Neutrophile to lymphocyte and platelet to lymphocyte ratios predict clinical response to bDMARD in naïve spondylarthritis patients

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Abstract

Objective: We aim to study association between neutrophile to lymphocyte (NLR) and platelet to lymphocyte (PLR) ratios and disease activity, and their value to predict bDMARD response.

Methods: A set of spondylarthritis (SpA) patients under bDMARD registered in the Reuma.pt registry was studied. Sociodemographic, clinical and laboratorial variables were assessed on bDMARD initiation, 6, 12, 18 and 24 months (M) thereafter. Univariable and multivariable generalized estimation equations models assessed associations with disease activity. The NLR and PLR predictive value was assessed using univariable and multivariable logistic regression models.

Results: A total of 170 patients were included. Most were male (54.7%), with a predominantly axial phenotype (84.7%). Significant associations were observed between NLR [B=1.55, 95% confidence interval (CI) = (1.38; 1.74)] and PLR [(B=1.16, 95% CI = (1.09; 1.24)] with ASDAS-CRP ($p<0.001$). Both baseline ratios predicted Δ ASDAS-CRP ≥ 1.1 at 6 months [OR = 2.20, 95% CI = (1.21, 4.00) for NLR; OR = 1.02, 95% CI = (1.01, 1.04) for PLR, $p<0.01$)]. PLR was a significant predictor of Δ ASDAS-CRP ≥ 1.1 in all timepoints [OR (12 M) = 1.02, 95% CI = (1.00, 1.03), $p<0.05$; OR (18M) = 1.02, 95% CI = (1.01, 1.03), $p<0.001$; OR (24M) = 1.01, 95% CI = (1.01, 1.02), $p<0.01$].

Conclusion: NLR and PLR were associated with disease activity during the follow up of these patients. They seem to be significant predictors of therapeutic response to bDMARD in naïve SpA patients.

Keywords: Spondylarthritis; Neutrophile to lymphocyte ratio; Platelet to lymphocyte ratio; Disease activity; Treatment response.

Introduction

Spondylarthritis (SpA) constitute a group of heterogeneous diseases characterized by inflammatory symptoms involving the axial and/or peripheral joints. There are consensual classification criteria defined by the ASAS (Assessment of Spondylarthritis International Society) describing the two clinical subsets of the disease: axial[1] and peripheral[2].

Several tools have been developed to assess disease activity, namely the BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) and ASDAS (Ankylosing Spondylitis Disease Activity Score) indices, the latter accounting for acute phase reagents such as C-reactive protein or the erythrocyte sedimentation rate.[3] Entheseal involvement is important as the site of inflammation onset, and several indices assess the degree of involvement of these structures in patients with spondylarthritis, namely MASES (Maastricht AS Enthesitis Score), MEI (Mander Enthesitis Index)[4,5] and SPARCC (Spondylarthritis Research Consortium of Canada). In assessing function and structural damage, BASFI[6] (Bath Ankylosing Spondylitis Functional Index) and BASMI[7] (Bath Ankylosing Spondylitis Metrology Index) are the most frequently used in clinical practice.

Some of the aforementioned assessment scores involve patient reported outcomes, subject to various biases, namely the patient's subjective interpretation of pain, which may not be correctly attributed to the underlying rheumatic disease, and may influence decision-making therapy. Several markers and indices with a potential surrogate role for clinical appraisal of these patients have been studied and described in literature, including the ratios of serum neutrophils/lymphocytes (NLR) and platelets/lymphocytes (PLR). The NLR is a numeric value representative of both the innate immune response (neutrophile-mediated) and the adaptative immune response (lymphocyte-mediated).[8] The pathogenesis of SpA includes amplified interleukin-17 and interleukin-22 activity, leading to recruitment and activation of neutrophiles at diverse locations (enthesis, eye, skin and gut), including axial and peripheral joints).[9] Serum increase of neutrophile levels mirrored histological elevation of Granulocyte-macrophage colony-stimulating factor (GM-CSF) in inflamed tissues in animal models.[10]

Platelets are important inflammation regulators, increasing in response to stress induced hypercortisolaemia.[11] The PLR may therefore constitute a surrogate marker of inflammation in SpA patients.

These laboratorial values have been previously assessed as valid markers of disease activity and response to therapy in various rheumatic diseases.[12,13,14,15,16,17] Most research projects have

focused on rheumatoid arthritis, with a positive correlation between NLR and PLR, and disease activity[18], with higher levels being associated with a higher risk of primary failure to anti-TNFα therapies, positively correlating with DAS-28, ESR and CRP values.[19]

With regard to SpA there is still little consensus in the literature. Some authors report the absence of a relationship between these ratios and disease activity[17], while others have revealed a positive correlation with ESR and CRP.[14,20]

We hypothesize that these ratios have important associations with disease activity and therapeutic response.

The main objective of our study was to determine the predictive value of NLR and PLR in ASDAS clinically important improvement (Δ≥1.1) at 6, 12, 18 and 24 months of bDMARD therapy. Secondary outcomes included assessing longitudinal associations between the ratios and clinical and sociodemographic variables.

