Original Research Article

The Egyptian Journal of Immunology

The Egyptian Journal of Immunology,
E-ISSN (2090-2506)
Volume 33 (2), April, 2026
Pages: 43–57.
www.Ejimmunology.org
https://doi.org/10.55133/eji.330205

Peripheral blood inflammatory cell ratios derived from complete blood count as predictors of multiple sclerosis disease activity and severity

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Abstract

Multiple Sclerosis (MS) is an autoimmune disorder that affects the central nervous system causing different types of disability. Complete blood count (CBC) parameters are considered as markers of systemic inflammation and were linked to many diseases as predictors of prognosis. This study aimed at evaluating the role of Neutrophil, Monocyte and Platelet-to-Lymphocyte Ratios in predicting MS severity and activity. This was a retrospective cohort study, performed through medical records analysis of 98 MS patients attended the hospital during 2025 for follow up. Disease activity and severity were estimated. The baseline CBC that performed shortly after MS diagnosis and prior to initiating disease modifying therapy was analyzed. High Neutrophil-Lymphocyte ratio (NLR) exhibited the strongest predictive value for both disease activity and severity, as confirmed by binary regression. A NLR cutoff of >2.681 yielded excellent sensitivity (97.6%) and specificity (85.7%) for predicting severe disease. High Monocyte-Lymphocyte ratio (MLR) also showed meaningful associations with disease severity and activity, although its predictive value was less pronounced. High Platelet-Lymphocyte ratio (PLR) was found to be predictive of high disease activity but not of disease severity, suggesting a more limited role compared to NLR. In conclusion, NLR is a strong and readily available biomarker for predicting clinical activity and severity of MS, outperforming MLR and PLR. These simple inflammatory indices may aid early risk stratification and clinical decisions in MS cases.

Keywords: Multiple sclerosis, Complete blood count, Inflammatory cell ratio, Activity, Severity.

Date received: 03 February 2026; **accepted:** 16 March 2026

Introduction

Multiple sclerosis (MS) is a long-term inflammatory demyelinating disorder of the neural tissue characterized by immune-driven damage, neurodegeneration, and variable neurological impairment. It manifests with a wide range of clinical signs and symptoms that lead to lifelong disability, reduced productivity,

and a negative impact on the quality of life of patients and their families.[1] The MS prevalence has risen significantly since 1990, particularly in developing countries, with considerable economic and healthcare implications.[2] Current understanding of MS pathogenesis emphasizes that auto-reactive T cells can initiate and regulate the entry and migration of inflammatory leukocytes into the central nervous system (CNS). In addition, growing evidence highlights a key role for B cells in the initiation and progression of multiple sclerosis.[3] Many studies have identified genetic susceptibility and infectious triggers as important predisposing factors for MS. [4] In terms of age, MS prevalence rises after adolescence and peaks between 25 and 35 years, particularly among females.[5] In addition, several environmental influences-including low vitamin D levels, obesity, early-life exposure to certain infectious agents, smoking, and other modifiable risk determinants have been linked to an increased risk of developing MS.[6]

Persistent neurodegeneration mediated by systemic inflammatory processes is a key contributor to MS pathogenesis. This process is mediated through release of pro-inflammatory cytokines and the activation of both innate and adaptive immune responses.[7] MS is frequently accompanied with other autoimmune disorders, including type 1 diabetes mellitus and rheumatoid arthritis.[8] Two principal hypotheses were proposed to explain MS pathophysiology. The inside–out hypothesis suggested that the inflammatory process originates within the CNS, whereas the outside–in hypothesis postulated that peripherally activated T cells cross the blood–brain barrier (BBB) and trigger inflammation within the CNS.[9] The resulting inflammatory cascade leads to myelin damage and the release of CNS antigens. Sustained inflammation subsequently contributes to ongoing neurodegeneration, clinical deterioration, and disease progression leading to functional disability.[10]

Several subtypes of MS exist, with relapsing–remitting MS (RRMS) representing the predominant form and comprising approximately 85% of all cases. RRMS is characterized by recurring neurological manifestations lasting from days to several weeks, ranging from mild manifestations to severe disability, followed by partial or near-full recovery after treatment.[11] Without adequate therapy, 10–15 years after onset, RRMS frequently progresses to secondary progressive MS (SPMS), leading to increasing disability.[12] Another form, primary progressive MS, presents with progressive disability from disease onset without relapses.[13] Diagnosis is typically based on magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis for oligoclonal bands and CSF-IgG index.[11]

