflammation and autoimmune illnesses has been clarified by the introduction of integrative immune-inflammatory markers, such as PLR and NLR, in recent years [20-21-22]

This current study, found that PLR was higher in MS patients during relapse than control volunteers with significant difference between them (P<0.001). Gokce et al. [23] found PLR to be statistically substantially higher in MS patients than in the control group, which is consistent with our findings.

The results of that study showed that high PLR was significantly associated with active lesions on MRI (P=0.006). The best cutoff of PLR to predict radiological activity of MS is ≥128.155 with area under curve 0.746 (95% CI; 0.598 to 0.894) but not with high sensitivity (76.9%) and specificity (60.2%).

In agreement to our results, Gokce et al. [23] found that PLR was higher in the active group with gadolinium-enhancing lesions in MRI than in the group without active lesions. Fathy et al. [24] found that higher activity among MS patients related significantly to high PLR.

Platelet inducing immune response is becoming increasingly recognized. Under inflammatory conditions, activated platelet has the ability to interact with different immune cells. The interplay between platelets and endothelial cells promote destruction of BBB and facilitate the recruitment of leukocytes and inflammatory cells to brain tissue Activated platelets activate leukocytes thus initiate auto-reactive T cells infiltration and creating a new inflammatory focus in the brain tissue. [25].

Recent evidences indicate the presence of platelet specific GlycoproteinIIb (CD41) in MS plaques [26]. CSF platelet activating factor (PAF) levels are related significantly with MS disease activity [27]. Callea et al. [28] reported that brain platelets could recognize ganglioside GT1b and GQ1b, and subsequently trigger immune response cascades. Furthermore, previous study proved that leukocyte migration to brain inflammatory focus is inactivated by the reduction of platelets number [29]

However, Carnero et al. [30] found that, as opposed to MS illness, patients with neuromyelitis optica spectrum condition may have worse outcomes when their PLR is high.

This current study showed high NLR in MS patients during relapse and there was statistically significant difference between MS patients and control subjects regarding NLR (P=0.031). The best cutoff of serum NLR to predict radiological activity of MS is ≥3.18 with area under curve 0.736 (95% CI; 0.563 to 0.909) with low sensitivity (70.6%) and specificity (61.5%).

In agreement with current study, Elgenidy et al. [31] found that compared to healthy controls, MS patients had a considerably greater NLR. Numerous other research, including Hemond et al. [6], have revealed a higher NLR in MS patients when compared to healthy individuals and there was a significant difference (P=0.003) between the MS patients and the healthy control group. Similar to current study, Yetkin and Mirza [9] found no relationship between NLR and radiological activity in MS patients

A possible early trigger mechanism for inflammation-induced BBB damage in MS patients is neutrophil infiltration of brain tissues. Neutrophils generate numerous inflammatory factors such as; nitric oxide, matrix metalloproteinases, and tumor necrosis factor α (TNF-α) that could mediate myelin degradation and damage of oligodendrocytes and axons [32-33].

In experimental autoimmune encephalitis (EAE) mice, within 24 hours of the disease being induced, neutrophils had already amassed at the meninges, and during the preclinical and peak stages, their numbers grew. Additionally, when neutrophils are depleted before but not after the commencement of the disease, the severity of EAE is decreased and its onset is delayed [34].

According to current study, there was no statistically significant difference in CRP between MS patients and control persons (P=0.079), but we found significant correlations between CRP and 9HPT scores of both right and left hands (P=0.01, 0.02) respectively.

Several earlier researches attempted to predict the shift to progressive disease types by

using inflammatory markers to predict disease activity and severity early on. They first looked at CRP, a classic marker of the acute phase response, but found conflicting results. In addition, other studies had declined the relationship between MS activity and CRP level [35-36]

On the other hand, previous studies reported CRP as a valuable marker [37-38]. Similar to current study, Soilu-Hänninen et al. reported in their study that CRP was used as a potent marker in assessing disease progression in MS patients [39]. In this context, Eren and Demir [40] found that MS patients with elevated CRP had high EDSS scores and clarified that the high CRP is a marker of systemic inflammation and oxidative stress that are mediating axonal damage and demyelinating lesions in MS.

CONCLUSIONS

A high PLR and NLR may be promising predictive markers that can detect activity in multiple sclerosis.

CONFLICT OF INTEREST

The authors declared that they have no conflicts of interest with respect to the authorship and/ or publication of this article.

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