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Neutrophil/lymphocyte and platelet/lymphocyte ratios as potential markers of disease activity in patients with Ankylosing spondylitis: a case-control study

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Abstract

Background: The neutrophil/ lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) have the potential to be inflammatory markers that reflect the activity of many inflammatory diseases. The aim of this study was to evaluate the NLR and PLR as potential markers of disease activity in patients with ankylosing spondylitis.

Methods: The study involved 132 patients with ankylosing spondylitis and 81 healthy controls matched in terms of age and gender. Their sociodemographic data, disease activity scores using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), erythrocyte sedimentation rate (ESR), and white blood cell, neutrophil, lymphocyte and platelet counts were recorded. The patients with ankylosing spondylitis were further divided according to their BASDAI scores into patients with inactive disease (BASDAI < 4) and patients with active disease (BASDAI ≥4). The correlations between the NLR, PLR and disease activity were analysed.

Results: There was a statistically significant difference in the NLR and PLR between the active and inactive ankylosing spondylitis patients (2.31 ± 1.23 vs. 1.77 ± 0.73, $p = 0.002$), (142.04 ± 70.98 vs. 119.24 ± 32.49, $p < 0.001$, respectively). However, there was no significant difference in both the NLR and PLR between the healthy control group and ankylosing spondylitis patients ($p > 0.05$). In addition, the PLR was significantly higher in both the active and inactive groups compared to those in the healthy control group (142.04 ± 70.98 vs. 99.32 ± 33.97, $p = 0.014$), (119.24 ± 32.49 vs. 99.32 ± 33.97, $p = 0.019$). The BASDAI scores were positively correlated with the PLR ($r = 0.219$, $p = 0.012$) and the NLR, but they were not statistically significant with the later ($r = 0.170$, $p = 0.051$). Based on the ROC curve, the best NLR cut-off value for predicting severe disease activity in ankylosing spondylitis patients was 1.66, with a sensitivity of 61.8% and a specificity of 50.6%, whereas the best PLR cut-off value was 95.9, with a sensitivity of 70.9% and a specificity of 55.5%.

Conclusion: The PLR may be used as a useful marker in the assessment and monitoring of disease activity in AS together with acute phase reactants such as the ESR.

Keywords: Ankylosing spondylitis, Neutrophil/lymphocyte ratio (NLR), Platelet/lymphocyte ratio (PLR), BASDAI

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Background

Ankylosing spondylitis (AS) is the main subtype of spondyloarthritides [1]. AS is a chronic, progressive, inflammatory rheumatic disease that primarily affects the sacroiliac joints and the axial skeleton. Oligoarthritis of the hips and shoulders, enthesopathy, and anterior uveitis are common conditions that can progress to significant functional disabilities that affect the quality of life with increased risk of comorbid conditions [2]. Disease activity is normally measured by using the Bath Ankylosing Spondylitis Activity Index (BASDAI), which is a patient-based questionnaire [3]. The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) indicate the proportions of absolute neutrophil count and platelet count, respectively, to the lymphocyte count, and are derived from a routine complete blood count (CBC) test. Elevated values of the NLR and PLR denote increased inflammation [4–6]. The 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 [7–11]. The PLR plays a key role in atherosclerosis and atherothrombosis in peripheral arterial occlusive disease [12]. In addition, it was found that the value of the PLR is not affected by smoking, unlike the value of the NLR, which is correlated with the pack/year [13].

Elevated levels of c-reactive protein (CRP) (or erythrocyte sedimentation ratio (ESR) have been found in only about 60% of clinically-active AS patients [14]. The clinical assessment of disease activity and response to treatment in AS is complex and difficult. Although the two traditional markers of an acute phase response, ESR and CRP, have been used for assessment, they may not often correlate with the patient's symptoms or radiological progression. Thus, it is important to find a new monitoring marker that can reflect disease activity. The NLR and PLR are readily available, simple, and inexpensive tools that may indicate disease activity in AS patients. This study was aimed to evaluate the differences between the NLR, PLR and disease activity among AS patients and the control group, and to examine the correlation between the NLR, PLR and disease activity in AS patients. In addition, this study was also conducted to assess the validity of the NLR and PLR in differentiating between active and inactive AS.

