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Galectin-3 and its correlation with carotid ultrasound in rheumatoid arthritis patients

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Abstract

Background Rheumatoid arthritis (RA) is a chronic inflammatory disease resulting in disability as well as joint damage. Early diagnosis and treatment are crucial for improving outcomes. RA patients have a twofold elevated risk of cardiovascular disease (CVD) development compared to the general population. Carotid ultrasound is a noninvasive imaging modality that can detect early signs of atherosclerosis and plaque buildup in the carotid arteries, which are strongly associated with CVD risk. Galectin-3 (Gal-3), a protein involved in inflammation and fibrosis, is suggested as one of the potential RA markers. Despite the growing interest in galectin-3 as a biomarker for CVD, few studies have investigated its role in RA patients. To our knowledge, only two studies have examined the correlation between galectin-3 and CVD in RA patients, and they have yielded conflicting results. This study aimed to determine the serum level of Gal-3 as well as its correlation with carotid ultrasound assessment for cardiovascular involvement in RA patients.

Results RA cases demonstrated substantially elevated Gal-3 levels than controls ($P < 0.001$), and a 3.38 pg/mL cut-off value was proven to be an excellent predictor of RA diagnosis (*AUC*, 0.98). Gal-3 levels were proven to be positively associated with DAS-28, Larsen score, and carotid intima-media thickness (CIMT) (*P*-value 0.006, 0.026, < 0.001, respectively). A positive association was also detected between right (RT) and left (LT) CIMT and disease duration (*P*-values of 0.040 and 0.042, respectively).

Conclusions Gal-3 is a biomarker for RA that is not only associated with activity and severity of the disease but it is also related to the chronicity of the disease and is a predictor of cardiovascular comorbidity.

Keywords Galectin-3, Carotid, Ultrasound, Rheumatoid arthritis, DAS, CIMT

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease impacting nearly 1% of the population globally. It primarily targets the joints, inducing swelling, stiffness, and pain, but it may also involve other organs, including blood vessels as well as the heart. Cardiovascular disease (CVD) is a prevalent comorbidity in RA patients and a significant reason for mortality as well as morbidity. RA patients have a twofold elevated risk of CVD development compared to general population and a higher likelihood of experiencing heart failure, stroke, and myocardial infarction [1].

The underlying mechanisms of the elevated cardiovascular risk in RA cases are not fully understood, but chronic inflammation and immune dysregulation are believed to have a significant role. Numerous inflammatory biomarkers are involved as predictors of CVD in RA patients, including C reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6). However, these biomarkers have limited sensitivity and

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specificity, and their clinical utility in RA patients is still under investigation [2].

Gal-3 is a protein binding to β-galactoside and is implicated in various pathological processes like cell proliferation, fibrosis, and inflammation. It has also been suggested as a potential CVD biomarker due to its involvement in atherosclerosis, myocardial remodelling, and heart failure. Gal-3 was proven to trigger immune cell activation and recruitment, proinflammatory cytokine generation, and the deposition of extracellular matrix proteins, all of which contribute to the development and progression of CVD [3].

Carotid ultrasound is a noninvasive as well as cost-effective imaging modality that can detect early signs of atherosclerosis and plaque buildup in the carotid arteries, which are strongly associated with CVD risk [4].

This study aimed to determine the serum level of Gal-3 and detect any correlation with carotid ultrasound assessment for cardiovascular involvement in RA patients.

Methods

A case-control study was conducted to assess serum levels of Gal-3 in RA patients and their association with carotid ultrasound. The subjects were grouped as

- *Group 1*: Thirty RA cases diagnosed based on the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA classification criteria [5]. All patients attended the inpatient and the Rheumatology, Rehabilitation, and Physical Medicine Department's outpatient clinics
- *Group 2*: Twenty apparently healthy subjects (matched sex and age) were enrolled as controls.

The study was done after the research ethics committee approval. All participants provided informed consent.

Inclusion criteria

All RA cases included were of both sexes (aged ≥ 20) and met the 2010 ACR/EULAR RA classification criteria [5].

Exclusion criteria

These were renal failure patients on dialysis, malignancy, and any comorbidities that may result in atherosclerosis, like hypertension, hyperlipidaemia, obesity, smoking, and diabetes mellitus (DM) and patients with prior CVD including myocardial infarction and stroke.

