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**ORIGINAL ARTICLE**

# Albumin to Fibrinogen Ratio and C- Reactive Protein to Albumin Ratio in Ankylosing Spondylitis Patients: Correlation with Disease Activity.

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## ABSTRACT

**Background:** The albumin to fibrinogen ratio (AFR) and C-reactive protein to albumin ratio (CAR) have emerged as useful biomarkers of systemic inflammation. The aim here was to investigate the relation between AFR/CAR and ASDAS-ESR Score in ankylosing spondylitis (AS).

**Methods:** This case control study included 30 patients with AS and 30 healthy controls. We calculated CAR and AFR in each group and comparison between both groups was done. The correlations between AFR, CAR and the disease activity were analyzed. Receiver operation characteristic (ROC) curves of albumin/fibrinogen ratio and CRP / albumin ratio were performed to set the best cutoff value for detecting disease activity of AS.

**Results:** The AFR was significantly lower in AS in AS patients than those in the control group while CAR was significantly higher in AS patients than those in the control group. ROC curve of CRP/albumin ratio to detect disease activity in AS patients showed AUC 0.71. So, CRP/albumin ratio was a fair parameter to discriminate disease activity among AS patients. ROC curve of albumin/fibrinogen ratio to detect disease activity in AS patients showed AUC 0.85. So, albumin/fibrinogen ratio was a good parameter to discriminate disease activity among AS patients.

**Conclusion:** AFR and CAR are two novel inflammatory markers for monitoring disease activity in AS patients. AFR and CAR are parameters that can be assessed quite simply, rapidly and inexpensively. CAR was a fair parameter while AFR was a good parameter to discriminate disease activity among AS patients.

**Keywords:** Ankylosing spondylitis, albumin, fibrinogen, C-reactive protein, disease activity

## 1-INTRODUCTION

Ankylosing spondylitis (AS) is a progressive, seronegative spondyloarthropathy, mainly affecting the sacroiliac (SI) joints and the axial skeleton. The diagnosis is made by merging clinical criteria of inflammatory back pain, enthesitis (inflammation at the location of bone insertion of ligaments and tendons) or arthritis with radiological findings. **(1)**

AS occurs as a result of an interplay between susceptibility genes, microbial causes, bone marrow inflammation, enthesial structures, and new bone development. Chronic spinal inflammation (spondylitis) can lead to complete

fusion (cementing) of the vertebrae, a condition known as ankylosis. **(2)**

Patients with AS often complain of pain, stiffness, and exhaustion. These clinical manifestations, as well as the radiological progression, lead to significant physical deficiencies, a lack of spinal mobility, and a reduction in quality of life (QoL). As a result, it's important to keep track of disease development in order to avoid symptoms and improve AS patients' outcomes. **(3).**

To measure disease activity, researchers used the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) **(4).** Six self-administered questions on fatigue, spinal discomfort, joint pain and swelling, regions of localized tenderness, and the severity and extent of morning stiffness are included in the self-administered instrument. The Bath Ankylosing Spondylitis Functional Index was used to determine function (BASFI) **(5, 6).** The Bath Ankylosing Spondylitis Global Score (BAS-G) is made up of two items that ask about the impact of the condition on the patients' general well-being in the past week and over the previous six months. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a more modern index for determining disease activity in AS patients. **(7).**

CRP is thought to be the most accurate indicator of disease activity and remission in AS patients. CRP levels can indicate the seriousness of AS, its clinical development, and treatment response **(8)**. Fibrinogen is an essential coagulation factor that has been shown to be higher in AS patients compared to controls and to be strongly associated with CRP. **(9).**

Albumin is regarded as a reliable predictor of nutritional status. In ankylosing spondylitis, albumin is often used as an acute phase response protein to indicate the systemic inflammatory status. **(10).**

The CRP/albumin ratio is calculated by dividing the CRP measurement by the albumin measurement. It is a well-established scoring method for determining the severity and behavior of an inflammatory disorder, and it is thought to be a more useful indication of the inflammatory status than CRP or albumin alone **(11)**. The albumin to fibrinogen ratio (AFR) and the C-reactive protein to albumin ratio (CAR) are two new biomarkers that may indicate the severity of chronic inflammation. **(12).**

In a previous study published in China in 2019, Liu et al. reported that fibrinogen, CRP, and ESR were all significantly higher in AS patients relative to stable controls ($p<0.05$), but albumin was significantly lower ($P<0.05$) **(13).** These ratios haven't been investigated in Egyptian AS patients yet. The aim of this study was to evaluate CAR and AFR in Egyptian AS patients and study their relation with disease activity.

