C-Reactive Protein/Albumin Ratio as a New Biomarker in Axial SpondyloArthritis and its Relation to Disease activity

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Abstract

Introduction: The C-reactive protein (CRP) to albumin (ALB) ratio (CAR) has emerged as a novel inflammatory biomarker. **Aim of the work:** This study was designed to detect the C-reactive protein/Albumin Ratio (CAR) as a new biomarker in Axial SpondyloArthritis and its relation to disease activity. **Subjects and Methods:** This study was Cross sectional study conducted on 72 Axial SpA patients attending the inpatient and outpatient clinics of Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig university hospitals after taking a written consent and after review and approval by the Institutional Review Board (IRB) Committee during a period of six months from February to August 2022. **Results:** there was a statistical significance increase in mean CAR among active compared to non-active cases (3.41±3.38) ;(2.09±1.91) respectively. There was a statistically significant +ve correlation between CAR and BASDAI, BASFI, ESR and CRP. Also, there was a statistically significant -ve correlation between CAR and albumin among the studied cases. **Conclusion:** CAR was increased in axSpA of the active group. It was an independent predictive factor for axSpA disease activity and may be a novel and reliable biomarker for assessing the disease activity of axSpA patients.

KeyWords: Axial SpondyloArthritis (axSpA); C-reactive protein (CRP); C-reactive protein/Albumin Ratio (CAR); biomarker.

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Introduction

Axial SpondyloArthritis (axSpA) is an autoimmune disease that produces inflammation in the spine, sacroiliac, and large peripheral joints, particular entheses and extra articular tissues such as the anterior uvea and aorta. Intervertebral and facet joint ankylosis is caused by the development of new bone in the axial skeleton, resulting in functional limitation (1) **(Pamukcu et al 2021).** Early diagnosis and administration of appropriate drug therapy have completely changed the prognosis of axSpA patients (2) **(Micheroli et al 2017).**

Biochemical markers and questionnaires, together with MRI scan, can aid in the analysis of axSpA disease activity. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Bath Ankylosing spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) are among them and frequently used (3) **(Lorenzin et al 2017).**

The acute phase reactant C-reactive protein (CRP) is well known, it's also a highly sensitive indicator of tissue injury and acute inflammation. CRP is used to track the severity of infectious, inflammatory, autoimmune, and rheumatologic illnesses, as well as their response to treatment. CRP is also utilized as a biomarker to predict mortality and morbidity in patients suffering from neurological and cardiovascular illnesses (4) **(Lee et al 2020).**

C-reactive protein (CRP) to Albumin Ratio (CAR) has been linked to the disease activity of inflammatory disorders like Crohn's disease and rheumatoid arthritis in several studies (5) **(Yang et al 2018).** When compared to isolated CRP levels, the CAR value more precisely indicates inflammation.

Subjects and Methods

This study was Cross sectional study conducted on 72 Axial SpA, patients, Patients attending the inpatient and outpatient clinics of Rheumatology and Rehabilitation Department, Faculty of Medicine, Zagazig university hospitals after taking a written consent and after review and approval by the Institutional Review Board (IRB) Committee during a period of six months from February to August 2022.

Inclusion criteria: Patients diagnosed as axSpA according to the ASAS classification criteria for axSpA(6) **(Rudwaleit et al., 2009).** The age of the patients was above 18 years and patients were divided into active groups which include (36) patients and inactive group that include (36) patients, based on cutoff value of 4, with BASDAI ≥4 in the active group and BASDAI < 4 in the inactive group (7) **(Garrett et al., 1994).**

Exclusion criteria: Patients with concomitant infections, cardiovascular diseases, diabetes mellitus, renal and hepatic dysfunction, liver cirrhosis, malignancy or tuberculosis and autoimmune diseases, like Systemic lupus erythematosus, Scleroderma, mixed connective tissue diseases.

Demographic data, duration of disease, and BASDAI and BASFI score of the patients with Ax-SpA were recorded. ESR (mm/hour), CRP (mg/dL), and albumin (g/dL) values were determined based on laboratory analysis. The CAR value was calculated by dividing the CRP level by the albumin level.

