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Serum Galectin-3 Level in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-analysis

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by synovial tissue transformation and fibroblast-like synoviocyte (FLS) proliferation. Galectin-3 is gaining attention as a diagnostic and prognostic biomarker for RA diagnosis. Elevated levels of Galectin-3 cause RA-FLSs to stimulate and generate proinflammatory agents, contributing to cartilage degradation and osteoclast formation. This systematic review and meta-analysis aimed to evaluate published evidence and support future investigation of Galectin-3 as an early biomarker for RA.

A systematic search was performed through four databases, including PubMed, the Web of Science, Scopus, and Embase, to find the studies examining Galectin-3 in individuals with RA compared to healthy controls. The risk of bias was evaluated using the Newcastle-Ottawa Quality Assessment Scale. Random-effects meta-analysis comparing serum/plasma Galectin-3 levels between individuals with RA and healthy control groups was performed to determine the standardized mean differences (SMD) along with 95% confidence intervals.

Following the initial search, studies went through screening. 12 studies, involving 773 patients with RA and 411 healthy controls, were included. Meta-analysis of the included studies revealed that individuals with RA had significantly higher levels of circulatory Galectin-3 compared to healthy control groups (SMD 0.957, 95% CI 0.393 to 1.520). Univariable meta-regression showed no significant association between age, publication year, sample size, or the male percentage with effect size.

According to the results, Galectin-3 might be useful as a biomarker for RA. To support these findings, further investigations of Galectin-3 as a possible early biomarker of RA is necessary.

Keywords: Inflammation; Galectin-3; Rheumatic diseases; Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic immune-mediated rheumatic disease that manifests as a symmetrical polyarthritis with stiffness, swelling, and pain in the joints.[1,2] This inflammatory disease is

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associated with relatively high morbidity and premature death.[1] The age-standardized global prevalence rate of RA was around 209 cases per 100,000 people in 2020, with an estimated 17.6 million individuals globally suffering from RA.[1] RA is characterized by a structural transformation of the synovial tissue and proliferation of fibroblast-like synoviocytes (FLSs), which are the core component of the synovial membrane.[2] Through their interactions with immune cells, activated RA-FLSs are increasingly recognized as key players in modifying the synovium and developing RA-related synovial pathologies.[3]

Complications of this disease significantly decrease the quality of life (QoL) in individuals with RA and may even increase their risk of mortality related to the disease.[4] The primary objectives of therapy for RA complications are to manage extra-articular complications and reduce the activity of the disease. Complications are typically strongly associated with prognosis, and necessitate early diagnosis and active treatment.[5] Thus, scientists are identifying biomarkers that might result in an earlier diagnosis, severity assessment, and even more effective therapies for RA.[6]

Galectin-3 (Gal-3) is a member of the β-galactoside binding lectins, possessing only one conserved carbon recognition domain (CRD) and one non-lectin N-terminal domain (ND).[7] Gal-3, the only chimera-type galectin, differs structurally from other galectins, which allows it to oligomerize.[7,8] Gal-3 demonstrates a distinct pleiotropic activity, contributing significantly to numerous physiological and pathological procedures in various tissues.[8] Gal-3 is gaining attention as a diagnostic and prognostic biomarker, as well as a potential new therapeutic target, due to the important roles it plays in many types of diseases.[8,9]

Gal-3 distinguishes itself from other galectins by its significant correlation with the RA pathophysiology influencing the inflammatory characteristics of FLSs, immune cells, and Osteoclasts.[10,11,12,13,14] Unlike Galectin-1, which acts as a negative immune response regulator in RA, substantial evidence suggests that Gal-3 serves as a proinflammatory agent in RA in both humans and animal models.[14,15,16] It has been demonstrated that elevated Gal-3 levels cause RA-FLSs to become stimulated and generate various proinflammatory agents.[17,18] Additionally, studies indicate that Gal-3 contributes to cartilage degradation and induces the expression of matrix metalloproteinase 3 (MMP3).[17,19] Moreover, this galectin can promote the formation of osteoclasts while preventing osteoblast development.[12,13] Due to its significant role in RA pathogenesis, Gal-3 has also been proposed as a biomarker for RA diagnosis.[20]

Given the potential for diagnostic and prognostic properties of Gal-3 as a biomarker of RA, this systematic review and meta-analysis aim to thoroughly evaluate the published evidence regarding Gal-3 circulating levels in RA patients to reduce uncertainty surrounding the role of this galectin in RA. Furthermore, we aim to support a future investigation of Gal-3 as a possible early biomarker of RA. To date, the authors have not identified any systematic reviews and meta-analyses of literature linking galectin-3 levels and RA.

