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Differential and Predictive Value of Galectin-3 and Soluble Suppression of Tumorigenicity-2 (sST2) in Heart Failure with Preserved Ejection Fraction

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Background: Galectin-3 and soluble suppression of tumorigenicity-2 (sST2) are promising biomarkers of cardiac fibrosis and ventricular remodeling. The purpose of this study was to investigate the diagnostic and predictive value of galectin-3 and sST2 for use in patients who have heart failure with preserved ejection fraction (HFpEF).

Material/Methods: A total of 217 hospitalized patients with HF and 30 controls from a physical examination center were included. Venous blood was collected for the detection of circulating expression of galectin-3 and sST2. All the included patients were followed up regularly for 1 year (12±1 months).

Results: The concentrations of galectin-3 and NT-proBNP were substantially higher following decreased ejection fraction (both P=0.000), except for sST2 (P=0.068 *vs.* control). In ROC analyses, galectin-3 and NT-proBNP distinguished HFpEF from controls with an area under the curve (AUC) of 0.819 (95% CI: 0.75-0.89, P=0.000) and 0.806 (95% CI: 0.66–0.82, P=0.000). In contrast, sST2 obtained a lower AUC of 0.584 (95% CI: 0.49–0.68, P=0.17) compared to galectni-3 and NT-proBNP. After adjustment for clinical factors and NT-proBNP, galectin-3 was strongly correlated with an increased risk of the endpoint events in HFpEF patients, and the hazard ratio per 1 SD increase of the galectin-3 level was 2.33 (95%CI: 1.72–2.94, P=0.009).

Conclusions: Galectin-3 is superior to sST2 in distinguishing HFpEF from controls and HFrEF.

MeSH Keywords: Biological Markers • Galectin 3 • Heart Failure • N-Terminal Acetyltransferase B

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Background

According to the 2016 ESC guidelines, heart failure (HF) can be divided into heart failure with preserved ejection fraction (HFpEF), heart failure mid-range ejection fraction (HFmrEF), and heart failure with reduced ejection fraction (HFrEF). At present, the incidence of HFpEF accounts for 40–70% of the total number of HF cases, which is rising compared with the incidence of 31–47% in previous years [1]. The pathophysiology of HFpEF is not yet clear. It is currently believed that impaired left ventricular diastolic function and decreased myocardial compliance result in impaired left ventricular diastolic filling and increased left ventricular end-diastolic pressure [2–4]. Age, sex, diabetes, obesity, hypertension, and cardiomyopathy are all related to the incidence of HFpEF [5]. Although large international clinical trials have focused on beneficial treatment strategies, little progress has been made in finding evidence-based and effective treatments for HFpEF [6–8]. Therefore, early risk stratification is essential for slowing the progression of heart failure and improving patient outcomes.

Biomarkers are an indispensable indicator of risk stratification in HF, especially in HFpEF. Galectin-3 and soluble suppression of tumorigenicity-2 (sST2) are emerging fibrotic biomarkers that are thought to be valuable in predicting HF [9]. Galectin-3 is a soluble galactoside-binding protein involved in cell adhesion, proliferation, migration, and apoptosis, and is closely related to the process of neovascularization, immune response, and inflammation. Galectin-3 is delivered by macrophages during myocardial stress and activates fibroblasts. Activated fibroblasts can lead to the deposition of collagen into the extracellular matrix and initiate a pro-fibrotic process. In the myocardium, this process promotes ventricular remodeling and eventually leads to heart failure [10]. Recent study revealed that galectin-3 plays a vital role in the pathophysiology of HF, such as myofibroblast proliferation, inflammation, fibrogenesis, and ventricular remodeling [11]. Moreover, circulating galectin-3 levels are a strong predicator of risk of HF hospitalization or death [12]. Soluble ST2 is a member of the interleukin (IL)-1 receptor family and consists of 2 isoforms, a transmembrane ligand (ST2L) and a soluble, circulating form (sST2). Binding of IL-33 to the ST2L protects against cardiac dysfunction by reduced remodeling, reduced fibrosis, and preserved LV function [9]. There is ample evidence showing that sST2 provides incremental value to N-terminal pro-B-type natriuretic peptide (NT-proBNP) in chronic heart failure (CHF) and acute heart failure (AHF) [13, 14]. Our previously study also verified the prognostic values of sST2 in different types of HF [15].

