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Heart Failure

Galectin-3 as a Biomarker to Predict Cardiorenal Syndrome in Patients with Acute Heart Failure

Serhan Ozyildirim,[1] Omer Dogan,[2] Hasan Ali Barman,[1] Selim Tanyolaç,[1] Adem Atıcı,[3] Rasim Enar[1] and Sait Mesut Doğan[1]

Background: Galectin-3 affects cardiac tissue inflammation as an inflammatory mediator. The development of cardiorenal syndrome in heart failure patients is associated with a poor prognosis. This study aims to investigate whether serum galectin-3 levels can be used as a biomarker to predict cardiorenal syndrome in heart failure patients with reduced left ventricular ejection fraction.

Methods: A total of 166 symptomatic heart failure patients [New York Heart Association (NYHA) functional class II-III] with reduced left ventricular ejection fraction (≤ 40%) were recruited prospectively. Cardiorenal syndrome type 1 was defined as an acute worsening of cardiac function leading to renal dysfunction. The patients were divided into two groups with and without cardiorenal syndrome. The galectin-3 levels of all patients were determined. The primary outcome of this study was the occurrence of cardiorenal syndrome.

Results: Cardiorenal syndrome developed in 41 patients. Galectin-3 levels were found to be higher in the patients with cardiorenal syndrome (+) compared to those without cardiorenal syndrome (–) (20.7 ± 2.9 ng/mL vs. 17.8 ± 3.1 ng/mL, $p < 0.001$). After performing a multivariable analysis, galectin-3 levels [odds ratio (OR): 3.21, $p = 0.001$], NYHA functional class (OR: 1.98, $p = 0.009$), creatinine (OR: 3.18, $p = 0.006$), furosemide dose (OR: 1.21, $p = 0.033$), and angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers usage (OR: 0.54, $p = 0.029$) were identified as independent predictors for the development of cardiorenal syndrome. Moreover, galectin-3 level demonstrated predictive capability for cardiorenal syndrome development (AUC = 0.761, $p < 0.001$).

Conclusions: Serum galectin-3 level showed an association with cardiorenal syndrome development in patients with heart failure, indicating potential usefulness as a prognostic biomarker.

Key Words: Cardiorenal syndrome • Galectin-3 • Heart failure

INTRODUCTION

A failing heart may induce dysfunction of the kidneys, which causes cardiorenal syndrome (CRS) due to complex heart-kidney interactions.[1] Hemodynamic cross-talk between the heart and kidneys is well known, but it is not the sole underlying mechanism. Several nonhemodynamic changes, including alterations in neurohormonal and inflammatory pathways that exacerbate the kidney injury, play a role in CRS, as with heart failure (HF) itself.[2] There is a complex bidirectional relationship between HF and inflammation, which involves interactions between the heart and multiple peripheral organs, such as the kidneys.[3] The value of inflammatory responses is well recognized as an important target in the diagnosis and management of HF.[4] Galectin-3 is involved in cardiac tissue inflammation as an inflammatory mediator. It is one of the 12 types of galectins that exist in humans, most of which have important metabolic and immune-modulating roles.[5]

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[1]Institute of Cardiology, Department of Cardiology, Istanbul University-Cerrahpaşa; [2]Department of Cardiology, Ministry of Health, Istinye State Hospital; [3]Istanbul Medeniyet University, Faculty of Medicine, Department of Cardiology, Goztepe Training and Research Hospital, Istanbul, Turkey.
Corresponding author: Dr. Omer Dogan, Department of Cardiology, Ministry of Health, Istinye State Hospital, Istanbul, Turkey. Tel: +90 5058976660; E-mail: omrdgn123@gmail.com

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
ADHERE	Acute Decompensated Heart Failure National Registry
AHF	Acute heart failure
AKI	Acute kidney injury
ARB	Angiotensin-receptor blockers
AUC	Area under the ROC curve
CI	Confidence interval
CRP	C-reactive protein
CRS	Cardiorenal syndrome
Gal-3	Galectin-3
GFR	Glomerular filtration rate
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
KDIGO	Kidney Disease: Improving Global Outcomes
LVEF	Left ventricular ejection fraction
NT-ProBNP	N terminal pro B type natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
ROC	Receiver operating characteristic

Biomarkers of cardiac and renal injury can be used to predict early CRS, differentiate CRS types, prognosticate CRS, and guide targeted treatment strategies. In previous studies, galectin-3 level has been shown to be an independent predictor of cardiovascular and all-cause mortality in addition to hospitalization for HF.[6] An elevated galectin-3 level has also been associated with impaired renal function in HF patients.[7,8]

We aimed to investigate whether serum galectin-3 level can be used as a biomarker to predict CRS in HF patients with reduced left ventricular ejection fraction (LVEF).