MATERIALS AND METHODS

Search Strategy

The PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed in the conduct of this systematic review and meta-analysis.[21] Four international databases, including PubMed, Embase, Scopus, and the Web of Science were comprehensively searched until 18 February 2024. The primary keywords included terms related to "rheumatoid arthritis" AND "galectin-3". Supplementary Table 1 shows the exact search queries and the number of records used in each database. The proposal of this systematic review is registered on the International Prospective Register of Systematic Reviews (PROSPERO) with registration code CRD42024533695.

Inclusion and Exclusion Criteria

The inclusion criteria were original studies that assessed 1) serum/plasma galectin-3 levels in individuals with RA and healthy controls, 2) the diagnostic role of galectin-3 serum/plasma levels in RA, and 3) the association between peripheral levels of galectin-3 and RA prognosis. Non-English studies, non-original articles, review studies, case reports, and meeting abstracts were excluded.

Screening and Data Extraction

Following the search, all results were imported into the EndNote 20 software for screening. First, duplicates were removed using "find duplicates" within this software. Afterward, 2 independent reviewers (MM and

RA) screened the included studies based on titles and abstracts. Following this step, full texts were screened independently to find studies that met our inclusion/exclusion criteria. Disagreements were resolved through discussion with a third person (AK).

A predefined Excel sheet was created for the data extraction. This sheet contained the following columns: first author, study country, sample size (total, RA, and controls), population characteristics for each group, mean age and sex distribution in each group, area under the curve (AUC), sensitivity, and specificity for diagnostic studies, main findings, and the mean and standard deviation of plasma/serum levels of galectin-3 for all individuals.

Risk of Bias Assessment

The risk of bias was independently assessed in the studies utilizing the "Newcastle-Ottawa Quality Assessment Scale" (NOS) (22) for observational research by two reviewers (MM and RA). The three primary areas of bias risk in the NOS system are outcome, selection, and comparability. The attributes of "very good", "good", "satisfactory", and "unsatisfactory" were assigned ratings of 9–10, 7–8, 5–6, and less than 5, respectively.

Statistical Analysis

All analyses were performed in R (R version 4.0.1, http://www.r-project.org). We conducted a random-effects meta-analysis (restricted maximum likelihood, REML) to compare serum/plasma galectin-3 levels between individuals with RA and healthy controls by calculating the standardized mean difference (SMD) and its 95% confidence interval (CI). In pooling galectin-3 levels, if median and interquartile ranges (IQR) were stated for serum/plasma galectin-3 levels, we utilized the methods by Luo et al, and Wan et al, to transform them to the mean and standard deviation (SD).[23,24] In addition, means and SDs were combined using the Cochrane Handbook formulas.[25] A *p* value of less than 0.05 was deemed statistically significant in all analyses.

The heterogeneity among the included studies in the meta-analysis was assessed using Higgins' I-square test based on Cochrane's *Q*. Studies were classified as having low, moderate, or high heterogeneity if their heterogeneity was ≤25%, 26% to 75%, or ≥75%, respectively. To find the cause of heterogeneity, meta-regression was employed, taking into account the sample size, mean age, male percentage, and publication year. The Galbraith plot was used to identify studies that were outliers. The sensitivity analysis was performed using "leave-one-out" in R to reperform the meta-analysis by removing one study. Lastly, Egger's statistical test and a visual inspection of funnel plots were performed to evaluate publication bias.[26]

RESULTS

Literature Search and Included Studies

The initial search resulted in 1168 records, comprised of 202 records from PubMed, 313 results from Scopus, 326 studies from the Web of Science, and 327 studies from Embase. After removing duplicates (n=542), these results went through title/abstract screening at which stage 35 studies remained. Among these, 12 were selected based on full-text screening to be included in the systematic review.[11,12,18,20,27,28-34] Figure 1 depicts the search results and screening process with a PRISMA flowchart.

Table 1 illustrates the characteristics of the included studies. Among these 12 studies, four were conducted in Denmark[12,30,31,33] and two were conducted in Greece,[28,29] and the United States.[27,32] Publication years ranged from 2003 to 2024. A total of 1184 individuals were included, comprised of 773 patients with RA and 411 healthy controls. Table 1 also indicates the main findings of each study. Based on NOS criteria, all studies had high quality, details of which are shown in Table 2.

