

Comparative assessment of the C-reactive protein-to-albumin ratio, platelet-to-albumin ratio, and prognostic nutritional index in rheumatoid arthritis

Nada M. Gamal¹ and Eman R. Badawy²

The Egyptian Journal of Immunology,
E-ISSN (2090-2506)

Volume 33 (4), October, 2026

Pages: 74–89.

www.Ejimmunology.org

<https://doi.org/10.55133/eji.330407>

¹Department of Rheumatology & Rehabilitation, Faculty of Medicine, Assiut University, Egypt.

²Department of Clinical Pathology, Faculty of Medicine, Assiut University, Egypt.

Corresponding author: Eman R. Badawy,
Department of Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt.
Email: e.badawy@aun.edu.eg

Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease that requires regular disease activity assessment to guide treatment and improve outcomes. Composite inflammatory and nutritional biomarkers are promising adjunctive tools for monitoring disease activity. This comparative study aimed to evaluate the levels of C-reactive protein-to-albumin ratio (CAR), platelet-to-albumin ratio (PAR), and prognostic nutritional index (PNI) in RA patients and healthy controls, and to compare their diagnostic performance and utility for disease activity assessment. The study included 165 RA patients and 167 age- and sex-matched controls. Disease activity of RA was assessed using the Disease Activity Score-28 based on erythrocyte sedimentation rate (DAS28-ESR) and classified into high (DAS28-ESR >5.1) and non-high (DAS28-ESR ≤5.1) disease activity groups. Complete blood count, serum albumin, and C-reactive protein (CRP) were measured to calculate CAR, PAR, and PNI. Rheumatoid arthritis patients had higher CAR and PAR, but lower PNI compared with controls (all $p < 0.001$). Patients with high disease activity had higher CAR and PAR, but lower PNI than those with non-high disease activity ($p < 0.001$, $p = 0.001$, $p = 0.018$ respectively). CAR and PAR correlated positively with DAS28-ESR, ESR and CRP, whereas PNI correlated negatively with these inflammatory measures. CAR showed the highest diagnostic performance for identifying RA patients (AUC=0.873), followed by PNI and PAR. CAR showed significantly superior performance, with no significant difference between PAR and PNI. CAR also showed the highest discriminatory performance for high disease activity (AUC=0.676) followed by PAR and PNI, although differences among them were not statistically significant. Higher CAR and PAR, whereas lower PNI were significantly associated with increased odds of high disease activity. Only CAR remained an independent predictor ($p = 0.005$) in multivariate analysis. In conclusion, CAR, PAR, and PNI are available composite biomarkers that provide complementary information regarding inflammatory burden and nutritional status in RA patients, with CAR showing the greatest utility.

Keywords: Rheumatoid arthritis; C-reactive protein-to-albumin ratio; platelet-to-albumin ratio; prognostic nutritional index.

Date received: 14 August 2026; **accepted:** 03 September 2026

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovial inflammation that results in progressive joint damage, functional disability, and reduced quality of life. It affects approximately 0.5–1% of the worldwide population.¹ Although extensive research has been conducted, the precise etiology and underlying pathogenic mechanisms of RA remain incompletely understood. Its development is believed to result from a complex interplay between genetic predisposition, environmental factors, and immune system dysregulation.² Current management strategies advocate a treat-to-target approach aimed at achieving and sustaining remission or low disease activity, underscoring the need for reliable and objective tools to monitor disease activity.³

Rheumatoid arthritis disease activity is routinely assessed using composite measures such as the Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR), Disease Activity Score 28-C-reactive Protein (DAS28-CRP), and Simplified Disease Activity Index (SDAI).^{4,5} These indices combine clinical evaluation, including tender and swollen joint counts, with inflammatory markers such as erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).⁶ Although ESR and CRP are incorporated into several of these assessment measures, they may not adequately represent the full inflammatory and metabolic burden of the disease, highlighting the need for additional objective biomarkers.⁷

Accordingly, several composite indices have been introduced to provide a more comprehensive evaluation of the systemic inflammatory and nutritional status of patients with RA. Among these, the C-reactive protein-to-albumin ratio (CAR), platelet-to-albumin ratio (PAR), and prognostic nutritional index (PNI) have gained increasing interest because they integrate routinely available laboratory parameters and provide complementary information regarding inflammation, immune function, and nutritional status.

The C-reactive protein-to-albumin ratio (CAR), calculated from serum CRP and albumin levels, is a composite biomarker of systemic inflammation. CRP and albumin are routinely measured laboratory parameters representing positive and negative acute-phase reactants, respectively, making CAR a useful indicator of inflammatory activity.⁸ Increasing evidence supports the clinical relevance of CAR as a reliable inflammation-related biomarker in a wide range of disorders, including cardiovascular, cerebrovascular, malignant, and infectious diseases.^{9–13}

The platelet-to-albumin ratio (PAR), derived by dividing the platelet count by the serum albumin concentration, is a readily available laboratory parameter that has been investigated in several inflammatory conditions. PAR has been associated with disease activity in ankylosing spondylitis, progression of IgA nephropathy, and the severity of endoscopic lesions in ulcerative colitis.^{14–16}

The prognostic nutritional index (PNI), derived from serum albumin concentration and lymphocyte count, is a well-established immuno-nutritional marker that has been widely investigated in malignancies and various autoimmune disorders.^{17–20} Given that hypoalbuminaemia and lymphopenia are common features of inflammation in rheumatoid arthritis, PNI may provide a useful indicator of both nutritional status and disease-related inflammatory burden.^{19,20}

Among these biomarkers, CAR has been the most widely studied in rheumatoid arthritis. Previous studies have consistently demonstrated its association with inflammatory burden and disease activity.^{21,22} Evidence has also suggested that CAR may have diagnostic value for identifying patients with RA.²³ Emerging evidence suggests that PAR may be a useful biomarker for RA, showing promising diagnostic performance and positive associations with disease activity.²⁴ Furthermore, PAR has also been independently associated with disease activity in patients with early RA.²⁵ More recently, PNI has been investigated as a potential biomarker in patients with RA. Lower PNI has been associated with

the presence of RA²⁶ and with increased disease activity in RA patients.^{27,28}

Despite the growing interest in these composite inflammatory and nutritional biomarkers, the available evidence remains limited and, in some cases, inconsistent. However, previous studies have primarily evaluated CAR, PAR, and PNI individually rather than directly comparing their clinical performance within the same cohort of patients with rheumatoid arthritis.

Therefore, this comparative study aimed to evaluate the levels of CAR, PAR, and PNI in patients with RA and healthy controls, and to compare their diagnostic performance and utility for disease activity assessment.

Patients and Methods

Study design and participants

This case-control study was based on previously collected clinical and laboratory data. It included 165 adult patients with RA who fulfilled the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria.²⁹ They were selected from a previously established dataset of patients with RA who had undergone clinical evaluation at the Rheumatology and Rehabilitation Department, Faculty of Medicine, Assiut University. The present analysis included patients with complete relevant clinical and laboratory data required for the study. The control group comprised 167 healthy individuals matched for age and sex, who had previously been recruited from hospital staff members and blood donors. They were selected from the previously established control dataset based on the availability of complete relevant data required for the present analysis. Participants with hematologic disorders, diabetes mellitus, renal or hepatic diseases, malignancies, infections, or other autoimmune diseases were excluded.

