



ORIGINAL ARTICLE

The Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio can be Considered as Valuable Markers of Disease Activity in Ankylosing Spondylitis

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ABSTRACT

Background: There is role of the platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) as laboratory biomarkers that detect the presence and activity of different diseases. Measuring the PLR and NLR levels as possible indicators of activity status among ankylosing spondylitis (AS) patients was the main goal of the current study. **Methods:** This study included 86 subjects divided into 43 AS patients and 43 apparently healthy volunteers serving as controls. For assessment of disease activity among AS patients we used the Bath AS Disease Activity Index (BASDAI), by which the studied AS patients were split to the following groups based on their level of activity; one group considered as inactive group (BASDAI < 4) and the second group considered as active group (BASDAI ≥ 4), laboratory data were collected from studied participants as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complete blood count including white blood cell count, neutrophil, lymphocyte and platelet counts. **Results:** PLR and NLR ratios were not significantly differ between AS patients and healthy control group as (P > 0.05), however both PLR and NLR ratios were significantly differ between inactive (BASDAI < 4) and active (BASDAI ≥ 4) studied AS patients (P<0.05). BASDAI score was significantly correlated with PLR, NLR, CRP and ESR among AS patients. **Conclusion:** PLR and NLR ratios are both useful indicators for determining and tracking disease activity among AS patients.

Keywords: Activity,NLR, PLR, Ankylosing Spondylitis.

INTRODUCTION

Ankylosing spondylitis (AS) is known to be a chronic systemic autoimmune seronegative disorder, that affects mainly the axial skeleton and sacroiliac joints, leaving

patients with functional disabilities [1]. One of the most reliable tools for assessing activity status of the disease among AS patients is the Bath AS Disease Activity Index (BASDAI) which is based on subjective

assessment and considered as a gold standard for measuring disease activity status among AS patients[2]. Numerous objective indicators used in assessing activity of the disease in AS, including CRP, ESR, different immunoglobulins as IgM, IgA and IgG, complements as C3 and C4, serum amyloid A and interferon-gamma IF γ [3].

The immune system components including neutrophil, lymphocyte, and platelet, which are measured as part of a routine complete blood test for the monitoring of rheumatological diseases, have been found to be linked to autoimmune disorders, cancer, inflammatory disorders and chronic illnesses[4].

The neutrophilic count and the platelet count, which are obtained from complete blood measuring test (CBC), are expressed as ratios, platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) representing ratios of absolute platelet count and neutrophilic count, respectively, to the lymphocytic count [4]. Elevated values of both ratios denote increased inflammation level[5].

It was proven that in several diseases involving systemic illness or local inflammatory reactions, like, familial Mediterranean fever (FMF), inflammatory arthritis, ulcerative colitis, coronary artery disease and cancers. The NLR has a

diagnostic value as its levels were higher among diseases patients in comparison to controls and might be also increased with disease activity status[6,7].

Only around 60% of Active AS patients have high CRP or ESR values, both ESR and CRP, are common laboratory biomarkers of an acute phase reaction, but there may be some discrepancies between them and the clinical manifestation or the radiological image. This makes the measurement of activity status of the disease and therapy responses in AS difficult and more complex. It is critical to discover a novel diagnostic marker to identify activity of the disease [8].

The recently used tool is NLR and PLR which are easily accessible, straightforward, and reasonably priced tools that could evaluate AS activity. Our study objectives are to assess the variations in PLR and NLR in AS patient group and controls, as well as the reasonability of the PLR and NLR in distinguishing patients with active disease from inactive patients.

METHODS

We conducted a case control study that was carried out in the Rheumatology, Rehabilitation and Physical Medicine Department Zagazig university Hospitals between 2021 and 2023. The total participants were 86 (divided into 2 equal groups, 43 patients in the AS group and 43 sex and age matched apparently healthy control group).

AS patients had been diagnosed by Modified New York Criteria [9]. Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Demographic data among AS patients group and other data as: duration of the disease, clinical symptoms (articular and other system manifestations), in addition to laboratory and inflammatory biomarkers like (ESR), (CRP) were noted. After receiving the patients' laboratory data, we manually computed both PLR and NLR ratios for each studied participant.

