Original Paper

Diagnostic Performance of Complete Blood Count-Derived Inflammatory Indices in Ankylosing Spondylitis: A Case-Control Study

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ABSTRACT: Ankylosing spondylitis (AS) is an inflammatory disease associated with persistent inflammation and progressive structural damage. Conventional markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), may remain normal despite active disease, highlighting the need for additional biomarkers. Hematological inflammatory markers from routine blood tests have emerged as inexpensive indicators of systemic inflammation. This study assessed the diagnostic performance of hematological inflammatory indices in AS and investigated their relationship with clinical status and functional capacity. This retrospective case-control pilot study included 17 radiographic AS patients and 16 controls. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI) were calculated. ROC analysis estimated discriminative ability, and Spearman correlation evaluated associations with BASDAI, ASDAS, and HAQ scores. NLR, PLR, SII, SIRI, and AISI were markedly elevated in AS versus controls, whereas MLR did not differ significantly. NLR had the best discriminative performance (AUC=0.930), followed by SII (AUC=0.912) and PLR (AUC=0.857). At the optimal cut-off (>3.028), NLR achieved 94.12% sensitivity and 93.75% specificity. None of the indices correlated significantly with disease activity or functional status. CBC-derived inflammatory indices, especially NLR and SII, exhibited good discriminative performance for AS, even when conventional inflammatory markers were not significantly different. Further large-scale, multicenter prospective studies are necessary to confirm these results and establish their clinical applicability.

KEYWORDS: *Ankylosing spondylitis. inflammation. biomarkers.*

Introduction

Ankylosing spondylitis (AS) is an inflammatory disease associated with persistent inflammation affecting the sacroiliac region, as well as the spine, potentially causing the progressive diseases status, new bone formation, and ankylosis [1-3].

It represents the radiographic form of axial spondyloarthritis (axSpA) [4].

AxSpA affects approximately 0.9%-1.4% of the global population and is more common in HLA-B27-positive individuals.

The use of imagistic techniques has increase the diagnosis ability of non-radiographic axSpA [5], and recent studies have reported increasing recognition of the disease among women and older adults [6,7].

Geographic and socioeconomic disparities contribute to diagnostic delays and unequal access to rheumatology care [8,9].

Because symptoms begin before the age of 30 years in more than 80% of patients, delayed diagnosis may result in irreversible structural damage, disability, reduced work capacity, absenteeism, and impaired productivity during the most active years of life [7,10,11].

Inflammatory low back pain, the hallmark symptom of axSpA, typically begins before the age of 40 years, persists for more than three months, worsens with rest, and improves with exercise [4].

Disease presentation varies according to the age at onset, with younger patients showing predominantly axial involvement and older patients more frequently presenting with peripheral manifestations [12].

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are currently used to evaluate AS severity, but they may remain within the normal range despite active axial inflammation, potentially leading to an underestimation of disease activity and influencing treatment decisions [13,14].

This limitation has prompted increasing interest in inexpensive and readily available

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inflammatory biomarkers calculated from routine blood test [15,16].

Among these, the Neutrophil/Lymphocyte Ratio (NLR) and Platelet/Lymphocyte Ratio (PLR) are highly investigated and may complete the puzzle of conventional inflammatory markers in the axSpA diseases management [14,17].

Other CBC-derived markers, such as MLR, SII, SIRI, and AISI, have also emerged as potential biomarkers because they integrate different inflammatory cell populations and are calculated from routine blood tests without additional cost.

Registry data have shown that NLR is associated with higher disease activity [18], NLR values >1.95 indicate high or very high disease activity [19], whereas both NLR and PLR decrease during biologic therapy and may help monitor treatment response [20].

Elevated baseline NLR has also been associated with TNF-α inhibitor discontinuation [21].

The clinical utility of these indices remains uncertain because of inconsistent findings across studies [22-24].

Although meta-analyses link NLR to disease activity [23,24], some observational studies found no correlation between NLR, PLR, and BASDAI scores [22].