Clinical evaluation

At the time of the original data collection, all patients underwent comprehensive history taking and detailed clinical examination. The collected clinical data included socio-

demographic characteristics, therapeutic history, tender joint count (TJC), swollen joint count (SJC), patient global assessment (PGA), and physician global assessment (PhGA), with the latter two assessed using visual analogue scale (VAS) scores. Disease activity had been assessed using the Disease Activity Score-28 based on erythrocyte sedimentation rate (DAS28-ESR).³⁰ Disease activity was classified as remission (<2.6), low activity (2.6–3.2), moderate activity (>3.2–5.1), or high activity (>5.1). For the present analysis, patients were further dichotomized into high disease activity (DAS28-ESR >5.1) and non-high disease activity (DAS28-ESR ≤5.1), with the latter group comprising patients with remission, low, and moderate disease activity. This dichotomization was performed to facilitate binary receiver operating characteristic (ROC) and logistic regression analyses. Functional status had been evaluated using the Modified Health Assessment Questionnaire (MHAQ).³¹

Laboratory evaluation

At the time of the original data collection, venous blood samples were collected from all participants under aseptic conditions. Laboratory investigations in patients with RA included erythrocyte sedimentation rate (ESR), liver enzymes; aspartate aminotransferase (AST), and alanine aminotransferase (ALT), kidney function tests; blood urea nitrogen (BUN) and serum creatinine, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Complete blood count (CBC) with differential, serum albumin and C-reactive protein (CRP) were performed for both patients with RA and healthy controls. The relevant laboratory parameters were used to calculate CAR, PAR, and PNI.

CAR was calculated by dividing CRP (mg/L) by albumin (g/L) whereas, PAR was calculated by dividing platelet count ($\times 10^3/\mu\text{L}$) by albumin level (g/L). PNI was calculated using the original formula:³² $\text{PNI} = 10 \times \text{serum albumin (g/dL)} + 0.005 \times \text{peripheral blood lymphocyte count/mm}^3$. In the present study, serum albumin levels were reported in g/L and were converted to g/dL by dividing by 10, while lymphocyte counts were reported as $\times 10^3/\mu\text{L}$ and were

converted to cells/mm³ by multiplying by 1000 before applying the formula.

Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 26. Categorical data were presented in form of frequencies and percentages, while numerical data were expressed as mean $\pm$ standard deviation (SD) or standard error (SE), as appropriate, after testing their distribution by Shapiro-Wilk test. The independent-samples-t-test or Mann-Whitney U test was used to compare differences between two groups. The Chi-Square test was used to compare proportions between groups. Spearman's correlation was performed to assess the correlation between CAR, PAR, PNI and other continuous variables. ROC curve analysis was performed to evaluate the diagnostic performance of CAR, PAR, and PNI for discriminating patients with RA from healthy controls. ROC curve analysis was also performed to evaluate the ability of CAR, PAR, and PNI to discriminate RA patients with high disease activity from those with non-high disease activity. Pairwise comparisons of areas under the curves (AUCs) were performed using DeLong's test. Univariate and multivariate

logistic regression analysis were performed to identify predictors of higher activity; high disease activity was the outcome variable.

A *p* value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population: The study included 165 patients with RA, comprising 145 females (87.9%) and 20 males (12.1%). The mean age of the patients was 45.2 ± 10.5 years (range: 20–65 years), while the mean disease duration was 9.4 ± 0.49 years (range: 0.5–30 years). The control group consisted of 167 age- and sex-matched healthy individuals (140 females and 27 males) with a mean age of 43.3 ± 11.8 years (range: 18–65 years). No significant differences were observed between patients and controls regarding age or sex distribution (*p* = 0.128 and *p* = 0.290, respectively). The mean body mass index (BMI) of the RA patients was 30.9 ± 8.1 kg/m² (range: 15–61.2 kg/m²). The clinical characteristics and therapeutic history of the patients are summarized in Table 1, whereas the laboratory findings of both patients and controls are presented in Table 2.

Table 1. Clinical manifestations and therapeutic history of rheumatoid arthritis patients.

	Variable Number (%)	RA patients (n=165)
Constitutional	Morning stiffness	125 (75.8)
	Fatigue	128 (77.6)
	Fever	44 (26.7)
	Anorexia	68 (41.2)
	Weight loss	77 (46.7)
Musculoskeletal	Arthralgia	156 (94.5)
	Arthritis	120 (72.7)
	Limitation of movements	104 (63)
	Deformity	62 (36.6)
	Myalgia	103 (62.4)
	Trigger finger	45 (27.3)
	Subcutaneous nodules	44 (26.7)
	De Quervain's tenosynovitis	4 (2.4)
CNS	Sleep disturbance	100 (60.6)
	Muscle weakness	9 (5.5)
	CTS	110 (66.7)
	TTS	64 (38.8)

Table 1. Continued.

	Variable Number (%)	RA patients (n=165)
Cardio-pulmonary	Dyspnea	99 (60)
	Cough	32 (19.4)
Renal	Burning micturition	54 (32.7)
	Loin pain	14 (8.5)
GIT	Diarrhea	7 (4.0)
	Abdominal colic	10 (5.7)
Eye	Dry eye	71 (43)
	Blurring of vision	57 (34.5)
Therapeutic history	NSAIDs	121 (73.3)
	Steroids	69 (41.8)
	Antimalarial drugs	159 (96.4)
	Methotrexate	111 (67.3)
	Leflunomide	127 (77)
	Sulfasalazine	38 (23)
	Cyclophosphamide	2 (1.2)
	Azathioprine	2 (1.2)
	Anti TNF- α drugs	25 (15.2)

RA: rheumatoid arthritis, CNS: central nervous system, CTS: carpal tunnel syndrome, TTS: tarsal tunnel syndrome.

GIT: gastrointestinal, NSAIDs: non-steroidal anti-inflammatory drugs, Anti-TNF- α drugs: anti-tumor necrosis factor- α drugs

Table 2. Laboratory investigations of rheumatoid arthritis patients and controls.