In HFpEF, the underlying phenotypic heterogeneity might be a key reason for the poor results of HFpEF clinical trials, which is characterized by an increase in cardiomyocytes stiffness and deposition of extracellular matrix. Although the American Heart Association (AHA) has recommended galectin-3 and sST2 as an adjunct to natriuretic peptide for risk stratification in HF [16], few data are available concerning their prognostic value in HFpEF. Therefore, in the present study we compared the circulating levels of sST2, galectin-3, and NT-proBNP in HFrEF, HFpEF, and controls and assessed their ability to predict adverse cardiovascular events in patients with HFpEF.

Material and Methods

Study population

We consecutively included patients at the Cardiology Department of the Tianjin Union Medical Center (Tianjin, PR. China) from April 2014 to August 2016. Three hundred inpatients diagnosed with heart failure were evaluated [17] and followed up for 1 year to evaluate clinical outcomes. Controls without HF were randomly selected from the physical examination center of the same hospital. Hospitalization with HF refers to a first diagnosis of HF or acute exacerbation of chronic stable HF requiring unplanned hospitalization. All HF episodes are determined by cardiologists based on the value of the biomarkers and validated according to the criteria of the European Society of Cardiology (ESC) guidelines [17]. A total of 55 patients were excluded (23 of whom were diagnosed with heart failure with moderate ejection fraction) and 28 were lost during the 1-year follow-up. Exclusion criteria included HF secondary to congenital heart disease and severe valve disease, severe renal and liver dysfunction, malignant diseases, autoimmune diseases, and other diseases resulting in <1-year life expectancy. Informed consent was obtained from all subjects, and the study was approved by the Ethics Committee board of Tianjin Union Medical Center.

Study procedures

All clinical data (including patients' demographic characteristics, accompanying diseases, clinical HF sign, and medication history and in-hospital biochemical data) were recorded by a single researcher and checked by a clinical specialist. After an overnight fast for >8 h, blood samples were collected from all participants and immediately centrifuged at 3000 rpm for 10 min to obtain plasma and serum. Then, the samples were separated into tubes and stored at –80 until analysis. LVEF were performed by transthoracic Doppler echocardiography using the standard protocol or biplane Simpson's method. Patients confirmed to have HF with an LVEF less than or equal to 40% were classified as HFrEF, and LVEF greater than or equal to 50% was classified as HFpEF. Patients with an LVEF ranging from 40% to 49% were considered as heart failure with mid-range ejection fraction (HFmrEF). Hence, 23 patients were classified

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as "grey zone", 172 patients were classified as HFpEF, and 45 patients were classified as HFrEF.

Follow-up and outcomes

All the patients were followed up regularly for up to 1 year (12±1 months). Data were collected from clinic visits, telephone interviews, medical records, and family members. Subsequent adverse events were cardiovascular death and rehospitalization due to HF exacerbation.

