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Associations of Neutrophil/lymphocyte ratio with disease activity indices in patients with ankylosing spondylitis

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Abstract

Background:Axial spondyloarthritis (axSpA) is a painful, inflammatory condition of the spine that usually manifests in young individuals with chronic back pain (less than 45 years of age). It may also be accompanied by extra-articular or periarticular (enthesitis, dactylitis) symptoms (uveitis, psoriasis, inflammatory bowel disease). AxSpA encompasses both ankylosing spondylitis (AS) with radiographic evidence of sacroiliitis and axSpA without radiographic evidence of sacroiliitis.Objective:to assess neutrophil/lymphocyte ratio (NLR) among AS patients and to evaluate its relation to disease activity. Methodology: The present investigation included thirty AS patients and thirty healthy controls. Disease Bath Ankylosing Spondylitis Disease Activity indicators were utilized to assess the disease activity of AS (BASDAI). Analyses were conducted on the relationship between NLR and disease activity.Results:There was a significant positive correlation between NLR and Duration of the disease (r=0.421, P=0.020), ESR (r=0.433, P=0.014), CRP (r=0.700, P< 0.001), BASDAI (r=0.433, P=0.017).There was an insignificant correlation between NLR and age. NLR had increased considerably among AS patients compared to controls (P-value <0.05).NLR can significantly predict AS disease activity (P-value <0.001, at cut off value ≥2.03 with 90% sensitivity, 88.89 % specificity, 94.7% PPV and 80% NPV).Conclusion:In conjunction with acute phase reactants, NLR might be a valuable marker for indicating inflammation.

Keywords: A.S, BASDAI, NLR.

1. Introduction

Axial spondyloarthritis (axSpA) is a painful, inflammatory condition of the spine that frequently shows as chronic back pain in those less than 45 years old. It may also be accompanied by periarticular/extraspinal (enthesitis, dactylitis) or extra-articular symptoms (uveitis, psoriasis, inflammatory bowel disease). AxSpA includes ankylosing spondylitis (AS) with radiographic evidence of sacroiliitis as well as axSpA without definite radiographic evidence of sacroiliitis **[1].** Genetic predisposition and intestinal dysbiosis lead to IL-17-mediated inflammation causing simultaneous bone erosions and bone formation resulting in the classic “bamboo spine.” In order to prevent persistent pain and impairment, the primary care physician plays a crucial role in identifying patients with inflammatory back pain early on **[2]**. AS is marked by low back pain and stiffness after lengthy periods of inactivity (inflammatory back pain). The insidious development of a common symptom such as low back pain, along with the gradual radiographic course of the illness, is projected to result in a diagnostic delay of five to ten years from the beginning of the initial symptoms **[3]**. The neutrophil/ lymphocyte ratio (NLR) has a diagnostic value in certain conditions with systemic or local inflammatory responses such as diabetes mellitus, coronary artery disease, ulcerative colitis, inflammatory arthritis, familial Mediterranean fever (FMF) and different malignancies **[4].** NLR has been linked to a variety of inflammatory disorders. Kaya et al. found that NLR is a sign of severe atherosclerosis and asserted that NLR is a valuable diagnostic tool for cardiac risk assessment **[5].** NLR has been shown to be related with coronary atherosclerosis, and it is characterized as an independent predictor in addition to CRP for predicting poorer hospital outcomes following myocardial infarction and failed first percutaneous coronary intervention **[6].** Duffy et al. discovered a correlation between NLR and long-term mortality in percutaneous coronary procedures patients. This relationship between systemic illness and its repercussions has been described **[7].** Furthermore, NLR has been found be an indicator for subclinical inflammation, and its association with prognosis is reported in CAD and cardiac failure **[8].** NLR is an independent risk factor for long-term mortality, as evidenced by MI with or without ST-elevation **[9].**