METHODS

Study population

Between February 2018 and December 2019, 166 symptomatic HF patients (New York Heart Association [NYHA] Functional class II-III) with reduced LVEF (≤ 40%) were recruited prospectively. Acute kidney injury (AKI) and related CRS were diagnosed according to the guidelines of Kidney Disease: Improving Global Outcomes. AKI was defined as either an increase in serum creatinine by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) within 48 hours or a urine volume ≤ 0.5 ml/kg/h for 6 hours.[9] The exclusion criteria were as follows: (a) chronic inflammatory diseases, which could involve the myocardium, (b) the presence of severe aortic stenosis and severe mitral stenosis, (c) history of recent acute coronary syndrome, (d) malignancy, and (e) electrocardiogram demonstrating depolarization disorders, such as Brugada syndrome, Wolff-Parkinson-White syndrome, or paced rhythms. The baseline demographic data are presented in Table 1. The NYHA functional classification was used to determine the patients' functional capacity and HF-related symptoms. Hemoglobin, fasting glucose, serum electrolytes, urea, creatinine, protein, and albumin levels were recorded as well as hs-troponin, N terminal pro B type natriuretic peptide (NT-ProBNP), C-reactive protein (CRP), and galectin-3 levels on admission. CRS was classified into five groups:[10] acute CRS type 1, an acute worsening of cardiac function leading to renal dysfunction; chronic CRS type 2, chronic abnormalities in cardiac function leading to renal dysfunction; acute reno-cardiac syndrome type 3, acute worsening of renal function causing cardiac dysfunction; chronic CRS type 4, chronic abnormalities in renal function leading to cardiac disease; and secondary CRS type 5, systemic conditions causing simultaneous dysfunction of the heart and kidneys. Only patients with CRS type 1 were included in this study.

Written informed consent was obtained from all patients. The study complies with the Declaration of Helsinki, and the trial protocol was approved by the local ethics committee. The treatment of HF was performed at the HF clinic by an experienced cardiologist team in accordance with the recent HF guidelines.[11]

Transthoracic echocardiography

Echocardiographic imaging through parasternal, apical, and subcostal windows was performed with a Philips Epiq-7 machine and X5-1 transducer (Philips Healthcare) in accordance with the latest American Society of Echocardiography guidelines.[12] LVEF was calculated by gathering and manually tracing through end-diastolic and end-systolic apical four-chamber views using Simpson's method.

Galectin-3 analysis

Galectin-3 levels were measured before treatment while the patients were hospitalized. Antecubital venous blood samples were obtained in the first 24 hours of ad-

Tablo 1. Baseline characteristics and outcomes of the CRS (+) and CRS (–) patients in study group

