ORIGINAL ARTICLE

May Neutrophil-Lymphocyte and Platelet-Lymphocyte Ratios Indicate Disease Activity in Ankylosing Spondylitis?

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ABSTRACT

Objectives: This study aims to evaluate the associations between neutrophil-lymphocyte ratio (NLR), mean platelet volume, and platelet-lymphocyte ratio (PLR) with disease activity in ankylosing spondylitis.

Patients and methods: The study included 103 patients (63 males, 40 females; mean age 40.7±12.0 years; range 20 to 70 years) with ankylosing spondylitis and 70 healthy controls (43 males, 27 females; mean age 42.7±15.3 years; range 18 to 66 years). All participants' age, sex, erythrocyte sedimentation rate, C-reactive protein and mean platelet volume levels, total white blood cell, neutrophil, lymphocyte, and platelet counts were recorded while patients' Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index and Bath Ankylosing Spondylitis Metrology Index scores, medication types, duration of disease and medication use were recorded. Patients were divided into three groups: healthy controls (group 1), patients having BASDAI scores <4 with mild disease activity (group 2, n=73), and patients having BASDAI scores ≥4 with moderate-severe disease activity (group 3, n=30). NLR and PLR values were calculated.

Results: Counts of neutrophil, NLR, C-reactive protein levels and PLR were significantly higher in group 3 compared to groups 1 and 2 (p<0.05). BASDAI scores were correlated weakly with neutrophil counts, NLR and PLR, and correlated moderately with C-reactive protein and erythrocyte sedimentation rate (p<0.05).

Conclusion: Our study results indicate that, in ankylosing spondylitis, mean platelet volume is not associated with disease activity, whereas NLR and PLR may reflect disease activity.

Keywords: Ankylosing spondylitis; disease activity; mean platelet volume; neutrophil-lymphocyte ratio; platelet-lymphocyte ratio.

Ankylosing spondylitis (AS) is a chronic inflammatory disease that mainly affects axial skeleton, leading to functional impairment and disability.[1] The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a self-administered subjective questionnaire which is also the gold standard to evaluate disease activity in AS.[2] Beside subjective scales such as Mander and Maastricht Ankylosing Spondylitis Enthesitis Indices,[3] a lot of objective laboratory markers like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulin A, G and M, complements C3 and C4, interferon-gamma,

interleukin-4, alpha-1-antitrypsin, and serum amyloid A were suggested to be used in evaluating disease activity in AS.[4-8]

The pathogenesis of AS is controversial but recent studies have revealed the roles of both neutrophils and lymphocytes.[1,9] Leukocyte count and its subtypes are also well-known inflammatory markers in several diseases.[10,11] Recently, neutrophil-lymphocyte ratio (NLR) has been calculated to evaluate inflammation in various chronic inflammatory diseases such as coronary chronic total occlusion,[10] psoriasis,[11] chronic kidney disease,[12] ulcerative colitis,[13]

gastric cancer,[14] chronic obstructive pulmonary disease,[15] familial Mediterranean fever,[16] and AS.[17] In addition, mean platelet volume (MPV) was reported to have a predictive value of inflammation in chronic obstructive pulmonary disease,[15] inflammatory bowel disease,[18] rheumatoid arthritis (RA) and AS.[19-21] On the other hand, platelet-lymphocyte ratio (PLR) was also suggested to be an inflammatory marker, and shown to be a valuable prognostic marker in several malignancies such as gastric,[14] colon,[22] and non-small cell lung cancers.[23] However, the relationships between NLR, MPV and disease activity in AS have not been fully understood yet and the associations between PLR and disease activity of AS was not investigated before. Therefore, in this study, we aimed to evaluate the associations between NLR, MPV, and PLR with disease activity in AS.

PATIENTS AND METHODS

One hundred and three consecutive patients with AS (63 males, 40 females; mean age 40.7±12.0 years; range 20 to 70 years) and 70 healthy controls (43 males, 27 females; mean age 42.7±15.3 years; range 18 to 66 years) were enrolled in this cross-sectional study after informed consents were obtained from all participants. The study was approved by the local ethics committee. All patients were diagnosed with AS according to the Assessment of Spondyloarthritis International Society classification criteria for spondyloarthritis.[24] The participants who had other inflammatory and infectious diseases, malignancies, cardiovascular diseases, diabetes mellitus, and liver/kidney diseases were excluded from the study.

