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Evaluation of Soluble ST2 and Galectin-3 Levels in Patients with Heart Failure

Kalp Yetersizliği Olan Hastalarda Çözünür ST2 ve Galektin-3 Düzeylerinin Değerlendirilmesi

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

ABSTRACT

Objective: Soluble stromelysin-2 (sST2) and galectin-3 have been found to be associated with prognosis in patients with heart failure (HF). However, there is no study evaluating the clinical importance of sST2 and galectin-3 in HF classification according to ejection fraction (EF). In the present study, we aimed to assess the diagnostic value of sST2 and galectin-3 in HF classification based on EF.

Method: Forty-one heart failure patients with reduced ejection fraction (HFrEF), 41 with mildly-reduced EF (HFmrEF), 41 with preserved EF (HFpEF), and 41 healthy controls were included in the study. EF ≤ 40% was defined as HFrEF, 41-49% as HFmrEF, and ≥ 50% as HFpEF. Levels of sST2 and galectin-3 were measured, and comparisons were performed.

Results: There were significant differences among the groups in terms of sST2 ($P < 0.001$) and galectin-3 ($P = 0.007$) levels. Post hoc analysis demonstrated that patients with HFmrEF and HFrEF had significantly higher sST2 ($P = 0.001$ and $P = 0.001$, respectively) and galectin-3 ($P = 0.043$ and $P = 0.007$, respectively) levels compared to the control group, whereas the HFpEF and control groups were similar in terms of sST2 and galectin-3 levels ($P = 0.645$ and $P = 0.436$, respectively). In correlation analysis, sST2 and galectin-3 levels were positively correlated with B-type natriuretic peptide (BNP) ($r = 0.240$, $P = 0.002$ and $r = 0.172$, $P = 0.028$, respectively) and negatively correlated with EF ($r = -0.403$, $P < 0.001$ and $r = -0.295$, $P < 0.001$, respectively).

Conclusion: sST2 and galectin-3 levels were higher in patients with HFrEF and HFmrEF compared to the control group, and these markers increased as EF decreased. However, these markers did not differ between patients with HFpEF and the control group.

Keywords: Heart failure, stromelysin 2, galectin-3

ÖZET

Amaç: Soluble Stromelysin-2 (sST2) ve galektin-3'ün kalp yetersizliği (KY) hastalarının prognozu ile ilişkili olduğu gösterilmiştir. Ancak, ejeksiyon fraksiyonu (EF) temelinde KY sınıflandırmasında sST2 ve galektin-3'ün klinik önemini değerlendiren hiçbir çalışma bulunmamaktadır. Mevcut çalışmada, EF temelinde KY sınıflandırmasında sST2 ve galektin-3'ün tanısal değerini incelemeyi amaçladık.

Yöntem: EF'si azalmış 41 KY hastası (HFrEF), EF'si hafif azalmış 41 hasta (HFmrEF), EF'si korunmuş 41 hasta (HFpEF) ve 41 sağlıklı kontrol grubu çalışmaya dahil edildi. EF ≤ 40% HFrEF, %41 ile %49 arası HFmrEF ve ≥5 0% HFpEF olarak tanımlandı. Hastaların sST2 ve galektin-3 düzeyleri ölçüldü ve karşılaştırmalar yapıldı.

Bulgular: Gruplar arasında sST2 ($P < 0.001$) ve galektin-3 ($P = 0.007$) düzeyleri açısından önemli farklar vardı. Post hoc analiz, HFmrEF ve HFrEF hastalarında sST2 (sırasıyla $P = 0.001$ ve $P = 0.001$) ve galektin-3 (sırasıyla $P = 0.043$ ve $P = 0.007$) düzeylerinin kontrol grubuna göre anlamlı derecede daha yüksek olduğunu, buna karşılık HFpEF ve kontrol gruplarının sST2 ve galektin-3 düzeyleri açısından benzer olduğunu (sırasıyla $P = 0.645$ ve $P = 0.436$) gösterdi. Korelasyon analizinde, sST2 ve galektin-3 düzeyleri BNP ile pozitif korelasyon gösterirken (sırasıyla $r = 0.240$, $P = 0.002$ ve $r = 0.172$, $P = 0.028$), EF ile negatif korelasyon gösterdi (sırasıyla $r = -0.403$, $P < 0.001$ ve $r = -0.295$, $P < 0.001$).

