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Serum fibrinogen to albumin ratio in patients with ankylosing spondylitis: correlation with disease activity and severity

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Abstract

Background: The fibrinogen to albumin ratio (FAR) has risen to prominence as a novel biomarker for various conditions, including systemic inflammation. Therefore, this study aims to assess the role of FAR in ankylosing spondylitis (AS) and its correlation with disease activity, severity, and functional status of AS patients. Thirty adult patients with AS were enrolled, along with 20 healthy age- and sex-matched subjects as controls. Bath Indices were used to determine the disease activity, severity, and functional status.

Results: The patients' mean age was 35.3 years, including 22 males (73.3%) and eight females (26.7%). The median disease duration was 10 years, ranging from 1 to 28 years. AS cases showed higher FAR than the control group ($P < 0.001$). Active cases were associated with significantly higher FAR when compared to cases in remission ($P < 0.001$). FAR showed significant positive correlations with Bath Indices including BASDAI, BASFI, and BASMI scores ($P = 0.002$, 0.002, < 0.001, 0.019, 0.022).

Conclusion: FAR has been increased in AS, particularly in active cases. FAR has also been associated with the impaired functional status of AS patients. FAR can represent a novel inflammatory parameter for monitoring disease activity and severity in AS.

Keywords: Ankylosing spondylitis, Fibrinogen to albumin ratio, Functional status, Disease activity

Background

Spondyloarthropathy (SpA) is a term used to refer to a group of various rheumatic disorders with similar clinical and genetic characteristics. They are categorized as peripheral (pSpA) or axial (axSpA) based on the most predominantly affected part of the body. Ankylosing spondylitis (AS), a type of SpA, is an autoimmune ailment that primarily affects the spines, sacroiliac joints (SIJs), and surrounding soft tissues, such as the tendons and ligaments. This inflammation causes fibrosis and soft tissue calcification in more advanced cases, resulting in subsequent loss of flexibility and spinal fusion, similar to "bamboo" with an immobile posture. The most common clinical symptoms are inflammatory back pain and progressive spinal stiffness, as well as arthritis of the hips, shoulders, peripheral joints, and fingers/toes. Acute anterior uveitis and inflammatory bowel disease (IBD) are examples of extra-articular symptoms [1]. Enthesitis is a prominent feature of axSpA, with entheses being well-recognized as the main target of musculoskeletal inflammation [2].

AS usually appears in the third decade of life and, in rare cases, after the age of 45. The prevalence of AS is estimated to be between 0.1 and 1.4% worldwide [3]. The outcome of AS varies and is partially influenced by some extra-articular features (such as uveitis, psoriasis, and IBD), age at diagnosis, and treatment [4].

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The liver produces fibrinogen, and its expression may increase in tandem with the inflammatory burden. Therefore, fibrinogen, like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), is classified as a positive acute-phase protein [4]. Serum albumin is likewise a liver protein, but its expression may be downregulated in case of systemic inflammation, in contrast to fibrinogen. Therefore, like transferrin, serum albumin is classified as a negative acute-phase protein [5]. The fibrinogen to albumin ratio (FAR) has recently been proposed as an inflammation-related index [6]

FAR has emerged as a novel biomarker for predicting the severity of different conditions, including esophageal squamous cell carcinoma [7], hepatocellular carcinoma [8], and retinal vein occlusion [9].

There is currently a scarcity of data on the role of FAR in AS disease. Therefore, this study focuses on the role of FAR in AS patients, as well as the relationship between FAR and AS disease activity and severity.

The current study's objective was to investigate the serum fibrinogen to albumin ratio in patients with ankylosing spondylitis and its correlation with disease activity, severity, and functional status.

Methods

Study design

This study is a case-control study.

Ethical consideration

The current study was carried out in accordance with the Helsinki Declaration, with signed informed consent obtained from all participants prior to participation. The Research Ethics Committee of the Faculty of Medicine-Benha University approved the current study.