Variables mean $\pm$ SD (range)	RA (n=165)	Controls (n=167)	p-value-
WBCs ($10^3/\mu\text{L}$)	6.5 $\pm$ 2.6 (2.1-26.8)	6.5 $\pm$ 2.1 (3.7-15.1)	NS
Neutrophils ($10^3/\mu\text{L}$)	3.5 $\pm$ 2.34 (0.6-25.1)	3.5 $\pm$ 1.4 (1.3-13.1)	NS
Lymphocytes ($10^3/\mu\text{L}$)	2.2 $\pm$ 0.76 (0.7-5.9)	2.5 $\pm$ 0.9 (1.07-5.4)	0.002
Monocytes ($10^3/\mu\text{L}$)	0.44 $\pm$ 0.02 (0.02-3.34)	0.3 $\pm$ 0.01 (0.1-0.9)	<0.001
Eosinophils ($10^3/\mu\text{L}$)	0.2 $\pm$ 0.02 (0-2.6)	0.2 $\pm$ 0.01 (0.05-0.5)	NS
Basophils ($10^3/\mu\text{L}$)	0.72 $\pm$ 0.04 (0-3.3)	0.6 $\pm$ 0.04(0-2.4)	0.018
Hemoglobin (g/dL)	12.1 $\pm$ 1.62 (7.4-16.6)	13.1 $\pm$ 1.5 (10.9-16.9)	<0.001
Platelets ($10^3/\mu\text{L}$)	317.7 $\pm$ 90.9 (160-749)	270.7 $\pm$ 57.1 (183-426)	<0.001
CRP (mg/l) (+ve in 135)	14.6 $\pm$ 1.7 (0.2-153.9)	2.3 $\pm$ 1.1 (0.5-5)	<0.001
Serum albumin (g/L)	41.1 $\pm$ 4.1 (28-50)	45.2 $\pm$ 3.9 (37-58)	<0.001
Serum albumin (g/dL)	4.1 $\pm$ 0.41 (2.8-5)	4.5 $\pm$ 0.39 (3.7-5.8)	
ESR (mm/1 st hr)	44.6 $\pm$ 2.5 (3-150)	-	
AST (U/L)	22.8 $\pm$ 1.3 (2-40)	-	
ALT (U/L)	23.9 $\pm$ 2.4 (6-45)	-	
BUN (mmol/L)	5.7 $\pm$ 0.6(1.8-8.2)	-	
Serum creatinine ($\mu\text{mol/l}$)	56.1 $\pm$ 15.3(30-95)	-	
RF (IU/ml) [+ve in 108]	127.2 $\pm$ 14.9(3.3-872)	-	
Anti CCP (U/mL) [+ve in 96]	75.5 $\pm$ 6.8 (0.5-200)	-	

RA: rheumatoid arthritis, WBCs: white blood cells, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, RF: rheumatoid factor, anti CCP abs: anti-cyclic citrullinated peptide antibodies. $p > 0.05$ is not significant (NS).

The mean TJC and SJC were 12.58 ± 0.69 and 4.27 ± 0.47 , with ranges of 0–28 and 0–24, respectively. The mean PGA score was 47.15 ± 24.95 (5–100), while the mean PhGA score was 45.18 ± 24.53 (5–100). According to DAS28-ESR, 14 patients (8.5%) were in remission, 15 (9.1%) had low disease activity, 43 (26.1%) had moderate disease activity, and 93 (56.4%) had high disease activity. For subsequent analyses, patients were dichotomized into a high ($n = 93$) and a non-high ($n = 72$) disease activity groups, the latter comprising patients in remission and

those with low or moderate disease activity. The mean MHAQ score was 0.69 ± 0.03 , ranging from 0 to 2.5.

Comparison of CAR, PAR, and PNI between study groups: Patients with RA had significantly higher mean CAR and PAR levels (0.38 ± 0.05 and 7.85 ± 2.67 , respectively) than healthy controls (0.05 ± 0.02 and 6.03 ± 1.36 , respectively); $p < 0.001$ for both. Conversely, the mean PNI was significantly lower in RA patients (52.09 ± 6.29) compared with controls (57.66 ± 5.90); $p < 0.001$, as illustrated in Figure 1.

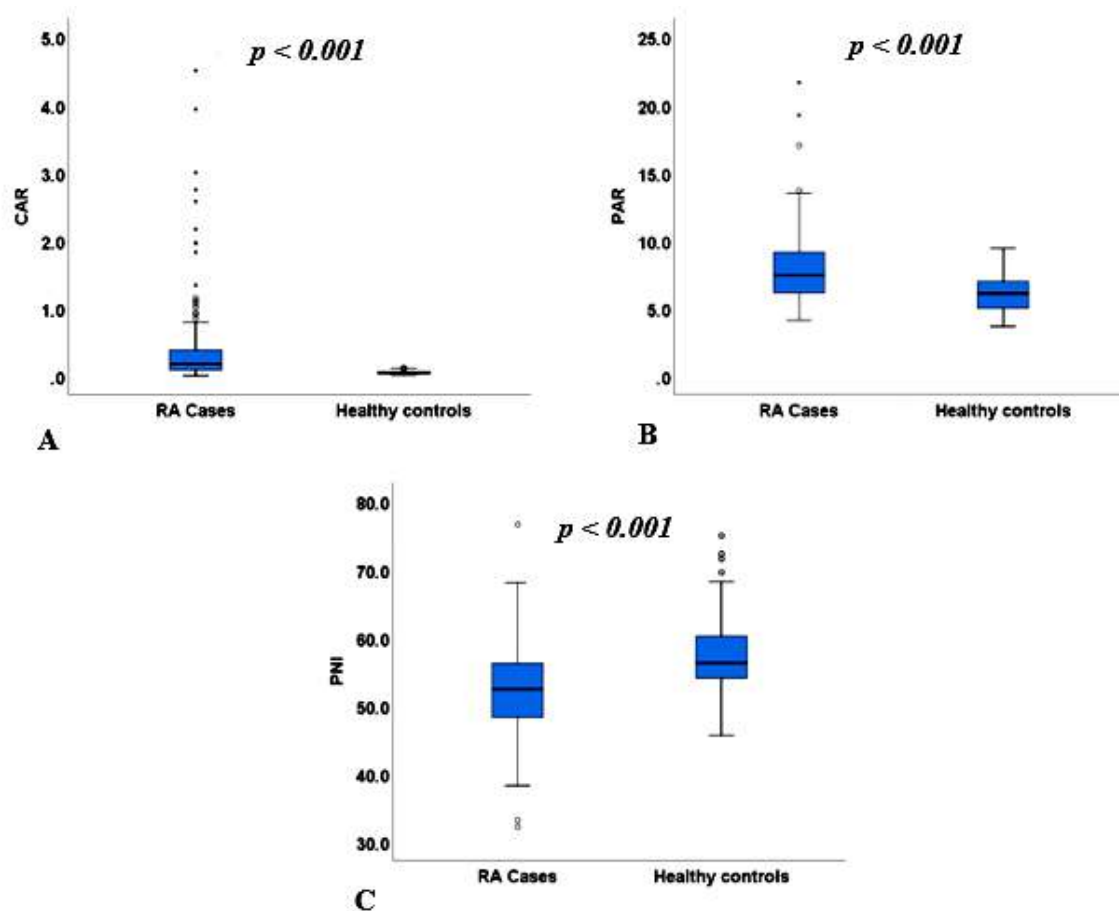


Figure 1. Box plots for the C-reactive protein-to-albumin ratio (CAR) [A], platelet-to-albumin ratio (PAR) [B], and prognostic nutritional index (PNI) [C] in rheumatoid arthritis (RA) patients and healthy controls.

Patients with high disease activity had significantly higher CAR levels than those with non-high disease activity (0.54 ± 0.08 vs. 0.16 ± 0.13 , $p < 0.001$). Similarly, PAR was significantly higher in patients with high disease activity

(8.47 ± 2.98 vs. 7.05 ± 1.94 , $p = 0.001$). In contrast, PNI was significantly lower in patients with high disease activity compared with the non-high disease activity group (51.08 ± 7.00 vs. 53.40 ± 4.96 , $p = 0.018$).