	CRS (+) (n = 41)	CRS (–) (n = 125)	p value
Age (years)	62.7 ± 11.0	64.2 ± 12.5	0.479
Female, n (%)	8 (19.5)	41 (32.8)	0.106
Systolic blood pressure (mmHg)	108 ± 20.1	124.6 ± 21.3	< 0.001
BMI (kg/m^2)	29.9 ± 7.9	28.3 ± 4.5	0.111
NYHA class	3.4 ± 0.6	2.8 ± 0.6	< 0.001
Smoker	17 (41.5)	57 (45.6)	0.644
Medical history, n (%)			
Hypertension	20 (48.8)	79 (63.2)	0.102
Diabetes mellitus	24 (58.5)	46 (36.8)	0.014
Hyperlipidemia	2 (4.9)	8 (6.4)	0.722
Ischaemic heart disease	23 (56.1)	77 (61.6)	0.532
COPD	4 (9.8)	14 (11.2)	0.796
Cerebrovascular disease	4 (9.8)	11 (8.8)	0.853
Laboratory findings			
Galectin-3 (ng/mL)	20.7 ± 2.9	17.8 ± 3.1	< 0.001
Creatinine (mg/dl)	1.50 (1.11-2.13)	1.15 (0.94-1.37)	0.001
Haemoglobin (g/dl)	11.4 ± 1.6	12.6 ± 2.6	0.009
Sodium (mmol/l)	135.1 ± 4.8	136.4 ± 4.9	0.171
Potassium (mmol/l)	4.4 ± 0.8	4.3 ± 0.7	0.494
Glucose (mg/dl)	139.7 ± 57.4	140.2 ± 74.9	0.972
Albumin (g/dl)	3.5 ± 0.56	3.6 ± 0.6	0.528
CRP (mg/l)	19 (4.65-49.50)	12 (4.77-27.45)	0.077
hs troponine (ng/L)	62 (18.5-105)	12 (6.2-27.6)	< 0.001
proBNP (pg/dl)	3865 (1834-10045)	826 (521-933)	< 0.001
Echocardiographic findings			
Ejection fraction (%)	23.3 ± 6.1	27.4 ± 6.0	< 0.001
Left atrial diameter (mm)	47.4 ± 8.2	44.7 ± 7.9	0.010
PASP (mmHg)	49.7 ± 14.7	44.2 ± 13.9	0.077
Mitral regurgitation degree	2.3 ± 1	1.86 ± 1	0.025
Treatment			
Beta-blocker, n (%)	31 (75.6)	95 (76)	0.960
ACE-i/ARB, n (%)	22 (57.3)	98 (78.4)	0.002
Anti-arrytmic drug, n (%)	20 (4.8)	44 (35.2)	0.121
Digoxin, n (%)	5 (12.2)	29 (23.2)	0.130
Statin, n (%)	12 (29.3)	53 (42.4)	0.135
Acetylsalicylic acid, n (%)	31 (75.6)	80 (64)	0.171
Oral anticoagulant, n (%)	16 (39)	43 (34.4)	0.591
Furosemide dose (mg/day)	300 (180-400)	180 (120-300)	0.001

ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRS, cardiorenal syndrome; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; proBNP, pro-brain natural peptide.

mission and stored at -80 C until analysis, following serum centrifugation at 3,000 rpm for 15 minutes at room temperature. Serum galectin-3 (35 kDa lectin) levels were measured using an E1951Hu Human Galectin-3 Enzyme-linked Immunosorbent Assay Kit (BT lab, Shangai Korain Biotech, Shangai, China) with a sensitivity of 2.49 pg/ml and a detection range of 5-2,000 pg/ml. Amino-terminal part concentrations of pro-brain natural peptide molecules (NT-proBNP) were detected in the core laboratory. The samples were analyzed and double-checked by the researchers, who were blinded to the clinical data of the patients.

