The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 5496-5502

CRP-Albumin Ratio as A Disease Activity Marker in RA Patients, Its Correlation with Musculoskeletal Sonography

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ABSTRACT

Background: Inflammatory rheumatoid arthritis (RA) worsens over time. Severe symptoms can be avoided with an early diagnosis. RA increases CRP-albumin ratio (CAR) as acute-phase reactants.

Objective: To validate the CAR inflammatory impact in RA and how it correlates with disease activity indices and musculoskeletal ultrasonography.

Methods: Seventy-five RA patients were involved in this cross-sectional research. 50 normal subjects were included as a control group. All participants were tested for CRP, albumin, and CAR. Disease activity indices "The Disease Activity Score 28 (DAS28) with erythrocyte sedimentation rate (ESR), the Modified Health Assessment Questionnaire (MHAQ), and the Clinical Disease Activity Index (CDAI)", and ultrasound, which was performed in both grayscale and power Doppler modes, were utilized to assess the patient's disease activity.

Results: CAR in the RA group was 2.25 (0 -13) and 0.41 (0 - 0.9) among controls (p< 0.001). ESR, albumin, CRP, DAS-28, CDAI, and HAQ scores were all found to be correlated with CAR. In patients with active RA, CAR levels were considerably greater than in patients in remission (P< 0.001). Cases who had synovial thickening and power Doppler alterations had higher CAR (p<0.001). At a cut-off of (2.6), sensitivity was 79.1%, specificity was 72.3%, and the area under the curve (AUC) was 0.77, as measured by the receiver operating characteristic (ROC) curve.

Conclusion: CAR is a measure that can be evaluated easily and affordably. CAR predicts disease activity among moderate to severely active RA patients.

Keywords: CAR, Rheumatoid arthritis, Disease activity indices, Ultrasonography.

INTRODUCTION

Damage to the synovial joints causes considerable impairment in daily life for those with rheumatoid arthritis (RA), a chronic inflammatory autoimmune illness. Epidemiology showed that disease activity and remission length affect RA progression**.** RA patients' clinical decisions and long-term outcomes depend on disease activity evaluation. Clinical symptoms, questionnaires, and laboratory testing are the most often utilized markers for RA disease activity **(1).**

Inflammatory activity levels in RA may be classified using the Disease Activity Score 28 (DAS28) in conjunction with erythrocyte sedimentation rate (ESR), the Modified Health Assessment Questionnaire (MHAQ), or the Clinical Disease Activity Index (CDAI) **(2-4).** Articular swelling and discomfort as well as CRP are often utilized in disease activity. In RA clinical studies, it predicted radiological damage and could replace ESR in DAS28 **(5)**. Inflammation alters albumin concentration. Hypoalbuminemia results from inflammation-induced albumin consumption in active RA **(6)**.

Chronic inflammation, cytokines, and articular activity in RA are linked to elevated ESR and CRP. Therefore, CAR ratios may be utilized as a simple laboratory measure to infer inflammation and disease activity. These ratios had consequently been frequently considered as outcome prediction indicators in a variety of illnesses as a result of the findings of a number of studies that have dispelled the allure regarding the CAR putative inflammatory effect in systemic diseases **(7).**

Finding a simple, dependable, and inexpensive disease activity biomarker and inflammation indicator for precise therapy targeting is a growing issue. (CAR) is a novel indicator of inflammation and nutrition. Lung cancer prognosis was strongly linked to CAR. In ankylosing spondylitis CAR ratios are reliable disease activity indicators **(8).**

Non-invasive, radiation-free musculoskeletal ultrasonography (MSUS) permits the evaluation of joint inflammation **(9).** MSUS has proven a reliable tool for identifying rheumatoid synovitis. MSUS is superior to clinical evaluation in detecting synovitis, as suggested by previous research **(10).**

This study aimed to validate the CAR inflammatory impact in RA and how it correlates with disease activity indices and musculoskeletal ultrasonography.