Methods

Study design

This was a case-control study conducted among AS patients at the Rheumatology Unit of the Baghdad Teaching Hospital/Medical City from August 2017 to the end of April 2018. A signed informed consent form was obtained from each participant in the study. The study protocol was approved by the University of Baghdad, College of Medicine, Rheumatology and Medical Rehabilitation Unit in accordance with the Declaration of Helsinki with ethical approval reference no.: 2017070-EA-7189.

Participants

A total of 132 Iraqi patients diagnosed with ankylosing spondylitis after fulfilling the modified New York criteria for ankylosing spondylitis [15] were consecutively selected. Eighty-one (81) healthy control participants matched for age and gender were obtained from medical staff volunteers. Subjects with acute or chronic infections, hypertension, diabetes mellitus, a history of coronary heart disease or impairment in thyroid functions, renal/hepatic dysfunction, malignancy, history of surgery in the last 3 months, current smokers or with a history of smoking in the past year, hematologic disorders or receiving blood transfusion during the past 3 months, steroid therapy, chronic obstructive pulmonary disease (COPD), and overlapping with other autoimmune diseases such as rheumatoid arthritis, psoriatic arthritis and inflammatory enteritis were excluded from the study.

Age, gender, disease duration, and disease activity was evaluated by using the Bath Ankylosing Spondylitis Disease Activity Index score [3], while the laboratory results for white blood cell count (WBC count), neutrophil count, lymphocyte count, platelet count and ESR were recorded. The blood neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) for each participant were calculated manually by dividing the neutrophil count and platelet count, respectively by the lymphocyte count after obtaining the laboratory results. The patients were categorized into 2 groups according to their BASDAI scores. Patients with BASDAI scores of less than 4 were considered to be having inactive or mild disease activity, while patients with scores of 4 or above were considered to be displaying active disease.

The BASDAI is a composite index ranging from 0 (no symptoms) to 10 (maximal symptoms) on a numeric scale. It is a patient-based questionnaire that includes questions about fatigue, pain in the spine, pain at the peripheral joints and entheses, and the quality and quantity of morning stiffness. A cut-off value of 4 has been accepted in the BASDAI scale and scores, equal to or above the cut-off value, indicate that the disease is more active. The Nihon Kohden®Japan (Celltacα) and Vital Microsed-System®Germany ESR automated analysers were used to obtain the final results of the CBC and ESR, respectively.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) software for Windows version 20. The descriptive statistics were presented as the mean ± standard deviation (SD) for the continuous variables, and as frequencies and proportions (%) for the categorical variables. A student's t-test was

used to compare the means of the continuous variables between the AS patients and the control group, and between the active and inactive AS patients. The parametric data of the three groups were compared using the one-way ANOVA test. For differences between the three groups, the post-hoc Tukey Test was utilized. The Pearson's correlation test was performed to determine the relationship between the NLR, PLR and BASDAI scores. A Receiver Operating Characteristic curve was used to assess the validity of the NLR and PLR to differentiate between the AS patients and the control group, and between the active and inactive AS. If the area under the curve (AUC) is 1.0, it is a perfect test; 0.9–0.99 indicates an excellent test; 0.8–0.89 is a good test; 0.7–0.79 is a fair test, 0.51–0.69 is a poor test, and 0.5 is of no value (Carter J V, 2016). $P < 0.05$ was considered as significant.

Results

Demographic, clinical and laboratory characteristics of the study population

The current study involved 213 participants comprised of 132 AS patients as well as 81 matched healthy controls. The ESR, and WBC, lymphocyte and platelet counts were significantly higher in the AS patients compared to the healthy controls ($p < 0.05$), whereas there was no significant difference with regard to their neutrophil count, NLR and PLR ($p > 0.05$). The other demographic and clinical characteristics are shown in Table 1.

Differences in mean values of NLR and PLR between active and inactive AS patients

The ankylosing spondylitis patients were categorised according to their disease activity into active disease ($n = 55$), and inactive or mild disease activity ($n = 77$). The mean BASDAI for the active group was 5.14 ± 0.92, range: 4–7.6, and for the inactive group it was 2.34 ± 0.91, range: 0.20–3.90.