## 2-SUBJECTS AND METHODS

### 2.1. Study design

This research was conducted in the Rheumatology, Rehabilitation, and Physical Medicine Department, Faculty of Medicine, Zagazig University Hospitals, after evaluation and acceptance by the Institutional Review Board (IRB) Committee (ZU-IRB #5972). Patients and controls were enrolled in the study after taking an informed consent. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. There are two groups in this case control analysis (AS group and control group). After receiving written informed consent, 30 patients with AS from the outpatient clinic and inpatient ward of Zagazig University Hospitals' Rheumatology Department were enrolled in this case control report. The Modified New York Criteria (1984) was used to diagnose patients with AS **(14)**.

Patients with SLE, Scleroderma, Overlap syndrome, and mixed connective tissue disorder, inflammatory bowel disease, reactive arthritis, psoriatic arthritis, RA, malignancies, and infections were excluded. The control group consists of 30 apparently healthy adults who were age and sex matched with the patients.

### 2.2. Disease activity Score

The Ankylosing Spondylitis Disease Activity Score (ASDAS) was used to measure the severity of AS at the time of entry. ASDAS was measured using ASDAS-ESR = 0.08 x Back Pain + 0.07 x Morning Stiffness Duration + 0.11 x Patient Global + 0.09 x Peripheral Pain/Swelling + 0.29 x $\sqrt{}$(ESR). On a metric ranking scale, back pain, patient global assessment, duration of morning stiffness, and peripheral pain/swelling are all evaluated (from 0

to 10). The score of ASDAS was used to classify a patient's AS operation status. ASDAS scores over 3.5 indicate extremely high disease activity, while ASDAS scores between 2.1 and 3.5 indicate moderate disease activity, and ASDAS scores between 1.3 and 2.1 indicate low disease activity and below 1.3 is associated with inactive disease **(15).** In our study ASDAS was translated, back-translated, revised and tested for our patients.

**Stages of Arabic translation:**

1) ***Initial Translation:*** The first stage was the forward translation. We performed two forward translations made from the original language to Arabic language, then compared and checked for discrepancies. Bilingual translators whose mother tongue is the target language produce the two independent translations.
2) **Back Translation:** Working from the latter version and totally blind to the original version, a translator then translated the questionnaire back into the original language. This process simply ensures consistent translation.
3) **Rheumatologists Revision & the final version:** Two rheumatologists consolidated all the versions and developed the pre-final version of it for field testing. A pilot study was conducted on 10% of the sample size to test the feasibility of the questionnaire, as well as the clarity of the tool and to estimate the time needed to fill it. The pilot study findings showed that the questionnaires were clear and relevant. The tools were finalized and made ready for use. The patients included in pilot study were included in the main sample.

**2.3. Laboratory Data**

Laboratory data measured for each patient included CRP, ESR, fibrinogen, and albumin. Peripheral venous blood samples were drawn from each patients for measuring ESR using Vision B analyzer (YHLO Biotech diagnostic, china), CRP by Immunoturbidometric technique on Cobas c501/6000 (Roche diagnostic , Germany), albumin by Bromocresol green (BCG) method on Cobas c702/8000 (Roche diagnostic , Germany) and plasma fibrinogen level using Clauss Clotting Time Method (Spectrum diagnostic , Egypt ). All the measurements were performed within 2 h after samples collection. CRP, serum albumin and plasma fibrinogen were measured for control group.

**2.4. Statistical analysis**

IBM SPSS Statistics for Windows, Version 23.0, was used to collect, tabulate, and statistically analyse all results. (Armonk, NY, USA: IBM Corporation). Mann Whitney U test was used to compare between two groups of non-normally distributed variable. The F-test (ANOVA) was used to measure more than two classes of normally distributed variables, and the least significant difference was used to identify significant differences between groups. The Kruskall Wallis test was used to evaluate non-normally distributed variables from more than two classes. Percentages of categorical variables were compared using the Chi-square test or Fisher's exact test.