PATIENTS AND METHODS

Seventy-five rheumatoid arthritis (RA) patients (10 men, 65 females) were enrolled at random in our cross-sectional study seeking routine follow-up care at the Rheumatology and Rehabilitation Department of Beni-Suef University Hospital. Inclusion criteria included conforming to the criteria for RA standards established in 2010 by the American College of Rheumatology and the European League Against Rheumatism **(11),** being of legal researchable age (in the United States) and having given informed consent. Cancer, pregnancy, breastfeeding, malignancy, hepatic impairment and renal deficit were exclusion criteria.

Received: 01/04/2023
Accepted: 01/06/2023

All patients were subjected to:

(1) Laboratory Investigations:

1. Complete blood picture.
2. Erythrocyte sedimentation rate (ESR) by the Westergren method, taking only first-hour's result.
3. C-reactive protein (CRP) by latex slide test.
4. Serum albumin.
5. C-reactive protein to albumin (CAR) was calculated.
6. Rheumatoid factor (RF).
7. Anti-cyclic citrullinated peptide antibodies (Anti-CCP).

(2) RA activity appraisal:

- **The DAS 28-ESR score:** EULAR validated the DAS 28-ESR score using painful and swollen joints number, ESR levels, and the visual analogue scale (VAS) assessment. The disease activity level may be classified as being in remission (DAS28 <2.6), low (2.6 ≤ DAS28 < 3.2), moderate (3.2 ≤ DAS28 ≤ 5.1), or high (DAS28 >5.1) for all DAS28 versions **(2).**
- **Clinical Disease Activity Index (CDAI):** The CDAI measures RA disease activity. It's evaluated by adding four parameters: 28 tender and swollen joints, patient and physician global
- disease activity rating on a 0–10 cm visual analogue scale, and it can be interpreted as remission (CDAI ≤2.8), low (2.8 < CDAI ≤ 10), moderate (10 < CDAI ≤ 22), or high (CDAI >22) **(3)**.
- **Modified Health Assessment Questionnaire (MHAQ):** The MHAQ is a drastically reduced HAQ (from 20 items in the original HAQ to eight items) to increase usability in clinical settings. Functional losses were classified as mild, moderate, or severe (MHAQ 1.3, 1.3 < MHAQ ≤ 1.8, and > 1.8, respectively) **(4).**

(3) Radiological Evaluation:

The wrist, metacarpophalangeal (MCPs) and proximal interphalangeal (PIPs) joints (as the most affected joints in RA) were examined using Gray Scale musculoskeletal ultrasonography (GS MSUS). According to EULAR recommendations, power Doppler ultrasonography (PDUS) was used to measure the size of the dorsal and palmar synovial hypertrophy (SH) and the number of blood vessels (12)**.**

PDUS: PD was rated using an established semi-quantitative grading method from 0–3: (Zero) No PD signal: (1) There are 1-2 blood vessels in smaller joints, and 1-3 in larger ones. (2) Synovial region that is less than half as big. (3) Over than half **(13).**

Ethical approval:

The Beni-Suef University Ethics Committee authorized the research protocol. Each patient signed informed consent according to the rules set out in the Helsinki Declaration.

Statistical analysis

After data collection and check for completeness and logical consistency. All statistical analyses were performed using two-tailed tests and an alpha error of 0.05. A p-value <_0.05 was considered statistically significant. Simple descriptive statistics (median value and interquartile range) were used to summarize the normally distributed quantitative data, and frequencies categorical variables. Comparisons between groups were done using the Mann–Whitney test and Chi-square test. Spearman test was used for correlations. Receiver operating characteristic (ROC) curve analysis was carried out to test the diagnostic performance of a test or the accuracy of a test to discriminate diseased cases from normal cases. The results were presented in tables and figures.

RESULTS

The study included 75 rheumatoid arthritis cases and 50 healthy controls. Both groups were matching regarding age and sex. The median disease duration value was 6±4.17 years. The medians of ESR, CRP, and CAR were significantly higher in the RA group than in the control group. While albumin value in the RA group was significantly lower than the control group. As regard disease activity indices, our patients were categorized into four groups: (Remission group, Mild activity, Moderate activity and severe activity). The DAS28 ESR index showed the highest number in the severe activity group (DAS28 >5.1), while the CDAI index revealed the greatest proportion in the moderate activity group (10 < CDAI ≤ 22). In contrast, the group with mild functional deficits (MHAQ ≤ 1.3) had the greatest proportion in the MHAQ index (Table 1).