The mean values of the NLR and PLR in the active AS group were significantly higher than the values in those with inactive or mild disease activity (2.31 ± 1.23 vs. 1.77 ± 0.73, $p = 0.002$), (142.04 ± 70.98 vs. 119.24 ± 32.49, $p < 0.001$), respectively, as shown in Figs. 1 and 2.

Disease activity and laboratory parameters

The laboratory parameters of the AS patients according to their BASDAI scores and the healthy controls are shown in Table 2. There were significantly different levels of WBC, neutrophil, lymphocyte and platelet counts, NLR, PLR and ESR among the three groups ($p < 0.05$).

By comparing the control group with the patients with BASDAI scores of < 4, there was a significant difference in the lymphocyte count, PLR and ESR ($p < 0.001$, $p = 0.019$, $p < 0.001$, respectively). Also, there was a significant difference in the WBC, neutrophil, lymphocyte and platelet counts, PLR and ESR on comparing the controls with those patients with BASDAI scores of ≥4 ($p < 0.001$, $p = 0.001$, $p = 0.019$, $p < 0.001$, $p = 0.014$, $p = 0.013$, respectively).

By comparing the two groups of AS patients (BASDAI ≥4 vs. BASDAI < 4), there was a significant difference in the WBC, neutrophil and platelet counts, NLR, PLR and ESR ($p = 0.040$, $p = 0.002$, $p < 0.001$, $p = 0.001$, $p < 0.001$, $p < 0.001$, respectively).

Correlation between BASDAI scores and laboratory parameters in ankylosing spondylitis patients

The BASDAI scores were moderately correlated with the platelet count and ESR in the AS patients (r = 0.304, $p < 0.001$; r = 0.394, p < 0.001, respectively). In addition, there was a weak correlation between the BASDAI scores and the WBC, neutrophil counts and PLR (r =

Table 1 Demographic, clinical and laboratory characteristics of AS patients and controls

	AS patients ($n = 132$)	Control ($n = 81$)	P value [a]
Age (years)	37.61 ± 10.0	35.98 ± 9.8	0.249
Male, *n* (%)	120 (90.9)	73(90.1)	0.849
Disease duration (years)	9.54 ± 7.3	–	–
BASDAI	3.51 ± 1.66	–	–
White blood cell count (10^9/L)	8.15 ± 1.75	7.31 ± 1.49	**< 0.001**
Neutrophil count (10^9/L)	4.85 ± 1.45	4.51 ± 0.98	0.066
Lymphocyte count (10^9/L)	2.71 ± 0.83	2.30 ± 0.51	**< 0.001**
Platelet count (10^9/L)	288.57 ± 89.47	263.08 ± 50.56	**0.020**
NLR	1.99 ± 1.00	2.02 ± 0.55	0.801
PLR	117.12 ± 56.51	119.24 ± 32.49	0.759
ESR (mm/hr.)	22.78 ± 21.03	8.24 ± 5.67	**< 0.001**

Values are means ± SD or numbers and percentages. [a], student t-test; AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Activity Index; ESR, erythrocyte sedimentation rate; *n*, number; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; *P* value, probability value (< 0.05)