Sonuç: sST2 ve galektin-3, kontrol grubuna kıyasla HFrEF ve HFmrEF hastalarında daha yüksekti ve bu belirteçler EF azaldıkça daha da arttı. Ancak, bu belirteçler HFpEF hastaları ile kontrol grubu arasında farklılık göstermedi.

Anahtar Kelimeler: Kalp yetersizliği, stromelysin-2 galektin-3

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Heart failure (HF) is a clinical syndrome defined as a functional and/or structural abnormality of the heart, resulting in elevated intracardiac pressures and/or inadequate cardiac output.[1] It is still the most important cause of mortality and morbidity worldwide. It places a substantial burden on both patients and society and leads to high healthcare costs.[2] The incidence and prevalence of HF increases with age, and this increase is even more pronounced in individuals over 60 years of age.[3] Because HF is associated with poor prognosis, the underlying pathophysiological mechanisms should be well understood, diagnosed early, and treated effectively.

Biomarkers can assist physicians in the diagnosis of heart failure, risk stratification, and treatment guidance. To date, many biomarkers have been investigated in patients with HF. Current guidelines state that B-natriuretic peptide (BNP or pro-BNP) can be used as an important biomarker for the diagnosis, follow-up, and prognosis of HF.[1] On the other hand, studies investigating additional biomarkers are still ongoing. Soluble suppression of tumorigenicity (sST2) and galectin-3 are biomarkers that have recently begun to be used in clinical practice.[4,5]

Galectin-3 is encoded by the LGALS3 gene, which is located on chromosome 14. This biomarker is a member of the beta-galactosidase-binding protein family and is secreted by macrophages. It is a multifunctional protein that plays a critical role in many pathophysiological processes, including cell growth, differentiation, programmed cell death, cell adhesion, angiogenesis, inflammation, fibrogenesis, and tumor progression.[4] On the other hand, ST2 is a member of the interleukin (IL)-1 receptor family and is synthesized on chromosome 2q12. ST2 exists in two different forms: the transmembrane receptor ST2 ligand (ST2L) and the soluble form (sST2).[5] Interaction between ST2L and IL-33 has been shown to have cardioprotective effects in experimental models, improving myocardial function and reducing myocardial fibrosis, myocyte hypertrophy, and apoptosis. The cardioprotective effect of this interaction is mediated only through the ST2L receptor and not through sST2. sST2 binds to ST2L by competing with IL-33 and inhibits IL-33 binding to ST2L. Thus, the ST2L/IL-33 interaction does not occur, and the cardioprotective effects described above are abolished.[6] Studies have shown that sST2 and galectin-3 levels are significantly elevated in patients with HF, and increased levels of these markers are significantly correlated with the severity of HF.[7-9] In the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for chronic HF, measurement of galectin-3 and sST2 is recommended to determine the risk level of patients with chronic HF.[10]

Although increased levels of sST2 and galectin-3 have been demonstrated in heart failure patients with reduced ejection fraction (HFrEF),[11,12] the clinical significance of these two biomarkers in HF patients with mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) has not been clarified. This study aimed to examine the clinical value of sST2 and galectin-3 levels in ejection fraction (EF)-based heart failure classification.

ABBREVIATIONS

BNP	B-type natriuretic peptide
EF	Ejection fraction
HF	Heart failure
HFmrEF	Heart failure patients with mildly-reduced EF
HFpEF	Heart failure patients with preserved EF
HFrEF	Heart failure patients with reduced ejection fraction
IL	Interleukin
sST2	Soluble stromelysin-2
ST2L	ST2 ligand
TTE	Transthoracic echocardiography

Materials and Methods

The study was initiated after approval from Harran University Clinical Research Ethics Committee (Approval Number: HRÜ/22.16.12, Date: 22.08.2022).

