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Galectins, Aspects in Cardiovascular Diseases

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Abstract. *The Galectins are proteins that belongs to Lectines family, ancient group that includes 15 types of Galectines, each with an specific role. Are involved in inflammatory processes, carcinogenesis, heart diseases, morbidity and mortality related to cardiovascular diseases being still in the first place worldwide. It is important to establish a link between Galectins (Galectin-3) and the process of heart failure, atherosclerosis, heart fibrosis. This review is done to determine the diagnostic performance of Galectin-3 parameters, total cardiac enzymes and their correlation.*

Keywords: Galectin, Cardiovascular Diseases, Heart Failure, Fibrosis.

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1. Introduction.

Cardiovascular disease is one of the main burdens of healthcare systems worldwide. Assessing cardiovascular risk in both apparently healthy individuals and low/high-risk patients remains a difficult issue. (Hogas et al., 2017). In cardiovascular diseases, a multifactorial pathological process with several triggering and etiopathogenic mechanisms in atherosclerosis. Its medium and long-term repercussions, however, invariably constitute a significant cause of morbidity and mortality (Rossi et al., 2021). Inflammations is one of the cornerstones and atherosclerosis, but it is also involved in heart fibrosis. The cardiac fibrosis is a tissue repair mechanism caused by a progressive accumulation of extracellular matrix in response to injury, inflammation or stress (Blândă, V. et al., 2020). Fibrotic diseases occur in a variety of organs and lead to continuous organ injury, function decline, and even failure (Li, L.et al., 2014).

Closely related to the fibrotic process, Heart Failure (HF) is a clinical syndrome caused by a cardiac structural/functional abnormality, resulting in a reduced cardiac output and/or elevated intra-cardiac pressure at rest or during stress, leading to typical symptoms and signs (e.g., breathlessness, fatigue, elevated jugular venous pressure, pulmonary crackles and peripheral edema) (Blândă, V. et al., 2020) (Ponikowsky, P., 2016). The two major pathophysiological processes contributing to HF development are inflammation and fibrosis (Blândă, V. et al., 2020). Understanding the mechanisms

responsible for initiation, progression, and resolution of cardiac fibrosis is crucial to design anti-fibrotic treatment (Kong, P., et al. 2014) and to find potential biomarkers for heart disease and detection of early stage pathology (Hara, A., 2020).

There are already established biomarkers like N-terminal prohormone of BNP (NT-proBNP), Troponin (Hogas et. al., 2017) – High sensitive Troponin-I, as well as myocardial enzymes Creatine Kinase (Creatine Phosphokinase) and Lactat Dehydrogenase. Numerous studies have demonstrated that Galectin-3 is a novel prognostic biomarker with high predictive value for cardiovascular mortality and readmission in HF patients (another existed HF prognostic biomarkers is NT-proBNP).

Galectin-3 acts in the inflammatory process stage. (Askin et all., 2021). Since 2014, the Food and Drug Administration (FDA) included Galectin-3 (Gal-3) on the list of validated cardiovascular biomarkers (Sun, R., R. et al. 2014).

2. Material and Methods. Analytes determined and used in the study.

The study was carried out in the Medical Analysis Laboratory of the "Alexandru Gafencu" Military Emergency Hospital of Constanta.

The values of selected analytes were taken in this study, for patients admitted to the Cardiology and Internal Medicine and Metabolic Diseases Departments. The framing, diagnosis and evolution of cardiovascular diseases were taken into account, considering that some of the patients presented for readmissions.

Analyses were performed using the laboratory's own equipment, instruments such as VIDAS and ARCHITECT, for quantitative analysis using the Enzyme-Linked Fluorescent Assay (ELFA) technique in human serum or plasma.

2.1. Galectin-3

Galectin-3 is a β-galactoside-binding protein involved in the regulation of several physiological cellular functions, such as cellular growth, proliferation, apoptosis, differentiation, cellular adhesion, and tissue repair (Blanda, V. et al., 2020). The Galectin family includes 15 members (Blanda, V. et al., 2020).

Galectin-3 overexpression and secretion are associated with several diseases and are extensively studied in the context of fibrosis, heart failure, atherosclerosis and diabetes mellitus (Suthahar, N., et al., 2018).

Galectin-3, which is secreted by macrophages under the influence of mediators like osteopontin, has been known for its significant role in mediating cardiac fibrosis and inflammation (Amin, Z., H., et al. 2017). The function of galectins varies with their tissue-specific and subcellular location, and their binding to carbohydrates makes them key players in several intra- and extracellular processes where they bind to glycosylated proteins and lipids. In humans, there are 12 identified galectins, some with tissue-specific distribution. Galectins are found inside cells and in the nucleus, cytosol, and organelles, as well as extracellularly. Galectin-1, -2, -3, -4, -7, -8, -9, and -12 can all induce T-cell apoptosis and modulate inflammation (Brinchmann, M., F.et al., 2018).

Galectine-3 is determined by an automatic quantitative test on the range of VIDAS instruments in human plasma. The principle of the test combines a one-step method of enzymatic immunological analysis in a single stage with fluorescence reading (ELFA), spectrophotometry.

