C-Reactive Protein to Albumin Ratio and Albumin to Fibrinogen Ratio in Rheumatoid Arthritis Patients

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Objective: *the albumin to fibrinogen ratio (AFR) and the C-reactive protein (CRP) to albumin ratio (CAR) have been proposed as markers of systemic inflammation.*
The goal of this study was to differentiate rheumatoid arthritis (RA) patients from healthy people and to study the association between AFR/CAR and DAS28 in RA.
Patients and methods. *A case control study including 30 RA patients and 30 healthy controls was performed. Fibrinogen, albumin, CRP and erythrocyte sedimentation rate (ESR) were measured. We calculated CAR and AFR in each group and compared them. Correlations of AFR, and CAR with disease activity were examined. Receiver operation characteristic (ROC) curves of AFR and CAR were also used to detect cutoffs for disease activity assessment.*
Results and discussion. *CAR was higher while AFR was lower in RA patients than in control group. ROC curve analyses showed that CAR can be used to detect disease activity of RA at cut off 2.66 with sensitivity 81.3% and specificity 64.3% with an area under the curve (AUC) 0.78. So, CAR was a fair parameter to discriminate disease activity among RA patients. AFR has AUC 0.62, sensitivity 87.5% and specificity 42.9% at cut-off value 5.96. So, in our group AFR was a poor indicator to discriminate disease activity among RA patients.*
Conclusion. *AFR and CAR have been recently proposed as inflammatory markers for assessment of disease activity in RA. AFR and CAR are simple, and inexpensive biomarkers, they also can be rapidly evaluated. CAR was found to be a fair parameter to depict disease activity in RA patients. AFR poorly depicted RA activity.*

Key words: *rheumatoid arthritis; albumin; fibrinogen; C-reactive protein.*
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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder of unknown etiology affecting mainly the joints and involving several other organs. RA affects 0.5–1% of adult population. The disease affects females three times more often than males [1].

Although RA is primarily thought to be a joint disease, involving small joints of the hands and feet, abnormal systemic immune response is also present and can cause a wide range of extra-articular manifestations such as vasculitis and nodules. Exact origin of RA is currently unknown, but it is almost likely that a combination of environmental and genetic variables is to blame; each one is required but not sufficient for complete disease development [2].

Disease activity indices can be used to classify different inflammatory activity levels in RA; such as the Disease Activity Score 28 (DAS28) with erythrocyte sedimentation rate (ESR), the Simplified Disease Activity Index (SDAI), and the Clinical Disease Activity Index (CDAI). These indices produce cut-off values that are used to categorize RA as remission, low, moderate, or high activity [3].

C-reactive protein (CRP) level is frequently used as an adjunct to articular swelling and tenderness in the assessment of the degree of disease activity. It is a component of the American College of Rheumatology (ACR) core set measuring clinical response in RA clinical trials. Moreover, it can be used as a component of DAS28 instead of ESR, and it was a predictor of radiological damage in RA clinical trials [4]. The concentration of albumin in inflammatory diseases also changes. In active RA excess of albumin consumption occurs at sites of inflammation and therefore hypoalbuminemia develops [5]. Fibrinogen is implicated in the cascade of blood coagulation, and its deposition in joints often accompanies chronic inflammation in RA. Circulating level of fibrinogen in RA patients is usually elevated and correlates with markers of inflammation [6].

CRP/albumin ratio (CAR) is calculated by dividing the CRP level by the albumin measurement value and is a recent index used to determine the degree of inflammation, which is a more useful indicator than CRP or albumin alone [7]. The albumin to fibrinogen ratio (AFR) and CAR have been recently proposed as new informative biomarkers which can be used to effectively monitor status of RA patients [8].

In a previous study done in China in 2018 W.M. Yang et al. [8] included 160 RA patients and 159 age- and sex-matched healthy controls. Authors found significant difference between control and RA regarding CAR and AFR ($p<0,001$).

So, we aimed to assess the correlation of CAR and AFR with disease activity in a group of Egyptian RA patients.

