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Clinical Utility of C-Reactive Protein/Albumin Ratio and Albumin/Fibrinogen Ratio in Patients with Rheumatoid Arthritis

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Abstract

The albumin-to-fibrinogen ratio (AFR) and the C-reactive protein-to-albumin ratio (CAR) have been served as inflammatory markers. However, their roles in rheumatoid arthritis remain unclear. To evaluate the clinical significance of CRP/Albumin ratio and Albumin / Fibrinogen ratio in patients with rheumatoid arthritis as inflammatory markers and its relation to disease activity and severity. A total of 60 RA patients were included in this cross-sectional study together with 30 healthy controls. The inclusion criteria were fulfilling the American College of Rheumatology/European League Against Rheumatism 2010 RA classification criteria, being over 18 years and accepting to participate in the study. Demographic and clinical parameters including serum erythrocyte sedimentation rate (ESR), CRP, fibrinogen, albumin, CAR and AFR measurement were recorded. Disease activity was measured using Disease Activity Score 28 (DAS28). Sixty RA patients were included,58 (96%) were females and 2(3.3%) were males. their age ranged from 23 to 70 years, with mean ± SD (48.10±7.85), and their duration of disease ranged from 1 to 34 years, with mean ± SD (13.85±7.64) together with 30 age and sex matched as a control group. Group I: They were subdivided according to disease activity into three groups: Group Ia: patients with severe disease activity: included 24 RA patients whose DAS score >5.1. Group Ib: patients with moderate disease activity: included 29 RA patients whose DAS score >3.2 but ≤ 5.1. Group Ic: patients with mild disease activity: included 4 RA patients whose DAS score ≤ 3.2. The data demonstrated significantly higher levels of fibrinogen and CRP in RA patients, compared to control, significantly higher levels of fibrinogen, CRP, ESR, and CRP/Alb ratio were noticed in patients with active disease compared to the remission subgroup. CRP/Alb ratio was highly statistically significant increased while Albumin /fibrinogen ratio decreased in RA patient compared to controls. CRP/Alb ratio was positively correlated with CRP, ESR and DAS Score 28 while Albumin /fibrinogen ratio showed negative correlation with them. CRP/albumin ratio was increased in all RA patients in comparison to control group while Alb/fibrinogen ratio was decreased.

Keywords: Rheumatoid arthritis, Albumin-fibrinogen ratio, C-reactive protein/albumin ratio.

1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune and inflammatory disease, which affects approximately 1% of the global population and occurs more in females, with a female-to-male ratio of 3:1 [1]. In general, the joints most frequently affected are those of the hands and wrists, followed by those of the feet, knees, elbows, and ankles, up to involving the wider joints of the shoulders, hips, jaws, and cervical spine [2] With overt disease, joint swelling occurs, caused by synovial effusion being associated to joint deformities and ankylosis [3]. C-reactive protein (CRP) and albumin are commonly used parameters for the measurement of the activity of inflammatory conditions and are known as positive and negative acute phase reactants (APRs). The CRP/albumin ratio is determined by dividing the CRP by the albumin measurement and is an established scoring system used to determine the degree and activity of the inflammatory disease, which is considered to be a more useful indicator of the status of inflammation than CRP or albumin alone [4)]. C-reactive protein to albumin ratio (CAR) ratio has been considered a useful biomarker for evaluating the disease activity in patients with Takayasu arteritis [5]. In a recent retrospective study on 160 patients with RA and 159 healthy controls, CAR was found to be higher than controls and positively correlated with DAS28-ESR. Therefore, CAR was proposed to be a novel inflammatory marker for monitoring disease activity in RA [6]. Several cases have been reported where the level of fibrinogen (Fib) was significantly increased, and the ALB level was lower in rheumatoid arthritis patients. This may be due to the fact that the albumin to fibrinogen ratio (AFR) emerged as a useful biomarker to predict inflammation conditions. AFR acting as a useful indicator for monitoring disease activity in systemic inflammatory diseases including RA has been scarcely studied [7]. Albumin /Fibrinogen Ratio has been reported to be increased in rheumatoid arthritis as an indicator of chronic inflammation [8]. There was another study on albumin to fibrinogen ratio (AFR) in autoimmune diseases [9] found that Albumin /Fibrinogen Ratio had correlation with DAS-28 in RA patients and can be used as an indicator to judge the activity of RA disease.