Materials and Methods

Study design and participants

A bicentric prospective open cohort study was conducted. We included patients classified as having spondylarthritis under bDMARD registered in Reuma.pt/Spondylarthritis until December 2021 in two Portuguese hospital centres. Data regarding the first 24 months under the first bDMARD was exported to an anonymized document.

Variables

Access was requested for sociodemographic data (age, sex, education level, smoking and drinking habits), psychosocial status (HADS), clinical data (diagnostic delay, bDMARD used and delay until use after diagnosis, HLA-B27 status, body mass index, comorbidities, ASDAS-ESR and CRP, BASDAI, BASMI, BASFI, MASES, SPARCC, LEI and DAS-28 CRP) and laboratorial data (neutrophile, lymphocyte and platelet count, ESR, CRP). NLR and PLR values were calculated, and clinical response to treatment was defined using ASDAS clinically important improvement (Δ≥1.1). [21] Clinical and laboratorial data were assessed on bDMARD initiation (t0), 6 months (t6), 12 months (t12), 18 months (t18) and 24 months (t24).

Outcomes

Our main outcome was observing higher NLR and PLR levels at baseline for patients with ASDAS clinically important improvement (Δ≥1.1) at 6 months of treatment. Secondary outcomes included higher levels of these ratios in patients with higher disease activity (assessed through

ASDAS or BASDAI) and in patients with higher degree of functional impairment (assessed through BASFI).

Exclusion criteria

Patients with less than three assessments for each clinical or laboratorial independent variables were excluded from the analysis.

Statistical analysis

Analysis was performed after normalization of continuous variables with non-normal distribution. Associations between independent variables and NLR and PLR were assessed through generalized estimation equations with linear and gamma with log-link models. The latter model was applied when the continuous dependent variable presented a non-normal distribution of values, with skewing towards 0, and was applied in assessing results for PLR[22]. Univariable models using NLR and PLR as dependent variables were built and variables with a p-value < 0.1 were selected to be used in multivariable GEE models, with the exception of ESR and CRP (to avoid redundancy). Three separate models were created according to the disease activity measure used (ASDAS-ESR, ASDAS-CRP and BASDAI + CRP), thus avoiding collinearity. Number of cases included in GEE analysis (total = 170 patients * 5 timepoints of assessment = 800 cases) was described for each model for both ratios. Assessment of baseline predictive value of NLR and PLR on ASDAS clinically important improvement at 6, 12, 18 and 24 months of bDMARD treatment was assessed using univariable logistic regressions. BASDAI wasn't used as an independent variable for predictive analysis since there are no consensual cut-offs of clinically significant variation in response to treatment, thus undermining the definition of a categorical variable. A p-value under 0.10 was considered significant for univariable models and those variables were used to build multivariable logistic regression models. Sensitivity analysis was conducted for the other definitions of disease activity (ASDAS-ESR and BASDAI). Controlling for ratio confounders (arterial hypertension and diabetes mellitus) was conducted.

Ethics approval

This project was approved by the Ethics Committee of both hospitals, and the study was approved by the national Reuma.pt committee. This study databases and the respective research processing were completely anonymised. All patients included in this analysis had previously signed informed consent in the Reuma.pt platform.

Results

From an initial pool of 469 individuals with SpA, a total of 170 patients were included in this analysis, after exclusion of 299 individuals with less than three assessments for each independent variable. Baseline characteristics have been described in Table I.

A majority were male (n=93; 54.7%), non-smokers (n=113; 68.9%), non-drinkers (n=140; 81.6%), with an average body mass index of 27.1 (±10.9) kg/m^2. A lower prevalence of common comorbidities was observed in comparison with the general population when weighed by age and gender: diabetes mellitus type 2 (n=7, 4.3%)[23] and hypertension (n=22; 13.4%)[24]. There was a predominantly axial phenotype (n=144; 84.7%), most individuals were HLA-B27 positive (n=100; 80.6%) with a mean age at bDMARD introduction of 41.8 (±12.2) years and a disease duration of15.9 (±11.3) years when the bDMARD treatment was started. Adalimumab was the most frequently administered bDMARD (n=69; 40.6%), followed by golimumab (n=39; 22.9%) and etanercept (n=34; 20.0%). When assessing disease related measures at baseline, patients generally presented high disease activity assessed through ASDAS-ESR and ASDAS-CRP (3.0 ±1.3 and 3.1 ±1.3, respectively), as well as with BASDAI (4.3±2.6). Psychosocial status at baseline was assessed through HADS (Hospital anxiety and depression scale) scores for anxiety and depression scores, averaging 6.3 (±5.3) and 4.6 ± (5.0), respectively, reflecting healthy levels of emotional distress.[25]

Univariable GEE models (supplementary Table I) demonstrated several significant variables in association with NLR [β value, (95% confidence interval)]: male gender [1.24, (0.95 to 1.62); p = 0.10], smoking [0.35, (0.05 to 0-66), p=0.08], hypertension [-0.27, (-0.48 to -0.06), p = 0.01], diabetes mellitus type II [-0.42, (-0.7 to -0.12) p=0.03], ESR [0.0, (0.0 to 0.03), p < 0.001], CRP [0.02, (0.01 to 0.03), p=0.03], BASMI [0.12, (0.06 to 0.19), p<0.001], BASFI [0.09, (0.05 to 0.12), p<0.001], BASDAI [0.09, (0.05 to 0.13), p<0.001], ASDAS-ESR [0.32, (0.24 to 0.40), p<0.001], and ASDAS-CRP [0.34, (0.25 to 0.42), p<0.001]. Multivariable models were created, one for each disease activity measure used: ASDAS-ESR, ASDAS-CRP and BASDAI (+CRP) (Table II).