Patients and methods

Type of study and sampling. After review and approval by the Institutional Review Board (IRB) Committee, this study was carried

Table 1. Demographic characteristics of RA patients and control group

Parameter	RA patients (n=30)		Control group (n=30)
Age, years, M±SD	35.8±8.1	F=0.006 p=0.99	35.8±8.2
Sex, n (%):			
female	21 (70,0)		17 (56.7)
male	9 (30,0)	χ^2=3.4 p=0.19	13 (43.3)
BMI, kg/m², M±SD	29.3±5.7	F=0.607 p=0.55	30.56±4.3

Note: BMI – body mass index.

Table 2. Clinical characteristics of RA patients

Parameter	RA patients (n=30)
BMI, kg/m², M±SD	29,3±5,7
BMI, n (%):	
normal	6 (20)
overweight	15 (50)
obese	9 (30)
Morning stiffness, n (%):	
yes	21 (70)
no	9 (30)
Median (range), min	30 [10; 120]
RA activity, n (%):	
low	3 (10)
moderate	11(36,7)
high	16 (53,3)
DAS28, M±SD	5,3±1,5
Patient global assessment, cm, M±SD	7,1±2,2
Systemic manifestations, n (%):	
Chest	19 (63,3)
GIT	14 (46,7)
CVS	4 (13,3)
CNS	3 (10)
Eye	5 (16,6)

Note: GIT – gastrointestinal tract; CVS – cardiovascular; CNS – central nervous system.

out in Rheumatology, Rehabilitation and Physical Medicine Department, Faculty of Medicine, Zagazig University Hospitals. The study was performed according to the Declaration of Helsinki for studies involving humans. It is a case control study which included 2 groups (RA group and control group). Sample size calculated by assuming that M±SD of albumin concentration in patients with RA versus normal individuals is 35.35±8,00 versus 39.27±5,00 g/l, so sample size was calculated to be 60 cases (30 patients with RA and 30 apparently healthy controls; age and sex matched with patients), using open EPI, power of test 80%, confidence interval (CI) 95%. RA patients from the outpatient clinic and inpatient ward of the rheumatology department of Zagazig University Hospitals were enrolled in this case control study after taking an informed written consent. All patients were adults (≥18 years of age) and fulfilled ACR/ European Alliance of Associations for Rheumatology (EULAR) 2010 classification criteria for RA [9].

Patients who had connective tissue diseases other than RA such as systemic lupus erythematosus, scleroderma, overlap syndrome and mixed connective tissue disease, inflammatory bowel disease, reactive arthritis, psoriatic arthritis, ankylosing spondylitis, malignancies, infections, chronic hepatic diseases and renal diseases were all excluded. The control group consisted of 30 age and sex matched apparently healthy individuals.

Disease activity score. RA disease activity was assessed by DAS28 at time of admission.

$DAS28=0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times PGA$.

TJC – tender joint count, SJC – swollen joint count, PGA – patient's global assessment measured on a visual analog scale [10].

DAS28 was used for classification of RA activity. Grading of DAS28 was low (DAS28 ≤3.2), moderate (3.2< DAS28 ≤5.1), high disease activity (DAS28 >5.1) and remission (DAS28 <2.6) [11].

Laboratory data. Laboratory parameters measured for each patient were CRP, ESR, fibrinogen and albumin. Peripheral venous blood samples were obtained from each patient. Serum albumin was assessed with Bromocresol green (BCG) method on Cobas c702/8000 (Roche diagnostic, Germany), plasma fibrinogen – with Clauss Clotting Time Method (Spectrum diagnostic, Egypt), CRP – with Immunoturbidometric technique on Cobas c501/6000 (Roche diagnostic, Germany) and ESR – with Vision B analyzer (YHLO Biotech diagnostic, China). All measurements were done within 2 h after sample collection. CRP, serum albumin and plasma fibrinogen were also measured for control group.