The study population was selected from outpatients admitted to the cardiology outpatient clinic of Harran University Medical Faculty Hospital who were not in acute respiratory distress and who underwent transthoracic echocardiography (TTE). A total of 123 HF patients (41 with HFrEF, 41 with HFmrEF, and 41 with HFpEF) and 41 control subjects (164 participants in total) were included in the study. All authors adhered to the Declaration of Helsinki and conducted the study appropriately. Furthermore, no artificial intelligence-supported applications were used in our study.

The diagnosis of HF and classification of subtypes were made according to the 2021 European Society of Cardiology (ESC) heart failure guideline. HF subtypes were determined based on left ventricular EF. According to these guidelines, HF classification based on EF is as follows: EF ≤ 40% indicates heart failure with reduced EF, EF between 41% and 49% indicates heart failure with mildly reduced EF, and EF ≥ 50% indicates heart failure with preserved EF.1 Patients aged ≥ 18 years who were diagnosed with HF based on medical evaluations were included in the study. Patients aged < 18 years; those with active infection, severe liver or kidney disease; pregnant women; patients diagnosed with acute coronary syndrome within the previous six months; patients with inflammatory or autoimmune diseases, malignancy, sepsis, or thyroid dysfunction; and patients who did not undergo TTE were excluded from the study. Written informed consent was obtained from all participants.

All patients included in the study underwent a detailed echocardiographic examination. All echocardiographic examinations were performed using the Vivid S6 device (GE Healthcare, Wauwatosa, USA). Echocardiographic measurements were obtained in the supine or left decubitus position using appropriate windows, in accordance with the American Society of Echocardiography recommendations. The modified Simpson's method was used for left ventricular EF measurements. End-systolic and end-diastolic diameters of the left ventricle (LVESD and LVEDD, respectively), left atrium (LA), interventricular septum (IVS), and right ventricle (RV), were measured and recorded.[13]

Statistical Analysis

The evaluations were performed using the SPSS (Statistical Package for the Social Sciences) version 22.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess the distribution of variables. Continuous data with normal distribution were presented as mean ± standard deviation (SD), whereas continuous data without normal distribution were presented as

Table 1. Comparison of baseline characteristics among heart failure subtypes and control patients

	Control (n = 41)	HFpEF (n = 41)	HFmrEF (n = 41)	HFrEF (n = 41)	*P*
Age (years), (mean±SD)	56.6 ± 8.9	56.6 ± 9.6	56.6 ± 12.6	58.6 ± 14.8	0.831
Gender, female (%)	20 (48.8)	26 (63.4)	10 (24.4)	15 (36.6)	**0.003**
BMI, kg/m²	29.4 ± 4.4	32.2 ± 6.7	28.3 ± 3.7	27.9 ± 4.6	**0.001**
SBP (mmHg)	125.9 ± 23.9	127.3 ± 20.1	123.4 ± 25.0	117.2 ± 20.5	0.192
DBP (mmHg)	69.0 ± 15.3	70.3 ± 12.2	69.8 ± 12.9	68.8 ± 13.3	0.955
HT (%)	17 (41.5)	24 (58.5)	24 (58.5)	18 (43.9)	0.244
DM (%)	12 (29.3)	12 (29.3)	7 (17.1)	8 (19.5)	0.425
HL (%)	7 (17.1)	9 (22)	10 (24.4)	2 (4.9)	0.088
Rhythm (%)					**0.021**
SR	41 (100)	41 (100)	37 (90.2)	36 (87.8)	
AF	0 (0)	0 (0)	4 (9.8)	5 (12.2)	
LBBB (%)	2 (4.9)	1 (2.4)	6 (14.6)	27 (65.9)	**<0.001**

AF, Atrial fibrillation; BMI, Body mass index; DBP, Diastolic blood pressure; DM, Diabetes mellitus; HFmrEF, Heart failure patients with mildly-reduced EF; HFpEF, Heart failure patients with preserved EF; HFrEF, Heart failure patients with reduced ejection fraction; HL, Hyperlipidemia; HT, Hypertension; LBBB, Left bundle branch block; SBP, Systolic blood pressure; SR, Sinus rhythm.

