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ORIGINAL PAPERS

PREDICTIVE VALUE AND ANALYSIS OF PATHOPHYSIOLOGICAL INTERDEPENDENCIES BETWEEN CARDIAC DAMAGE MARKERS AND PARAMETERS OF COMPLEX METABOLIC DYSFUNCTION PATHWAYS OF MYOCARDIAL FIBROSIS AND REMODELING MEDIATED BY GALECTIN-3 IN HEART FAILURE

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Abstract. In heart failure and metabolic dysfunction, biomarkers can provide an overview of pathophysiological correlations and mechanisms. The study employed an observational design and was conducted on a sample consisting of two groups: a group of patients with cardiovascular disease, specifically heart failure, with or without comorbidities, and a control group. Biological variables relevant to cardiovascular status and metabolic dysfunction were analyzed, with a focus on the emerging biomarker, Galectin-3. The distribution of biomarker values was evaluated using statistical analyses. The ARCHITECT Galectin-3 immunoassay is a two-step test that utilizes Chemiflex CMIA technology, a technology with flexible testing protocols. When used in conjunction with the ARCHITECT iSYSTEM, it is a test for the quantitative determination of galectin-3 in human serum and EDTA plasma. It is indicated for prognostic assessments in heart failure. In the present study, values of established and emerging cardiovascular biomarkers relevant to cardiovascular status were evaluated and statistically correlated. Other biochemical parameters (lipid profile, blood glucose, liver enzymes, and cardiac markers) relevant to metabolic dysfunction were also included. Galectin-3 is an indicator of cardiac fibrosis and remodeling. The distribution of biomarker values was evaluated using descriptive analysis and coefficients for parametric data and non-Gaussian distributions (Spearman), normality tests (Kolmogorov–Smirnov and Shapiro–Wilk), or tests for comparing biological variables between the two groups. Key correlations of Galectin-3 are relevant for risk stratification in heart failure and reflect the evolving status of the

patient's condition. Established markers such as NT-proBNP/BNP are used in assessing hemodynamic status and correlate with Galectin-3, an indicator of long-term fibrosis. Within the same fibrosis-inflammation axis, it correlates also, with early predictors of cardio-renal syndrome (creatinine/urea) or markers of glycemic status.

Keywords: Biomarker, Galectin-3, Cardiac Remodeling, Fibrosis, Methabolic Disorders.

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OBJECTIVES

1. Primary objective

The primary objective is to establish the relationship between established biomarkers, emerging biomarkers, and markers of metabolic dysfunction, to evaluate correlations and interpret the results.

2. Secondary objectives

a) Relationships analyses between established cardiovascular biomarkers, such as those used in heart failure, and novel biomarkers;
b) Relationships analyses between emerging biomarkers in heart failure and metabolic dysfunction, with a focus on the links between inflammation and fibrosis in heart failure.

INTRODUCTION

Cardiovascular and metabolic diseases should be approached using a multimarker strategy in order to highlight key pathophysiological processes such as systemic inflammation, necrosis, endothelial dysfunction, and myocardial wall stress. The integration of metabolic and renal markers with cardiac biomarkers provides a more comprehensive systemic analysis. Within this framework, the integration of biomarkers related to the fibrosis–inflammation axis, myocardial stress, and metabolic dysfunction is particularly useful.

Among cardiac conditions in which galectin-3 has been extensively studied, two major groups are of particular interest: patients with acute coronary syndrome and those with heart failure (Lupu, A. et al., 2021). Therefore, a multimarker approach in these conditions is feasible. A higher risk of developing heart failure has been observed in patients with elevated levels of both the established biomarker BNP and galectin-3 (Grandin E.W. et al., 2012; de Boer R.A. et al., 2011; Ho J. et al., 2012; Abbot.Arch.).

Galectin-3 is a structural member of a unique group of proteins. It belongs to the family of multifunctional lectins that bind beta-galactosides. Its main roles include regulation of inflammation, cancer, and immune responses. It has been

extensively studied and remains of significant interest due to its relevance in cardiovascular diseases in general. In this context, inflammation and fibrosis are essential pathophysiological mechanisms in the development and progression of heart failure. Cardiac remodeling has a key underlying component, namely fibroblast proliferation. There is a well-established link between this proliferation and the upregulation of galectin-3 (Lupu (Surlea) A. et al., 2025; de Boer R.A. et al., 2009; Dumic J. et al., 2006; Gabius H.J. et al., 2006; Henderson N.C. et al., 2006; Kuwabara I. et al., 1996; Liu Y.H., 2009; Papaspyridonos M., 2008; Sano H., 2000; Sharma U.C. et al., 2004).