Age, sex, ESR, CRP, MPV and total white blood cell (WBC), neutrophil, lymphocyte and platelet counts, BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index scores, medication types and, durations of diseases and medications were recorded. Patients were divided into three groups: healthy controls (group 1, n=70), patients having BASDAI scores <4 with mild disease activity (group 2, n=73), and patients having BASDAI scores ≥4 with moderate-severe disease activity (group 3, n=30). NLR and PLR levels were calculated.

Erythrocyte sedimentation rate was measured by spectrophotometric assay (Alifax Test-1 THL, 950 nm, Italy). CRP was determined by turbidimetric method (TOSHIBA ACCUTE/TBA-40FR, Tokyo, Japan). Complete blood count analysis was measured by the method of flow cytometry (LH 780 Analyzer, Beckman Coulter Inc., Brea, CA, USA). ESR normally ranges between 2-8 mm/h for males and 2-20 mm/h for females, and CRP ranges between 0 to 3 mg/dL in both sexes.

The disease activity was assessed by using the Turkish version of BASDAI.[25] BASDAI is a self-administered questionnaire consisting of six questions relating to five major symptoms including fatigue, spinal pain, joint pain/swelling, areas of localized tenderness, and morning stiffness. In each of the five questions, the patients were asked to rate what they felt over the previous week on a 10 cm horizontal visual analog scale. The scale for degree of morning stiffness is graded every 15 minutes for 0-2 hours. The mean of two scores for morning stiffness is calculated. visual analog scale has no distinguishing marks except the word 'easy' and 'impossible' at either ends of the line to indicate the direction of severity. Total BASDAI score is the mean of the total of five scores with higher scores indicating higher disease activity.

Functional status of the patients was evaluated with the Turkish version BASFI.[26] BASFI consists of eight questions on daily activities and two additional questions to assess patients' ability to cope with everyday life. Each question was answered on a 10 cm horizontal visual analog scale reflecting status over previous month. BASFI score is the mean of the total of 10 scores, with higher scores indicating more severe impairment.

The clinical status was evaluated by Bath Ankylosing Spondylitis Metrology Index which was calculated with the measurements of wall to tragus distance, lumbar flexion, cervical rotation, lumbar lateral flexion, and intermalleolar distance.[27] Lateral flexion of lumbar spine was measured bilaterally and the mean of right and left flexion values was accepted as a single value. Each measurement either received 0 (mild disease involvement), 1 (moderate disease involvement), or 2 (severe disease involvement) points. The sum of 5 scores is in between 0 and 10 with higher scores indicating higher disease involvement.

Statistical analysis

Statistical analysis was performed by SPSS version 15.0 software program (SPSS Inc., Chicago, IL, USA). The normality of distribution for continuous variables was tested with Kolmogrov-Smirnov test. Continuous variables were presented as mean ± standard deviations. Categorical variables were shown as frequency and percentages. For the comparisons of parametric data of two groups, Student's t test was used for parametric variables and Mann-Whitney U test was used for non-parametric variables. For the evaluation of categorical variables, Chi-square test and if needed, Fisher's exact test were used. Pearson or Spearman rank correlation test was performed to determine the relationships between continuous variables. Comparisons of parametric data of three groups were performed with one-way ANOVA testing. Levene's test was used to determine homogeneity of variances and in case of homogeneity of variance, post hoc Tukey test was used. All probability values were calculated by assuming a two-sided p value of <0.05.

RESULTS

Demographic features and laboratory findings of the patients and healthy controls were summarized in Table 1. ESR, CRP and counts of WBC and neutrophil were significantly higher in patients compared to healthy controls (p<0.001) whereas there was no significant difference regarding lymphocyte counts, NLR, PLR and MPV levels (p>0.05). Twenty-seven of 40 female patients and 47 of 63 males had higher levels of ESR. Also, 25 of 40 females and 44 of 63 males had higher levels of CRP.