Measurement of biomarkers

Fasting venous blood samples were collected on the day after admission and centrifuged to collect serum and plasma. In our Core Laboratory, the concentration of galecin-3 was measured in serum with a Human Galectin-3 Assay Kit (Immuno-Biological Laboratories Co., Japan). Soluble ST2 concentrations were detected in serum with the human sST2 enzyme-linked immunosorbent assay (ELISA) (Qiyi Biological Co., Shanghai, China). NT-proBNP was measured by a Roche Diagnostics® electrochemiluminescent immunoassay (Roche Diagnostics, Mannheim, Germany). The range of detection was 8–400 pg/ml for sST2 and 0.7–22 ng/ml for galectin-3.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) version 19.0. Categorical variables are expressed as percentages or numbers. Continuous variables with normal distribution are expressed as mean ±SD and as medians and interquartile range (IQR) for variables with skewed distribution. Comparisons of biomarkers used the Mann-Whitney U test or Kruskal-Wallis test. Spearman rho correlation coefficient was used to assess relationships among biomarkers. The sensitivity and specificity of biomarkers were assessed by receiver operating characteristic (ROC) curve, and the optimum cut-off points were calculated using the Youden index. Logarithmic transformation was carried out to normalize the distribution of NT-proBNP, sST2, and galectin-3. Multivariable Cox regression analysis with a backward selection procedure was used to identify predictors of adverse cardiac events. Two sets of models were predefined: Model 1 was adjusted for age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart function of grade NYHA, LVEF, coronary artery disease (CAD), hypertension, β-blockers treatment, aldosterone receptor antagonist, eGFR, and LDL cholesterol, while Model 2 added NT-proBNP. All statistical tests were 2-tailed, and p values <0.05 were considered statistically significant.

Results

Baseline characteristics

Table 1 provides an overview of the clinical characteristics of all 247 patients (135 females, 54.7%) enrolled in this study: 172 (69.6%) patients were classified as HFpEF and 45 (18.2%) as HFrEF, while the remaining 30 patients from the physical examination center were used as a control group. Patients with HFpEF tended to be older and female, and to have a higher proportion of NYHA II, a higher SBP, and worse hypertension morbidity. Known coronary heart disease and diabetes were more prevalent in the HFrEF group. Reduced renal function was observed in HFpEF and HFrEF, manifested by elevated creatinine and decreased estimated glomerular filtration rate (eGFR). It is noteworthy that the mitral E/e' ratio was significantly higher in both HF groups, especially in HFpEF.

Expression levels of biomarkers and the correlation with clinical parameters

As shown in Figure 1, galectin-3 and NT-proBNP levels were significantly raised with the decrease of ejection fraction, except sST2 (P=0.068 *vs.* control). Patients with higher plasma galectin-3 levels were more likely to have elevated hsCRP (r=0.138, p=0.042) and E/e' ratio (r=0.153, p=0.000), and lower systolic blood pressure (r=–0.248, p=0.001) and eGFR (r=–0.346, p=0.000). Elevated sST2 was correlated with hsCRP (r=0.163, p=0.016) and reduced ejection fraction (r=–0.57, p=0.000). In the total cohort, NT-proBNP was correlated with both galectin-3 and sST2 (r=0.379, p=0.000; r=0.322, p=0.000). In addition, NT-proBNP was also related to eGFR (r=–0.245, p=0.000) and LVEF (r=–0.488, p=0.000) (Table 2).

Distinguishing HFpEF from HFrEF and the general population

As show in Figure 2A, compared with controls, HFpEF groups had the greatest area under the ROC curve of galectin-3 (0.819), and the optical cut-off value was 9.55 ng/ml (sensitivity 65%, specificity 86%). The AUC for NT-proBNP was 0.806 (sensitivity 60.5%, specificity 80%), which was different from that of sST2 (AUC=0.584, sensitivity 48%, specificity 57%). The optical cut-off value of NT-proBNP and sST2 were 295.85 pg/ml and 68.6 pg/ml, respectively. With respect to patients from different HF groups, the areas under the curve were NT-proBNP (AUC=0.901), galectin-3 (AUC=0.863) and sST2 (AUC=0.824) (Figure 2B). These results suggest that galectin-3 is better than sST2 in identifying HFpEF from HFrEF and controls (Table 3).

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Table 1. Demographic and clinical baseline characteristics and treatments.