All participants were subjected to (I) complete history taking, (II) full clinical examination, and (III) assessment of diseases activity and severity: DAS-28 score interpretation [6]:

- < 2.6 (disease remission)
- 2.6–3.2 (low activity of the disease)
- 3.2–5.1 (moderate activity of the disease)
- 5.1 (high activity of the disease)

Severity: Modified Larsen's scoring method

As per a global score for 2nd to 5th PIP, 2nd to 5th MCP, four quadrants in the wrist in each hand, and 2nd to 5th MTP in each foot, score ranges 0–160 [7].

Radiological investigations

1. Conventional radiography: Plain x-rays of the feet (antero-posterior), as well as both hands (postero-anterior) views, were obtained from all patients and assessed (based on modified Larsen's scoring) [7].
2. Carotid ultrasound: Subclinical atherosclerosis evaluation as well as carotid intima-media thickness measurement. All patients included in the study underwent radiological evaluation by a consultant at the radiology department in our hospital.

Intima-media thickness measurement

The probe was placed along the left common carotid artery's longitudinal axis. The IMT appears as a double-line pattern on both common carotid artery (CCA) walls. These two parallel lines (two anatomical boundary leading edges) represent lumen-intima interfaces as well as media-adventitia. Measurement of the distance between media-adventitia as well as lumen-intima interfaces was done along the CCA medial wall at three different points and calculation of the mean of these measurements [8].

Type of equipment

It is a GE Logiq P6 ultrasound machine, linear probe (5–11 MHz).

Equipment settings

Frame rate (> 15–25 Hz), focus depth (20–30 mm), gain, and dynamic range settings are adjusted optimally to facilitate the detection of edges.

Laboratory investigations

Laboratory investigations: Routine laboratory investigations included the following:

(I) Hematological tests

1. *Complete blood picture*: These are hemoglobin (Hb %), RBCs count, WBCs (total and differential count), platelets count.

2. *Erythrocyte sedimentation rate* (*ESR*): The first-hour reading was taken using the Westergren method recorded in mm/h [9]
3. C-reactive protein (CRP): Utilizing latex agglutination slide test [10]
4. Total lipid profile: Total cholesterol, LDL, HDL, and triglyceride

(II) Chemical tests

a. Kidney function test: Serum creatinine and blood urea
b. Liver function tests: Alanine transaminase (ALT) and aspartate transaminase (AST)
c. Fasting blood sugar (FBS)

(III) Serological tests

a. Rheumatoid factor (by Latex agglutination test) [11]
b. Anti-citrullinated protein antibody (ACPA): It was detected utilizing the ELISA technique.
c. Serum Gal-3 concentrations in serum were determined utilizing a commercially available ELISA kit (SunRed Biotechnology Company; REF of kits DZE201121952) according to the manufacturer's protocol.

Methodology

Sampling

Venous blood (3 ml) was withdrawn from each subject utilizing clean venepuncture as well as disposable plastic syringes. Samples were placed on plain tubes, with no anticoagulants, to separate serum. The tubes were left for 30 min at an ambient temperature until coagulation before centrifugation (for 15 min; at 1500 rpm). The resultant serum was kept at −20 °C for additional Gal-3 testing.

Assay principle: Gal-3

In this kit, a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) was utilized for assaying human Gal-3 levels in samples. Serum samples were added to wells of the microplate (precoated with human Gal-3 monoclonal antibodies) and incubated; Gal-3 antibodies labeled with biotin were added. After washing to remove any unbound biotinylated antibody, streptavidin-HRP (horseradish peroxidase-conjugated streptavidin) was added. Samples were incubated before rewash. Chromogen solutions A and B were subsequently added. The liquid color changed into blue, and after adding an acidic stop solution, the color finally became yellow. The yellow color density is proportional to the quantity of Gal-3 amount of sample captured in the plate. The absorbance of OD was read (at 450 nm) in a microplate reader before calculating Gal-3 concentration.

Statistical analysis

On an "investigation report form," the data were recorded and subsequently analyzed, coded, and tabulated utilizing the 26th version of the SPSS software. The descriptive statistics for the data were calculated as percentages, numbers, mean, and standard deviation (±SD). Student's *t*-test was utilized to identify the significance of the difference between the means of two groups of numerical (parametric) data (in the statistical comparison) between groups. A comparison of the categorical data between groups was made utilizing the chi-square test (X^2 value). The Pearson correlation coefficient (r) test was used to correlate various parameters—the model of regression for identifying which of these factors is an influential indicator of RA disease activity. *P*-value ≤ 0.05 was considered statistically significant.