median (25th–75th percentiles). Categorical data were presented as numbers (%). Continuous data with normal distribution were compared using the t-test, while the Mann-Whitney U test was used for data without normal distribution. Comparisons of more than two independent groups were performed using analysis of variance (ANOVA) for normally distributed variables. In the presence of differences between groups, Bonferroni and/or Tukey post hoc tests were applied to determine which groups accounted for the differences. The Kruskal-Wallis test was used to compare more than two independent groups that did not follow a normal distribution. In the presence of a difference between groups, the Mann-Whitney U test with Bonferroni correction was applied to determine the source of the difference. Correlation analyses were performed using Pearson and Spearman correlation coefficients. Receiver operating characteristic (ROC) curve analyses were conducted to determine the area under the curve and cut-off values of soluble ST2 and galectin-3 levels for predicting heart failure subtypes. The predictive validity of sST2 and galectin-3 was quantified using the area under the ROC curve (AUC), and comparisons were performed using MedCalc version 16 statistical software (trial version) with the DeLong test. A post hoc power analysis was performed and indicated that the power of the study was 97% for sST2 and 75% for galectin-3. A p value < 0.05 was considered statistically significant.

Results

A total of 123 HF patients and 41 control subjects were included in the study, with 41 patients each in the HFrEF, HFmrEF, and HFpEF groups. A comparison of baseline characteristics among the groups is presented in Table 1. There were significant differences among the four groups in terms of sex (P = 0.003) and body mass index (BMI) (P = 0.001). Subgroup analyses showed that the frequency of female sex (P < 0.001 and P = 0.015, respectively) and BMI (P = 0.003 and P = 0.001, respectively) were significantly higher in patients with HFpEF compared to those with HFmrEF and HFrEF.

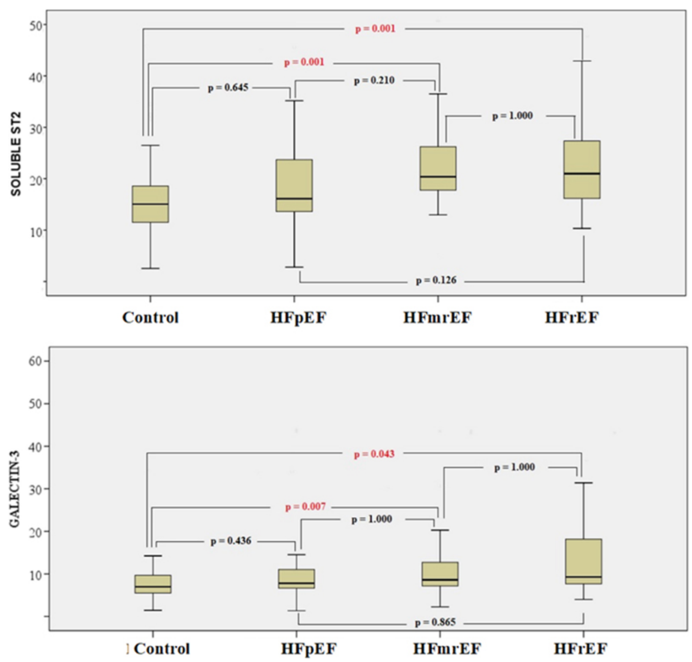


Figure 1. Comparison of sST2 and galectin-3 levels among heart failure subtypes and the control group.

HFmrEF, Heart failure patients with mildly-reduced EF; HFpEF, Heart failure patients with preserved EF; HFrEF, Heart failure patients with reduced ejection fraction.