Table 1. Characteristics of studies evaluating Galectin-3 levels in patients with RA

Author	Year	Design	Location	Population	Sample size	Groups	Mean Age (years)	% Female	Main Findings
Andonian et al	2018	Cross-sectional	United States	Previously sedentary patients with RA based on 1987 ACR criteria with no previous medications or prednisolone 5 mg or less and exercising<2 days per week/ cohort of patients with prediabetes (HBA1C 5.6-6.5%) who underwent similar exercise training/age-gender- and BMI-matched healthy controls	21	RA (HIIT):12 Prediabetes (HIIT):9	RA (HIIT): 63.9±7.2 Prediabetes (HIIT): 71.4±4.9	RA (HIIT): 91.6 Prediabetes (HIIT):55.6	Plasma Gal-3 was significantly higher in older people with RA, compared to age-, gender-, and BMI-matched controls (8.80±3.5 vs. 6.89±1.9 ng/mL, p=0.042). Patients with RA had higher plasma Gal-3 compared with prediabetic cases before HIIT.
Anyfanti et al	2018	Cross-sectional	Greece	Patients with diagnosis of RA based on 1987 ACR criteria/ healthy volunteers	124	RA: 85 Controls: 39	RA: 60.6 ± 11.9 Control: 57.2 ± 8.6	RA: 76.9 Control: 83.5	Blood Gal-3 was significantly higher in patients with RA, compared with controls (17.7 [9.8-33.5] vs. 9.1 [6.0-12.0] ng/dL, p<0.001)
Anyfanti et al	2023	Case-control	Greece	Adult patients with RA based on 1987 revised ACR criteria at remission or with low disease activity/ non-RA individuals	48	RA: 24 Controls: 24	RA: 54.6 ± 9.6 Controls: 52.1±7.5	RA: 22.5 Controls: 20.8	Patients with RA had increased levels of circulating Gal-3 compared with controls (6.9 ± 6.7 vs. 4.6 ± 4.7 ng/dL, p=0.015)
Gruszewska et al	2020	Cross-sectional	Poland	Patients with RA based on ACR 2010 criteria/ healthy subjects	112	RA: 82 Control: 30	RA: 58.8 [range 20-85] Controls: 25 [range 21-54]	RA: 84.1 Controls: 63.3	RA patients had increased levels of Gal-3 when compared with controls (18.75 [range 3.8-50.3] vs. 9.45 [range 7.3-15] ng/mL, p<0.001). Gal-3 had an AUC of 0.911 with sensitivity and specificity of 71.1% and 95%, respectively.

Table 1. Continued...

Author	Year	Design	Location	Population	Sample size	Groups	Mean Age (years)	% Female	Main Findings
Issa et al	2015	Prospective cohort	Denmark	Newly diagnosed RA patients based on 1987 ACR criteria (DMARD naïve and disease duration less than 6 months) [ERA]/long-standing RA [LRA] with erosions on X-ray in at least one joint	Circadian cohort: 35 Exercise cohort: 34	Circadian ERA: 11 LRA: 10 Controls: 14 Exercise: ERA: 10 LRA: 10 Controls: 14	Circadian ERA: 63[38-72] LRA: 61.5 [54-65] Controls: 47 [45-49] Exercise: ERA: 45.5 [38-52] LRA: 54 [50-55] Controls: 49.5 [38-55]	Circadian ERA: 72.7 LRA: 70 Controls: 71.4 Exercise: ERA: 80 LRA: 70 Controls: 71.4	In circadian variation cohort, patients with ERA and LRA had higher levels of gal-3, compared to healthy controls (6.03 [4.44-7.61] and 5.95 [4.44-7.47] vs. 4.51 [3.48-5.53] µg/L, p=0.08 for both comparisons). In physical exercise group, LRA group (Gal-3: 6.18 [4.46-7.89] µg/L) had significantly higher levels than controls (4.00 [3.10-4.91] µg/L) (p <0.01). However, there was no difference between ERA (4.27 [3.32-5.30] µg/L) and controls (P = 0.68). Following exercise, gal-3 increased by 9%, 15%, and 10% in controls, ERA, and LRA groups.
Issa et al	2017	Prospective cohort	Denmark	Newly diagnosed RA patients based on 1987 ACR criteria (<6 months duration) and DMARD naïve/ self-reported healthy blood donors aged 20-70 years	279	RA: 160 (Anti-CCP positive: 93, Anti-CCP negative: 67) Controls: 119	RA: 53 [42-63] Anti-CCP positive: 53 [44-60] Anti-CCP negative: 52 [38-65]	RA: 66.9 Anti-CCP positive: 63.4 Anti-CCP negative: 71.6	While gal-3 was higher in RA patients, this was not statistically significant (4.2 [3.2-5.7] vs. 3.8 [3.0-4.8], p=0.06). Gal-3 had significant correlations with smoking, anti-CCP status, CRP, and HAQ.
Lee et al	2007	Cross-sectional	South Korea	Patients with active RA/age- and sex-matched healthy controls	70	RA: 20 Controls: 50	RA: 52.5±1.7	RA: 95	Serum gal-3 was significantly higher in RA patients, compared with healthy controls.
Mendez-Huergo et al	2018	Cross-sectional	Argentina	Established RA patients (ACR 2010)/ sex-, and age-matched healthy controls	77	RA: 48 Control: 29	NR	NR	Patients with RA had significantly lower levels of circulatory gal-3, compared with controls. Also, higher gal-3 levels were associated with higher disease activity (p=0.0037) and HAQ score (p=0.0098). Gal-3 had AUC of 0.88 for discrimination of RA from controls (sensitivity: 80%, specificity: 73.3%)