Target population

Patients and controls

This study included 50 subjects recruited from Benha University Hospitals' Rheumatology, Rehabilitation, and Physical Medicine outpatient clinic and inpatient department. These 50 subjects were divided into two groups:

- Group (I): 30 ankylosing spondylitis patients
- Group (II): 20 apparently healthy subjects with matching age and sex as the control group

Inclusion criteria

All ankylosing spondylitis patients above 18 years of age fulfilled the modified New York criteria for the classification of AS. The criteria require the presence of at least one clinical criterion plus evidence of radiographic sacroiliitis [10].

Exclusion criteria

Participants were excluded in the case of the following:

1. Other systemic inflammatory or autoimmune disorders.
2. History of corticosteroid medication in the last 6 months.
3. Liver diseases.
4. Malignancy.

Complete history taking and a comprehensive clinical examination were performed on all patients.

Clinical assessment

1. The visual analog scale (VAS) was used to assess pain severity: the patient rated his pain from 1 to10. The VAS-zero score is the least pain, while the VAS 10.0 refers to the worst [11].
2. Assessment of AS disease activity, severity, and functional status:
   The Bath Indices: a set of functional and disease activity indices used to diagnose and track disease activity in AS patients [12].
   –Assessment of AS disease activity: by BASDAI score (Bath Ankylosing Spondylitis Disease Activity Index), which is a subjective method of assessment by the patient on a scale of 1–10 [13].

Patients were categorized into the remission group (BASDAI score < 4) and the active group (BASDAI score ≥ 4).

- Bath Ankylosing Spondylitis Metrology Index (BASMI): BASMI is a globally used composite index of spinal mobility. The BASMI scale spans from 0 to 10, with 0 representing no mobility limitation and 10 representing a severe limitation [14].
- Bath Ankylosing Spondylitis Functional Index (BASFI): BASFI represents a visual analog scale (VAS) index. The patient was asked to rate his/her capability to achieve tasks (BASFI) by drawing a vertical line on a 10-cm horizontal line. A score of 0 indicates that the task was simple, while a score of 10 indicates that the task was impossible to complete [15].
- Bath Ankylosing Spondylitis Patient Global Score (BAS-G): It reflects the effect of AS on the patient's quality of life. It includes two questions for the patients to rate the impact of the condition on their well-being during the previous week and 6 months on a 10-cm VAS. The BAS-G score ranges from 0 to 10 based on the average of the two scores [16].

C-Laboratory investigations

Complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum fibrinogen, and albumin levels were collected. Albumin levels were measured using the modified Bromocresol green colorimetric method. Fibrinogen levels were measured using the clotting time method. FAR = plasma fibrinogen (g/dl)/serum albumin (g/dl) [7].

E-Radiographic assessment

Plain radiographs and MRI of both right and left sacroiliac joints (oblique view or P/A view) were obtained to evaluate the early structural changes in the form of evidences and degree of sacroiliitis [17].

Statistical analysis

The Statistical Package for Social Science, version 25 (IBM Corp. Released 2017), was used to code, tabulate, and feed the obtained data into the computer (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY).

Descriptive statistics

For parametric numerical data, mean and standard deviation (SD) were utilized; for non-parametric numerical data, median and range were used. For non-numerical data, frequency and percentage were used.

Analytical statistics Student's *t*-test or Mann-Whitney *U* test was utilized to compare the differences of continuous variables, whereas the chi-square test or Fisher's exact test was utilized for categorical variables. The receiver operating characteristic (ROC curve) was applied to assess the sensitivity and specificity of quantitative diagnostic measures that categorize cases into one of two groups.

Probability of results

A *P*-value is considered significant if ≤ 0.05 at a confidence interval of 95%.

Table 2 Indices of disease activity and severity in all studied cases

		AS	
		***N* = 30**	
BASDAI score	Mean ± SD	4.7	± 1.4
Remission	*N*, %	10	33.3%
Activity	*N*, %	20	66.7%
BASFI score	Mean ± SD	4.7	± 1.5
BASMI score	Mean ± SD	5.2	± 1.6
BAS-G score	Mean ± SD	4.4	± 1.4

SD Standard deviation, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *BAS-G* Bath Ankylosing Spondylitis Global Score

Results

The present study was conducted on 30 AS cases, with a mean age of 35.3 years (Table 1). They were 22 males (73.3%). The median disease duration was ten and ranged from 1 to 28 years, in addition to 20 healthy control subjects of matched age and gender.