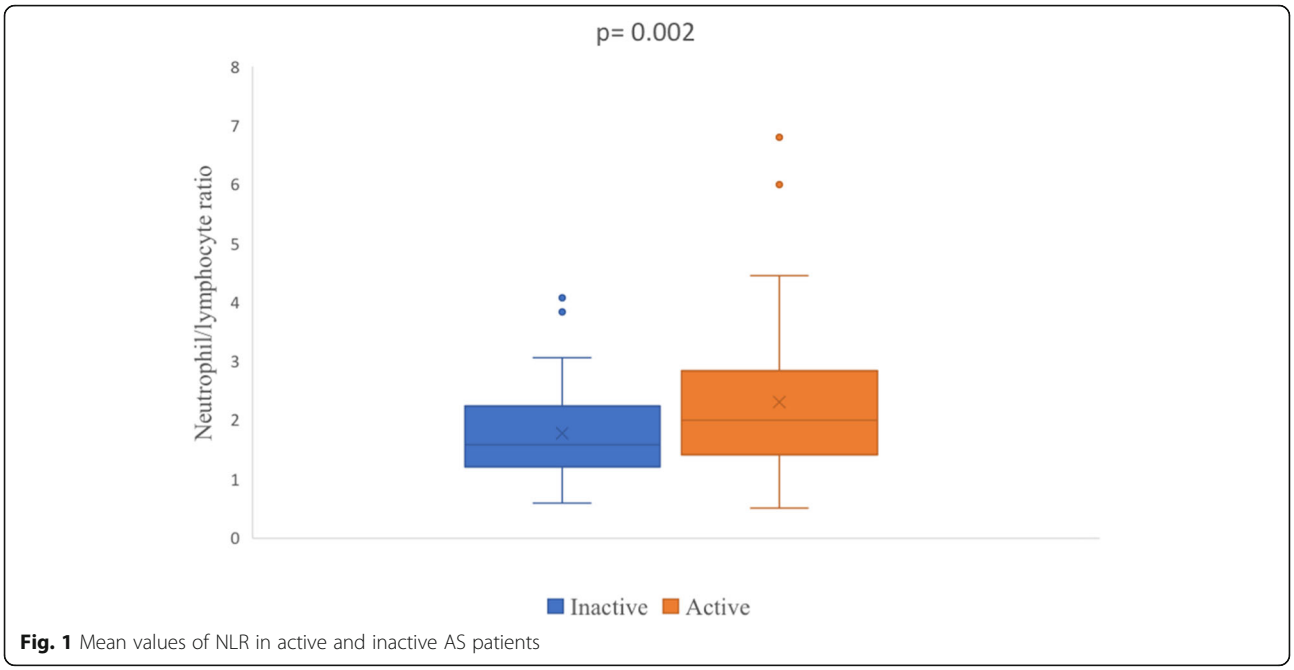

Fig. 1 Mean values of NLR in active and inactive AS patients

0.201, $p = 0.021$; r = 0.228, $p = 0.009$; r = 219, $p = 0.012$, respectively), while the NLR showed a very weak positive correlation with the BASDAI scores but it did not achieve statistical significance (Table 3, Figs. 3 and 4).

ROC analysis and validity of NLR, PLR and ESR between AS patients according to disease activity

Furthermore, the ESR and PLR were valid fair tests to differentiate the active AS from inactive AS, where the AUC for them were 0.726 and 0.702, respectively, with $p < 0.001$ (Fig. 5). The optimum cut-off value for the ESR was ≥15.5 mm/hr. (sensitivity of 70.9%, specificity 64.9%) and 95.9 for the PLR (sensitivity 70.9%, specificity 55.5%). However, the AUC for the NLR was 0.626 with a cut-off value of ≥1.66, sensitivity of 61.8%, and specificity of 50.6%. These validity parameters are shown in Table 4.

Discussion

The main findings of the current study were that the NLR, PLR and ESR were significantly higher in the active

