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Research Article

Correlation of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and mean platelet volume with disease activity in patients with ankylosing spondylitis

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Abstract

Objectives: The indices that are currently used to determine the disease activity in patients with ankylosing spondylitis (AS) are either patient- or physician-oriented. The neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR) and mean platelet volume (MPV) are new markers of systemic inflammation and correlate with disease severity in many rheumatological disorders. However, their relationship with disease activity in patients with AS has not been thoroughly studied in the Indian subcontinent.

Methods: This cross-sectional observational study was performed on 60 patients with definite AS in a tertiary care hospital in New Delhi, India. Healthy, age- and sex-matched individuals identified from the same demographic population were subjected to clinical assessment and investigations as per protocol.

Results: The mean values of NLR, PLR and MPV were 3.13±1.1, 168.36±69.43 and 10.07±1.28, respectively, in cases with high disease activity as compared to 2.58±1.05, 127.02±55.65 and 10.07±1.64 in cases with low disease activity. A statistically significant correlation was found between NLR and PLR and disease activity as calculated by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Ankylosing Spondylitis Disease Activity Score-C-reactive protein/erythrocyte sedimentation rate (ASDAS-CRP/ESR). However, multivariate linear regression revealed a significant correlation only between NLR and BASDAI, BASFI and ASDAS-CRP. PLR was found to be significantly lower in cases on biological therapy. No correlation of PLR and MPV with disease activity was found on multivariate regression analysis.

Conclusion: NLR and PLR correlate significantly with disease activity indices in patients with AS. Patients with the extra-spinal disease had higher NLR, PLR and MPV with only NLR being statistically significant. NLR was significantly lower in patients on biologics than those on Disease modifying antirheumatic drugs (DMARDs). Therefore, NLR and PLR can be used as potential parameters for the assessment of disease activity and extra-spinal disease and treatment response monitoring in patients with AS.

Keywords: Ankylosing spondylitis, BASDAI, mean platelet volume, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio

Ankylosing spondylitis (AS) is chronic inflammatory arthritis, which mainly affects the axial skeleton with characteristic involvement of the spine and sacroiliac joints. The inflammation affects not only the axial skeleton but also the peripheral joints, entheses, large bowel, eyes, lungs and heart in patients with AS [1].

The currently used single-component indices that measure the disease activity in AS, including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Metrology Index (BASMI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Ankylosing Spondylitis Disease Activity Score-C-reactive protein/erythrocyte sedimentation

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rate (ASDAS-CRP/ESR), are fully patient or physician oriented and lack face validity [2].

Other objective laboratory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complements C3 and C4, interferon-gamma, interleukin-4, alpha-1-antitrypsin, immunoglobulin A, G and M and serum amyloid A have also been suggested but they lack reliability, reproducibility and are expensive [3].

Dysregulated immune system plays an important role in the activation and progression of the disease. Being important components of the immune system, the neutrophils, platelets and lymphocytes play a role in cascading inflammation in many rheumatological disorders [4]. Recently, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been found to be predictive of disease severity in various chronic inflammatory diseases such as coronary artery disease, psoriasis, chronic kidney disease, ulcerative colitis, gastric cancer, chronic obstructive pulmonary disease (COPD), familial Mediterranean fever (FMF) and many rheumatological disorders [5].

The mean platelet volume (MPV) may also be used as a marker for platelet activation and severity of inflammation. Recently, it has been shown that increased platelet size is associated with inflammatory diseases such as rheumatoid arthritis, AS, juvenile Systemic Lupus Erythematosus , systemic sclerosis, Inflammatory Bowel Disease and Familial Mediterranean Fever [6]. NLR, PLR and MPV are simple, cost-effective and readily available tools as compared to ESR and CRP and can be used at primary and secondary health centres with minimal expertise. However, the relationship of NLR, PLR and MPV with disease activity in AS has not been thoroughly studied in the Indian subcontinent. Finding newer markers to assess inflammation in AS may herald the development of simple, economical and better measures. The present study evaluated the association and validation of NLR, PLR and MPV in predicting the disease activity in patients with AS.