Clinical characteristics of the AS patients according to BASDAI scores and healthy controls were shown in Table 2. Twenty-seven patients were administered disease modifying drugs (sulfasalazine and/or methotrexate), 36 patients anti-tumor necrosis factor-alpha (anti-TNF-α) therapies, 29 patients non-steroidal anti-inflammatory drugs, and 11 patients anti-TNF-α therapies with one of the disease modifying drugs. We demonstrated significantly different levels of WBC, neutrophil and platelet counts, ESR and CRP between group 3, group 2 and group 1 (p<0.05). The counts of neutrophil, NLR, CRP and PLR levels were higher in group 3 when compared to group 1 and group 2 (p<0.05). The platelet counts were significantly higher in group 3 compared to group 1 (p=0.033). There were significantly higher levels of WBC counts and ESR levels in group 2 compared to group 1 (p<0.05). Additionally, we showed that BASDAI scores were significantly but weakly correlated with neutrophil and platelet counts, NLR and PLR,

Table 1. Demographic features and laboratory findings of study groups

| | AS patients (n=103) | | Healthy controls (n=70) | | |
	n	Mean±SD	n	Mean±SD	p
Age (years)		40.7±12.0		42.7±15.3	0.469
Gender					
Female	40		27		0.972
Male	63		43		
White blood cell count (cell/mm³)		7963±1690		7127±1056	<0.001
Neutrophil count (cell/mm³)		4815±1442		4210±794	0.001
Lymphocyte count (cell/mm³)		2272±709		2171±596	0.316
Platelet count (cell/μL)		256718±68885		239414±46849	0.069
Erythrocyte sedimentation rate (mm/h)		26.0±21.4		7.2±4.7	<0.001
C-reactive protein (mg/dL)		12.5±18.3		3.0±1.5	<0.001
Neutrophil-to-lymphocyte ratio		2.36±1.16		2.07±0.65	0.226
Platelet-to-lymphocyte ratio		126.4±59.1		116.7±34.3	0.534
Mean platelet volume (fL)		8.2±1.3		8.2±0.9	0.750
Disease duration (years)		9.2±8.2		–	
BASDAI		2.9±1.9		–	
BASMI		1.9±1.9		–	
BASFI		1.9±1.6		–	

AS: Ankylosing spondylitis; SD: Standard deviation; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index.

Table 2. Demographic features and laboratory findings of ankylosing spondylitis patients according to BASDAI scores (n=103) and healthy controls (n=70)

	Group 1 (Healthy controls) (n=70)		Group 2 (BASDAI <4.0) (n=73)		Group 3 (BASDAI ≥4.0) (n=30)		
	n	Mean±SD	n	Mean±SD	n	Mean±SD	p
Age (years)		42.7±15.3		41.9±12.1		58.1±10.1	0.296
Gender							0.153
Female	27		24		16		0.054
Male	43		49		14		
White blood cell count (cell/mm^3)		7127±1056*‡		7778±1565*		8413±1914‡	<0.001
Neutrophil count (cell/mm^3)		4210±794‡		4563±1247*		5426±1705*‡	<0.001
Lymphocyte count (cell/mm^3)		2171±596		2301±747		2200±613	0.489
Platelet count (cell/µL)		239414±46849*		244370±52752		286766±91994*	0.001
Erythrocyte sedimentation rate (mm/h)		7.2±4.7*‡		23.9±20.8‡		31.0±22.4*	<0.001
C-reactive protein (mg/dL)		3.0±1.5*¶		9.7±13.8‡¶		19.4±25.2*‡	<0.001
Neutrophil-to-lymphocyte ratio		2.07±0.65*		2.21±1.04‡		2.70±1.37*‡	0.061
Platelet-to-lymphocyte ratio		116.7±34.3*		121.8±63.1‡		137.6±46.9*‡	0.090
Mean platelet volume (fL)		8.2±0.9		8.2±1.5		8.1±1.0	0.676
BASMI		–		2.1±2.1		1.3 ±1.3	0.083
BASFI		–		1.7±1.5		2.4±1.7	0.047
BASDAI		–		1.9±1.1		5.3±1.0	<0.001
Disease duration (years)		–		9.4±9.2		8.7±5.3	0.470
Medication duration (years)		–		8.2±8.7		6.9±5.0	0.695

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; SD: Standard deviation; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASFI: Bath Ankylosing Spondylitis Functional Index; *, ‡, ¶: There is a significant difference between the parameters marked with the same letter (p<0.05) Comparisons of parametric data of three groups were performed with One-Way ANOVA testing. Levene's test was used to determine homogeneity of variances and in case of homogeneity of variance, post hoc Tukey test was used. All probability values were calculated by assuming a two-sided p-value of <0.05.

and moderately correlated with CRP and ESR values in patients with AS (p<0.05) (Table 3).