Moreover, FAR may assess disease activity more accurately than NLR and PLR [25], limiting their routine use in axial spondyloarthritis.

Their associations with disease activity measured by ASDAS and BASDAI and with functional status assessed by the Health Assessment Questionnaire (HAQ) also remain insufficiently defined [4,13,14,18,22-25].

Objective

The present study aims to assess the diagnostic performance of hematological inflammatory indices in ankylosing spondylitis and to investigate their relationship with the severity of the clinical status and functional capacity.

In this light, we evaluate the strength of CBC-derived markers and their associations with BASDAI, ASDAS, or HAQ scores in AS, compared them with CRP and ESR.

We hypothesized that complete blood count-derived inflammatory indices would distinguish AS from healthy people, as well as will stratify AS by better distinguish between clinical and functional status.

Methods

Our retrospective, single-center case-control pilot study cohort contain 17 adults with radiographic ankylosing spondylitis (AS) receiving biologic disease-modifying antirheumatic drugs (bDMARDs) and 16 age-and sex-matched healthy people.

Clinical, and laboratory data were collected and analyzed.

The following inclusion conditions was applied for the AS cohort: (i) age over 18 years; (ii) axAS classification according to the 1984 Modified New York criteria or the Assessment of SpondyloArthritis International Society (ASAS); (iii) treatment with bDMARDs; and (iv) ability to complete the clinical questionnaires.

Exclusion criteria were: (i) active bacterial or viral infection at the time of blood sampling; (ii) malignancy; (iii) other autoimmune/chronic inflammatory disorders; (iv) severe hepatic and renal failure; and (v) recent high-dose systemic glucocorticoid therapy that could affect leukocyte counts and hematological inflammatory indices.

Clinical Assessment

All patients underwent a rheumatological evaluation. Disease activity was assessed using ASDAS-CRP and BASDAI, and functional status using the Health Assessment Questionnaire (HAQ).

Laboratory Parameters and Calculation of Hematological Indices

Hematological inflammatory markers calculated from routine blood test using absolute number (abs. no.) of neutrophil, lymphocyte, monocyte, and platelet as follows: NLR as abs. no of neutrophil divided by abs. no of lymphocyte, PLR as abs no. of platelet divided by abs no. of lymphocyte, MLR as abs. no. of monocyte divided by abs. no. of lymphocyte, SII as abs. no. of platelet × abs. no. of neutrophil divided by abs. no. of lymphocyte, SIRI as abs. no. of neutrophil × abs. no. of monocyte divided by abs. no. of lymphocyte and AISI as abs. no. of neutrophil × abs. no. of monocyte × abs. no. of platelet divided by abs. no. of lymphocyte.

Conventional inflammatory markers were also evaluated.

Statistical Analysis

Statistical tests were used to evaluate this data (jamovi software version 2.7.37; The jamovi Project, Sydney, Australia).

The distribution of data and variability was analysed by running the *Shapiro-Wilk test for normality*.

Continuous variables are represented as mean±standard deviation (mean±SD) or median (interquartile range [IQR]), depending on appropriateness, while categorical variables are indicated as frequencies and percentages.

Comparisons between groups were carried out using Student's t-test or Welch's t-test for normally distributed variables, the Mann-Whitney U test for non-normally distributed variables, and the chi-square (χ^2) test for categorical variables.

The relationship between hematological inflammatory indices (NLR, PLR, MLR, SII, SIRI, and AISI) and BASDAI, ASDAS, and HAQ scores were also analysed using Spearman's rank correlation coefficient (ρ).

Discriminative performance was evaluated by ROC analysis, area under the curve (AUC), 95% confidence interval (95% CI), optimal cut-off value, sensitivity, specificity, and diagnostic accuracy.

For box-and-whisker plots GraphPad Prism (version 10.0; GraphPad Software, Boston, MA, USA) were used, as well as a p value cut-off of 0.05 was establish for significance.