To measure the activity status among studied AS participants; the BATH AS Disease Activity Index (BASDAI) was used. A pair of groups were created for the patients based on their BASDAI scores. Patients with BASDAI scores equal 4 or higher were considered to have active disease, while those with scores of less than 4 were regarded to have mild activity status or considered as inactive [10].

Regarding the BASDAI, it is a composite index with a numeric range from (0), which indicates no symptoms, to (10), which indicates the worst symptoms. It is a

questionnaire that asks about fatigue, back discomfort, tenderness in joints and entheses across the body and severity and length of morning stiffness. The BASDAI scale has a cut-off value of 4, and scores that are equal to or higher than that number signify that the disease is more active and the patient has more severe symptoms [11].

Statistical analysis was done by the Statistical Package for Social Sciences (SPSS) computer software for Windows version 20. For continuous variables, the descriptive data were presented as mean and standard deviation (SD), while categorical variables were shown in the form of frequencies and proportions from total number (%). When data had normal distribution, a student's t-test was applied to compare means of the continuous data and Mann-Whitney test was employed if the data were skewed after applying Shapiro-Wilk test. Associations of PLR, NLR, and BASDAI scores were examined using the Pearson's correlation test. The PLR and NLR's ability to distinguish between AS patients and controls as well as patients having active disease and inactive or mild disease activity patients was assessed using a Receiver Operating Characteristic (ROC) curve. The Area Under the Curve (AUC) values obtained by ROC analysis between 0.9 and 0.99 classified as excellent, 0.8 and 0.89 classified as good test, 0.7 and 0.79 classified as fair test, 0.51 to 0.69

classified as poor test. P value greater than 0.5 is of no significance while equal 0.05 or lower was considered as significant [12].

RESULTS

Eighty-six studied participants in total were separated into two equal groups for the current study. The 43 AS patients ages in Group I (AS group) ranged from 19 up to 48 years, with a mean age 31.2 years 7.2 SD. Their disease duration started from 2 up to 12 years, with a mean of 5.9 years 2.7 SD. Thirty of them were males (69.8%) and thirteen were females (30.2%). Group II (Control group): consisting of 43 seemingly healthy volunteers, 28 of whom were males (65.1%) and 15 of whom were females (34.9%), their ages ranged from 19 to 59 years, with mean age 30.6 years 8.54 SD.

Table 1 show that the range of BASDAI scores among AS patients was 1 to 9 with a median score of 5. With a BASDAI score of 4, 13 of the 43 AS patients were assorted as having minimal or no disease activity, whereas the remaining 30 patients were assorted as active patients. When the two groups' ESR and CRP levels were compared, there was statistically significant difference ($P > 0.001$) between them. ESR and CRP values in ankylosing spondylitis patients were substantially more than in the controls. Patients with ankylosing spondylitis had NLR values ranging from 0.95 to 5.24, with a median of 1.67. In contrast, the NLR value for

the control group ranged from 0.9 to 4.89 with a median of 1.18; this difference was considered as not statistically significant ($P=0.07$).

The variation in PLR value between ankylosing spondylitis patients and healthy controls was also considered as not statistically significant ($P = 0.09$). Otherwise, as in (Figures 1 and 2), it was reported a statistically significant difference between patients with active disease status and inactive ankylosing spondylitis as regards PLR and NLR values (1.89 ± 0.23 vs. 2.29 ± 0.4 , $p = 0.003$) and (115.12 ± 25.11 vs. 149.09 ± 34 , $p < 0.001$, respectively).

Table 2 show the correlations studies between the BASDAI and various laboratory results in AS patients found positive statistically significant correlation with ESR ($r = 0.5$ _ $p=0.001$), CRP ($r = 0.6$ _ $p=0.02$), NLR ($r = 0.3$, $p=0.03$), and PLR ($r= 0.31$, $P = 0.04$) values in determining disease activity, which highlighting the adding role of both PLR and NLR values as markers in assessing disease activity status.

ROC curve was applied to discriminate between patients having activity and inactive patients by NLR and PLR value. NLR at cut-off point ≥ 1.89 shows 55.17% sensitivity and 93.33% specificity with AUC 0.8, while PLR shows 71.21% sensitivity and 67.69% specificity at cut-off point ≥ 104 , with AUC 0.73 (Figure 4).

Table 1: Demographic and laboratory data among studied groups.