2. Patients and Methods

This study is a cross-sectional case-control study conducted on 90 participants; they are divided into two groups. Group I: 60 patients fulfilling the 2010 ACR- EULAR criteria for diagnosis of RA [10]. They were subdivided according to disease activity into three groups: Group Ia: patients with severe disease activity: including 24 RA patients whose DAS score > 5.1. Group Ib: patients with moderate disease activity: included 29 RA patients whose DAS score >3.2 but ≤ 5.1. Group Ic: patients with mild disease activity: included 4 RA patients whose DAS score ≤ 3.2. All patients were recruited from rheumatology outpatient clinic and inpatients in the internal medicine department (Al-Zahraa University Hospital) after obtaining oral consent to participate in the study during the period from June to November 2021. Group II Control group: This group included 30 apparently healthy volunteers whose age and sex matched as a control group.

2.1 Inclusion Criteria

Adult rheumatoid arthritis patients ≥18 yrs old.

2.2 Exclusion Criteria

Current Infectious disease, Malignant diseases, Chronic liver and kidney diseases, ischemic heart disease and other autoimmune diseases (such as SLE).

2.3 Method

All patients were subjected to the following: Complete medical history with

special emphasize on disease duration, pattern of joint involvement and drug in use. Full clinical examination including musculoskeletal examination (number of affected joints, number of joint swelling and extra-articular examination). Assessment of rheumatoid arthritis disease activity state using disease activity score Das28 score (11). Scoring of DAS28, after the complex calculation, has been made DAS 28 > 5.1 = high disease activity. DAS 28 > 3.2 ≤ 5.1 = moderate activity. DAS28 > 2.6< 3.2 = low disease activity. DAS28 <2.6 = remission (12). Laboratory investigations include Complete blood count and erythrocyte sedimentation rate (ESR) 1ST hour by Westegren method. Liver function test (Albumin, bilirubin, ALT and AST) and Renal function test (Blood urea, serum creatinine.). Anti-citrullinated peptide antibody (ACPA) by ELISA. Rheumatoid factor (RF) IgM by latex agglutination slide test, C- reactive protein (CRP) by latex agglutination slide test, Plasma fibrinogen. C-reactive protein (CRP)/ albumin ratio and Albumin /Fibrinogen ratio X-ray on both hands.

2.4 Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA). The quantitative data were presented as mean± standard deviation and ranges when their distribution was parametric (normal) while non-normally distributed variables (non-parametric data) were presented as median with inter-quartile range (IQR). Also, qualitative variables were presented as number and percentages. Data were explored for normality using Kolmogorov-Smirnov and Shapiro-Wilk Test. The significance of the test was determined based on P values: P value less than or equal to 0.05 was considered significant, while P value more than 0.05 was considered non-significant.

2.5 Ethical Considerations

Written consent was attained from patients before enrollment into the study. The study protocol was approved by the institutional review board of the Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. Every patient can refuse participation or withdraw from the study at any time without any clarification of the reason and without troubling their rights of medical care. Moreover, data were nameless and coded to guarantee the privacy of patients**.**