Results

Biologic profile of AS group and control group are summarized below (Table 1).

Table 1. Biologic profile of AS group versus control group.

Parameter	Group	Mean	+/- SD
Age (years)	AS group	55.35	12.34
	Control group	48.06	6.57
Disease Duration (years)	AS group	14.88	5.12
	Control group	N/A	N/A
Hemoglobin (g/dL)	AS group	14.58	1.64
	Control group	13.69	1.24
WBC ($x10^9$ /L)	AS group	7.52	0.67
	Control group	6.61	2.06
Neutrophils ($x10^9$/L)	AS group	5.38	0.62
	Control group	3.73	1.69
Lymphocytes ($x10^9$/L)	AS group	1.65	0.40
	Control group	2.38	0.68
Monocytes ($x10^9$/L)	AS group	0.51	0.32
	Control group	0.53	0.14
Platelets ($x10^9$/L)	AS group	276.41	35.32
	Control group	268.19	69.47
Glucose (mg/dL)	AS group	101	8.81
	Control group	110.94	19.68
ALT (U/L)	AS group	27.65	8.62
	Control group	24.2	8.31
AST (U/L)	AS group	28.02	9.25
	Control group	27.47	9.99
Creatinine (mg/dL)	AS group	0.84	0.19
	Control group	0.74	0.19
BASDAI (score)	AS group	0.97	0.17
	Control group	N/A	N/A
ASDAS (score)	AS group	1.47	0.33
	Control group	N/A	N/A
HAQ (score)	AS group	0.69	0.29
	Control group	N/A	N/A

Patients with ankylosing spondylitis showed an increased total white blood cell and neutrophil absoute number and decreased lymphocyte absolute number than controls, whereas monocyte and platelet absolute number remain unchanged between groups.

Comparison of Conventional Inflammatory Markers

To evaluate differences between AS group and controls, the conventional CRP and ESR were analyzed in Table 2.

Table 2. Comparison of CRP and ESR.

Parameter	AS group	Control group	P value
CRP ≥6mg/L	6 (35.3%)	5 (31.3%)	p=0.805
CRP <6mg/L	11 (64.7%)	11 (68.7%)	
ESR (mm/h)	15.53±7.26	21.9±11.1	p=0.059

CRP and ESR values are summarized in Table 2. CRP did not differ significantly between groups (p=0.805).

Although the mean ESR was numerically higher in healthy controls than in patients with ankylosing spondylitis, the difference was not statistically significant (p=0.059).

Association Between CRP and Clinical Indices

BASDAI, ASDAS, and HAQ scores did not differ significantly between patients with CRP levels ≥6mg/L and those with CRP levels <6mg/L (Mann-Whitney U=26.5, p=0.529; U=30.5, p=0.839; and U=22.5, p=0.414, respectively).

These findings indicate no association between CRP levels and disease activity or functional status in the present cohort.

Simple and composite CBC-derived markers in AS

Simple and composite CBC-derived markers in AS versus control analysis data are summarized in Table 3.

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Table 3. Descriptive statistics and comparison of hematological inflammatory indices.

Parameter	Group	Median	IQR	P value
NLR	AS group	3.402	0.395	<0.001
	Control group	1.389	0.368	
PLR	AS group	161.074	52.3	<0.001
	Control group	109.538	34.6	
MLR	AS group	0.299	0.383	0.191
	Control group	0.223	0.0899	
SII	AS group	902.183	209	<0.001
	Control group	375.385	273	
SIRI	AS group	1.769	1.82	0.041
	Control group	0.705	0.653	
AISI	AS group	480.644	490	0.045
	Control group	190.009	260	

The simple hematological inflammatory indices differed in AS versus control groups.

NLR and PLR median were significantly increased in the AS (3.402 vs. 1.389; respectively 161.074 vs. 109.538) with p<0.001 Although the median MLR has an increased trend in the AS (0.299 vs. 0.223), without statistical significance (p=0.191).

