C-Reactive Protein-to-Albumin Ratio: A Novel Inflammatory Marker and Disease Activity Sign in Early Rheumatoid Arthritis

C-reaktives Protein-Albumin-Verhältnis: Ein neuer Entzündungsmarker und Krankheitsaktivitätszeichen bei früher rheumatoider Arthritis

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ABSTRACT

Objective A novel inflammation-based score, C-reactive protein (CRP)-to-albumin ratio (CAR), has been shown to have an association with the inflammatory status in several diseases. We aimed to analyse the association between CAR and disease activity in patients with early rheumatoid arthritis (RA) and to determine the cut-off value of CAR in early and established RA.

Methods A total of 177 patients with RA and 111 age and gender-matched healthy controls were included in this study. Cases with a disease duration of less than 1 year were classified as early RA. Serum albumin, CRP, erythrocyte sedimentation rate (ESR), Disease Activity Score-28 (DAS-28-ESR), Clinical Disease Activity Index (CDAI) and Health Assessment Questionnaire (HAQ) scores were recorded.

Results CAR was 2.44 (0.21–30.83) in the RA group and 0.45 (0.21–10.47) in the control group ($p < 0.001$). Eighty-seven (49.15 %) of the RA cases were classified as early RA. The analyses indicated that the ESR, CRP and CAR values were higher in patients with early RA than in those with established RA and controls. CAR was correlated with albumin, CRP, ESH, DAS-28 and HAQ scores in both early RA and established RA groups. The receiver operating characteristic curves revealed a CAR cut-off value of 2.67 (80 % sensitivity and 85 % specificity) and 1.63 (77 % sensitivity and 72 % specificity) for the prediction of early and established RA, respectively.

Conclusion CAR, a formulated ratio, has been described as a predictor for disease activity in patients with early RA as well as in those with established RA. However, CAR has higher sensitivity and specificity for early RA than for established RA.

ZUSAMMENFASSUNG

Ziel der Arbeit Das C-reaktive Protein (CRP)-zu-Albumin-Verhältnis (CAR), ein neuartiger entzündungsbasierter Score, zeigte eine Korrelation mit dem Entzündungsstatus bei verschiedenen Krankheiten. Unser Ziel war es, die Assoziation zwischen CAR und Krankheitsaktivität bei Patienten mit früher rheumatoider Arthritis (RA) zu analysieren und den cut-off-Wert von CAR bei früher und etablierter RA zu bestimmen.

Methoden Insgesamt wurden 177 Patienten mit RA zu 111 alters- und geschlechtsgematchten gesunden Personen in diese Studie aufgenommen. Fälle mit einer Krankheitsdauer von weniger als 1 Jahr wurden als frühe RA klassifiziert. Die Werte für Serumalbumin, CRP, Erythrozytensedimentationsrate (ESR), Disease Activity Score-28 (DAS-28-ESR), Clinical Disease Activity Index (CDAI) und Health Assessment Questionnaire (HAQ) wurden aufgezeichnet.

Ergebnisse CAR war 2,44 (0,21–30,83) in der RA-Gruppe und 0,45 (0,21–10,47) in der Kontrollgruppe ($p < 0,001$). Siebenundachtzig (49,15 %) der RA-Fälle wurden als frühe RA klassifiziert.

Die Analysen zeigten, dass die ESR-, CRP- und CAR-Werte der Patienten mit früher RA höher waren als die der Patienten mit etablierter RA und die der Kontrollpersonen. CAR korrelierte mit Albumin, CRP, ESH, DAS-28 und HAQ-Scores sowohl in den Gruppen mit früher RA als auch mit etablierter RA. Die Empfängerkennlinien ergaben einen cut-off-Wert für CAR von 2,67 (80 % Sensitivität und 85 % Spezifität) und von 1,63 (77 % Sensitivität und 72 % Spezifität) für die Vorhersage einer frühen bzw. etablierten RA.