3. Results

Demographic data of our study revealed that out of 60 RA patients, 58 (96%) were females and 2(3.3%) were males. Their age ranged from 23 to 70 years, with mean ± SD (48.10±7.85), and their duration of disease ranged from 1 to 34 years, with mean ± SD (13.85±7.64). Out of 60 patients, 55 had a tender joint range from 1 to 22 with mean ± SD (7.84±5.17), 40 had swollen joint range from 0 to 8 with mean ± SD (1.12±1.95), 50 had a morning stiffness range from 15 to 90 with mean ± SD (43.30±14.45) and 35 had extra-articular manifestation, 10 (16.7%) had pulmonary manifestation, 2 (3.3%) had neurological manifestation, 2 (3.3%) had skin manifestation, 7 (11.7%) had hematological manifestation, and 4 (6.7%) patients had ocular manifestation as shown in Table .1. Out of 60 patients, 3 patients were in remission, 4 patients were in mild disease activity, 29 patients in moderate disease activity, and 24 patients in severe disease activity as shown in Table .2. Out of 60 patients, 40(60%) patients had RF positive, and 20(40%) patients were negative, and 50(80%) patients had positive ACPA, and 10 (20%) patients were negative as shown in Table .3. There was highly significant increase of CRP, fibrinogen, CRP/Albumin ratio and decrease in Albumin fibrinogen ratio in RA patients when compared to control group with (p−values were <0.001) Table .4.

Table (1): The main clinical manifestation of RA patients.

Variable	no. of patients	Range	Mean ± SD
Tender joint number	55	1-22	7.84±5.17
Swollen joint number	40	0-8	1.12±1.95
Morning stiffness	50	15-90	43.30±14.45
Extra articular manifestation	35	------	------
	No of patients (n= 60)		Percentage
ILD	10		(16.7%)
Anemia	7		(11.7%)
Ocular	4		(6.7%)
PN	2		(3.3%)
Skin	2		(3.3%)
Anemia & ILD	1		(1.7%)

Table (2): Disease Activity Score (DAS28) among studied RA patients.

DAS score 28	NO of Patients *(n=60)*	Percentage%
Remission ≤ 2.6	3	(5.0%)
Mild disease activity >2.6 - ≤3.2	4	(6.7%)
Moderate disease activity >3.2 - ≤5.1	29	(48.3%)
Severe disease activity >5.1	24	(40.0%)

Table (3): Serology tests in RA patients.

Variable	Seropositive patients%		Seronegative patients%	
	NO	Percentage	NO	Percentage
RF(IU/ml)	40	60%	20	40%
Anti CCP(IU/ml)	50	80%	10	20%

Table (4): Comparison between patients' group and control group according to inflammatory markers.

Inflammatory markers	Patients *(n=60)*	Control *(n=60)*	Test value	p-value
CRP				
Mean ± SD	14.71±10.87	6.00±1.95	U=4.344	<0.001**
Range	3.5-50	3-10		
Fibrinogen				
Mean ± SD	4.65±1.26	2.77±0.67	U=7.652	<0.001**
Range	2.8-8.6	1.50-4.0		
CRP albumin ratio				
Mean ± SD	3.56±2.57	1.44±0.52	U=4.449	<0.001**
Range	0.8-11.1	0.7-2.6		
Albumin fibrongen ratio				
Mean ± SD	0.92±0.24	1.56±0.41	U=-9.316	<0.001**
Range	0.45-1.5	1-2.5		

Using: U=Mann-Whitney test *p-value <0.05 S; **p-value <0.001 HS

Table (5): Comparison between groups Ia, Ib, Ic as regards, CRP / Albumin ratio and Albumin/fibrinogen ratio.

Variable	Group 1a	Group 1b	Group 1c	F-test	p-value
	Mean ±SD	Mean ±SD	Mean ±SD		
CRP albumin ratio	2.58±1.84	3.70±2.95	3.79±2.27	0.375	0.689
Albumin fibrinogen ratio	1.25±0.19	0.91±0.20	0.82±0.20	7.981	0. 921

Using: F-One Way Analysis of Variance
p-value >0.05 NS.