Statistical analysis. Collection, tabulation and statistical analysis of all data were done using IBM SPSS Statistics for Windows, Version 23.0. (IBM Corporation, Armonk, NY, USA). F-test (ANOVA) was used for comparing more than two groups of normally distributed variables. Mann–Whitney U test was used to compare between two groups of non-normally distributed variables. While comparing between more than two groups of non-normally distributed variables we used Kruskall–Wallis test (KW). We compared between percentages of categorical variables by Chi-square test or Fisher's exact test whenever appropriate.

Results

Characteristics of patients and the control group are shown in tables 1–3. The RA group included 21 females (70%) and 9 males (30%), with the mean age of 35.8±8.1 years, the control group – 17 females (56.7%) and 13 males (43.3%) with mean age of 35.8±8.2 years. No significant differences were found regarding age (p=0.99) and sex (p=0.19) between the two groups.

Table 4 shows that there was a statistically significant difference between RA patients and control group regarding CAR and AFR (p<0.001). CAR was higher in RA patients than in control. The median of CAR in RA patients was 2.7 [0.19; 20.96] while that in control group – 0.38 [0.02; 0.88]. Also, table 3 shows that AFR was decreased in RA patients in comparison with control group. The median of AFR in RA patients was 5.2 [4.09; 9.43] while that in control group – 16.9 [1.76; 29].

The relation of DAS28 with CAR and AFR in RA patients is shown in table 5. There was statistically significant relation of CAR and DAS28 in RA patients (p<0.05). Whereas relation of AFR and DAS28 was statistically insignificant (p>0.05). Mann–Whitney test showed that CAR was significantly different between different activity levels according to DAS28 (for low and moderate

Table 3. Laboratory investigation of RA patients

Parameter	Value
ESR, mm/h, Median (range)	27,5 [3; 81]
CRP, mg/l, Median (range)	12,35[1; 87]
Complete blood count, M±SD	
Hemoglobin, g/dl	11,8±2,1
Red blood cells, $\cdot 10^6$/cmm	4,6±0,57
White blood cells, $\cdot 10^3$/cmm	7,6±2,3
Platelets, $\cdot 10^3$/cmm	276±83
Liver function test	
Serum ALT, U/L, Median (range)	17,1 [6,5; 46,1]
Serum AST, U/L, M±SD	19,3±6,4
Serum albumin, mg/dl, M±SD	4,3±0,39
Kidney function test	
BUN, mg/dl, Median (range)	10,25 [5,1; 183]
Creatinine, mg/dl, M±SD	0,72±0,17
Serology test	
RF, n (%):	
positive (≥14 IU/ml)	27 (90)
negative (<14 IU/ml)	3 (10)
RF, IU/ml, Median (range)	78,4 [10; 468]
Anti-CCP, n (%):	
positive (>20 U/ ml)	17 (56,7)
negative (<20U/ ml)	13 (43,3)
Anti-CCP, U/ml, Median (range)	159,4 [6,64; 483,5]

Note: ALT – alanine transaminase; AST – aspartate transaminase; BUN – blood urea nitrogen; RF – rheumatoid factor; Anti-CCP – anti-cyclic citrullinated peptide.

Table 4. Comparison between RA patients and control group regarding CAR and AFR, Median (range)

Parameter	RA patients (n=30)	Control group (n=30)	p
Serum albumin, g/dl	4.3 [3.55; 5.23]	4.49 [3.7; 5.52]	0.054
ESR, mm/h	27,5 [3; 81]	–	–
CRP, mg/l	12.35 [1; 87]	1.77 [0.07; 4.5]	<0.001
Fibrinogen, g/dl	0.8 [0.46; 0.99]	0.26 [0.18; 0.39]	<0.001
CAR	2.7 [0.19; 20.96]	0.38 [0.02; 0.88]	<0.001
AFR	5.2 [4.09; 9.43]	16.9 [1.76; 29]	<0.001

Note: p – comparison between groups by Mann–Whitnney U test.