Neutrophils are bone marrow–generated immune cells and constitute the most predominant leukocyte population in peripheral blood. They can form neutrophil extracellular traps, which may promote inflammation and act as a plausible origin of autoantigens, thereby contributing to the initiation of autoimmune responses.[14] The role of neutrophils in autoimmune diseases of the CNS was initially proposed based on findings from studies using experimental autoimmune encephalomyelitis, in which neutrophils disrupt the BBB by exerting cytotoxic effects, amplifying inflammation, and activating adaptive immune responses.[15] Neutrophil dominance and accelerated lymphocyte apoptosis elevate neutrophil–lymphocyte ratio (NLR) and monocyte–lymphocyte ratio (MLR), reflecting innate–adaptive immune imbalance, particularly during early MS.[16] Neutrophils also contribute to disease activity, especially during relapses, through infiltration across the BBB.[17] Deterioration of the disease from relapsing to progressive stages is also linked to shift from adaptive to innate immune dominance, demonstrated by elevated NLR and MLR.[18]

Platelets, although anucleated, play a crucial role in inflammatory conditions by regulating the vascular microenvironment through the secretion of immune mediators.[19] Platelet–lymphocyte ratio (PLR) was reported as a poor prognostic marker in cancer and COVID-19.[20] Platelets express cytokines such as interleukin-1β and chemokines (CCL5, CCL3), and can cross a disrupted BBB, contributing to MS plaque formation.[21] Likewise, leukocytes, particularly T lymphocytes, are implicated in MS progression.

Activated T cells and cytokines are found at sites of tissue damage and in circulation.[22] Their adhesion to cerebral endothelial cells enables migration through vessel walls into the CNS parenchyma.[23] This extravasation is thought to precede demyelination.[15]

Hematological alterations are frequently observed in MS, making complete blood count (CBC) a routine tool to assess patients' overall health.[13] Derived ratios such as the NLR, MLR, and PLR are increasingly recognized as simple yet effective markers in autoimmune or inflammatory disorders, including MS.[24] Baseline CBC parameters were shown to correlate with MS disease activity, MRI lesion burden, disability progression, and brain atrophy.[25] Given the rising prevalence of MS, its social burden, and the high costs of disease modifying therapies (DMTs) in the context of ongoing economic challenges, there is a pressing need for cost-effective biomarkers to predict disease severity and prognosis. Therefore, this study aimed to evaluate the predictive value of NLR, MLR and PLR in assessing MS severity.

Patients and Methods

This was a retrospective cohort study performed through analysis of medical records of 172 cases with MS and attended clinic in Prince Mohammed Bin Abdelaziz hospital, Riyadh city, Saudi Arabia during 2025 for follow-up. Eligible patients were over 18 years of age and had follow up data of approximately three years, which was considered adequate for evaluating relapse rate and disability progression. Inclusion criteria required also the availability of a CBC prior to initiating steroids or disease modifying therapy. Patients were excluded if they lacked baseline CBC data at disease onset, had a disease follow up period shorter or longer than three years, incomplete medical records, diagnosed with additional autoimmune diseases, or had known hematological disorders. Sample size was calculated using the OpenEpi program. The study included 98 patients, comprising males 41 (41.8%) and females 57 (58.2%), with a mean age of years was 33.2 ± 8.29.

The data obtained from patient's records included the age of disease onset, Body Mass Index (BMI), frequency of relapses, and the administration of DMT. Radiological data about disease activity including the CNS lesions were also considered. Disability was evaluated using the Expanded Disability Status Scale (EDSS), and the patients were divided into two cohorts based on EDSS scores interpreted as follow: mild disability for EDSS ≤ 3.5 and moderate to severe disability for EDSS ≥ 4.[26] Patients were also divided according to disease activity into two other cohorts high and low disease activity. High disease activity was defined as having ≥2 relapses during the year before study enrollment and the presence of at least one gadolinium-enhancing lesion at the time of evaluation. Baseline CBC was performed shortly after MS diagnosis and prior to initiating DMT, and analyzed as follows:

White blood cell indices included total leukocyte count, neutrophil–lymphocyte ratio (NLR), and monocyte–lymphocyte ratio (MLR), both obtained by dividing the absolute neutrophil or monocyte count by the lymphocyte count, respectively.[22]

Platelet indices included platelet count and platelet–lymphocyte ratio (PLR), the latter obtained by dividing the platelet count by the lymphocyte count.[15]