The comparison of laboratory data between the patient and control groups is shown in Table 2. There were significant differences among the groups in urea (P = 0.014), creatinine (P < 0.001), uric acid (P = 0.007), N-terminal pro–B-type natriuretic peptide (NT-pro BNP) (P < 0.001), sST2 (P < 0.001), and galectin-3 (P = 0.007) (Table 2). Post hoc analyses revealed that sST2 (P = 0.001 and P = 0.001, respectively) and galectin-3 levels (P = 0.043 and P = 0.007, respectively) were significantly higher in the HFmrEF

Table 2. Laboratory characteristics of heart failure subtypes and the control group

	Control (n = 41)	HFpEF (n = 41)	HFmrEF (n = 41)	HFrEF (n = 41)	*P*
Urea (mg/dL) (median [Q1-Q3])	32.1 (24.6-38.5)	29.9 (26.3-38.5)	29.9 (25.6-36.3)	38.5 (29.9-52.4)	**0.014**
Creatinine (mg/dL) (mean±SD)	0.79 ± 0.14	0.8 ± 0.19	0.89 ± 0.19	0.95 ± 0.20	**< 0.001**
Glucose (mg/dL) (median [Q1-Q3])	112 (93.5-135.0)	103 (92.5-130.5)	100 (93.5-125.5)	103 (90.5-130.0)	0.667
Uric acid (mg/dL) (mean±SD)	4.9 ± 1.2	5.3 ± 1.4	5.3 ± 1.4	6.0 ± 1.5	**0.007**
Sodium (mmol/L) (mean±SD)	139.9 ± 3.0	140 ± 2.1	139.9 ± 2.1	140.1 ± 2.0	0.976
Potassium (mmol/L) (mean±SD)	4.3 ± 0.3	4.4 ± 0.3	4.3 ± 0.4	4.3 ± 0.4	0.942
Albumin (g/dL) (mean±SD)	4.4 ± 0.2	4.4 ± 0.2	4.3 ± 0.3	4.3 ± 0.2	0.584
LDL-C (mg/dL) (median [Q1-Q3])	101.8 (83.0-132.2)	103 (81.3-131.3)	91 (72.4-103.8)	105.8 (73.1-123.6)	0.104
TSH (uIU/dL) (median [Q1-Q3])	1.3 (0.9-1.6)	1.3 (0.9-2.2)	1.1 (0.7-1.7)	1.0 (0.7-2.0)	0.255
CRP (mg/dL) (median [Q1-Q3])	0.4 (0.1-0.6)	0.7 (0.2-1.1)	0.3 (0.1-0.8)	0.5 (0.2-1.0)	0.105
Leukocytes (x10³/uL) (median [Q1-Q3])	8.4 (6.7-10.8)	7.6 (6.6-9.2)	7.7 (6.4-9.7)	8.6 (7.4-9.9)	0.188
Hematocrit (%) (mean±SD)	41.9 ± 5.5	42.6 ± 4.1	43.7 ± 3.9	43.2 ± 4.9	0.329
Hemoglobin (g/dL) (mean±SD)	13.4 ± 1.8	14.1 ± 1.5	14.2 ± 1.6	14.1 ± 1.6	0.148
Platelets (x10³/uL) (median [Q1-Q3])	288 (236.0-331.5)	275 (217.0-344.0)	245 (211.5-327.5)	255 (232.0-312.5)	0.254
NT pro-BNP (pg/mL) (median [Q1-Q3])	88.8 (53.2-167.0)	85.8 (50.4-162.5)	138 (105.0-510.0)	769 (321.0-1289.5)	**< 0.001**
Soluble ST2, ng/L (median [Q1-Q3])	15.0 (9.6-20.2)	16.1 (13.5-26.9)	20.3 (17.1-26.6)	20.9 (16.1-28.4)	**< 0.001**
Galectin-3, ng/Ml (median [Q1-Q3])	7.0 (5.4-9.7)	7.8 (6.4-12.4)	8.6 (6.9-13.2)	9.2 (7.5-18.6)	**0.007**

AF, Atrial fibrillation; BMI, Body mass index; CRP, C-reactive protein; DBP, Diastolic blood pressure; DM, Diabetes mellitus; HFmrEF, Heart failure patients with preserved ejection fraction; HFpEF, Heart failure patients with reduced ejection fraction; HL, Hyperlipidemia; HT, Hypertension; HFrEF, Heart failure patients with reduced ejection fraction; LDL-C, Low-density lipoprotein cholesterol; LBBB, Left bundle branch block; NT pro-BNP, N-terminal pro b-type natriuretic peptide; SBP, Systolic blood pressure; SR, Sinus rhythm; TSH, Thyroid-stimulating hormone.