Results

Regarding the study groups' demographic data, there were no substantial differences as regard the age, sex, systolic, diastolic blood pressure, and pulse between the studied groups (*P*-value 0.07, 0.8, 0.6, 0.6, 0.2, respectively).

Regarding RA group clinical data, the mean disease duration was 11.33 ± 5.87 years, the tender joint number was 7.37 ± 2.75, the swollen joint number was 4.100 ± 1.24, the modified Larsen score was 32.40 ± 18.42, and the DAS-28 score was 5.54 ± 0.43.

Regarding our patients' medications, 67% were on methotrexate, 26% on corticosteroids, 14% on hydroxychloroquine, 13% on leflunomide, and 10 % on biologic therapy.

Highly statistically substantial differences were observed between studied groups in terms of haematocrit, platelet, ESR, CRP, RT CIMT, LT CIMT, and Gal-3 serum level (all *P*-values < 0.001) (Table 1).

ROC curve analysis revealed that the Gal-3 cut-off value of 3.38 pg/mL could be an excellent predictive test of RA diagnosis with 96.7% sensitivity and 95% specificity (*AUC*, 0.98 and 95% *CI*, 0.94–1.00) (Fig. 1).

A highly statistically marked positive correlation was observed between the Gal-3 level and (RT CIMT, LT CMIT) (*P*-value < 0.001). A statistically positive marked correlation was detected between the Gal-3 level and (modified Larsen score, DAS28) (*P*-value 0.026, 0.006, respectively) (Fig. 2).

Marked carotid intima medial thickness (CIMT) difference was shown between A. normal control measuring

Table 1 Comparison between study groups regarding laboratory data, CIMT

	Cases ($n = 30$)		Control ($n = 20$)		*t*	*p*-value
	Mean	SD	Mean	SD		
WBC/mcL	6.62	2.07	6.58	2.02	0.1	0.9
HB g/dL	11.78	1.42	12.34	1.00	1.5	0.1
RBC mil/mcl	4.28	0.47	4.52	0.50	1.7	0.1
Hematocrit	32.86	4.01	38.20	2.86	5.1	< 0.001*
Platelet	264.90	95.73	187.50	36.47	4.01	< 0.001*
ESR	53.70	24.92	6.30	2.54	10.3	< 0.001*
CRP	18.63	20.52	3.30	1.66	4.1	< 0.001*
AST	21.67	5.13	19.95	5.55	1.1	0.3
ALT	21.23	5.43	20.95	5.53	0.2	0.9
Creatinine	0.70	0.15	0.80	0.20	1.9	0.07
Cholesterol	133.67	18.14	133.30	18.77	0.1	0.9
LDL	78.53	12.002	72.65	10.95	1.8	0.09
HDL	41.57	4.97	43.95	4.45	1.7	0.09
Triglyceride	94.77	12.24	92.45	10.61	0.7	0.5
F Bl. sugar	87.70	6.47	86.15	8.77	0.7	0.5
CIMT						
RT CIMT	0.73	0.25	0.44	0.04	6.4	< 0.001*
LT CIMT	0.72	0.23	0.44	0.04	6.4	< 0.001*
Galectin-3						
Galectin-3	7.05	2.88	2.31	0.55	8.8	< 0.001*

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *HB* hemoglobin, *WBC* white blood cells, *RBC* red blood cells, *CIMT* carotid intima-media thickness