	Control (n=30)	HFpEF (n=172)	HFrEF (n=45)	*P* value
Clinical characteristics				
Age, years	67±4.79	73±9.19	71.14±8.59	.265
Female, %	12 (40)	96 (55.8)	27 (39.3)	.015
BMI, kg/m^2	24 (19.3, 28.7)	24.2 (22.1, 26.3)	24.3 (22, 26.6)	.892
Heart rate, beats/min	71.2 (67.5, 75.8)	76.2 (70, 84)	80 (70, 91)	.374
Systolic blood pressure, mmHg	120 (115, 125)	140 (125, 150)	120 (111, 135)	.002
Diastolic blood pressure, mmHg	73.5±6.34	72±11.01	63.26±14.01	.071
Hypertension, %	–	124 (72)	25 (31.8)	.029
Diabetes mellitus, %	–	52 (30.2)	24 (54.5)	.007
Coronary artery disease, %	–	128 (74.4)	40 (90.9)	.051
Atrial fibrillation, %	–	36 (21)	11 (25)	.056
NYHA class, %	–			
II	–	41	21	
III	–	23	34	
IV	–	8	44	
Laboratory values				
Hemoglobin, g/dl	148.72±16.57	131.87±19.85	130.32±27.56	.549
hsCRP, mg/L	2.7 (1.2, 7.8)	5.3 (2.7, 10.6)	11.9 (6.6, 11.6)	.041
Creatinine, mg/dl	62 (54, 71.3)	81.6 (54, 83)	101 (65, 113)	.016
eGFR, ml/min/1.73 m^2	97.98±10.48	85.41±32.16	67.45±27.16	.001
LDL-c, mg/dl	3.0±0.54	2.81±0.71	2.57±0.75	.021
sST-2, pg/ml	61.7 (50, 70)	63.48 (49.55, 86.54)	140.2 (81.14, 164.7)	.068
Galectin-3, ng/ml	6.96 (6.2, 8.51)	9.42 (8.15, 10.55)	12.9 (10.64, 16.2)	.000
NT-proBNP, pg/ml	189 (132.5, 213.75)	614 (242.5, 1478.5)	4330 (1746.5, 10013)	.000
Echocardiographic data				
LVEF, %	58.5 (56.8, 60)	60 (56.3, 62)	31 (28, 34.5)	.034
Mitral E/e' ratio	7.2 (5.4, 12.6)	17.7 (12.7, 22.6)	14.3 (11.5, 17)	.026
Medication				
Beta blocker, %	2 (7)	69 (40)	29 (65.9)	.314
ACEI or ARB, %	5 (16.7)	68 (39.5)	20 (44.5)	.130
Dioxin, %	–	9 (5.2)	20 (45.5)	.000
Aldosterone antagonist, %	–	58 (33.7)	36 (81)	.000
Statin, %	7 (23.3)	108 (62.8)	32 (72.7)	.532
Adverse events				
Adverse events, %	–	15 (9)	17 (38.6)	.015

HFrEF – heart failure with reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; hsCRP – high sensitivity C reactive protein; eGFR – estimated glomerular filtration rate; LDL-c – low-density lipoprotein cholesterol; LVEF – left ventricular ejection fraction; ACEI – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; NT-proBNP – N-terminal pro B-type natriuretic peptide; sST2– soluble suppression of tumorigenicity-2. Data are presented as the mean ±SD, median (interquartile range) or %. P<0.05 means a statistically significant difference between groups. * p<0.05 *vs.* control, # p<0.05 *vs.* HFpEF.

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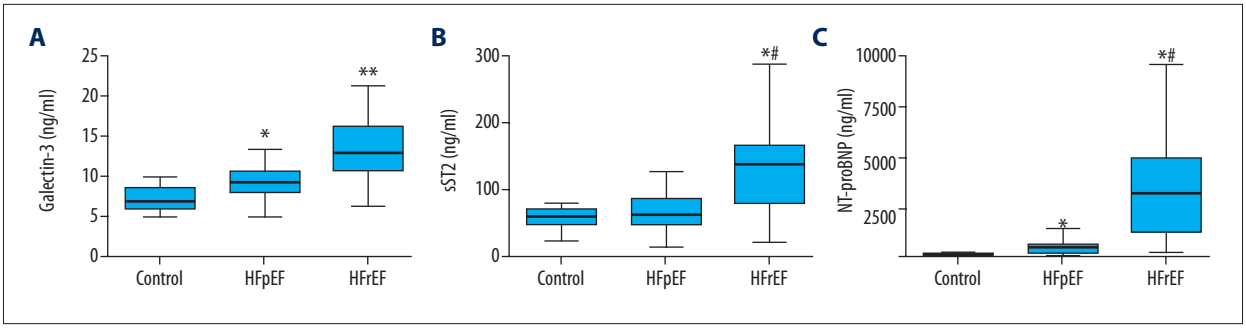