As is evident in the abovementioned table, only type II diabetes was associated with NLR in the different models (β = -0.47, -0.45 and -0.49, p < 0.05). In the ASDAS-ESR and ASDAS-CRP models, male sex (β = 0.38 and 0.29, p< 0.01 and p=0.02, respectively) and BASMI (β = 0.08 and 0.09, p=0.04 and p=0.02, respectively) were significantly associated with NLR. ASDAS-ESR (β = 0.39, p<0.001), ASDAS-CRP (β = 0.44, p<0.001) and CRP in the BASDAI model (β = 0.02, p<0.001) were all associated with higher NLR.

A similar analysis was conducted for the PLR. Univariable GEE models (supplementary Table II) demonstrated several significant variables in association with PLR [β value, (95% confidence interval)]: diabetes mellitus type II [-0.25, (-0.49 to -0.01), p=0.04], csDMARD use [0.15, (0.05 to 0.25), p=0.01], corticosteroid use [0.14, (0.03 to 0.6), p=0.02], NSAID use [0.10, (0.0 to 0.18), p=0.02], ESR [0.01, (0.00 to 0.01), p<0.001], CRP [0.01, (0.00 to 0.01), p<0.001], BASMI [0.02, (0.00 to 0.05), p=0.07], BASFI [0.04, (0.03 to 0.06), p<0.001], MASES [0.02, (0.00 to 0.04), p=0.02], SPARCC [0.03, (0.01 to 0.05) p <0.001], BASDAI [0.04, (0.03 to 0.06), p<0.001], ASDAS-CRP [0.12, (0.09 to 0.15), p<0.001], ASDAS-ESR [0.13, (0.10 to 0.15), p<0.001], physician visual analogue scale [0.01, (0.00 to 0.01), <0.001] and nocturnal pain visual analogue scale [0.002, (0.001 to 0.004), p=0.01].

Multivariable models were created, one for each disease activity measure used: ASDAS-ESR, ASDAS-CRP and BASDAI (+CRP) (Table III).

The only variable with a statistically significant association in all models was the physician visual analogue scale (β = 0.01, p< 0.01). ASDAS-ESR (β = 0.13, p<0.001), ASDAS-CRP (β = 0.15, p<0.001) and CRP in the BASDAI model (β = 0.01, p<0.01) were all associated with higher N/L. Nocturnal pain visual analogue scale was only significant in the ASDAS-CRP model (β = -0.01, p=0.03).

Regarding clinically significant therapeutic response (ASDAS-ESR and CRP ≥ 1.1), univariable and multivariable logistic regressions were conducted at the four time sets of follow-up (Table IV). Both NLR and PLR had a positive predictive value in therapeutic response at 6 months (OR 2.20, p-value = 0.01, OR 1.02 = 1.02, p-value <0.01, respectively), an effect lost in multivariable analysis. At 12 months, both ratios were significant in predicting response to treatment in univariable and multivariable ASDAS-CRP models, while only PLR in the ASDAS-ESR model. (table IV).

At 18 months of treatment, both ratios were significant in predicting therapeutic response in the univariable ASDAS-CRP model (p<0.001), and NLR was the only one significant in both univariable and multivariable analysis. In the ASDAS-ESR model at 18 months, only PLR ratio was significant, with no significance in multivariable analysis. After 24 months there was only univariable significance of PLR in both ASDAS models. Regarding covariables for the multivariable models, bDMARD timing (age at introduction and time until treatment; p=0.02) and nocturnal pain (p<0.01) were significantly associated with clinically important improvement in the first 12 months of treatment. Indexes such as BASMI (p=0.88 at 12 months; p=0.53 at 18 months) and MASES (p=0.85 at 12 months;|p=0.10 at 18 months) weren't significant covariates

in predicting therapeutic response. Physician VAS ($p<0.01$) was more important on later evaluations.

Analysis was performed after normalization of continuous variables with non-normal distribution. Results were similar for both GEE and regressive models.