Comparison between groups Ia, Ib, Ic as regards, CRP/ Albumin ratio and Albumin/fibrinogen ratio revealed no significant difference in different RA groups with mild, moderate or severe disease activity as shown in Table .5. There was a significant increase in ESR, highly significant increase of each DAS score 28, CRP and CRP /Albumin ratio in active disease of RA patients when compared to remission. There was a significant decrease in albumin and albumin/ fibrinogen ratio in active disease of RA patients when compared to remission as shown in Table .6. There was a statistically significant positive correlation between CRP and each of Fibrinogen, CRP /Albumin ratio and negative correlation between CRP and Albumin/ Fibrongen ratio. There was a statistically significant positive correlation between fibrinogen and each of CRP, CRP /Albumin ratio and a negative correlation with Fibrinogen and Albumin/ Fibrongen ratio. There was a statistically significant positive correlation between CRP /Albumin ratio and each of CRP and fibrinogen and a negative correlation with Albumin/ Fibrongen ratio. There was a statistically significant negative correlation between Albumin/ Fibrongen ratio and each of CRP, Fibrinogen and CRP / Albumin ratio as shown in Table .7.

Table (6): Comparison between the active disease subgroup and remission subgroup according to different parameters.

Parameters	Rheumatoid Arthritis Subgroups		Test value	p-value
	Active Disease Subgroup (n=57)	Remission Subgroup (n=3)		
Age (years)	48.30±12.01	44.33±9.29	U=0.561	0.577
Duration of disease	13.40±7.30	22.33±10.79	U=-2.025	0.272
Tender joint number	10 (6-13)	2 (1-3)	U=2.494	0.015
Swollen joint number	4 (2-6)	0 (0-0)	U=2.278	0.026
DAS score 28	4 (4-6)	2 (2-3)	U=4.402	<0.001**
HB	10.83±1.19	10.60±0.72	t=0.326	0.746
PLT	253.39±80.15	250.33±54.26	U=0.065	0.948
Albumin	4.08±0.28	4.63±0.29	t=-1.145	0.023*
ALT	21.12±10.82	28.33±14.57	U=-1.109	0.272
AST	26.46±13.20	32.67±12.50	U=-0.795	0.430
WBC	7.10±2.50	8.10±1.25	U=-0.683	0.497
RBC	4.76±0.66	4.43±0.45	t=0.852	0.398
HTC	30.66±3.40	28.83±0.29	t=0.922	0.360
MCV	76.99±8.01	77.00±2.65	t=-0.002	0.999
MCH	22.46±3.50	21.00±1.00	t=0.717	0.476
Urea	30.03±9.32	30.00±2.00	U=0.005	0.996
Creat	0.65±0.21	0.57±0.15	U=0.655	0.515
ESR	50 (35-70)	35 (30-40)	U=0.021	0.021*
RF	27.70±34.67	17.77±9.75	U=0.491	0.625
Anti CCP	200.71±152.74	287.33±213.43	U=-0.942	0.350
Crp	14.71±10.87	6.00±1.95	U=4.321	<0.001**
Crp /albumin ratio	3.56±2.57	1.44±0.52	U=4.411	<0.001**
Albumin /fibrinogen ratio	0.92±0.24	1.56±0.41	U=-0.942	<0.001**

Using: t-Independent Sample t-test; U=Mann-Whitney test
p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

There was a statistically significant positive correlation between CRP /Albumin ratio and each of DAS score and ESR and negative correlation with albumin. There was a statistically significant negative correlation between Albumin/ fibrinogen ratio and each of DAS scores and ESR as shown in Table .8.

Receiver operating characteristics (ROC) curve was performed for CRP/Albumin Ratio and demonstrated an area under the curve of 0.750 with P value <0.05. The best cut-off value for the prediction of RA disease activity was ≥1.5 with a sensitivity of 81% and specificity 69%. As for the Albumin / Fibrinogen Ratio and demonstrated an area under the curve of 0.820 with P-value <0.001. The value set cut-off value for the prediction of RA disease activity was ≤1.19 with a sensitivity of 89% and specificity 76% as shown in Table .9.