Lymphocytes are one of the most important cellular immune. Theyare playinga crucial role in the pathogenesis, progression and prognosis of AS through releasing inflammatory agents **[10].** Neutrophils, more than 50% of which are produced by bone marrow, are at the front line of the defense system. They are responsible for the production of many lytic enzymes, free oxygen radicals, and cytokines **[11].** The relation between higher levels of NLR and systemic inflammation is not clear yet. Systemic inflammation has deleterious effects on vascular endothelial cells through decreased production

of nitric oxide and prostacyclin, which causes decreased vasodilation and anti-thrombosis. Also, stimulated leukocytes have increased adherence to the vascular endothelium **[12].** Cytokines, like PDGF,IL-1ra, IL-6, IL-7, IL-8 and IL-12play a considerable role in inflammation and may have an effect on increased NLR **[13]** NLR indicate the proportions of absolute neutrophil count to the lymphocyte count and are derived from a routine CBC test.They are readily available, simple, and inexpensive tools **[14].** Elevated values of the NLR denote increased inflammation **[15].** Some studies have suggested that neutrophils and lymphocytes may had a role in AS pathogenesis **[16-17].**

The connection between AS and NLR has not yet been studied. In this study, we intended to determine if NLR has a role in predicting inflammation in AS patients, as well as its connection with BASDAI, ESR, and CRP.

2.Subjects and methods

Thirty individuals with ankylosing spondylitis who satisfied the modified New York criteria for the diagnosis of AS were evaluated **[18].** Patients were collected from those attending the Rheumatology, Rehabilitation and Physical medicine department Benha University hospitals and Rheumatology unite / internal medicine department in Kobry El-kobba Military Hospitals.All patients were subjected to complete history taking, Full clinical examination**,** Assessment of disease activity usingThe Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score**[19].**

Laboratory investigations including:Complete blood count (CBC) and the total & differential leucocyte counts will be recorded, The blood neutrophil/lymphocyte ratio (NLR) for each participant was calculated manually by dividing the neutrophil count by the lymphocyte count after obtaining the laboratory results, ESR and CRP titer.

3. Results

This study included 30 ankylosing spondylitis (AS) patients. (A) group of 30 age matched volunteers were also included as a control group (B).

Table (1): Associated comorbidities between the studied groups.

	Group A (N=30)	Group B (N=30)	P value
HTN	7 (23.33%)	5 (16.67%)	0.748
DM	7 (23.33%)	4 (13.33%)	0.506
Hyperlipidemia	7 (23.33%)	4 (13.33%)	0.579

HTN: hypertension, DM: diabetes mellitus, *: significant as P value <0.05. Associated comorbidities were insignificantly different between both studied groups **Table (1).**

Table (2) : Neutrophil and lymphocyte count between the studied groups.

		Group A (N=30)	Group B (N=30)	P value
Neutrophil (cells/mm^3)	**Mean ± SD**	3483.3± 1762.8	2383.5 ± 625.01	0.002*
	Range	589 – 6600	1517 – 3535	
Lymphocyte (cell/ µL)	**Mean ± SD**	2626 ± 925.31	1821 ± 522.36	<0.001*
	Range	971 – 4500	990 – 2591	

Hb: hemoglobin, TLC: total leukocyte count. Regarding the laboratory investigations, neutrophil, lymphocyte, were significantly higher in group A compared to group B (P value <0.05).

Table (3): Comparison between AS patients and the healthy control group regarding NLR.

NLR	**Mean ± SD**	**1.6 ± 1.28**	**0.7 ± 0.21**	<0.001*
	Range	**0.19 - 4.63**	**0.19 - 0.91**	

NLR: Neutrophil to lymphocyte ratio**.** Regarding the NLR there was considerably higher in group A compared to group B (P value <0.05).

Table (4): Diagnostic performance of NLR for prediction of Ankylosing spondylitis disease activity.

	Cut off	Sensitivity %	Specificity %	PPV	NPV	AUC	P value
NLR	≥2.03	90	88.89	94.7	80	0.942	**<0.001***

NLR: Neutrophil to lymphocyte ratio, NPV: negative predictive value,PPV: positive predictive value, CI: confidence interval,AUC: area under the curve, *: significant as P value <0.05.

NLR can significantly predict the AS disease activity with 0.942 and P value <0.001, at cut off value ≥2.03 with 90% sensitivity, 88.89 % specificity, 94.7% PPV and 80% NPV.

Table (5): Correlation between NLR and demographics and clinical presentation in the studied patients.

	NLR	
	R	**P**
Age (years)	0.240	0.202
Duration of the disease	0.421	0.020*

NLR: Neutrophil to lymphocyte ratio*: statistically significant as P value <0.05.