## RESULTS

The demographic and clinical characteristics for the patients and control groups are shown in Table 1 and 2. The patients included 14 females (46.7 %) and 16 males(53.3%),with the mean age of 35.6±8.4 years, while the control group included 17 females (56.7%) and13 male(43.3%) ,with the mean age of 35.8±8.2 years. No significant differences were observed in age ($p=0.99$) and sex ($p=0.19$) between the two groups.

Table 3 shows that there was statistically significant difference between AS patients and control group regarding serum level of fibrinogen, CRP/albumin ratio and albumin/fibrinogen ratio ($p<0.001$). As shown in table 3, CAR increased in AS patients than control. The median of CAR in AS patients was 3.2(0.11-25.14) while in control group was 0.38(0.02-0.88). Also table 3 shows that AFR decreased in AS patients than control group. The median of AFR in AS patients was 5.1(3.56-11.5) while in control group was 16.9(1.76-29).

The Relation between ASDAS level and CRP albumin/ratio and Albumin/fibrinogen ratio in AS patients was shown in Table 4. There was statistically insignificant relation between serum CAR and ASDAS Score of AS patients $p>0.05$. Whereas, there was statistically significant relation between serum Albumin/fibrinogen ratio and ASDAS Score in AS patients $p<0.05$. Mann Whitney test define serum AFR was (low & moderate ASDAS; p=0.43 (NS)), (low & high ASDAS; p=0.024 (S)), (moderate & high ASDAS; p=0.004 (S)).

CAR may be used as marker to detect disease activity in AS at cut off (≥2.625) with sensitivity (88.2%) and specificity (53.8%) and AFR may be used as marker to detect disease activity in AS at cut off (≤5.845) with sensitivity (100%) and specificity (61.5%) as shown in table 5.

**Table (1): Demographic characteristics of studied AS patients and control group**

| | AS patients (n=30) | Control group (n=30) | F | p |
|---|---|---|---|---|
| **Age per year** Mean± SD | 35.6±8.4 | 35.8±8.2 | F=0.006 | 0.99 |
| | | | $\chi^2$ | P |
| **Sex** *no (%)* | | | 3.4 | 0.19 |
| Female | 14(46.7) | 17(56.7) | | |
| Male | 16(53.3) | 13(43.3) | | |
| **BMI** *Mean± SD* | 29.3±5 | 30.56±4.3 | F=0.607 | 0.55 |

F=Anova test $\chi^2$ = Chi square test f=Fisher Exact test

**Table (2): Clinical manifestations of AS patients**

| | AS patients (n=30) |
|---|---|
| **BMI** | |
| *Mean± SD* | 29.3±5 |
| **Normal** No (%) | 7(23.33) |
| **Overweight** | 10(33.33) |
| **obese** | 13(43.33) |
| **Occiput wall test** *No (%)* | |
| not touch | 14(46.7) |
| touch | 16(53.3) |
| **Pelvic compression test** *No (%)* | |
| negative | 11(36.7) |
| positive | 19(63.3) |
| **FABER** *test No (%)* | |
| negative | 9(30) |
| positive | 21(70) |
| **Gaenslens test No** *(%)* | |
| negative | 14(46.7) |
| positive | 16(53.3) |
| **Chest expansion test (cm)** *Mean± SD* | 3.4±1.2 |
| **Modified Schober test (cm)** *Mean± SD* | 18.6±3.1 |
| **ASDAS-ESR SCORE NO** *(%)* | |
| Low | 2(6.7) |
| Moderate | 11(36.7) |
| high | 17(56.6) |
| *Mean± SD* | 3.6±1.02 |
| **Systemic manifestations** *No (%)* | |
| Chest | 3(10) |
| GIT | 14(46.7) |
| | 14(46.7) |

| | |
|---|---|
| CVS | 11(36.7) |
| CNS | 4(13.3) |
| EYE | |

ASDAS-ESR SCORE: Ankylosing Spondylitis Disease Activity Score - Erythrocyte sedimentation rate, GIT: gastrointestinal tract, CVS: cardiovascular, CNS: central nervous system. BMI: Body Mass Index.