Table 1. Continued...

Author	Year	Design	Location	Population	Sample size	Groups	Mean Age (years)	% Female	Main Findings
Nielsen et al	2023	Cross-sectional	Denmark	Patients aged >17 years with diagnosis of RA based on EULAR/ACR 2010 criteria who had disease duration of less than 6 months (mean 3 months) with moderate-to-severe disease/ chronic RA/healthy controls	164	Early RA: 98 Chronic RA: 18 Controls: 48	Early RA: 56 [46-65] Chronic RA: 47 [37-61] Controls: 49 [45-58]	Early RA: 73 Chronic RA: 70 Controls: 57	Patients with early RA and chronic RA had significantly higher levels of gal-3, compared with healthy controls. Baseline gal-3 correlated with number of swollen joints (p<0.01).
Nussdorf et al	2024	Cohort	United States	RA patients diagnosed based on EULAR/ACR 2010 criteria.	124	Gal-3 first tertile: 42 Gal-3 second tertile: 42 Gal-3 third tertile: 42	All: 56.5±12.26 Gal-3 first tertile: 51.76 ± 13.38 Gal-3 second tertile: 55.07±11.43 Gal-3 third tertile: 57.10±11.55	Gal-3 first tertile: 73.81 Gal-3 second tertile: 85.37 Gal-3 third tertile: 85.37	In univariable analysis, older age, race, longer RA disease duration, current prednisone use, type of treatment, higher triglyceride level, presence of diabetes, and higher levels of ascending aorta inflammation as measured by SUV were all associated with increased gal-3 levels. In multivariable analysis, higher galectin-3 level remained significantly associated with greater arterial inflammation as measured by SUV MDS max in the ascending aorta, after adjusting for treatment type and BMI.
Ohshima et al	2003	Case-control	Switzerland	RA patients based on revised ACR 1987 criteria	40	RA: 20 Controls: 20	NR	NR	Serum gal-3 was significantly higher in RA patients, compared with healthy controls (p<0.001). Serum gal-3 had significant association with CRP levels.
Pedersen et al	2023	Cross-sectional	Denmark	Patients with RA/healthy controls	56	RA: 41 Controls: 15	RA: 52.3 ±4.51 Controls: 40.5 ±7.76	RA: 67.5 Controls: 53.3	There was no significant difference between RA and controls in terms of plasma gal-3 levels.

Data are presented as mean±standard deviation, median [interquartile range], or percentage. RA: rheumatoid arthritis; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; HBA1C: hemoglobin A1C; HIIT: high-intensity interval training; DMARD: disease-modifying antirheumatic drugs; CRP: C-reactive protein; HAQ: health assessment questionnaire; SUV: standardized uptake values; BMI: body mass index; AUC: area under the receiver operating characteristic curve; CI: confidence interval; NR: not reported

Table 2. Qualities of included studies based on Newcastle-Ottawa Quality Assessment Scale (NOS)

Study	Selection				Comparability	Outcome		Overall Score
	Representation	Sample size	Non-Respondents	Exposure		Outcome	Statistical test	
Andonian et al (2018)	*	*	*	*	**	**	*	10
Anyfanti et al (2018)	*	*	*	*	-	**	*	8
Anyfanti et al (2023)	*	*	*	*	-	**	*	8
Gruszewska et al (2020)	*	*	*	*	-	**	*	8
Issa et al (2015)	*	*	*	*	-	**	*	8
Issa et al (2017)	*	*	*	*	-	**	*	8
Lee et al (2007)	*	*	*	*	**	**	*	10
Mendez-Huergo et al (2018)	*	*	*	*	**	**	*	10
Nielsen et al (2023)	*	*	*	*	-	**	*	8
Nussdorf et al (2024)	*	*	*	*	-	**	*	8
Ohshima et al (2003)	*	*	*	*	-	**	*	8
Pedersen et al (2023)	*	*	*	*	-	**	*	8

