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Original Research Article

Association between Serum Galectin-3 Levels and Left Ventricular Remodeling in Heart Failure with Reduced Ejection Fraction

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Abstract

Background: Heart failure with reduced ejection fraction (HFrEF) is characterized by progressive left ventricular (LV) remodeling driven by maladaptive fibrotic and inflammatory processes. Galectin-3 (Gal-3), a β-galactoside-binding lectin implicated in myocardial fibrosis and inflammation, has emerged as a promising biomarker for risk stratification in heart failure. However, the precise relationship between circulating Gal-3 concentrations and echocardiographic parameters of LV remodeling across varying HFrEF severities remains insufficiently characterized.

Methods: This cross-sectional analytical study enrolled 286 patients with established HFrEF (left ventricular ejection fraction [LVEF] ≤40%) at a tertiary cardiac center. Serum Gal-3 levels were quantified using enzyme-linked immunosorbent assay (ELISA). Comprehensive transthoracic echocardiography was performed to assess LV end-diastolic volume index (LVEDVi), LV end-systolic volume index (LVESVi), LV mass index (LVMi), LVEF, left atrial volume index (LAVi), and global longitudinal strain (GLS). Correlation and multivariable regression analyses were performed to evaluate associations between Gal-3 and remodeling parameters.

Results: The median serum Gal-3 level was 21.4 ng/mL (IQR: 15.8–29.6). Patients in the highest Gal-3 tertile (>26.2 ng/mL) demonstrated significantly greater LVEDVi (118.4 ± 32.6 vs. 86.2 ± 24.8 mL/m²; $p < 0.001$), LVMi (148.6 ± 38.4 vs. 112.8 ± 28.6 g/m²; $p < 0.001$), and worse GLS (−8.2 ± 2.4% vs. −12.6 ± 3.1%; $p < 0.001$) compared to the lowest tertile. In multivariable analysis, Gal-3 remained independently associated with LVEDVi ($\beta = 0.34$; $p < 0.001$), LVMi ($\beta = 0.31$; $p < 0.001$), and GLS ($\beta = 0.28$; $p = 0.001$) after adjustment for age, NT-proBNP, estimated glomerular filtration rate, and NYHA functional class.

Conclusion: Elevated serum Gal-3 levels are independently associated with adverse LV remodeling parameters in HFrEF patients, suggesting that Gal-3 may serve as a clinically informative biomarker reflecting the degree of myocardial structural deterioration beyond conventional markers.

Keywords: Galectin-3; heart failure; reduced ejection fraction; left ventricular remodeling; cardiac fibrosis; biomarker; echocardiography.

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Introduction

Heart failure represents one of the most significant global public health challenges, affecting an estimated 64 million individuals worldwide and accounting for substantial morbidity, mortality, and healthcare resource consumption [1]. Heart failure with reduced ejection fraction, defined by a left ventricular ejection fraction of 40% or less, constitutes approximately half of all heart failure cases and is characterized by impaired systolic contractile function with progressive chamber dilatation and geometric distortion [2]. Left ventricular remodeling, encompassing changes in cardiac mass, volume, geometry, and composition, represents the central pathophysiological mechanism driving disease progression from initial myocardial injury to overt clinical decompensation [3]. The molecular and cellular processes underlying adverse LV remodeling involve a complex interplay of neurohormonal activation, oxidative stress, inflammatory signaling, cardiomyocyte hypertrophy and apoptosis, extracellular matrix expansion, and interstitial and replacement fibrosis [4]. Despite the transformative impact of guideline-directed medical therapy—including renin-angiotensin-aldosterone system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and more recently sodium-glucose cotransporter-2 inhibitors—on clinical