Table (1): Demographics and other data of cases and control

Parameter		RA Group (N=75)	Control (N=50)	P-value
Age (years) Mean±SD		43±10.01	41.58±10.02	0.134
Sex (Gender)	Male	N 10 (%) (13.3)	6 (12)	0.916
	Female	N 65 (%) (86.7)	44 (88)	
Disease duration in years (Median)		6±4.17		
Disease onset in years		35±7.98		
Articular Manifestations (AMS)	Morning stiffness, N (%)	**Yes** 25 (33.3) **No** 50 (66.7)		
	Tender joints count	6±5.51		
	Swollen joints count	5±4.20		
Extra-articular Manifestations	Eye	N 9 (%) (12)		
	Chest (ILD)	N 19 (%) (25.3)		
	Sjogren S	N 7 (%) (9.3)		
Laboratory	ESR Median (range)	29.5 (7-85)	7 (4-27)	**<0.001**
	CRP Median (range)	11.7 (0-52)	1.77 (0-5)	**<0.001**
	Albumin Median (range)	3.9 (3.5 - 5)	4.4 (3.5-5.5)	**<0.001**
	CAR Median (range)	2.25 (0-13)	0.41 (0-0.9)	**<0.001**
DAS28	NO	N 14 (%) (18.7)		
	Mild	N 9 (%) (12)		
	Moderate	N 22 (%) (29.3)		
	Severe	N 30 (%) (40)		
MHAQ	NO	N 7 (%) (9.3)		
	Mild	N 49 (%) (65.3)		
	Moderate	N 10 (%) (13.3)		
	Severe	N 9 (%) (12)		
CDAI	NO	N 9 (%) (12)		
	Mild	N 17 (%) (22.7)		
	Moderate	N 25 (%) (33.3)		
	Severe	N 24 (%) (32)		

Median and range: non-parametric test. DAS, disease activity score; ILD, interstitial lung disease; CRP, C-reactive protein; CAR, CRP/albumin ratio**.**

CAR was positively associated with joint swelling among cases who had interstitial lung disease, ESR, and CRP. Serum albumin levels were negatively linked to CAR levels. Nevertheless, neither RF nor anti-CCP titers were associated with CAR (Table 2).

Table (2): Correlation of CAR with articular and extra-articular manifestations

Parameters		CAR	
		R-value	P-value
Age in years		.182	.118
Articular Manifestations	Morning stiffness	.164	.160
	Tender joints count	.198	.089
	Swollen joints count	.295	<0.001
Extra-articular Manifestations	Raynaud's	.164	.160
	Eye	-.096	.414
	Chest (ILD)	.247	<0.001
	Sjogren's syndrome	.166	.190
	Cardiovascular	-.111	.343
	Neurological	.119	.310
	Gastrointestinal	.170	.145
	Constitutional	.051	.665
LABS	Hemoglobin	.138	.083
	WBCs	.095	.418
	PLT_S	.064	.586
	ESR	.247	<0.002
	CRP	.999	<0.001
	Albumin	-.431	<0.002
	Rheumatoid factor	.152	.193
	Anti-CCP	.188	.521
DRUGS	MTX	-.206	.096
	LFN	.118	.760
	HCQ	.100	.392
	Steroids	.148	.205
	Biologics	-.090-	.440

Anti-CCP, Anti-cyclic citrullinated peptide antibodies; MTX, Methotrexate; LFN, Leflunamide; HCQ, Hydroqueine

High levels of CAR were correlated with elevated levels of the DAS 28-ESR, CDAI, and MHAQ, particularly for higher disease activity scores (severe grade score) (Table 3).

Table (3): Correlation of CAR with disease activity indices

Disease activity indices		CAR	
		R-value	P-value
DAS28 -ESR	No	_	_
	Mild	0.093	0.812
	Moderate	0.330	<0.001
	Severe	. 390	<0.001
	(As a whole)	.353	<0.001
MHAQ	No	.645	.117
	Mild	.074	.614
	Moderate	-.219	.543
	Severe	.254	.009
	(As a whole)	.224	<0.001
CDAI	No	_	_
	Mild	.413	.099
	Moderate	.382	<0.001
	Severe	.300	<0.001
	(As a whole)	.264	<0.001

DAS28-ESR, The Disease Activity Score-28 with ESR; MHAQ, the Modified Health Assessment Questionnaire; CDAI, The Clinical Disease Activity Index.