Correlation of CAR, PAR, and PNI with clinical and laboratory parameters: CAR and PAR showed significant positive correlations with DAS28-ESR and inflammatory markers, whereas PNI showed significant negative correlations with disease duration, DAS28-ESR, and

inflammatory markers but a positive correlation with BMI. Correlations of CAR, PAR and PNI with selected demographic, laboratory and clinical parameters in patients with RA presented in Table 3.

Table 3. Correlations of CAR, PAR and PNI with selected demographic, laboratory and clinical parameters in rheumatoid arthritis patients.

Parameter	CAR		PAR		PNI	
	r	p	r	p	r	p
Age	0.162	0.037	0.039	NS	-0.081	NS
Disease duration	0.250	0.001	0.172	0.027	-0.228	0.003
BMI	-0.047	NS	-0.134	NS	0.265	0.001
ESR	0.429	<0.001	0.406	<0.001	-0.321	<0.001
CRP	0.994	<0.001	0.424	<0.001	-0.298	<0.001
RF	0.226	0.004	0.129	NS	-0.191	0.014
Anti CCP abs	0.323	<0.001	0.300	<0.001	-0.152	NS
DAS-28 ESR	0.321	<0.001	0.273	<0.001	-0.160	0.040
MHAQ	0.237	0.002	0.079	NS	-0.081	NS

CAR: C-reactive protein to albumin ratio, PAR: platelet to albumin ratio, PNI: prognostic nutritional index, BMI: body mass index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, RF: rheumatoid factor, anti CCP abs: anti-cyclic citrullinated peptide antibodies, DAS28- ESR: disease activity score 28 based on erythrocyte sedimentation rate, MHAQ: modified health assessment questionnaire. $p > 0.05$ is not significant (NS).

Diagnostic performance of CAR, PAR, and PNI for discriminating RA patients from healthy controls: ROC curve analysis demonstrated that CAR had the highest diagnostic performance for discriminating patients with RA from healthy controls (AUC = 0.873, 95% CI: 0.833–0.907), followed by PNI (AUC = 0.745, 95% CI: 0.695–0.792) and PAR (AUC = 0.730, 95% CI: 0.679–0.777). All three biomarkers significantly discriminated RA patients from controls (all $p < 0.001$). Pairwise comparisons using DeLong's test showed that CAR had a significantly higher AUC than both PAR and PNI ($p < 0.001$, $p = 0.001$, respectively), whereas no significant difference was observed between PAR and PNI ($p = 0.683$). The detailed diagnostic performance indices are presented in Table 4, and the corresponding ROC curves are illustrated in Figure 2A.

Diagnostic performance of CAR, PAR, and PNI for discriminating high from non-high

disease activity in RA patients: For discriminating patients with high disease activity, CAR showed the highest discriminatory performance (AUC = 0.676, 95% CI: 0.599–0.747), followed by PAR (AUC = 0.656, 95% CI: 0.578–0.728) and PNI (AUC = 0.605, 95% CI: 0.526–0.680). All biomarkers significantly discriminated RA patients with high disease activity (CAR and PAR: $p < 0.001$; PNI: $p = 0.016$). However, pairwise comparisons of the ROC curves using DeLong's test revealed no statistically significant differences among the three markers (CAR vs. PAR, $p = 0.698$; CAR vs. PNI, $p = 0.174$; and PAR vs. PNI, $p = 0.843$). The detailed performance indices are presented in Table 4, and the corresponding ROC curves are illustrated in Figure 2B.

Logistic regression analysis for predictors of high disease activity: In the univariate logistic regression analysis, higher CAR (OR = 24.69, 95% CI: 3.91–155.92, $p = 0.001$) and PAR (OR =

1.29, 95% CI: 1.11–1.50, $p = 0.001$) were significantly associated with increased odds of high disease activity, whereas lower PNI was associated with higher odds of high disease activity (OR = 0.94, 95% CI: 0.89–0.99, $p = 0.021$). After adjustment for age, disease

duration, BMI and mutual adjustment for the three biomarkers, only CAR remained an independent predictor high disease activity (AOR = 17.45, 95% CI: 2.33–130.45, $p = 0.005$), whereas the associations for PAR and PNI were no longer statistically significant.

Table 4. Receiver operating characteristic (ROC) analysis of CAR, PAR and PNI for diagnosis of rheumatoid arthritis and prediction of high disease activity.

	Prediction of RA		
	CAR	PAR	PNI
AUC, 95% CI	0.873 (0.833-0.907)	0.730 (0.679-0.777)	0.745 (0.695-0.792)
Cut off	> 0.086	> 7.19	≤ 53.97
Accuracy	84.0	69.0	71.2
Sensitivity %	74.5	53.3	62.8
Specificity %	92.8	84.4	79.6
PPV %	91.1	77.2	75.4
NPP %	78.7	64.7	68.6
p value	<0.001	<0.001	<0.001
	Prediction of high disease activity		
	CAR	PAR	PNI
AUC, 95% CI	0.676 (0.599-0.747)	0.656 (0.578-0.728)	0.605 (0.526-0.680)
Cut off	> 0.381	> 7.25	≤ 50.68
Accuracy	65.5	66.7	60.5
Sensitivity %	37.6	66.7	46.2
Specificity %	93.1	66.7	74.6
PPV %	87.5	72.1	70.5
NPP %	53.6	60.8	51.5
p value	<0.001	<0.001	0.016

RA: rheumatoid arthritis, CAR: C-reactive protein to albumin ratio, PAR: platelet to albumin ratio, PNI: prognostic nutritional index, AUC: area under curve, CI: confidence interval, PPV: positive predictive value, NPP: negative predictive value.

$p \leq 0.05$ is significant.

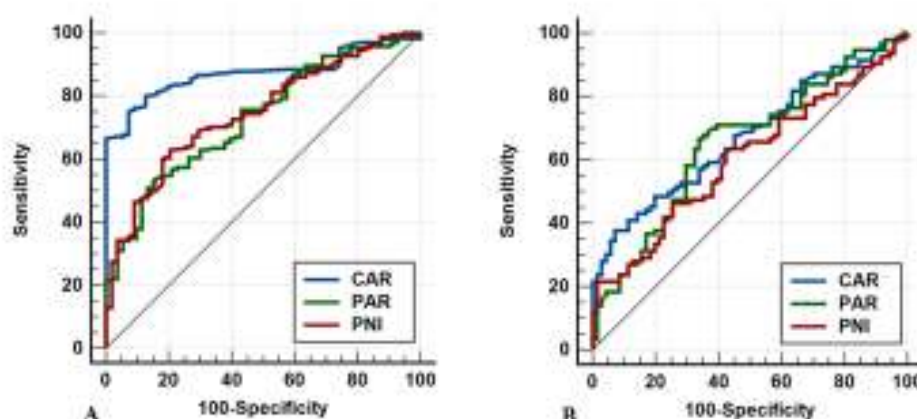


Figure 2. Receiver operating characteristic (ROC) curve for prediction rheumatoid arthritis [A], high rheumatoid arthritis disease activity [B] by the C-reactive protein-to-albumin ratio (CAR), platelet-to-albumin ratio (PAR), and prognostic nutritional index (PNI).