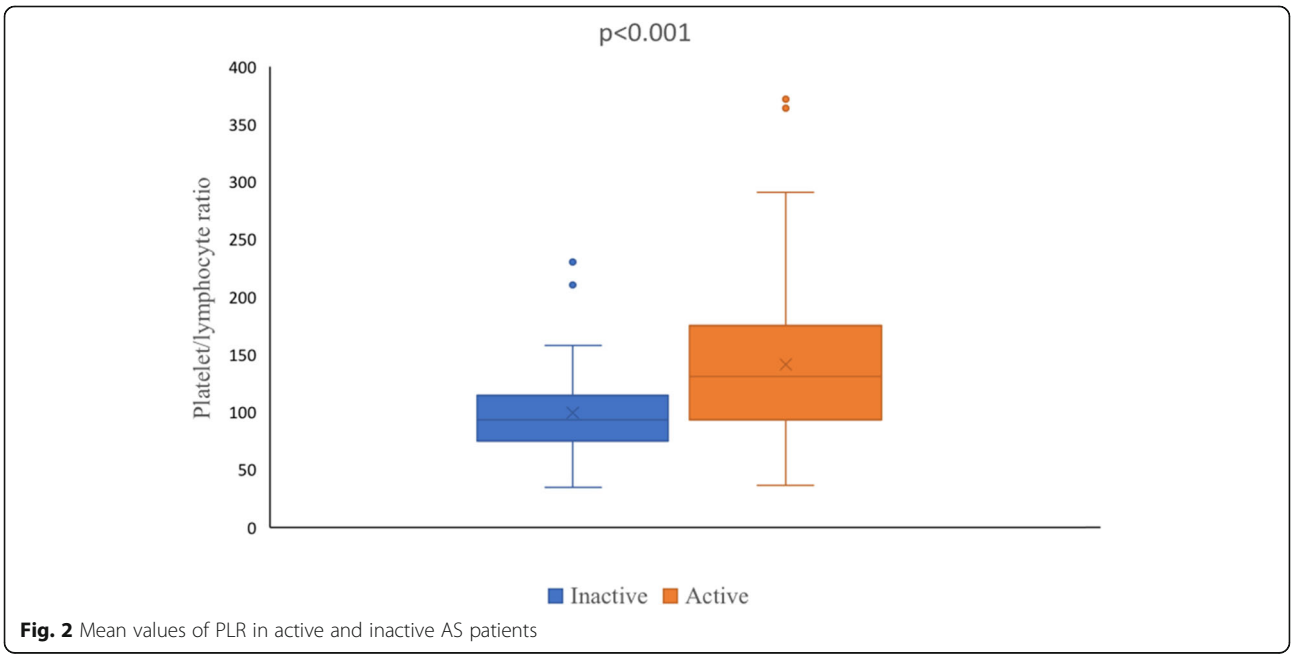

Fig. 2 Mean values of PLR in active and inactive AS patients

Table 2 Laboratory parameters of study groups based on disease activity

	Control ($n = 81$)	BASDAI< 4 ($n = 77$)	BASDAI≥4 ($n = 55$)	*P* value
White blood cell count (10^9/L)	7.31 ± 1.49	7.85 ± 1.65	8.56 ± 1.81	**< 0.001** P1 = 0.097 **P2 < 0.001** **P3 = 0.040**
Neutrophil count (10^9/L)	4.51 ± 0.98	4.53 ± 1.33	5.30 ± 1.51	**0.001** P1 = 0.994 **P2 = 0.001** **P3 = 0.002**
Lymphocyte count (10^9/L)	2.30 ± 0.51	2.76 ± 0.76	2.65 ± 0.92	**< 0.001** **P1 < 0.001** **P2 = 0.019** P3 = 0.661
Platelet count (10^9/L)	263.08 ± 50.56	257.58 ± 62.38	331.96 ± 103.22	**< 0.001** P1 = 0.879 **P2 < 0.001** **P3 < 0.001**
NLR	2.02 ± 0.55	1.77 ± 0.73	2.31 ± 1.23	**0.002** P1 = 0.138 P2 = 0.131 **P3 = 0.001**
PLR	99.32 ± 33.97	119.24 ± 32.49	142.04 ± 70.98	**< 0.001** **P1 = 0.019** **P2 = 0.014** **P3 < 0.001**
ESR (mm/hr.)	1.40 ± 3.48	15.31 ± 33.23	12.31 ± 25.86	**< 0.001** **P1 < 0.001** **P2 = 0.013** **P3 < 0.001**

AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; ESR, erythrocyte sedimentation rate; *n,* number; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; *P* value, probability value (< 0.05); P1, Control vs. BASDAI < 4; P2, Control vs. BASDAI ≥4; P3, BASDAI ≥4 vs. BASDAI < 4

Comparisons of parametric data of three groups were performed with One-Way ANOVA test. Post-hoc Tukey Test was used for differences between the three groups

disease patients compared to the inactive disease patients. However, there was an insignificant difference between the healthy controls and AS patients in terms of the NLR and PLR, whereas the ESR was significantly higher in the group of AS patients. In addition, the ESR and PLR were significantly higher in the active and inactive disease patients compared to the healthy control group. Also, it was found that there was a significant but weak positive correlation between the BASDAI scores and the PLR, and a moderate correlation with the ESR values. Also, there was a very weak positive correlation between the BASDAI scores and the NLR, but it was not statistically significant. ESR and PLR were fair valid significant tests that can differentiate between active and inactive AS.

Table 3 Correlation between BASDAI scores and laboratory parameters in ankylosing spondylitis patients ($n = 132$)

Parameter	Pearson's correlation	*P* value
White blood cell count (10^9/L)	0.201	**0.021**
Neutrophil count (10^9/L)	0.228	**0.009**
Lymphocyte count (10^9/L)	−0.014	0.876
Platelet count (10^9/L)	0.304	**< 0.001**
NLR	0.170	0.051
PLR	0.219	**0.012**
ESR	0.394	**< 0.001**

ESR, erythrocyte sedimentation rate; *n,* number; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; *P* value, probability value (< 0.05)

The patients' demographic data in this study showed no significant difference when compared with the healthy control individuals. This indicated that the patients were correctly matched with the control group, and the effect of confounding variables that may influence the results was avoided.