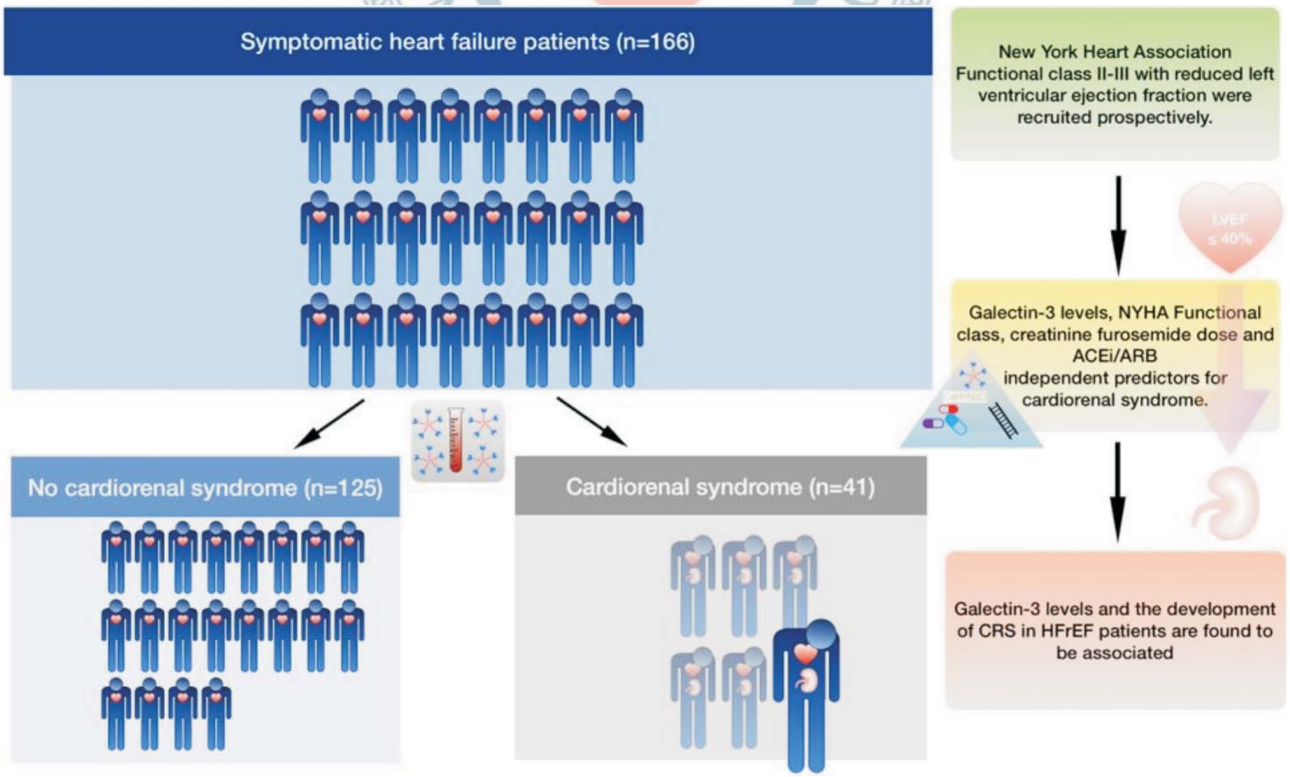
Statistical analysis

SPSS version 19.0 for Windows was used to analyze the data statistically. The normality of distribution was tested using the Kolmogorov-Smirnov test. Quantitative variables were expressed as the mean and standard deviation or median and interquartile range. Continuous data were expressed as mean ± standard deviation, and categorical data were expressed as percentages. Pearson's or Spearman's correlation analysis was used when appropriate to evaluate the relationships among parameters. The Student's t test or Mann-Whitney U test was used to compare unpaired samples. Univariate and multivariate logistic regression analyses were used to identify independent variables. Independent variables in the univariate analysis were NT-proBNP, galectin-3, NYHA class, presence of atrial fibrillation, age, and LVEF. These variables were utilized in a multivariate logistic regression analysis with the stepwise method. The results of the univariate and multivariate regression analyses were presented as odds ratio (OR) with a 95% confidence interval. The predictive ability of galectin-3 and NT-proBNP for the presence of CRS was evaluated using receiver operating characteristic (ROC) analysis. ROC curves were compared using the De-Long method. C statistics were calculated to compare galectin-3 and creatinine in the ROC curve analysis. The results were expressed as relative risk with 95% confidence intervals. Significance was assumed at a two-sided $p < 0.05$.

RESULTS

The study included 166 patients with heart failure with reduced ejection fraction (HFrEF), of whom 41 (24%) had CRS (CRS [+]) (Central Illustration). In the CRS (+) group, 19.5% were female, compared to 32.8% in the CRS (–) group, with no statistically significant difference in gender distribution. Systolic blood pressure was lower in the CRS (+) group than in the CRS (–) group ($p < 0.001$). The average BMI was higher in the CRS (+) group, but the difference was not statistically significant. NYHA class was higher in the CRS (+) group ($p < 0.001$).

The prevalence of chronic diseases including hypertension, chronic obstructive pulmonary disease, cere-



Central Illustration. *Galectin-3 levels and the development of cardiorenal syndrome (CRS) in heart failure with reduced ejection fraction (HFrEF) patients are found to be associated.*

brovascular disease, hyperlipidemia, and ischemic heart disease did not significantly differ between the two groups. However, diabetes mellitus was more frequent in the CRS (+) group (p = 0.014). Galectin-3 levels were higher in the CRS (+) group (p < 0.001), along with lower serum hemoglobin and higher hs-troponin, proBNP, creatinine, and CRP levels compared to the CRS (–) group. LVEF was lower in the CRS (+) group (p < 0.001), and left atrial diameter and mitral regurgitation severity were higher in the CRS (+) group (p = 0.01 and p = 0.025, respectively). There was no significant difference in pulmonary artery systolic pressure (PASP) level between the two groups.