BASDAI was used to evaluate disease-specific symptoms such as fatigue, spinal and peripheral joint pain, swelling, and morning stiffness duration and severity and interpreted based on a score ranging from 0 to 10, The data of the two groups, which were divided based on BASDAI score (BASDAI ≥4 = high activity, <4 = low activity), were compared statistically.

Statistical analysis:

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 27.0(8) **(IBM, 2020).** Qualitative data were represented as frequencies and relative percentages. Chi square test was used to calculate difference between qualitative variables. Mann Whitney (MW) test was used to calculate difference between quantitative variables in two groups in not normally distributed data. Kruskal Wallis test was used to calculate difference between quantitative variables in more than two groups in not normally distributed data. Spearman's correlation coefficient used to calculate correlation between quantitative variables.

Results

Seventy-two axSpA patients (42 male, 30 female), mean age (37.13 ± 9.14) were enrolled in this study. Diagnosis of axSpA was performed according to the Assessment of SpondyloArthritis international Society (ASAS). Which divided into

two groups according to the disease activity active group (BASDAI≥4) included 36 patients and the mean ±Sd of age of this group (38.72±8.36) and 19(52.8%) female, and 17(47.2%) male, the mean ± Sd of disease duration was (7.64±6.06). while non active groups (BASDAI < 4) included 36 patients, the mean ± Sd of age was (35.53± 9.71) and 11(30.6%) females and 25(69.4%) males, the mean ± Sd of disease duration was (7.91±5.72).

According to clinical and radiological data shows that there were no statistically significant differences between the studied groups in back pain, sacroiliitis, skin rash, anterior uveitis or GIT symptoms or MRI finding, but there was a statistically significant increase in frequency of peripheral joints and enthesitis among active cases compared to non-active. which are presented in the **table (1)**:

Table (1): Clinical data among the studied groups:

Variable		Group I (Active cases) (*n*=36)		Group II (Non-active cases) (n=36)		χ^2	P
		No	%	No	%		
Back pain:	LBP Neck pain LBP+ Neck pain	32 2 2	88.9 5.6 5.6	36 0 0	100 0 0	4.24	0.12 NS
Sacroiliitis:	Unilateral Bilateral	8 28	22.2 77.8	2 34	5.6 94.4	2.90	0.08 NS
Peripheral joints:	No Yes	5 31	13.9 86.1	25 11	69.4 30.6	**22.86**	**<0.001 ****
Skin rash:	No Yes	35 1	97.2 2.8	35 1	97.2 2.8	0	1 NS
Enthesitis:	No Yes	18 18	50 50	32 4	88.9 11.1	**12.83**	**<0.001 ****
Anterior Uveitis:	No Yes	33 3	91.7 8.3	32 4	88.9 11.1	0.16	0.69 NS
GIT Symptom:	No Yes	34 2	94.4 5.6	35 1	97.2 2.8	0.35	0.56 NS
MRI:	Not done Uni Sacroiliitis Bi Sacroiliitis	2 6 28	5.6 16.7 77.8	1 1 34	2. 2.8 94.4	4.49	0.11 NS

χ^2:Chi square test NS: Non significant (P>0.05)
*: Significant (P<0.05) **: Highly significant (P<0.001).
MRI: Magnetic Resonance Imaging, Uni: Unilateral, Bi: Bilateral

According to BASDAI and BASFI score analysis we found that there was a statistically significant increase in mean BASDAI and BASFI score among active cases compared to non-active cases. Which are presented in the **table (2).**

Table (2): Disease activity score among the studied groups:

Variable		Group I (Active cases) (n=36)	Group II (Non-active cases) (n=36)	MW	P
BASDAI:	Mean ± Sd Median Range	5.82±1.27 5.75 4-8.1	2.49±0.87 2.7 1.2-3.5	**7.31**	**<0.001****
BASFI:	Mean ± Sd Median Range	4.78±2.28 4.8 1-9.2	2.92±2.08 2.3 1-7.7	**3.38**	**0.001***

SD: Standard deviation MW: Mann Whitney test *: Significant (P<0.05), **: highly significant (P<0.001). BASDAI; Bath Ankylosis Spondylitis Disease Activity Index,Bath Ankylosis Spondylitis Functional Index.