Table 5. The relation of DAS28 with CAR and AFR in RA patients, Median (range)

Parameter	DAS28 low (n=3)	DAS28 moderate (n=11)	DAS28 high (n=16)	KW	p
CAR	0.78 [0.58; 2.43]	2.39 [0.19; 6.69]	4.52 [1.78; 20.96]	7.5	0.024
AFR	5.6 [4.09; 7.3]	5.37 [4.49; 9.43]	5.1 [4.29; 6.83]	1.4	0.49

RA activity p=0.55, for low and high activity p=0.01, for moderate and high activity p=0.04).

We have done ROC curve analyses (fig. 1) and showed that CAR can be used to detect disease activity of RA at cut off ≥2.66

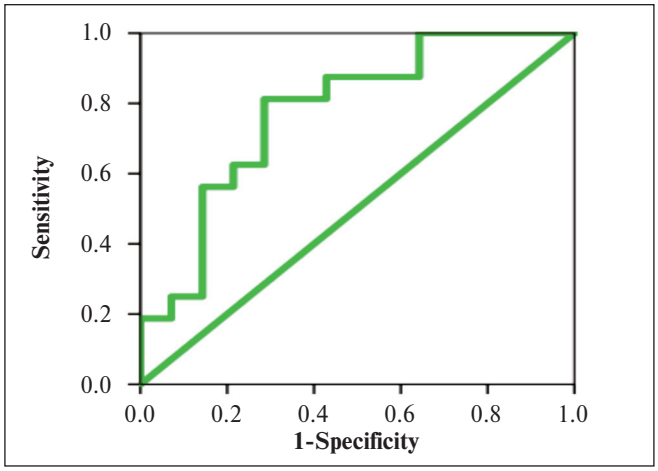

Fig. 1. *ROC curve of CAR to detect disease activity of RA (AUC 0.78)*

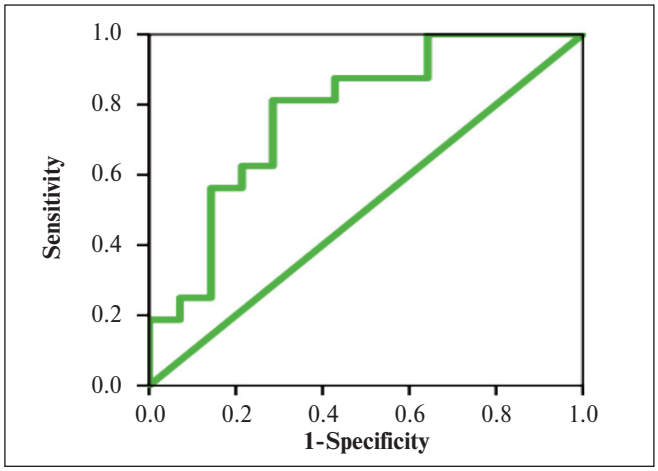

Fig. 2. *ROC curve of AFR to detect disease activity of RA (AUC 0.62)*

with sensitivity 81.3% and specificity 64.3% with an area under the curve (AUC) 0.78. So, CAR was a fair parameter to discriminate disease activity among RA patients. As shown in table 6, CAR may be used as marker to detect disease activity in RA at cut off ≥2.66 with sensitivity 81.3% and specificity 64.3%. AFR has AUC 0.62 with sensitivity 87.5% and specificity 42.9% at cut-off value ≤5.96 (fig. 2). So, in our group AFR was a poor parameter to discriminate disease activity among RA patients.

Discussion

The present study was designed to assess the correlation of AFR and CAR with disease activity in RA patients. We have revealed a statistically significant differences between RA patients and control group regarding CAR and AFR (p<0.001). This was in agreement with the results of previous investigations [8, 12, 13]. In our study, we found that fibrinogen was increased in RA patients compared with controls. This finding was in agreement with publications of P.A. Varisco et al. [6], T. Rooney et al. [14], P. Zhang et al. [15].

