Original Article

Serum C-Reactive Protein/Albumin Ratio and its Correlation with Disease Activity in Rheumatoid Arthritis Patients

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune disorder affecting joints with a progressive symmetric inflammation leading to bone erosion, cartilage destruction and disability. Usually, RA activity is measured by using RA Score of Disease Activity involving 28-joint count (DAS-28). C-reactive protein (CRP) to albumin ratio (CAR) has been recently used as a new indicator to assess inflammation and predict prognosis of certain malignancies with Some studies demonstrated its correlation with disease activity of some inflammatory diseases, particularly Crohn's disease and RA. **Objectives:** to assess the role of serum C-reactive protein to albumin ratio (CAR) in RA as a marker for activity of this disease. **Materials and Methods:** This cross-sectional study included 84 RA patients. Each patient was tested for albumin and CRP in addition to erythrocyte sedimentation rate (ESR). CAR was calculated mathematically by dividing CRP on albumin value. RA activity was assessed by applying DAS-28-ESR scoring system. **Results:** The mean of CAR was 4.25. Significant correlation was found between CAR and DAS-28 CRP disease activity index, CRP, ESR and patient VAS and serum albumin. CAR was showing significant differences among high, medium and low-remission groups of disease activity. However, positive but nonsignificant correlation was found between CAR and the DAS-28-ESR disease activity scoring system, CDAI and the physician VAS. **Conclusion:** CAR, can be considered as useful initial simple investigation which can give an idea about degree of disease activity and the need for further evaluation and management with less time, cost and effort especially in areas with low medical resources and facilities.

Keywords: CAR, disease activity, rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is an autoimmune systemic disease that mainly affects joints. Joint involvement is usually symmetric and progressive resulting in synovitis, bone erosions, cartilage destruction and disability.[1] Generally, RA patients suffer from stiffness and pain in more than five joints and linked to lower quality of life. During active exacerbations of the diseases, Erythrocyte sedimentation rate (ESR) and CPR levels usually increased.[2] The progression of RA fluctuates with exacerbations and remission and in the absence of appropriate care, symptoms progressively worsen over time, leading to irreversible joint damage that impairs physical and psychological functions.[3] Additionally, comorbidities and complications that related to RA shorten the patient's expected survival time by a few years. Early diagnosis, appropriate nonpharmacological and pharmaceutical treatment with periodic evaluation of therapeutic efficacy, compliance and safety are the most effective therapeutic approaches.[4] Pharmacological agents includes: conventional synthetic (DMARDs), biologic (DMARDs) and targeted synthetic (DMARDs).[5]

For evaluation of disease activity in RA patients, disease activity scoring system which involved 28-joint count

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(DAS-28) is commonly applied. The calculation of scores, which range from 0 to 9.4, takes into account several factors such as overall health, number of swollen and tender joints, and laboratory tests results for acute inflammation.[6] DAS-28 uses either ESR or CRP,[7] both of them are well validated and the agreement between them is very high, however as CRP become widely accessible, and is more responsive to inflammatory activity alteration so the DAS-28-CRP is gaining more popularity nowadays. It has been demonstrated that the DAS-28-CRP yields somewhat lower scores than this involved the ESR.[8]For ESR the clinical value remains useful in assessing response in selected clinical conditions. Specifically, in the diagnostic criteria and monitoring of disease progression.[9,10]

It is commonly known that CRP has a significant role in the defense mechanism of the host against infections and inflammatory responses. When it binds to immunoglobulin receptor, it promotes proinflammatory cytokines production creating amplification loop of inflammatory response.[11] CRP is produced by the liver as a response to a variety of cytokines. Increased levels were also found in the RA patients' synovial fluid.[12]

Albumin (ALB) is the most important human plasma protein, maintaining nutrition and osmotic pressure.[13] It is synthesized by the liver and can be downregulated in response to malnutrition and intense inflammatory reaction, which are both identified in RA patients with active disease. Albumin is a negative acute phase reactant and an acute inflammation marker, lower levels are associated with more severe inflammatory response.[14,15]