METHODOLOGY

The study was conducted on a group of patients for whom clinical and biological parameters with cardiometabolic, inflammatory, and renal relevance were analyzed. The analysis focused in particular on assessing the relationship between galectin-3 and a series of commonly used biological markers in clinical practice, such as BNP, NT-proBNP, blood glucose, creatinine, urea, CRP, HDL-cholesterol, and CK-MB. Data were statistically processed using IBM SPSS Statistics 25 software.

Categorical variables were expressed as absolute frequencies and percentages, while quantitative variables were evaluated using descriptive and non-parametric methods. The association between Galectin-3 and the analyzed biological markers—NT-proBNP, BNP, glucose, creatinine, urea, CRP, HDL-cholesterol, and CK-MB—was assessed using the Spearman correlation coefficient. Differences in galectin-3 levels according to age groups, NYHA class, and type of metabolic dysfunction were analyzed using the Kruskal–Wallis test. The threshold for statistical significance was set at $p < 0.05$.

MATERIALS AND METHODS

The determination of the main biomarker included in the study was performed using the ARCHITECT Galectin-3 assay, applied together with the ARCHITECT iSYSTEM. This is a chemiluminescent microparticle immunoassay (CMIA) used for the quantitative determination of galectin-3 in human serum and EDTA plasma. The assay is based on monoclonal antibodies specific for galectin-3, 87B5 and M3/38. The ARCHITECT Galectin-3 test is indicated for use in the prognostic assessment of patients with chronic heart failure.

The ARCHITECT Galectin-3 immunoassay is a two-step test that uses CMIA Chemiflex technology, a flexible assay protocol system. It was used for the quantitative determination of galectin-3 in EDTA plasma. Galectin-3 present in the plasma binds to microparticles coated with anti–galectin-3 antibodies.

Disposable pipettes were used for sample handling. Calibration and standardization of the assay were performed in accordance with the manufacturer's protocol.

Quality control procedures were strictly followed, including the use of additional controls and adherence to the laboratory's quality control policy regarding the use of controls to verify test results.

The results of the analyses are recommended to be interpreted together with clinical data, including manifestations, signs, symptoms, and medical history. In cases of inconsistency, additional confirmatory testing may be performed. Furthermore, in patients with other conditions such as advanced-stage cancer or organ fibrosis, the test may not be indicated for evaluation.

Reference intervals were used for data interpretation. Classification ranges were established according to categories of risk for hospitalization and risk of death from any cause, as follows.

-Low risk = Galectin-3 value	17,8 ng/ml
-Mediu risk = Galectin-3 value	17,8 – 25.9 ng/ml
-High risk = Galectin-3 value	25.9 ng/ml

Table 1. Reference classification intervals for Galectin-3 determined from plasma(Adapted after Abbot Lab).

The quantitative determination of Galectin-3 in plasma uses the immunoassay based on chemiluminescence (CMIA technology), optimized for the use of integrated protocols (CHEMIFLEX).

The cut-off values of Galectin-3 used in this study were considered according to the recommendations between 17.8 ng/ml and 25.9 ng/ml. The detection limit for which the test was quantified was 1 - 4 ng/mL (Abbot Lab.)

The values of Galectin-3 obtained, expressed in ng/mL, were classified with the division into 3 risk categories for the causes of morbidity and mortality, as follows:

a) Low risk ≤ 17,8 ng/mL, values considered suggestive of low risk of heart failure;

b) Medium risk > 17,8 ng/ml ≤ 25,9 ng/mL values considered suggestive of medium risk of heart failure.

c) High risk > 25,9 ng/mL values considered suggestive of increased risk of heart failure (Tabel 1).