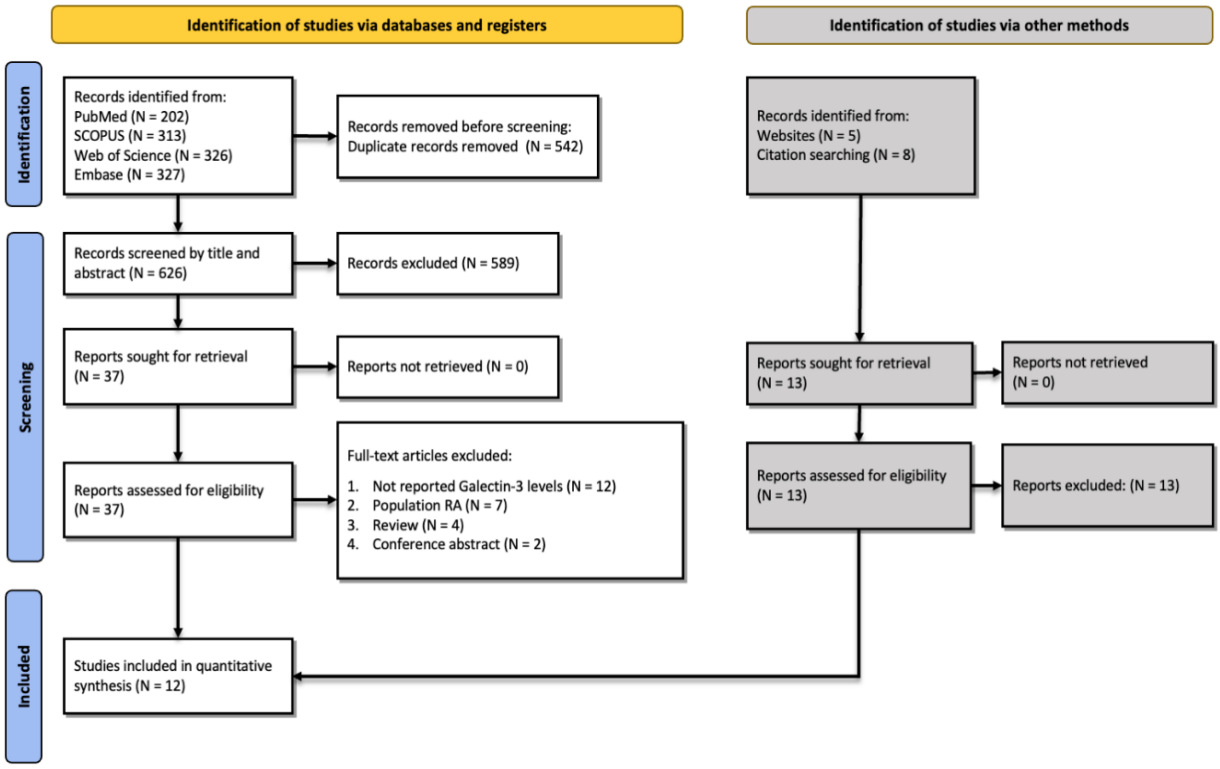

Figure 1. The PRISMA flowchart of the identification, screening, and inclusion of the studies evaluating circulatory Galectin-3 levels in patients with rheumatoid arthritis.

Gal-3 in Patients with RA vs. Healthy Controls

According to the random-effects meta-analysis performed on the nine studies, it has been shown that circulatory Gal-3 was significantly higher in patients with RA, compared with healthy individuals (SMD 0.957, 95% CI 0.393 to 1.520, p=0.0009). As shown in a forest plot in Figure 2, the heterogeneity was high in this analysis (I^2: 87.1%). After removing the outlier study, Lee et al,[34] the same higher serum Gal-3 levels were observed in individuals with RA (SMD 0.671, 95% CI 0.416 to 0.925, p<0.0001). The forest plot for this analysis is demonstrated in Supplementary Figure 1.

Supplementary Figure 2 shows sensitivity analysis by the leave-one-out method. The removal of none of the studies had a significant impact on the overall effect size. Publication bias was assessed using a funnel plot by trim and fill method. As shown in Supplementary Figure 3, there was no significant asymmetry in the funnel plot. Moreover, Egger's test did not demonstrate any significant publication bias (Intercept=4.219, 95% CI 0.14 to 8.58, t=1.898, p=0.113).