Our research showed a significant positive correlation between CAR and ultrasound findings with gray scale and power Doppler in the wrist joint and the third, fourth, and fifth PIP joints (Table 4).

Table (4): CAR correlation with ultrasound findings

SONAR		CAR	
		R-value	P-value
Synovial Hypertrophy (SH) (Active disease GS =1)	RC	**0.**289	<0.001
	1MCP	-0.194	.095
	2MCP	.148	.542
	3MCP	.158	.174
	4MCP	.061	.603
	5MCP	-.054	.645
	1PIP	-.034	.771
	2PIP	-.144	.218
	3PIP	.358	<0.001
	4PIP	.219	<0.001
	5PIP	.240	<0.001
PDUS signal (Active disease PD ≥1)	RC	.301	<0.001
	1MCP	-.079	.500
	2MCP	.032	.786
	3MCP	.121	.621
	4MCP	.020	.865
	5MCP	.006	.962
	1PIP	-.120-	.304
	2PIP	-.062-	.595
	3PIP	.284*	<0.002
	4PIP	.269*	<0.002
	5PIP	.187	<0.001

PIP, proximal interphalangeal joint; MCP, Metacarpophalangeal joint; PDUS, power Doppler ultrasonography

The accuracy of the CAR ratio in predicting RA activity was evaluated using ROC curve analysis. Area under the curve (AUC) (0.77) was highest for the DAS28 ESR at a cut-off point of (≥2.6). At a threshold value of (≥3.4), the CDAI has an AUC of 0.768. While MHAQ had a lower specificity (55.6%) at a cut-off point of (≥0.7) (Table 5 and figure 1).

Table (5): Validity data of CAR as a marker for RA activity

Parameter		DAS28	CDAI	MHAQ
CAR	Cut-off	≥ 2.6	≥ 3.4	≥ 0.7
	Sensitivity, %	79.1	78.4	78.9
	Specificity, %	72.3	74	55.6
	AUC	0.77	0.768	0.769
	Accuracy	83.4	82.1	81.8

DAS28-ESR, The Disease Activity Score-28 with ESR; MHAQ, the Modified Health Assessment Questionnaire; CDAI, The Clinical Disease Activity Index; AUC, Area under the curve.

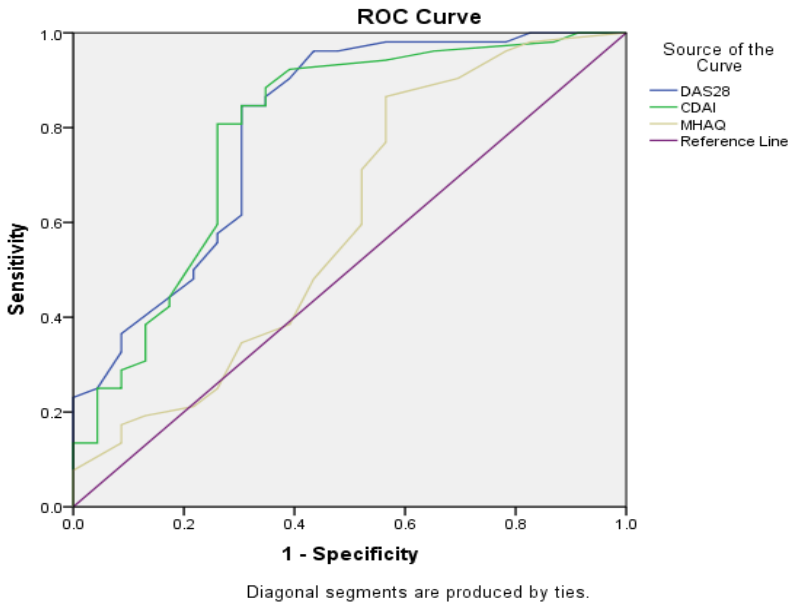

Figure (1): Predicting RA patients with moderate to high disease activity using CAR levels: receiver operating characteristic (ROC) curve

Figures 2 and 3 show some manifestations of RA using musculoskeletal ultrasonography.