High CRP and low albumin may correlate with severe chronic inflammation. It has been shown by several studies that the ratio between CRP and ALB (CAR), is associated with inflammatory response and may have prognostic value in stroke and cardiovascular disease. CAR value more accurately reflects inflammatory response than isolated serum CRP.[15,16]

Recently, CAR has emerged as a marker to evaluate inflammation and predict prognosis of different types of malignancies as Ewing sarcoma, colorectal and esophageal carcinoma. Some studies have also demonstrated its correlations with disease activity in some inflammatory disorders including Crohn's disease and RA.[17]

Objectives

To assess the role of Serum C-Reactive Protein to Albumin Ratio as a disease activity marker in RA.

Materials and Methods

This cross-sectional study was conducted at rheumatological outpatient clinic in Merjan teaching hospital over a period from June 2022 to July 2023.

Patients

The study comprised eighty four participants, twenty four of them were male and sixty of them were female. All of the participants had previously been received a diagnosis of RA by a rheumatology specialists and were actively undergoing treatment. Inclusion criteria for participation required individuals to meet the 2010 RA classification guidelines developed by the European League Against Rheumatism and by the American College of Rheumatology, age of patients above 18 years, and provide their informed consents to participate in the study. Patients with mental issues or psychiatric disorders were excluded from this study.

Methods

The study collected data had several variables, including: sex, age, disease duration, educational level, employment, smoking, alcohol, drugs used for treating RA and global evaluation for RA activity by physicians. The activity of RA was assessed using DAS-28-ESR scoring system which including the number of tender and swollen joints, global assessment of RA disease activity by patient and ESR level.[18,19] According to the DAS-28-ESR values, the studied patients were divided into the following subgroups:

1. Remission (≤2.6)
2. Low level of RA disease activity (>2.6 and ≤3.2)
3. Moderate level of RA disease activity (>3.2 and ≤5.1)
4. High level of RA disease activity (>5.1)

Materials

About 5 mL of venous blood was collected from each patient for testing ESR, CRP and albumin. ESR was measured by the Westergren technique, CRP levels were determined using the AFIAS-6, which is an automated fluorescent immunoassay system manufactured by WELDON BIOTECH. On the other hand, albumin levels were assessed with the assistance of the Mindray BS-240 clinical chemistry analyzer, which employs the bromocresol green method based on the formation of complexes with green colored using bromocresol. The CRP to albumin ratio (CAR) for each patient was calculated mathematically through dividing the value of CRP by the value of albumin.

Statistical analysis

Statistical analysis for this study was conducted using Statistical Package for Social Sciences (SPSS) Software (version 26.0). Qualitative data were represented as numbers and percentages, while continuous numerical data were represented as mean ± standard deviation. Categorical variables were compared using Chi-square test. Spearman's rho correlation coefficient, Kruskal–Wallis Test and Mann–Whitney *U* test had been calculated in order to assess the correlation between discrete numerical

variables. *P* value was considered statistically significant when if <0.05.

Ethical approval

The study was carried out in compliance with the ethical standards found in the Helsinki Declaration. Before any samples were taken, the patients' verbal approval was obtained. The consent form, subject information, and study protocol were examined and approved by the local ethics committee by document No. 233 on May 22, 2022.

Results

Of 84 patients included in this study 24 were male and 60 were females. The mean age for the study group was 52.97 and disease duration mean was 7.38 years, the mean and median for CRP was 18.63 and 9.9, for the ESR was 43.47 and 38.0 mm/h, for the albumin 4.53 and 4.50 g/dL and for CRP/ albumin ratio (CAR) 4.25 and 2.10, respectively as shown in Table 1.