Table (7): Correlation between inflammatory markers in 60 patients of RA, using Spearman's rank correlation coefficient (rs).

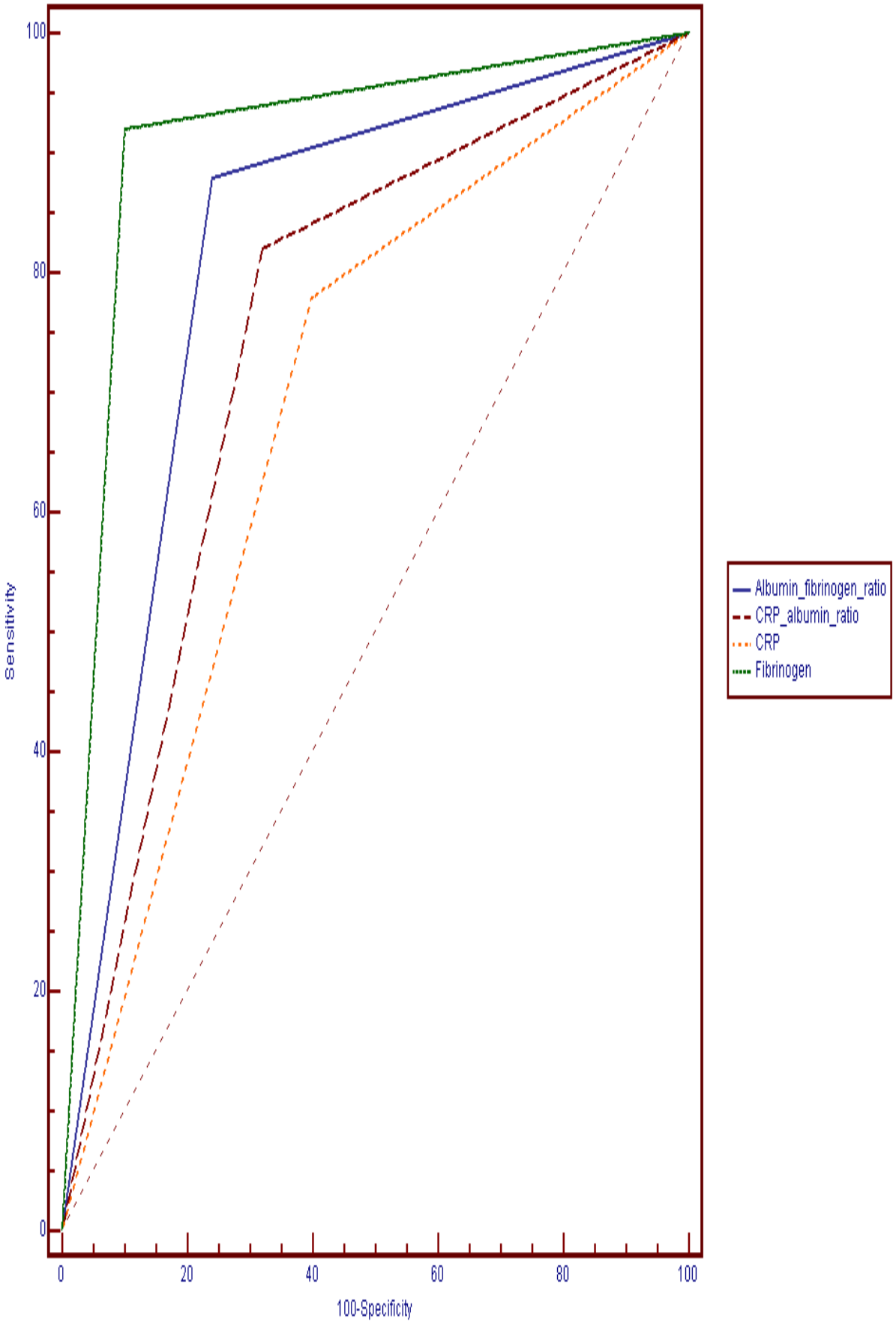
Inflammatory markers	CRP		Fibrinogen		CRP albumin ratio		Albumin fibrongen ratio	
	Rs	p-value	Rs	p-value	Rs	p-value	Rs	p-value
CRP			0.280	0.049*	0.992	<0.001**	-0.486	<0.001**
Fibrinogen	0.280	0.049*			0.258	0.047*	-0.967	<0.001**
CRP albumin ratio	0.992	<0.001*	0.258	0.047*			-0.275	0.033*
Albumin fibrongen ratio	-0.249	<0.001*	-0.967	<0.001**	-0.275	0.033*		