The mean scores for all studies cases in terms of BASDAI, BASFI, BASMI, and BAS-G were 4.7, 4.7, 5.2, and 4.4, respectively. Furthermore, 10 patients (33.3%) were in remission, whereas 20 patients (66.7%) were active (Table 2).

AS cases demonstrated significantly lower albumin, significantly higher fibrinogen, and FAR compared to the control group ($P < 0.001$ for each) (Table 3).

The receiver operating characteristic (ROC) curve of albumin, fibrinogen, FAR, ESR, and CRP was conducted for discrimination between the AS and control groups (diagnosis of AS). Albumin, fibrinogen, FAR, and ESR showed high accuracy AUCs (AUC = 0.987, 0.988, 0.998, 0.917, respectively), while CRP showed moderate accuracy AUC (AUC = 0.877) (Table 4 and Fig. 1).

Table 1 Comparison of demographic and anthropometric data between the studied groups

		AS		Control		*P* value
		***N* = 30**		***N* = 20**		
Age (years)	35.3	36.4	36.4	35.3	± 9.1	0.711
Males	22	14	14	22	73.3%	0.797
Females	8	6	6	8	26.7%	
Weight (kg)	76.8	79.2	79.2	76.8	± 16.8	0.603
Height (cm)	168.3	171.7	171.7	168.3	± 8.9	0.208
BMI (kg/m^2)	27.1	26.9	26.9	27.1	± 5.5	0.911
Duration (years)	**Median, range**	–	–			–

Numerical data are compared using the Student *t* test; categorical data are compared using the chi-square test

$P \leq 0.05$: significant; $P \leq 0.01$: highly significant

SD Standard deviation, *BMI* Body mass index

Table 5 shows that active cases had significantly associated with substantially lower albumin and significantly higher fibrinogen and FAR than cases in remission ($P = 0.002$, < 0.001, < 0.001, respectively).

ROC curve of albumin, fibrinogen, FA, ESR, and CRP was conducted to predict activity. Fibrinogen and FAR showed high accuracy AUCs (AUC = 0.917, 0.985, respectively); CRP, ESR, and albumin showed moderate accuracy AUCs (AUC = 0.897, 0.813, 0.793, respectively) (Table 6 and Fig. 2).

FAR showed significant positive correlations with ESR, CRP, BASDAI, BASFI, and BASMI scores ($P =$ 0.035, 0.006, 0.002, 0.002, < 0.001, 0.019, 0.022).

FAR demonstrated significant positive correlations with ESR, CRP, BASDAI, BASFI, and BASMI scores (P = 0.035, 0.006, 0.002, 0.002, < 0.001, 0.019, 0.022). All studied cases were subjected to plain X-ray and MRI on SIJ. Plain X-ray showed bilateral sacroiliitis: grade 2 in 53.3%, grade 3 in 26.7%, and grade 4 in 20%. In addition, MRI showed bilateral sacroiliitis: grade 2 in 53.3%, grade 3 in 26.7%, and grade 4 in 20%, indicating a statistically insignificant correlation with FAR (Table 7).

No significant differences were found in relation to albumin, fibrinogen levels, and FAR according to the received medications among all studied cases (Table 8).

Discussion

The present study aimed to determine fibrinogen level and albumin level, calculate FAR in a patient with ankylosing spondylitis, and study their correlation with disease activity and severity. AS cases showed significantly lower albumin, as well as significantly higher fibrinogen and FAR when compared to the control group ($P <$ 0.001).

In our study, FAR demonstrated significant positive correlations with ESR, CRP, BASDAI, BASFI, BASMI scores (P = 0.035, 0.006, 0.002, 0.002, < 0.001, 0.019, 0.022), which is consistent with the results of Liu et al. [18], who reported a positive correlations between FAR and BASDAI score ($r = 0.488$, $P < 0.001$), CRP ($r = 0.858$, $P < 0.001$), and ESR ($r = 0.817$, $P < 0.001$).