DISCUSSION

In the present study, we have found three main results. Firstly, there was no significant difference between healthy controls and AS patients in terms of NLR and PLR, whereas ESR, CRP, WBC and neutrophil counts were significantly higher in the

Table 3. Correlation between BASDAI scores and laboratory parameters in ankylosing spondylitis patients (n=103)

	r	p
White blood cell count (cell/mm^3)	0.153	0.122
Neutrophil count (cell/mm^3)	0.264	0.007
Lymphocyte count (cell/mm^3)	-0.131	0.186
Platelet (cell/µL)	0.242	0.014
Erythrocyte sedimentation rate (mm/h)	0.316	0.001
C-reactive protein (mg/dL)	0.350	<0.001
Neutrophil-to-lymphocyte ratio	0.256	0.009
Platelet-to-lymphocyte ratio	0.213	0.030
Mean platelet volume (fL)	-0.082	0.413

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

patient group. Secondly, neutrophil counts, NLR, CRP and PLR values were significantly higher in patients with moderate to severe disease activity compared to those both in healthy controls and in patients with mild disease activity. Finally, we have demonstrated significantly but weakly positive correlations between BASDAI scores with neutrophil counts, NLR and PLR, and moderate correlations with ESR and CRP values.

Patients with AS may complain about peripheral or axial joint involvements and extra articular manifestations such as enthesitis and uveitis. These variations in clinical symptomatology make evaluation of the disease activity challenging and there is no objective gold standard for this issue yet.[4] The precise pathogenesis of AS is unknown, but inflammation and new bone formation are the two main features to be held accountable.[1] T cells and macrophages were also shown to be the predominant cells in the inflammation areas of patients with AS.[28] Thus, estimation of the level of inflammatory status may help to predict which patients have more severe disease. Previously acute phase reactants such as ESR and CRP had weakly to moderately but significant
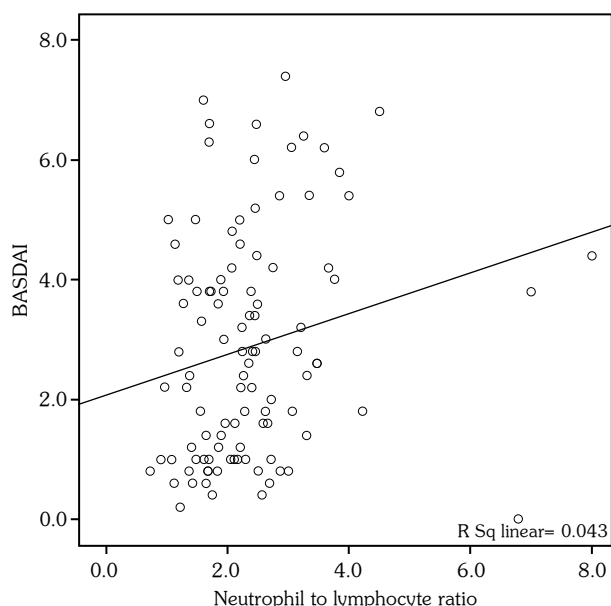
Figure 1. Correlation between BASDAI scores and neutrophil to lymphocyte ratio in patients with ankylosing spondylitis (p<0.001). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

Figure 2. Correlation between BASDAI scores and platelet to lymphocyte ratio in patients with ankylosing spondylitis (p<0.05). BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