The daily furosemide dose was higher in the CRS (+) group (p = 0.001), while angiotensin-converting enzyme inhibitor (ACEi)/angiotensin-receptor blockers (ARB) usage was lower in the CRS (+) group (p = 0.002). No significant differences were observed in the use of beta-blockers, statins, acetylsalicylic acid (ASA), digoxin, antiarrhythmic drugs, and oral anticoagulants between the two groups.

Logistic regression was carried out by univariate and multivariate analyses to predict the occurrence of CRS in the HFrEF patients. Galectin-3 level (OR: 3.21, p = 0.001), NYHA class (OR: 1.98, p = 0.009), creatinine (OR: 3.18, p = 0.006), furosemide dose (OR: 1.21, p = 0.033), and ACEi/ARB usage (OR: 0.54, p = 0.029) were identified to be independent predictors of CRS development (Table 2).

The specificity and sensitivity of galectin-3 level, NYHA, creatinine, and furosemide dose in predicting the development of CRS were evaluated using ROC analysis. The area under the curve (AUC) of galectin-3 level was 0.761 (0.676-0.847; p < 0.001) to predict the development of CRS, and a cut-off galectin-3 level of 19.7 ng/mL had 74% sensitivity and 70% specificity (Figure 1). In addition, the AUC values of NYHA class, creatinine level, and furosemide dose were 0.732 (0.64-0.824 p < 0.001) 0.656 (0.545-0.767, p = 0.003) and 0.68 (0.573-0.787, p = 0.001), respectively (Figure 1). Through the ROC analysis, all predictors (galectin-3 levels, NYHA, creatinine, and furosemide dose) were combined in a single model. The AUC for the model was 0.861 (0.800-0.921), with 79% sensitivity and 75% specificity (Figure 2). In addition, C statistics were calculated to compare galectin-3 and creatinine in the ROC curve analysis. There was no statistically significant difference between galectin-3 and creatinine (Z = 1.499, AUC = 0.099, p = 0.134).

DISCUSSION

The relationship between galectin-3 levels and de-

Table 2. Univariate and multivariate logistic regression analyzes to identify independent predictors of CRS development in HFrEF patients

Variable	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Galectin-3 levels	3.31	2.01-5.82	< 0.001	3.21	1.74-5.96	0.001
NYHA class	3.81	2.11-6.87	< 0.001	1.98	1.28-3.29	0.009
Gender (female)	2.01	0.85-4.75	0.110			
LVEF	0.90	0.84-0.96	0.001	0.90	0.84-1.09	0.089
Hemoglobin	0.79	0.66-0.94	0.008	0.88	0.67-1.15	0.242
HT	1.80	0.89-3.68	0.105			
hs troponine	1.01	0.98-1.03	0.785			
proBNP	1.05	0.45-4.07	0.970			
DM	0.41	0.20-0.85	0.016	0.69	0.32-2.14	0.592
Creatinine	3.60	1.90-6.83	< 0.001	3.18	1.37-6.95	0.006
CRP	1.14	1.05-1.21	0.009	1.03	0.95-1.09	0.693
Furosemide dose	1.34	1.09-1.71	< 0.001	1.21	1.06-1.49	0.033
ACEi/ARB	0.32	0.15-0.67	0.003	0.54	0.29-0.85	0.029

ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blockers; CI, confidence interval; CRP, C-reactive protein; CRS, cardiorenal syndrome; DM, diabetes mellitus; HT, hypertension; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio; proBNP, pro-brain natural peptide.