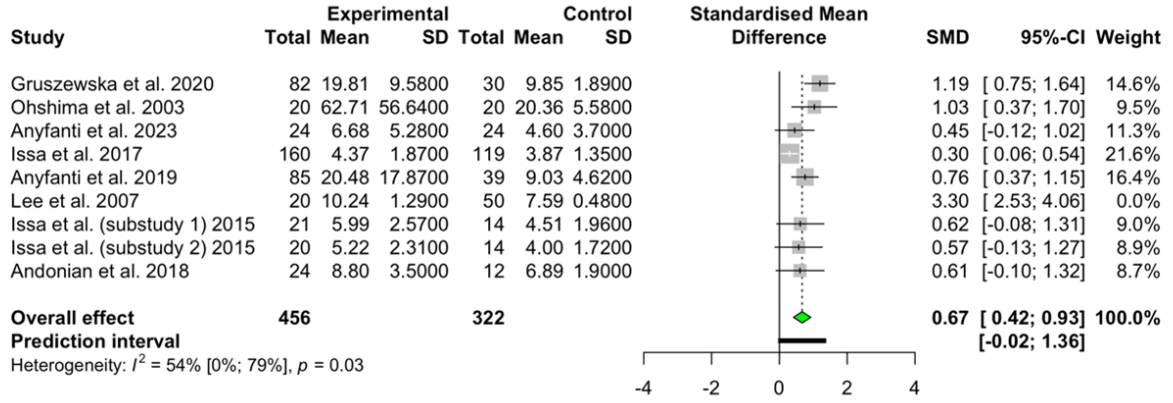

Figure 2. Forest plot comparing circulatory Galectin-3 levels in patients with rheumatoid arthritis versus healthy controls. SMD: standardized mean difference; standard deviation; CI: confidence interval

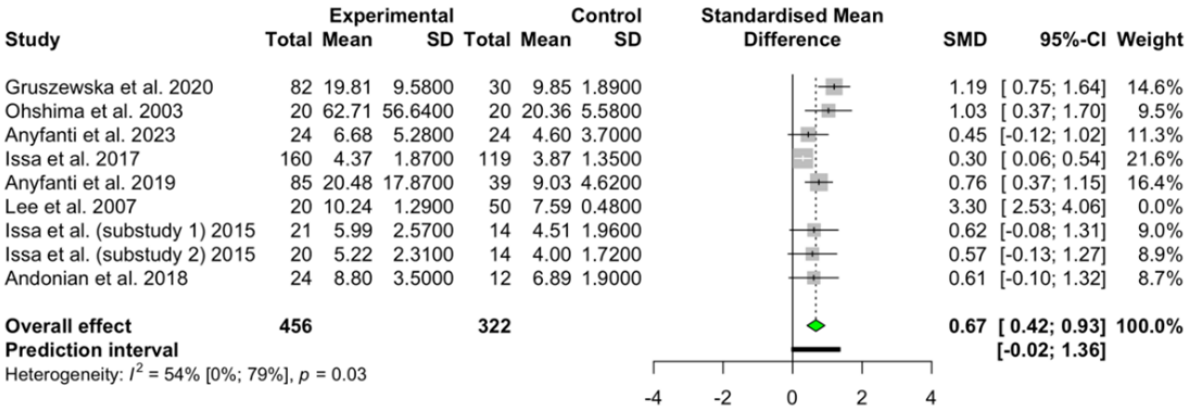

Figure 3. Forest plot comparing circulatory Galectin-3 levels in patients with rheumatoid arthritis vs. healthy controls after removal of outlier studies. SD: standard deviation; SMD: standardized mean difference; CI: confidence interval

For assessment of the effect of each variable on the effect size observed, univariate meta-regression was performed. As shown in Table 3, none of the age, publication year, sample size, and male percentage had a significant association with the effect size. Bubble plots are presented in Supplementary Figures 4–7. The publication year and male percentage accounted for 23.25% and 14.20% of the heterogeneity, respectively.

Diagnostic Ability of Gal-3 for RA

The diagnostic ability of Gal-3 for RA has been investigated in two studies.[11,20] Gruszewska et al,[20] assessed 82 patients with RA and compared their results with those of 30 healthy controls. At a threshold of 15 ng/mL, Gal-3 demonstrated an AUC of 0.911 for the diagnosis of RA, with a sensitivity and specificity of 71.1% and 95%, respectively. Moreover, a positive predictive value (PPV) of 98.2% and a negative predictive value (NPV) of 46.3% were reported in this study. Similarly, Gal-3 discrimination power for distinguishing RA from healthy controls was assessed in the Mendez-Huergo et al.[11] The AUC of Gal-3 was reported to be 0.88 with a sensitivity of 85.42% and a specificity of 71.43%.