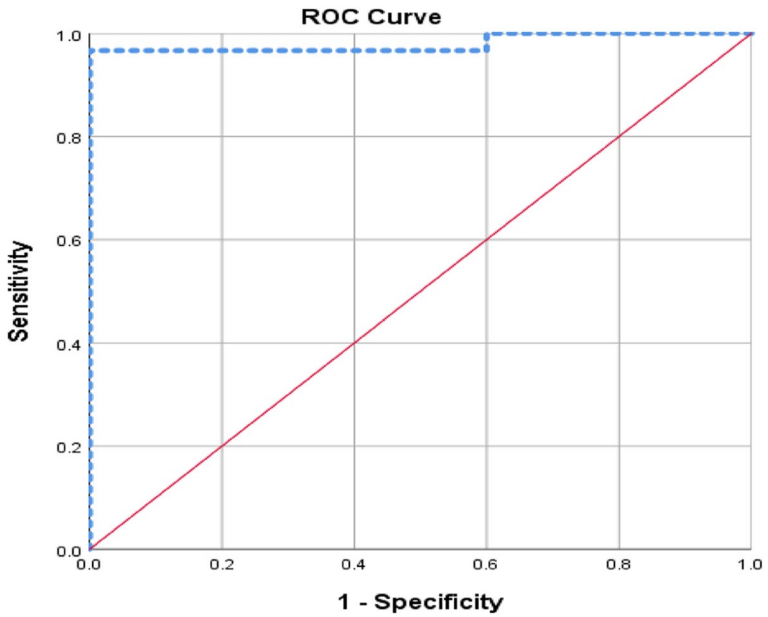

Fig. 1 Receiver Operating Characteristic (ROC) curve analysis of galectin-3 cut-off values for prediction of RA

ROC curve analysis revealed that the galectin-3 cut-off value of 3.38 pg/mL could be an excellent predictive test of RA diagnosis with 96.7% sensitivity and 95% specificity (AUC, 0.98 and 95% CI, 0.94-1.00)

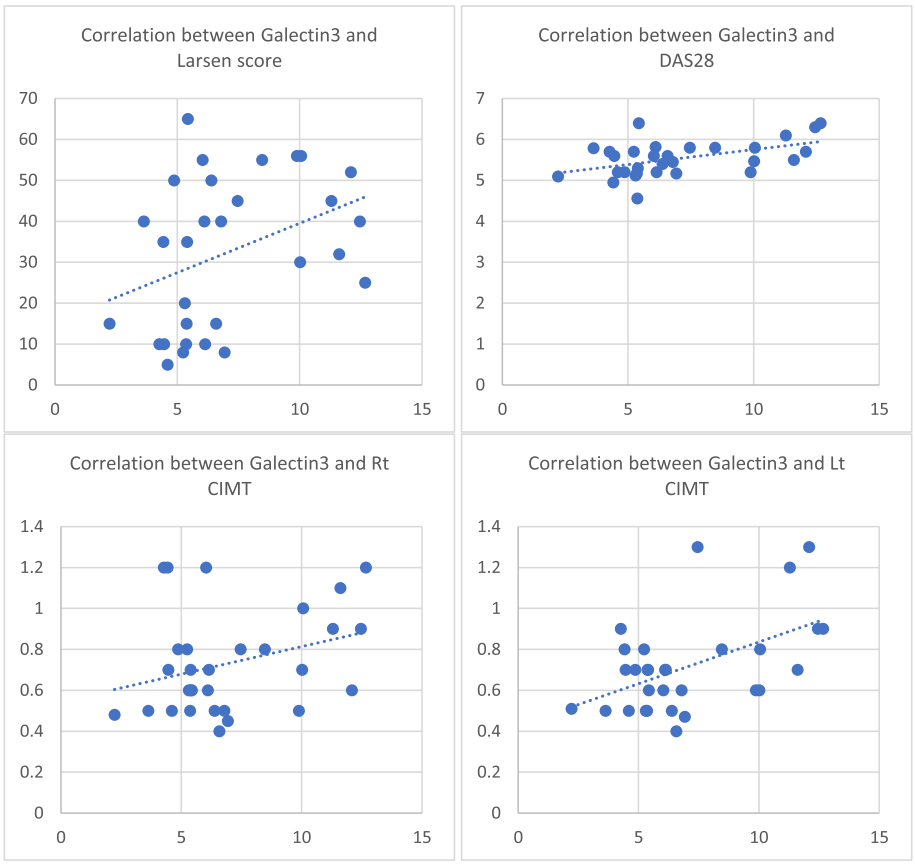

Fig. 2 Correlation between Galectin3 and severity, activity scores & CIMT in RA patients

A highly statistically significant positive correlation was observed between galectin-3 level and (RT CIMT, LT CMIT) (*P*-value <0.001). A statistically positive marked correlation was detected between galectin-3 level and (Modified Larsen score, DAS28) (*p*-value 0.026, 0.006, respectively). DAS28: disease activity score28, RT: right, LT: left, CIMT: carotid intima-media thickness