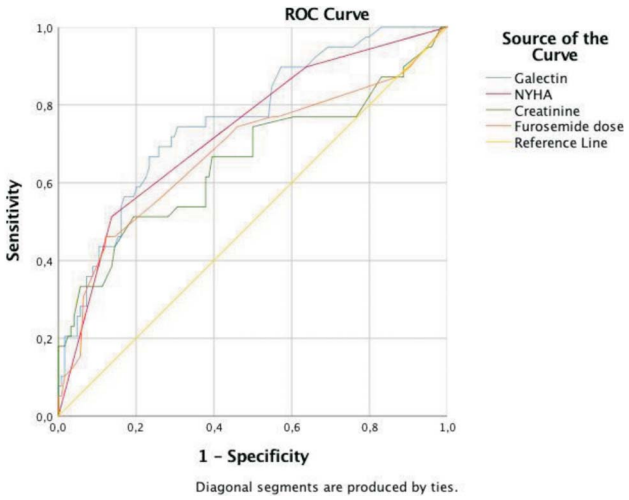


Figure 1. *The receiver operating characteristic (ROC) curves for galectin-3 levels, New York Heart Association (NYHA) Class, creatinine and furosemide dose.*

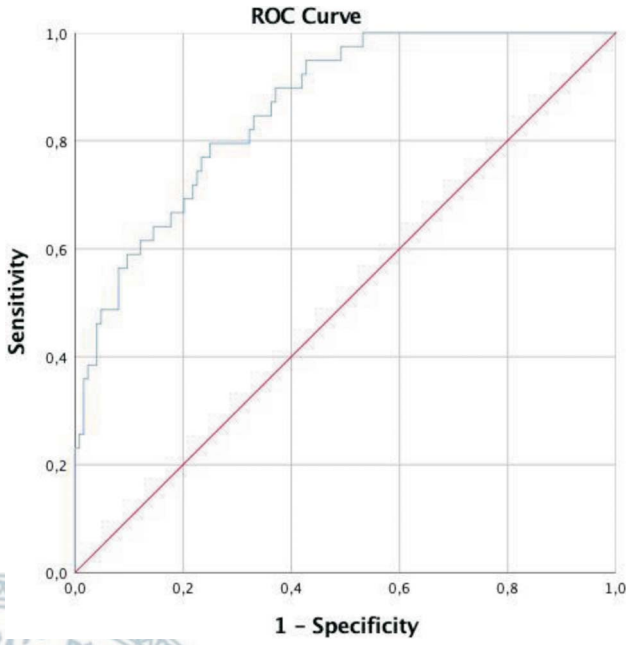


Figure 2. *Receiver operating characteristic (ROC) analysis with a single model created with all of the combine data [galectin-3 levels, New York Heart Association (NYHA) class, creatinine, furosemide dose].*

velopment of type-1 CRS in patients with acute HF and reduced LVEF was investigated in this study. The main finding is that the patients who developed CRS had a significantly higher galectin-3 level than those who did not develop CRS. The cut-off value for galectin-3, as an independent predictor of CRS development, was determined to be 19.7 ng/mL, with 74% sensitivity and 70% specificity. When the other predictors of CRS (NYHA class, creatinine, furosemide dose, and ACEi/ARB use) were combined with galectin-3 in a single model, the sensitivity and specificity increased to 79% and 75%, respectively, with an AUC value of 0.861 (0.800-0.921).

CRS defines a spectrum of disorders in which dysfunction of the heart or kidneys causes the dysfunction of the other. It is mainly grouped into five subtypes, and type 1 and 2 define that the kidney disease is induced by acute or chronic HF, respectively. The development of CRS during the course of HF is associated with worse clinical outcomes. In a study of the Acute Decompensated Heart Failure National Registry (ADHERE) database, which included 118,465 patients hospitalized with acute decompensated heart failure, only 9% of all patients had normal renal function, and more severe renal dysfunction was associated with worse in-hospital clinical outcomes.[13]

Creatinine is a biomarker that mainly reflects function of the glomeruli and does not reflect tubular function. Consequently, its level may stay within normal limits during an acute tubular injury. In addition, fluctuations in serum creatinine and urine output may not represent renal tubular injury (and therefore early CRS) in the setting of acute heart failure (AHF). A previous study reported that contrary to the decreased renal flow caused by HF, glomerular filtration rates can still be preserved.[14] The underlying mechanism in CRS cannot simply be explained with the hemodynamic alterations as hypoperfusion of the kidneys, but rather, it includes inflammatory pathways. A study of the ADHERE database reported that the incidence of kidney dysfunction was similar among AHF patients with reduced and normal systolic function.[13] A biomarker with a particular role in inflammation and fibrosis in both organs may define the risk of CRS before it becomes overt. Galectin-3 is an inflammatory protein that may provoke fibrosis in both organs, resulting in CRS during the course of CHF. It is important to determine which HF patients are at higher risk of developing AKI and CRS to prevent morbidity and mortality. Therefore, the possible predictive power of galectin-3 for type 1 CRS presented in this study may be valuable.