Table 3. Echocardiographic characteristics of heart failure subtypes and control patients

	Control (n = 41)	HFpEF (n = 41)	HFmrEF (n = 41)	HFrEF (n = 41)	*P*
LVEF (%) (mean±SD)	60.0 ± 2.2	57.7 ± 2.7	44.3 ± 1.5	29.2 ± 4.2	**< 0.001**
LVEDD (cm) (mean±SD)	4.8 ± 0.4	5.0 ± 0.5	5.1 ± 0.5	6.2 ± 0.7	**< 0.001**
LVESD (cm) (mean±SD)	3.3 ± 0.2	3.5 ± 0.4	3.9 ± 0.4	5.1 ± 0.6	**< 0.001**
IVS (cm) (mean±SD)	0.9 ±0.1	1.0 ± 0.3	1.0 ± 0.1	0.9 ± 0.2	**0.042**
LA (cm) (mean±SD)	3.4 ± 0.2	3.7 ± 0.3	3.6 ± 0.5	4.1 ± 0.5	**< 0.001**
Ascending Aorta (cm) (mean±SD)	3.4 ± 0.3	3.6 ± 0.4	3.4 ± 0.3	3.6 ± 0.4	0.104
RV (cm) (mean±SD)	3.5 ± 0.2	3.5 ± 0.2	3.6 ± 0.3	3.7 ± 0.5	**0.026**
E/e' (mean±SD)	7.0 ± 0.9	14.6 ± 0.9	12.0 ± 2.1	15.9 ± 1.0	**< 0.001**

HFmrEF, Heart failure patients with mildly-reduced EF; HFpEF, Heart failure patients with preserved EF; HFrEF, Heart failure patients with reduced ejection fraction; IVS, Interventricular septum; LA, Left atrium; LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameter; RV, Right ventricle.

and HFrEF groups than in the control group. On the other hand, sST2 and galectin-3 levels (P = 0.645 and P = 0.436, respectively) were similar between the HFpEF and control groups (Figure 1).

A comparison of echocardiographic parameters among the study groups is shown in Table 3. As expected, there was a significant difference in EF among the groups. Additionally, LVEDD, LVESD, and LA differed significantly among the groups. Post hoc analysis indicated that these differences were mainly between the HFrEF group and the other groups.

Correlation analysis was performed to evaluate the relationships between galectin-3 and sST2 levels and laboratory and echocardiographic variables. We observed that sST2 levels were positively correlated with BNP (r = 0.240, P = 0.002) and negatively correlated with EF (r = -0.403, P < 0.001). Similarly, galectin-3 levels showed a positive correlation with BNP (r = 0.172, P = 0.028) and a negative correlation with EF (r = -0.295, P < 0.001) (Figure 2).

In our study, ROC analysis was performed to determine the AUC, optimal cut-off values, sensitivities, and specificities of galectin-3 and sST2 levels in predicting HFrEF and HFmrEF compared to the control group. ROC curve analyses of sST2 and galectin-3 for predicting HFrEF are shown in Figure 3. An sST2 value ≥ 18.62 predicted HFrEF with 73.2% sensitivity and 75.6% specificity (AUC: 0.751, 95% confidence interval [CI]: 0.646-0.856, P < 0.001). A galectin-3 value ≥ 7.61 predicted HFrEF with 75.6% sensitivity and 61% specificity (AUC: 0.708, 95%