Discussion and Conclusions

Our study has revealed the presence of longitudinal association between NLR and PLR with disease activity assessed through ASDAS-ESR and ASDAS-CRP indexes after bDMARD introduction in naive spondylarthritis patients. Additional sociodemographic variables with significant association were seen mainly for NLR, namely male sex, hypertension, diabetes mellitus type II and active smoking. Baseline PLR presented as a constant univariable predictor of therapeutic response to first bDMARD in all time sets assessed, while NLR was only significant in predicting earlier response up to 18 months of treatment, and solely on ASDAS-CRP models at 12 and 18 months. Age at bDMARD introduction and nocturnal pain VAS were significant covariate predictors of response at 12 months of treatment for both ratios in the ASDAS-CRP models only. SPARCC score was only a significant predictor on the ASDAS-CRP model at 12 months for NLR. Physician VAS was a significant predictor of therapeutic response at 12 months for PLR in the ASDAS-ESR model, and at 18 months for NLR in the ASDAS-CRP model.

This study assessed a more extended spectrum of SpA patients than previous studies, including predominantly axial and undifferentiated SpA phenotypes, and a residual subset of IBD associated SpA. Age at bDMARD introduction was within the range assessed in the literature (41.8 ±12.2 years), but male predominance was minimal (n=93; 54.7%) when comparing with the other studies.[26,] Comorbidities with a possible confounding effect in NLR or PLR values such as essential hypertension (n=22, 13.4%)[24] or diabetes mellitus type 2 (n=7, 4.3%)[23] were less reported than in the global Portuguese population. In the GEE multivariable models constructed, DM type 2 had a negative association with NLR over the follow-up course, which may be explained by good glycaemic control in this population, as traditional cardiovascular risk factors are closely monitored on our SpA patients. Our population demonstrated healthy levels of anxiety and depression, which may prove a bias for assessing mental health domains of the patient reported outcomes assessed.[25] Regarding disease activity measures, ASDAS-ESR, ASDAS-CRP and CRP in a BASDAI model all presented a significant association with higher NLR and PLR ($p<0.001$), thus supporting previously reported findings, and sustaining these ratios value as inflammation surrogate markers and their association with disease activity in SpA. Male sex was

only a significant covariable in the NLR multivariable model, with no significant association with PLR in univariable models. When assessing the ratios predictive value in clinically important improvement (Δ ASDAS ≥ 1.1), both were significant predictors of response for ASDAS-CRP models at 6 and 12 months, while PLR maintained significance for both disease activity models at all-time sets of evaluation. NLR showed an increased OR relative to PLR in models where both were significant predictors of therapeutical response, sustaining previous evidence of neutrophilia as a more expressive marker of inflammation vs lymphopenia or thrombocytosis in SpA.[15,27] Age at bDMARD introduction was a significant covariable in ASDAS-CRP models for absence of response at 12 months of treatment (p=0.02), but not further on due to absence of significance on univariable models.

The Covid19 pandemic proved to be a clinical challenge far broader than the obvious constraints of a global infectious disease with significant mortality and disability burden. Rheumatic patients, namely patients with spondylarthritis, had a more difficult access to presential consultations and intercurrences were more dependent on patient reports than on actual physical examination.[28] This context led to a rise in interest and development of long distance tools for assessment of disease activity and treatment response, and laboratorial markers that could be globally easily accessible were studied in this setting.

The N/L and P/L ratios are feasible in most countries due to the low cost of acquiring a hemogram with white blood cell count, and are regularly assessed in rheumatology consultations.

The N/L ratio constitutes a simple serum biomarker capable of reflecting aspects of both the innate and adaptative immune systems. Neutrophils are the main effector cells in primary response against pathogens and play an important mediator role in adaptative immunity, especially during extensive inflammatory responses.[29] Different subpopulations of neutrophils are developed in response to different stimuli, with further activation of other effector cells and pathologic mechanisms: macrophage increase in chronic inflammation and obesity and associated T-cell inhibition[29]; release of S100 calcium-binding proteins A8 and A9 with downstream granulocyte colony stimulator factor (G-CSF) stimulation and consequent neutrophilia in hyperglycaemia, with consequent atherogenesis and reticulated thrmobocytosis[30]; elevated reactive oxygen species (ROS) and myeloperoxidase (MPO) in hypercholesterolemia.[31]

NLR is also higher in patients with impaired glucose tolerance and diabetes mellitus (DM) type 2, especially in those with poor disease control.[32] Similarly, PLR, despite seemingly decreasing in the earlier phases of DM type 2, is higher in later stages.[32] NLR and PLR have also been observed at higher values in patients with non-dipper hypertension profiles.[33,34]

Neutrophile to lymphocyte ratio's role in rheumatology has been more extensively studied in rheumatoid arthritis and systemic lupus erythematosus, with a particular focus in diagnosis.

Gasparyan AY. *et al*[11] reviewed publications on the role of the PLR in inflammatory rheumatic diseases. Rheumatoid arthritis patients were retrospectively assessed in four large cohorts, controlling for comorbidities and corticosteroid use. Exclusive association of PLR with RA diagnosis was only independently observed in one study[16], while in other papers it was globally associated with inflammatory activity when in combination with NLR.[13,35]

NLR and PLR were also assessed in SLE patients, and both were positively correlated with SLEDAI scores ($r = 0.471$ and $r = 0.44$, $p<0.01$, respectively).[36]

Al-Osami MH. *et al*[20] were among the first authors to show significant elevation of NLR and PLR mean values in ankylosing spondylitis patients with active disease. They also demonstrated presence of weak correlations between NLR and PLR and BASDAI scores, although only the latter was significant ($r=0.219$, $p=0.012$).