These differences are illustrated in Figure 1.

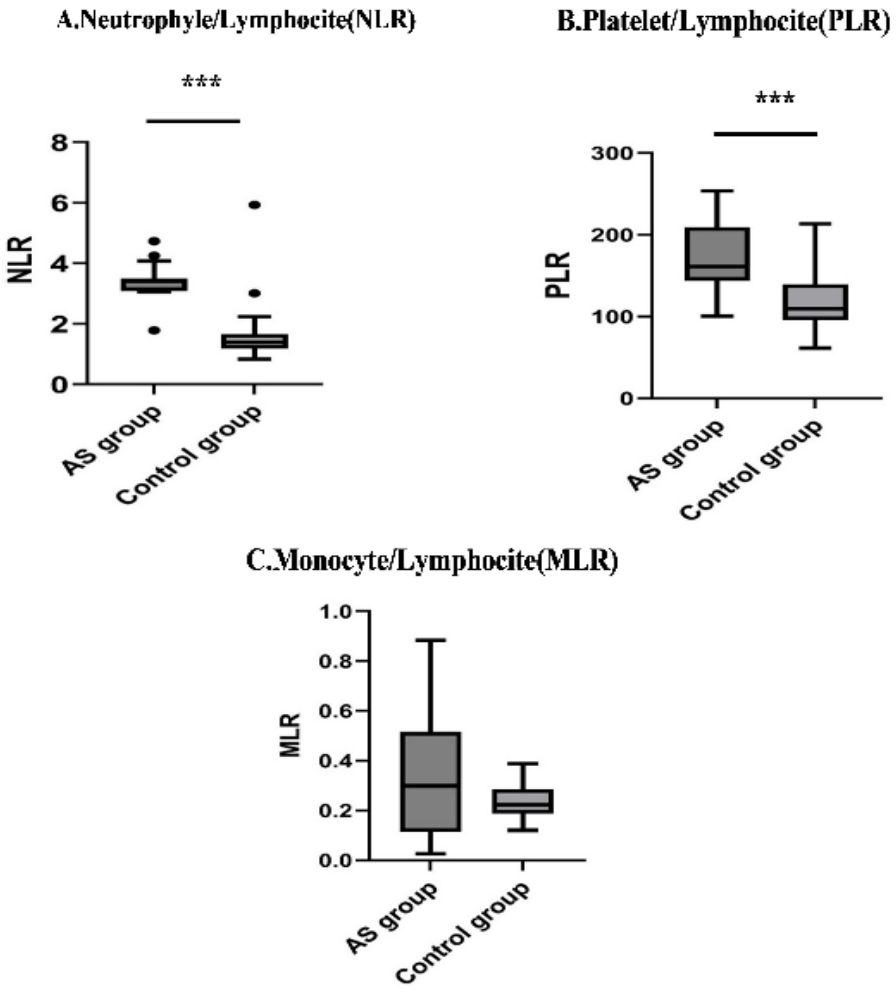


Figure 1. Simple hematological inflammatory pattern in AS compared with controls: (A) NLR; (B) PLR; (C) MLR. ***p<0.05

The composite indices also differed in AS versus controls.

SII showed the greatest between-group difference (p<0.001), whereas SIRI and AISI were also increased in the AS group (p=0.041 and p=0.045, respectively).

These differences are illustrated in Figure 2.

