Al-Azhar International Medical Journal

Volume 5 | Issue 6 Article 36

7-1-2024
Section: Neurology

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How to Cite This Article

Hussin, Hussin Mohamed; Mansour, Fathy Mahmoud; and Abdullatif, Haitham Mohamed (2024) "Neutrophil/Lymphocyte Ratio (NLR) as a Possible Marker for MS Activity in a Sample of Egyptian Patient," *Al-Azhar International Medical Journal*: Vol. 5: Iss. 6, Article 36.
DOI: https://doi.org/10.58675/2682-339X.2497

ORIGINAL ARTICLE

Neutrophil/Lymphocyte Ratio (NLR) as a Possible Marker for MS Activity in a Sample of Egyptian Patient

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Abstract

Background: ***Multiple sclerosis (MS) is a persistent autoimmune disorder affecting the central nervous system (CNS), characterized by inflammation, loss of myelin, as well as damage to nerve fibres, resulting in a range of neurological symptoms and different degrees of clinical impairment.***

Aim and objectives: ***To detect if there is a relationship between Multiple sclerosis activity and Neutrophil/Lymphocyte Ratio.***

Patients and methods: This prospective trial was done on 100 persons with MS patients (either known as Multiple sclerosis or newly diagnosed) presented to the neurology department and Multiple sclerosis unit of Al-Azhar university hospitals during relapse. The duration of the recruiting period was 6 months.

Results: ***The mean Neutrophil-lymphocyte ratio was 3.17±0.85 and 1.87±0.41 in patients before and after steroid therapy, respectively. Data showed significant differences between groups in NLR. A significant positive association was discovered among MS activity and NLR in addition to between NLR and C-reactive protein (CRP), secondary progressive multiple sclerosis (SPMS), relapsing remittent multiple sclerosis (RRMS), and primary progressive multiple sclerosis (PPMS). NLR showed 67% sensitivity and 82 % specificity. CRP showed 58% sensitivity and 70% specificity. Erythrocyte sedimentation rate (ESR) showed 62% sensitivity and 65 % specificity.***

Conclusion: ***The presence of NLR revealed a strong correlation with both the level of disability activity in individuals with Multiple sclerosis. Our findings indicate that NLR can be used as a straightforward, quick, and cost-effective indicator of inflammation in relation to disability and activity in Multiple sclerosis. An increased NLR is linked to Multiple sclerosis; hence, studying the involvement of neutrophils in people with Multiple sclerosis could offer fresh perspectives on the development of Multiple sclerosis.***

Keywords: Multiple sclerosis; Neutrophil/Lymphocyte Ratio; Expanded Disability Status Scale

1. Introduction

Multiple sclerosis is a long-lasting inflammatory illness that affects the central nervous system. It causes damage to the protective covering of nerve fibres (demyelination), inflammation, and loss of nerve fibres (axonal loss). These changes result in a range of neurological symptoms as well as different levels of clinical disability.[1]

It has been proposed that low-grade systemic inflammation has an impact on the development of multiple sclerosis by increasing harmful immune activation.[2]

The absence of easily obtainable dependable biomarkers for systemic inflammation is a hindrance in accurately forecasting the activity in addition to the advancement of MS.[3]

Neutrophils play an increasingly acknowledged role in both starting and sustaining autoimmune neuro-inflammation. [4]

The peripheral blood neutrophil-to-lymphocyte ratio has been proposed as an inexpensive and effective surrogate marker for the systemic inflammatory state, in addition to disease activity in many autoimmune disorders.[5]

The persistent proinflammatory milieu in individuals with multiple sclerosis results in the activation of neutrophils, leading to an increase in their population and the subsequent generation of inflammation and damage to tissues. Furthermore, the neutrophil count exhibited an increase during the clinical relapse period in comparison to the remission phase.[6]

In addition to enhancing T-cell activation, neutrophils may release proinflammatory cytokines, reactive oxygen species, as well as proinflammatory enzymes, which in turn may cause inflammation in the brain's parenchyma as well as compromise the blood-brain barrier. [7]

Accepted 21 June 2024.
Available online 31 June 2024

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https://doi.org/10.58675/2682-339X.2497

Finding an association between Multiple sclerosis activity and the Neutrophil/Lymphocyte Ratio was the primary goal of this research.