A recent study by Rouhin S. *et al*[37] assessed PLR and NLR predictive value in radiographic sacroiliitis and active disease in axial SpA patients. Multivariable logistic regression analysis controlled for sociodemographic factors and disease duration demonstrated NLR (OR 1.459, $p=0.034$) and PLR (OR 4.842, $p<0.001$) as independent predictors of radiographic sacroiliitis. Only NLR had an independent predictor value (OR 6.931, $p = 0.002$) for active disease (BASDAI ≥4). Use of anti-TNFα therapies significantly reduced previously predetermined cut-offs for prediction of the dependent outcomes.

The novelty in our work relates to the assessment of bDMARD naïve patients, inclusion of patients with both axial and peripheral involvement and use of GEE, thus accounting for diverse inter-variable interactions and allowing us to establish more life-like statistical models. Additionally, we assessed therapeutic response based on ASDAS scores, the most reliable and consensual method of assessment, and created multivariable models at different time sets after biotechnological drug introduction, thus allowing for more reliable assessment of the predictive value of NLR and PLR at baseline for therapeutic response. Several limitations can be pointed out in this study. Firstly, the number of patients included in this analysis, despite significant, is not ideal for extrapolation for other clinical contexts. Secondly, the exclusion of an elevated number of patients due to missing data or low number of assessments limits the interpretation

of our results. Thirdly, inclusion of patients with peripheral involvement, although representing a minority, may restrict comparison against studies focused on axial spondylarthritis. Additionally, assessment of 6 monthly spaced time sets, according to monitoring protocols established in our country, may exclude important variations in the ratios.

Our study has shown good longitudinal association between NLR and PLR, and disease activity, as well as proving to be predictors of therapeutic response to bDMARD at 6 months of treatment. PLR was a more consistent predictor of ASDAS-CRP or ASDAS-ESR improvement, thus constituting further evidence for this ratio value in rheumatic patients.

Our results provide additional insight into NLR and PLR role in representing inflammation and consequently disease activity in SpA patients. A bDMARD naïve population helps equalizing therapeutical contribution in ratio variation, and a 24-month follow-up period allows for hypothesizing on long term impact of using NLR and PLR for monitoring these patients.

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Tables and Figures

Table I. Baseline population characteristics.

Variable		N valid
Male sex (n, %)	93 (54.7)	170
SpA subtype (n, %)		170
• **Axial SpA**	144 (84.7)	
• **Undifferentiated SpA**	17 (10)	
• **IBD SpA**	9 (5.3)	
Age at bDMARD initiation (mean, ±SD)	41.8 (±12.2)	170
Years until bDMARD initiation (mean, ±SD)	15.9 (±11.3)	170
HLA B27 positive (n, %)	100 (80.6)	124
BMI (mean, ±SD)	27.1 (±10.9)	158
University education (n, %)	41 (26.3)	156
Smoking status (n, %)		
• **Current smokers**	50 (31.1)	161
Alcohol status (n, %)		
• **Current drinkers**	31 (19.4)	160
Comorbidities (n, %)		
• **Hypertension**	22 (13.4)	164
• **Diabetes mellitus type 2**	7 (4.3)	162
Uveitis (n, %)	37 (22.0)	168
NSAID use	80 (47.1)	161
csDMARD use	32 (18.8)	158
bDMARD (n, %)		170
• **Adalimumab**	69 (40.6)	
• **Golimumab**	39 (22.9)	
• **Etanercept**	34 (20.0)	
• **Infliximab**	23 (13.5)	
• **Certolizumab**	5 (3.0)	
Laboratorial values (mean, ±SD)		170
• **ESR**	20.5 (±21.8)	
• **CRP (mg/L)**	14.7 (±29.4)	
• **NLR**	2.1 (±2.0)	
• **PLR**	113.2 (±58.1)	
Disease related measures (mean, ±SD)		
• **BASMI**	4.3 (±1.8)	144
• **BASFI**	4.6 (±2.9)	158
• **MASES**	1.1 (±2.1)	144
• **BASDAI**	4.3 (±2.6)	160
• **ASDAS-ESR**	3.0 (±1.3)	147
• **ASDAS-CRP**	3.1 (±1.3)	148
• **DAS-28 CRP***	3.0 (±1.1)	28
• **SPARCC**	1.4 (±2.7)	128
• **LEI**	0.5 (±0.9)	128
HADS (mean, ± SD)		
• **Anxiety score**	6.3 (±5.3)	52
• **Depression score**	4.6 (±5.0)	64

**only for peripheral involvement; N-valid represents the number of individuals with data for each variable at baseline. Abbreviations: ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARD – biotechnological disease modifying anti-rheumatic drug; BMI – body mass index; CRP - C-reactive protein; csDMARD – conventional DMARDs; DAS-8: Disease Activity Score 28 joints; ESR – erythrocyte sedimentation rate; LEI – Leeds Enthesitis Index; HADS – Hospital Anxiety and Depression Score; IBD – inflammatory bowel disease; HADS – Hospital Anxiety and Depression HLA-B27 – Human Leukocyte Antigen B27; MASES – Maastricht Ankylosing Spondylitis Enthesitis Score; NLR – neutrophile to lymphocyte ratio; PLR – platelet to lymphocyte ratio; SD – Standard Deviation; SpA – spondylarthritis; SPARCC - Spondylarthritis Research Consortium of Canada Enthesitis Index.*

Table II. Multivariable GEE models to study the association between the neutrophile/lymphocyte ratio (NLR, dependent variable) and clinical and demographic variables.