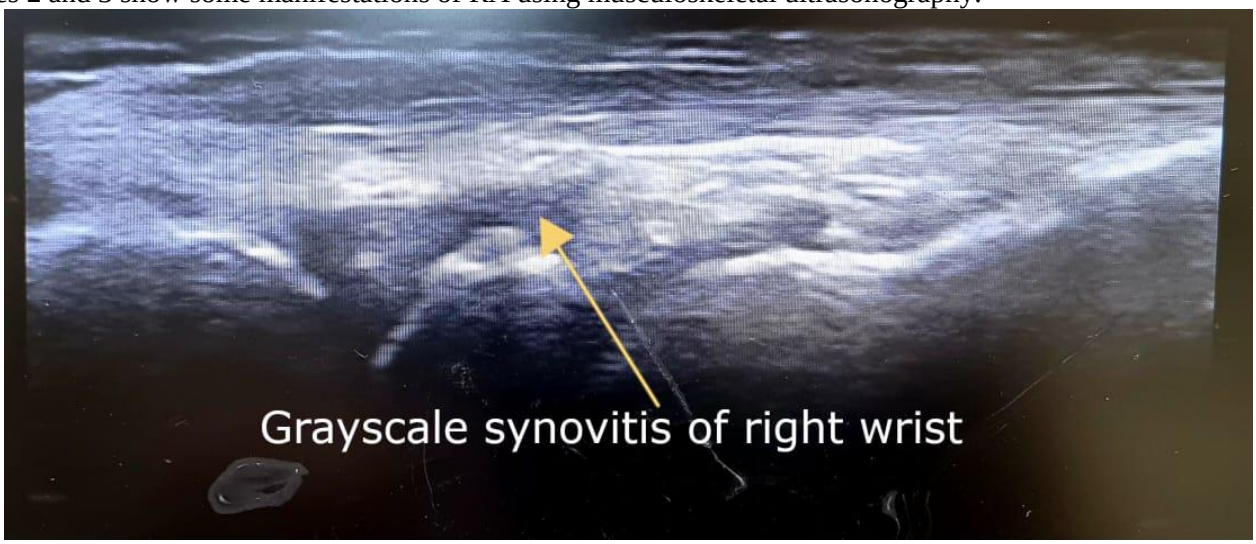

Figure (2): Grayscale musculoskeletal ultrasound of the long axis of the dorsal aspect of the right wrist of one patient involved in our study showing synovial hypertrophy (GS =1).