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 25) software. Continuous variables were assessed for normality using distribution characteristics and are reported as mean ± standard deviation (SD) for normally distributed variables or median with interquartile range (IQR) for non-normally distributed variables. Categorical data are reported as frequencies and percentages. The relations between two independent groups are revealed with the independent samples t-test for normally distributed continuous variables, while the Mann–Whitney U test was applied for non-parametric data. Associations between categorical variables were evaluated using the Chi-square test. The Receiver Operating

Characteristic (ROC) curve was performed to evaluate the diagnostic value of NLR, MLR, and PLR in detecting disease activity and severity, and optimal cutoff values were determined based on sensitivity and specificity. Binary logistic regression was used to detect independent predictors of disease activity and disease severity, with results expressed as odds ratios (ORs) and 95% confidence intervals (CIs). A *p*-value ≤ 0.05 was considered statistically significant.

Results

This work involved 98 RRMS cases with a mean age of 33.2 years. The sample comprised 58.2% females and 41.8% males. The mean Body Mass Index (BMI) was 27 kg/m^2**.** The majority of participants (68.4%) exhibited low number of relapses. Laboratory values, including neutrophil–lymphocyte ratio (N/L), monocyte–lymphocyte ratio (M/L), and Platelet–lymphocyte ratio (P/L) ratios, showed variation across participants, with mean N/L ratio of 2.7, M/L ratio of 0.25, and P/L ratio of 141.95. The mean red blood cells and hematocrit were 4.8 and 0.4%, respectively. The Expanded EDSS indicated that 57.1% of participants had mild disability, and 42.9% had moderate to severe disability. Various DMTs were used with Ocrelizumab being the most frequently prescribed (28.6%) (Table 1).

Table 1. Demographic and Laboratory investigations data of the 98 participants.

Patients characteristics	No.	%
Gender		
Female	57	58.2
Male	41	41.8
Age		
Mean ± SD.	33.2 ± 8.29	
Range	20.0 – 58.0	
Age of onset		
Mean ± SD.	28.9 ± 8.19	
Range	18.0 – 55.0	
BMI		
Mean ± SD.	27.0 ± 7.00	
Range	15.0 – 45.0	
Relapses		
Low number of relapse (< 2)	67	68.4
High number of relapse (≥ 2)	31	31.6
EDSS		
Mild (≤ 3.5)	56	57.1
Moderate to severe (≥ 4)	42	42.9
Treatment with DMT		
None	7	7.1
Ocrelizumab	28	28.6
Teriflunomide	9	9.2
Interferon beta-1a	7	7.1
Fingolimod	12	12.2
Natalizumab	12	12.2
Dimethyl fumarate	16	16.3
Interferon beta-1b	7	7.1

Table 1. Continued.

Patients characteristics	
N/L	
Mean ± SD.	2.7 ± 0.62
Range	1.26 – 3.95
M/L	
Median (IQR)	0.25 (0.17 – 0.37)
Range	0.095 – 3.52
P/L	
Median (IQR)	141.95 (101.05 – 183.12)
Range	41.04 – 1295.0
WBCs	
Mean ± SD.	5.0 ± 1.12
Range	2.88 – 7.9
Platelets	
Median (IQR)	284.5 (240.5 – 343.0)
Range	92.0 – 631.0

SD: Standard deviation; BMI: Body mass index; EDSS: Expanded disability status scale; DMT: Disease modifying therapy; N\L: Neutrophil/lymphocyte; M\L: Monocyte/lymphocyte; P\L: Platelet/lymphocyte; WBC: White blood cells, IQR: Interquartile range

The relation between clinical activity and different demographic and laboratory data was examined. Age and gender were not significantly related to disease activity. However, participants with high activity had a significantly elevated N/L, M/L, and P/L ratios, and white blood cell count (WBC) compared to those with low activity. Additionally, EDSS scores were higher in the high-activity group, indicating more severe disability. The analysis also revealed that participants with high disease activity had a higher mean BMI, suggesting potential association between higher BMI and more active disease (Table 2).

Table 2. Relation between disease activity (relapse) and Demographic data, Laboratory investigations of the 98 participants.