Discussion

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease with a complex and incompletely understood pathogenesis. Growing evidence suggests that immune dysregulation and nutritional status play pivotal roles in the development and progression of RA.^{33,34} Activation of various immune cells contributes to adaptive immune responses, leading to synovial angiogenesis, tissue remodeling, and progressive joint destruction.³⁵ In addition, patients with RA commonly exhibit malnutrition, which has been associated with poor prognosis and increased all-cause mortality.^{36,37}

Accordingly, composite biomarkers that simultaneously reflect inflammatory and nutritional status have gained attention as simple and readily available tools for disease evaluation. Among these, the C-reactive protein-to-albumin ratio (CAR), platelet-to-albumin ratio (PAR), and prognostic nutritional index (PNI) have shown promising value in the diagnosis and assessment of disease activity in RA.^{22-25,27,28} Based on these considerations, the study provided a comparative evaluation of CAR, PAR, and PNI in patients with RA, including their diagnostic performance and utility for disease activity assessment.

In the present study, patients with RA exhibited significantly higher CAR and PAR, but significantly lower PNI levels compared with healthy controls. Our findings regarding CAR are consistent with previous studies^{21,38-41} which demonstrated significantly higher CAR levels in RA patients compared with controls. Similarly, in the large population-based study using data from the National Health and Nutrition Examination Survey (NHANES) by Yang et al.²³ further reported an independent association between elevated CAR and the presence of RA. Likewise, our finding of increased PAR levels in patients with RA agreed with the results of Liu et al. study²⁴ reported significantly higher levels of PAR in RA. In contrast, Sahin et al.⁴¹ found non-significant difference in PAR between patients and controls, suggesting that the evidence regarding PAR remains less consistent than that for CAR. In agreement with our

results, Wang et al.²⁶ demonstrated that lower PNI was independently associated with the presence of RA in a large NHANES study, supporting the potential role of impaired nutritional and immunological status in patients with RA.

In this study, all three composite biomarkers (CAR, PAR, and PNI) demonstrated significant diagnostic performance in differentiating patients with RA from healthy controls. Among them, CAR achieved the highest diagnostic accuracy, followed by PNI and PAR. Pairwise comparisons showed that CAR was significantly superior to both PAR and PNI, whereas no significant difference was observed between PAR and PNI. Our findings regarding CAR are consistent with previous studies of Afifi et al.,³⁸ Hussein et al.,⁴⁰ and Sahin et al.⁴¹ reported diagnostic AUCs of 0.789, 0.750 and 0.949 respectively, supporting the ability of CAR to distinguish patients with RA from healthy controls. Similarly, Yang et al.²³ using NHANES data, demonstrated an independent association between elevated CAR with the presence of RA. Regarding PAR, Liu et al.²⁴ reported a diagnostic AUC of 0.887, which was higher than that observed in this study. Evidence regarding the diagnostic utility of PNI remains limited; however, Wang et al.²⁶ demonstrated that lower PNI was independently associated with the presence of RA in a large population-based study, supporting its potential diagnostic value.

The observed alternations of CAR, PAR, and PNI in patients with RA likely reflect the complex interplay between inflammation, immune dysregulation, and nutritional impairment.

The higher CAR observed in patients with RA can be attributed to the persistent systemic inflammatory state that characterizes the disease. CAR is calculated from CRP and albumin, two complementary acute-phase reactants that change in opposite directions during inflammation, with CRP increasing while albumin decreases.^{42,43} CRP is synthesized by the liver in response to pro-inflammatory cytokines, particularly IL-1, IL-6, and TNF- α , making it a highly sensitive marker of systemic inflammation.⁴⁴ Conversely, albumin decreases during inflammatory states and reflects

nutritional status.⁴⁵ Thus, by integrating these two biomarkers into a single index, CAR simultaneously reflects both inflammatory and nutritional status, providing a more comprehensive assessment of the inflammatory burden in RA than either marker alone.^{46,47} The elevated PAR observed in RA is closely linked to platelet activation induced by chronic inflammation. Platelets are increasingly recognized as active participants in innate immunity and play an important role in RA pathogenesis. During disease initiation, platelets are recruited to inflamed synovial tissues, where they promote local inflammatory responses.^{48,49} Pro-inflammatory cytokines activate fibroblast-like synoviocytes (FLS), stimulating pannus formation and matrix metalloproteinases (MMPs) release, which contribute to cartilage destruction and bone erosion.⁵⁰ In addition, systemic inflammation increases capillary permeability, resulting in albumin extravasation into the interstitial space, shortening its half-life, and ultimately leading to hypoalbuminemia, a recognized marker of inflammation.⁵¹ The lower PNI observed in patients with RA reflects the close interaction between chronic inflammation, immune dysregulation, and nutritional impairment. As a chronic inflammatory autoimmune disease, RA is characterized by persistent immune activation throughout its course.⁵² In addition, patients with RA become increasingly susceptible to malnutrition as the disease progresses.⁵³ Notably, inflammation and malnutrition have a bidirectional relationship, whereby chronic inflammation promotes insulin resistance and catabolism, leading to nutritional deterioration,⁵⁴ while malnutrition further impairs mitochondrial function, enhances reactive oxygen species generation, and activates inflammatory signaling pathways.⁵⁵ Serum albumin, one of the two components of PNI, is an important indicator of nutritional status, in addition to its anti-inflammatory and antioxidant properties.⁵⁶ The second component of PNI, lymphocytes, plays a fundamental role in adaptive immune responses and is critically involved in the pathogenesis of autoimmune diseases.⁵⁷ Alternations in peripheral lymphocyte count may reflect the

persistent immune dysregulation that characterizes of RA.⁵⁸

When patients were categorized according to disease activity, patients with high disease activity had significantly higher CAR and PAR but significantly lower PNI levels than those with non-high disease activity. These findings are supported by previous studies evaluating the association of these biomarkers with RA disease activity. Higher CAR levels were consistently reported in patients with higher disease activity, supporting its potential value in assessing disease activity.^{21,22,39,40,59-61} Similarly, higher PAR levels were significantly associated with increased disease activity as demonstrated in previous studies.^{24,25} Regarding PNI, significantly lower PNI levels were observed in RA patients with more active disease in agreement with recent studies.^{27,28}

Regarding the ability of these biomarkers to discriminate patients with high disease activity, all three biomarkers demonstrated significant discriminatory performance, with CAR achieving the highest AUC, followed by PAR and PNI. However, pairwise comparisons showed no statistically significant differences among the three biomarkers in predicting high disease activity. These findings are comparable to those reported in previous studies evaluating the discriminatory performance of these biomarkers for predicting disease activity in RA. Several studies^{21,38-40,60,61} demonstrated the ability of CAR to discriminate patients with higher disease activity. Recently, Öz et al.²⁷ and Pamukcu et al.²⁸ reported the discriminatory performance of PNI for identifying patients with high disease activity. Based on the available literature, no previous studies have evaluated the discriminatory performance of PAR for predicting high disease activity in RA, precluding direct comparison with our findings.