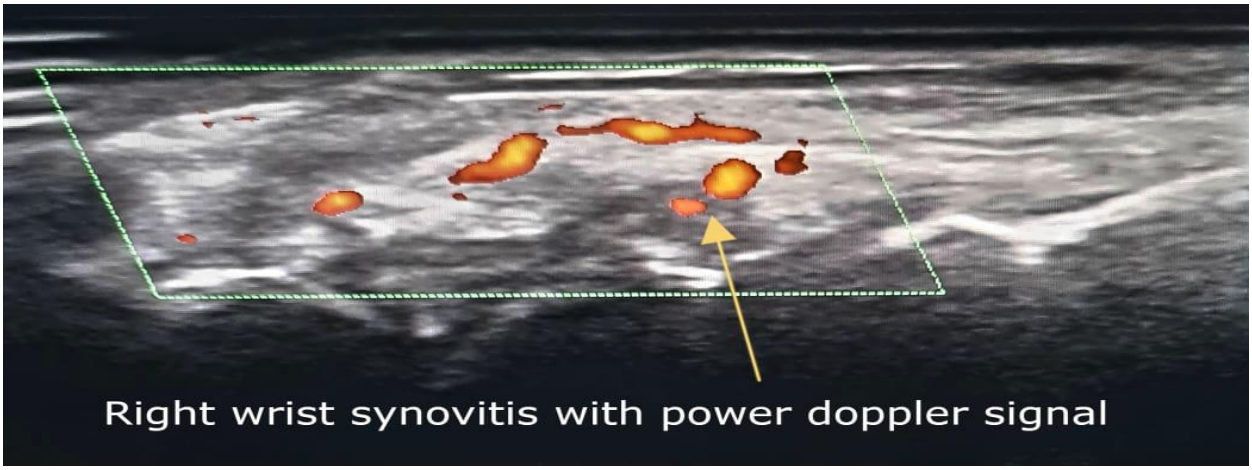

Figure (3): Power Doppler musculoskeletal ultrasound of the long axis of the dorsal aspect of the right wrist of the same patient showing hyper-vascularization with denoting synovial inflammation with grade 2 power Doppler signal.

DISCUSSION

Multiple varieties of cancer, Crohn's disease [14], and vasculitides [15] have been linked to CAR as a crucial determinant of poorer general survival. It was reported that CAR can predict mortality independently and performed superior to CRP alone. Albumin is a negative acute phase reactant that contributes to CRP in assessing inflammation [16]. Innovative marker CAR is derived by dividing CRP/albumin.

Because of its progressive nature, rheumatoid arthritis necessitates regular monitoring for signs of disease activity. Elevated CRP, fibrinogen, and ferritin are prevalent signs of autoimmune disorders as acute phase reactants, pointing to inflammation [17].

In the present research when compared to healthy controls, RA patients had significantly higher ESR and CRP levels, as well as lower albumin levels; these observations are quite consistent with any inflammatory condition [18–20].

The RA group had considerably higher CRP levels than the control group, coming in at median (Range) 11.7(0-52) mg/l as opposed to 1.77(0-5) mg/l. Patients with RA had a CAR that ranged from 0 to 13 while those in the control group only had 0.41 (0-0.9). The findings of **Yang and colleagues [21], Sunar and Ataman [22]** and **Erkut and colleagues [23]** are consistent with this observation.

In our study, serum albumin was marginally lower in our RA patients, with a median of 3.9 (3.5 -5) mg/dl versus 4.4 (3.5-5.5) mg/dl in the controls. **Ganeb *et al.* [24]** discovered a similar result, with RA patients having reduced blood albumin levels median of 3.9 (3.5- 4.35) mg/dl) than controls. Patients with RA have a lower albumin level, as demonstrated by the work of **Zhang *et al.* [25], Ben-Hadj-Mohamed *et al.* [26],** and **Tsuji *et al.* [27]** since albumin targets inflamed joints, active RA patients commonly develop hypoalbuminemia [6].

Despite, the lack of correlation with RF or anti-CCP titers, RA active groups had significant alterations in CAR according to DAS 28-ESR and CDAI indices score (as a whole, moderate and severe subgroups only), which were positively correlated with CAR ($p<0.001$), as was the MHAQ index score (as a whole, severe subgroup only) ($p<0.001$, 0.009 respectively).

These findings support those of **Sunar and Ataman [22],** who discovered that CAR differed significantly ($p=0.008$) among remission, high, middle, and low patients groups, as well as **Erkut and colleagues [23],** who found that in early and established RA, CAR linked with DAS-28, CDAI, and HAQ scores. We concur with results of both **Afifi *et al.* [28]** and **Elsabagh *et al.* [29]** who found a correlation between a high DAS28 ESR group and disease activity ($p=0.024$ and p 0.001, respectively).

In the attempt to correlate MSUS findings with CAR, patients with more vascular change (as measured by power Doppler ultrasonography) and synovial hypertrophy (as measured by gray scale ultrasonography) had substantially higher levels of CAR than those without. These results coincides with those of **Afifi *et al.* [28],** who discovered that CAR was significantly elevated in patients with Doppler changes compared to those without. Consistent with previous studies [30], these findings suggest that CAR can serve as a predictor of RA activity.