2. Patients and methods

This prospective study was performed on 100 individuals with Multiple sclerosis patients (either known MS or newly diagnosed) presented to the neurology department and Multiple sclerosis unit of Al-Azhar University Hospitals during relapse. The duration of the recruiting period was 6 months.

Inclusion criteria: Any MS patient diagnosed according to the McDonald criteria 2017 comes to the Multiple Sclerosis unit with relapse and before starting steroid therapy.[8]

Exclusion criteria: Any MS patients with a history of acute or chronic infections, patients on DMT less affecting lymphocytes, concomitant autoimmune diseases, malignancy, short-term steroid therapy in the last one month, pregnancy, diabetes mellitus, hypertension, heart disease, hepatic, coronary renal diseases & deficiency in thyroid functions, cases with a history of operation in the last three months& current smokers or with a history of smoking, health issues related to blood or having received a blood transfusion in the last 90 days.

All patients underwent History taking, clinical examination, radiological investigations, neurological examination, visual evoked potential (VEP), CSF examination for oligoclonal bands (OCB) and IgG index when indicated, Expanded Disability Status Scale (EDSS), CBC with counting NLR two times (during relapsing, before starting steroid therapy, and one month later), routine and specialized lab according to clinical data, and ECG and echocardiography.

Mental status: A clinician might get a sense of the patient's overall health by evaluating their cognitive abilities, which include things like language usage, the order in which events were remembered, and the importance of their responses. "Awake," "alert" (responsive appropriately), and "oriented" (self-aware, location-aware, and time-aware) were the characteristics of a healthy person.

Cranial Nerves: Problems with the regular functioning of the cranial nerves help pinpoint exactly where in the brain or brainstem the lesion is located.

Olfactory nerve (Cranial nerve I): Evaluating the individual's olfactory abilities is one way to check their functioning. Proper detection of any aberrant findings requires starting with one nostril while covering the opposing nostril.

Optic nerve (Cranial nerve II): Visual acuity and visual field tests are part of an evaluation of the optic nerve's function. Directly shining a light into an eye is one way to evaluate the pupillary light reaction. The optic disk was also visualized during a fundoscopic examination. Warning signs of potentially fatal disorders, including elevated intracranial pressure subarachnoid haemorrhage, include anomalies, for example, pa, papilledema or retinal haemorrhages.

Trochlear, Oculomotor, and abducens nerves (Cranial nerve III, IV, in addition to VI): As part of the evaluation, the patient is asked to follow an invisible "H" drawn in front of them. Double vision or disconjugate gaze is a sign of an abnormality.

Trigeminal nerve (Cranial nerve V): For the purpose of evaluating this nerve, it is common practice to have the patient clamp their jaw while simultaneously feeling for the ophthalmic, maxillary, and mandibular branches. Muscle weakness in the area of chewing or loss of sensation on the opposite side may indicate its involvement.

The facial nerve (Cranial nerve VII): The ocular, maxillary, and mandibular branches are tested for sensation when the patient is asked to clench their jaw as part of the evaluation of this nerve. As a result, its participation is suggested by ipsilateral sensory deficits or weakening of the masticatory muscle.

The vestibulocochlear nerve (Cranial nerve VIII): One way to make a general evaluation of function is to whisper some words behind the person's back, rub their hair or fingers together near their ear, and then ask them if they can hear.

The glossopharyngeal and vagus nerves (Cranial nerves IX & X): Listening carefully for hoarseness or nasal speech is an important part of evaluating these nerves while a person is speaking. It may be helpful to have the individual swallow some water to monitor for any signs of coughing or gurgling speech.

The spinal accessory nerve (Cranial nerve XI): As part of the evaluation, an individual is asked to shrug their shoulders and turn their head to the side, even if they may resist.

The hypoglossal nerve (Cranial nerve XII): During the assessment, the tongue is examined in its relaxed position within the mouth.

Motor Exam: One way to determine if a muscle or joint is injured or diseased is to measure its range of motion (ROM). As a measure of strength and pain, an active range of motion can help pinpoint the source of limited mobility. The evaluation of muscular strength was completed lastly. A cortical lesion (hemiplegia from a stroke), a spinal cord lesion (presence of dermatomal level), a brainstem lesion (crossed deficits from Multiple sclerosis plaques), a peripheral nerve lesion (neuropathy or radiculopathy), or a muscular disease (myasthenia gravis) can be distinguished based on the location of the weakness in relation to other neurologic deficits.