Association of Gal-3 with Vascular Inflammation in Patients with RA

Anyfanti et al, (2019)[28] examined the association between Gal-3 levels and hemodynamic variables. In this study, a strong association was reported between Gal-3 levels and both pulse wave velocity (PWV) and carotid intima-media thickness (cIMT) in individuals with RA. Similarly, there was a considerable relation between serum Gal-3 with central systolic blood pressure and peripheral pulse pressure. In another investigation by Anyfanti et al, (2023)[29] Gal-3 was associated with PWV and subendocardial variability ratio (SEVR). Nussdorf et al,[32] demonstrated that higher Gal-3 levels were related to higher 18Fluorodeoxyglucose aortic standardized uptake values as a marker of aortic inflammation.

Association of Gal-3 and Serum Inflammatory Markers in RA

Based on Gruszewska and colleagues' findings,[20] there was a positive association between Gal-3 level and erythrocyte sedimentation rate (ESR). Similarly, as reported by Ohshima et al,[18] serum Gal-3 was associated with C-reactive protein (CRP) levels. Regarding anti-CCP seropositivity; patients who tested positive for anti-CCP had higher levels of Gal-3, compared to seronegative patients.[31] It was also shown that Gal-3 levels were related to anti-CCP status and CRP levels.[31]

Effect of Exercise on Gal-3 in Patients with RA

Andonian et al,[27] measured Gal-3 levels in individuals with RA before and after high-intensity interval training (HIIT) and showed that mean levels of Gal-3 were not affected by HIIT. However, significant increases in Gal-3 levels were observed in patients with early RA and long-standing RA, with increases of 15% and 10%, respectively.

Table 3. Meta-regression analysis for meta-analysis of Galectin-3 levels in patients with rheumatoid arthritis vs. healthy controls

Moderator	No. of Comparisons		Meta-regression				R^2 Analog (proportion of variance explained)
	RA	Control	Slope	95% CI		*p*	
Mean Age (years)	412	290	-0.042	-0.265	0.181	0.710	0%
Publication Year	456	322	-0.076	-0.161	0.009	0.079	23.25%
Male percentage	412	290	0.017	-0.006	0.040	0.153	14.20%
Sample Size	456	322	-0.005	-0.017	0.007	0.408	0%

RA: Rheumatoid arthritis; CI: confidence interval

DISCUSSION

The emerging role of Gal-3 as a crucial mediator in rheumatologic diseases, such as RA, influencing disease progression and clinical outcomes in addition to heterogeneity between the results of studies investigating Gal-3 levels in patients urged us to conduct this systematic review and meta-analysis. In summary, the results of our meta-analysis indicated that individuals with RA had significantly higher levels of Gal-3 compared to healthy controls. Due to the high level of interstudy heterogeneity, we implemented cautionary measures, including the trim-and-fill method and the analysis excluding outliers, which did not alter the significance of the results. Moreover, meta-regression results did not demonstrate any significant association between the calculated effect sizes and the suspected confounders including age, the percentage of male participants, publication year, or sample size.

Although it is commonly recognized as a novel cardiac biomarker in the general population[35] and especially in patients with heart failure, Gal-3 is a multifunctional β-galactoside binding protein involved in various biological processes and diseases. It plays a significant role in rheumatologic diseases such as SLE and RA and involved in immune responses, inflammation, and fibrosis.[11,36,37] In this context, findings of the included studies[28,29,32] have shown that Gal-3 levels in the context of RA had strong associations with hemodynamic variables like blood pressure, PWR, and SEVR as well as markers of vascular inflammation like cIMT which may increase the risk of cardiovascular incidents in these patients. Moreover, previous investigations suggest that measuring Gal-3 serum concentration could serve as a valuable indicator of active fibrosis in the progression of rheumatic diseases.[38,39] Similarly, studies have indicated an association between elevated levels of serum Gal-3 and both inflammatory conditions and rheumatologic disorders.[39,40]

The results of this meta-analysis demonstrated increased serum concentration of Gal-3 in RA patients than in healthy controls which has been proposed to have a noteworthy role in the pathogenesis of this disease. It is well-established that RA-FLSs have a crucial role with central players of inflammation within the joint affected by RA and are a significant origin of extracellular Gal-3.[33] In addition, the attachment of RA-FLSs to cartilage oligomeric matrix protein (COMP), which was coated to the cell culture plates, was observed to enhance the intracellular level of Gal-3.[41] Conversely, after being exposed to TNF-α, resulted in a reduction of intracellular galectin-3 levels.[41] Similar findings support an association between Gal-3 and the functionality of differentiated osteoclasts and aggressive FLSs within the inflammatory synovial environment of RA acting via pathways such as activation of programmed death-1 (PD-1) receptors, thereby facilitating bone erosions.[12,33] Therefore, it has been proposed that the administration of the Gal-3 inhibitor has the potential to impede the link between Gal-3 and PD-1, consequently leading to a reduction in the activation levels of T cells and osteoclasts leading to decreased disease activity.[33,42]