In the current study, CAR and PAR showed significant positive correlations with disease activity measures, assessed by DAS28-ESR, as well as with the inflammatory markers ESR and CRP. These findings are comparable to those reported in previous studies demonstrating positive correlations between CAR and disease activity, together with conventional inflammatory markers.^{21,38-41,59,61} Similar

significant positive correlations have also reported for PAR.^{24,25} In contrast, PNI showed significant negative correlations with DAS28-ESR, ESR, and CRP. These findings consistent with those of Pamukcu et al.²⁸ who demonstrated significant inverse correlations between PNI and disease activity measures including; DAS-CRP, ESR, and CRP.

The observed differences in CAR, PAR and PNI across disease activity categories, together with their discriminative performance and significant correlations with disease activity measures, may likely reflect the underlying inflammatory and immunological process involved in RA. The positive association between CAR and disease activity may be explained by its close relationship with the inflammatory process underlying RA. Disease activity in RA is largely driven by pro-inflammatory cytokines, particularly IL-6, which stimulate hepatic CRP synthesis while simultaneously suppressing albumin production, leading to higher CAR values with increasing disease activity.^{44,45} Elevated CAR levels have also been associated with greater synovial hypertrophy on grayscale ultrasonography and increased vascularity on power Doppler imaging, suggesting that CAR reflects not only systemic inflammation but also local synovial inflammatory activity.^{38,39,62} The association between elevated PAR and increased disease activity may be explained by the underlying inflammatory and immune mechanisms of RA. Cytokines play a central role in RA by mediating communication between immune cells and amplifying inflammatory responses.⁶³ Activated platelets further contribute to this process by releasing pro-inflammatory mediators, including IL-1, IL-6, and TNF- α , which activate the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway, a key mediator of inflammatory cytokine signaling.⁶⁴ The clinical efficacy of biologic therapies targeting cytokines, particularly TNF- α , further supports the pivotal role of these inflammatory pathways in RA pathogenesis.⁶⁵

Moreover, persistent inflammation suppresses hepatic albumin synthesis, leading to reduced serum albumin concentrations.⁶⁶ The inverse association between PNI and

disease activity is biologically plausible because active inflammation directly affects both components of PNI. Albumin, a negative acute-phase reactant that is downregulated by pro-inflammatory cytokines, including IL-6, TNF- α , and IL-1 β ,⁶⁷ whereas lymphopenia may result from cytokine-driven redistribution of lymphocytes to inflamed tissues, increased apoptosis, and treatment-related effects.^{68,69} Therefore, lower PNI reflects the combined effects of heightened inflammatory activity, nutritional impairment and immune dysregulation.

In the present study, univariate logistic regression analysis demonstrated that higher CAR and PAR, as well as lower PNI, were significantly associated with increased odds of high disease activity. However, after adjustment for age, disease duration, BMI, and mutual adjustment among the three biomarkers, only CAR remained independently associated with high disease activity, whereas the associations of PAR and PNI were no longer statistically significant. These findings are consistent with the previous studies^{22,60} which identified CAR as an independent predictor of active disease in patients with RA. In contrast, Leng et al.²⁵ reported that PAR remained independently associated with both DAS28-ESR and DAS28-CRP after adjustment for potential confounding factors. Regarding PNI, conflicting findings have been reported. Öz et al.²⁷ identified PNI as an independent predictor of disease activity. Whereas, Pamukcu et al.²⁸ reported that PNI lost its independent association after adjustment for inflammatory markers, in agreement with our findings.

In the present study, although both PAR and PNI were significantly associated with disease activity, neither remained an independent predictor of high disease activity after multivariable analysis. This suggests that their associations with disease activity may be influenced by other inflammatory and clinical variables rather than reflecting independent effects of the biomarkers themselves. Nevertheless, their significant associations with disease activity indicate that both PAR and PNI remain valuable adjunctive markers reflecting the inflammatory burden in RA.

Both PAR and PNI are derived from simple, inexpensive, and routinely available laboratory parameters, making them readily applicable in daily clinical practice, particularly in resource-limited settings. Rather than replacing established composite disease activity measures, they may provide complementary information regarding the inflammatory, nutritional, and immunological status of patients. Regarding PAR, integrating platelet count and serum albumin into a single index may provide a more comprehensive assessment of inflammatory and nutritional status than either parameter alone. Therefore, PAR may serve as a practical adjunctive biomarker to complement conventional disease activity assessment in patients with RA.²⁵ Concerning PNI, markedly reduced values of PNI may alert clinicians to uncontrolled systemic inflammation or unrecognized nutritional deficiencies. In addition, low PNI has been associated with an increased risk of adverse outcomes, including infections and poor treatment tolerance.⁷⁰ Therefore, patients with low PNI may benefit from nutritional assessment, dietary counseling, nutritional support, and closer follow-up.⁷¹

Taken together, the present findings demonstrated the superiority of CAR over PAR and PNI. CAR not only showed the highest discriminatory performance for distinguishing patients with RA from healthy controls and identifying those with high disease activity, but also emerged as the only independent predictor of high disease activity. This superior performance of CAR may be explained by its distinct biological characteristics. CAR combines CRP, a positive acute-phase reactant, with albumin, a negative acute-phase reactant, thereby capturing both inflammatory and nutritional changes through two complementary biomarkers that respond in opposite directions to systemic inflammation.^{21,23,39,59} From a clinical perspective, these findings highlight the potential utility of CAR as an adjunctive biomarker in RA. Because it is derived from two inexpensive and routinely available laboratory parameters, CAR is readily applicable in daily clinical practice and may facilitate disease

activity assessment and risk stratification in patients with RA.

To the best of our knowledge, this is the first study to simultaneously evaluate and compare CAR, PAR, and PNI for the diagnosis of RA and the assessment of disease activity, including their independent predictive value for high disease activity. Nevertheless, several limitations should be acknowledged. First, this was a single-center study with a relatively small sample size, which may limit the generalizability of the findings. Second, the cross-sectional design precluded assessment of the prognostic value of these biomarkers over time or the establishment of causal relationships. Therefore, larger multicenter prospective studies are warranted to validate these findings and explore the clinical utility of these biomarkers in RA.

In conclusion, CAR, PAR, and PNI are readily available composite biomarkers for the assessment of RA. They provide complementary information regarding inflammatory burden, nutritional status, and immune function in patients with RA. Their integration into routine clinical assessment may improve the comprehensive evaluation of RA patients, with CAR showing the greatest potential for clinical application.

Author Contributions

Both authors contributed to the study conception, design, data interpretation, manuscript review, and final approval. NMG: performed clinical examination, collection of data, and writing the original draft of manuscript. ERB: performed laboratory investigation, manuscript editing and revision.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for the present study was obtained from the Institutional Review Board of the Faculty of Medicine, Assiut University, Egypt (IRB registration No. 04-2026-300889). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Informed consent

Written informed consent had been obtained from the participants at the time of the original data collection.