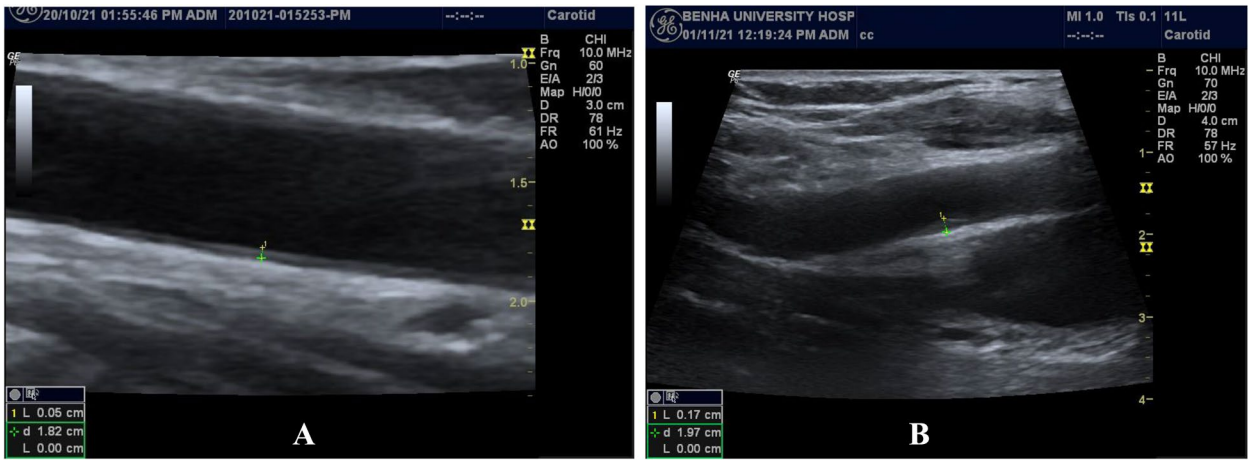

Fig. 3 Marked carotid intima medial thickness (CMIT) difference between **A**. normal control and **B**. RA patient

Marked carotid intima medial thickness (CMIT) difference between **A**. normal control measuring 0.5 mm and **B**. a patient with RA measuring 1.7 mm. The corresponding Gal-3 levels were 2.22 pg/ml for **A** and 12.67 pg/ml for **B**

Table 2 Correlation between CIMT and different variables

	Rt. CIMT		Lt. CIMT	
	r	*p*-value	*r*	*p*-value
Disease duration	0.377	0.040*	0.373	0.042*
Anti-CCP	0.185	0.327	0.130	0.493
RF	0.095	0.616	0.026	0.98
Larsen score	0.152	0.424	0.298	0.110
DAS28	0.296	0.112	0.422	0.020*

Anti-CCP anti-cyclic citrullinated peptide, *RF* rheumatoid factor, *DAS28* Disease Activity Score 28

0.5 mm and B. a patient with RA measuring 1.7 mm. The corresponding Gal-3 levels were 2.22 pg/ml for A and 12.76 pg/ml for B (Fig. 3).

A positive statistically marked correlation existed between mean Rt CIMT, Lt CIMT, and disease duration (*P*-value 0.040, 0.042, respectively). Moreover, there was a substantial positive correlation between LT CIMT and DAS28 score (*P*-value = 0.20). However, no substantial association was detected between mean Rt CIMT and Lt CIMT (anti-CCP, RF, and Larsen score) (*P*-value 0.327, 0.493, 0.616, 0.98, 0.424, 0.110, 0.112, respectively) (Table 2).

Univariate regression analysis reveals that age, Gal-3 level, disease duration, NTJ, NSJ, and Lt CIMT were significant predictors for RA activity. Conversely, the multivariate regression analysis shows that none of the variables was a significant predictor for RA activity (Table 3).

Discussion

The complex pathogenesis of RA involves the interaction of both adaptive and innate immune cells that generate anti-inflammatory and proinflammatory factors, inflammatory mediators, chemokines, and other chemicals affecting the patient's joints and synovial tissue [12].

Various members of the galectin family have effects on myeloid lineage cells and T and B lymphocytes and have demonstrated a negative or positive role in RA progression [13].