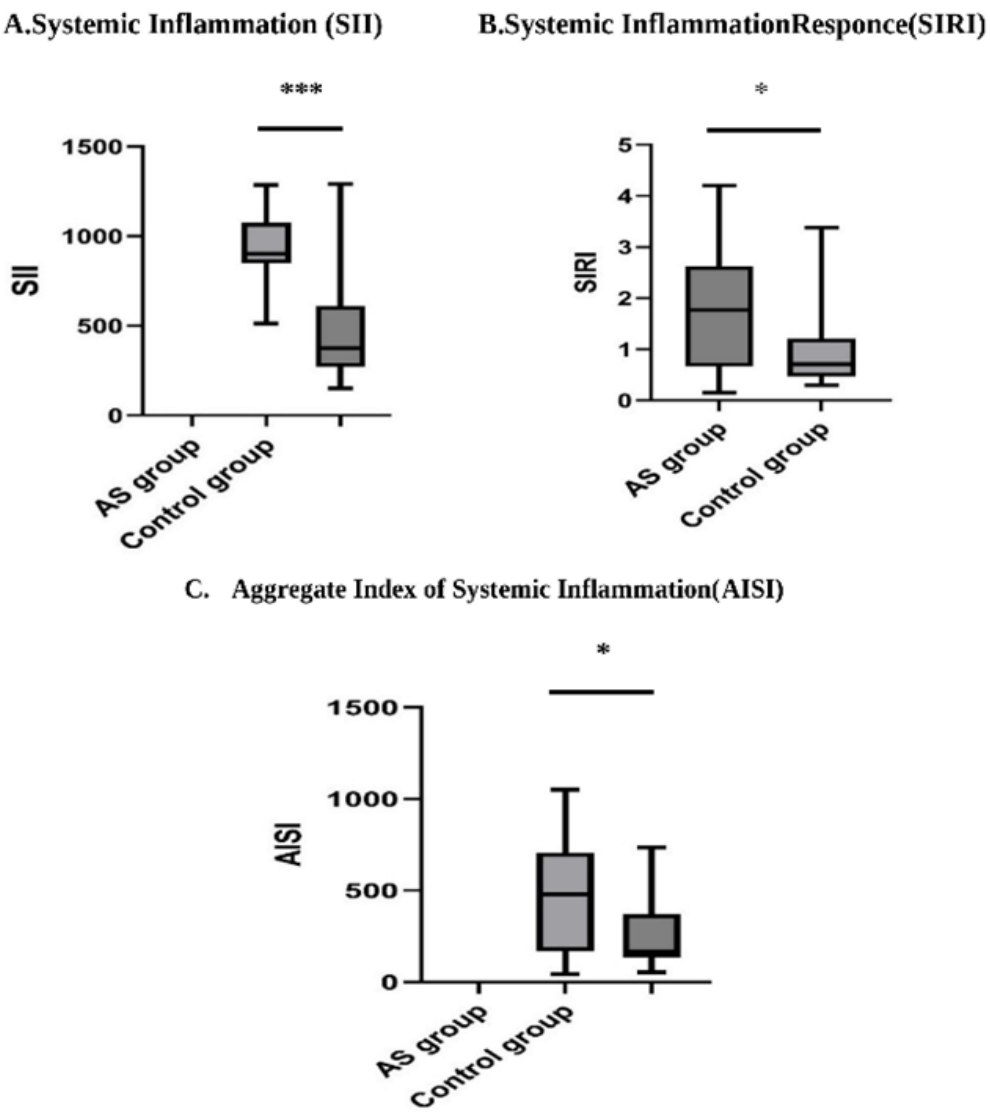


Figure 2. Level of composite inflammatory indices in AS versus controls: (A) SII; (B) SIRI; (C) AISI. *p<0.05; ***p<0.001.

SII, SIRI, and AISI were increased in patients with AS than in healthy controls.

SII has the greatest discrimination between groups, whereas SIRI and AISI demonstrated greater variability and partial overlap.

Correlation Between Hematological Inflammatory Indices and Clinical Scores (BASDAI, ASDAS, and HAQ)

In our study, Spearman's correlation analysis showed no significant associations of hematological inflammatory indices and BASDAI, ASDAS, or HAQ scores (all p>0.05) (Table 4).

Table 4. Correlation Between Hematological Inflammatory Indices (NLR, PLR, MLR, SII, SIRI, and AISI) and Clinical Scores (BASDAI, ASDAS, and HAQ) in AS.