References

- Pamukcu M, İzci Duran T, Ulusoy H, Altınbaş K. (2021). Investigation of the correlation between mood disorder symptoms and disease activity and functional status in rheumatoid arthritis patients. *Turk J Med Sci*; 51:3008-16.
- McInnes IB, Schett G. (2011). The pathogenesis of rheumatoid arthritis. *N Engl J Med*; 365:2205-19.
- Smolen JS, Landewé RBM, Bergstra SA, et al. (2023). EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis*; 82:3-18.
- van Riel PLCM. (2014). The development of the Disease Activity Score (DAS) and the Disease Activity Score using 28 joint counts (DAS28). *Clin Exp Rheumatol*; 32(Suppl 85):S65-S74.
- Aletaha D, Smolen JS. (2005). The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. *Clin Exp Rheumatol*; 23(Suppl 39):S100-S108.
- Wells G, Becker JC, Teng J, et al. (2009). Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. *Ann Rheum Dis*; 68(6):954-60.
- Yazici Y, Bergman M, Pincus T. (2008). Time to score quantitative rheumatoid arthritis measures: 28-joint count, Disease Activity Score, Health Assessment Questionnaire (HAQ), Multidimensional HAQ (MDHAQ), and Routine Assessment of Patient Index Data (RAPID) scores. *J Rheumatol*; 35:603-9.
- Ranzani OT, Zampieri FG, Forte DN, Azevedo LCP, Park M. (2013). C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. *PLoS One*; 8(3):e59321.
- Kayapinar O, Ozde C, Kaya A. (2019). Relationship between the reciprocal change in inflammation-related biomarkers (fibrinogen-to-albumin and hs-CRP-to-albumin ratios) and the presence and severity of coronary slow flow. *Clin Appl Thromb Hemost*; 25:1076029619835383.
- Zhang D, Yan H, Wei Y, et al. (2019). C-reactive protein/albumin ratio correlates with disease severity and predicts outcome in patients with aneurysmal subarachnoid hemorrhage. *Front Neurol*; 10:1186.
- Tsujino T, Komura K, Hashimoto T, et al. (2019). C-reactive protein-albumin ratio as a prognostic factor in renal cell carcinoma - A data from multi-institutional study in Japan. *Urol Oncol*; 37(11):812.e1-812.e8.
- Zavalaga-Zegarra H, Palomino-Gutierrez J, Ulloque-Badaracco J, et al. (2022). C-reactive protein-to-albumin ratio and clinical outcomes in COVID-19 patients: a systematic review and meta-analysis. *Trop Med Infect Dis*; 7:186.
- Luo B, Sun M, Huo X, Wang Y. (2021). Two new inflammatory markers related to the CURB-65 score for disease severity in patients with community-acquired pneumonia: the hypersensitive C-reactive protein-to-albumin ratio and fibrinogen-to-albumin ratio. *Open Life Sci*; 16:84-91.
- Cui R, Wang YL, Tao YL, Tong Q, Chen Z, Dai SM. (2023). Platelet-to-albumin ratio is an independent indicator for disease activity in ankylosing spondylitis. *Clin Rheumatol*; 42(2):407-13.
- Tan J, Song G, Wang S, et al. (2022). Platelet-to-albumin ratio: a novel IgA nephropathy prognosis predictor. *Front Immunol*; 13:842362.
- Huang J, Lu J, Jiang F, Song T. (2023). Platelet/albumin ratio and plateletcrit levels are potential new biomarkers for assessing endoscopic inflammatory bowel disease severity. *BMC Gastroenterol*; 23(1):393.
- Tan X, Chen H. (2023). The prognostic value of prognostic nutritional index in patients with ovarian cancer: a systematic review and meta-analysis. *Nutr Cancer*; 75:73-81.
- Tobing E, Tansol C, Tania C, Sihombing AT. (2024). Prognostic nutritional index as an independent predictor of poor survival in prostate cancer: a

- systematic review and meta-analysis. *Clin Genitourin Cancer*; 22:102142.
19. Klein A, Molad Y. (2021). Hematological manifestations among patients with rheumatic diseases. *Acta Haematol*; 144:403-12.
 20. Fessler J, Fasching P, Raicht A, et al. (2021). Lymphopenia in primary Sjögren's syndrome is associated with premature aging of naïve CD4+ T cells. *Rheumatology* (Oxford); 60:588-97.
 21. Yang W, Zhang W, Ying H, 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. Kaplan H, Cengiz G, Sas S, Eldemir YO. (2023). Is the C-reactive protein-to-albumin ratio the most remarkable simple inflammatory marker showing active disease in patients with axial spondyloarthritis, psoriatic arthritis, and rheumatoid arthritis? *Clin Rheumatol*; 42:2959-69.
 23. Yang F, Sang W, Liu Y, Wang J. (2025). The C-reactive protein-to-albumin ratio as a diagnostic biomarker for rheumatoid arthritis: a cross-sectional NHANES analysis. *Front Med* (Lausanne); 12:1624527.
 24. Liu Y, Huang Y, Huang Z, Huang Q, Li T. (2020). AB0204 A new inflammatory marker associated with disease activity in patients with rheumatoid arthritis: platelet-to-albumin ratio. *Ann Rheum Dis*; 79(Suppl 1):1402.
 25. Leng L, Shen J, Li L, Li J, Li X, Liu D. (2024). Nonlinear association between platelet-to-albumin ratio and disease activity in patients with early rheumatoid arthritis. *Sci Rep*; 14:27112.
 26. Wang J, Zhu R, Fang H, Xing X, Ge L, Cai G. (2024). Association of prognostic nutritional index with the presence and all-cause mortality of rheumatoid arthritis: the National Health and Nutrition Examination Survey 2003-2018. *BMC Public Health*; 24(1):3281.
 27. Öz N, Gezer HH, Cilli Hayiroğlu S, Duruöz MT. (2024). Evaluation of the prognostic nutritional index (PNI) as a tool for assessing disease activity in rheumatoid arthritis patients. *Clin Rheumatol*; 43(5):1461-7.
 28. Pamukcu M, Duran TI, Baltacı MA, Demir ME. (2026). Association between prognostic nutritional index and disease activity in patients with rheumatoid arthritis: a retrospective cohort study. *Mediterr J Rheumatol*; 1:37(2):357-63.
 29. Aletaha D, Neogi T, Silman AJ, et al. (2010). Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*; 69:1580-8.
 30. Prevoo MLM, van't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PLet. (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 Rheum*; 38:44-8.
 31. Pincus T, Summey JA, Soraci SA Jr, Wallston KA, Hummon NP. (1983). Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum*; 26(11):1346-53.
 32. Onodera T, Goseki N, Kosaki G. (1984). Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi*; 85(9):1001-5.
 33. Hayashi H, Satoi K, Sato-Mito N, et al. (2012). Nutritional status in relation to adipokines and oxidative stress is associated with disease activity in patients with rheumatoid arthritis. *Nutrition*; 28(11-12):1109-14.
 34. Edilova MI, Akram A, Abdul-Sater AA. (2021). Innate immunity drives pathogenesis of rheumatoid arthritis. *Biomed J*; 44(2):172-82.
 35. Tardito S, Martinelli G, Soldano S, et al. (2019). Macrophage M1/M2 polarization and rheumatoid arthritis: a systematic review. *Autoimmun Rev*; 18(11):102397.
 36. Cano-García L, Redondo-Rodríguez R, Manrique-Arija S, et al. (2023). Prevalence of malnutrition and associated factors in older patients with rheumatoid arthritis: a cross-sectional study. *Nutrients*; 15(16):3500.
 37. Tian P, Xiong J, Wu W, et al. (2022). Impact of malnutrition on mortality in rheumatoid arthritis patients: a cohort study from NHANES 1999-2014. *Front Nutr*; 9:993061.
 38. Afifi N, M Medhat B, Abdel Ghani AM, Mohamed Ali Hassan HGE, Behiry ME. (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.
 39. Fathy HM, Rafat S, Abd-ElAzeem MI, Abdou LM, Abd Elbaset AS, Tantawy M. (2023). CRP-albumin ratio as a disease activity marker in RA patients, its correlation with musculoskeletal sonography. *Egypt J Hosp Med*; 92:5496-502.