Materials and Methods

This cross-sectional observational study included 60 cases with ankylosing spondylitis, diagnosed using Assessment of SpondyloArthritis international Society (ASAS) criteria and attending a rheumatology clinic at a tertiary care hospital in New Delhi, India, for 1 year. Sixty age- and sex-matched healthy volunteers were also identified as controls. The study was conducted after obtaining permission from the Ethical and Institutional Review Board (letter number: 732/16, obtained on 20 October 2016).

Individuals who had active infectious diseases, such as tuberculosis, HIV, Hepatitis B, Hepatitis C and any acute infection or febrile illness within the last 3 months, were excluded from the study. Also, patients with diabetes, metabolic syndrome, hypertension, coronary artery disease, chronic liver and kidney diseases, thyroid disorders, COPD or any malignancies were excluded. Those with a history of smoking, steroid intake or surgery within the last 3 months were also excluded.

The cases and controls were subjected to investigations as per the defined protocol. Details including the mode of onset, the joints and entheses involved, duration of early morning stiffness, family history of AS and extra-articular and extra-spinal symptoms were recorded. A detailed report of drug intake was elicited. A general physical and systemic examination was performed on each patient.

BASDAI [7], BASFI [8], BASMI [9] and ASDAS [10] scores were calculated as per standard questionnaires and protocols.

Fasting venous blood sample was withdrawn and evaluated for blood glucose (fasting and postprandial), complete blood counts (including NLR, PLR and MPV), liver and kidney function tests, CRP, ESR in cases as well as controls. Routine clinical assessments such as involvement of entheseal sites, extra-articular manifestations and radiological investigations including x-rays were conducted. Absolute neutrophil count (cells/mm^3), absolute lymphocyte count (cells/mm^3) and platelet count (cells/mm^3) were verified by manual counting. NLR was calculated by dividing the total neutrophil count by the total lymphocyte count. Similarly, PLR was calculated by dividing the total platelet count by the total lymphocyte count. MPV was calculated by an automated haematology cell counter.

Cases were divided into groups based on whether they were in remission, low, moderate or high disease activity as per BASDAI and ASDAS. Patients were divided into four groups based on ASDAS scores: inactive disease (ASDAS <1.3) (group A), moderate (ASDAS=1.3-2) (group B), high (ASDAS=2.1-3.5) (group C) and very high disease activity (ASDAS >3.5) (group D).

Statistical analysis

Categorical variables were presented in number and percentage, and continuous variables were presented as mean±SD and median. Univariate and multivariate linear regression was used to calculate the significance of NLR, PLR and MPV in predicting the disease activity. A p-value of <0.05 was considered statistically significant. The data were entered in MS EXCEL spreadsheet, and analysis was made using the Statistical Package for Social Sciences (SPSS), version 21.0.

Results

The study included 60 cases (52 males and 8 females) with definite ankylosing spondylitis and 60 age- and sex-matched controls (50 males and 10 females). The age of cases and controls ranged from 18 to 58 years with a mean age of 33 years. Out of the total 60 cases, 36 (60%) had BASDAI <4 and 24 (40%) had BASDAI >4 (i.e. high disease activity). When assessed on the basis of ASDAS-ESR, 8.4% had an inactive disease, 26.7% had moderate disease activity, 43.3% had high disease activity and 21.6% had very high disease activity. On the basis of ASDAS-CRP, the proportion of patients with inactive disease, mod-

Table 1. Mean value of parameters amongst cases and controls

Parameter	Cases (n=60)	Controls (n=60)	p
NLR	2.8±1.09	2.04±0.69	<0.001
PLR	143.55±64.29	131.55±45.51	<0.02
MPV (fL)	10.01±1.5	9.0±1.3	<0.01

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MPV: Mean platelet volume.