relations with the disease activity in AS.[4,6-8] On the other hand, NLR has been proposed to be a marker to evaluate systemic inflammatory condition in various chronic inflammatory diseases.[10-17] However, the relationship between disease activity in AS and NLR has not been fully demonstrated yet. NLR is also an objective measurement and does not lead to any additional cost to the patients. In the present study, there was no significant difference regarding the number of patients who were on anti-TNF-α therapies between the patients with mild disease activity and those with moderate to severe disease activity. Also, it was previously shown that there was no direct interaction between anti-TNF-α therapies and neutrophil counts.[29,30] According to the present results which are consistent with previous studies regarding certain chronic inflammatory diseases,[11-13,15] we have detected significantly higher levels of NLR, CRP and neutrophil counts in AS patients with moderate to severe disease activity compared to those in patients with mild disease activity and healthy controls. Expectedly, ESR and CRP values were shown to have good correlation with disease activity of AS patients in this study similar to previous studies.[6,17,19] In addition, NLR was
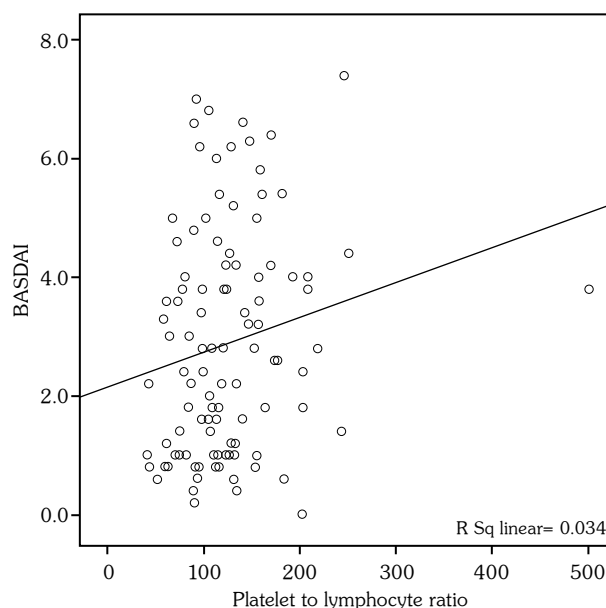
shown to be correlated weakly but significantly with BASDAI scores of AS patients in this study similar to a previous study by Gökmen et al.[17] These results likely indicate that NLR may be a parameter to measure disease activity in AS.

Inflammation is characterized by interactions among platelets, leukocytes and endothelial cells.[31] MPV is an indicator of platelet function and activation.[32] Enhanced platelet reactivity was shown in patients with RA, psoriatic arthritis and seronegative spondyloarthritis. This reactivity pathway was also suggested to be a target in the treatment of these diseases.[33] Moreover, significantly decreased levels of MPV were reported after anti-TNF-α therapy in patients with AS.[20] Recently, MPV that was investigated in inflammatory bowel disease,[18] chronic obstructive pulmonary disease,[15] RA and AS[19-21] and PLR which was evaluated in some cancers like gastric,[14] colon,[22] and non-small cell lung cancers[23] have become to be prominent markers to indicate inflammatory status and prognosis of several diseases, but there is no cut-off level reported before for PLR and MPV as well as NLR. In the same way, we investigated if there were relationships between PLR and MPV values and disease activity in AS or not.

Inconsistently with previous studies about several chronic inflammatory diseases including chronic obstructive pulmonary disease,[15] inflammatory bowel disease,[18] RA and AS,[19-21] we found that MPV did not reflect disease activity in AS since its levels were similar in healthy controls as well as patients with mild and moderate to severe disease activity. Similar to the present results, no significantly different levels of MPV were reported in patients of hemodialysis, renal transplanted, peritoneal dialysis and chronic renal failure patients when compared to each other[34] as well as in patients with advanced stage endometriosis.[35] Accordingly to the reported studies about colon and non-small cell lung cancers,[22,23] PLR was found to be significantly higher in patients with moderate to severe disease activity when compared to patients with mild disease activity and healthy controls and it had a weakly but significant correlation with BASDAI scores in the present study. Albeit, the level of inflammation in advanced stage endometriosis that is proven to develop with severe inflammation was shown to have no significant association with PLR.[35] Nevertheless, these results also may indicate that PLR reflects disease activity in AS.

The present study has several limitations including the relatively small study population. Cross-sectional design which is not the best way to evaluate any causal relations also limited the results. The current study could not demonstrate the pathogenesis of the relationship between NLR and PLR and disease activity. Since this study is a single-center study, we were unable to generalize the results to the public population. However, to the best of our knowledge, this was the first study to evaluate the relationships between PLR and disease activity in patients with AS.

Conversely to NLR and PLR, MPV has been found to have no association with disease activity in this study population. The data that are needed to calculate NLR and PLR already exist in complete blood count analysis which is routinely performed during diagnosis and follow-up of the rheumatic diseases. Thus clinicians may use NLR and PLR to evaluate disease activity in AS since these easily determinable measurements are objective, simple and readily available and also do not lead to any additional cost. Albeit NLR

and PLR may reflect the disease activity in AS according to the present study, we have found weak correlations between BASDAI and NLR and PLR. Further studies with larger patient populations and longer follow-up periods should be designed to enlighten the relationships more precisely.

Declaration of conflicting interests

Funding

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