This study showed that males were more predominant than females at a ratio of 10:1 with regard to AS. This was comparable with another Iraqi study conducted at a Baghdad teaching hospital by Abdul-Wahid K. M. et al. [16] in which a ratio of 11:1 was obtained. However, the findings of this study and the other Iraqi study [16] were inconsistent with those of other studies [17–19]. This inconsistency might be attributed to the following factors: the small sample size, and the fact that the number of women diagnosed with AS is less than the men, since,

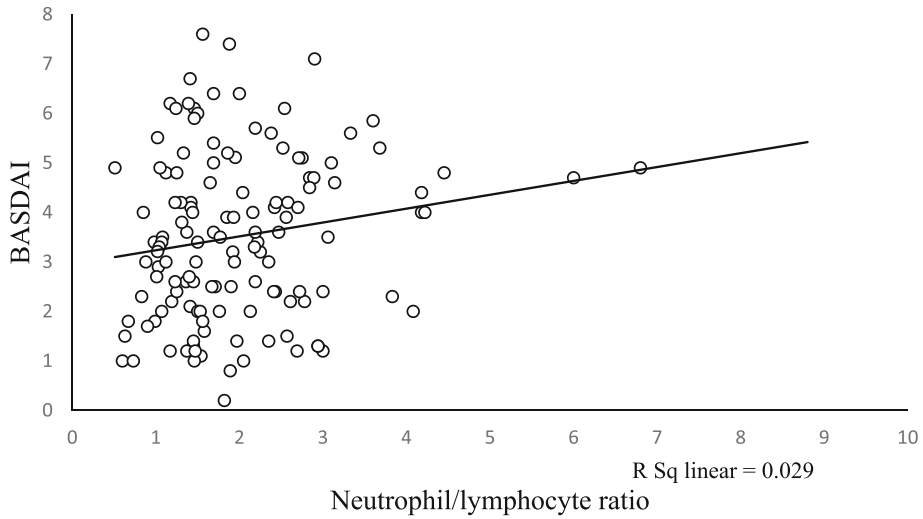

Fig. 3 Correlation between BASDAI scores and neutrophil/lymphocyte ratio in patients with ankylosing spondylitis ($p = 0.051$)

for reasons that are unclear, women seem to develop chronic changes later and less often [1]. In addition, some female patients were excluded from this study due to either their use of steroids or their being diabetic.

Although the pathogenesis of AS is unknown, some studies have suggested that neutrophils and lymphocytes may play a role in the pathogenesis of AS [1, 20]. In the literature, five studies [21–25] showed no significant difference in the NLR when comparing the AS patients with the healthy controls, and similar findings were also obtained with regard to the PLR [21, 25, 26], which were consistent with the results of this study. However, these results disagreed with the findings of four other studies with regard to the NLR [27–30] and one study concerning the PLR [24], which might have been related to the involvement of either newly-diagnosed patients with no previous treatment or only patients with active AS in their studies.

For individual AS patients, a disease activity assessment is a critical step in the management of the disease. Currently, the CRP and ESR are the most widely used laboratory indices for the estimation of AS disease activity. However, an increase in these indices may relate more to disease activity in the peripheral joints than to axial disease [31]. Therefore, a novel index is needed to improve the accuracy of currently available disease activity estimation tools. To further assess whether the higher NLR and PLR in AS were associated with clinical disease activity, the patients were divided into active and inactive subgroups based on the BASDAI scores. The patients with high BASDAI scores had significantly higher NLR and PLR levels. These results were in agreement