The accuracy of the CAR ratio in predicting RA activity was evaluated using ROC curve analysis. Area under the Curve (AUC) (0.77) was highest for the DAS28 ESR at a cut-off point of (≥2.6), where the sensitivity was 79.1% and the specificity was 72.3%. At a threshold value of (≥3.4), the CDAI hadan AUC of 0.768, a sensitivity of 78.4%, and a specificity of 74%. While MHAQ had a lower specificity (55.6%) for an area under the curve of 0.769 and sensitivity of (78.9%), as well as a cut-off point of (≥0.7). These findings are comparable to those of **Afifi *et al.* [28]**, who discovered that CAR had a specificity of 66.67%, AUC of 0.789, a cut-off of ≥1.66, and a sensitivity of 81.58% in their study. These results coincide with those of **Elsabagh *et al.* [29]** who discovered the greatest AUC (AUC 0.78) at a cut-off of ≥2.66, a sensitivity of 81.3% and specificity of 64.3%, as well as **Erkut and associates [23]** whence the finding based on the ROC curve, the optimal CAR cut-off value for predicting early rheumatoid arthritis was 2.67 (80%, 85% in sensitivity and specificity) while for predicting established RA, it was 1.63 (77% sensitivity and 72% specificity).

CONCLUSION

CAR is a measure that can be evaluated easily and affordably. CAR, a derived ratio, can reflect activity in RA patients. This result lends support to CAR usage as a dependable predictor of RA inflammation.

The negative aspects of our research include the single-centre cross-sectional design, the lack of a follow-up assessment, and the lack of an evaluation of the correlation between CAR and RA outcomes.

RECOMMENDATION

We recommend larger-scale research and the use of an organized model comprised of various ratings and factors to improve the precision of predicting RA disease activity.

Disclosure statement: No author has any financial interest or received any financial benefit from this research.

Conflict of interest: The authors state no conflict of interest.

REFERENCES

1. **McInnes I, Schett G (2011):** The pathogenesis of rheumatoid arthritis. N Engl J Med., 365(23): 2205–2219.