Table 4 Validity of albumin, fibrinogen, FAR, ESR, and CRP for the discrimination between the AS and control groups (diagnosis of AS)

	Albumin	Fibrinogen	FAR	ESR	CRP
AUC	0.987	0.988	0.998	0.917	0.877
Cutoff	< 4	316	77.9	15.5	5.5
Sensitivity (%)	90	90	96.7	86.7	83.3
Specificity (%)	95	100	100	100	100
PPV (%)	90	90	96.7	86.7	83.3
NPV (%)	95	100	100	100	100
Accuracy (%)	92	94	98	92	90

AUC Area under the ROC curve, *PPV* Positive predictive value, *NPV* Negative predictive value

In our study, fibrinogen and FAR had high accuracy AUCs (AUC = 0.917, 0.985, respectively); CRP, ESR, and albumin had moderate accuracy AUCs (AUC = 0.897, 0.813, 0.793, respectively), while albumin had a sensitivity of 95% and a specificity of 60% at optimal cutoff value (< 3.8 g/dl). Regarding fibrinogen, it had a sensitivity of 85% and a specificity of 90% at an optimal cutoff value (= 354 g/dl). Regarding FAR, it had a sensitivity of 90% and a specificity of 100% at an optimal cutoff value (= 93.2).

In contrast, Slouma et al. [19] stated that FAR has a significant potential to differentiate between patients with high disease activity and those with low disease activity, with an area under the curve (AUC) of 0.819. The best FAR cutoff value with the highest accuracy was 0, 1065 with a sensitivity of 0.792 and a specificity of 0.852.

According to Liu et al. [20], FAR was also considerably higher in active AS patients than in inactive patients ($P <$ 001). Spearman's correlation test revealed a positive relationship between FAR and BASDAI in AS patients ($r =$ 0.594, $P < 0.001$). According to the ROC curve analysis, FAR had a greater AUC than albumin and fibrinogen. The optimal FAR cutoff value for AS diagnosis was 78.84, with 88.2% specificity and 77.0% sensitivity.

Table 3 Comparison of albumin, fibrinogen, and FAR between the studied groups

		AS		Control		*P* value
		N = 30		*N* = 20		
Albumin level (g/dl)	**Mean ± SD**	3.7	0.2	4.3	0.2	**< 0.001**
Fibrinogen level (g/dl)	**Mean ± SD**	357.3	30	277.5	20	**< 0.001**
FAR	**Mean ± SD**	96.7	10.2	64.5	5.4	**< 0.001**