Patients' characteristics	Low activity (n=67)		High activity (n=31)		*p*-value
	No.	%	No.	%	
Gender					
Female	39	58.2	18	58.1	$NS^{\chi 2}$
Male	28	41.8	13	41.9	
Age					
Mean ± SD.	32.9 ± 8.36		34.0 ± 8.23		NS^{t}
Range	21.0 – 58.0		20.0 – 55.0		
Age of onset					
Mean ± SD.	28.7 ± 8.40		29.5 ± 7.81		NS^{t}
Range	18.0 – 55.0		18.0 – 48.0		
N/L					
Mean ± SD.	2.4 ± 0.49		3.3 ± 0.50		$<0.001^{t}$
Range	1.26 – 3.44		2.12 – 3.95		

Table 2. Continued.

Patients' characteristics	Low activity (n=67)		High activity (n=31)		*p*-value
M/L					
Median (IQR)	0.20 (0.16 – 0.28)		0.47 (0.30 – 0.95)		<0.001[U]
Range	0.1 – 0.47		0.095 – 3.52		
P/L					
Median (IQR)	125.48 (97.08 – 147.90)		205.20 (147.31 – 350.0)		<0.001[U]
Range	41.04 – 297.53		77.31 – 1295.0		
EDSS					
Mild (≤ 3.5)	53	79.1	3	9.7	<0.001[χ2]
Moderate to severe (≥ 4)	14	20.9	28	90.3	
BMI					
Mean ± SD.	25.9 ± 6.50		29.6 ± 7.50		0.014[t]
Range	15.0 – 43.0		20.0 – 45.0		
WBCs					
Mean ± SD.	4.7 ± 1.10		5.7 ± 0.88		<0.001[t]
Range	2.88 – 7.9		3.18 – 6.6		

χ2: Chi square test. t: Independent t test. IQR: Interquartile range. U: Mann Whitney U test. SD: Standard deviation. N\L: Neutrophil/lymphocyte. M\L: Monocyte/lymphocyte. P\L: Platelet/lymphocyte. EDSS: Expanded disability status scale. BMI: Body mass index. WBC: White blood cells. $p > 0.05$ is not significant (NS).

The relationship between disease severity (as assessed by EDSS) and various demographic and laboratory measures was also investigated. Gender, age, and age of onset were not significantly related to disease severity. However, a significant difference in laboratory markers was observed, with participants in the moderate-to-severe EDSS group having higher N/L, M/L, and P/L ratios. Higher BMI and WBC were also associated with increased disease severity (Table 3).

Table 3. Relation between disease severity (EDSS) and Demographic data, Laboratory investigations of the 98 participants.

Patients characteristics	Mild (≤ 3.5) (n=56)		Moderate to severe (≥ 4) (n=42)		*p*- value
	No.	%	No.	%	
Gender					
Female	35	62.5	22	52.4	NS[χ2]
Male	21	37.5	20	47.6	
Age					
Mean ± SD.	32.9 ± 8.30		33.6 ± 8.36		NS[t]
Range	21.0 – 58.0		20.0 – 55.0		
Age of onset					
Mean ± SD.	28.8 ± 8.47		29.1 ± 7.89		NS[t]
Range	18.0 – 55.0		18.0 – 48.0		
N/L					
Mean ± SD	2.3 ± 0.41		3.3 ± 0.38		<0.001[t]
Range	1.26 – 3.44		2.39 – 3.95		

Table 3. Continued.

Patients characteristics	Mild (≤ 3.5) (n=56)	Moderate to severe (≥ 4) (n=42)	*p*- value
M/L			
Median (IQR)	0.20 (0.15 – 0.27)	0.38 (0.26 – 0.65)	<0.001[U]
Range	0.1 – 0.38	0.095 – 3.52	
P/L			
Median (IQR)	125.4 (96.58 – 148.53)	163.85 (132.54 – 231.05)	<0.001[U]
Range	41.04 – 350.0	72.18 – 1295.0	
BMI			
Mean ± SD.	25.3 ± 6.66	29.4 ± 6.84	0.004[t]
Range	15.0 – 43.0	18.0 – 45.0	
WBCs			
Mean ± SD.	4.5 ± 1.09	5.7 ± 0.79	<0.001[t]
Range	2.88 – 7.9	4.0 – 6.6	

χ2: Chi square test. t: Independent t test. IQR: Interquartile range. U: Mann Whitney U test. SD: Standard deviation. N\L: Neutrophil/lymphocyte. M\L: Monocyte/lymphocyte. P\L: Platelet/lymphocyte. BMI: Body mass index. WBC: White blood cells. *p* > 0.05 is not significant (NS).