According to manufacturers, citing authors of several studies, there have been investigations into the prognostic role of galectin-3 in chronic heart failure over long periods of time. In the three studies mentioned, increased values of galectin-3 are associated with severe prognosis. It also refers to increased values of natridiuretic peptides correlated with Galectin-3 values, not separately

analyzed. This correlation provides significant data in the acute form of heart failure as well. (van Kimmenade, R.R., et. al.,2006; Felker, G.M., et. al., 2012; Lok, D.J.A., et. al., 2010; de Boer, R.A., 2011)

In the PRIDE (Pro-BNP Investigation of Dyspnea in the Emergency Department) study, in selected patients, a higher correlation was shown in those at high risk of death versus readmission. In the COACH (Coordination of Outcomes of Counseling and Consulting in Heart Failure) study, for patients with heart failure with preserved ejection fraction, Galectin-3 showed a greater prognostic significance than in patients with heart failure with reduced ejection fraction, the former being more difficult to diagnose or treat (de Boer RA, et. al., 2011). The PREVENT (Prevention of End-Stage Renal and Vascular Disease) study showed an association between higher Galectin-3 levels and all-cause mortality in the general population studied over a period of approximately 10 years (de Boer, R.A., et. al., 2011). The CORONA (Controlled Rosuvastatin Multinational Trial in HF) study also showed a correlation between Galectin-3 levels in patients treated with statins. (Gullestad, L., et. al., 2012).

Among the biomarkers recommended and used in the evaluation of cardiovascular diseases, those with indications for heart failure and acute coronary syndrome were selected. Heart failure involves complex hemodynamic, inflammatory, metabolic, and fibrotic pathways and is described as a complex syndrome. In the metabolic context, the evolution of the disease also differs. Due to the need for a stratified statistical approach in both major disease categories, patients with heart failure were selected. The values of established biomarkers are altered in both conditions; however, the underlying pathophysiological mechanisms differ, being mainly chronic-progressive rather than acute. In heart failure, Galectin-3 is an potential marker of remodeling with indications for:

-Identification of patients at high risk of hospitalization

-Monitoring the degree of myocardial fibrosis, independent of filling pressure (BNP).

In such a framework, where a new marker is introduced into the assessment, additional elements are brought to a risk model.

In the context of Galectin-3 measurement at the time of myocardial infarction, studies have shown that it may serve as an independent predictor of mortality. Post-infarction, plasma galectin-3 has been demonstrated to provide information related to vascular dysfunction (Asleh R. et al., 2019; Huttin O. et al., 2020; Blanda V. et al., 2020).

RESULTS AND DISCUSSIONS

Common biomarkers are the most accessible and frequently used in clinical evaluations. In addition to these, key elements have also been identified that are

the subject of extensive and diverse studies regarding their involvement in pathophysiological processes. One such biomarker is galectin-3, a protein belonging to the lectin family that has emerged as a key mediator in inflammation, fibrosis, and cardiac remodeling.

Metabolic disorders and dysregulations may interfere with its activity. Cardiac natriuretic peptides are central elements in clinical assessment, and current research is also focusing on future multimarker approaches. From the perspective of medical biology, this approach is based on molecular and cellular mechanisms in pathophysiology. In biology, a biomarker is defined as a signal indicating intra- or extracellular levels of a given process.

Based on pathophysiological mechanisms that can provide an overall picture of cardiometabolic assessment, the analyzed biomarkers were grouped into:

1. Hemodynamic and Cardiac Remodeling Axis.

Myocardial Stress Biomarkers for Hemodynamic and Myocardial Injury. NT-proBNP / BNP – markers of ventricular wall distension

Natriuretic peptides include N-terminal proBNP (NT-proBNP) and Brain Natriuretic Peptide (BNP), which are measured in blood plasma as quantitative biomarkers for the assessment of cardiac hemodynamic stress. They provide both diagnostic and prognostic accuracy that is considered comparable. NT-proBNP and BNP are widely used in cardiovascular conditions such as heart failure (Mueller C. et al., 2019; Lupu, Surlea A. et al., 2023).

According to Mueller et al. (2019), the use of natriuretic peptide markers is based on several principles:

-their use in the clinical evaluation of patients with symptoms of heart failure, including dyspnea;

-their role in differentiating acute dyspnea due to heart failure from chronic heart failure or dyspnea in obese patients;

-their use in risk stratification in heart failure;

Many studies have shown that Galectin-3 has less prognostic relevance than established biomarkers such as NT-proBNP. However, Galectin-3 has been demonstrated to potentially serve as a prognostic marker for cardiovascular mortality in heart failure. It could be considered an indicator of remodeling and fibrosis. Furthermore, in patients with heart failure, it can also be an indicator of renal failure. Crucial for studies regarding risk stratification in high-risk heart failure patients is the combined model of biomarkers with a prognostic role, such as the association of NT-proBNP and Galectin-3 (Amin, H.Z., et al., 2017).