2.2. Creatine phosphokinase (CPK)

Creatine phosphokinase (CPK) is an enzyme predominantly localized in skeletalmuscle and myocardium, being a key of muscle metabolism (Roșoiu, 2010).

CPK, also known by the name creatine kinase (CK), is the enzyme (Aujla, R., S., et al.2021) that catalyzes the reversible reaction of creatine and adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and phosphocreatine (Bong, S.M., et al., 2021). The phosphocreatine created from this reaction is used to supply tissues and cells that require substantial amounts of ATP, like the brain, skeletal muscles, and the heart, with their required ATP (Aujla, R., S., et al.2021).

It is an established biomarker that allows to establish the unfavorable prognosis if the values remain high for more than 3-4 days. Dosages performed in dynamics, at regular intervals, have shown that, starting from the obtained curves, it is possible to extrapolate with the extent of the necrotic tissue. (Roșoiu, 2010). Many centers are now going by troponin levels instead of CK (Aujla, R., S., et al.2021).

2.3. Lactate dehydrogenase (LDH)

Lactate dehydrogenase (LDH) is involved in carbohydrate metabolism. Catalyses the reversible conversion reaction of pyruvate to lactate in the final cycle of the anaerobic phase of glycolysis. It is of semiological importance due to the existence of different isoenzymes, some of myocadic origin, others of muscular or hepatic origin (Roșoiu, 2010).

Cells of tissues are direct source of lactate dehydrogenase isoenzymes that are naturally distributed in blood plasma/serum, producing characteristic profile**.** The activity and release of LDH have been evaluated as prognostic and monitoring tools of the disease development, activity, and progression (Tzouvelekis A., et al., 2005)

The persistence of elevated values for more than 14 days makes this determination a retrospective prognosis of a heart attack when the other enzyme activities have returned to their normal value (Roșoiu, 2010).

2.4. NT-proBNP

It is a quantitative test used in the diagnosis of heart failure. Elevated NT-proBNP levels are associated with ventricular dysfunction and severe heart failure, but are also increased in mild HF (Hn., et al., 2011). They are recommended in the suspicion of HF, thus helping alongside clinical assessment (Howlet, M., G., et al., 2007). Studies have shown that including NT-proBNP in the diagnostic strategy in suspected HF has led to reduced costs and length of hospital stay (JH, R., et al. 2008).

Results and Discussions.

Eighteen pacients aged between 36 and 82 years were taken in this study in almost all of their periods of hospitalization, with cardiovascular diseases, diagnostics like heart failure or atherosclerosis. The mean age of patients with cardiovascular diseases was 66,72 years.

For Galectin-3, the clinical interpretation of the results is performed according to three risk categories related to all causes of morbidity: “low risk” – is for a Galectin

concentration values between 3-17,8 ng/mL, "medium risk' for values between 17,8 and 25,9 ng/mL, and "high risk" for concentration values higher than 25,9 ng/mL (Blândă, V. et al., 2020).

Tabel 1. Descriptives

	Statistic						
	Mean	Median	SD	Min	Maxi	Range	IQR
LDH seric (UI/L)	421.17	407.50	109.35	266.00	615.00	349.00	161.00
CK-NAC (UI/L)	178.67	184.00	106.06	38.00	390.00	352.00	167.50
Galectin-3 (ng/mL)	13.71	13.40	2.76	8.80	18.80	10.00	3.90
NT-proPBN2 (pg/mL)	248.22	233.50	151.50	40.00	490.00	450.00	276.25
D-Dimer (ng/mL)	318.34	295.00	115.97	122.71	487.00	364.29	194.65
TGO/ASAT (UI/L)	31.39	22.00	26.17	16.00	126.00	110.00	11.75
TGP/LAT (UI/L)	29.89	23.00	21.80	11.00	91.00	80.00	17.75
R. RITIS (TGO/TGP)	1.05	1.16	.27	.57	1.40	.83	.54

Tabel 2. Pearson Correlations Galectin-3 and LDH, NT-proPBN2, D-dimer

		LDH seric (UI/L)	NT-proPBN2 (pg/mL)	D-Dimer (ng/mL)
Galectin-3 (ng/mL)	Pearson Correlation (r)	.493	.546	.657
	Sig. (2-tailed) (p)	.038	.019	.003
	N	18	18	18

Galectin-3 (ng/mL) correlates with LDH (UI/L) ($r = 0.493$, $p = 0.038 < \alpha = 0.05$, Correlation is positive, low to moderate, statistically significant.