The ROC curve analysis for N/L, M/L, and P/L ratios in diagnosing moderate to severe disease demonstrated the highest ability (AUC = 0.965) for N/L ratio, with an optimal cutoff of >2.681, providing excellent sensitivity (97.6%) and specificity (85.7%). The M/L ratio showed good performance (AUC = 0.817) as well as the P/L ratio (AUC = 0.727), however, was less reliable for diagnosing severe disease compared to N/L and M/L ratios. This reinforces the importance of N/L and M/L ratios in detecting disease severity (Table 4) (Figure 1).

The ROC curve analysis for N/L, M/L, and P/L ratios in diagnosing high disease activity indicated that N/L ratio had the highest area under the curve (AUC = 0.878), with a cutoff value of >2.911, demonstrating good sensitivity (87.1%) and specificity (86.6%). The M/L and P/L ratios also showed significant ability, with AUC values of 0.856 and 0.827, respectively. These results suggested that these ratios are reliable biomarkers for identifying high disease activity in MS (Table 5) (Figure 2).

Table 4. Receiver Operating Characteristic (ROC) curve for neutrophil–lymphocyte ratio (N/L), monocyte–lymphocyte ratio (M/L) and platelet–lymphocyte ratio (P/L) ratio in diagnosis of severe multiple sclerosis disease.

	AUC	*p*-value	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
N/L	0.965 (Excellent)	<0.001	>2.681	97.6%	85.7%	83.7%	98.0%	90.8%
M/L	0.817 (Good)	<0.001	>0.2291	81.0%	64.3%	63.0%	81.8%	71.4%
P/L	0.727 (Fair)	<0.001	>142.91	69.0%	66.1%	60.4%	74.0%	67.3%

AUC: Area Under the Curve; PPV: Positive predictive value; NPV: Negative predictive value; *p* ≤ 0.05 is significant.

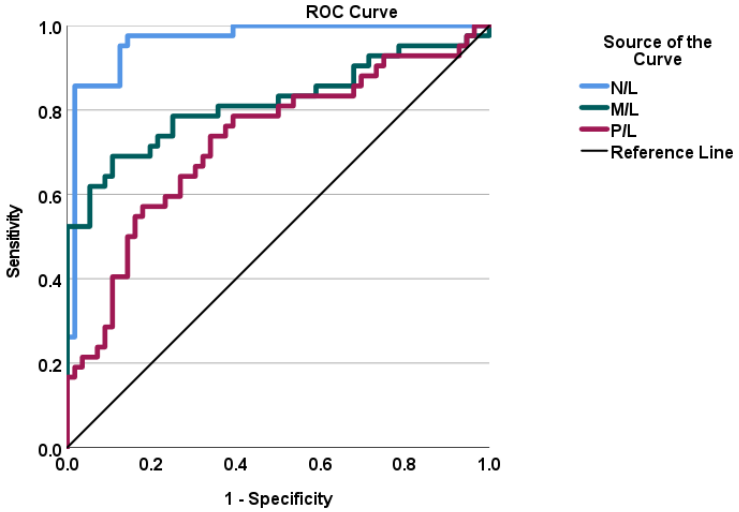

Figure 1. Receiver Operating Characteristic (ROC) curve showing performance of neutrophil–lymphocyte ratio (N/L), monocyte–lymphocyte ratio (M/L) and platelet–lymphocyte ratio (P/L) in diagnosis of severe multiple sclerosis (MS) disease.

Table 5. Receiver Operating Characteristic (ROC) curve for neutrophil–lymphocyte ratio (N/L), monocyte–lymphocyte ratio (M/L) and platelet–lymphocyte ratio (P/L) ratio in diagnosis of high multiple sclerosis disease activity.

	AUC	*p*-value	Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
N/L	0.878 (Good)	<0.001	>2.911	87.1%	86.6%	75.0%	93.5%	86.7%
M/L	0.856 (Good)	<0.001	>0.2904	80.6%	76.1%	61.0%	89.5%	77.6%
P/L	0.827 (Good)	<0.001	>147.248	77.4%	74.6%	58.5%	87.7%	75.5%

AUC: Area Under the Curve; PPV: Positive predictive value; NPV: Negative predictive value; $p \leq 0.05$ (Statistically significant)