outcomes, progressive remodeling and adverse prognosis persist in a substantial proportion of patients, underscoring the need for improved risk stratification and mechanistically targeted therapies [5]. Galectin-3 is a 30-kDa chimeric lectin of the galectin family, predominantly expressed by activated macrophages and fibroblasts within the myocardium [6]. It functions as a critical mediator of tissue fibrosis through the activation of resident cardiac fibroblasts, stimulation of collagen deposition, and modulation of inflammatory cell trafficking [7]. Experimental studies have demonstrated that Gal-3 expression is markedly upregulated in failing myocardium, and that pharmacological inhibition or genetic deletion of Gal-3 attenuates adverse cardiac remodeling in animal models of heart failure [8]. The United States Food and Drug Administration has cleared Gal-3 as a prognostic biomarker in heart failure, and the 2017 ACC/AHA heart failure guidelines assign a Class IIb recommendation for its use in additive risk stratification [9].

Clinical studies have consistently demonstrated associations between elevated circulating Gal-3 concentrations and increased risk of hospitalization, mortality, and composite cardiovascular endpoints in heart failure populations [10]. The DEAL-HF study reported that Gal-3 levels predicted all-cause mortality independently of established clinical predictors and NT-proBNP in chronic heart failure patients [11]. Similarly, data from the COACH trial demonstrated incremental prognostic value of Gal-3 beyond conventional risk factors in predicting rehospitalization and death [12].

However, while the prognostic significance of Gal-3 in heart failure is relatively well established, the relationship between circulating Gal-3 concentrations and specific echocardiographic parameters of LV remodeling has received comparatively limited investigation [13]. The majority of existing studies have focused on clinical outcome prediction rather than on correlating Gal-3 levels with quantitative imaging markers of structural cardiac deterioration.

Furthermore, studies examining this biomarker-remodeling relationship specifically within HFrEF populations—as opposed to mixed or undifferentiated heart failure cohorts—are scarce [14]. Understanding whether Gal-3 concentrations reflect the extent of structural remodeling could enhance its clinical utility as a monitoring tool and potentially guide therapeutic intensity or intervention timing.

The aim of this study was to investigate the association between serum Gal-3 levels and echocardiographic parameters of LV remodeling in a well-characterized cohort of patients with HFrEF, and to determine whether these associations remain significant after adjustment for established clinical and biochemical confounders.

Materials and Methods

Study Design and Setting: This cross-sectional analytical study was conducted at the tertiary cardiac center.

Study Population: Consecutive adult patients (aged ≥18 years) with an established diagnosis of HFrEF (LVEF ≤40% confirmed on transthoracic echocardiography within the preceding 3 months) attending the outpatient heart failure clinic or admitted for heart failure management were screened for enrollment. Inclusion criteria required stable clinical status defined as no change in heart failure medications, hospitalization for acute decompensation, or intravenous diuretic therapy within the preceding 4 weeks. Exclusion criteria comprised acute coronary syndrome within 3 months, prior cardiac surgery or percutaneous coronary intervention within 6 months, significant primary valvular heart disease (moderate or severe), congenital heart disease, hypertrophic or restrictive cardiomyopathy, active myocarditis, severe chronic kidney disease (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73 m²), hepatic cirrhosis, active malignancy, systemic inflammatory or autoimmune diseases, and ongoing immunosuppressive therapy.

Clinical Assessment and Data Collection: Comprehensive clinical data were obtained through structured interviews and medical record review. Variables documented included age, sex, body mass index, heart failure etiology (ischemic vs. non-ischemic), New York Heart Association (NYHA) functional classification, duration of heart failure diagnosis, cardiovascular comorbidities (hypertension, diabetes mellitus, atrial fibrillation, chronic kidney disease), and concurrent medications (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists, sacubitril/valsartan, SGLT2 inhibitors, diuretics, and cardiac device therapy including implantable cardioverter-defibrillators and cardiac resynchronization therapy).