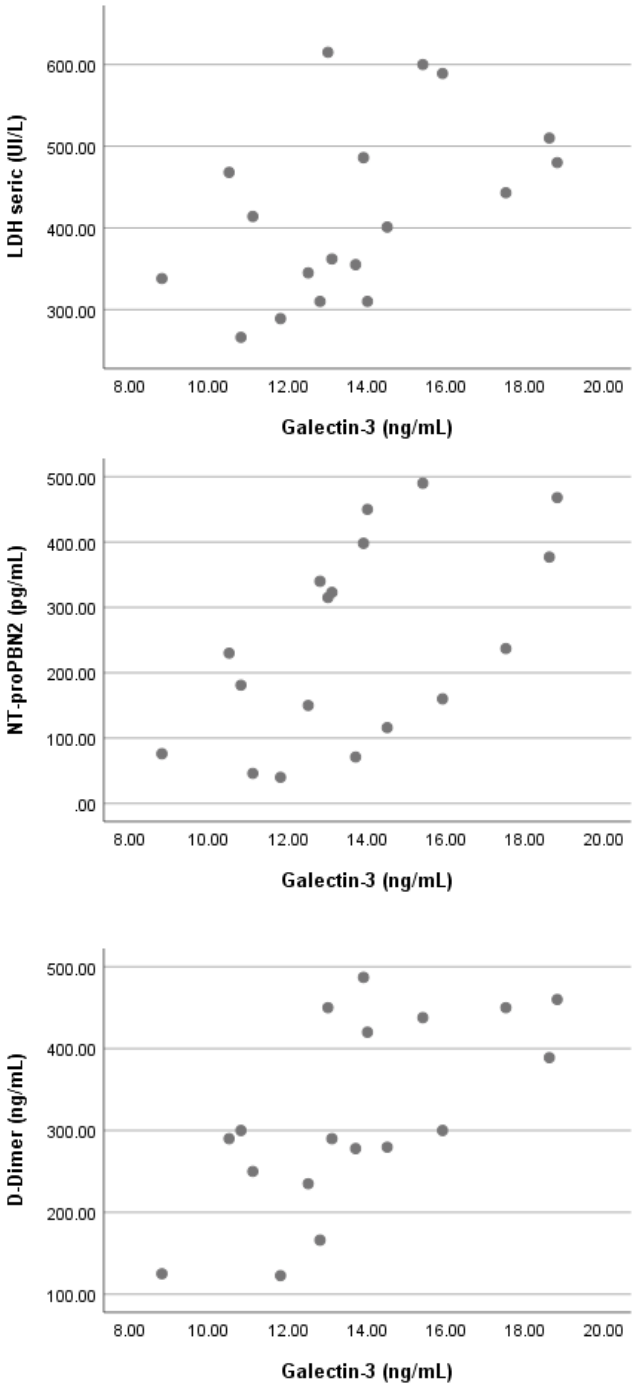

Fig. 1. Scatter-Plot Graphic representation of Galectin-3 / LDH / NT-proPBN2 / D-dimer values.

Tabel 3. D-Dimer/ R.Ritis correlations

		R. RITIS (TGO/TGP)
D-Dimer (ng/mL)	Pearson Correlation (r)	.767
	Sig. (2-tailed) (p)	.000
	N	18

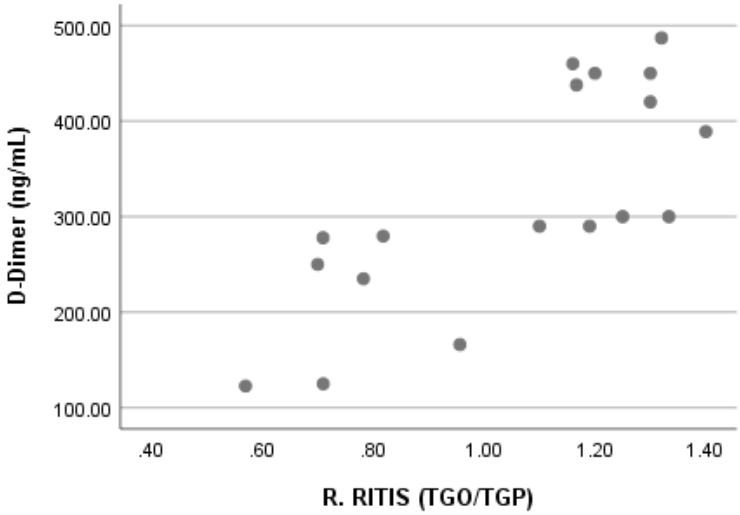

Fig. 1. Scatter-Plot Graphic representation of R.Ritis /D-dimer values.

D-Dimer (ng/mL) correlates with R. RITIS (TGO/TGP) ($r = 0.767$, $p < 0.0001 < \alpha = 0.05$, Correlation is positive, statistically significant.

The study showed correlations between Galectin-3 and LDH that is direct, low to moderate (r=0.493) and significant (p=0.038).

Pearson correlation between D-Dimer and R.Ritis is positive, strong (r=0.767) and significant (p<0.0001).

The association of Galectin-3 and NT-proBNP with D-dimer is superior NT-proBNP or D-Dimer and LDH in the identification of patients with acute forms of heart failure.

3. Conclusions

1. The positive correlations of biomarkers taken in the study demonstrate that a multimarker approach could be a superior predictor of cardiovascular disease, heart failure.

2. Galectin-3 is a marker with important prognostic value in cardiovascular disease; serum levels of Galectin-3 and NT-proBNP are directly correlated with strong statistical significance and is important in the risk assessment of patients with heart failure.

3. The statistical results of our study lead to assessment of the poor prognosis of patients with cardiovascular disease in whom the values of the two analytes are increased (high values of analytes are associated with poor prognosis).

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