Table 2. Difference between NLR, PLR and MPV amongst cases with low and high disease activity as measured by BASDAI

Parameter	BASDAI <4	BASDAI >4	p
NLR	2.58±1.05	3.13±1.1	<0.001
PLR	127.02±55.65	156.8±69.43	<0.01
MPV (fL)	10.07±1.64	10.07±1.28	NS

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MPV: Mean platelet volume; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; NS: Not significant.

erate, high and very high disease activity was 11.7%, 21.7%, 38.3% and 28.3%, respectively.

While only 15.1% of the patients received NSAIDs alone, 76.6% received DMARDs (sulfasalazine and a few additionally received methotrexate) and 8.3% underwent TNF-α inhibitor therapy. A total of 53.4% had disease limited to the spine whereas 46.6% had spinal as well as extra-spinal and extra-articular manifestations. The mean values of NLR, PLR and MPV among cases and controls are depicted in Table 1.

The mean values of NLR, PLR and MPV were 2.49±0.8, 130.79±53.53 and 10.01±1.57 in cases with only axial involvement against 3.08±1.25, 154.72±71.38 and 10.12±1.45 in cases with concomitant spinal as well as extra-spinal or extra-articular manifestations. However, only NLR and PLR statistically correlated with the presence of extra-spinal disease (p<0.023 and p<0.04, respectively). NLR and PLR also correlated with the number of entheseal site involvement and early morning stiffness (p<0.03 and p<0.05, respectively).

Significantly higher NLR (p<0.001) and PLR (p<0.005) were found in cases with AS of radiological evidence of erosions and ankylosis.

Univariate analysis showed a statistically significant relationship of NLR with BASDAI (p=0.0002), BASFI (p<0.0001), BASMI (p=0.001), ASDAS-ESR (p=0.002) and ASDAS-CRP (p=0.001). PLR was found to have a significant association with BASDAI (p=0.0004), BASFI (p=0.0003), BASMI (p=0.001), ASDAS-ESR (p=0.008) but not with ASDAS-CRP (p=0.144). However, MPV did not correlate with any of the indices: BASDAI (p=0.766), BASFI (p=0.406), BASMI (p=0.631), ASDAS-ESR (p=0.476) and ASDAS-CRP (p=0.671).

However, multivariate linear regression analysis found NLR to have a significant association with only BASDAI (p=0.043), BASFI (p=0.019) and ASDAS-CRP (p=0.001) and not BASMI (p=0.129) and ASDAS-ESR (p=0.076). No correlation was found to exist between PLR and MPV and these differentiated disease activity parameters (Tables 2, 3).

While computing and analysing the type of treatment received, we observed that NLR, PLR and MPV were significantly lower in patients on biological therapy, slightly higher in those on DMARD and highest in cases who were taking NSAID only (Table 4), showing that TNF inhibitor therapy is most effective in suppressing inflammation and disease activity followed by DMARD and NSAID. However, statistical significance was observed with only NLR and PLR (p<0.002 and p<0.05, respectively) and not MPV (Table 4).

Discussion

With the increase in the number of cases of AS and the lack of a sufficient number of rheumatologists, newer, handy, economical tools, which can rapidly and accurately quantify the disease and do not require any special training, application or expertise, and also eliminate the subjective error of visual analog scale, are required for physicians. NLR, PLR and MPV are simple, readily available and cost-effective methods and thus can provide an alternative, easy and objective ways to assess the disease activity in remote areas, where the facility of ESR and

Table 3. Difference in values of NLR, PLR and MPV amongst different disease activity as measured by ASDAS