Biomarker Assessment: Venous blood samples were collected after a 12-hour overnight fast and processed within 60 minutes. Serum was separated by centrifugation at 3000 rpm for 15 minutes and stored at −80°C until batch analysis. Serum Gal-3 levels were measured using a commercially available quantitative sandwich ELISA kit (BG Medicine, Waltham, MA, USA) with an analytical measurement range of 1.4–94.8 ng/mL and intra-assay and inter-assay coefficients of variation of 3.2% and 5.6%, respectively. Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) was

measured using an electrochemiluminescence immunoassay on the Cobas e601 analyzer (Roche Diagnostics, Basel, Switzerland). Additional laboratory assessments included serum creatinine, eGFR (CKD-EPI equation), hemoglobin, high-sensitivity C-reactive protein (hs-CRP), and serum albumin.

Echocardiographic Assessment: Comprehensive two-dimensional and Doppler transthoracic echocardiography was performed by experienced sonographers using a Vivid E95 ultrasound system (GE Healthcare, Horten, Norway) equipped with an M5Sc-D phased-array transducer. All measurements followed current American Society of Echocardiography (ASE) recommendations. LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LVEF were measured using the biplane Simpson's method of discs from apical four-chamber and two-chamber views. Volumes were indexed to body surface area (LVEDVi, LVESVi). LV mass was calculated using the ASE-recommended linear method and indexed to body surface area (LVMi). Left atrial volume was assessed using the biplane area-length method and indexed (LAVi).

Global longitudinal strain was analyzed offline using two-dimensional speckle-tracking echocardiography from standard apical views using EchoPAC software (GE Healthcare). Wall motion score index (WMSI) was calculated from a 17-segment model. All echocardiographic measurements represented the average of three consecutive cardiac cycles, and studies were interpreted by two board-certified cardiologists blinded to Gal-3 results.

Sample Size Estimation: Assuming a moderate correlation coefficient ($r = 0.25$) between Gal-3 and primary echocardiographic parameters, a minimum sample size of 250 patients was estimated to provide 90% power at a significance level of 0.05, accounting for multivariable adjustment with up to eight covariates.

Statistical Analysis: Continuous variables with normal distribution were expressed as mean ± SD and compared using independent samples t-tests or one-way analysis of variance with Bonferroni post-hoc testing. Non-normally distributed variables were presented as median with interquartile range and compared using Mann-Whitney U or Kruskal-Wallis tests.

Categorical variables were expressed as frequencies and percentages and analyzed using chi-square tests. Gal-3 levels were analyzed both as a continuous variable and categorized into tertiles. Bivariate correlations between Gal-3 and echocardiographic parameters were assessed using Pearson or Spearman correlation coefficients.

Multivariable linear regression models were constructed to evaluate independent associations between Gal-3 and each primary echocardiographic parameter, adjusting for age, sex, BMI, heart failure etiology, NYHA class, NT-proBNP, eGFR, and hs-CRP. Standardized regression coefficients (β) were reported. Collinearity diagnostics were performed using variance inflation factors (VIF), with VIF >5 considered indicative of significant multicollinearity.

All analyses were two-tailed with $p < 0.05$ considered statistically significant, performed using SPSS version 28.0 and R version 4.3.1.

Results

Patient Characteristics: A total of 312 patients were screened, of whom 286 met all eligibility criteria and were included in the final analysis. Baseline clinical, biochemical, and echocardiographic characteristics are presented in Table 1. The mean age was 62.4 ± 11.8 years, with a male predominance (72.4%). Ischemic cardiomyopathy was the underlying etiology in 58.7% of patients. The mean LVEF was 29.6 ± 7.4%, and the median NT-proBNP was 1842 pg/mL (IQR: 876–3648). The median serum Gal-3 level was 21.4 ng/mL (IQR: 15.8–29.6).