There was a significant positive correlation between NLR and Duration of the disease (r=0.421, P=0.020).

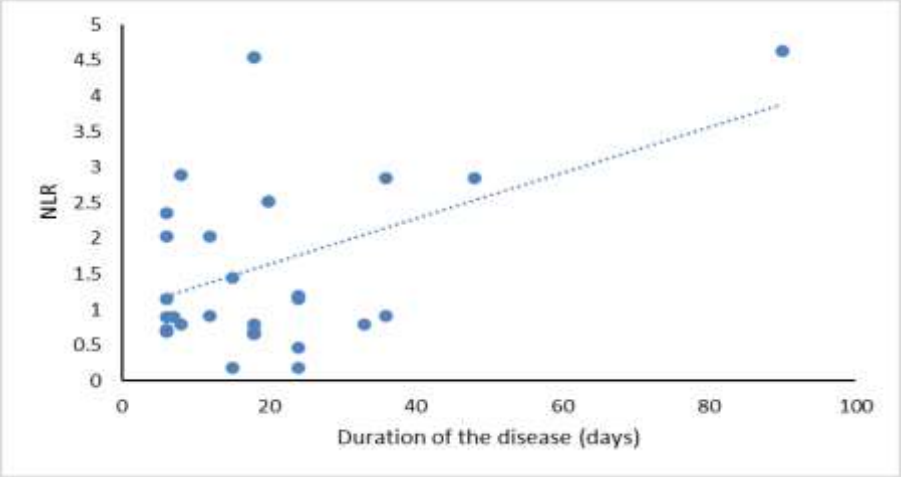

Fig (1): A significant positive correlation between NLR and duration of disease.

Table (6) Correlation between NLR and inflammatory markers in the studied patients.

	NLR	
	R	**P**
ESR	0.433	0.014*
CRP	0.700	<0.001*

ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, NLR: Neutrophil to lymphocyte ratio, *: statistically significant as P value <0.05.

There was a significant positive correlation between NLR and ESR (r=0.433, P=0.014), CRP (r=0.700, P< 0.001). There was an insignificant correlation between NLR and age

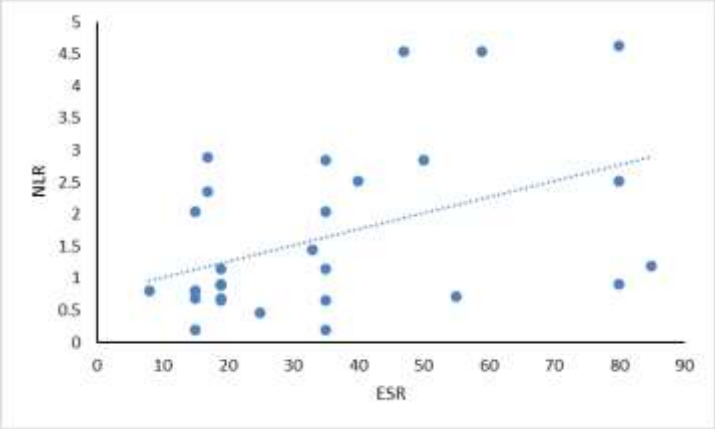

Fig (2): A significant positive correlation between NLR and ESR.

