The Role of Galectin-3 in The Diagnosis and Evaluation of Disease Activity in *Rheumatoid arthritis*

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ABSTRACT
Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects small joints, leading to joint inflammation, pain, and limited mobility. New biomarkers specific to RA could facilitate early diagnosis and treatment, while also enabling better monitoring of disease activity and treatment response. By ELISA, galectin-3 (gal-3) level was measured in 133 patients with inflammatory arthritis to determine the diagnostic value of gal-3 in the diagnosing of RA and evaluate the disease activity. Serum gal-3 levels were significantly higher in RA patients compared to patients with other types of inflammatory arthritis. According to CDAI, DAS-28 ESR, and DAS-28 CRP, gal-3 showed positive correlations with disease activity scores. Galectin-3 at a cut-off value of ≥ 2.4 ng/ml, revealed 89% sensitivity, 91% specificity, and an AUC of 0.893. There was a significant correlation between gal-3 and the age of RA patients, while no significant correlations were observed with gender, BMI, and smoking index., gal-3 levels correlated significantly with CRP, RF titer, and ACPA levels. Therefore, gal-3 can be considered a valuable biomarker for the diagnosis of RA and evaluating the disease activity.

Key words: *CDAI; DAS-28 CRP; DAS-28 ESR; Galectin-3; Rheumatoid arthritis.*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation affecting multiple systems, and its etiology remains uncertain. The condition predominantly affects synovial joints, causing persistent inflammation and subsequent degradation of both cartilaginous and bony components, resulting in pain and impairment of function. In addition, the disease has a variety of extra-articular manifestations that affect a variety of organs (Mohammed, 2020).

Rheumatoid arthritis is the most frequent inflammatory autoimmune arthritis. It is estimated to affect approximately 0.24 to 1% of the population. In Iraq, the incidence of RA in patients who attend the rheumatology centers increased from 1.1% in 2014 to 10% in 2019 (Albidri et al., 2016).

Rheumatoid arthritis is a disease of unknown origin, but in recent years, it has become evident that RA arises due to genetic and epigenetic components (Scherer et al., 2020). Significant advancements have been made in the past decade regarding the understanding of RA's pathogenesis. However, studies still lack a comprehensive understanding of the molecular network that predisposes individuals to develop the disease, exacerbates symptoms, or leads to a favorable response to specific treatments (Gavrilă et al., 2016).

The heterogeneity of clinical manifestations and the variability of therapeutic response serve as evidence of the intricate nature of this disease. The advancements made in comprehending the pathogenesis of RA have sparked a surge of interest in investigating the biomarkers implicated in various disease stages. Consequently, novel biomarkers continue to be identified and studied in this field (Heidari, 2011).

Biomarkers play a crucial role in guiding the clinical and therapeutic management of all stages of RA. They offer valuable insights by aiding in the prediction of disease development in individuals at risk, bridging the serological gap to enhance diagnosis, providing prognostic information to inform therapeutic decisions, assessing treatment responses and outcomes, and enabling the monitoring of disease activity and progression (Atzeni et al., 2017).

The major role of biomarkers can be objectified by comparing the diagnostic criteria. The only American College of Rheumatology (ACR) 1987 criteria biomarker is the rheumatoid factor (RF). The new ACR/EULAR 2010 criteria for the early diagnosis of RA use four serological tests including RF, anti-citrullinated protein antibodies (ACPA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) (Schneider & Krüger, 2013).

The biomarkers currently available for the diagnosis, activity, prognosis, and management of *Rheumatoid arthritis* (RA) have several limitations. Rheumatoid factor (RF) lacks specificity, as positive RF testing can be triggered by any condition that causes chronic antigenic stimulation. While anti-citrullinated protein antibodies (ACPA) are more specific, both tests fail to identify 20%-25% of patients with seronegative RA (Van Der Linden et al., 2011). Although analyzing the fine specificity of ACPA does not provide additional information regarding disease activity or the calculation of the progression score, it may contribute to predicting extra-articular in-

volvement. Due to the lack of adequate biomarkers for this purpose, disease activity monitoring still relies on clinical evaluation. Moreover, ESR and CRP are nonspecific acute-phase reactants that can be elevated for various reasons (Morozzi et al., 2007).