Schlussfolgerung CAR, ein formulierter Quotient, wird als Vorhersagewert für die Krankheitsaktivität sowohl bei Patienten mit früher RA als auch bei Patienten mit etablierter RA beschrieben. CAR hat jedoch eine höhere Sensitivität und Spezifität für frühe RA als für etablierte RA.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease in which autoimmune processes and impaired cytokine cycle play a role in its pathophysiology [1]. The inflammation process is triggered by various cytokines, affects synovial joints, and causes irreversible articular damage and functional impairment [2, 3]. Disease activity and remission duration are associated with joint damage, and thus functional competence. The close monitoring of disease activity is the main factor for treatment decision and affects long-term results. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are inflammation markers commonly used in laboratory measurements to assess disease activity in RA [4]. On the other hand, these laboratory markers have known limitations, such as short duration of inflammation and possibility of indicating various inflammatory conditions [5, 6].

There is evidence that various current biomarkers reflect inflammatory processes regarding malignancy. Some studies have also reported that these new markers can show recanalization in myocardial infarctions [3]. Since circulating blood cell composition is related with systemic inflammation, researchers have investigated blood cell components such as derived neutrophil to lymphocyte ratio (dNLR) as a sign of inflammatory activity [6, 7]. Data available in the literature have established that systemic inflammation and malnutrition may be related to disease activity and contributed to the progression of RA. Albumin is a negative inflammatory marker indicating both nutritional status and systemic inflammation. In addition, serum albumin acts as an antioxidant in the immune system [2, 8]. Based on this information, it has been shown that the albumin-dNLR score reflects systemic inflammation and disease activity in patients with RA [2]. A novel inflammation-based score, the CRP-to-albumin ratio (CAR), was initially shown to be associated with inflammatory status in patients with cancer [9, 10]. To date, only a few studies have analyzed CAR as an inflammation marker and useful indicator of disease activity in patients with established RA [3, 4].

It is known that the early diagnosis and treatment of RA in the period defined as "window of opportunity" changes the long-term results of the disease and reduces functional loss [11]. In this context, close monitoring of disease activity is critical in patients with early RA. To the best of our knowledge, there is no study investigating CAR as an inflammatory marker in patients with early RA. In this study, we aimed to explore the association between CAR and disease activity in patients with early RA and to determine the cut-off value of CAR in early and established RA.

Materials and Methods

This was a case-control study performed between January 2020 and March 2021. The study was approved by the local ethics committee. Written consent was taken from all participants. All procedures were undertaken in compliance with the current version of the Declaration of Helsinki.

The study included 177 patients who presented to the rheumatology outpatient clinic and met the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA, and 111 age- and gender-matched healthy controls. The exclusion criteria were as follows: age below 18 years, coexistence of other autoimmune and/or inflammatory connective tissue diseases, overlap syndromes, diabetes mellitus, surgery, infections, malignancy, pregnancy, renal or hepatic function disorders, chronic obstructive pulmonary disease, proteinuria in spot urinalysis, weight loss more than 5 % of their body weight within the last three months, and trauma. Patients with RA accompanied by vasculitis and myositis were also excluded, as these conditions can influence the analyzed data. In addition, patients with juvenile-onset arthritis were not included in the study.

Age, gender and body mass index (BMI) values of patients and controls were recorded. In addition to blood tests for liver and kidney functions, urinalysis of all the patients with RA were evaluated. Medical treatments [glucocorticoids, conventional and biological disease-modifying anti-rheumatic drugs (DMARD)] that the patients were receiving were recorded. For the RA group, the ages of the patients at the onset of disease were also noted. The RA cases with a disease duration of less than 1 year were classified as early RA [12].

The activity of the disease was assessed using the Disease Activity Score (DAS28-ESR) and Clinical Disease Activity Index (CDAI). The disease activity scores were interpreted as remission (≤ 2.6 and ≤ 2.8), low disease activity ($2.6 <$ and ≤ 3.2; $2.8 <$ and ≤ 10), moderate disease activity ($3.2 <$ and ≤ 5.1; $10 <$ and ≤ 22), and high disease activity (> 5.1 and > 22) for DAS28 and CDAI, respectively [13–15]. The Health Assessment Questionnaire (HAQ) was applied for functional evaluation [16].