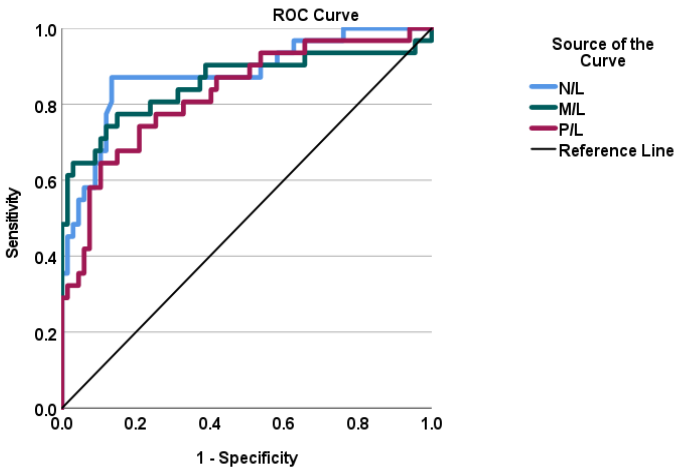

Figure 2. Receiver Operating Characteristic (ROC) curve showing performance of neutrophil–lymphocyte ratio (N/L), monocyte–lymphocyte ratio (M/L) and platelet–lymphocyte ratio (P/L) in prediction of active multiple sclerosis (MS) disease.

The results of binary logistic regression for predicting disease activity and severity showed that the N/L ratio was a significant predictor of both disease activity and severity, with an odds ratio (OR) of 11.725 for disease activity and 623.603 for disease severity, indicating its strong role in predicting clinical outcomes. The M/L ratio was marginally significant for disease activity (OR = 418.189), but not for disease severity. The P/L ratio was found to be a significant predictor only for disease activity (OR = 1.013). These findings highlighted the potential of N/L and P/L ratios as biomarkers for monitoring progression of MS (Table 6).

Table 6. Binary logistic regression for prediction of multiple sclerosis disease activity and severity.

Multiple sclerosis		Wald	*p*-value	OR	95% CI of OR	
					Lower	Upper
Disease activity	N/L	7.835	0.005	11.725	2.092	65.721
	M/L	3.669	NS	418.189	0.869	201154.534
	P/L	5.805	0.016	1.013	1.002	1.024
Disease severity	N/L	16.362	<0.001	623.603	27.585	14097.762
	M/L	0.610	NS	25.199	0.008	82787.255
	P/L	0.145	NS	1.003	0.988	1.017

OR: Odds ratio; *p* > 0.05 is not significant (NS).

Discussion

Multiple sclerosis is a long standing, disabling, immune-precipitated neurodegenerative central nervous system disorder, involving more than two million individuals over the world.[27] The disease is marked by diverse clinical presentations and variable disease courses. This underscores the need for reliable biomarkers that can facilitate early disease detection, accurate staging, and prognostic stratification. These biomarkers could also guide the therapeutic decision-making particularly in light of recent advances in highly effective disease-modifying therapies.[28] A wide range of biomarkers was employed to evaluate MS activity and progression, encompassing radiological and immunological markers measured in serum or cerebrospinal fluid. Several studies explored the utility of acute-phase markers, like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR); however, findings were inconsistent, with some studies supporting their prognostic value e.g. Nazeri, et al., 2022[29] while others failed to demonstrate a significant association e.g. Pierson, et al., 2018.[30]

The complete blood count is routinely used as a basic clinical investigation to assess overall patient health and is valued for its wide availability, low cost, and ability to reflect systemic inflammatory responses.[31] Few previous studies examined the association between all CBC ratios and MS severity and activity, but most were case control or cross sectional studies with limited short time follow up period. To address these limitations, we conducted a retrospective cohort study involving 98 MS patients with three years follow up period to assess the predictive role of CBC-derived parameters for MS progression. White blood cells, NLR, MLR, and PLR were assessed for all patients, alongside EDSS scores and disease relapses.

Our study demonstrated that all the analyzed immune markers including NLR, MLR and PLR were significantly elevated in MS patients with higher disease relapse and disability. Among the three ratios, NLR was the superior biomarker, demonstrating the highest predictive power for both disease activity and

severity, even after adjusting for other covariates. In contrast, while MLR and PLR demonstrated discriminatory ability, only PLR was a significant predictor of MS disease activity in the multivariate analysis. Additional findings included a significant relationship between higher BMI and greater MS disease activity/severity, as well as elevated WBCs in patients with more severe disability. In contrast, demographic variables such as age and sex showed no significant associations with MS disease relapse or severity.