Despite the growing interest in Gal-3 as a biomarker for CVD, few studies have investigated its role in RA patients. To our knowledge, only two studies have studied the correlation between Gal-3 and CVD in RA patients, and they have yielded conflicting results. One study revealed that Gal-3 levels were more elevated in RA cases with CVD than those without, while the other study reported no significant difference [14].

In the current study, we found that the mean ± SD of Gal-3 was 7.05 ± 2.88. There were statistically significant differences between studied groups regarding Gal-3 serum level (*P*-value < 0.001). Consistent with our results, Ohshima et al. [15] illustrated that Gal-3 as well as its binding protein are overexpressed in RA synovial membranes, specifically at the cartilage invasion site. In addition, the levels of Gal-3 were elevated in synovial fluid and blood long-term RA cases compared to controls and osteoarthritis. Neidhart et al. [16] illustrated that Gal-3 was elevated intracellularly due to synovial fibroblast adhesion to cartilage oligomeric matrix protein (COMP) in RA patients. Inconsistent with our findings, Kaur et al. [17], Issa et al. [18, 19], and Baki et al. [20] reported that serum Gal-3 levels were substantially elevated in the RA group than in controls ($P < 0.001$). Moreover, Anyfanti et al. [21] reported that the variation in the levels of Gal-3 between RA and non-RA subjects was proven to be induced by cardiovascular comorbidities.

Conversely, Mendez-Huergo et al. [22] reported that RA cases demonstrated diminished Gal-3 concentrations compared to controls. However, Hu et al. [23] reported

Table 3 Regression analyses of various variables for prediction of rheumatoid arthritis disease activity

	Univariate analysis				Multivariate analysis			
	ß	*p*-value	95% *CI* of ß		ß	*p*-value	95% *CI* of ß	
Age	0.02	0.043*	0.000	0.031	0.01	0.600	−0.021	0.035
Sex	0.14	0.452	−0.229	0.500				
Galectin-3	0.07	0.006*	0.023	0.123	0.03	0.533	−0.056	0.105
Disease duration	0.02	0.049*	0.000	0.053	0.01	0.469	−0.023	0.048
NTJ	0.09	0.001*	0.041	0.140	0.06	0.094	−0.010	0.119
NSJ	0.17	0.004*	0.059	0.289	0.06	0.400	−0.087	0.211
ESR	0.006	0.066	0.000	0.012				
Rt CIMT	0.51	0.112	−0.126	1.135				
Lt CIMT	0.78	0.020*	0.132	1.430	0.09	0.869	−1.134	0.965

NTJ number of tender joints, *NSJ* number of swollen joints, *ESR* erythrocyte sedimentation rate, *RT* right, *LT* left, *CIMT* carotid intima-media thickness

no differences in Gal-3 levels between patients and controls in the Taiwanese population.

In concordance with our study, elevated levels of Gal-3 have been observed in case-control studies of various other autoimmune diseases, Ezzat et al. [24] in JIA cases, Koca et al. [25] in systemic sclerosis, Cao et al. [26] in ankylosing spondylitis, and Lee et al. [27] in Behcet's disease.

In this study, ROC curve analysis revealed that the Gal-3 could be an effective predictive test of RA diagnosis with 96.7% sensitivity and 95% specificity (*AUC*, 0.98 and 95% *CI*, 0.94–1.00).

Similarly, Gruszewska et al. [28] and Baki et al. [20] demonstrated that Gal-3 demonstrated elevated diagnostic sensitivity, specificity, and a discriminative value in RA, denoting its efficiency as a beneficial diagnostic marker. In addition, Mendez-Huergo et al. [22] illustrated that serum Gal-3 is a significant parameter for distinguishing RA cases from healthy individuals and differentiating between non-RA and pre-RA.

CIMT measurement is a potent as well as noninvasive cardiovascular event marker. Additionally, CIMT is regarded as an indicator of future vascular and subclinical atherosclerosis events. Research revealed that CIMT values in rheumatologic cases are considerably greater than in the general population. Specifically, RA is an independent risk factor for the development of CIMT [29].

In this study, highly statistically substantial differences were detected between studied groups regarding mean RT CIMT and LT CIMT. RT CIMT and LT CIMT were substantially elevated in the RA group than in the controls (P-value < 0.001). Furthermore, Özişler et al. [30] reported that CIMT (thickest and mean) were markedly elevated in the patients and substantially associated with age. Moreover, Alper et al. [31] meta-analysis reported that RA cases had a statistically higher CIMT.