ESR was estimated using the Westergren method. CRP and rheumatoid factor (RF) were quantified with the immuno-turbidimetric method. Blood biochemical test analyses were performed with a biochemistry analyzer (Dimension RXL system, Siemens, Munich, Germany). Values of > 14 IU/L and 5 mg/L were accepted as positive for RF and CRP, respectively. Anti-cyclic citrullinated peptide was measured with the AxSYM analyzer (Abbot, Wiesbaden, Germany) using the enzyme-linked fluorescent assay method, and val-

ues > 5 U/mL were accepted as positive. The patients' blood count was analyzed with the Sysmex XE-2100 device (Sysmex, Kobe, Japan), and the peripheral venous blood analysis was performed within 1 hour.

Statistical analysis

All analyses were carried out using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows. Categorical variables were presented as number and percentages, and continues variables as mean ± standard deviation or median (interquartile range) values. The Kolmogorov-Smirnov test was used to determine whether the data followed a normal distribution. According to the results, parametric and non-parametric tests were used. Student's t-test and the Mann-Whitney U test were used in the comparison of two independent groups for continuous variables. Categorical variables were compared between the groups with the chi-square test. The Kruskal-Wallis test and one-way analysis of variance were performed for multiple-group comparisons. The Games-Howell test was used as a post hoc method in pairwise comparisons. The Spearman correlation analysis was undertaken to examine the relationship between CAR and laboratory and clinical variables. The receiver operating characteristic (ROC) curve was drawn to determine the cut-off value of CAR in determining moderate to high disease activity. Significance was evaluated at the level of $p < 0.05$.

Results

A total of 177 patients with RA and 110 controls were included in the study. The mean age was 56.23 ± 13.94 and 52.77 ± 13.04 years in the RA and control groups, respectively ($p = 0.182$). The percentage of females was 79.1 and 75.7 % in the RA and control groups, respectively ($p = 0.591$). The median [interquartile range (IQR)] value of disease duration was 26 (4–96) months. Except three patients using bDMARD as monotherapy, all the remaining patients with RA were receiving at least one cDMARD agent (methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine) as monotherapy or in combination. A total of 20 patients with RA were on bDMARD therapy (tumor necrosis factor blockers in 15, tocilizumab in three, and rituximab in two). The median (IQR) CAR value was 2.44 (0.89–6.01) in the RA group and 0.45 (0.25–0.95) in the control group, revealing a significant difference ($p < 0.001$).

Of the total 177 cases with RA, 87 (49.15 %) were classified as early RA and 90 as established RA (50.85 %). There was no statistically significant difference between the two RA groups in terms of mean age, sex, and BMI. Fourteen (15.6 %) patients in the early RA group and six (6.7 %) in the established RA group were taking glucocorticoids at a dose of lower than 7.5 mg/day, with no statistically significant difference ($p = 0.163$). Six patients with early RA and 14 with established RA were on bDMARD therapy, indicating no statistically significant difference ($p = 0.070$). It is important that no difference was detected between the early and established RA groups concerning medical treatments, as the drugs that used for the treatment of RA affect not only the disease activity, but also may have an influence on the albumin balance. The analyses indicated that the ESR, CRP and CAR values of the patients with early RA were significantly higher than those of the patients with established RA and controls. In addition, the DAS28, CDAI and HAQ scores were significantly higher in the early RA group than in the established RA group ($p < 0.001$ for all). The demographic, clinical and laboratory characteristics of the 3 groups (early RA, established RA, and controls) are summarized in ▶ **Table 1**.