There was a statistical significant increase in mean CRP and decrease in mean Albumin among active compared to non-active cases. That shows in the **table (3):**

Table (3): ESR, CRP & Albumin among the studied groups:

Variable		Group I (Active cases) (n=36)	Group II (Non-active cases) (n=36)	MW/t	P
ESR: (mm/h)	Mean ± Sd Median Range	32.58±20.28 29.5 3-90	30.89±19.24 30 3-68	0.30	0.76 NS
CRP: (mg/dl)	Mean ± Sd Median Range	14.09±13.05 7.92 0.6-58.98	6.85±5.42 5.92 0.22-25.64	**2.61**	**0.009***
Albumin: (gm/dl)	Mean ± Sd Range	4.18±0.43 3.09-5.15	4.41±0.4 3.42-5.32	**2.35**	**0.02***

SD: Standard deviation t: Independent t test MW: Mann Whitney test NS: Non significant (P>0.05), *: Significant (P<0.05), ESR; Erythrocyte Sedimentation Rate CRP; C-Reactive Protein.

The comparison of CAR value of patients with Ax-SpA stratified based on disease activity shows that there was a statistical significance increase in mean CAR among active compared to non-active cases. Correlation analysis between CAR and BASDAI, BASFI, ESR and CRP, Albumin revealed that there was a statistically significant +ve correlation between CAR and BASDAI, BASFI, ESR and CRP. Also, there was a statistical significant -ve correlation between CAR and albumin among the studied cases. As shown in **table (4):**

Table (4): Correlation between CAR and age, duration, disease activity score, inflammatory markers and albumin among the studied cases:

Variable	CAR (n=72)	
	r	P
Age: (years)	0.11	0.35 NS
Disease duration: (years)	0.03	0.80 NS
BASDAI	**0.33**	**0.005***
BASFI	**0.45**	**<0.001****
ESR: (mm/h)	**0.41**	**<0.001****
CRP: (mg/dl)	**0.91**	**<0.001****
Albumin: (gm/dl)	**-0.42**	**<0.001****

r: Spearman's correlation coefficient, NS:Non significant (P>0.05 *:Significant (P<0.05) **: highly significant (P<0.001)

CAR had significant validity for differentiation between active and non-active cases at cut off 2.04 with sensitivity 72.2%, specificity 61.1% and accuracy 66.7%.

Discussion

Even in the era of new treatment strategies that make remission or "inactive disease" an achievable target in Ax-SpA, a persisting need for standardized and easily applicable and reliable tools for the

evaluation of disease activity has been reported. In clinical studies, it is seen that the BASDAI composite score is commonly used to evaluate disease activity in Ax-SpA. CAR value has been investigated in many diseases as a value that reflects the systemic inflammation **(Sunar and Ataman, 2020)**(9), **Kalyoncuoglu and Durmus, 2020)**(10).

There were no statistically significant differences between the studied groups according to sex distribution, age, occupation and smoking.

Our results were in line with study of **Pamukcu and Duran, 2021**(1) as they reported that there was no statistically significant difference between low active group and high active group as regard age, sex distribution and disease duration.

The current study showed that as regard Clinical and radiological data among the studied groups; there were no statistical significance differences between the studied groups in back pain, skin rash, Anterior uveitis, GIT symptoms or MRI findings but there was a statistical significance increase in frequency of peripheral joints and enthesitis among active cases compared to non-active. There was a statistically significant increase in mean BASDAI and BASFI score (5.82±1,27),(4.78±2.28) among active cases compared to (2.49±0.87),(2.92±2.08) respectively in non-active cases.