Variables	BASDAI (ρ)	P value	ASDAS (ρ)	P value	HAQ (ρ)	P value
NLR	-0.288	0.263	-0.209	0.421	0.038	0.889
PLR	0.298	0.245	-0.132	0.614	0.164	0.543
MLR	0.301	0.241	-0.203	0.436	-0.171	0.527
SII	0.043	0.868	-0.164	0.529	-0.016	0.954
SIRI	0.303	0.237	-0.276	0.284	-0.247	0.357
AISI	0.335	0.189	-0.224	0.388	-0.171	0.527

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Abbreviations**:** Spearman's correlation coefficient (ρ), $p<0.05$ was considered significant. Correlations were calculated using available cases (BASDAI and ASDAS: $n=17$; HAQ: $n=16$).

Although NLR, PLR, SII, SIRI, and AISI were increased in AS, none correlated with BASDAI, ASDAS, or HAQ scores.

MLR neither differed between groups nor correlated with any clinical parameter, suggesting that these biomarkers are more useful for distinguishing patients with AS than for assessing disease activity or functional impairment in this cohort.

ROC Curve Analysis

Following the comparison of inflammatory indices between groups, ROC curve analysis was conducted to determine their discriminative capacity of AS versus healthy controls.

The corresponding data are shown in Table 5.

Table 5. ROC analysis data of hematological inflammatory indices (NLR, PLR, MLR, SII, SIRI, and AISI) in AS versus control.

Marker	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	Accuracy (%)
NLR	0.930	0.807-1.000	3.028	94.12	93.75	93.94
PLR	0.857	0.724-0.990	143.655	82.35	81.25	81.82
SII	0.912	0.786-1.000	826.594	82.35	93.75	87.88
AISI	0.706	0.516-0.896	469.188	58.82	87.50	72.73
SIRI	0.710	0.512-0.907	1.488	58.82	93.75	75.76
MLR	0.636	0.424-0.848	0.391	41.18	100.00	69.70

ROC curve analysis pattern reveals that NLR had a higher discriminative capacity in AS) versus controls (AUC=0.930; 95% CI: 0.807-1.000).

At the optimal cut-off value (>3.028), NLR achieved 94.12% sensitivity, 93.75% specificity, and 93.94% diagnostic accuracy.

SII also demonstrated an increased discriminative capacity (AUC=0.912), followed by PLR (AUC=0.857).

In contrast, SIRI (AUC=0.710) and AISI (AUC=0.706) has only modest discriminative ability, whereas MLR had the lowest diagnostic performance (AUC=0.636), despite achieving 100% specificity at the optimal cut-off (>0.391).

Overall, NLR and SII were the best-performing biomarkers, followed by PLR (Figure 3).

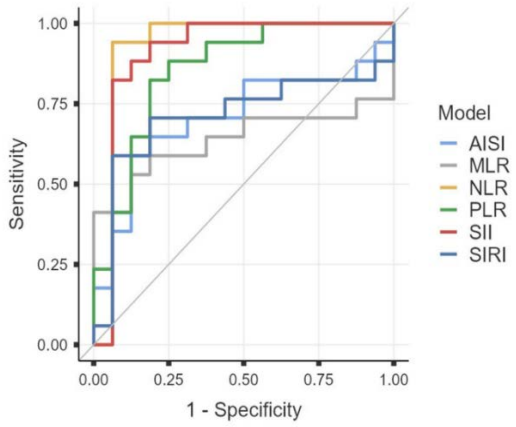


Figure 3. ROC curves of hematological inflammatory indices (NLR, PLR, MLR, SII, SIRI, and AISI) in AS versus control.

Univariate Logistic Regression Analysis

The associations between each hematological inflammatory index and the presence of AS were examined using univariable logistic regression models.

The resulting odds ratios (ORs), corresponding 95% confidence intervals (CIs), and statistical significance levels are presented in Table 6.