All the patients with RA (both early and established) were further categorized into three groups based on their DAS28 score: remission or low disease activity (DAS28 ≤ 3.2), moderate disease activity (3.2 < DAS28 ≤ 5.1), and high disease activity (DAS28 > 5.1). In the early RA group, remission and low, moderate and high disease activity were seen in four, 17, 45 and 21 patients, respectively. The median (IQR) values of ESR, CRP and CAR and the mean HAQ score were significantly higher in the high disease activity group than the low disease activity-remission and moderate disease activity groups ($p < 0.001$ for all). The laboratory parameters and HAQ scores of the patients with early RA according to disease activity with DAS28 are demonstrated in ▶ **Table 2**. According to the CDAI score, remission, low, moderate and high disease activity was seen in two (2.3 %), 18 (20.7 %), 40 (46.0 %), and 27 (31.0 %) patients, respectively.

Of the total 90 patients in the established RA group, 19 were in remission, 26 had low disease activity, 33 had moderate disease activity, and 12 had high disease activity. Further analysis of the disease activity groups revealed that the median ESR, CRP and CAR values and the mean HAQ scores were significantly higher in the high disease activity group than the low disease activity-remission and moderate disease activity groups (▶ **Table 3**). The CDAI scores of the established RA group indicated that two (2.2 %) patients were in remission, 40 (44.4 %) had low disease activity, 32 (35.6 %) had moderate disease activity, and 16 (17.8 %) had high disease activity.

The correlation between CAR and laboratory variables, disease activity, and HAQ score was also investigated. The results showed that CAR was correlated with albumin, CRP, ESR, DAS28 and HAQ score in both the early RA and established RA groups (▶ **Table 4**). Lastly, the patients with both early RA and established RA were evaluated in two groups according to the DAS28 scores being ≤ 3.2 ($n = 66$ and 45 for the early and established RA groups, respectively) and > 3.2 ($n = 21$ and 45 for the early and established RA groups, respectively). ROC curves were drawn for the CAR levels in the determination of moderate to high disease activity in the early and established RA groups (▶ **Fig. 1** and **2**). The area under the curve was 0.883 ± 0.041 and 0.886 ± 0.034 for the early and established RA groups, respectively. The sensitivity (probability that a patient with moderate or high disease activity had a CAR level over the determined cut-off value) and specificity (probability that a patient with remission or low disease had a CAR level below the determined cut-off value) of CAR were calculated. For the early RA group, the best Youden index was 0.66, and at a cut-off value of 2.67, CAR showed 80 % sensitivity and 85 % specificity. For the established RA group, the best Youden index was 0.55, and at the cut-off value of 1.63, CAR had 77 % sensitivity and 72 % specificity.

The cut-off values of CAR were also calculated according to the CDAI score. The patients in both the early and established RA groups were further divided into 2 groups according to the CDAI scores being ≤ 10 and > 10. The area under the ROC curve values were 0.889 ± 0.039 and 0.912 ± 0.029 for the early and established

▶ **Table 1** Clinical and laboratory variables in the rheumatoid arthritis and control groups.

	Early RA (n = 87)	Established RA (n = 90)	Healthy controls (n = 111)	*p value*
Age (years)	56.53 ± 16.07	55.93 ± 11.60	52.77 ± 13.04	*0.109*
Sex (female)	64 (73.6 %)	76 (84.4 %)	84 (75.7 %)	*0.176*
BMI (kg/m²)	29.37 ± 4.88	30.75 ± 4.48	29.76 ± 4.61	*0.097*
Disease duration (months)	4 (3–8)	94.50 (50–150)	NA	***< 0.001***
RF positive	65 (74.7 %)	63 (70 %)	NA	*0.485*
Anti-CCP positivity	64 (73.6 %)	63 (70 %)	NA	*0.600*
Neutrophil count (×10³/μL)	5.66 ± 1.88	4.88 ± 1.78	4.79 ± 1.74	***< 0.001***
				p1 = 0.015
				p2 < 0.001
				p3 = 0.001
Lymphocyte count (×10³/μL)	2.06 ± 0.66	2.19 ± 0.73	2.48 ± 1.44	***0.016***
				p1 = 0.458
				p2 = 0.020
				p3 = 0.153
Platelet count (×10³/μL)	319.87 ± 78.15	288.50 ± 69.23	272.06 ± 59.69	***< 0.001***
				p1 = 0.015
				p2 < 0.001
				p3 = 0.180
Albumin (g/L)	4.09 ± 0.36	4.18 ± 0.36	4.40 ± 0.27	***< 0.001***
				p1 = 0.207
				p2 < 0.001
				p3 < 0.001
ESR (mm/hr)	31 (20–46.30)	26 (15–40)	13 (7–21)	***< 0.001***
				p1 = 0.038
				p2 < 0.001
				p3 < 0.001
CRP (mg/L)	15.70 (6–40)	6.65 (2.30–14.75)	2.1 (1.10–3.80)	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				p3 < 0.001
CAR	3.64 (1.51–9.46)	1.63 (0.58–3.92)	0.46 (0.25–0.95)	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				p3 < 0.001
DAS28	4.19 ± 1.19	3.44 ± 0.80	NA	***< 0.001***
CDAI	17.77 ± 8.47	12.84 ± 8.73	NA	***< 0.001***
HAQ score	1.20 ± 0.48	0.89 ± 0.47	NA	***< 0.001***
Medications				
cDMARD	87	87		*NA*
bDMARD	6	14		*0.070*
Glucocorticoid	16	11		*0.176*