Figure 1. Biomarker values according to left ventricular ejection fraction. Comparison of galectin-3 (**A**), sST2 (**B**), and NT-proBNP (**C**) between HFpEF, HFrEF, and controls. Soluble suppression of tumorigenicity-2 (sST2), N-terminal pro-B-type natriuretic peptide (NT-proBNP). * P<0.05 *vs.* Control, # P<0.05 *vs.* HFpEF.

Table 2. Spearman correlation coefficient among galectin-3, sST-2 and NT-proBNP and clinical parameters.

Parameter	Galectin-3	sST2	NT-proBNP
Galectin-3	n.a.	r=0.279 p=0.000	r=0.379 p=0.000
sST-2	r=0.279 p=0.000	n.a.	r=0.322 p=0.000
NT-proBNP	r=0.379 p=0.000	r=0.322 p=0.000	n.a.
Age	r=0.148 p=0.051	r=0.003 p=0.562	r=0.055 p=0.398
Sex	r=0.088 p=0.14	r=0.027 p=0.677	r=0.077 p=0.231
Systolic blood pressure	r=–0.248 p=0.001	r=–0.104 p=0.106	r=0.021 p=0.742
eGFR	r=–0.346 p=0.000	r=–0.105 p=0.103	r=–0.245 p=0.000
hsCRP	r=0.138 p=0.042	r=0.163 p=0.016	r=0.108 p=0.111
LVEF	r=–0.085 p=0.16	r=–0.57 p=0.000	r=–0.488 p=0.000
E/e'	r=0.153 p=0.000	r=0.047 p=0.351	r=0.036 p=0.484

eGFR – estimated glomerular filtration rate; hsCRP – high sensitivity C reactive protein; LVEF – left ventricular ejection fraction; sST2 – soluble suppression of tumorigenicity-2; NT-proBNP – N-terminal pro B-type natriuretic peptide.

Associations of biomarkers with adverse events of different types HF

In Cox regression analyses, both galectin-3 and sST2 were strong predictors of 1-year adverse events in HF patients, regardless of adjustment for Model 1 (clinical data) and Model 2 (Model 1 +NT-proBNP) (Table 4). For patients with HFrEF, sST2 also showed strong predictive power (HR: 2.36, 95% CI: 1.82–3.01, P=0.000; adjusted for NT-proBNP, HR: 2.08, 95% CI: 1.56–2.72, P=0.023), but not galectin-3. For patients with HFpEF, galectin-3 regained significant prognostic value (HR: 2.57, 95% CI: 2.18–2.84, P=0.000; adjusted for NT-proBNP, HR: 2.33, 95% CI: 1.72–2.94, P=0.009). When NT-proBNP was included in multivariate analysis, sST2 lost a statistically significant association with adverse events, which is contrary to galectin-3.

Discussion

HFpEF is a very common entity with distinct features from HFrEF. However, there is scant data on the use of biomarkers to diagnose HFpEF, and natriuretic peptide levels alone may