	AS Group (n=43)	Control group (n=43)	P-value
Age (years)			
<i>Mean±SD</i>	31.2±7.2	30.6±8.54	0.5
<i>Range</i>	(19-48)	(19-59)	
Sex N. %			
Males	23 (53.5%)	25 (58.1%)	0.3
Females	20 (46.5%)	18 (41.9%)	
ESR (mm/hr)			
<i>Mean ± SD</i>	40.3±19.4	10.9±2.9	<0.001
CRP (mg/l)			
<i>Mean ± SD</i>	11.5±7.13	5.2±0.8	<0.001
NLR			
<i>Median (range)</i>	1.67 (0.95-5.24)	1.18 (0.9-4.89)	0.07
PLR			
<i>Median (range)</i>	119.4 (72-392.3)	105 (60.2-355)	0.09
BASDAI:			
<i>Median (range)</i>	5 (1-9)	-	-

Table 2: Correlation between BASDAI, and laboratory parameters in ankylosing spondylitis patients.

Variable	BASDAI	
	r	P
ESR	0.52	<0.001
CRP	0.61	0.02
NLR	0.34	0.03
PLR	0.31	0.04

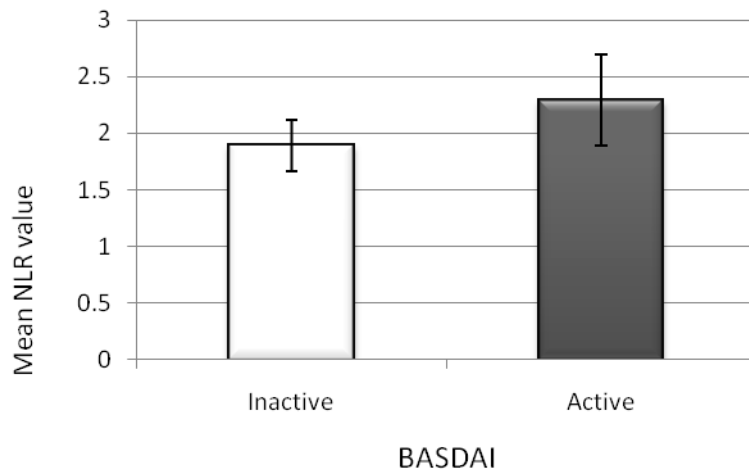


Figure 1: NLR values in active and inactive ankylosing spondylitis patients

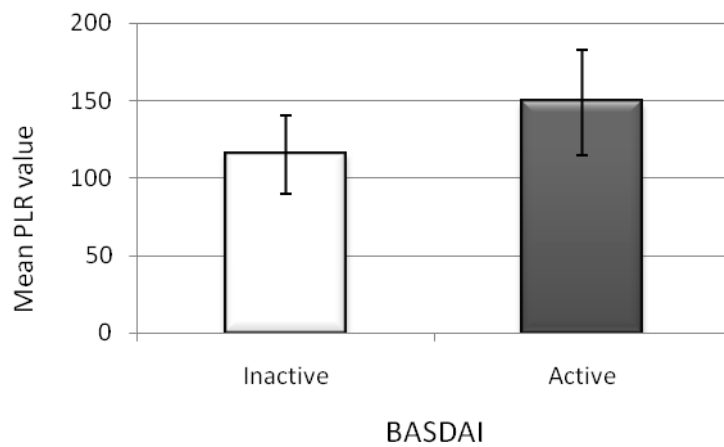


Figure 2: PLR values in active and inactive ankylosing spondylitis patients

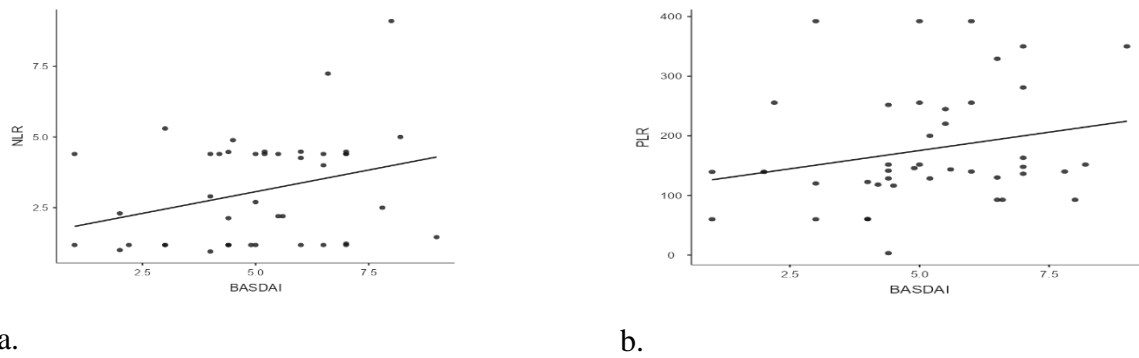


Figure 3: Correlation between BASDAI score and (a.) NLR and (b.) PLR.