Data presented as n (%) for categorical variables and mean ± standard deviation or median (interquartile range) for continuous variables depending on distribution. RA: rheumatoid arthritis; BMI: body mass index; RF: rheumatoid factor; Anti-CCP: anti-cyclic citrullinated peptide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CAR: C-reactive protein-to-albumin ratio; DAS28: Disease Activity Score with 28-Joint Counts; CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire; cDMARD: Conventional disease-modifying anti-rheumatic drugs; bDMARD: Biological disease-modifying anti-rheumatic drugs; NA: not applicable. $P < 0.05$ considered statistically significant; p1, p value for the comparison of early RA and established RA; p2, p value for the comparison of early RA and controls; p3, p value for the comparison of established RA and controls. Significant p values presented in **bold**.

▶ **Table 2** Laboratory parameters and HAQ scores in disease activity groups of early rheumatoid arthritis.

Early RA	Group 1 Remission + low disease activity (n = 21)	Group 2 Moderate disease activity (n = 45)	Group 3 High disease activity (n = 21)	*p value*
Neutrophil count (×10³/μL)	5.05 ± 1.52	5.77 ± 2.06	6.03 ± 1.73	*0.206*
Lymphocyte count (×10³/μL)	2.31 ± 0.51	1.93 ± 0.62	2.09 ± 0.82	*0.097*
Platelet count (×10³/μL)	301.95 ± 68.23	316.76 ± 75.52	344.76 ± 95.08	*0.198*
Albumin (g/L)	4.32 ± 0.36	4.11 ± 0.31	3.81 ± 0.25	***< 0.001***
				p1 = 0.065
				p2 < 0.001
				p3 < 0.001
ESR (mm/hr)	15 (8.5–19.5)	29 (24–42)	62 (42.50–66)	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				p3 < 0.001
CRP (mg/L)	3 (1.1–7.6)	16 (10.20–33)	46 (26.50–73)	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				p3 = 0.001
CAR	0.67 (0.25–1.83)	3.72 (2.43–8.44)	12.70 (6.72–19.23)	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				p3 = 0.001
HAQ score	0.61 ± 0.31	1.26 ± 0.36	1.61 ± 0.24	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				P3 < 0.001

RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CAR: C-reactive protein-to-albumin ratio; HAQ: Health Assessment Questionnaire. Data given as mean ± standard deviation for parametric variables and median (interquartile range) for non-parametric variables. P < 0.05 considered statistically significant; p1, p value for the comparison of Group 1 and Group 2; p2, p value for the comparison of Group 1 and Group 3; p3, p value for the comparison of Group 2 and Group 3. Significant p values shown in **bold**.

RA groups, respectively. For the early RA group, the best Youden index was 0.72, and at a cut-off value of 2.47, CAR showed 81 % sensitivity and 88 % specificity. For the established RA group, the best Youden index was 0.60, and at the cut-off value of 1.68, CAR had 77 % sensitivity and 82 % specificity.