Table 1: Demographic data of the study population

Number	Mean	Median
Patients		
84 total		
60 females		
24 males		
Marital status		
76 married		
2 singles		
6 widowed		
Educational level		
22 illiterate		
30 primary school		
22 secondary school		
10 college		
Smoking		
68 nonsmokers		
8 ex-smokers		
8 smokers		
BMI		
58 Normal weight		
2 Overweight		
24 Obese		
Age (year)	52.97	54
Disease duration (year)	7.38	4.5
CRP (mg/L)	18.63	9.9
ESR (mm/h)	43.47	38.0
Albumin (g/dL)	4.53	4.50
CRP/albumin (CAR)	4.24	2.10

CRP = C-reactive protein, CRP to albumin ratio (CAR) values varied significantly among patient's groups of high level, medium level and (low-remission) level of disease activity (*P* value = 0.025) according to Kruskal–Wallis test. Analysis with Mann–Whitney *U* test revealed that CAR was significantly differ in patients with remission—low activity than patients with moderate activity (*P* = 0.09) or patients with high activity (*P* = 0.023)

According to the DAS-28-ESR, 12.05% of patients had low RA activity or were in remission, 37.35% had moderate level of RA activity, and 50.60% had high disease activity as in Figure 1.

Using Spearman's rho correlation, there was positive but nonsignificant correlation between CAR and the DAS-28-ESR scoring system, CDAI and the physician VAS (*P* value = 0.060, rs = 0.207; *P* value = 0.593, rs = 0.059 and *P* value = 0.170, rs = 0.152, respectively). And there was significant correlation between the CAR and DAS-28 CRP disease activity index, CRP, ESR and patient VAS (*P* value = 0.011, rs = 0.279; *P* value < 0.001, rs = 0.993; *P* value < 0.001, rs = 0.676 and *P* value = 0.005, rs = 0.304, respectively) and significant negative correlation with serum albumin (*P* value, 0.001 and rs = −0.393) as in Table 2.

Discussion

Recent years showed a growing use of various inflammatory markers and prognostic scores to evaluate disease activity and predict outcomes in inflammatory medical conditions. These markers include neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and Glasgow prognosis score (modified one), in addition to the C-reactive protein/ albumin ratio (CAR).

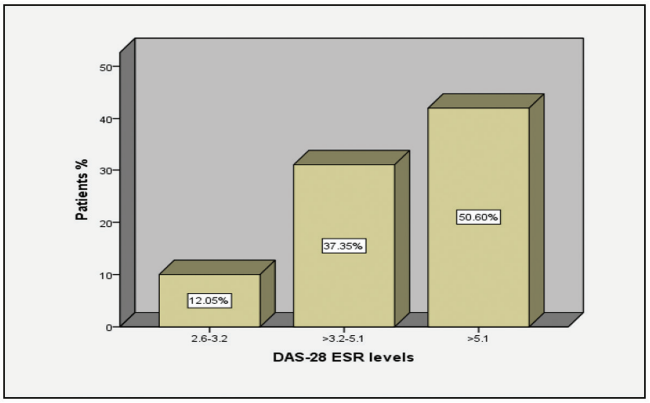

Figure 1: Patients' disease activity according to DAS-28-ESR

Table 2: C-reactive protein/Albumin correlations with other disease activity parameters

	P value	rs
DAS-28-ESR	0.060	0.207
DAS-28 CRP	0.011	0.011
CDAI	0.593	0.059
ESR	0.000	0.676
CRP	0.000	0.993
Albumin	0.000	−0.393
Patient VAS	0.005	0.304
Physician VAS	0.170	0.152

CRP = C-reactive protein

CAR has emerged as a notable predictor of poor survival in several cancer types.[20,21] It also exhibits a significant correlation with disease activity in various inflammatory disorders, such as Crohn's disease,[22] rheumatological disorders like vasculitis,[23] and psoriatic arthritis.[24] Furthermore, CAR has been identified as an independent predictor of mortality and has demonstrated superior predictive performance compared to CRP alone.[25] This superiority stems from CAR's reliance on two inflammatory markers rather than just one, providing a more comprehensive assessment of the inflammatory impact of many diseases.

