AJ J Med Sci 2025;2(2):77–82

Online ISSN: 3049-2742

AJ Journal of Medical Sciences

ORIGINAL ARTICLE

Assessment of C-reactive Protein/Albumin Ratio (CAR), Calcium, and Parathyroid Hormone Levels among Sudanese Rheumatoid Arthritis Patients in White Nile State

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ARTICLE INFO

Article history:
Received 24.04.2025
Accepted 20.05.2025
Published 17.07.2025

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https://doi.org/10.71325/ajjms.v2i2.25.24

ABSTRACT

Background: Rheumatoid arthritis (RA) is a long-lasting inflammatory condition characterized by inflammation of the synovial membrane in the joints and may lead to reduced mobility, joint deformities, and disability. The development of precise diagnostic tools remains a persistent challenge in the effective management of the disease, aiming to improve patient outcomes. The present study was conducted to assess the diagnostic values of serum biomarkers among rheumatoid patients. **Materials and Methods:** An analytical case-control study conducted at Kosti Teaching Hospital included 100 rheumatoid patients as the case group and 100 healthy individuals as controls. Blood samples were collected and analyzed for the C-reactive protein (CRP), rheumatoid factor (RF) erythrocyte sedimentation rate (ESR), C-reactive protein /albumin ratio (CAR), Calcium, parathyroid hormone (PTH) and Albumin. Data was analyzed using SPSS version (27). **Results:** Our findings indicated that levels of RF, PTH, ESR, and CAR were significantly elevated in cases compared to controls, (P<0.001). Additionally, CAR and CRP exhibited a strong positive correlation with disease activity (r=0.915, P=0.000 and r=0.850, P=0.000, respectively), but showed no correlation with disease duration (r=0.069, P=0.495, and r=0.075, P=0.461). Serum calcium levels did not correlate with disease activity or duration. Sensitivity and specificity of CAR (sen: 97% and spec: 98%), CRP (sen:96% and spec: 91%) ESR (sen: 54% and spec: 93%), ALB (sen: 92% and spec: 87%), PTH (sen: 27% and spec: 98%). **Conclusion:** Elevated levels of RF, ESR, CRP, CAR, and PTH have been linked to rheumatoid arthritis. Furthermore, CAR has the potential to serve as a cost-effective and readily implementable diagnostic biomarker for rheumatoid arthritis.

Keywords: Rheumatoid; Inflammation; Calcium; Albumin; Biomarkers

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease that impacts approximately 0.5-1% of the adult population and presents two- to three-fold more frequently in women than in men[1]. RA with a symptom duration of fewer than six months is defined as early RA, and when the symptoms have been present for more than six months, it is described as established RA[2]. There is no pathognomonic laboratory test for rheumatoid arthritis, making diagnosis challenging in the early stages. A comprehensive clinical approach is required to make the diagnosis and prevent debilitating joint damage[2,3].

Several autoantibodies, including rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), and anti-carbamylated protein antibodies, have been identified in the serum of RA patients[4]. The role of these autoantibodies is critical as they may form immune complexes in the joint that contribute to the inflammatory processes that lead to articular cartilage damage. Depending on the presence or absence of RF and ACPA in RA patients' serum, two forms

of the disease have been established: Seropositive RA, which represents the most common form and is characterized by the presence of RF and or ACPA antibodies, while seronegative RA is determined by the absence of both RF and ACPA[5].

The RF test measures IgM autoantibodies that are directed against the Fc portion of IgG. Patients whose tests are positive for RF are described as being seropositive. Although about 85% of patients become seropositive at some point, this test alone is neither sufficient nor necessary to make the diagnosis[6].

Other laboratory abnormalities in rheumatoid arthritis include elevations in test results that are indicative of acute phase reactants. Such as increases in the erythrocyte sedimentation rate and C - reactive protein levels. These indicators are less specific than RF or anti-CCP antibodies, but they may help distinguish rheumatoid arthritis from non-inflammatory diseases such as osteoarthritis when physical signs are not prominent. Erythrocyte sedimentation rate and C-reactive protein level are also used to monitor therapy, unlike the RF value; these measurements do fluctuate with disease activity. Antinuclear antibodies may be detected in about 40% of patients with RA, further contributing to the complexity of the disease's laboratory profile[7].

Laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and disease activity score-28 (DAS-28) are used to evaluate disease activity in RA patients. Although ESR and CRP are the most used acute phase reactants, they are non-specific, show short-term inflammation, and can be affected by many factors. In this sense, other biomarkers indicating inflammation are needed. CRP/albumin ratio (CAR) is a new laboratory indicator and CAR concentration increased in cancer and cardiovascular disease and is associated with inflammation. As a new predictive biomarker, CAR might be used to assess disease activity in RA patients, it correlates with DAS-28 in RA patients and can be used as an indicator to assess the activity of RA and give more precise results in mortality compared to CRP alone[8].

The present study was conducted to evaluate the diagnostic utility of C-reactive protein albumin ratio (CAR), acute phase reactant, calcium, and parathyroid hormone among Sudanese rheumatoid arthritis patients, and to compare the levels of RF, CRP, CAR, and Calcium between different disease activity levels (low, medium and high activity).

MATERIALS AND METHODS

Study population

Analytical, case-control, and hospital-based study was conducted in Kosti Teaching Hospital in White Nile State, Sudan. It included 100 rheumatoid patients as the case group (with a mean age of 46.1 $\pm$ 7.9) which included 82 females and 18 males and 100 healthy individuals as a control group (with a mean age of 40.1 $\pm$ 6.4). Patients diagnosed with short-term rheumatoid arthritis of both genders and healthy individuals matched the cases in age and gender were included. The sample size was determined using the following equation: $n_1 = (\sigma_1 + \sigma_2 / K) (Z_{1-\alpha/2} + Z_{1-ß})^2 / \delta^2$, with K defined as $n_2/n_1 = 1$. In this context, n_1 and n_2 represent the sample sizes of the respective groups, σ_1 and σ_2 denote the variances of the means, α signifies the probability of a type I error (set at 0.05), ß indicates the probability of a type II error (set at 0.2), Z refers to the critical Z value corresponding to the specified α or ß, δ represents the absolute difference between the two means, and K is the ratio of the sample sizes, which is equal to 1. According to this equation, the minimum sample size for each group was found to be 40 participants. Patients with chronic renal failure, liver disease, diabetes mellitus, systemic illness, and immune disease or on calcium and vitamin D supplements were excluded from the study.

Data collection and sampling

The primary data were collected by using a structured questionnaire, the questionnaire was based on the objectives of the study and explained to the participants in the local language, and the secondary data were collected from laboratory results. A venous blood sample was collected directly into ESR and a plain container. The serum was obtained immediately after being separated by centrifuge at 5000 rpm for 5 minutes. Then, the serum was tested for rheumatoid factors, C-reactive protein, calcium, albumin, and parathyroid hormone following standard procedures and using full automated analyzers. The C-reactive protein/albumin ratio was then calculated.

The disease activity was determined according to the disease activity score (DAS-28), which depended on the number of joints involved and serum inflammatory markers.

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

TJC – tender joint count, SJC – swollen joint count, PGA – patient's global assessment measured on a visual analog scale[9]. DAS28 was used for classification of RA activity. Grading of DAS28 was low (DAS28$\leq$3.2), moderate (3.2<DAS28$\leq$5.1), and high disease activity (DAS28>5.1).

Ethical considerations

The research proposal was approved by the research board of the Faculty of Medical Laboratory Sciences, University of EL Imam EL Mahdi. Permission was taken from Kosti Teaching Hospital, and written informed consent was obtained from all the study participants before sampling.

Statistical analysis

The collected data were analyzed using SPSS version 27 (IBM Inc., Chicago, USA). Numerical data were expressed as mean ± standard deviation. Qualitative data were expressed as frequency and percentage. The chi-square test was used to examine the relation between qualitative variables. ANOVA was used in multi-comparison analysis of data. Pearson's correlation was used to measure the correlation coefficients. The P value < 0.05 was considered significant for all tests.