Discussion

The current study was conducted to investigate the association between CAR and disease activity in patients with early RA and to determine the cut-off value of CAR in early and established RA. The results indicated that CAR was higher in the patients with RA than in the healthy controls and positively correlated with ESR, CRP, and DAS28 and HAQ scores. We identified an increase in CAR among the patients with active disease in both the early and established RA groups. The cut-off values of CAR were 2.67 and 1.63 in the early and established RA groups, respectively. We detected noticeably higher sensitivity and specificity for CAR at the determined cut-off value in the early RA group compared to established RA.

RA is a progressive articular disease in which an impaired cytokine cycle plays a role in pathophysiology and causes irreversible joint damage and functional impairment. Acute phase reactants (increased CRP, ESR, fibrinogen, ferritin, and decreased albumin) indicate an inflammatory state in autoimmune diseases [17]. CAR, a novel marker, is obtained by dividing CRP by albumin, components that are both closely related to inflammation. While serum albumin is considered to have anti-inflammatory and immunomodulating properties, it also reflects nutritional status. There is a multifaceted association between albumin with inflammation and malnutrition. Malnutrition, a common symptom in patients with RA, may have an impact on immune system and lead to an increase in inflammatory cytokines. On the other hand, systemic inflammation decreases albumin synthesis [18, 19]. Therefore, increased CRP and decreased albumin levels have attracted the attention of researchers as systemic inflammation markers, and CAR has been used to prognosticate disease severity and outcomes in various diseases, particularly cancer [20, 21]. Higher CAR levels have been demonstrated in patients with active RA than those in remission.

▶ **Table 3** Laboratory parameters and HAQ scores in disease activity groups of established rheumatoid arthritis.

Established RA	Group 1 Remission + low disease activity (n = 45)	Group 2 Moderate disease activity (n = 33)	Group 3 High disease activity (n = 12)	*p value*
Neutrophil count (×10³/μL)	4.44 ± 1.62	4.84 ± 1.69	6.46 ± 1.89	***0.001***
				p1 = 0.536
				p2 = 0.007
				p3 = 0.037
Lymphocyte count (×10³/μL)	2.14 ± 0.66	2.31 ± 0.77	2.05 ± 0.88	*0.450*
Platelet count (×10³/μL)	278.42 ± 59.59	303.59 ± 75.63	286.23 ± 82.21	*0.291*
Albumin (g/L)	4.39 ± 0.28	3.96 ± 0.32	3.88 ± 0.17	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				p3 < 0.407
ESR (mm/hr)	17 (9.5–27)	34 (22–47.50)	46.5 (39–66)	***< 0.001***
				p1 = 0.001
				p2 < 0.001
				p3 = 0.002
CRP (mg/L)	4 (1–6.3)	11 (6.55–26)	47 (37–61.25)	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				p3 = 0.001
CAR	0.83 (0.24–1.51)	3.14 (1.69–6.37)	12.26 (9.31–15.04)	***< 0.001***
				p1 < 0.001
				p2 < 0.001
				p3 < 0.001
HAQ score	0.59 ± 0.35	1.10 ± 0.35	1.44 ± 0.29	***< 0.001***
				< 0.001
				p1 < 0.001
				p2 < 0.001
				P3 < 0.001

RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CAR: C-reactive protein-to-albumin ratio; HAQ: Health Assessment Questionnaire Data given as mean ± standard deviation for parametric variables and median (interquartile range) for non-parametric variables. P < 0.05 considered statistically significant; p1, p value for the comparison of Group 1 and Group 2; p2, p value for the comparison of Group 1 and Group 3; p3, p value for the comparison of Group 2 and Group 3. Significant p values shown in **bold**.