RA is a progressively disabling articular condition that requires vigilant monitoring and early detection of disease activity to start appropriate early interventions preventing joint damage. One prominent characteristic of RA is an increase in CRP and ESR levels, coupled with a decrease in albumin levels. This study, along with several others,[26] clearly demonstrates this phenomenon.

There have been limited studies investigating the role of CAR as an inflammatory marker in RA and its correlation with scoring system of RA disease activity, primarily DAS-28-ESR, as seen in the 2023 study by Kaplan *et al*.[26] Consistent with their findings, this study according to DAS-28-ESR also reveals positively correlated relation between CAR and activity of RA disease.

DAS-28-ESR is a widely recognized and dependable score for assessing disease activity in RA. It is one of the most commonly used measures in rheumatology to evaluate RA.

However, in busy clinical settings, computing DAS-28-ESR can be somewhat time-consuming. Therefore, many researchers are currently exploring alternative biochemical inflammatory tests that can save time and effort.

A case–control study conducted by Onder ME and colleagues in 2022[27] found that Patients with early RA had higher CRP, ESR, and CAR when compared to those who had established disease or controls. Correlations was found between CAR and CRP, albumin and DAS-28 in both groups of early RA and established one. The study concluded that CAR has been identified as a predictor of RA disease activity in early RA group and in established RA patients group, with a notable stronger correlation in early-stage disease.

CAR was found to have a positive correlation with DAS-28-ESR in a retrospective study by Yang *et al*.[16] that included 160 RA patients and 159 controls. The authors came to the conclusion that CAR might be used as a straightforward parameter to assess inflammation in RA, potentially valuable for monitoring disease activity. In another study by Sunar and Ataman,[28] they saw a significantly weak correlation between CAR and DAS-28 ESR. This study identified a positive but statistically nonsignificant correlations between CAR and the DAS-28-ESR disease activity score, CDAI, and the physician VAS.

The relatively positive weak correlation between the DAS-28-ESR and CAR in this study could be explained by two indirectly related factors. Firstly, tenderness, which can result from secondary osteoarthritis, joint damage, and or subluxation, may induce pain even in the absence of active inflammation. This means that possible in patients who had established RA, their joints damage and secondary pain could elevate DAS-28 level despite lower CRP value. Secondly, it's worth noting that CRP measurements can be influenced by different factors rather than inflammatory condition such as obesity, pregnancy and anemia.[27] Consequently, higher CRP levels with lower disease activity in some cases may contribute to a decrease in the significance of the correlation between CAR and DAS-28-ESR.

This study also demonstrated a significant correlation between CAR and the DAS-28 CRP disease activity index. This correlation can be explained by the fact that both the CAR ratio and this disease activity index rely on the same biochemical inflammatory marker, C-reactive protein (CRP). As mentioned earlier, they are subject to similar related and unrelated inflammatory factors discussed in the previous paragraphs.

DAS-28-ESR categorizes disease activity into different groups (high, medium, and low-remission), and these categories influence the management plan accordingly. When correlating CAR with these various disease activity groups, this study observed that CAR significantly differed among these groups. Specifically, CAR was notably different in patients how had remission or low disease activity in comparison to those who had disease activity categorized as moderate or high level of activity. This implies that CAR may be useful as a preliminary test to assess the inflammatory activity in RA patients. and differentiate between various levels of disease activity. It may require less effort than calculating the DAS-28-ESR score, making CAR a valuable, simple investigation for providing insights into disease activity and the need for further evaluation and management. This is particularly beneficial in regions with limited medical resources and facilities, where efficiency and cost-effectiveness are essential considerations.

In conclusion, CAR, can be considered as useful initial simple investigation which can give idea about the level of disease activity and the need for further evaluation and management with less time, cost and effort especially in areas with low medical resources and facilities. Further studies with more strict evaluation criteria to eliminate effect of other inflammatory and noninflammatory conditions on CAR are required for more clarification of the strength of use of CAR as strong indicator of RA

disease activity as alternative or in addition to DAS-28-ESR score.

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Conflicts of interest
There are no conflicts of interest.

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