However, it should be noted that while early investigations in both murine models and human subjects suggested a positive association between levels of Gal-3 and joint inflammation.[14,18,31] Gal-3 did not exhibit any connection with indicators of disease activity related to RA or broader systemic inflammation in the study by Nussdorf et al,[32] Consistent with their results, Anyfanti et al, did not detect any link between Gal-3 levels and erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or Disease Activity Score (DAS) in their cohort, all of whom were undergoing treatment with disease-modifying antirheumatic drugs (DMARDs).[28] Patients with positive anti-CCP also had higher Gal-3 compared to negative ones.[31] Conversely, in the study by Oshima et al, a positive relationship was identified between circulating Gal-3 levels and CRP.[18] However, crucial information regarding the subjects' treatment status was omitted in the publication, and this study was conducted nearly twenty years ago with a relatively limited sample size, during a period when choices for biologic DMARDs were constrained.[18] Similarly, Mendez-Heurgo et al, did not establish an association between Gal-3 serum levels and various metrics of RA activity, such as ESR, DAS-28, or Visual Analog Scale (VAS), among their participants, all of whom were administered at least one DMARD.[11]

Understanding the various and even contrasting roles of Gal-3 is important, as its impact appears to rely on the surrounding microenvironment, specific disease type, and possibly the extent of ligand-induced Gal-3 multimerization.[33] Within RA, Gal-3 is mostly linked to the severity of the disease and the presence of inflammation, whereas a contrasting outcome has been noted in various forms of cancer. In neoplasia, the presence of Gal-3 in the tumor microenvironment has been demonstrated to exert immunosuppressive

properties, thereby facilitating the evasion of immune surveillance by the tumor.[43,44] Additionally, while previous studies have presented that there are independent relationships between higher levels of Gal-3 and higher inflammation based on sex and race in RA and non-RA studies,[32,45] our meta-regression analysis did not indicate any significant influence of age and sex on calculated effect sizes.

The challenge of diagnosing rheumatic diseases, particularly in their initial phases caused growing interest in identifying circulating biomarkers that could aid in the early detection of rheumatic disorders and provide insights into their progression. Accordingly, two studies by Gruszewska et al,[20] and Mendez-Heurgo et al,[11] investigated the diagnostic ability of Gal-3 in RA, which revealed promising performance for this marker with desirable sensitivity and specificity. In this context, risk assessment in patients with RA is progressively gaining significance in enhancing the effectiveness of treatment outcomes.[12] The question revolves around the potential of Gal-3 measurements to assist in making decisions regarding treatment options. For instance, the study by Andonian et al,[27] evaluated the response of Gal-3 levels in patients with RA to HIIT, which shows the potential for Gal-3 to be applied prognostically.

This study had several limitations that should be addressed. The relatively low number of eligible studies included in the current systematic review is the main shortcoming that limited the ability to perform subgroup analyses which might diminish the generalizability of the findings. Furthermore, the lack of specific prognostic indicators constrained our ability to argue for the appropriateness of Gal-3 as a prognostic biomarker in RA. Moreover, despite the significantly elevated levels of Gal-3 observed in this meta-analysis, the diagnostic efficacy of Gal-3 remains undetermined. Only studies reporting serum levels of Gal-3 in patients with RA were included in the current review. However, integrating findings from studies measuring gene expression and tissue expression of Gal-3 in these individuals may provide a more comprehensive interpretation of the results. Although the meta-analysis was conducted meticulously accounting for potential confounders using tools like meta-regression, the high level of heterogeneity indicates that the results should be interpreted cautiously.

The findings of the current systematic review and meta-analysis indicated significantly higher serum levels of Gal-3 in individuals with RA compared to healthy controls which highlights the potential diagnostic and prognostic properties of this protein as an early biomarker of RA that can even be further investigated as a therapeutic target in reduction of disease activity. However, further evidence is needed to support these hypotheses, along with the identification of possible pitfalls, such as specific confounders or comorbidities.

STATEMENT OF ETHICS

This study exclusively utilized data from previously published articles and did not involve any new data collection. As such, ethics committee approval was not required.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

Data Availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

AI Assistance Disclosure

Not applicable.

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