Sensory Exam: entails evaluating the symptoms that the individual has reported, which may include a reduced or exaggerated impression of feeling. A sterile pin was used to evaluate the sense of pain, and it was tested to see whether it was sharp or dull. A tuning fork could be utilized to evaluate vibration sense. The evaluation of light touch could be performed using a piece of cotton, and the evaluation of position sense could be carried out by testing the distal phalanx and soliciting the patient's opinion regarding the position of the digit. In contrast, the patient's eyes are closed.

Gait: Gait assessment includes evaluating posture, the length of steps, equilibrium, and the initial contact with the heel. To further assess balance and strength, the patient can be instructed to walk on tiptoes or heels or walk in tandem.

Deep Tendon Reflexes: Deep tendon reflexes can be evaluated by striking a particular tendon with a reflex hammer and observing for a subsequent muscular contraction. A diminished deep tendon reflex typically indicates a lower motor neuron injury, which includes radiculopathy but can also be observed in cases of spinal shock. Conversely, the existence of hyperreflexia and clonus indicates an upper motor neuron injury.

Visual evoked potential: The VEP test measures the electrical activity in the brain. During this test, the patient was shown high-contrast patterns that flash and alternate. While this happened, the patient had electrodes attached to the scalp. Using the electrodes, a computer measures the timing of the flashing patterns as well as the timing of the electrical activity in the brain. We used these measurements to figure out how long it takes for the flashing lights to turn into electrical impulses in the retinas and then travel down the optic nerves. If the patient has MS, the immune system attacks the myelin sheath that insulates the neurons. This is called demyelination. If the myelin along the optic nerves is damaged, a VEP test is to find the delay called latency between when you're shown a pattern and when the signal reaches the back of the brain.

Administrative and Ethical Design: Official authorization was acquired from the Faculty of Medicine at Al-Azhar University. Authorization was acquired from the Neuro-Psychiatry Department at Al-Azhar University hospitals. During the enrollment process, the patients or their families were required to provide written informed consent. Obtain approval from the Institutional Review Board (IRB) of the faculty of medicine's ethical committee.

3. Results

Table 1. Demographic data

	VALUE
AGE (YEARS)	31.7±7.61
BMI (KG/M2)	25.8±5.9
SEX	
FEMALE	70
MALE	30

Mean age in studied patients was 31.7±7.61. Mean BMI in studied patients was 25.8±5.9. 70 patients were females while 30 patients were male. Data showed no significant change among groups. (Table 1)

Table 2. NLR in line with disease activity

	BEFORE STEROID THERAPY	1 MONTH AFTER STEROID THERAPY	P VALUE
NLR (MEAN±SD)	3.17±0.85	1.87±0.41	<0.01

Mean Neutrophil-lymphocyte ratio was 3.17±0.85 and 1.87±0.41 in patients before and after steroid therapy respectively. Data showed significant variance amongst groups in NLR. (Table 2)

Table 3. NLR according to type

TYPE	N	%	NLR	P VALUE
NEWLY DIAGNOSED	40	40%	2.96±0.65	NP
RELAPSING REMITTENT MULTIPLE SCLEROSIS	80	80%	3.29±0.87	
SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS	8	8%	3.19±0.75	>0.05
PRIMARY PROGRESSIVE MULTIPLE SCLEROSIS	12	12%	2.89±0.94	

Among all diseased patients, all patients had active disease (100%), 40 patients were newly diagnosed. 80 patients had RRMS. 8 patients had SPMS. 12 patients had primary progressive multiple sclerosis. Mean Neutrophil/Lymphocyte Ratio was 3.29±0.87 and 3.19±0.75 and 2.89±0.94 in relapsing remittent multiple sclerosis, SPMS and PPMS groups respectively. Data displayed no significant alteration. (Table 3)

Table 4. Correlation amongst MS activity & other parameters

CORRELATIONS		MS activity
AGE	r	0.125
	P	0.155
BMI	r	0.298
	P	0.12
ESR	r	0.160
	P	0.0554
CRP	r	0.220
	P	0.121
NLR	r	0.720**
	P	<0.0001
AGE OF DISEASE ONSET	r	0.34
	P	0.88
DISEASE DURATION	r	0.54
	P	0.56
SEX MALE	r	0.87
	P	0.76