	GEE models					
Variables	**Model 1**		**Model 2**		**Model 3**	
	β (CI 95%)	**p-value**	**β (CI 95%)**	**p-value**	**β (CI 95%)**	**p-value**
Male sex	0.38 (0.13, 0.63)	<0.01	0.29 (0.04, 0.53)	0.02	0.21 (-0.03, 0.44)	0.08
Active smoker	0.31 (0.00, 0.63)	0.05	0.30 (-0.03, 0.62)	0.07	0.31 (-0.01, 0.62)	0.06
HTN	-0.04 (-0.30, 0.22)	0.76	-0.04 (-0.29, 0.21)	0.76	-0.02 (-0.26, 0.22)	0.87
DM type II	-0.47 (-0.89, -0.05)	0.03	-0.45 (-0.82, -0.07)	0.02	-0.49 (-0.91, -0.08)	0.02
BASMI	0.08 (0.00, 0.15)	0.04	0.09 (0.01, 0.16)	0.02	0.06 (-0.01, 0.13)	0.08
BASFI	-0.04 (-0.09, 0.01)	0.14	-0.06 (-0.11, -0.01)	0.02	0.03 (-0.03, 0.09)	0.33
ASDAS-ESR	0.39 (0.29, 0.49)	<0.001	-		-	
ASDAS-CRP	-		0.44 (0.32, 0.55)	<0.001	-	
BASDAI	-		-		0.02 (-0.05, 0.08)	0.63
CRP	-		-		0.02 (0.02, 0.03)	<0.001

Cells with a green filling represent significant variables in multivariable models. Model 1 – ASDAS-ESR as the disease activity measure, 579 cases included; Model 2 – ASDS-CRP as the disease activity measure, 579 cases included; Model 3 – BASDAI + CRP as the composite disease activity measure, 579 cases included. CRP was excluded in the first two models to avoid redundancy. Use of "-" reflects exclusion from a model. Abbreviations: ASDAS – Ankylosing Spondylitis Disease Activity Score; B – unstandardized beta coefficient; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index, CRP - C-reactive protein; HTN - hypertension; DM - Diabetes Mellitus; GEE - generalized estimated equations.

Table III. Multivariable GEE models to study the association between the platelet/lymphocyte ratio (PLR, dependent variable) and clinical and demographic variables.

	GEE models					
Variables	**Model 1**		**Model 2**		**Model 3**	
	β (CI 95%)	**p-value**	**β (CI 95%)**	**p-value**	**β (CI 95%)**	**p-value**
DM type II	-0.14 (-0.46, 0.17)	0.37	-0.10 (-0.39, 0.20)	0.52	-0.12 (-0.42, 0.17)	0.43
BASMI	-0.01 (-0.05, 0.02)	0.41	-0.01 (-0.04, 0.02)	0.39	-0.02 (-0.05, 0.02)	0.36
BASFI	-0.01 (-0.03, 0.02)	0.88	0.00 (-0.03, 0.03)	0.99	0.01 (-0.02, 0.05)	0.53
SPARCC	-0.01 (-0.02, 0.01)	0.38	-		0.01 (-0.01, 0.03)	0.44
MASES	-		-0.01 (-0.02, 0.01)	0.35	-	
Physician VAS	0.01 (0.00, 0.01)	<0.001	0.01 (0.001, 0.01)	<0.01	0.01 (0.00, 0.01)	<0.01
Nocturnal pain VAS	-0.01 (-0.01, -0.01)	0.05	-0.01 (-0.01, 0.00)	0.03	-0.001 (-0.001, 0.001)	0.21
ASDAS-ESR	0.13 (0.08, 0.19)	<0.001	-		-	
ASDAS-CRP	-		0.15 (0.09, 0.21)	<0.001	-	
BASDAI	-		-		0.01 (-0.03, 0.05)	0.72
CRP	-		-		0.01 (0.00, 0.01)	<0.001

Cells with filling represent significant variables in multivariable models. Model 1 – ASDAS-ESR as the disease activity measure, 360 cases included; Model 2 – ASDS-CRP as the disease activity measure, 361 cases included; Model 3 – BASDAI + CRP as the composite disease activity measure, 359 cases included. CRP was excluded in the first two models to avoid redundancy. Use of "-" reflects exclusion from a model. Abbreviations: ASDAS – Ankylosing Spondylitis Disease Activity Score; B – unstandardized beta coefficient; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index, CRP - C-reactive protein; HTN - hypertension; DM - Diabetes Mellitus; GEE - generalized estimated equations; VAS – visual analogue scale.