The Student *t* test was used for comparison

$P \leq 0.05$: significant; $P \leq 0.01$: highly significant

SD Standard deviation, *FAR* Fibrinogen/albumin ratio

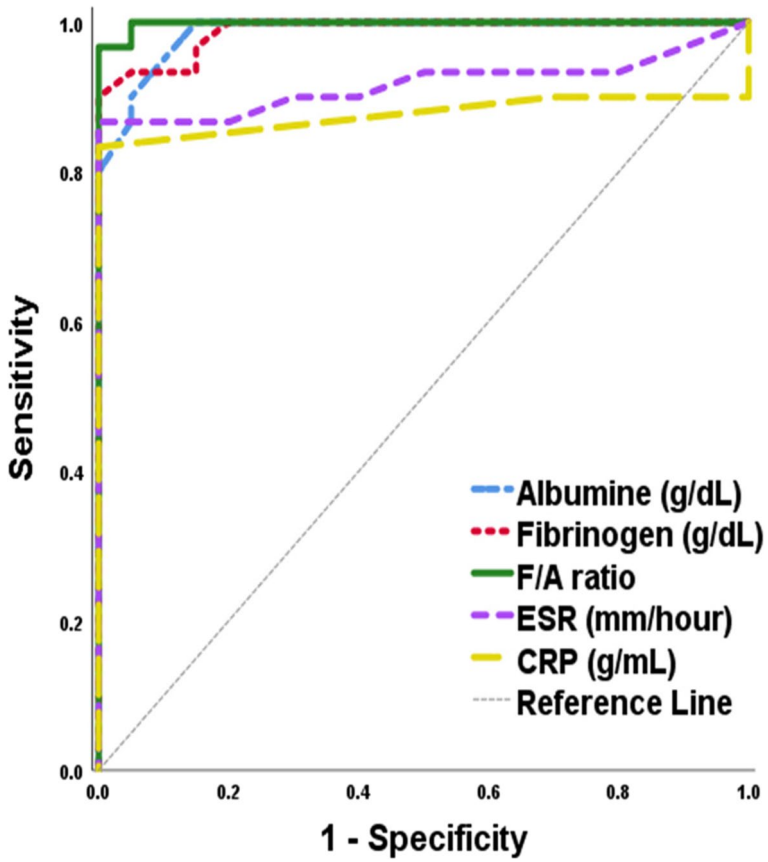

Fig. 1 ROC of albumin, fibrinogen, FAR, ESR, and CRP for discrimination between the AS and control groups

Table 5 Comparison of albumin, fibrinogen, and FAR according to activity in all studied cases

		Remission		Active		*P* value
		N = 10		*N* = 20		
Albumin level	**Mean ± SD**	3.8	0.2	3.6	0.1	**0.002**
Fibrinogen level	**Mean ± SD**	328.1	24.8	372.0	20.1	**< 0.001**
FAR	**Mean ± SD**	85.8	5.9	102.1	6.9	**< 0.001**

The Student *t* test was used for comparison

$P \leq 0.05$: significant; $P \leq 0.01$: highly significant

SD Standard deviation, *FAR* Fibrinogen/albumin ratio

Albumin levels are lower in severe malnutrition, chronic inflammation, and autoimmune disease. Compared to the control group, AS patients had significantly lower albumin and significantly higher fibrinogen and FAR. Albumin levels showed a significant negative correlation with BASDAI, BASMI, and BAS-G scores.

In contrast, active cases were significantly associated with substantially lower albumin and higher fibrinogen and FAR than cases in remission

This finding is consistent with the findings of Zhang et al. [21], who found that ESR, CRP, BASIDI, and BASIFI were significantly higher in the active group compared to the inactive group, while albumin was lower. Slouma et al. [19] found that fibrinogen levels were elevated in 45% of patients, and albumin levels were decreased in 51% of cases.

Fibrinogen is a glycoprotein complex formed by the liver, but studies have proved that it represents opposite

Table 6 Validity of albumin, fibrinogen, FAR, ESR, and CRP for the prediction of activity

	Albumin	Fibrinogen	FAR	ESR	CRP
AUC	0.793	0.917	0.985	0.813	0.897
Cutoff	< 3.8	354	93.2	26.5	18.4
Sensitivity (%)	95	85	90	90	85
Specificity (%)	60	90	100	60	90
PPV (%)	95	85	90	90	85
NPV (%)	60	90	100	60	90
Accuracy (%)	83.3	86.7	93.3	80	86.7

AUC Area under the ROC curve, *PPV* Positive predictive value, *NPV* Negative predictive value

expressions in inflammatory conditions. Therefore, fibrinogen is not only a critical coagulation factor but also a major acute-phase reactive protein in cases of chronic inflammation. During systemic inflammation, the immune system interacts with all components of the coagulation system and activates the production of fibrinogen by the liver and itself, resulting in high levels of fibrinogen expression [8].

In our study, fibrinogen levels showed significant positive correlations with CRP, BASDAI, and BASFI scores, which is in accordance with the results of Zhang et al. [21] who showed that ESR, CRP, and fibrinogen were positively correlated with BASIDI score with the goodness of fit of CRP, ESR, and fibrinogen to BASDAI of $r=0.763$, $r=0.689$, and $r=0.549$, respectively.