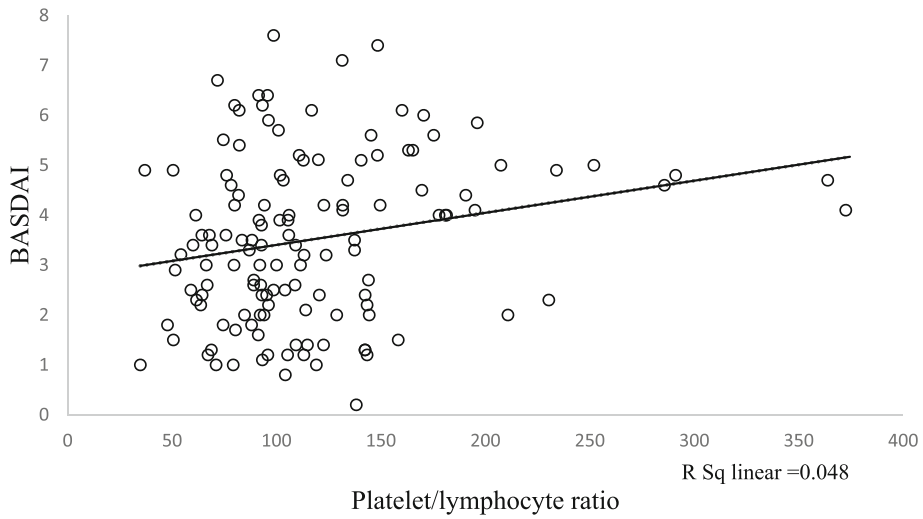

Fig. 4 Correlation between BASDAI scores and platelet/lymphocyte ratio in patients with ankylosing spondylitis ($p = 0.012$)

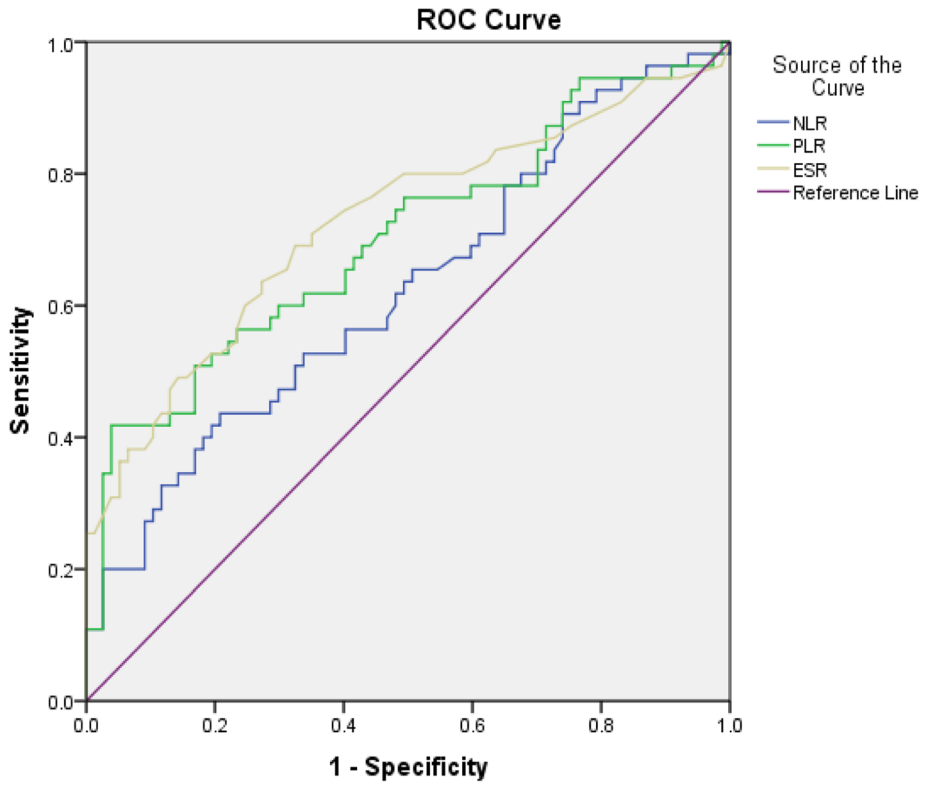

Fig. 5 ROC curve of NLR, PLR and ESR differentiating active AS from inactive AS

with the finding of Esraa et al. [21] and Kucuk et al. [30] that the NLR and PLR were significantly higher in patients with severe disease activity compared to mild disease activity.