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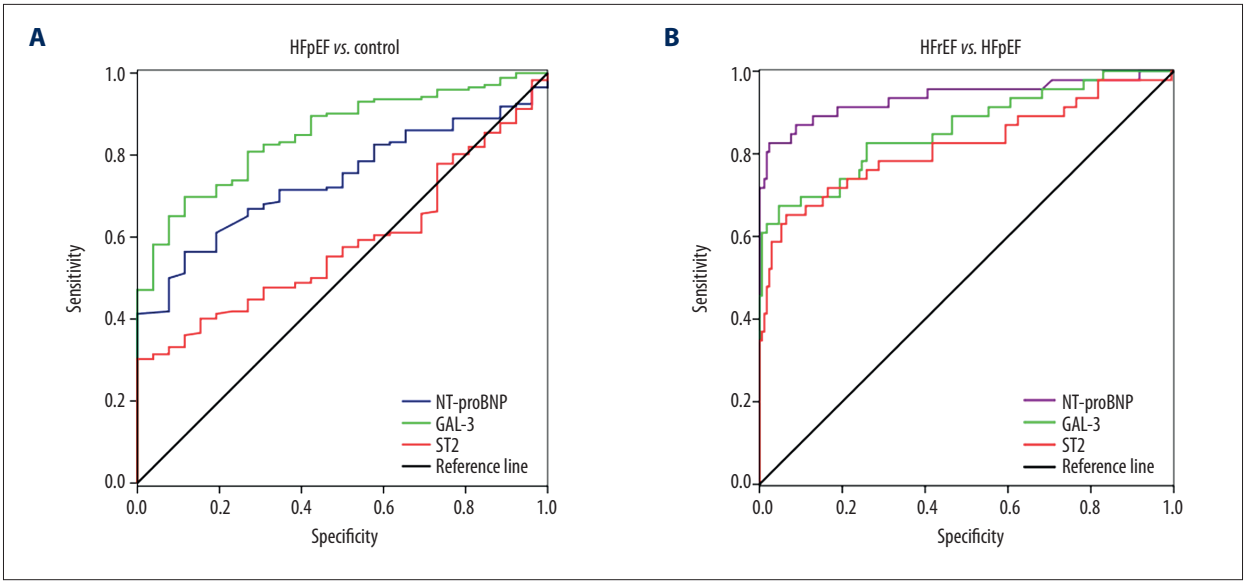

Figure 2. Receiver operating characteristic (ROC) curve analyses for the different conditions of HF and differentiation of HFrEF *vs.* HFpEF. (**A**) HFpEF *vs.* Control. (**B**) HFrEF *vs.* HFpEF.

Table 3. ROC curves for distinguish HFpEF from controls and HFrEF.

	AUC (95% CI)		P-value	Sensitivity	Specificity
HFpEF *vs.* Control					
NT-proBNP	0.806	(0.66, 0.82)	0.000	60.5%	80%
Galectin-3	0.819	(0.75, 0.89)	0.000	65%	86%
sST2	0.584	(0.49, 0.68)*	0.17	48%	57%
HFrEF *vs.* HFpEF					
NT-proBNP	0.901	(0.85, 0.96)	0.000	95%	60%
Galectin-3	0.863	(0.79, 0.93)	0.000	89%	60%
sST2	0.824	(0.73, 0.90)	0.000	82%	56%

ROC – receiver operating characteristic curve; NT-proBNP – N-terminal pro brain natriuretic peptide; sST2 – soluble suppression of tumorigenicity-2; HFrEF – heart failure with reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction. * P<0.05 *vs.* NT-proBNP.

not be sensitive to diastolic dysfunction. Biomarkers that reflect collagen homeostasis have been shown to correlate with the presence and severity of HFpEF in the PARAMOUNT trial [18], which focused on the identification and predication capability of galectin-3 and sST2 to distinguish HFpEF from HFrEF. All of the markers had similar associations with HFrEF compared to HFpEF. Both galetin-3 and sST2 were significantly associated with adverse cardiovascular events in patients with HF after correction for clinical factors and NT-proBNP, but only galectin-3 maintained the strong prognostic ability for HFpEF and sST2 did not. Our study demonstrates that galectin-3 might be a potential biomarker in the identification of HFpEF.

Galectin-3, a biomarker of heart failure, is controversial because of its impact on many variables, such as NT-proBNP and renal function [19,20]. However, recent studies indicated that serum galectin-3 levels are directly related to left ventricular end-diastolic pressure and heart function in patients with HFpEF [21,22]. In the COACH study, 592 patients with retained and reduced left ventricular function were studied, and de Boer et al. showed that elevated galectin-3 levels were strongly negatively correlated with adverse cardiovascular outcomes in patients with HFpEF [23]. Our results indicated that elevated galectin-3 in HFpEF was accompanied by increasing diastolic dysfunction (higher E/e') and systolic dysfunction (lower LVEF), which are associated with frequent rehospitalization

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Table 4. Multivariable Cox regression analysis for 1-year outcome prediction.