To the best of our knowledge, no previous studies have assessed the relation between sacroiliac joint affection radiologically and FAR. In the current study, all studied cases were subjected to plain X-ray and MRI on SIJ; however, the correlation with FAR was statistically insignificant. This may be attributed to the fact that radiographic structural severity is a marker of long-term damage in patients with AS.

The current study demonstrated statistically insignificant differences in relation to albumin, fibrinogen levels, and FAR according to the received medications among all studied cases; this may be attributed to the relatively small sample size.

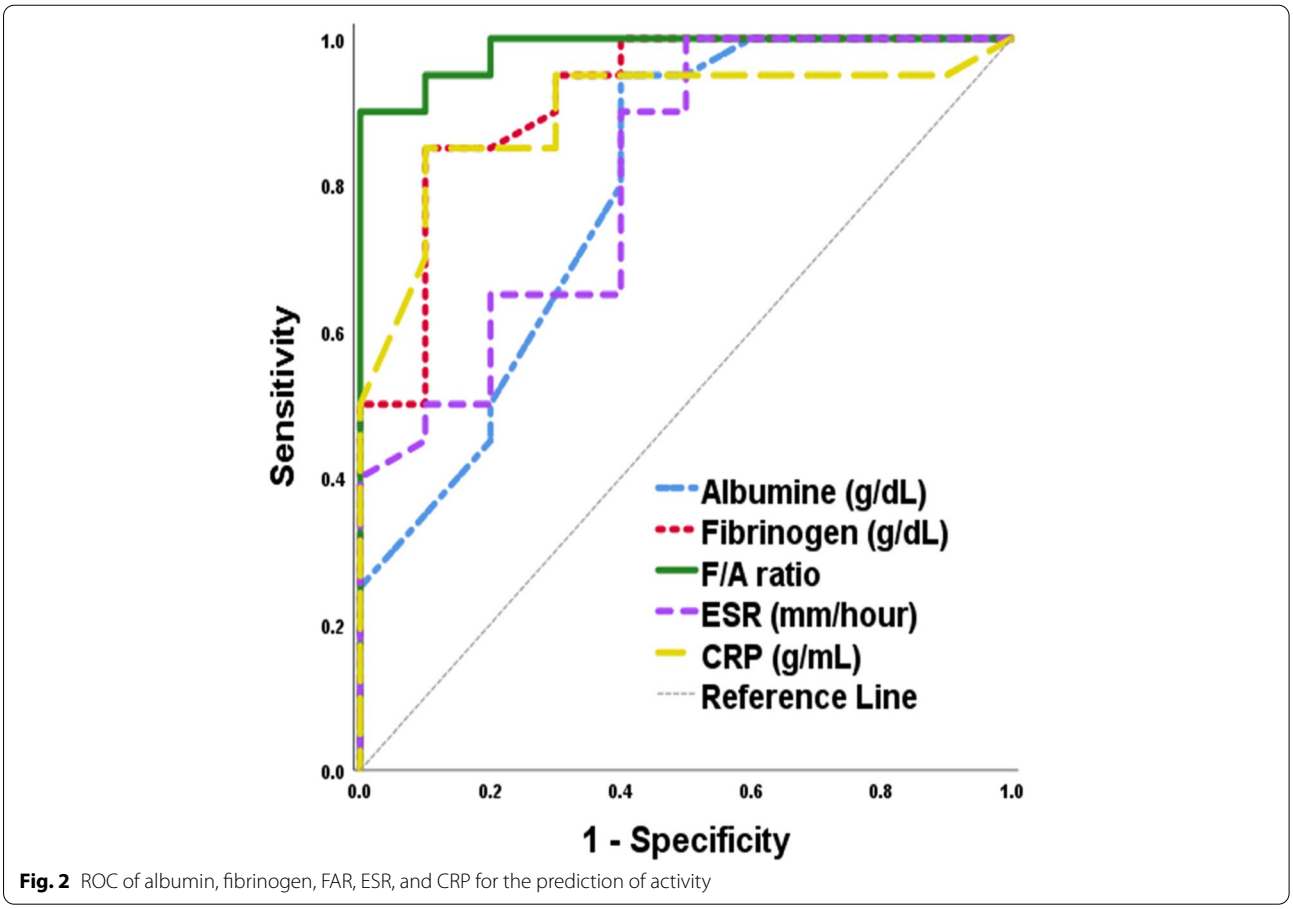

Fig. 2 ROC of albumin, fibrinogen, FAR, ESR, and CRP for the prediction of activity