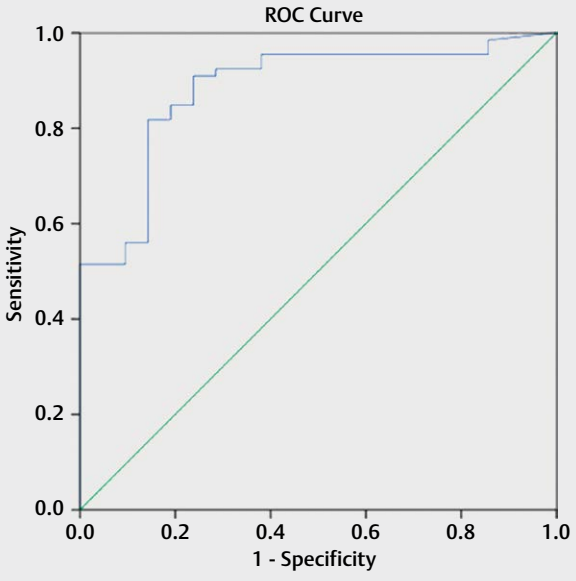
In the current study, in order to prevent the effect of any possible reasons on the albumin value other than RA [3, 4], diabetes, infection, cancer, liver and kidney dysfunction, and autoimmune and other chronic inflammatory diseases were not included in the sample. Therefore, the current study was designed to rule out factors that could affect albumin value other than RA. As expected, the CAR value was found to have a strong correlation with CRP and ESR (other acute phase reactants) and DAS28 scores, which also included acute phase reactants in its calculation [3, 4]. Our results were similar, indicating higher CAR values in the patients with RA than in the healthy controls and association of CAR with disease activity in the RA group. Similarly, there was a strong correlation between CDAI, a disease activity score calculated without a laboratory value, and CAR. Moreover, to our knowledge, this is the first study that evaluated the association between disease activity and CAR in patients with early RA. We determined CAR to be a valuable marker for monitoring disease activity in this patient group.

Early diagnosis and treatment without delay are associated with better long-term outcomes for patients with RA. It is suggested that the treat-to-target principle, in which treatment is concentrated until remission or low disease activity may prevent progressive damage in early RA [22]. An appropriate follow-up of the patient is absolutely dependent on the specialist's ability to measure disease activity. Therefore, different laboratory markers are frequently addressed as a current issue in addition to clinical evaluation in disease monitoring. ESR and CRP are the most commonly used laboratory values associated with inflammation and arthritis in RA. However, it is known that both of these measures are also affected by factors other than inflammation (e. g., pregnancy, obesity, and anemia) [23], and therefore research has focused on various ration-

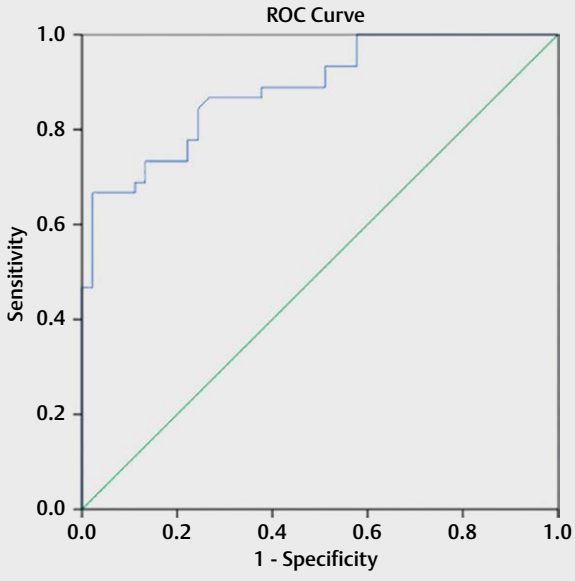
▶ **Table 4** Correlation between CAR and laboratory parameters, disease activity, and functional status.