RESULTS

This case-control study included 100 cases of rheumatoid arthritis patients as study group and 100 age and sex matched healthy individual as controls. The mean value of disease duration and disease activity among cases were (8.4 ±4.6) and (4.2 ±0.821) respectively.

The mean values of RF, PTH and ESR in cases were (46.5 ± 13.8 IU/ml, 43.4 ± 21.3, pg/ml, and 28.8±12.52 mm/hr) respectively, while in controls were (5.7 ± 5.9 IU/ml, 39.8 ± 16.7 pg/ml, and 18.6 ± 6.4 mm/hr) respectively. There was significant increase in RF, PTH and ESR levels among cases compared to controls (P<0.001). Moreover, the rheumatoid patients showed significant increase in CRP (20.3 ± 7.2 mg/dl), and CAR (6.7±2.4) levels compared to controls, CRP (4.1 ± 3.4 mg/dl), and CAR (0.960 ± 0.837), (P= 0.000).

Calcium and albumin levels decreased in RA cases (6.8 ± 0.629 mg/dl and 3 ± 0.383 g/dl) respectively, compared to controls (8.8 ± 1.7 mg/dl and 4.4 ± 0.809 g/dl), (P< 0.001) as shown in Table 1 and Figure 1.

Table 1: Levels of biochemical parameters in the study groups

Variables	Group: Mean ± SD		P value
	Cases (N=100)	Control (N=100)	
Calcium (mg/dl)	6.8 ± 0.629	8.8 ± 1.7	0.001
Serum albumin (g/dl)	3.0 ± 0.383	4.4 ± 0.809	0.000
ESR (mm/h)	28.8±12.52	18.6 ± 6.4	0.000
RF (IU/ml)	46.5 ± 13.8	5.7 ± 5.9	0.000
CRP (mg/dl)	20.3 ± 7.2	4.1 ± 3.4	0.000
PTH (pg/ml)	43.4 ± 21.3	39.8 ± 16.7	0.001
CAR	6.7 ± 2.4	0.960 ±0.837	0.000

The serum calcium was not correlated with disease duration (r= -0.004, P 0.972) or disease activity (r= 0.028, P=0.779). The CAR was strongly and positively correlated with disease activity (r= 0.915, P=0.000), but not with disease duration. CRP also correlated positively with disease activity (r= 0.850, P=0.000), but not correlated with disease duration as shown in Table 2 and Figure 2 (**A and B**).

ROC is a plot of the sensitivity (true positive rate) at y-axis against the 1-specificity (false positive rate) at x-axis for the different possible cut-points of Albumin, CRP and CAR

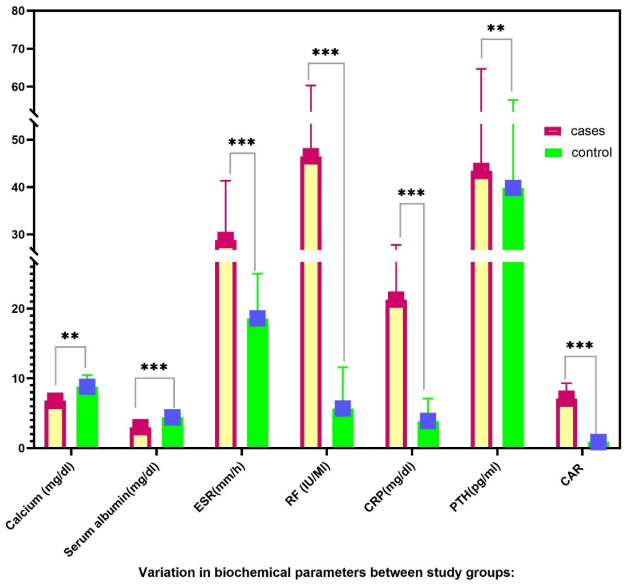

Fig. 1: Levels of the study parameters in cases and controls. Calcium, Albumin, ESR: Erythrocyte sedimentation rate, RF: Rheumatoid factor, CRP: C - reactive protein, PTH: Parathyroid hormone, and CAR: CRP/Albumin Ratio