Previous reports regarding heart and kidney interactions have revealed that interstitial cells, such as macrophages, T lymphocytes, fibroblasts, and myofibroblasts, have common communication systems that utilize galectin-3, provoking the proliferation and activation of fibro-

blasts and myofibroblasts. This process results in fibrosis and the consequent dysfunction of both organs. Previous studies have concluded that galectin-3 is a strong predictor of adverse events in patients with HF, and that an elevated level of galectin-3 is associated with higher NYHA class and worse prognosis.[15] In our study, the HFrEF patients who developed CRS in follow-up had higher creatinine (1.5 mg/dl vs. 1.15 mg/dl, p = 0.001) and galectin-3 levels (20.7 ± 2.9 ng/mL vs. 17.8 ± 3.1 ng/mL, respectively; p < 0.001) than the CRS (–) group. The mean proBNP level of the CRS (+) group was 4.6 times higher than that of the CRS (–) group (3,865 vs. 826 pg/dl, respectively, p < 0.001), and the CRS (+) group had worse functional capacity (NYHA class 3.4 vs. 2.8, p < 0.001), lower systolic blood pressure (108 mmHg vs. 124 mmHg, p < 0.001), and lower LVEF with a larger left atrium accompanied by more severe mitral regurgitation. Anemia was more common in the CRS (+) group, with a mean hemoglobin value of 11.4 g/dl, than in the CRS (–) group, with an hemoglobin of 12.6 g/dl (p = 0.009). All of these features were indicative of more severe HF. Worsening HF and the risk of adverse events are possibly related to worsening renal function in a bidirectional manner. Therefore, increased galectin-3 levels may reflect the progression of the dysfunction of both organs. However, a cohort study on the predictive value of galectin-3 level in HF patients showed that a higher galectin-3 level was associated with poor renal function in patients with both normal and reduced LVEF, although there were no relationships between galectin-3 and hemodynamic or echocardiographic indexes.[15]

In our study, the cut-off value for galectin-3, as an independent predictor of CRS development, was determined to be 19.7 ng/mL, with 74% sensitivity and 70% specificity, and when the other predictors of CRS (NYHA class, creatinine, furosemide dose, and ACEi/ARB use) were combined with galectin-3 in a single model, the sensitivity and specificity increased to 79% and 75%, respectively, with an AUC value of 0.861 (0.8-0.921) (Figure 2). A multi-center study to determine galectin-3 assay performance characteristics revealed that galectin-3 could be detected in the plasma of healthy adults, and a central 95% normal reference was 3.8-21 ng/ml. In AHF patients, the galectin-3 level ranged from 4-75 ng/mL, and a cut-off level of 22.1 ng/mL was associated with increased mortality in this population. Galectin-3 was also associated with the severity of HF.[16]

In a post-hoc analysis of the AKINESIS study, which included 790 patients with AHF, a galectin-3 level over 25.9 ng/mL on admission was associated with more common renal tubular damage and AKI.[17] Perez et al. reported a sub-analysis of the Redinscor-II registry, and found that galectin-3 concentrations were negatively correlated with the renal function of patients with AHF, and were associated with an increased risk of 1-year mortality. The median value of galectin-3 in their study population was 23.2 ng/mL (17.3-32.1 ng/mL).[18] An independent association between galectin-3 level and kidney dysfunction with microalbuminuria in CHF patients was reported by Iacoviello et al. They reported that a galectin-3 cutoff value of 14.2 ng/mL could detect microalbuminuria with 74% sensitivity and 56% specificity.[19]