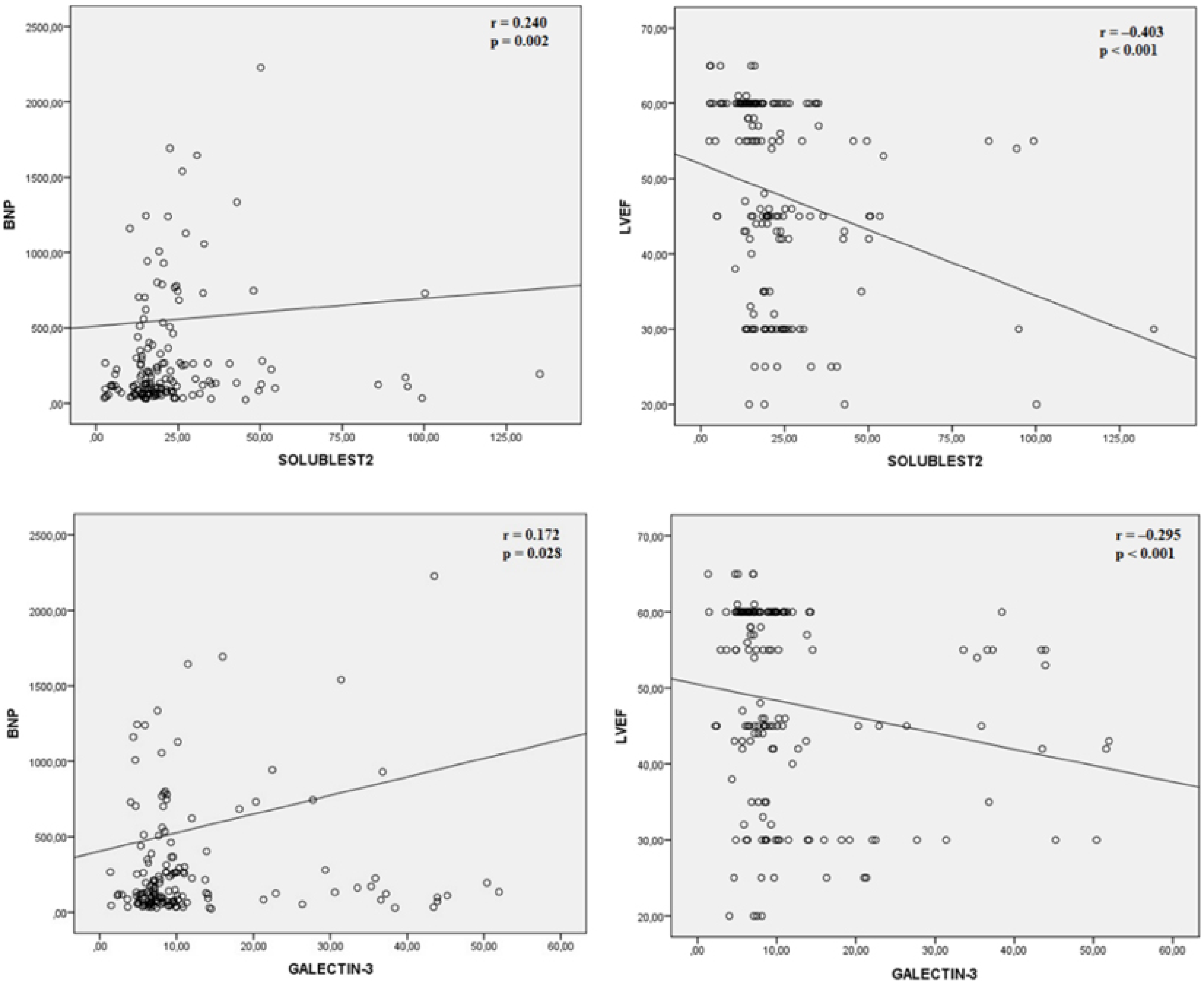


Figure 2. Correlation of sST2 and galectin-3 with BNP levels and left ventricular ejection fraction.