There is a subset of patients diagnosed with RA who exhibit erosive disease despite testing negative for RF, ACPA, and human leukocyte antigen (HLA). The absence of serological markers in these individuals poses a challenge in initiating early and appropriate treatment (Sokka & Pincus, 2009). Therefore, there is a critical need for more reliable predictors of disease outcomes, such as soluble biomarkers that can be detected at an early stage of the disease progression.

Galectin-3 (gal-3), a chimera-type member of the galectin family, increases monocyte chemotaxis and macrophage activation as well as neutrophil activation, degranulation, and superoxide production, implying that they play a role in the development of innate immune (Abdel Baki et al., 2022).

Galectin-3 is predominantly located in the cytoplasm and shuttles into the nucleus. In addition, it is secreted to the cell surface and into biological fluids. The different locations of gal-3 contribute to its various functions. Thus, it is involved in cell differentiation, inflammation, fibrogenesis, and host defense. Previous evidence has indicated that gal-3 is involved in the pathogenesis of various autoimmune and inflammatory processes (Chen & Kuo, 2016; Dong et al., 2018).

This research aimed to study the value of gal-3 as an ideal biomarker for the diagnosis of RA and differentiate it from other types of inflammatory arthritis. In addition, study its role in the evaluation of RA activity.

Materials and Methods

A cross-sectional study on 133 patients with inflammatory arthritis (*Rheuma-*

toid arthritis and other inflammatory arthritis), was conducted from September 2022 to January 2023. All the patients were recruited from Al–Sader Teaching Hospital in Najaf city. The age range of the patients was 20–70 years. The sample included 116 females and 17 males. Patients at the time of their clinic visit were randomly selected and classified into:

1. Group 1 consists of patients with RA who are classified as remission, mild, moderate, or severe based on their disease activity score measured by CDAI, DAS-28 ESR, and DAS-28 CRP.
2. Group 2 consists of patients with other types of inflammatory arthritis.

Inclusion criteria:

a. Patients who are diagnosed with RA by a rheumatologist according to the 2010 ACR/EULAR criteria get a score > or:6 on these criteria and their ages are between 20 and 70 years.
b. Patients with other inflammatory arthritis.

Exclusion criteria:

Patients with other autoimmune diseases, central nervous system diseases, cardiovascular diseases except for hypertension, immunodeficiency disease, malignancy, and chronic infections, patients who have had recent surgery, wound, or acute local inflammation, and patients older than 70 years and younger than 20 years.

The serum levels of gal-3 and ACPA in patients with inflammatory arthritis were measured using the Enzyme-Linked Immunosorbent Assay technique (ELISA) (Sunlong, China). Additionally, ESR was measured using the Westergren method, while RF and CRP were assessed using the sandwich immunodetection method (Boditech/Korea).

All data from both study groups were collected and analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 26, developed by Inc. in Chicago, USA.

Results and Discussion

The higher median (IQR) value of gal-3 was observed among the RA patients [4.6 (3.5-6.2) ng/ml] when compared to that of the other inflammatory arthritis patients [1.9 (1.7- 2.0) ng/ml] with a highly significant difference (P = <0.0001) between the two groups of patients as shown in table 1.

Table 1. Comparison of Gal-3 Values between the RA Patients and the Other Inflammatory Arthritis Patients.

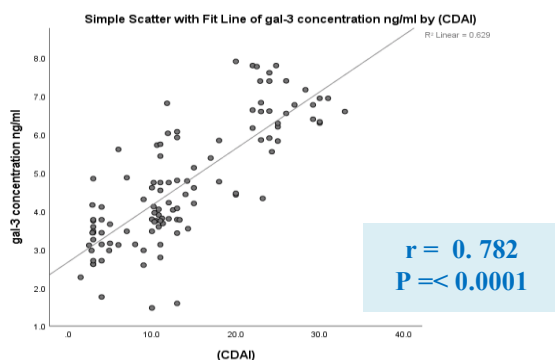| Characteristic	RA patients	Other Inflammatory Arthritis Patients	P- value
Gal-3 (ng/ml), median (IQR)	4.6 (3.5-6.2)	1.9 (1.7- 2.0)	<0.0001