The pathophysiology of MS is partly driven by complex imbalances in the natural and acquired immune system reactions. While the innate immune system cells such as neutrophils and monocytes are typically the initiators of the BBB disruption and the subsequent neural tissue damage, adaptive immune cells such as lymphocytes can also partake in this pathological process.[32] In active phases of MS, peripheral leukocytosis can be present, reflecting the exaggerated underlying systemic inflammatory response, while lymphopenia can also be frequently observed due to either increased apoptosis or migration of lymphocytes from the peripheral circulation to the CNS.[33] It was hypothesized that this systemic disequilibrium between the innate and adaptive immunity can be utilized in the quantification of the systemic inflammatory response occurring in MS. Furthermore, using the ratios of these immune cells rather than the absolute counts, enables physicians to account and control for each patient baseline immune status, and thus can provide more sensitive metric of the inflammatory response.[34]

In the present study, elevated baseline NLR was significantly linked to a higher relapse rate over a three-year follow-up period, as well as with increased MS disease severity evaluated by the EDSS. These findings are in harmony with several previous studies that identified NLR as a predictor of both relapse frequency and MS disease severity.[24, 22, 35, 36] Several mechanisms may explain this association. NLR echoes the interaction between neutrophil-associated innate immune activation and lymphocyte-dependent adaptive immunity. Increased neutrophil counts in MS patients were linked to enhanced expression of toll-like receptor-2, cluster of differentiation-43, and phenotypic alterations in formyl peptide receptor-1, all of which contribute to pro-inflammatory immune responses. Moreover, lymphopenia is a recognized marker of immune dysregulation and chronic inflammatory conditions.[37] These pathophysiological mechanisms support the findings of Fahmi et al., 2021, who reported significantly higher NLR values in MS patients compared with healthy controls, with the highest levels observed among those with progressive disease courses.[24]

Conversely, Yetkin et al., 2020, in a prospective study with a three-year follow-up, found no significant association between elevated NLR and MS relapse frequency.[38] Similarly, Gelibter and colleagues, 2021, demonstrated that NLR was slightly higher in MS patients than in healthy individuals and it did not correlate with disease activity.[39] NLR was also proved to be the most significant predictor of both MS disease severity (AUC 0.965, Cutoff >2.681) and activity (AUC 0.878, Cutoff >2.911). In consistent with our results, previous studies also reported significant association between NLR level and MS clinical status.[40,41] However Demirci et al., 2016, reported that NLR at cutoff 3.90 was a significant predictor of MS diagnosis.[42] Another large Danish cohort study reported that high NLR correlated with MS, however; the power of the correlation with MS severity was weak (R2.0.019).[43] Notably, the exceedingly high AUC reported in our analysis could be related to a plethora of factors, including use of binary categories rather than continuous outcome regression, relatively small sample size, inclusion of MS patients before any DMT or steroid initiation, as well as the inclusion of RRMS-only cohort, which eliminates heterogeneity from other MS phenotypes.

Generally, the superiority of NLR over other predictors in our analysis highlights the role of neutrophil, as the first responders in the immune-related CNS infiltration. The activation of neutrophils leads to the release of oxidative stress factors (such as reactive oxygen species, matrix metalloproteinases and myeloperoxidase), all of which result in the

disruption of BBB integrity and the eventual influx of inflammatory cells and demyelinating antibodies.[44] Moreover, recent reports stated that neutrophils can directly exert cytotoxic effects on neurons and oligodendrocytes via their ability to form neutrophil extracellular traps.[45] Therefore, our study could suggest that among MS patients with a neutrophil-dominant immune profile, the risk of rapid progression of the disease severity is amplified. This also indicates that the innate immune system in these patients can be the main potent accelerator of relapses, independent of the adaptive immune system cycles that are typically associated with disease recurrences and relapses.

The process of antigen presentation and myelin phagocytosis within the CNS in MS is related to the monocyte migration theory, where monocytes are driven into the CNS during the acute phase of inflammation to mature into macrophages and dendritic cells.[46] Our analysis reported that while MLR was initially elevated among MS patients in the high activity/severity groups in the univariate analysis, it did not remain a significant predictor of either disease severity or activity in the multivariate regression model. In contrast to our results, Hemond et al., 2019, reported that elevated MLR was an independent significant predictor of disease progression, after adjusting other clinical and demographic variables. However, the study by Hemond et al., 2019, pooled data from a relatively larger sample size (n=483) and included MS patients with a progressive pattern, which could explain some of the discrepancies in the results.[6]

Alongside their homeostatic activity, platelets also have a physiological role in neuro-inflammation; they are potent pro-inflammatory cells that have the ability to adhere into the inflamed endothelium of the affected CNS lesion, releasing a large amount of cytokines and chemokines, forming a bridge that eventually help the extravasation of other immune cells.[47, 48]