Table (8): Correlation between inflammatory markers with different parameters in patients' group, using Spearman's rank correlation coefficient (rs).

Different parameters	CRP		Fibrinogen		CRP albumin ratio		Albumin fibrongen ratio	
	Rs	p-value	Rs	p-value	Rs	p-value	Rs	p-value
Age (years)	-0.104	0.429	-0.058	0.661	-0.076	0.566	-0.336	0.082
Duration of disease	-0.072	0.587	0.009	0.944	-0.083	0.528	0.014	0.918
Tender joint number	0.195	0.136	0.263	0.042*	0.218	0.094	-0.329	0.010*
Swollen joint number	0.197	0.132	0.346	0.007*	0.221	0.090	-0.425	<0.001**
DAS score 28	0.225	<0.001**	0.369	0.004*	0.272	0.036*	-0.469	<0.001**
HB	-0.003	0.983	-0.190	0.145	0.019	0.884	0.141	0.282
PLT	0.167	0.201	-0.097	0.461	0.148	0.260	0.161	0.219
Albumin	-0.082	0.533	-0.148	0.258	-0.369	0.014*	0.355	0.005*
ALT	0.235	0.071	-0.109	0.408	0.208	0.110	0.106	0.420
AST	0.058	0.661	0.031	0.813	0.024	0.856	0.010	0.942
WBC	0.148	0.259	-0.192	0.142	0.146	0.264	0.197	0.131
RBC	-0.191	0.145	-0.030	0.821	-0.198	0.130	0.043	0.746
HTC	0.309	0.016	-0.188	0.151	0.298	0.021	0.227	0.082
MCV	0.058	0.662	-0.211	0.106	0.065	0.622	0.221	0.089
MCH	0.165	0.207	-0.269	0.038	0.169	0.197	0.258	0.947
Urea	-0.019	0.884	0.104	0.429	-0.020	0.877	-0.101	0.444
Create	-0.103	0.435	-0.127	0.334	-0.087	0.508	0.150	0.252
ESR	0.465	<0.001**	0.325	0.013*	0.444	<0.001**	-0.502	<0.001**
RF	0.014	0.918	-0.022	0.866	0.016	0.903	0.044	0.736
Anti-CCP	0.007	0.959	-0.014	0.914	0.018	0.893	-0.036	0.786

Table (9): Roc curve analysis of the inflammatory markers for the prediction of RA disease activity.

Inflammatory markers	Cut-off	Sen.	Spe.	PPV	NPV	AUC	p-value
CRP	≥7	78.0%	61.0%	66.1%	73.2%	0.690	<0.05 Sig.
Fibrinogen	≥3.7	93.0%	89.0%	90.2%	91.8%	0.910	<0.001 highly Sig.
CRP albumin ratio	≥1.5	81.0%	69.0%	71.9%	79.1%	0.750	<0.05 Sig.
Albumin fibrinogen ratio	≤1.19	89.0%	76.0%	78.6%	86.4%	0.820	<0.001 highly Sig.