Figure 1. Correlation between Gal-3 and RA Activity According to CDAI. Results for Gal-3 are Expressed as nanograms per milliliter.
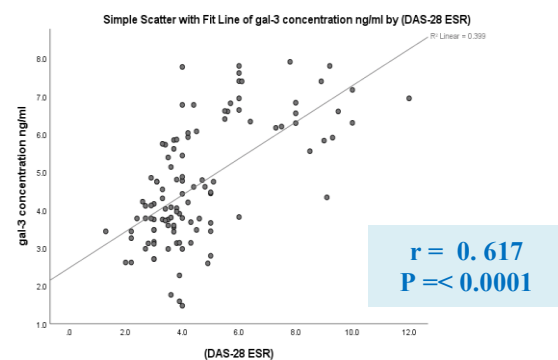

Figure 2. Correlation between Gal-3 and RA Activity According to DAS-28 ESR. Results for Gal-3 are Expressed as nanograms per milliliter.
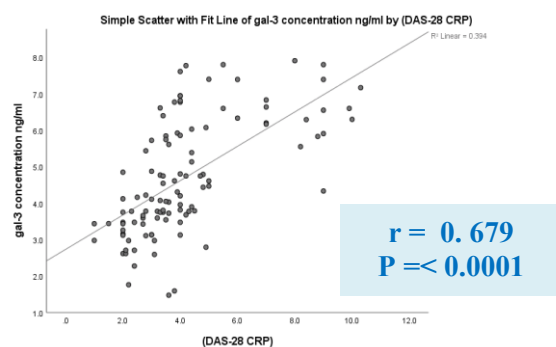
Figure 3. Correlation between Gal-3 and RA Activity According to DAS-28 CRP. Results for Gal-3 are Expressed as nanograms per milliliter.

In the RA patients, a highly significant difference in the median (IQR) level of gal-3 was observed among the disease activity groups according to CDAI, DAS-28 ESR, and DAS-28 CRP (P= <0.0001) as shown in table 2. Furthermore, a highly significant positive correlation was observed between the disease activity score according to CDAI, DAS-28 ESR, and DAS-28 CR and the level of gal-3 (P= <0.0001), as shown in figure 1, figure 2, and figure 3.

Table 2. Comparison of Gal-3 Values among Disease Activity Groups of the RA Patients According to CDAI, DAS-28 ESR, and DAS-28 CRP.

Character-istic	CDAI				P-value
	Remission n: 1	Low Activity n: 28	Moderate Activity n: 50	High Activity n: 30	
	2.27 (2.27-2.27)	3.34 (2.97-3.72)	4.43 (3.77-5.19)	6.80 (6.38-7.43)	
	DAS-28 ESR				
Gal-3 (ng/ml), median (IQR)	Remission n: 1	Low Activity n: 28	Moderate Activity n: 50	High Activity n: 30	<0.0001
	3.2 (2.6-3.4)	3.7 (3.1-4.3)	4.1 (3.5-5.3)	6.8 (6.3-7.3)	
	DAS-28 CRP				
	Remission n: 19	Low Activity n: 20	Moderate Activity n: 50	High Activity n: 20	
	3.2 (2.7-3.4)	3.7 (3.2-4.6)	4.7 (3.8-6.0)	6.7 (6.3-7.5)	

Table 3. Correlations of Demographic Characteristics and BMI with Gal-3 Value in the RA Patients

Characteristic		Gal-3
Age (years)	Correlation Coefficient (r)	0.323
	P-value	0.001
Gender	Correlation Coefficient (r)	0.128
	P-value	0.185
BMI	Correlation Coefficient (r)	0.173
	P-value	0.072
Smoking index, (pack per year)	Correlation Coefficient (r)	0.130
	P-value	0.544

A statistically significant correlation was observed between the level of gal-3 and age (p-value = 0.001). Nevertheless, no statistically significant correlations were identified between gal-3 levels and gender,

BMI, and smoking index, as evidenced by the respective p-values [(P = 0. 185), (P = 0. 072), (P = 0.544), respectively], as presented in table 3.

There was a statistically significant correlation of gal-3 value with CRP titer, RF titer, and ACPA level (P = 0.031, P = 0.0001, P = 0.0001, respectively) but there was no significant correlation between gal-3 level and the level of ESR (P = 0.127) as shown in table 4.