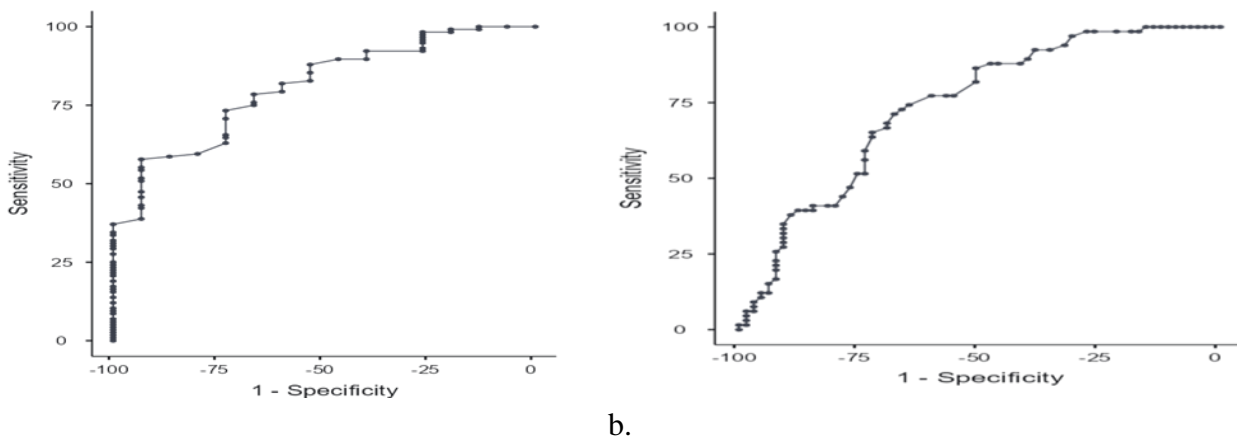


Figure 4: ROC curve analysis of (a.) NLR and (b.) PLR to discriminate between active and inactive AS patients.

DISCUSSION

Patients with AS may complain of extra-articular symptoms such as enthesitis and uveitis as well as peripheral or axial joint involvements. Due to the disparities in clinical presentations, assessment of disease activity is difficult. For this issue, there is no impartial gold standard yet [13]. There is no known specific pathophysiology for AS, nevertheless, the development of new bone and inflammation are considered as the two

key elements that must be held responsible. T lymphocytes and macrophages cells are the most prominent cells at the inflammation sites [14].

Previously, there were modest but significant connections between AS disease activity and ESR and CRP [5]. However, in a variety of chronic inflammatory diseases, NLR has been proposed as a marker to measure the severity and activity of the systemic diseases [15]. The relation between the severity of the AS

disease and NLR is yet unclear. Another impartial metric that doesn't cost the patients any more money is NLR. By dividing the platelet and neutrophil counts by the number of lymphocytes, respectively, one may quickly calculate PLR and NLR. Full blood counts are a standard, inexpensive test. According to certain research, PLR and NLR are regarded to be effective markers and can be used to measure the disease activity status in patients with SLE [16,17]. NLR can be used as an indicator of the disease activity and infection differentiation among patients with SLE [18].

It was proven that PLR and NLR are associated with active disease status among RA patients and NLR aids in early detection of RA [19,20]. A study by Mercan et al. showed that high NLR ratios among RA and AS patients was associated with highly active diseases [21].

The demographic data showed no associated differences statistically between the two studied groups AS and controls, proving that the patients and controls were well matched and reducing the impact of potential confounding factors. On comparing patients with high disease activity status, inactive disease and healthy controls, we have found that AS patients having active disease had considerably higher levels of NLR and PLR ratios. These findings corroborated another research for Sen et al. & Gunay et al. [22,23].

This study demonstrated a strong association between AS patients' ESR and CRP readings and disease activity.