Table 1: Baseline Clinical, Biochemical, and Echocardiographic Characteristics (N = 286)

Variable	Value
Age (years), mean ± SD	62.4 ± 11.8
Male sex, n (%)	207 (72.4)
BMI (kg/m²), mean ± SD	28.2 ± 4.6
Ischemic etiology, n (%)	168 (58.7)
NYHA Class II, n (%)	112 (39.2)
NYHA Class III, n (%)	138 (48.3)
NYHA Class IV, n (%)	36 (12.6)
HF duration (months), median (IQR)	36 (18–72)
Hypertension, n (%)	186 (65.0)
Diabetes mellitus, n (%)	98 (34.3)
Atrial fibrillation, n (%)	82 (28.7)
eGFR (mL/min/1.73 m²), mean ± SD	58.4 ± 21.6
Hemoglobin (g/dL), mean ± SD	12.8 ± 1.9

hs-CRP (mg/L), median (IQR)	4.2 (1.8–8.6)
NT-proBNP (pg/mL), median (IQR)	1842 (876–3648)
Galectin-3 (ng/mL), median (IQR)	21.4 (15.8–29.6)
ACEi/ARB or ARNI use, n (%)	248 (86.7)
Beta-blocker use, n (%)	264 (92.3)
MRA use, n (%)	198 (69.2)
SGLT2 inhibitor use, n (%)	124 (43.4)
ICD/CRT, n (%)	86 (30.1)
LVEF (%), mean ± SD	29.6 ± 7.4
LVEDVi (mL/m²), mean ± SD	98.4 ± 30.2
LVESVi (mL/m²), mean ± SD	70.6 ± 26.8
LVMi (g/m²), mean ± SD	128.4 ± 34.6
LAVi (mL/m²), mean ± SD	42.8 ± 14.2
GLS (%), mean ± SD	−10.8 ± 3.4

Echocardiographic Parameters Stratified by Galectin-3 Tertiles: Patients were divided into tertiles based on serum Gal-3 levels: Tertile 1 (<17.2 ng/mL; n = 96), Tertile 2 (17.2–26.2 ng/mL; n = 94), and Tertile 3 (>26.2 ng/mL; n = 96). Table 2 summarizes the echocardiographic remodeling parameters across Gal-3 tertiles. Significant graded increases in LVEDVi, LVESVi, LVMi, LAVi, and WMSI, along with progressive deterioration of LVEF and GLS, were observed across ascending Gal-3 tertiles (all p-trend < 0.01).

Table 2: Echocardiographic Parameters Stratified by Galectin-3 Tertiles

Parameter	Tertile 1 (<17.2 ng/mL; n = 96)	Tertile 2 (17.2–26.2 ng/mL; n = 94)	Tertile 3 (>26.2 ng/mL; n = 96)	p-trend
LVEF (%), mean ± SD	33.2 ± 5.8	29.4 ± 6.8	26.1 ± 7.6	< 0.001
LVEDVi (mL/m²), mean ± SD	86.2 ± 24.8	96.8 ± 28.4	118.4 ± 32.6	< 0.001
LVESVi (mL/m²), mean ± SD	58.2 ± 20.4	69.4 ± 24.6	88.6 ± 30.2	< 0.001
LVMi (g/m²), mean ± SD	112.8 ± 28.6	126.4 ± 32.8	148.6 ± 38.4	< 0.001
LAVi (mL/m²), mean ± SD	36.4 ± 11.8	42.2 ± 13.6	50.8 ± 15.4	< 0.001
GLS (%), mean ± SD	−12.6 ± 3.1	−10.8 ± 2.8	−8.2 ± 2.4	< 0.001
WMSI, mean ± SD	1.62 ± 0.34	1.84 ± 0.38	2.12 ± 0.42	< 0.001
E/e' ratio, mean ± SD	12.4 ± 4.8	15.6 ± 5.4	19.8 ± 6.2	< 0.001