Our results were in agreement with study of **Zhong et al., 2021**(11) as they reported that in comparison with the inactive group BASDAI, and BASFI were significantly higher in the active group.

In the study in our hands, there was a statistically significant increase in mean CRP and decrease in mean Albumin among active compared to non-active cases.

In accordance with our results is a study of **Zhong et al., 2020**(11), **Pamukcu and Duran, 2021**(1), which demonstrated that there was a statistically significant increase in mean CRP and decrease in mean Albumin among high-active compared to low-active cases.

The acute phase reactant C-reactive protein (CRP) is well known, it's also a highly sensitive indicator of tissue injury and acute inflammation. CRP is used to track the severity of infectious, inflammatory, autoimmune, and rheumatologic illnesses, as well as their response to treatment. CRP is also utilized as a biomarker to predict mortality and morbidity in patients suffering from neurological and cardiovascular illnesses. Albumin is a negative acute phase reactant, low albumin has been examined as a predictor of systemic inflammation, and is regularly used as an indication of nutritional status. C-reactive protein (CRP) to Albumin Ratio (CAR) has been linked to the disease activity of inflammatory disorders like Crohn's disease and rheumatoid arthritis in several studies **(Yang et al., 2018)**(5).

The present study showed that there was a statistical significance increase in mean CAR among active compared to non-active cases.

Our results were in agreement with study of **Zhong et al., 2021** (11),**Pamukcu and Duran, 2021**(1), as they reported that in comparison with the inactive group, CAR was significantly higher in the active group of axSpA patients.

Also, in the study of **Abdou et al., 2021**(12), CAR was significantly higher in AS patients than those in the control group.

The current study showed that there was a statistically significant +ve correlation between CAR and BASDAI (r =0.33,p=0.005).BASFI(r =0.45,p=<0.001), ESR(r =0.41,p=< 0.001) and CRP(r=0.91,p=< 0.001). Also, there was a statistically significant -ve correlation between CAR and albumin (r = -0.42, p=< 0.001) among the studied cases.

These results were supported by **Pamukcu and Duran, 2021**(1) which There was a statistically significant positive correlation between BASDAI and CAR, ESR, CRP. Further, it was noted a high correlation between CAR and CRP (rho: 0.998, p <0.001), low-to-moderate correlation between CAR and ESR (rho: 0.377, p <0.001).

Previous studies have demonstrated that TNF and IL-6 are involved in the initiation and maintenance of inflammation of axSpA, which may account for the associations between increased CAR and inflammation and disease activity of axSpA **(Levitova et al., 2016)**(13).

Our results showed that regarding Validity of CAR in differentiation between active and non-active cases among the studied groups; using ROC curve; CAR had significant validity for differentiation between active and non-active cases at cut off 2.04 with sensitivity 72.2%, specificity 61.1% and accuracy 66.7%, CAR yielded the AUC (0.65,95% CI:0.52-0.78).

Also, **Abdou et al., 2021**(12) revealed ROC curve of CRP/albumin ratio to detect disease activity in AS

patients showed AUC 0.71.

Furthermore, in a study of **Tamer and Avcı, 2020**(14), which included patients with psoriasis reported that CAR could be used as an inflammatory biomarker of psoriatic arthritis in addition to being an inflammatory biomarker of psoriasis in patients treated with biological agent.

This study has some limitations. The first limitation of this study is that it was a single-centre study and the number of patients was not very large. Secondly, other important indices used in the evaluation of disease activity in Ax-SpA (e.g., the ankylosing spondylitis disease activity score (ASDAS), ASDAS - CRP and ASDAS - ESR) were not included in the study, and correlation calculations could not be made. Finally, the effect of treatment on CAR value was not evaluated. Further detailed investigations should be conducted to determine the applicability of CAR as an early diagnostic marker of inflammation in Ax-SpA.

Conclusion

In conclusion, CAR was increased in axSpA of the active group and it was an independent predictive factor for axSpA disease activity and may be a novel and reliable biomarker for assessing the disease activity of axSpA patients.

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