Table 4. Correlations between Gal-3 level and Levels of other Biomarkers in the RA Patients

Parameters		Gal-3 (ng/ml)	ESR (mm/h)	CRP titer (mg/L)	RF titer (IU/mL)	ACPA (U/ml)
Gal-3 (ng/ml)		1				
ESR (mm/h)	r	0.147	1			
	P	0.127				
CRP	r	0.207	0.463	1		
	P	0.031	0.0001			
RF (IU/mL)	r	0.398	0.111	0.122		
	P	0.0001	0.248	0.205	1	
ACCP (U/ml)	r	0.493	0.143	0.155		1
	P	0.0001	0.138	0.107	0.416	

A receiver operating characteristic (ROC) curve was used to quantify the diagnostic utility of gal-3 and the other two routine biomarkers (RF and ACPA) in the RA patients proven by ACR criteria (the current gold standard) and to differentiate RA patients from the other inflammatory arthritis patients, as shown in figure 4. At ≥ 2.4 ng/ml as a cutoff value, gal-3 was considered a good predictor of RA because of an area under the curve of more than 0.8 and highly significant P value (P = 0.0001) and the level of accuracy was more than 70%. In addition, the sensitivity of gal-3 for the diagnosis of RA was 89% which is higher than the sensitivity of RF and ACPA, while the specificity was 91% which is higher than the specificity of RF but lower than the specificity of ACPA. The positive and negative predictive values were clarified in table 5.

Table 5. Characteristics of Receiver Operator Characteristic (ROC) Curve of the Inflammatory Arthritis Patients.

Characteristic	Gal-3	RF	ACPA
AUC	0. 893	0.820	0.908
SE	0. 041	0.048	0.032
Sig.	0.0001	0.0001	0.0001
95% Confidence Interval	0.813-0.974	0.727- 0.914	0.846- 0.971
Optimal Cut-Point Value	2.4 ng/ml	18.1 IU/mL	19.0 U/ml
Sensitivity (%)	89	70	84
Specificity (%)	91	83	95
PPV (%)	98	95	98
NPV (%)	66	38	57
Diagnostic effectiveness (accuracy)	78.4	72.9	86.4
Youden's index	0.95	0.70	0.87

Note: AUC (Area under the Curve); SE, stander error, PPV (Positive Predictive Value), NPV (Negative Predictive Value); Youden's index is a measure for evaluating the biomarker effectiveness.
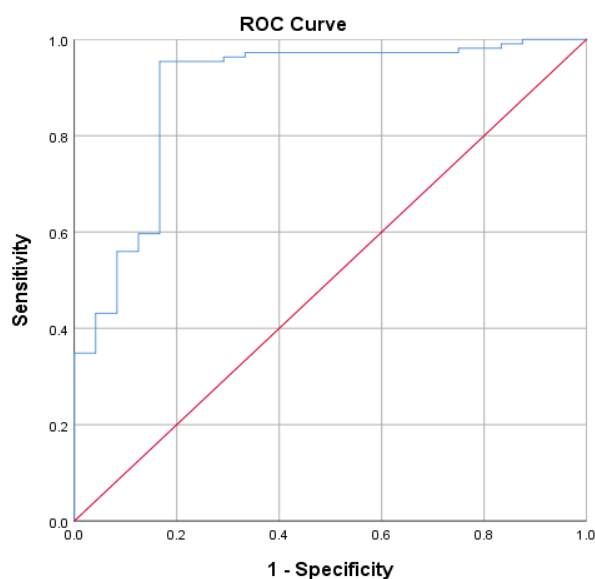
Figure 4. Receiver Operator Characteristic (ROC) Curve Analysis to Find the Best gal-3 Cutoff Value that can Diagnose RA, and Differentiate it from Other Inflammatory Arthritis.

According to CDAI, DAS-28 ESR, and DAS-28 CRP, the present study showed significant differences in gal-3 among the four groups of disease activity. *Rheumatoid arthritis* patients in the high-activity group had significantly the highest median gal-3 level followed by the moderate activity group, then the intermediate activity group, while the lowest median gal-3 level was in the low-activity group. So, the gal-3 level had significant associations with the disease activity group progression, and this finding was confirmed by the presence of a highly positive correlation between the gal-3 level and the disease activity score. This finding is compatible with Baki (Abdel Baki et al., 2022).