	ASDAS									
	CRP					ESR				
	Remission (low disease activity)	Moderate disease activity	High disease activity	Very high disease activity	p	Remission (low disease)	Moderate disease activity	High disease activity	Very high disease activity	p
NLR	2.11±0.67	2.38±0.99	2.69±1.01	3.57±1.04	0.002	2.33±1.05	2.4±0.93	2.6±0.95	3.89±0.94	0.001
PLR	130.45±59.32	138.28±68.93	127.63±54.88	174.53±68.82	0.119	112.9±51.7	117.53±57.15	142.56±56.9	189.37±70.96	0.017
MPV	9.0±0.66	10.09±2.02	10.36±1.23	10.1±1.52	0.189	9.6±2.07	10.07±1.85	10.1±1.21	12.1±1.45	0.791

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MPV: Mean platelet volume; ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 4. Effect of different type of therapy on NLR, PLR and MPV

Parameter	NSAIDs alone	DMARD's	Anti TNF therapy	p
NLR	3.3±1.07	2.82±1.06	1.79±0.87	<0.002
PLR	159.97±91.17	143.6±56.48	113.59±82.03	<0.05
MPV (fL)	10.41±1.52	10.01±1.52	10.02±1.45	NS

NLR: Neutrophil-lymphocyte ratio; PLR: Platelet-lymphocyte ratio; MPV: Mean platelet volume; DMARD's: Disease modifying antirheumatic drugs; TNF: Tumor necrosis factor; NS: Not significant.

CRP is absent. High NLR, PLR and MPV have been shown to correlate with disease severity in many connective tissue disorders such as RA; however, similar studies in AS are miniscule.

We found significantly higher NLR, PLR and MPV in patients with AS compared with the healthy general population. In 2015, Gokmen et al. [11] also found that NLR was significantly higher in patients with AS than controls [mean NLR of 2.24±1.2 and 1.73±0.70, respectively (p<0.0001)].

NLR and PLR are affected by neutrophil count and platelet count, respectively. On the one hand, the count of neutrophil and platelet increases in acute inflammation as a part of acute phase reaction as well as response to stress. On the other hand, the lymphocyte count decreases because of physiological stress. In addition, IL-17 and IL-23, which are key cytokines in the pathogenesis of AS, have been found to play a major role in neutrophil homeostasis [12]. This provides a possible explanation of increased NLR, PLR and MPV in patients with ankylosing spondylitis and the ratios found to increase progressively with higher grades of severity.

On the contrary, in 2015, Mercan et al. [13] concluded that only a moderate correlation exists between NLR, PLR and other acute phase reactants, and none of these measures correlated with BASDAI. They concluded that NLR is elevated in patients with inflammatory arthritis, but the correlation could not reach statistical significance in patients with AS (as compared to RA).

Ozsahin et al. [14] in 2014 and Illeez et al. [15] in 2018 also concluded that NLR and PLR levels were not significantly higher in patients with AS than in healthy individuals, and therefore they cannot be appropriate measures to detect systemic inflammation in these individuals. The reason is that NLR, PLR and MPV are affected by many pathological and physiological conditions, and a clearly defined range is not available even in healthy individuals. We strictly enforced our exclusion criteria to eliminate conditions that affect these parameters. In fact, choosing controls was a more difficult task than identifying cases. This meticulous selection of controls has provided us with the statistical significance of these tools.

In our study, MPV was found to be significantly higher in cases than in controls; however, this parameter was not associated with the severity of the disease. The mean MPV in patients with BASDAI <4 was 10.03±1.64, whereas it was 10.07±1.28 in cases with BASDAI ≥4. No correlation of MPV (p=0.766) was found with BASDAI and ASDAS. Although numerically MPV was higher in cases with higher disease activity, it was not found to correlate with different disease activities. This was also found by Ustun et al. [16] in 2014, who stated that MPV showed no significant association with any disease activity indices (i.e. BASDAI, ESR and CRP) (p>0.05). Contrary to that, Gorial [17] observed that MPV was significantly higher in patients with severe AS, and there was a direct correlation between MPV and ESR, CRP and BASDAI. In 2017, Sezgin et al. [6] also stated that MPV was significantly higher in patients with AS than in the control group. In 2016, Bozan et al. [18] also observed that the value of MPV was higher in patients with AS than in healthy controls although the difference was not statistically significant (p=0.390).