2. **Prevoo M, van 't Hof M, Kuper H *et al.* (1995):** Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis and Rheumatism, 38 (1): 44-48.
3. **Aletaha D, Smolen J (2005):** The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clinical and Experimental Rheumatology, 23 (39): 100-8.
4. **Pincus T, Summey J, Soraci S *et al.* (1983):** Assessment of patient satisfaction in activities of daily living using a modified Stanford health assessment questionnaire. Arthritis Rheum., 26: 1346–53.
5. **Giles J, Bartlett S, Andersen R (2008):** Association of body fat with C-reactive protein in rheumatoid arthritis. Arthritis Rheum., 58(9):2632-41.
6. **Ren K, Dusad A, Dong R *et al.* (2013):** Albumin as a delivery carrier for rheumatoid arthritis. J Nanomed Nanotechnol., 4: 176-79.
7. **Tsujino T, Komura K, Hashimoto T *et al.* (2019):** C-reactive protein-albumin ratio as prognostic factor in renal cell carcinoma – A data from multi-institutional study in Japan. Urol Oncol., 37(11): e1812. doi:10.1016/j.urolonc.2019.04.0028.
8. **Liu M, Huang Y, Huang Z *et al.* (2019):** AB1326 increased fibrinogen to albumin ratio in ankylosing spondylitis: correlation with disease activity. Ann Rheum Dis., 78:2126–27.
9. **Naredo E, Collado P, Cruz A *et al.* (2007):** Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. Arthritis Rheum., 57: 116–24.
10. **Magni-Manzoni S, Epis O, Ravelli A *et al.* (2009):** Comparison of clinical versus ultrasound-determined synovitis in juvenile idiopathic arthritis. Arthritis Rheum., 61: 1497–504.
11. **Aletaha D, Neogi T, Silman A *et al.* (2010):** Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis., 69(9):1580–8.
12. **Backhaus M, Burmester G, Gerber T *et al.* (2001):** Guidelines for musculoskeletal ultrasound in rheumatology. Annals of the Rheumatic Diseases, 60(7):641-9.
13. **D'Agostino M, Wakefield R, Berner-Hammer H *et al.* (2016):** Value of ultrasonography as a marker of early response to abatacept in patients with rheumatoid arthritis and an inadequate response to methotrexate: results from the APPRAISE study. Annals of the Rheumatic Diseases, 75: 1763-69.
14. **Qin G, Tu J, Liu L *et al.* (2016):** Serum albumin and C-reactive protein/albumin ratio are useful biomarkers of Crohn's disease activity. Med Sci Monit., 22: 4393-4400.
15. **Moon J, Ahn S, Park Y *et al.* (2018):** C-reactive protein to serum albumin ratio is an independent predictor of all-cause mortality in patients with ANCA-associated vasculitis. Yonsei Med J., 59:865-71.
16. **Bruschi M, Candiano G, Santucci L *et al.* (2013):** Oxidized albumin. The long way of a protein of uncertain function. Biochim Biophys Acta., 1830: 5473-9.
17. **Singh H, Shrivastava A, Raizada A *et al.* (2013):** Atherogenic lipid profile and high sensitive C-reactive protein in patients with rheumatoid arthritis. Clin Biochem., 46:1007–1012.
18. **Göbel K, Eichler S, Wiendl H *et al.* (2018):** The coagulation factors fibrinogen, thrombin, and factor XII in inflammatory disorders—a systematic review. Front Immunol., 9:1731. doi:10.3389/fimmu.2018.0173119.
19. **Tominaga T, Nonaka T, Sumida Y *et al.* (2016):** The C-reactive protein to albumin ratio as a predictor of severe side effects of adjuvant chemotherapy in stage III colorectal cancer patients. PLoS One, 11(12):e0167967. doi:10.1371/journal.pone.016796721.
20. **Ishizuka M, Nagata H, Takagi K *et al.* (2016):** Clinical significance of the C-reactive protein to albumin ratio for survival after surgery for colorectal cancer. Ann Surg Oncol., 23(3):900–907. doi:10.1245/s10434-015-4948-7.
21. **Yang W, Zhang W, Huang Z *et al.* (2018):** Two new inflammatory markers associated with disease activity score 28 in patients with rheumatoid arthritis: Albumin to fibrinogen ratio and C-reactive protein to albumin ratio. Int Immunopharmacol., 62: 293-8.
22. **Sunar I, Ataman S (2020):** Serum C-reactive protein/albumin ratio in rheumatoid arthritis and its relationship with disease activity, physical function, and quality of life. Arch Rheumatol., 35(2): 247-53.
23. **Erkut M, Orucoglu N, Omar F *et al.* (2022):** C-reactive protein-to-albumin ratio: A novel inflammatory marker and disease activity sign in early rheumatoid arthritis. Aktuelle Rheumatologie, 47(03): 239-247.
24. **Ganeb S, Egaila S, Hamed A *et al.* (2020):** Significance of serum albumin and derived neutrophil-to-lymphocyte ratio score in assessment of disease activity in rheumatoid arthritis patients. Egypt Rheumatol Rehabil., 47: 5. DOI:10.1186/s43166-020-00010-9
25. **Zhang P, Liu J, Tan B *et al.* (2016):** Hypercoagulable state is associated with NF-kappa B activation and increased inflammatory factors in patients with rheumatoid arthritis. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi., 32(3):364-8.
26. **Ben-Hadj-Mohamed M, Khelil S, Ben Dbibis M *et al.* (2017):** Hepatic proteins and inflammatory markers in rheumatoid arthritis patients. Iran J Public Health, 46(8): 1071-78.
27. **Tsuji H, Hashimoto M, Harada T *et al.* (2020):** Persistent anemia and hypoalbuminemia in rheumatoid arthritis patients with low serum triiodothyronine level. Mod Rheumatol., 30(4): 640-7.
28. **Afifi N, Medhat B, Abdel Ghani A *et al.* (2020):** Value of albumin-fibrinogen ratio and CRP-albumin ratio as predictor marker of disease activity in Egyptian RA patients, correlated with musculoskeletal sonography. Open Access Rheumatol., 12: 241-8.
29. **Elsabagh A, Abd-Elwahab H, Mohamed A *et al.* (2022):** C-reactive protein to albumin ratio and albumin to fibrinogen ratio in rheumatoid arthritis patients. Modern Rheumatology Journal, 16(2): 21–25.
30. **Hameed B, Pilcher J, Heron C *et al.* (2008):** The relation between composite ultrasound measures and the DAS28 score, its components, and acute phase markers in adult RA. Rheumatology, 47(4): 476–480.