When compared to patients with higher scores of BASDAI, the NLR and PLR levels were noticeably high. Al-Osami et al. findings, which compared the PLR, NLR and ESR among AS group, were in agreement with these findings. Additionally, they note that there was significant difference in the PLR, NLR and ESR between the two studied groups of AS patients (BASDAI ≥ 4 vs. BASDAI < 4), there was significant difference in the NLR, PLR and ESR ($p = 0.001$, $p < 0.001$, $p < 0.001$, respectively) [24]. Another study by Kucuk et al. who found that individuals with severe disease activity had NLRs that was considerably higher than those with mild activity status (2.72 ± 1.41 , 2.20 ± 1.19 ; respectively; $p = 0.001$) [13]. The PLR and NLR, however, did not statistically differ significantly between the studied controls and AS patients, although the ESR and CRP were significantly greater in AS patient in comparison to controls.

Although the etiology of AS is unclear, both lymphocytes and neutrophils may have a participation in its pathogenesis [26]. A number of earlier studies that compared AS patients with controls found no appreciable difference in the NLR and got equivalent results for the PLR [24,21]. These results were disagreed with the results of other studies regarding the NLR ratio done by Zhu et al. and Zeb et al. [27,28] and one study regarding

the PLR by Song & Lee, they reported a statistically significant higher levels of PLR and NLR among AS patients in comparison to controls [29]. This may be due to the patients included in these studies only with active AS disease or newly diagnosed who had not received any prior treatment.

The current study demonstrated that BASDAI with ESR and CRP were significantly correlated ($r=0.5$, $P < 0.001$ and $r=0.6$, $p=0.02$), respectively in the studied AS patients. In addition, NLR was demonstrated to have a weak but significant correlation ($r=0.34$, $p=0.03$) with the BASDAI scores of AS patients in this study, which is comparable to another study performed by Inal et al. that found weak but significant correlations ($r: 0.256$, $P:0.009$) between NLR and BASDAI score. [25].

These findings suggest that NLR might be a criterion to evaluate activity of the disease. PLR and NLR might be used by clinicians to measure activity in AS disease since they are straightforward, objective measurements that are simple, already available and do not incur any extra costs.

PLR and NLR ratios are influenced by platelet count and neutrophil count separately. While the acute phase reactant response, stress and acute inflammation cause an increase in neutrophil and platelet counts and physiological stress causes the number of lymphocytes to decrease. This offers an explanation for the higher NLR and PLR

ratios, which rise with increasing activity of the disease. Furthermore, to maintain the neutrophil regulation requires IL-23 and IL-17, which are important cytokines in the development of AS [30].

In the current study, it was conducted by ROC analysis that NLR had significant validity to discriminate inactive and active patients, as at NLR cut off point ≥ 1.89 it shows sensitivity 55.2% and specificity 93.3%. The AUC of NLR was 0.8. PLR also proved validity for discrimination between inactive and active AS patients at cut off ≥ 104 , with AUC 0.73, sensitivity 71.2% and specificity 67.7%.

Another study by Elfitouri, assessed the accuracy of PLR and NLR in identifying patients having active versus inactive AS disease status. They reported NLR at cutoff point 1.78 had sensitivity 75% and specificity 91.1% with AUC 0.67, while PLR at cut-off point 113.6 had sensitivity and specificity of 61.1% and 72.2% with AUC 0.65. [31]. Al-Osami et al. establish that a sensitivity 70.9% and specificity 65.5% for the optimal PLR cutoff level were 95.9. With sensitivity 61.8% and specificity 90.6%, optimal NLR cutoff value for identifying patients had AS with considerable high activity status was 1.66. [24].

Limitation of the study: the small sample size was considered as a possible limitation of our study. Additionally, we did not elicit the results of the study from a single center to a larger population, and the therapy's effect on the PLR and NLR ratios was not assessed.

CONCLUSIONS

Significant correlations between PLR and NLR were found among active AS patients that differentiate active from inactive disease. However, no significant correlation of these ratios between control group and diseased AS group. The ESR, CRP, PLR, and NLR have been demonstrated to be a reliable test that discriminate between active disease and inactive AS. Additional studies should be conducted by a greater number of participants and patients had longer durations of follow-up should be planned in order to corroborate our findings.

Declaration of interest

The authors report no conflicts of interest.

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