P value< 0.05 is significant, P value< 0.01 is

highly significant

There was significant positive connection amongst Multiple sclerosis activity & NLR, however there were no significant relationship with age, sex, BMI, disease duration, Age of disease onset, CRP & ESR. (Table 4)

Table 5. Correlation among Neutrophil/Lymphocyte Ratio & other parameters

CORRELATIONS

		NLR
AGE	r	0.23
	P	0.25
BMI	r	0.318
	P	0.152
MALE SEX	r	0.1
	P	0.54
CRP	r	0.74
	P	0.042
AGE OF DISEASE ONSET	r	0.28**
	P	0.76
DISEASE DURATION	r	0.234
	P	0.07
CURRENT MS MEDICATION	r	-0.43
	P	0.76
RELAPSING REMITTENT MULTIPLE SCLEROSIS	r	0.87
	P	0.034
SPMS	r	0.88
	P	0.035
PPMS	r	0.78
	P	0.04
REMISSION	r	-0.98
	P	0.043

There was significant positive relationship amongst Neutrophil/Lymphocyte Ratio & CRP, SPMS, RRMS, as well as primary progressive multiple sclerosis. (Table 5)

Table 6. Correlation between NLR and EDSS

CORRELATIONS

		NLR
EDSS	r	-0.68
	P	0.003

There was significant negative connection among NLR & EDSS or remission patients. (Table 6)

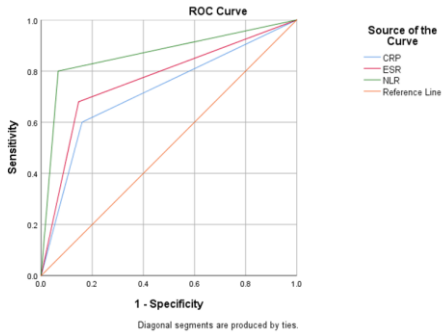

Figure 1. ROC curve

Neutrophil/Lymphocyte Ratio presented 67% sensitivity in addition 82 percent specificity. CRP showed 58 percent sensitivity in addition to 70% specificity. ESR exposed 62 percent sensitivity & 65 percent specificity. (Figure 1)

4. Discussion

Our results showed that the mean age in the participating cases was 31.7±7.61. The mean BMI in the studied patients was 25.8±5.9. Seventy cases were females, while thirty patients were male. The data showed no significant change amongst groups.

In concordance with the current trial, Fahmi et al. presented that MS persons were 97 (69.3%) female and 43 (30.7%) males with female to male ratio of 2.26:1, their age varied from 18 to 51 years with a mean age (±SD) of 31.82 (+ or -7.36) years. The controls involved 97 women and 43 males with a mean age of 33.05 (±7.46) years. There were no significant variances regarding demographic data.[4]

The current trial also revealed that the mean Neutrophil-lymphocyte ratio was 3.17±0.85 and 1.87±0.41 in cases before and after steroid therapy, respectively, with statistical change. The above outcomes suggested that both CRP and Neutrophil/Lymphocyte Ratio can be used to monitor treatment response in Multiple sclerosis.

In line with the current study, Hasselbalch et al. reported that steroid medication has an impact on the number of white blood cells, namely causing an increase in neutrophil count, which in turn alters the neutrophil-to-lymphocyte ratio.[9]

The Neutrophil/Lymphocyte Ratio has a well-established short-term response to both endogenous and exogenous corticosteroids among MS patients.[10]

In the current study, all patients had active disease (100%), and 40 patients were newly diagnosed. 80 patients had RRMS. 8 patients had SPMS. 12 patients had primary progressive multiple sclerosis. Mean NLR was 3.29±0.87 and 3.19±0.75 2.89±0.94 in relapsing remittent multiple sclerosis, SPMS, and PPMS groups, respectively. Data showed no significant alteration.

In line with the current trial, Vivchar et al. initiated no variance in the Neutrophil/Lymphocyte Ratio originated amongst relapsing remittent multiple sclerosis progressive MS patients and neither among SPMS and primary progressive multiple sclerosis patients.[11]

Concerning the correlation between Multiple sclerosis activity and other parameters, the current study revealed that there was a significant positive correlation between MS activity and NLR. However, there were no significant associations with age, BMI, sex, Age of disease onset, CRP, disease duration, and ESR.