Galectin-3 is an important independent predictor for rehospitalization and prognosis in heart failure (Meijers, W.C., et al., 2014). Patients with heart failure who presented Galectin-3 measured values higher than 17.8 ng/ml had higher

chances of readmission within 1 to 4 months, even after adjustment, including for BNP levels (Meijers, W.C., et al., 2014, Amin, H.Z., et al., 2017).

An association and correlation between Galectin-3 and NT-proBNP levels are demonstrated in heart failure patients, who exhibit higher plasma levels. In heart failure cases, these elevated plasma levels of Galectin-3 and NT-proBNP are potentially linked to cardiac remodeling, and Galectin-3 is useful for its prognostic potential in these patients. A significant contribution to describing this role was made by Sharma et al., who show that Galectin-3 appears in early myocardial dysfunction (Yılmaz, Ürün, Y., et al., 2020).

		BNP	NT-proBNP	Uree
Galectina	Correlation Coefficient	,313*	,401*	,321*
	Sig. (2-tailed)	,049	,010	,043
	N	40	40	40

*. Correlation is significant at the 0.05 level (2-tailed).
**. Correlation is significant at the 0.01 level (2-tailed).

Spearman correlation analysis revealed statistically significant associations between galectin-3 and the natriuretic markers BNP and NT-proBNP, as well as between galectin-3 and urea. Galectin-3 showed a positive correlation with BNP (*rho* = 0,313; *p* = 0,049), NT-proBNP (*rho* = 0,401; *p* = 0,010) and Urea (*rho* = 0,321; *p* = 0,043), suggesting a possible relationship between this biomarker and the cardio-renal status. NT-proBNP showed a positive correlation with creatinine and urea, while BNP showed a positive correlation with CK-MB.

Both BNP and NT-proBNP are recommended biomarkers for the evaluation of dyspneic patients in whom heart failure needs to be ruled out. (Ponikowski, P, V. et.al., 2016)

-BNP can provide information related to ventricular function with preserved or reduced ejection fraction, the former having lower values (van Veldhuisen, D.J. et.al., 2013)

-NT-proBNP has a better predictive factor than BNP in the case of prognosis related to mortality or rehospitalization (Masson, S., et.al, 2006)

Both BNP and NT-proBNP are considered independent prognostic factors for rehospitalization and death in heart failure (Linssen, G.C.M., et.al., 2018).

Pathophysiology of cardiac remodeling.

Cardiac fibrosis involves regulators, including Galectin-3. The evolution of heart failure is linked to the pathophysiology of cardiac remodeling, and Galectin-3 is known to correlate with prognosis in cases of heart failure related to readmission or severe prognosis. Cardiac remodeling has among its factors stress, metabolic dysfunction such as diabetes mellitus, myocardial injury. After the

occurrence of injuries, whether acute or chronic, the immune response at the myocardial level and the appearance of cell signaling proteins may occur. Subsequent activation of macrophages initiates fibroblast activity. Galectin-3 is linked to fibroblast activation, being secreted extracellularly. Extracellular collagen is deposited, which is linked to cardiac fibrosis (Bošnjak, I.,et., al. 2015).

Actions	
Upregulation of cytoskeletal proteins	
Synthesis of matrix components	Type I collagen synthesis
Inhibition for degradation of extracellular matrix components	Downregulation of matrix metalloproteinases

Table 2. The role of Galectin-3 in fibroblast activation after De Boer, 2009 Blanda, V.2020; Adapted after Grande, D.; 2017,

1. Inflammation – fibrosis axis.

Alongside to fibrosis, another mechanism that contributes to the development of heart failure is inflammation. (Bošnjak, I, et., al. 2015). Activated macrophages secrete Galectin-3. This becomes a mediator in remodeling as we have shown previously, but it is also a mediator for inflammation and its processes). It is therefore related to macrophage regulation and injury signaling, but is context-dependent, either pro-immune response or with immunosuppressive effects in other situations. (Martuszewski, A.; 2025)

The molecular mechanisms are supported by the ability of this lectin to:

- Interact with nuclear or plasma proteins through the carbohydrate recognition domain (CRD), namely through Asparagine-Tryptophan-Glycine-Arginine (NWGR)
- Binds sugars through the carbohydrate recognition domain (CRD).
- Regulate pre-mRNA processes – in the nucleus, in interaction with proteins.