Median of serum albumin level in our patients was 4.3 [3.55; 5.23] mg/dl in RA patients while in control group –

Table 6. Validity data of AFR and CAP as marker to detect disease activity of RA patients

Parameter	Cut off	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy	AUC
CAR	≥2.66	81.3	64.3	72.2	75	73.3	0.78
AFR	≤5.96	87.5	42.9	63.6	75	66.7	0.62

Note: PPV – positive predictive value; NPV – negative predictive value.

4.49 [3.7; 5.52] mg/dl, so albumin was slightly decreased in RA patients in comparison with control group. Nearly to our results, S. Ganeb et al. [16] found that serum albumin level was lower (median 3.9 [3.5; 4.35] mg/dl) in their RA patients than in control group. P. Zhang et al. [15], M. Ben-Hadj-Mohamed et al. [17] and H. Tsuji et al. [18] also showed decreased albumin level in RA patients. This may be attributed to the fact that albumin is an attractive carrier targeting inflamed joints and patients with active RA frequently develop hypoalbuminemia [5].

RA patients had higher CRP concentration than control group (12.35 [1; 87] and 1.77 [0.07; 4.5] mg/l respectively). In addition to ESR, CRP is a component of the American College of Rheumatology core set for assessment of clinical response in RA clinical trials and it is also a parameter for calculation of DAS28-CRP [4]. The median of CAR in RA patients was 2.7 [0.19; 20.96] and in control group – 0.38 [0.02; 0.88]. This is in agreement with the results of W.M. Yang et al. [8].

We evaluated the performance of CAR and AFR to predict the disease activity The current study revealed that CAR was significantly different between different levels of RA activity according to DAS28 (low and high, p=0.01, moderate and high, p=0.04). These findings are matching with those previously reported by I. Sunar and S. Ataman [19] who declared that CAR was significantly different between high, medium and low remission disease activity groups (p=0.008). It has been observed that there was statistically insignificant relation between AFR and DAS28 level (p>0.05). W.M. Yang et al. [8] and N. Afifi et al. [12] were different with us when reported that DAS 28 negatively correlated to AFR (p<0.001) and that patients with higher DAS28 had smaller AFR level. Number of patients in our study was lower than in these studies. So, we need to increase number of patients in further studies.

In our study, ROC curve analysis to detect the discriminate validity of these ratios as markers of RA disease activity was performed. The highest AUC was that of CAR (AUC 0.78) at a cut-off of ≥2.66 with sensitivity 81.3% and specificity of 64.3%. So, CAR was a fair parameter to discriminate disease activity among RA patients. While AFR has area under curve of 0.62 with sensitivity and specificity 87.5 and 42.9% respectively at cut-off ≤5.96. So, AFR was a poor measure to discriminate disease activity among RA patients.

These findings are rather close to the results of N. Afifi et al. [12] who declared that AFR had area under curve of 0.826 with sensitivity and specificity 86.84% and 75%, respectively at cut-off 1.461. CAR in that study had less specificity (66.67%) with area under curve of 0.789, at a cut-off 1.66 and sensitivity 81.58%.

There were some limitations in our study. First, this was a single center study. Second, we did not examine the correlations of AFR and CAR with important in RA inflammatory mediators like tumor necrosis factor-α and interleukin-1β.

Conclusion

In conclusion, there are scanty studies examining correlations of AFR and CAR with RA disease activity, despite the fact that AFR and CAR are parameters that can be assessed simply and at an affordable cost. AFR was lower while CAR was higher in RA patients. DAS 28 showed a strong correlation with CAR but not with AFR.

We suggest that CAR and AFR are very good variables to discriminate healthy subjects from RA patients. CAR was also a fair measure to discriminate disease activity among RA patients but AFR was a very poor parameter for activity level assessment. Their use in clinical practice to follow up RA patients seems promising. CAR was a more reliable indicator of activity in RA patients than AFR.

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Conflict of Interest Statement

The investigation has not been sponsored. There are no conflicts of interest. The authors are solely responsible for submitting the final version of the manuscript for publication. All the authors have participated in developing the concept of the article and in writing the manuscript. The final version of the manuscript has been approved by all the authors