**Table (3): Laboratory data of AS patients and healthy controls**

| | **AS patients (n=30)** | **Control group (n=30)** | ***P** |
|---|---|---|---|
| **Serum albumin(gm/dl)** Median (range) | 4.1(3.5-5.8) | 4.49(3.7-5.52) | 0.017 |
| **ESR (mm/hr)** Median (range) | 27(3-100) | - | |
| **CRP (mg/l)** Median (range) | 13(0.5-88) | 1.77(0.07-4.5) | <0.001 |
| **Fibrinogen(gm/dl)** Median (range) | 0.8(0.3-1.6) | 0.26(0.18-0.39) | <0.001 |
| **CRP/albumin ratio(mg/gm)** Median (range) | 3.2(0.11-25.14) | 0.38(0.02-0.88) | <0.001 |
| **Albumin/fibrinogen ratio(gm/gm)** Median (range) | 5.1(3.56-11.5) | 16.9(1.76-29) | <0.001 |

p<0.05 significant, * Comparison between each group by Mann Whitney U test

**Table (4): Relation between ASDAS score and CRP albumin/ratio and Albumin/fibrinogen ratio in AS patients**

| | **ASDAS Score** | | | **K W** | **p-value** |
|---|---|---|---|---|---|
| | low n=2 | moderate n=11 | high n=17 | | |
| **CRP/albumin ratio (mg/gm) Median (range)** | 2.5(1.95-3.13) | 2.8±2.2 (0.11-6.79) | 3.28(1.71-25.14) | 3.7 | 0.15 |
| **Albumin/fibrinogen ratio(gm/gm)** Median (range) | 6.47(5.97-6.97) | 5.9(4.2-11.5) | 4.61(3.56-5.79) | 11.1 | 0.004 |

ASDAS: Ankylosing spondylitis disease activity score, KW: Kruskal Wallis test

**Table (5): Validity data of Albumin fibrinogen ratio & CRP/albumin ratio as marker to detect disease activity of AS patients**

| | **Cut off** | **sensitivity** | **specificity** | **PPV** | **NPV** | **Accuracy** | **AUC** |
|---|---|---|---|---|---|---|---|
| **CAR** | ≥2.625 | 88.2% | 53.8% | 71.4% | 77.8% | 73.3% | 0.71 |
| **AFR** | ≤5.845 | 100% | 61.5% | 77.3% | 100% | 83.3% | 0.85 |

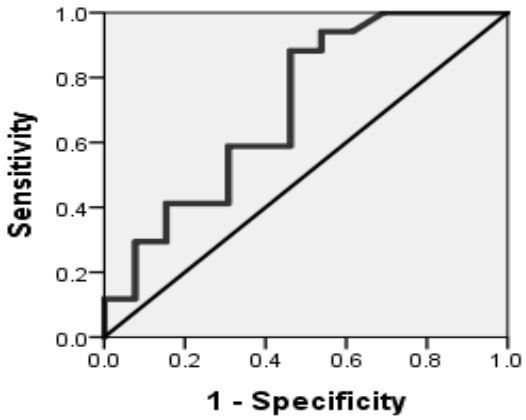


**Figure (1): ROC curve of CRP/albumin ratio to detect disease activity of AS (AUC 0.71). So, CRP/albumin ratio was a fair parameter to discriminate disease activity among AS patients.**

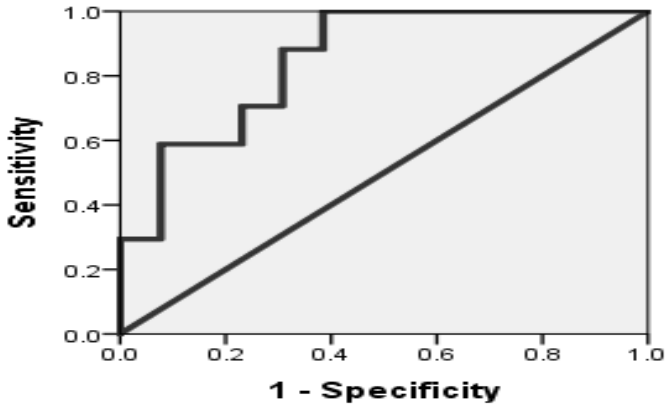


**Figure (2): ROC curve of albumin/fibrinogen ratio to detect disease activity of AS (AUC 0.85). So, albumin/fibrinogen ratio was a good parameter to discriminate disease activity among AS patients.**

## DISCUSSION

The aim of this research was to see whether there was a relation between albumin to fibrinogen ratio (AFR) and C-reactive protein to albumin ratio (CAR) and disease activity in ankylosing spondylitis patients. The present research found a statistically important discrepancy in AFR between AS patients and the control group ($p<0.001$).