In accordance with our findings, Alian et al. [32], Ebraheem et al. [33], Breda et al. [34], Głowińska-Olszewska et al. [35], Ilisson et al. [36], and Ahmad et al. [37] reported an elevated CIMT of the left and right carotid arteries among JIA cases as compared to healthy controls (with statistically substantial differences, P-value < 0.001). Conversely, Satija et al. [38] and Evenesen et al. [39] did not detect variations in IMT between healthy and JIA children.

This study showed a highly statistically positive significant correlation between Gal-3 level (mean LT CMIT, CIMT, tender joint numbers, swollen joint numbers, and ESR) (P < 0.001). A statistically positive substantial correlation was detected between the Gal-3 level and (Larsen score, DAS-28). There was no marked association between Gal-3 level and (disease duration, anti-CCP, and RF). In accordance with our findings, Gruszewska et al. [28] reported that Gal-3 concentration had a significant relationship with ESR (P = 0.004) in RA cases. Nonetheless, they reported that the correlation between DAS-28 as well as Gal-3 concentrations was not significant (P = 0.060). Similarly, Ayfanti et al. [21] reported a relationship between Gal-3 and both CIMT and arterial stiffness. Nevertheless, they revealed that Gal-3 was not correlated with disease-associated parameters in their study's RA population, including disease duration, inflammatory markers, and disease activity. Likewise, Baki et al. [20] revealed that Gal-3 correlated with ESR, TJC, DAS-28, and SJC but not with RF and anti-CCP.

In contrast, Issa et al. [18] reported that galectin-3 demonstrated a marked association with anti-CCP and DAS-28 but no correlation with SJC and TJC. Furthermore, Mendez-Huergo et al. [22] did not detect any correlation between concentrations of Gal-3 serum and DAS-28 and ESR score (P-value = 0.69and 0.31), respectively.

Consistent with our results, Ohshima et al. [15] demonstrated a positive correlation between galectin-3 and long-standing RA disease, supporting the hypothesis of Gal-3 as a structural joint damage mediator. Furthermore, Issa et al. [19] reported that Gal-3 is correlated with risk factors for erosive progression.

In this study, we detected a positive statistically marked relationship between mean disease duration, Lt CIMT, and Rt CIMT and a positive marked correlation between DAS-28 and LT CIMT score. However, there was no marked association between mean Lt CIMT and Rt CIMT and (Larsen score, anti-CCP, and RF). Consistent with our findings, Alian et al. [32] detected a substantial positive correlation between the JADAS-27 and Rt CIMT (P-value < 0.001). Nevertheless, they differed from our results as they found a negative correlation between CIMT and disease duration. Contrary to our results, Baki et al.' [20] study reported no significant correlation between CIMT and DAS-28.

Finally, our study's univariate regression analysis revealed that age, Gal-3 level, disease duration, NTJ, NSJ, and Lt CIMT were significant predictors for RA activity. In contrast, multivariate regression analysis reveals that none of the variables was a reliable predictor for RA activity.

Further larger-scale longitudinal studies are warranted to explain role of galectin-3 in RA pathogenesis and its role in cardiovascular involvement. Limitation of the study was as follows: DM was excluded by history taking and FBS assessment, but we recommend further evaluation of HbA1C.

Conclusion

Our findings revealed the involvement of Gal-3 in disease severity as well as disease activity in RA patients. RA leads to an elevated intima-media thickness linked to the disease duration, and Gal-3 would be a predictor of cardiovascular involvement in RA patients.

Abbreviations

RA	Rheumatoid arthritis
DAS-28	Disease activity score
CIMT	Carotid intima-media thickness
RT	Right
LT	Left
CVD	Cardiovascular disease
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor-alpha
DM	Diabetes mellitus
FBS	Fasting blood sugar

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Authors' contributions
Idea suggestion and study design, AFS, ASA, ASMAT, and M"MH"F. Data collection and analysis, SAH, ASA, M"MH"F, and SMAT. Manuscript writing and final revision, ASA, SAH, and AFS.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
An informed written consent was taken from all patients and subjects participating in this study, and the protocol was approved by the ethical committee of Benha Faculty of Medicine no. MS 28.4.2021.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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