Correlations and Multivariable Regression Analysis: Bivariate correlation analysis revealed significant positive correlations between serum Gal-3 levels and LVEDVi ($r = 0.46$; $p < 0.001$), LVESVi ($r = 0.44$; $p < 0.001$), LVMi ($r = 0.42$; $p < 0.001$), LAVi ($r = 0.38$; $p < 0.001$), E/e' ratio ($r = 0.36$; $p < 0.001$), and WMSI ($r = 0.34$; $p < 0.001$), and significant negative correlations with LVEF ($r = −0.40$; $p < 0.001$) and GLS ($r = 0.39$; $p < 0.001$; noting that less negative GLS indicates worse function). Gal-3 also correlated significantly with NT-proBNP ($r = 0.52$; $p < 0.001$), hs-CRP ($r = 0.31$; $p < 0.001$), and inversely with eGFR ($r = −0.36$; $p < 0.001$). Multivariable linear regression results are presented in Table 3. After adjustment for age, sex, BMI, heart failure etiology, NYHA class, NT-proBNP, eGFR, and hs-CRP, serum Gal-3 remained independently associated with LVEDVi ($\beta = 0.34$; $p < 0.001$), LVMi ($\beta = 0.31$; $p < 0.001$), GLS ($\beta = 0.28$; $p = 0.001$), LVESVi ($\beta = 0.27$; $p = 0.002$), and LAVi ($\beta = 0.22$; $p = 0.008$). The association with LVEF, while significant in bivariate analysis, was attenuated after multivariable adjustment ($\beta = −0.14$; $p = 0.062$). All VIF values were below 3.2, indicating acceptable absence of multicollinearity.

Table 3: Multivariable Linear Regression: Independent Associations between Galectin-3 and Echocardiographic Parameters

Echocardiographic Parameter	Standardized β	95% CI for β	p-value	Model Adjusted R^2
LVEDVi (mL/m²)	0.34	0.21–0.47	< 0.001	0.42
LVESVi (mL/m²)	0.27	0.14–0.40	0.002	0.38
LVMi (g/m²)	0.31	0.18–0.44	< 0.001	0.40
LAVi (mL/m²)	0.22	0.09–0.35	0.008	0.34
GLS (%)	0.28	0.15–0.41	0.001	0.36
LVEF (%)	−0.14	−0.28–0.01	0.062	0.31
E/e' ratio	0.19	0.06–0.32	0.018	0.29
WMSI	0.18	0.05–0.31	0.024	0.28

Discussion

The findings of this study demonstrate that elevated serum Gal-3 levels are significantly and independently associated with adverse echocardiographic parameters of LV remodeling in patients with HFrEF. Specifically, higher Gal-3 concentrations were associated with greater LV cavity dilatation, increased LV mass, enlarged left atrial dimensions, impaired myocardial deformational mechanics, and elevated filling pressures, even after comprehensive adjustment for established clinical and biochemical confounders including NT-proBNP and renal function. These findings provide important mechanistic insight linking circulating Gal-3 to the structural myocardial processes underlying disease progression in HFrEF.

The observed positive correlation between Gal-3 and LVEDVi ($r = 0.46$) and the persistence of this association in multivariable analysis ($\beta = 0.34$) suggest that Gal-3 reflects processes driving chamber dilatation beyond those captured by natriuretic peptides, which primarily reflect myocardial wall stress. This distinction is biologically plausible given the mechanistically distinct roles of these biomarkers: while NT-proBNP is released in response to cardiomyocyte stretch, Gal-3 is secreted by activated macrophages and fibroblasts during the fibrogenic cascade, representing the profibrotic arm of the remodeling process [15]. De Boer et al. demonstrated in preclinical models that intrapericardial infusion of Gal-3 induced cardiac fibrosis and ventricular dysfunction, establishing a direct causal link between Gal-3 and adverse remodeling [16].

The independent association between Gal-3 and LV mass index ($\beta = 0.31$) is particularly noteworthy, as increased LV mass in HFrEF reflects the combined contributions of cardiomyocyte hypertrophy and interstitial fibrotic expansion. Cardiac magnetic resonance studies employing T1 mapping and extracellular volume quantification have correlated Gal-3 levels with diffuse myocardial fibrosis in heart failure patients, providing imaging validation for the biomarker-fibrosis relationship [17]. Our echocardiographic findings complement these MRI-based observations and extend their applicability to clinical settings where advanced cardiac imaging may not be readily available.