Table 2: Pearson Correlation between study parameters and disease duration and activity

Variables	Correlation coefficient (r)	P value
Ca^{+2} vs Disease Activity	0.028	0.779
Ca^{+2} vs Disease duration	-0.004	0.972
CAR vs Disease Activity	0.915	0.000
CAR vs Disease duration	0.069	0.495
CRP vs Disease Activity	0.850	0.000
CRP vs Disease duration	0.075	0.461

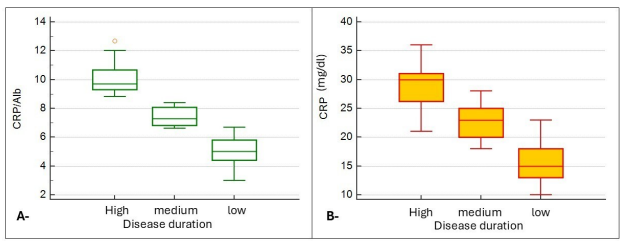

Fig. 2: CAR and CRP in low, medium, and high disease duration

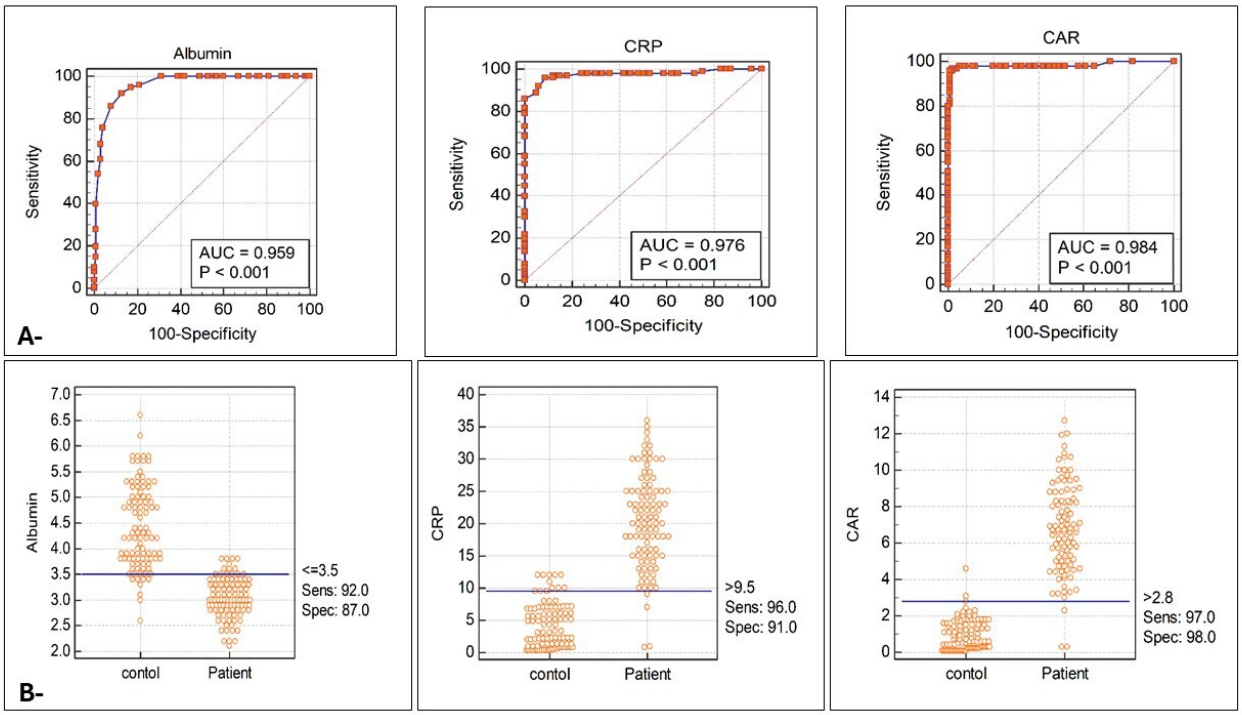

Fig. 3: A- The Receiver Operating Characteristic (ROC) curve of serum levels of Albumin, CRP and CAR of studied subjects. B- Interactive dot diagrams of studied parameters. Sens: sensitivity; spec: specificity. Blue lines indicate the cut-off value of each parameter

respectively. The area under the curve = 0.959, 0.976, and 0.984 are indicating the good accuracy of Albumin, CRP and CAR respectively, as shown in Figure 3**(A and B)**.