MPV shows the platelet size and platelet production in bone marrow as an indicator of platelet activation. Large platelets produce more proinflammatory cytokines and prothrombotic factors than small-sized platelets. In addition, cytokines are believed to amongst platelet activation PDGF leading to higher MPV. Therefore, MPV may be used as an indicator of platelet activation and severity of inflammation [17] and hence is higher in cases with AS than in controls.

In our study, mean NLR and PLR were found to be significantly higher in cases with higher grades of disease activity and correlated significantly with the functional and mobility outcomes.

In 2015, Kucuk et al. [4] also observed that NLR was significantly higher in severe AS disease activity (BASDAI >4) compared to mild AS disease activity (BASDAI <4) (2.72±1.41 vs 2.20±1.19, respectively; p=0.001). There was a positive direct correlation found between NLR and BASDAI.

In 2015, Inal et al. [5] also concluded that NLR and PLR were significantly higher in patients with BASDAI ≥4 as compared to healthy controls and patients with BASDAI <4 (p<0.05). They also concluded that NLR and PLR may reflect disease activity in patients with AS. This can be explained by the fact that cytokine production is more in cases with higher grades of disease activity. IL-17, IL-23 and TNF are known to shift the balance from lymphocyte to neutrophilia and therefore may explain higher NLR and PLR in high disease activity.

NLR in patients receiving biologics, DMARDs and NSAIDs was 1.79±0.87, 2.82±1.06 and 3.3±1.07, respectively, and NLR was significantly lower in patients receiving biologics (p=0.044) than those receiving DMARDs and NSAIDs.

TNF-α plays a major role in the pathogenesis of AS as it affects the granulocyte macrophage colony-stimulating factor, interleukin IL-1, IL-6 and IL-8. PDGF and cytokines IL-1ra, IL-6, IL-7, IL-8, IL-12 play important roles in inflammation and cause neutrophilia and hence increased NLR in patients with ankylosing spondylitis [19]. Therefore, TNF inhibitors reduce neutrophilia by reducing inflammation and hence NLR.

Similar findings were observed by Coskun et al. [19] in 2014, who concluded that the mean NLR value of the healthy controls and patients with ankylosing spondylitis was 1.90±0.89

and 2.67±1.17, respectively ($p<0.05$). After a 3-month course of TNF-α inhibitor, the patient group had a mean NLR value of 1.8±0.7, which was significantly lower than the pre-treatment values.

Significantly higher NLR and PLR were found in cases with concomitant extra-spinal or extra-articular disease and in cases with radiological evidence of bone erosion. This can be explained by the fact that these cases have a higher disease burden, with high disease activity and longer duration of disease and an expectedly higher load of cytokines leading to higher NLR and PLR. Being an observational (but not prospective) study, our study could not see the effect of treatment over time by repeated testing of NLR and PLR. In addition, the lack of TNF or other cytokine levels was a major drawback. Small sample size with unequal distribution of cases for different disease activities was also a drawback, which requires further validation with a larger sample size.

Conclusion

NLR and PLR are found to be new emerging tools for assessing the disease severity in patients with AS. These new indices not only properly correlate with the disease activity but can also be used in the objective assessment of disease activity, presence of extra-spinal disease and bone erosions and treatment response monitoring in patients with AS. In primary centres, where CRP (as well as ESR) is a remote thought, NLR and PLR can find a place as a primary choice of disease severity assessment markers as only Complete Blood Count (CBC) is needed and no special training or app is required with an added advantage of objectivity, reproducibility and simple test procedure.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by the Atal Bihari Vajpayee Institute of Medical Sciences and Dr. Ram Manohar Lohia Hospital Ethics Committee (No: 732/16, Date: 20/10/2016).

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