The significant association between Gal-3 and global longitudinal strain ($\beta = 0.28$) is clinically meaningful, as GLS represents a sensitive measure of subclinical systolic dysfunction that detects myocardial impairment earlier and more precisely than conventional LVEF [18]. The mechanistic link between fibrotic myocardial infiltration and impaired longitudinal deformation has been well characterized, with fibrosis disrupting the helical architecture of subendocardial myocardial fibers that are the primary determinants of longitudinal contractile function [19]. The correlation between Gal-3 and GLS observed in our study thus supports the hypothesis that Gal-3 reflects, at least in part, the myocardial fibrotic burden contributing to subclinical contractile impairment.

The attenuation of the Gal-3–LVEF association after multivariable adjustment ($p = 0.062$) is noteworthy and may reflect the recognized limitations of LVEF as a remodeling marker. LVEF is a volumetric ratio dependent on both loading conditions and chamber geometry, and may remain relatively preserved despite substantial structural deterioration, particularly in eccentric remodeling patterns [20]. The superior sensitivity of volumetric and deformation parameters in capturing Gal-3-related remodeling processes reinforces the growing consensus that LVEF alone insufficiently characterizes the complexity of ventricular remodeling.

The significant correlation between Gal-3 and E/e' ratio ($\beta = 0.19$) suggests an association between fibrosis-mediated processes and diastolic dysfunction, which commonly accompanies systolic impairment in HFrEF. Fibrotic infiltration of the myocardial interstitium increases passive chamber stiffness, impairs relaxation, and elevates filling pressures, contributing to the symptom burden and hemodynamic compromise observed in advanced heart failure [21]. This dual systolic-diastolic impact of Gal-3 underscores its relevance as a comprehensive marker of myocardial structural deterioration.

Our results are consistent with findings from several prior investigations. Lok et al. reported significant correlations between Gal-3 and echocardiographic measures of LV remodeling in a cohort of chronic heart failure patients, though their study included both HFrEF and HFpEF subtypes [22]. The PROTECT trial biomarker substudy demonstrated that higher baseline Gal-3 levels were associated with larger LV volumes and greater LV mass in chronic heart failure patients [23]. Our study extends these observations by specifically examining these relationships within a pure HFrEF population and employing comprehensive echocardiographic assessment including speckle-tracking strain analysis.

Several limitations merit acknowledgment. The cross-sectional design precludes establishment of temporal or causal relationships between Gal-3 elevation and progressive remodeling; longitudinal studies with serial Gal-3 measurements and echocardiographic assessments are needed to address this limitation. Gal-3 concentrations are influenced by renal function, and despite statistical adjustment for eGFR, residual confounding cannot

be entirely excluded [24]. The study excluded patients with severe chronic kidney disease, which limits generalizability to this high-risk subgroup. Cardiac magnetic resonance imaging with tissue characterization, the reference standard for myocardial fibrosis assessment, was not performed, and thus direct correlation between Gal-3 and quantified fibrosis burden was not possible. Finally, the single-center design and enrollment from a tertiary heart failure service may introduce referral bias, limiting generalizability to broader heart failure populations [25].

Conclusion

This study demonstrates that elevated serum Gal-3 levels are significantly and independently associated with adverse echocardiographic indices of left ventricular remodeling in patients with heart failure with reduced ejection fraction. Higher Gal-3 concentrations are associated with greater left ventricular cavity dilatation, increased left ventricular mass, enlarged left atrial volumes, impaired global longitudinal strain, and elevated diastolic filling pressures, independent of established clinical and biochemical confounders. These findings position Gal-3 as a clinically informative biomarker that captures dimensions of myocardial structural deterioration not fully reflected by natriuretic peptides or conventional ejection fraction measurements. Integration of Gal-3 into multimarker assessment strategies may enhance risk stratification, facilitate early identification of progressive remodeling, and potentially guide therapeutic intensification in heart failure management. Prospective longitudinal studies evaluating the relationship between serial Gal-3 changes, progressive remodeling, and clinical outcomes, as well as interventional studies targeting Gal-3-mediated fibrotic pathways, are warranted to further define the clinical and therapeutic implications of this biomarker.

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