Extracellular matrix dynamics, endothelial activation and markers involved in inflammation – PCR, Fibrinogen. The molecular correlation of some inflammation factors shows the immuno-inflammatory axis and the previously demonstrated fibrotic modeling axis. This association may demonstrate that a complex disease like this can overcome the cardiocentric analytical matrix.

The correlation of Gal-3 – PCR and Fibrinogen, demonstrates that HF is a systemic disease, not a pump function defect.

1. Metabolic Dysfunction Axis – Glycemia, Transaminases, Renal Damage

There are numerous studies linking galectin-3 to the pathophysiology of diabetes. As referenced by Martuszewski, A et., al. 2025, study results suggest a correlation with the impact of elevated blood glucose, less with plasma glucose values. In other studies, it has either been shown to be an independent predictor of heart failure or a potential role in diabetic cardiomyopathy has been suggested (Martuszewski, A et., al. 2025).

Kruskal-Wallis Test

Ranks

Disfunction metabolic		N	Mean Rank
Galectina	DZ	10	7,00
	BRD	9	13,33
	Total	19	

Rank analysis indicated higher galectin-3 values in the renal disease group compared to the group of patients with diabetes mellitus, with a mean rank of 13.33 for chronic kidney disease and 7.00 for diabetes mellitus. This result descriptively suggests a possible increase in galectin-3 levels in patients with chronic renal impairment.

Test Statistics a,b

	Galectina
Kruskal-Wallis H	6,000
df	1
Asymp. Sig.	,014

a. Kruskal Wallis Test

b. Grouping Variable: Disfunction metabolic

Galectin-3 was significantly different between the two categories of metabolic dysfunction analyzed ($p = 0.014$), with higher values in the renal impairment group compared to the diabetes mellitus group. However, the interpretation should be made with caution, given the small size of the subgroups.

Correlations

			Galectina	Disfunction metabolic
Spearman's rho	Galectina	Correlation Coefficient	1,000	,577**
		Sig. (2-tailed)	.	,010
		N	40	19
	Disfunction metabolic	Correlation Coefficient	,577**	1,000
		Sig. (2-tailed)	,010	.
		N	19	19

**. Correlation is significant at the 0.01 level (2-tailed).

Galectin-3 was significantly associated with the type of metabolic dysfunction, showing higher values in the chronic kidney disease group compared to the diabetes mellitus group. However, the interpretation should be made with caution, given the small size of the analyzed subgroups.

2.Cardio-Renal Axis.

Galectin-3 is not only a cardiac marker; it is directly involved in renal fibrosis.

		Creatinina	Uree
NT-proBNP	Correlation Coefficient	,327*	,365*
	Sig. (2-tailed)	,039	,020
	N	40	40

The strongest association was observed between creatinine and urea (*rho = 0.796; p < 0.001*), confirming the biological relationship between renal function markers.

The results suggest that **galectin-3 is mainly associated with cardiac and renal biomarkers, particularly NT-proBNP, BNP, and urea**. NT-proBNP is cleared passively by the kidneys. An increase in creatinine (a decrease in eGFR) will therefore lead to an automatic increase in NT-proBNP, independent of cardiac status. The NT-proBNP–Creatinine ratio is a more reliable indicator of true cardiac stress in patients with metabolic and renal dysfunction**.**

STUDY LIMITATIONS

This study has several limitations. It was based on a relatively small number of patients with heart failure, without stratification according to ventricular functional parameters such as ejection fraction.

CONCLUSIONS

1. Metabolic dysfunction (Glycemia) is not merely a risk factor, but a direct modulator of inflammatory intensity (CRP) and the rate of fibrogenesis (Gal-3).

2. Galectin-3 represents a complex biomarker, situated at the intersection of inflammation, fibrosis, and cardiorenal dysfunction. Its correlations with natriuretic peptides, renal markers, inflammatory markers, and metabolic parameters support the feasibility of its use both in assessing the severity of heart failure and its potential for evaluating the prognosis of patients with cardiorenal syndrome and associated metabolic diseases.

3. Serum levels of Galectin-3 are differentially influenced by comorbidities, and the results underscore the importance of an integrated, cardiometabolic approach..

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