Table 6. Univariable Logistic Regression Analysis for the Association Between Hematological Inflammatory Indices and Ankylosing Spondylitis.

Inflammatory Marker	Odds Ratio (OR)	95% Confidence Interval	p value
NLR	5.20	1.92-14.11	0.001
PLR	1.04	1.01-1.06	0.007
MLR	32.68	0.33-3190.61	0.136
SII	1.007	1.003-1.011	0.001
SIRI	2.57	1.04-6.37	0.041
AISI	1.003	1.0003-1.010	0.034

The univariable logistic regression analysis revealed that NLR, PLR, SII, SIRI, and AISI were each associated with the presence of ankylosing spondylitis, whereas MLR did not reach statistical significance (p=0.136).

Among all evaluated biomarkers, NLR demonstrated the strongest association with AS diagnosis, as reflected by the highest odds ratio (OR=5.20), indicating that each unit increase in NLR was associated with a more than fivefold higher odds of AS.

Discussion

ROC analysis showed that an NLR cut-off value >3.028 identified patients with ankylosing spondylitis with 94.12% sensitivity, 93.75% specificity, and an overall diagnostic accuracy of 93.94% (AUC=0.930; 95% CI: 0.807-1.000).

These findings indicate high diagnostic performance.

The AUC observed in our study was higher than that reported in the meta-analysis by Xu et al. [24] which found a pooled AUC of 0.768.

However, this difference should be interpreted with caution because of the heterogeneity of the populations included in the meta-analysis and the specific characteristics of our study cohort.

Moreover, the higher diagnostic performance observed may partly reflect our small cohort and the potential overestimation of ROC curve parameters, a well-recognized limitation of pilot studies.

The best fit NLR cut-off identified in our study (>3.028) was also higher than that reported by Almirall et al. [19], who proposed cut-off values of 1.61 for the diagnosis of axial spondyloarthritis and 1.95 for patients with high disease activity.

This discrepancy may be explained by the characteristics of our study cohort, in which patients had an average of disease period approximately 15 years over the course of which received anti-inflammatory and/or biologic therapy.

Overall, they had low disease activity, as reflected by BASDAI, ASDAS, and HAQ scores, suggesting well-controlled disease or remission/low disease activity. In this setting, a higher NLR threshold may be required to distinguish patients with ankylosing spondylitis from healthy individuals.

Moreover, complete blood count-derived inflammatory indices may better reflect residual systemic inflammation, even when conventional inflammatory markers remain within the normal range or are only minimally elevated.

Our findings differ partly from those reported by Wu et al. [26], who found a significant association between SII and disease activity measured by the BASDAI and ASDAS scores.

This difference can be attributed to the characteristics of the study populations.

Wu et al. included patients with a broader spectrum of disease activity, including individuals with highly active inflammatory disease, whereas our cohort consisted predominantly of patients receiving effective anti-inflammatory and/or biologic therapy.

Consequently, most patients had low clinical disease activity and normal or only mildly elevated CRP and ESR levels.

Under these conditions, the limited variability of BASDAI and ASDAS scores, together with the effects of treatment on systemic inflammation, may have reduced the strength of the associations between hematological inflammatory indices and clinical disease activity.

In our cohort, NLR and SII appeared to reflect residual systemic inflammation rather than clinical disease activity as assessed by the BASDAI, ASDAS, and HAQ scores.

This interpretation is consistent with findings from the PULSAR registry [18], which demonstrated the influence of treatment on NLR and PLR values and supported their use as complementary biomarkers in patients with axial spondyloarthritis.

Likewise, studies including patients with higher inflammatory disease activity and less treatment-related suppression have shown NLR to be associated with both disease diagnosis and activity [19,20,27].

The higher diagnostic performance of SII observed in our study (AUC=0.912, sensitivity 82.35%, specificity 93.75%, and diagnostic accuracy 87.88%) further supports the value of integrating neutrophil, lymphocyte, and platelet numbers into a single marker of systemic inflammation.