Sensitivity
100
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80
100
100-Specificity
Albumin_fibrinogen_ratio
CRP_albumin_ratio
CRP
Fibrinogen

4. Discussion

The current study was carried out to evaluate the clinical significance of CRP /Albumin ratio and Albumin/fibrinogen ratio in patients with rheumatoid arthritis as inflammatory markers and its relation to disease activity and severity.

The present study showed that out of 60 RA patients, 58 (96%) were females and 2 (3.3%) were males (male: female ratio 1:7) The prevalence of extra-articular manifestation (ExRA) in the studied patients was 54%. This was close to a study that reviewed 262 medical reports of rheumatoid arthritis patients, they found a prevalence of extra-articular manifestation in 45.8% of their patients [13].

In the current study, we found that there was a significant increase in serum levels of ESR, CRP, RF and Anti-CCP among RA patients in comparison to the control group; this agreed with El Tokhey et al (2011) who showed a significant increase in mean serum level of Anti-CCP and RF antibodies in all established RA patients compared to the control group [14].

There was highly significant increase of CRP, fibrinogen, ESR and decrease in Albumin in RA patients when compared to control group. This agreed with Göbel et al (2018) who revealed that raised fibrinogen, ESR, and CRP and reduced albumin among rheumatoid arthritis [15].

In the present study we found that there was a significant increase in CRP /Albumin ratio and decrease in Albumin/ fibrongen ratio in active disease of RA when compared to remission. There was significant positive correlation between CRP /albumin ratio and each of CRP, ESR and DAS score whereas albumin/ fibrongen ratio show negative correlation with them.

This agreed with previous study which conducted on 160 patients with RA and 159 healthy controls. They divided the RA patients into two groups according to the DAS 28-ESR score. Group 1 included 40 patients with a score of lower than 2.6 (patients in remission) and Group 2 included 120 patients with a score of 2.6 or higher (patients with active disease). They found that RA patients, the Albumin/ fibrongen ratio was lower than those in the control group. Patients in group 2 had a higher CRP /Albumin ratio than those in group 1. The Albumin/ fibrongen ratio was lower in group 2 than that in group 1. A positive correlation was observed between DAS 28-ESR score and CRP /Albumin ratio while the correlation between DAS 28-ESR and Albumin/ fibrongen was negative [9].

Also, this agreed with He et al (2019) who studied 196 RA patients, 200 patients with systemic lupus erythematosus (SLE), and 200 healthy controls. The percentage of Th17 cells in peripheral blood of RA patients was detected by flow cytometry, and the relative expression of TNF-α, IL-6 and IL-17A was detected by RT-Qpcr [8]. As regard RA patients, they found that albumin/ fibrongen ratio was significantly lower ($P < 0.01$) in RA patients, while CRP /Albumin ratio was significantly increased ($P < 0.01$) in RA patients when compared to healthy control. Albumin/ fibrongen ratio showed negative correlation with CRP, ESR, Th17 cells and IL-17. CRP /Albumin ratio was positively correlated with CRP and ESR. Similar to our finding, Naglaa et al (2020) found that RA patients had lower albumin/ fibrongen ratio and higher CRP /Albumin ratio than those in the control group. Positive correlation was demonstrated between CRP /Albumin ratio and DAS score, whilst there was a negative correlation between albumin/ fibrongen ratio and DAS 28-ESR [16]. In the current study, we found that there was no correlation between CRP /Albumin ratio and Albumin / Fibrinogen ratio and each of Anti-CCP and RF. This agreed with Naglaa et al (2020) who found that these ratios were not correlated with either rheumatoid factor (RF) or anti-citrullinated protein antibodies (ACPA) on the other hand this disagreed with Yang et al (2018) who found that these ratios are significantly correlated to RF concentrations.

5. Conclusion

RA patients exhibit a higher CRP /Albumin ratio and lower Albumin / Fibrinogen ratio than healthy subjects. CAR and AFR may be easily, rapidly detected and prognostically useful markers of ongoing inflammation and joint affection.

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