Biomarkers such as troponin and NT-proBNP are used as prognostic indicators in patients with HF. Galectin-3 is a marker of tissue inflammation and fibrosis in various organs, including the heart.[20] HF is a syndrome involving multiple organs, and other organs such as the kidneys can contribute to increased galectin-3 levels in HF. Inflammation is closely related to the onset and progression of HF, and the progression of HF is related to higher levels of galectin-3. Another reason for an increase in galectin-3 and accompanying CRS could be related to the renal handling of galectin-3, which appears to be altered in HF patients. Fractional galectin-3 clearance is reduced in HF patients, resulting in a further increase in plasma galectin-3 levels. Therefore, there is a complex and probably bidirectional relationship between galectin-3 level and kidney function in patients with HF. An elevated galectin-3 level in HF may be both a reason for and a consequence of further worsening of kidney function.[21] Furthermore, comorbidities such as diabetes, chronic kidney disease, and obesity are common in patients with HF, and they potentiate the chronic low-grade inflammation of HF through the activation of both innate and humoral immune systems, endothelial inflammation, and inflammatory mediators.[3]

Compatible with these findings, diabetes frequency was higher in the CRS (+) group when compared with the CRS (–) group in our study (58.5% vs. 36.8%, respectively; p = 0.014). This result was expected, as diabetes is an established risk factor for type 1 CRS.[1] Our results are also compatible with the ADHERE database, in which a higher

diuretic dose, inotrope use, nesiritide use, and less ACEi/ARB use were associated with worse renal function. Our results showed that among all medications, the frequency of ACEi/ARB use was significantly lower in the CRS (+) group than in the CRS (–) group (57.3% vs. 78.4%, respectively; p = 0.002). All other drugs, including beta-blockers, anti-arrhythmic drugs, digoxin, statins, acetylsalicylic acid, and oral anticoagulants were similar in both groups. The anti-inflammatory properties of ACEi/ARB may explain this result, because angiotensin II has pro-inflammatory effects via the production of reactive oxygen species, proinflammatory cytokines, and adhesion molecules.[22]

Hanberg et al. reported a lower concentration of galectin-3 at admission in HF patients under beta-blocker and spironolactone treatment. In addition, the daily furosemide dose was significantly higher in CRS (+) patients (300 vs. 180 mg; p = 0.001). Diuretic resistance accompanying a decrease in renal function may explain this finding. Progression of inflammation may constitute another mechanism for diuretic resistance in HF patients.[23] Loop diuretics may further activate the renin-angiotensin system and worsen intrarenal hemodynamics, and they have been identified as a modifiable in-hospital determinant of CRS type 1.[1] The higher loop diuretic dose in the CRS (+) group in our study was consistent with these data. De Boer et al. reported that galectin-3 levels were correlated with higher CRP levels in HF patients.[14] However, this inflammatory mechanism in relation to CRS was not supported by the CRP levels in our study. Although the mean CRP level in the CRS (+) group (19 mg/l) was higher than that in the CRS (–) group (12 mg/l), the difference was not statistically significant (p = 0.077). This could be due to low-grade inflammation that could not be detected solely by CRP, the sample size or other factors. However, in both cases, galectin-3 may be superior to CRP in detecting low-grade inflammation, which may constitute a possible mechanism for CRS. Moreover, inflammation in HF appears to be chronic from the outset; that is, monocytes and macrophages, the main source of galectin-3, are the predominant cellular responders in contrast with the polymorphonuclear leukocytes seen in acute inflammation. Therefore, the factors that initiate and regulate chronic inflammatory processes differ from those involved in acute inflammation, and probably link HF with kidney dysfunction.[24]

Galectin-3 level can be used as a useful biomarker to predict the development of CRS in patients with reduced LVEF and symptomatic HF. This information can aid clinicians in identifying high-risk patients and implementing appropriate interventions to improve their outcomes. Additionally, this study provides insight into the role of galectin-3 in cardiac tissue inflammation and its association with the development of CRS. Further research is needed to fully understand the underlying mechanisms and potential therapeutic targets related to galectin-3 in this population.

Limitations

Our study has some limitations. First, the study was single center. Second, there was a small number of patients. Third, there were no follow-up data, such as post-discharge death and rehospitalization. Fourth, patients with HFrEF were included in the study, but patients with heart failure with preserved ejection fraction (HFpEF) were excluded. In addition, the absence of a validation cohort is another limitation of the study.

CONCLUSIONS

In conclusion, there appears to be an association between galectin-3 level and the development of CRS in HFrEF patients. The early detection of CRS holds significance in HF patients, given the poor prognosis in those with CRS. Consequently, serum galectin-3 level may help to detect CRS early in patients with severe left ventricular dysfunction.

AUTHOR CONTRIBUTIONS

All authors contributed substantially to study conception and design, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

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DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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