In our analysis, PLR was found to be a significant independent predictor of high disease activity (OR = 1.013, *p*=0.016) but failed to predict disease severity in the multivariate regression analysis. In accordance with our findings, a previous study reported a significant but weak association between PLR and EDSS score.[49] Other studies found no significant association between PLR and disease severity and reported that PLR was generally weaker than NLR and MLR.[6, 11]

Our results suggested that the use of these markers, particularly NLR in the stratification of RRMS patients at baseline, could help physicians in the treatment-decision process. Their high-yield low-cost and practical-ease can help physicians in choosing MS patients who might benefit better by initiating high-efficacy therapy earlier in the treatment course. Moreover, although evidence supporting their use for longitudinal patient monitoring remains limited, these indices may still serve as useful surrogate markers, particularly in resource-limited settings. In contrary, some guidelines recommend the use of relatively expensive fluid biomarkers (oligoclonal bands, neurofilament light chain), with frequent MRI imaging as the preferred markers for longitudinal monitoring and prognosis of MS, while dismissing the use of blood count-derived indices (NLR, MLR, PLR) due to limited longitudinal evidence and their non-specificity.[50, 51]

Another noticeable finding in our study was the significant association between BMI and high disease activity/severity. The association between obesity and MS was established, with high BMI reported to be associated with a consistent state of chronic low-grade inflammation.[52] Adipose tissue is a biologically active endocrinal organ with the ability to secrete pro-inflammatory chemicals such as leptin and resistin, while surprising the release of other anti-inflammatory proteins such as adiponectin.[53]

In our study we also found that patients with higher disease activity and severity had significantly elevated total WBC counts ($p < 0.001$). This finding aligns with Liu et al., 2025, who reported that peripheral leukocytosis predicted disease exacerbation.[54] However, other reports did not confirm a strong association, arguing that WBC values can fluctuate with infections or treatments.[55] Our methodological decision to include baseline

counts prior to steroid or DMT initiation strengthens the argument that the observed differences reflect disease-related inflammation rather than treatment effects.

Interestingly, we observed no significant associations between age, sex, and either disease activity or severity. This is in contrast to earlier reports. For instance, Mouresan et al., 2024, showed that older age at onset predicted faster disability progression, and Kalincik et al., 2013, found female sex to be associated with higher relapse rates. The lack of associations in our cohort may be due to relatively narrow age distribution (mean ~33 years).[56, 57]

The main limitations of this study included its retrospective design, the limited study cohort, and the fact that it was conducted at a single center. Another limiting factor was the deficiency of recording of other relevant biomarkers that could be correlated with the CBC ratios to strengthen the validity of our results. Nevertheless, we highlighted that this study presents a cost-effective, readily available, and easily applicable biomarkers, particularly valuable in settings where more advanced or expensive biomarkers are not accessible. The use of such a marker may support improved clinical decision in managing MS cases, thereby optimizing treatment strategies and potentially enhancing patient outcomes.

In conclusion, this study introduced highly effective, inexpensive, and easily applicable biomarkers that may aid in the early identification of MS disease course. Among these biomarkers, NLR has emerged as the strongest, most practical predictor of MS activity and severity. Assessment of NLR at the time of initial diagnosis may assist clinicians in predicting future disease severity and progression. Particular attention to patients with elevated NLR may facilitate earlier risk stratification, leading to improved patient outcomes and a reduction in overall disease burden. Such an approach may benefit both patients and the broader community by enhancing productivity and reducing healthcare expenditures related to advanced therapies and hospital admissions. Nevertheless, we recommend further comprehensive evaluation through well-designed prospective multicenter studies to boost the evidence supporting the clinical utility of these biomarkers.

Acknowledgements

This study was supported by the Deanship of Postgraduate and Scientific Research, Dar Al- Uloom University, Riyadh, Saudi Arabia. We would also like to thank Dr. Maysoon Bawazir, consultant neurology at PMAH for his help in collecting patient's data.

Author Contributions

NMM, OM, HA, BA, AA performed Data Collection/Data Processing/ analysis. RAM, NMM performed Drafting of the manuscript and critical review of the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

Ethical approval

The study protocol was reviewed and approved by the Institutional Review Board, Dar Al Uloom University and Prince Mohammed bin Abdelaziz Hospital in Riyadh, Saudi Arabia (IRB No: 25-003, 25th February 2025).

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