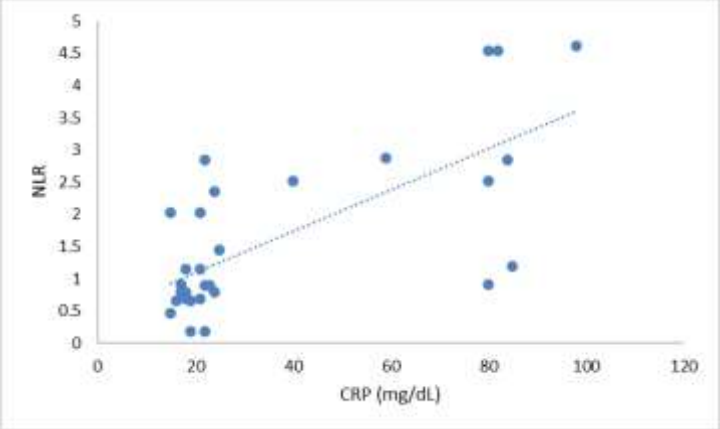

Fig (3): A significant positive correlation between NLR and CRP

4. Discussion

axSpA is a chronic inflammatory disease of the spine that manifests as persistent back pain in those younger than 45. It may also be accompanied by extra-articular or periarticular (enthesitis, dactylitis) symptoms (uveitis, psoriasis, inflammatory bowel disease). AxSpA encompasses both AS with radiographic evidence of sacroiliitis and axSpA without radiographic evidence of sacroiliitis **[1].** Genetic predisposition and intestinal dysbiosis lead to IL-17-mediated inflammation causing simultaneous bone erosions and bone formation resulting in the classic "bamboo spine." In order to prevent chronic pain and impairment, the primary care physician plays a critical role in the early diagnosis of patients with inflammatory back pain **[2]**. This study aimed to evaluate the relationshipbetween NLR and disease activity parameters among AS patients.Patients were subjected to full medical history, general and musculoskeletal examinations, assessment of disease activity using the BASDAI score, laboratory investigations including, blood NLR. Our study addresses an area of immense importance and practical utility by evaluating the NLR as a biomarker of inflammation in AS.

This study included 30 AS patients. The examined groups showed no statistically significant differences were reported between the studied groups regarding demographic data. According to Comorbidities (HTN, DM and Hyperlipidemia, smoking) there were insignificantly different between both groups.

ESR and CRP are the most widely used markers for measuring acute phase response due to their reliability, reproducibility, and cost effectiveness. Both of these markers correlate closely with clinical disease activity of RA and to a lesser extent with AS **[20].**

NLR has been proposed as a marker for evaluating the systemic inflammatory state in chronic inflammatory diseases. Notwithstanding, a conclusive link between disease activity in AS and NLR has not yet been established. NLR is an objective examination that does not impose any additional costs for patients **[21].**

In the present study, TLC, neutrophil, lymphocyte, were significantly higher in A.S patients compared to healthy control(P value

<0.05). NLR there was significantly higher in A.S patients. NLR can significantly predict the Ankylosing spondylitis disease activity with 0.942 and P value <0.001, at cut off value ≥2.03 with 90% sensitivity, 88.89 % specificity, 94.7% PPV and 80% NPV.There was a significant positive correlation between NLR and Duration of the disease (r=0.421, P=0.020), BASDAI (r=0.433, P=0.017). There was a significant positive correlation between NLR and ESR (r=0.433, P=0.014), CRP (r=0.700, P< 0.001). There was an insignificant correlation between NLR and age.

Leukocyte subtype and NLR are straightforward, basic indicators of systemic inflammation. The NLR has been proposed as a surrogate marker for endothelial dysfunction and inflammation since it is a new, affordable, and routine signal **[22]**. The NLR has been considered an effective biomarker for predicting rheumatic illness. Recent research has utilized the NLR in conjunction with other inflammatory markers to diagnose inflammation in AS. Recent research by Gokmen et al. found an elevated NLR in AS patients and suggested that the NLR may be a valuable indicator of inflammation. Mercan et al. recently revealed that AS patients had a greater NLR than healthy controls **[23-24].**

This study revealed that the NLR is greater in AS patients compared to healthy controls. Our findings correspond to these prior observations. Esra et al. reported weakly positive but statistically significant relationships between BASDAI scores and neutrophil counts, NLR, and moderate correlations with ESR and CRP concentrations **[25]**. The NLR, CRP, and neutrophil counts of disease-active AS patients were considerably greater than those of healthy controls. In this study, similar to previous research, it was shown that ESR and CRP levels showed a significant relationship with the disease activity of AS patients **[24,26]**.

Similar to a recent trial by Gokmen et al., this study found a significant association between NLR and BASDAI scores among AS patients. These results show that NLR may serve as a metric for assessing disease activity in AS **[24].**

The present study has a number of limitations, including a small sample size. The cross-sectional design, which is not the ideal way for examining causal linkages, further constrained the results. This study was unable to identify the pathophysiology of the connection between NLR and disease activity. We were unable to generalize the results to the general population.

5. Conclusion

NLR may be a useful marker for demonstrating inflammation together with acute phase reactants.

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