40. Hussein SM, Elrefaei KE, El-Bagoury IMS, El-Senosy FM. (2024). Clinical utility of C-reactive protein/albumin ratio and albumin/fibrinogen ratio in patients with rheumatoid arthritis. *Al-Azhar Univ J Virus Res Stud*; 6(2):94-103.
41. Sahin M, Uzumcu M, Melikoglu MA. (2025). Could complete blood count sub-parameters to albumin ratios be biomarkers of disease activity in rheumatoid arthritis? *Van Med J*; 32(2):216-23.
42. Sproston N, Ashworth J. (2018). Role of C-reactive protein at sites of inflammation and infection. *Front Immunol*; 9:754.
43. Arroyo V, García-Martínez R, Salvatella X. (2014). Human serum albumin, systemic inflammation, and cirrhosis. *J Hepatol*; 61:396-407.
44. Strang F, Schunkert H. (2014). C-reactive protein and coronary heart disease: all said—is it not? *Mediators Inflamm*; 2014:757123.
45. Caraceni P, Tufoni M, Bonavita M. (2013). Clinical use of albumin. *Blood Transfus*; 11:S18-25.
46. Tominaga T, Nonaka T, Sumida Y, Hidaka S, Sawai T, Nagayasu T. (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:e0167967.
47. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Shibuya N, Kubota K. (2016). Clinical significance of the C-reactive protein-to-albumin ratio for survival after surgery for colorectal cancer. *Ann Surg Oncol*; 23:900-7.
48. Boilard E, Nigrovic PA, Larabee K, et al. (2010). Platelets amplify inflammation in arthritis via collagen-dependent microparticle production. *Science*; 327(5965):580-3.
49. Wright HL, Lyon M, Chapman EA, Moots RJ, Edwards SW. (2020). Rheumatoid arthritis synovial fluid neutrophils drive inflammation through production of chemokines, reactive oxygen species, and neutrophil extracellular traps. *Front Immunol*; 11:584116.
50. Bartok B, Firestein GS. (2010). Fibroblast-like synoviocytes: key effector cells in rheumatoid arthritis. *Immunol Rev*; 233(1):233-55.
51. Soeters PB, Wolfe RR, Shenkin A. (2019). Hypoalbuminemia: pathogenesis and clinical significance. *JPEN J Parenter Enteral Nutr*; 43(2):181-93.
52. Alpizar-Rodríguez D, Finckh A. (2020). Is the prevention of rheumatoid arthritis possible? *Clin Rheumatol*; 39(5):1383-9.
53. Fukuda W, Yamazaki T, Akaogi T, et al. (2005). Malnutrition and disease progression in patients with rheumatoid arthritis. *Mod Rheumatol*; 15:104-7.
54. Wunderle C, Stumpf F, Schuetz P. (2024). Inflammation and response to nutrition interventions. *JPEN J Parenter Enteral Nutr*; 48(1):27-36.
55. Bañuls C, de Marañón AM, Veses S, et al. (2019). Malnutrition impairs mitochondrial function and leukocyte activation. *Nutr J*; 18(1):89.
56. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. (2012). Human serum albumin: from bench to bedside. *Mol Aspects Med*; 33(3):209-90.
57. Horwood N. (2008). Lymphocyte-derived cytokines in inflammatory arthritis. *Autoimmunity*; 41(3):30-8.
58. Ridgley LA, Anderson AE, Pratt AG. (2018). What are the dominant cytokines in early rheumatoid arthritis? *Curr Opin Rheumatol*; 30(2):207-14.
59. Sunar I, Ataman Ş. (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.
60. Öz N, Duruöz MT. (2023). Predictive value of C-reactive protein/albumin ratio (CAR) for disease activity in patients with rheumatoid arthritis: a prospective cohort study. *Ann Rheum Dis*; 82(Suppl 1):1312.
61. Uslu S, Tasgöz FC. (2024). Role of the C-reactive protein-to-albumin ratio in assessing disease activity in elderly patients with rheumatoid arthritis. *Cureus*; 16(8):e66929.
62. Hameed B, Pilcher J, Heron C, Kiely PD. (2008). The relation between composite ultrasound measures and the DAS28 score, its components, and acute phase markers in adult rheumatoid arthritis. *Rheumatology*; 47(4):476-80.
63. Jang S, Kwon EJ, Lee JJ. (2022). Rheumatoid arthritis: pathogenic roles of diverse immune cells. *Int J Mol Sci*; 23(2):905.
64. Morrell CN, Aggrey AA, Chapman LM, Modjeski KL. (2014). Emerging roles for platelets as immune and inflammatory cells. *Blood*; 123(18):2759-67.
65. Schett G, Stach C, Zwerina J, Voll R, Manger B. (2008). How antirheumatic drugs protect joints from damage in rheumatoid arthritis. *Arthritis Rheum*; 58(10):2936-48.
66. Don BR, Kaysen G. (2004). Serum albumin: relationship to inflammation and nutrition. *Semin Dial*; 17(6):432-7.

67. Bode JG, Albrecht U, Häussinger D, Heinrich PC, Schaper F. (2012). Hepatic acute phase proteins: regulation by IL-6- and IL-1-type cytokines involving STAT3 and its crosstalk with NF- κ B-dependent signaling. *Eur J Cell Biol*; 91:496-505.
68. Kondo N, Kuroda T, Kobayashi D. (2021). Cytokine networks in the pathogenesis of rheumatoid arthritis. *Int J Mol Sci*; 22(20):10922.
69. Ding Q, Hu W, Wang R, et al. (2023). Signaling pathways in rheumatoid arthritis: implications for targeted therapy. *Signal Transduct Target Ther*; 8:68.
70. Isoda K, Tsuji S, Harada Y, et al. (2023). Potential of the prognostic nutritional index to determine the risk factor for severe infection in elderly patients with rheumatoid arthritis. *Mod Rheumatol*; 33:88-95.
71. Olsen MN, Halse AK, Skeie E, Lein RK, Nilsen RM, Tangvik RJ. (2024). Effect of dietary interventions on nutritional status in patients with rheumatoid arthritis and spondyloarthritis: a systematic review and meta-analysis. *Clin Nutr*; 43(4):926-35.