Table 7 Correlations of albumin, fibrinogen, FAR with ESR, CRP, BASDAI, BASFI, BASMI, BAG-G scores, and sacroiliac joint radiological findings in AS cases

	Albumin		Fibrinogen		FAR	
	rs	*P* value	*rs*	*P* value	*rs*	*P* value
ESR	−0.294	0.115	0.258	0.168	0.387	0.035
CRP	−0.172	0.364	0.510	0.004	0.489	0.006
BASDAI score	−0.517	**0.003**	0.785	**< 0.001**	0.847	**< 0.001**
BASFI score	−0.287	0.124	0.404	**0.027**	0.427	**0.019**
BASMI score	−0.532	**0.002**	0.276	0.140	0.416	**0.022**
BAS-G score	−0.357	**0.043**	0.227	0.228	0.339	0.067
Plain X-ray on SIJ bilateral sacroiliitis	−0.151	0.425	0.175	0.356	0.218	0.247
MRI on SIJ bilateral sacroiliitis	0.120	0.528	−0.168	0.375	−0.173	0.360

rs correlation coefficient, *SIJ* sacroiliac joint

$P \leq 0.05$: significant, $P \leq 0.01$: highly significant

Table 8 Comparison of albumin, fibrinogen levels, and FAR according to the received medications among all studied cases

		Albumin		Fibrinogen		FAR	
		Mean	SD	Mean	SD	Mean	SD
NSAIDs	**No**	3.78	0.16	358.08	22.61	95.10	8.23
	Yes	3.66	0.14	356.83	34.63	97.70	11.41
		0.157		0.913		0.504	
Etanrecept	**No**	3.72	0.19	358.00	31.19	96.64	11.14
	Yes	3.68	0.09	356.00	28.88	96.70	8.50
		0.581		0.867		0.988	
Sulfasalazine	**No**	3.69	0.16	360.90	29.88	97.98	10.19
	Yes	3.74	0.17	350.20	30.36	94.01	10.17
		0.497		0.366		0.323	
Adalimumab	**No**	3.70	0.16	356.75	30.91	96.78	10.53
	Yes	3.85	0.21	365.50	9.19	95.01	2.84
		0.196		0.697		0.817	
Methotrexate	**No**	3.73	0.16	354.92	30.50	95.46	10.08
	Yes	3.58	0.10	373.00	23.28	104.43	7.94
		0.175		0.269		0102	

However, our study has limitations, such as the small sample size with a relatively wide range of patient disease duration and single opportunity participation.

Conclusion

FAR is significantly higher in active cases of ankylosing spondylitis than in remission, with a positive correlation with the BASIDI score. FAR serves as an available marker for detecting and assessing the severity of AS disease activity. Furthermore, FAR showed a significant positive correlation with BASIFI and BASIMI scores, indicating its significance in detecting the impaired functional activity of AS patients. FAR has the potential to predict the impaired functional activity and disease activity but not the radiological severity of sacroiliitis, as determined by X-ray and MRI.

Abbreviations

FAR: Fibrinogen to albumin ratio; AS: Ankylosing spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BAS-G: Bath Ankylosing Spondylitis Patient Global Score; SpA: Spondyloarthropathy; axSpA: Axial spondyloarthropathy; SIJs: Sacroiliac joints; IBD: Inflammatory bowel disease; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: Visual analog scale.

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Authors' contributions
All authors have read and approved the final manuscript. Idea suggestion, study design, data collection and analysis, and sharing in writing of the manuscript: NH, MS, EA, and AS. Manuscript writing and final revision: NH, EA, and AS.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Done, the Ethical committee's approval: number: MS1292020, date:12/9/2020.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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