	Early RA-CAR (n = 87)		Established RA-CAR (n = 90)	
	r	p	r	p
Neutrophils (×10³/μL)	0.271	0.11	0.400	< 0.001
Lymphocytes (×10³/μL)	− 0.600	0.579	− 0.051	0.634
Platelet (×103/μL)	0.302	0.004	0.053	0.620
Albumin (g/L)	− 0.520	< 0.001	− 0.504	< 0.001
ESR (mm/hr)	0.593	< 0.001	0.521	< 0.001
CRP (mg/L)	0.996	< 0.001	0.996	< 0.001
DAS28	0.721	< 0.001	0.741	< 0.001
CDAI	0.879	< 0.001	0.828	< 0.001
HAQ score	0.539	< 0.001	0.667	< 0.001

RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CAR: C-reactive protein to albumin ratio; DAS28: Disease Activity Score with 28-Joint Counts; CDAI: Clinical Disease Activity Index; HAQ: Health Assessment Questionnaire.



▶ **Fig. 1** Receiver operating characteristic curve (ROC) for prediction of moderate to high disease activity based on the levels of CAR for the patients with early RA. AUC (Area under the curve): 0.883.



▶ **Fig. 2** Receiver operating characteristic curve (ROC) for prediction of moderate to high disease activity based on the levels of CAR for the patients with established RA. AUC (Area under the curve): 0.886.

al laboratory values with the aim of minimizing exposure to causes other than inflammation [2–4]. Our results demonstrated a correlation between the CAR value and the DAS28 and CDAI score which is calculating without any laboratory value. Moreover, CAR was strongly correlated with the HAQ score, which reflects long-term damage. CAR, which is associated with composite indexes, clinical assessments, and functional status, presents as a promising marker of inflammation in patients with early RA, as well as those with established RA.

Cut-off values as predictors of disease activity are helpful in the practical use of laboratory markers. Afifi et al. [3] performed ROC curve analyses for CAR in patients with RA with a median disease duration of eight years. The authors found a cut of value 1.66 (specificity 66.67 % and sensitivity 81.58 %) for an area under curve of 0.789. We investigated the cut-off levels for both early and established RA. In the established RA group, the cut-off value of CAR was 1.63, at which it had 77 % sensitivity and 72 % specificity while in

the early RA patients, CAR showed 80 % sensitivity and 85 % specificity at a cut-off value of 2.67. Furthermore, the cut-off values of CAR according to the CDAI score were similar to the results of the analysis we conducted with the DAS28 scores, in which we determined these values as 2.47 for early RA and 1.68 for established RA. Our result for established RA is similar to the value reported by Afifi et al. [3]. On the other hand, the CAR cut-off value we determined for early RA was higher than the established RA group, and sensitivity and specificity were also higher in the former. This finding indicates that the use of CAR in early RA is even more valuable than in established RA.

Composite disease activity scores include particular parameters (tender joint count, swollen joint count, patient and physician global assessment and inflammatory markers, such as CRP and ESR) in different combinations. While these parameters may reflect active inflammation one by one, it is necessary to consider some specific parameters (tender joint count and patient global assessment values) from different perspectives. The possibility for irreversible joint damage may lead to confusion concerning the disease activity of established RA, unlike early RA. Joint tenderness is normally expected as a result of the increased innervation of pain fibers due to inflammation. However, tenderness may also be an outcome of joint damage, secondary osteoarthritis, or subluxation and can induce pain even when there is no active inflammation [24, 25]. In view of this information, it can be considered that possible joint damage and secondary pain in patients with established RA can increase the DAS28 scores despite lower CRP scores, which can explain the different cut-off values of CAR in the early and established RA groups.

Some limitations of our study are the cross-sectional and single-center design, absence of a follow-up evaluation, and relationship between CAR and RA prognosis not being evaluated. In addition, diet types and dietary adjustment after diagnosis which can lead to major changes in the course of the process were not evaluated in this study; future studies considering these dietary factors may provide better results. Finally, albumin values may better reflect systemic inflammation in studies to be planned by performing appropriate nutritional risk screening and providing appropriate nutritional support.

In conclusion, CAR, a formulated ratio, can be considered as a predictor of disease activity in patients with early RA, as well as established RA. Furthermore, at the determined cut-off value, CAR has higher sensitivity and specificity for patients with early RA than those with established RA. This finding supports the use of CAR as a reliable indicator of inflammation in early RA.

Conflict of Interest

The authors declare that they have no conflict of interest.

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