As both NLR and SII are readily derived from routine complete blood counts without additional cost, they may provide useful complementary information, particularly in patients with normal CRP and ESR despite persistent inflammatory disease.

Overall, NLR and SII demonstrated the best diagnostic performance, with PLR also showing good discriminative ability, whereas SIRI, AISI, and particularly MLR had more limited diagnostic value.

None of the evaluated indices correlated with BASDAI, ASDAS, or HAQ scores, indicating that these biomarkers may be more useful for identifying residual systemic inflammation than for assessing clinical disease activity in this cohort.

The results of the univariable logistic regression analysis were consistent with those of the ROC analysis.

NLR showed the strongest association with the presence of AS (OR=5.20), whereas PLR, SII, SIRI, and AISI were also significantly associated with the disease.

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In contrast, MLR was not significantly associated with AS, consistent with its lower diagnostic performance in the ROC analysis.

These results futher support the potential role of NLR as the most informative CBC-derived inflammatory marker evaluated in this study.

Study limitations

Although the findings of the present study support the potential discriminative power of complete blood count-derived inflammatory indices in ankylosing spondylitis, they should be interpreted in light of several limitations.

First, the small study cohort (17 patients with AS and 16 healthy controls), characteristic of a pilot study, may have led to an overestimation of diagnostic performance and highlights the need for external validation of the proposed cut-off values, including the NLR threshold of >3.028, in larger independent cohorts.

Second, the retrospective, observational, single-center study limits the power of the results and precluded multivariable analyses to adjust for confounding such as age, sex, disease duration, and treatment.

In addition, most patients had long-standing disease (approximately 15 years), low clinical disease activity, and were receiving anti-inflammatory and/or biologic therapy, all of which may have influenced NLR, PLR, SII, SIRI, and AISI values while reducing the variability of BASDAI and ASDAS scores.

Consequently, the absence of significant correlations between hematological indices and clinical disease activity must be interpreted carefully, as these biomarkers could reflect both residual systemic inflammation and treatment-related changes in peripheral blood cell populations [27-31].

Finally, the cross-sectional design did not enable assessment of longitudinal changes in these biomarkers in relation to disease progression or treatment response.

Therefore, larger prospective multicenter studies are needed to establish their clinical applicability.

Conclusions

The present study showed that NLR, PLR, SII, SIRI, and AISI were increased in patients with AS versus healthy controls, as well as MLR has not a switable marker to distinguish between the two groups.

Among the evaluated biomarkers, NLR and SII demonstrated the best diagnostic performance and appear to be promising complementary biomarkers for distinguishing patients with ankylosing spondylitis from healthy individuals.

In contrast, none of the hematological indices was significantly associated with BASDAI, ASDAS, or HAQ scores, suggesting that, in this cohort, these biomarkers are more useful for detecting residual systemic inflammation than for assessing clinical disease activity or functional impairment.

Do to the small sample cohort, the retrospective single-center design, and the lack of longitudinal follow-up, a larger prospective, multicenter studies are needed to confirm the discriminative cut-off values, and better establish their role in AS management.

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None to declare.

Author Contributions

Conceptualization, A.L.B. and A.M.B.; Methodology, A.M.B., A.L.B and C.A.B.; Investigation, C.A.B, A.L.B, C.C.D and Ax.M.B; Data analysis, C.A.B and Ax.M.B; Manuscript writing and initial draft preparation, C.A.B, A.M.B. and Ax.M.B; Manuscript review and editing, A.M.B and C.C.D; Supervision, A.M.B and A.L.B.

All authors read and approved the final manuscript".

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Conflicts of interest

The authors declare no competing interests.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki.

This retrospective, cross-sectional, single-center pilot study and the protocols utilized therein were approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova (Approval No. 207/20.09.2023).

Consent Statement

Written informed consent was obtained from all participants prior to their inclusion in the study.

Data availability

All data presented in the manuscript are available from the authors upon request.

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