DISCUSSION

Rheumatoid arthritis (RA) is identified as the most prevalent inflammatory arthritis, significantly contributing to disability and increasing the risk of cardiovascular and pulmonary disorders[10]. The present study indicated that most RA patients exhibited medium disease activity, with a higher prevalence in females, as reported in previous studies[11]. İsmihan. S, et al., 2018, reported that 38% of rheumatoid patients had low disease activity or were in remission, 50.4% had moderate disease activity, and 11.6% had high disease activity[12].

The study revealed significant elevations in rheumatoid factor (RF), parathyroid hormone (PTH), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels among RA patients compared to controls. This suggests a strong inflammatory response, as these markers are known immune regulators[13]. The low plasma calcium stimulates the section of parathyroid hormone so it increases according to this compensatory mechanism[9]. Additionally, serum calcium and albumin levels were notably lower in RA patients, potentially due to inadequate dietary intake and the effects of chronic inflammation and steroid treatment, which can lead to osteoporosis. RA is associated with collection of chronic inflammatory cells occurring adjacent to bone with subsequent bone destruction. Furthermore, the catabolic effect of steroids treatment may contribute occasionally in liver disease, hypoalbuminemia and osteoporosis[14,15].

A significant increase in the C-reactive protein/albumin ratio (CAR) was observed in RA patients, indicating a potential link between inflammation and CAR as a long-term biomarker for disease activity[16,17]. Some studies suggested that CAR was a long term biomarker and it would give more precise results in mortality compared to CRP alone[18,19].

The study found a strong positive correlation between CAR and CRP levels as reported in previous work[12]. Additionally, our findings suggest high predictive value of CAR in identifying RA cases. This suggests that CAR may serve as a more reliable indicator of RA and disease activity. Furthermore, the study concluded that patients with high disease activity exhibited significantly greater levels of ESR, RF, CRP, CAR, and calcium compared to those with low or medium activity, reinforcing the relationship between disease severity and inflammatory markers[12,20].

Table 3: Diagnostic data of serum levels of Albumin, CRP and CAR using ROC curve

	AUC	SE	Asymptotic Significance	Asymptotic 95% Confidence Interval		Cut-off value	Sensitivity (%)	Specificity (%)
				Lower	Upper			
Albumin	0.959	0.0132	< 0.001	0.922	0.982	3.5 g/dl	92%	87%
CRP	0.976	0.0113	< 0.001	0.944	0.922	9.5 g/dl	96%	91%
CAR	0.984	0.00984	< 0.001	0.955	0.996	2.8	97%	98%

CONCLUSION

The RF, ESR, CRP, CAR and PTH levels were significantly higher while serum calcium and albumin levels were lower among rheumatoid patients than in control. CAR was strong positively correlated with disease activity. The high CAR levels and low albumin levels were associated with the severity of RA and may be used as a good predictive biomarker for RA.

DECLARATIONS

Ethical approval and consent to participate

The study was approved by the Ethics Committee at Kosti teaching hospital – Kosti -Sudan, informed consents were obtained from all participants in the study.

Availability of data and material

Please contact the authors for data requests.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Funding

No funding to be declared for this publication.

Acknowledgment

The authors would like to thank the head and staff of Rheumatoid unit in Kosti teaching hospital for their valuable support.

The authors would like to express sincerest gratitude to Bashar Abdalla, from Gezira College of Medical Science and Technology for his valuable support in preparing figures and tables.

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