	Model 1 HR (95% CI)	P-value	Model 2 HR (95% CI)	P-value
Patients with HF				
Log galectin-3	2.69 (2.09, 2.82)	0.003	2.15 (1.74, 2.58)	0.045
Log sST2	2.33 (1.96, 2.71)	0.002	2.09 (1.54, 2.64)	0.026
Patients with HFrEF				
Log galectin-3	1.46 (1.20, 1.67)	0.613	1.11 (0.98, 1.27)	0.678
Log sST2	2.36 (1.82, 3.01)	0.000	2.08 (1.56, 2.72)	0.023
Patients with HFpEF				
Log galectin-3	2.57 (2.18, 2.84)	0.000	2.33 (1.72, 2.94)	0.009
Log sST2	1.34 (1.14, 1.57)	0.089	1.29 (1.17, 1.42)	0.156

Model 1 is adjusted for age, sex, systolic blood pressure, diastolic blood pressure, heart function of grade NYHA, left ventricular ejection fraction, coronary artery disease, hypertension, β-blockers treatment, aldosterone receptor antagonist, LDL cholesterol and eGFR. Model 2 is additionally adjusted for NT-proBNP. eGFR – estimated glomerular filtration rate; NT-proBNP – N-terminal pro-B type natriuretic peptide.

and increased mortality [24]. Galectin-3 is controversial due to its vulnerability to some variables, like NT-proBNP and renal function. Zhang et al. [20] reported that both sST2 and galectin-3 were strongly associated with death in patients with HF with an eGFR ≥60 ml/min/1.73 m^2, but the association between galectin-3 and death was not significant in patients with eGFR <60 ml/min/1.73 m^2. In our study, Cox regression analyses showed that galectin-3 could be used as a reference to predict one-year adverse events in patients with HFpEF, even after adjusting for clinical parameters and NT-proBNP. The reason for the difference between the 2 studies may be that the renal function of the HF patients in this study was acceptable, especially in patients with HFpEF with an average of 85.41 ml/min/1.73 m^2.

Since sST2 is less influenced by natriuretic peptides, renal function, and LV function, and it can be a strong predictor of stable and acute HF prognosis [25]. Our study showed that sST2 predicts prognosis of patients with HFrEF but not HFpEF. In addition, serum sST2 concentration was significantly negatively correlated with LVEF, which means sST2 measurement provides a serologic overview of cumulative myocardial fibrotic and systolic dysfunction processes.

Our study has certain limitations. Firstly, gelectin-3 distinguished HFpEF from controls with a cut-off value of 9.55 ng/ml and distinguished HFpEF from HFrEF with a cut-off value of 12.8 ng/ml, which differs from results of the ALDO-DHF study (cut-off value of 12.1 ng/ml to distinguish HFpEF from controls) [22]. The small sample size and differences in kits used might be the reason of the differences in cut-off values. Secondly, we lacked a dynamic observation of galectin-3 to assess its changes in heart failure progression. Thirdly, galectin-3 is not a cardiac-specific biomarker, its levels were susceptible to many factors, and aggregating multiple clinical indicators may provide reliable predictive information for HFpEF. Both galetin-3 and sST2 were significantly associated with adverse cardiovascular outcomes in HF after correction for clinical factors and NT-proBNP, but only galectin-3 showed the optimal capacity in patients with HFpEF.

Conclusions

The comparison of 2 new-generation fibrosis biomarkers revealed that circulating galectin-3 was obviously elevated in HFrEF and HFpEF patients, but not in patients with sST2. Both galectin-3 and sST2 predicted the occurrence of adverse cardiac events, but only galectin-3 has a clear advantage in predicting HFpEF. These findings suggest that the detection of circulating galectin-3 changes might be an early sign leading to clinical diagnosis of HFpEF.

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