Liu et al. tested the relation between Fibrinogen to Albumin Ratio (FAR) with disease activity in AS patients. Their ratio differed from ours in the arrangement, as we conducted Albumin to Fibrinogen Ratio (AFR) rather than Fibrinogen to Albumin Ratio (FAR). They found that fibrinogen was higher in AS patients relative to stable controls, but albumin was lower causing the ratio to increase with AS activity **(13)**.

In our research, we found a statistically important discrepancy in CAR between AS patients and the control group. This was in line with the findings of Zhong et al. (16), who

discovered that CAR, ESR, and CRP were significantly higher in axSpA patients than in the control group, although Albumin was significantly lower. In our research, we found that fibrinogen levels in AS patients were substantially higher than in the control group. This was in agreement with Chapin and Hajjar **(9)** and Liu et al. **(17)**

In the present study we found that the median of CRP was 13(0.5-88) in AS patients while in control group was 1.77(0.07-4.5) so CRP is higher in AS patients than control group. This is in line with the findings of Benhamou et al. **(18),** who found that patients with painful axial AS often had elevated CRP. As a result, CRP levels represent the seriousness of AS, its clinical development, and therapeutic response **(8).** We found in this study that serum albumin was lower in AS patient than control group as the median of serum albumin in control group was 4.49(3.7-5.52) while in AS patients was 4.1(3.5-5.8). This result was in agreement with Liu et al.**(17)** who found that serum albumin was significantly lower in AS patient than control group**.** Serum AFR also differed significantly with different ASDAS levels where AFR in patients with high ASDAS score was significantly different than that in patients with low and moderate scores ( p value was 0.024 on comparing low & high ASDAS and 0.004 on comparing moderate & high ASDAS).

Liu et al. **(13)** found that FAR, fibrinogen, CRP and ESR in active group were higher than remission group ($P < 0.05$), while albumin was lower ($P < 0.05$). They also found that there was a positive correlation between FAR and BASDAI ($r = 0.488$ - $P < 0.001$).

In the present study we found that ROC curve of albumin/fibrinogen ratio to detect disease activity of AS (AUC 0.85). So, albumin/fibrinogen ratio was a good parameter to discriminate disease activity among AS patients. While Liu et al. **(13)** reported that ROC results showed that area under curve (AUC) of FAR (0.818). So, FAR was a marker of disease activity in AS patient.

Zhong et al. **(16)** performed ROC and concluded that the area under the curve (AUC) of CAR was 0.701. CAR's optimum cutoff point was 0.3644, with 58.5 percent sensitivity and 79.0 percent accuracy. The findings of the logistic study showed that elevated CAR was an independent marker for axSpA. This is consistent with our findings, which showed that a ROC curve of the CRP/albumin ratio could be used to detect disease activity in AS patients (AUC 0.71), at a cutoff of 2.625, with sensitivity and accuracy of 88.2% and 53.8 percent, respectively.

There were some limitations in this research. To begin with, the sample size was limited, and this was a single-center analysis. Second, we did not investigate the links between AFR, CAR, and inflammatory cytokines such as tumor necrosis factor (TNF)-alpha & Interleukin (IL)-1b, which are essential mediators in AS.

In conclusion, despite the fact that AFR and CAR are markers that can be tested quickly and inexpensively, there are few studies demonstrating the associations of AFR and CAR with disease activity in patients with AS. In AS patients, AFR was lower while CAR was higher in AS patients as compared to healthy controls. The ASDAS –ESR score had a close association with AFR. Our findings confirmed that CAR and AFR were very good parameters to discriminate healthy subjects from AS patients. Among AS patients, CAR was a fair parameter to discriminate disease activity among AS patients but AFR was a good parameter. Their use in clinical practice to follow up AS patients seems promising; AFR was a stronger parameter for activity in AS patients.

**Declarations**

**Consent for publication**

All authors have approved all parts of the manuscript and a consent for publication has been taken from all authors

**Competing interests**

We all authors confirm that we have no competing interests. There is no conflict of interest to declare.

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