In agreement with our results, Fahmi et al. showed that Neutrophil/Lymphocyte Ratio was elevated in Multiple sclerosis cases with disease activity (3.21±0.87) than in those with no activity (2.41±0.65) & this was significant (t=6.19;

P<0.001). Multivariable analysis showed that NLR was an independently significant factor related to activity. However, contrary to the current research, ESR & CRP were increased in MS cases with disease activity (21.96±10.23 & 6.06±3.62 respectively) than in those without activity (17.46±10.85 & 4.79±3.28 respectively) as well as this was significant (t=2.46; P=0.015 & t=2.07; P=0.04 respectively).[4]

Also, consistent with the present trial, D'Amico et al. revealed that there was a significant relation between the Neutrophil/Lymphocyte Ratio value and multiple sclerosis disease activity (p = 0.013).[5]

Regarding the relationship between Neutrophil/Lymphocyte Ratio and other parameters, it was revealed that there was a significant positive relationship between NLR and CRP, RRMS, SPMS and PPMS. There was a significant negative link between the Neutrophil/Lymphocyte Ratio and EDSS or remission persons.

Giovannoni et al. This indicates that the presence of systemic inflammation may lead to disability only after a prolonged period of multiple sclerosis illness; in addition, this might explain the association between the neutrophil/lymphocyte ratio and multiple sclerosis disability. This explains the negative correlation between NLR and EDSS among our patients.[12]

As well, Demirci et al. showed that increased Neutrophil/Lymphocyte Ratio was correlated with relapses or disabilities in MS.[13]

Also, Guzel et al. Discovered an association between NLR and the Expanded Disability Status Scale.[14]

A receiver operating characteristics curve analysis was performed to assess the accuracy of the Neutrophil/Lymphocyte Ratio compared to traditional inflammatory markers (ESR and CRP) in predicting multiple sclerosis disability and activity. The study revealed that Neutrophil/Lymphocyte Ratio showed 67% sensitivity and 82 % specificity. CRP showed 58% sensitivity and 70% specificity. ESR showed 62% sensitivity and 65 % specificity.

The above results showed that the Neutrophil/Lymphocyte Ratio was more reliable and accurate than traditional inflammatory markers (ESR and CRP) in assessing MS disability and activity.

The superiority of NLR over ESR and CRP was confirmed by Fahmi et al., who demonstrated that a Neutrophil/Lymphocyte Ratio cutoff value of 3.12 effectively differentiated MS impairment, with a sensitivity of 63.89% and a specificity of 80.77%. A Neutrophil/Lymphocyte Ratio threshold value of 3.12 was found to effectively differentiate Multiple sclerosis activity, with a sensitivity of 61.54% and a specificity of 87.50%. The area under the curve (AUC) for the Neutrophil/Lymphocyte Ratio as a measure of disability was 0.737 (95% confidence interval [CI]: 0.656-0.808), which was substantially greater than the AUC for CRP (0.545; CI: 0.459-0.630; p-value: 0.012) and ESR (0.595; CI: 0.509-0.677; p-value: 0.027). The area under the curve (AUC) for the neutrophil-to-lymphocyte ratio as a measure of activity was 0.767 (95% confidence interval: 0.688-0.834), which was substantially greater than that of C-reactive protein (AUC: 0.600; CI: 0.514-0.682; p: 0.019) & erythrocyte sedimentation rate (AUC: 0.617; CI: 0.532-0.698; p: 0.017).[4]

4. Conclusion

The Neutrophil/Lymphocyte Ratio exhibited a substantial correlation with the disability and activity levels of Multiple Sclerosis. Our findings indicate that NLR could be employed as a straightforward, quick, and cost-effective indicator of inflammation in relation to disability and activity in multiple sclerosis. The findings from our research, as well as other studies, indicate that an increased Neutrophil/Lymphocyte Ratio is linked to multiple sclerosis. Consequently, exploring the involvement of neutrophils in Multiple sclerosis patients could offer fresh perspectives on the development of MS.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

Funding

No Funds : Yes

Conflicts of interest

There are no conflicts of interest.

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