There was a very weak positive correlation between the BASDAI scores and NLR but it was not statistically significant (r = 0.170, $p = 0.051$). This result was in agreement with the finding of Mercan et al. [22] and Gokmen et al. [29], but was in contrast to the findings of three other studies [21, 28, 30]. Meanwhile, there was a weak positive correlation between the PLR and the BASDAI scores, and this result was in agreement with the finding of Esraa et al. [21]. A further analysis showed a strong overall performance characteristic of the PLR in the diagnosis of severe AS patients. Based on the ROC curve, it was found that the PLR had an optimal sensitivity of 70.9%, specificity of 55.5%, and accuracy of 61.36%, and these were nearly similar to the sensitivity and accuracy of the ESR, which were 70.91 and 61.61%, respectively. Meanwhile, the NLR at a cut-off value of 1.66 showed poor validity as an inflammatory marker of severe disease activity in AS patients with an AUC of 0.626, sensitivity of 61.8%, specificity of 50.6%, and accuracy 56.82%. In addition, the ESR showed a moderate positive correlation with the BASDAI scores. This suggested that the PLR together with the ESR can be used as potential complementary assessment tools for the diagnosis of disease activity in AS patients. Similar findings regarding the NLR were reported by other two studies [30, 32]. Moreover, there is a lack of data in the literature about the performance of the PLR and the severity of disease activity in AS.

An estimation of patients with increased systemic inflammation would be useful to predict those patients with severe disease activity and who have developed comorbidities. Therefore, it is believed that it is important

Table 4 ROC curve analysis and validity of NLR, PLR and ESR to differentiate between active and inactive AS patients

Variable	AUC	95% CI	Cut-off value	Sensitivity	Specificity	Accuracy	*P* value
NLR	0.626	0.528–0.723	1.66	61.8%	50.6%	56.82%	**0.014**
PLR	0.702	0.608–0.795	95.9	70.9%	55.5%	61.36%	**< 0.001**
ESR	0.726	0.634–0.817	15.5	70.9%	64.9%	61.61%	**< 0.001**

AS, ankylosing spondylitis; AUC, area under curve; CI, confidence interval; ESR, erythrocyte sedimentation rate; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; *P* value, probability value (< 0.05)

to practically demonstrate the level of systemic inflammation in patients with AS. Thus, combined with the findings of this study, it is suggested that a high PLR level in AS may correlate with heightened disease activity in AS patients. The PLR together with the ESR are useful markers in the assessment of the inflammatory response and disease activity in AS patients.

There were some limitations to this study. This was a cross-sectional case-control study in a single centre, and the sample was smaller than samples used in previous studies, which did not permit the establishment of causality between the NLR, PLR and disease activity. Also, the possible effects of treatment on the NLR and PLR were not considered due to incomplete or unavailable treatment records, and the relationship between the NLR, PLR and cytokines was not investigated. However, this was the first study in Iraq to evaluate the NLR and PLR as potential tools for assessing the disease activity of AS. These are simple, rapid and inexpensive tools whose values can be easily calculated as common components of the complete blood count (CBC) test that is nowadays widely carried out in nearly every healthcare facility and by an automated machine.

Conclusions

There was a significant statistical difference in the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) between active and inactive AS patients. However, there was no statistically significant difference in these ratios between the patients and the control group. There was a significant weak positive correlation between ankylosing spondylitis disease activity with the platelet/lymphocyte ratio (PLR), whereas there was no statistically significant correlation with the neutrophil/lymphocyte ratio (NLR). The PLR proved to be a fair and valid significant test that can differentiate between active and inactive AS. However, the NLR was shown to have poor validity. The PLR might be integrated into an assessment of AS disease activity. Further studies with a larger sample size and longer follow-up periods should be designed to validate the findings of this study and to further demonstrate their relation to the medications received and the disease outcome.

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Authors' contributions

This paper is a part of NA board certification of rheumatology and medical rehabilitation in Iraq. The research was conducted by NA and supervised by MO. NA, and MO designed the project. Date collection was done by NA. AA contributed in the statistical analysis, and KK helped in drafting the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study protocol was approved by the University of Baghdad, College of Medicine, Rheumatology and Medical Rehabilitation Unit in accordance with the Declaration of Helsinki with ethical approval reference no.: 2017070-EA-7189.

Before becoming involved in the study, all participants who agreed to be involved in the study were given a cover letter describing the study objectives as well as a written informed consent form.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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