The precise cause for the increase in median gal-3 level in RA patients with the increase in the disease activity is not entirely understood. However, it is believed that gal-3 plays a role in the inflammatory response and tissue remodeling in RA. *Rheumatoid arthritis* is characterized by notable alterations in synovial tissue, including synovial hyperplasia, infiltration of inflammatory cells, and neovascularization. The expression of galectin-3 is noticeable in the epithelial layer, macrophages, and fibroblasts of synovial tissue among patients diagnosed with RA. Galectin-3 is believed to play a role in the inflammatory response within synovial tissue through its facilitation of immune cell migration and stimulation, as well as its induction of pro-inflammatory cytokine production. Furthermore, gal-3 may potentially exert influence on the modulation of programmed cell death and restructuring of tissues in the context of RA. Studies have shown that the gal-3 can stimulate the production of matrix metalloproteinases (MMPs), the enzymes responsible for the breakdown of extracellular matrix components, and hence increase the viability of synovial fibroblasts. In RA patients, the above-mentioned processes may exacerbate disease activity by contributing to the degeneration of synovial tissue and, ultimately, joint destruction (Abdel Baki et al., 2022; Filer et al., 2011; Hu et al., 2017).

The present study's results suggest that the elevation of gal-3 levels is a significant marker for the progress of the disease in patients diagnosed with RA. In addition, gal-3 levels can be monitored to evaluate the success of treatment and monitor disease progression. Therefore, monitoring this specific biomarker can help in the treatment of RA by providing important information about the disease's activity. Consistently checking this biomarker can help in optimizing disease care and guiding therapy choices.

The existing study exposed a significant positive association between serum gal-3 levels and age, this is in accordance with Baki's findings (Abdel Baki et al., 2022). This may be because gal-3 is involved in tissue repair and regeneration, which may be more relevant in older patients with RA who may have more advanced disease and require more tissue repair. A further possible explanation for the correlation between gal-3 and age in RA is

that aged patients may have a prolonged duration of disease, which may result in more tissue damage and consequently, higher levels of gal-3 (Issa et al., 2017).

This study found no significant correlation between gal-3 levels and gender, BMI, or smoking index. The present result is similar to the results of Issa and Alaaraji (Alaaraji, 2020; Issa et al., 2017). These findings of the current study demonstrate many ideal features of gal-3 as a diagnostic biomarker for RA because this biomarker is not affected by gender, BMI, and smoking index.

Based on the findings of this study, there was a significant correlation between the gal-3 level and the CRP titer, RF titer, and ACPA level. These findings are supported by the studies of Issa, Alaaraji, and Oliveira (Alaaraji, 2020; de Oliveira et al., 2015; Issa et al., 2017). The significant positive correlation between gal-3 and CRP may reflect the role of gal-3 in promoting inflammation and disease activity in RA. Elevated levels of gal-3 may lead to increased production of CRP as part of the inflammatory response. In addition, gal-3 modulates the activity of several cytokines and chemokines implicated in the pathogenesis of RA, including TNF-, IL-6, and IL-8. These cytokines and chemokines stimulate CRP production, which may also explain the observed correlation between gal-3 and CRP in RA (de Oliveira et al., 2015).

The significant positive correlation of gal-3 with RF and ACPA in patients with RA indicates that gal-3 may play a role in the production or regulation of these autoantibodies. One possible explanation is that gal-3 promotes the survival and activation of immune cells, such as B cells, which produce autoantibodies. Another possibility is that gal-3 directly interacts with RF and ACPA, leading to their increased production or activity (Alaaraji, 2020; Issa et al., 2017).

Galectin-3 had a higher sensitivity for the diagnosis of RA compared to RF and ACPA. It had a higher AUC, accuracy, and specificity compared to RF but lower than that for ACPA. The present result is similar to the result of the ROC curve analysis of gal-3 in studies conducted by Mendez and Gruszewska (Gruszewska et al., 2020; Mendez-Huergo et al., 2019). Therefore, the obtained results in the current study suggest that the determination of serum gal-3 concentration may be a useful tool in the diagnosis of RA disease. Moreover, if it is available as a routine test; due to its high diagnostic accuracy and cheapness, gal-3 can be a valuable surrogate marker for the diagnosis of patients with RA disease.

Conclusion

Galectin-3 can be considered a good biomarker for the diagnosis of RA and can be used to evaluate disease activity.

Approval of the Ethical Committee

Before commencing the research project, this study received ethical approval from the Faculty of Medicine's ethical committee at the University of Kufa. Informed consent was obtained from all participating patients, and permission was acquired from the Rheumatology Unit.

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