Table IV: Predictive value of NLR and PLR in clinically important improvement (Δ ASDAS ≥ 1.1) using ASDAS-ESR and ASDAS-CRP.

Univariable models								
	T6*		T12*		T18*		T24*	
Disease activity measure	ASDAS-CRP	ASDAS-ESR	ASDAS-CRP	ASDAS-ESR	ASDAS-CRP	ASDAS-ESR	ASDAS-CRP	ASDAS-ESR
NLR	2.20 (1.21; 4.00), 0.01	2.77 (1.43; 5.36), <0.01	2.62 (1.02; 6.73), <0.05		2.44 (1.59; 3.76), <0.001			
PLR	1.02 (1.01; 1.04), <0.01	1.03 (1.01; 1.05), <0.001	1.02 (1.00; 1.03), 0.02	1.02 (1.00;1.04), <0.05	1.02 (1.01; 1.03), <0.001	1.01 (1.01; 1.02), <0.01	1.01 (1.00; 1.02), <0.01	1.01 (1.00; 1.02), 0.01

Multivariable models					
	T12			T18	
Disease activity measure	ASDAS-CRP		ASDAS-ESR	ASDAS-CRP	
Age at bDMARD introduction	0.87 (0.78; 0.98), 0.02	0.91 (0.85; 0.98), 0.02	-	-	
Years until bDMARD	1.06 (0.96; 1.17), 0.24	1.03 (0.96; 1.10), 0.45	-	-	
BASMI	-	-	1.04 (0.60; 1.82), 0.88	1.14 (0.76; 1.071), 0.53	
BASFI	1.07 (0.74; 1.56), 0.71	-	1.06 (0.73; 1.53), 0.76	0.98 (0.70; 1.37), 0.91	
MASES		-	0.96 (0.65; 1.44), 0.85	1.23 (0.99; 1.02), 0.10	

SPARCC	1.83 (1.05; 3.19), 0.03	-	-	-
Physician VAS	-	-	1.08 (1.04; 1.13), <0.001	1.04 (1.01; 1.06), <0.01
Nocturnal pain VAS	1.05 (1.01; 1.08), <0.01	1.04 (1.02;1.07), <0.001	-	1.00 (0.98; 1.03), 0.84
NLR	2.62 (1.02, 6.73), 0.04	-	-	2.50 (1.011, 5.63), 0.03
PLR	-	1.02 (1.00, 1.03), 0.02	1.02 (1.00, 1.04), 0.04	-

*Results shown as odds-ratio (95% confidence interval), p-value; Univariable analysis: beige filling corresponds to absence of significance in univariable analysis; light grey filling corresponds to loss of statistical significance of NLR or PLR in multivariable models. Multivariable models presented if ratio significance was maintained. Use of "-" reflects exclusion from a model. NLR and PLR were assessed separately; Abbreviations: ASDAS - Ankylosing Spondylitis Disease Activity Score; BASMI - Bath Ankylosing Spondylitis Metrology Index; BASFI - Bath Ankylosing Spondylitis Function Index; bDMARD - biotechnological disease modifying antirheumatic drug; CRP - C-reactive protein; ESR -erythrocyte sedimentation rate; MASES - Maastricht Ankylosing Spondylitis Enthesitis Score; NLR - neutrophile to lymphocyte ratio; PLR - platelet to lymphocyte ratio; SPARCC - Spondylarthritis Research Consortium of Canada Enthesitis Index; VAS - visual analogue scale.

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Supplementary material

Supplementary Table I. Univariable GEE analysis to study the association between the neutrophile/lymphocyte ratio (NLR, dependent variable) and clinical and demographic variables

Variable	β (95% CI)	P value
Male gender	1.50 (0.90 - 2.40)	0.09
Age at bDMARD initiation	1.00 (0.99 – 1.02)	0.97
Years until bDMARD initiation	0.99 (0.97 – 1.01)	0.35
HLA B27 positive	1.18 (0.75 – 1.84)	0.48
University education	0.88 (0.54 – 1.44)	0.62
Smoking	2.03 (0.92 – 4.48)	0.08
Alcohol use	0.87 (0.57 – 1.38)	0.59
BMI	1.00 (0.99 – 1.01)	0.91
Hypertension	0.68 (0.48 – 0.94)	0.02*
Diabetes mellitus type II	0.59 (0.20 – 0.50)	< 0.001*
HADS anxiety	1.01 (0.98 – 1.05)	0.47
HADS depression	1.03 (0.99 – 1.07)	0.15
Diabetes	0.59 (0.20 – 0.50)	< 0.001*
Uveitis	2.14 (0.77 – 6.01)	0.15
csDMARD	0.94 (0.59 – 1.50)	0.79
Corticosteroid	1.32 (0.80 – 2.15)	0.28
NSAID	1.32 (0.88 – 1.97)	0.18
Patient VAS	1.01 (1.01 – 1.02)	<0.001*
Physician VAS	1.02 (1.01 – 1.02)	<0.001*
Nocturnal VAS	1.01 (1.00 – 1.01)	0.02*
Spine VAS	1.01 (1.00 – 1.02)	0.02*
ESR	1.02 (1.00 – 1.03)	0.03*
CRP	1.02 (1.01 – 1.03)	<0.001*
BASMI	1.11 (1.03 – 1.21)	0.01*
BASFI	1.07 (1.02 – 1.12)	0.004*
MASES	0.96 (0.89 – 1.04)	0.34
SPARCC	0.98 (0.90 – 1.05)	0.52
BASDAI	1.10 (1.03 – 1.17)	0.002*

ASDAS ESR	1.31 (1.19 – 1.44)	< 0.001*
ASDAS CRP	1.44 (1.27 – 1.62)	< 0.001*

Results presented as odd ratio (O.R.) ± 95% confidence interval (CI); variables with p-values < 0.05; Abbreviations: ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARD – biotechnological disease modifying anti-rheumatic drug; BMI – body mass index; CRP - C-reactive protein; csDMARD – conventional DMARDs; DAS-8: Disease Activity Score 28 joints; ESR – erythrocyte sedimentation rate; LEI – Leeds Enthesitis Index; HADS – Hospital Anxiety and Depression Score; IBD – inflammatory bowel disease; HADS – Hospital Anxiety and Depression HLA-B27 – Human Leukocyte Antigen B27; MASES – Maastricht Ankylosing Spondylitis Enthesitis Score; NLR – neutrophile to lymphocyte ratio; PLR – platelet to lymphocyte ratio; SD – Standard Deviation; SpA – spondylarthritis; SPARCC - Spondylarthritis Research Consortium of Canada Enthesitis Index; VAS – visual analogue scale.

Supplementary Table II. Univariable GEE analysis to study the association between the platelet/lymphocyte ratio (PLR, dependent variable) and clinical and demographic variables

Variable	β (95% CI)	P value
Male gender	1.00 (0.90; 1.11)	0.95
Age at bDMARD initiation	1.00 (1.00; 1.00)	0.70
Years until bDMARD initiation	1.00 (1.00; 1.01)	0.75
HLA B27 positive	1.11 (0.96; 1.28)	0.15
University education	1.10 (0.96; 1.26)	0.16
Smoking	0.99 80.88; 1.12)	0.87
Alcohol use	1.01 (0.87; 1.17)	0.95
BMI	1.00 (0.99; 1.00)	0.32
Hypertension	0.93 (0.80; 1.08)	0.35
Diabetes mellitus type II	0.78 (0.61; 0.99)	0.04*
HADS anxiety	1.00 (0.98; 1.02)	0.96
HADS depression	1.00 (0.96; 1.03)	0.87
Uveitis	1.10 (0.95; 1.27)	0.21
csDMARD	1.17 (1.05; 1.29)	0.01*
Corticosteroid	1.15 (1.03; 1.30)	0.02*
NSAID	1.10 (1.02; 1.19)	0.02
Patient VAS	1.00 (1.00;1.00)	<0.001*
Physician VAS	1.01 (1.00; 1.01)	<0.001*
Nocturnal VAS	1.00 (1.00; 1.00)	0.01*
Spine VAS	1.00 (1.00;1.00)	<0.001*
ESR	1.01 (1.01; 1.01)	<0.001*
CRP	1.01 (1.00; 1.01)	<0.001*
BASMI	1.03 (1.00; 1.05)	0.07
BASFI	1.04 (1.03; 1.06)	<0.001*
MASES	1.02 (1.00; 1.04)	0.02*
SPARCC	1.03 (1.01; 1.05)	<0.01*
BASDAI	1.04 (1.03; 1.06)	<0.001*
ASDAS ESR	1.14 (1.10; 1.17)	<0.001*
ASDAS CRP	1.13 (1.10; 1.16)	<0.001*

Results presented as odd ratio (O.R.) ± 95% confidence interval (CI); variables with p-values < 0.05; Abbreviations: ASDAS – Ankylosing Spondylitis Disease Activity Score; BASDAI – Bath Ankylosing Spondylitis Disease Activity Index; BASFI – Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARD – biotechnological disease modifying anti-rheumatic drug; BMI – body mass index; CRP - C-reactive protein; csDMARD – conventional DMARDs; DAS-8: Disease Activity Score 28 joints; ESR – erythrocyte sedimentation rate; LEI – Leeds Enthesitis Index; HADS – Hospital Anxiety and Depression Score; IBD – inflammatory bowel disease; HADS – Hospital Anxiety and Depression HLA-B27 – Human Leukocyte Antigen B27; MASES – Maastricht Ankylosing Spondylitis Enthesitis Score; NLR – neutrophile to lymphocyte ratio; PLR – platelet to lymphocyte ratio; SD – Standard Deviation; SpA – spondylarthritis; SPARCC - Spondylarthritis Research Consortium of Canada Enthesitis Index; VAS – visual analogue scale.