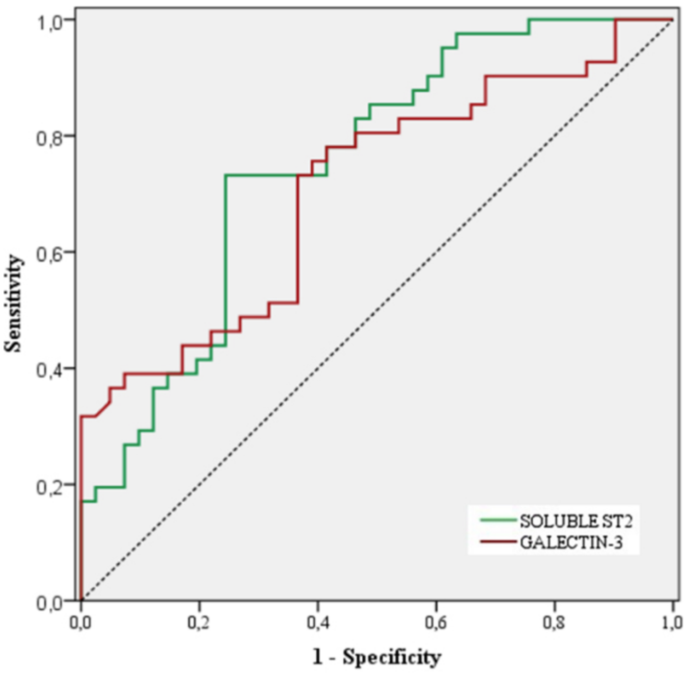
BNP, B-type natriuretic peptide; SOLUBLEST2,Soluble stromelysin-2.

CI: 0.595-0.820, P = 0.001). When we compared the AUC values of sST2 and galectin-3 for predicting HFrEF, we found that the AUCs of sST2 and galectin-3 were comparable (0.751 vs. 0.708, P = 0.455). ROC curve analysis of soluble ST2 and galectin-3 levels for predicting HFmrEF is shown in Figure 4. Accordingly, an ST2 value ≥ 18.78 predicted HFmrEF with 68.3% sensitivity and 75.6% specificity (AUC: 0.740, 95% CI: 0.632-0.848, P < 0.001). A galectin-3 value ≥ 7.17 predicted HFmrEF with 75.6% sensitivity and 58.5% specificity (AUC: 0.672, 95% CI: 0.555-0.789, P = 0.007). When the AUC values of sST2 and galectin-3 were compared for predicting HFmrEF, the AUC of sST2 tended to be higher than that of galectin-3 (0.740 vs. 0.672, P = 0.098).

Discussion

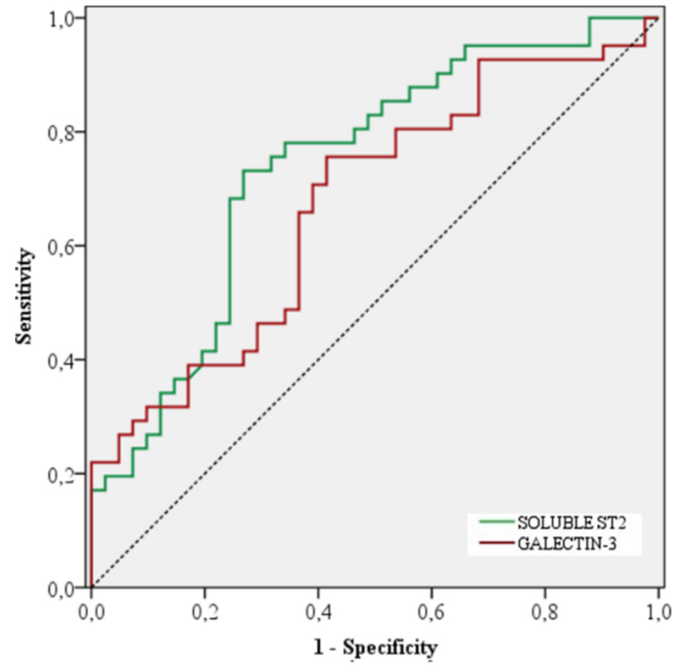
The results of the current study can be summarized as follows: (I) galectin-3 and sST2 levels were significantly increased in HF patients compared to the control group; (II) galectin-3 and sST2 levels were significantly higher in the HFrEF and HFmrEF subgroups compared to the control group, whereas no significant difference was observed between the HFpEF and control groups in terms of these two biomarkers; and (III) galectin-3 and sST2 levels were positively correlated with BNP and negatively correlated with left ventricular ejection fraction (LVEF). EF-based heart failure classification was first defined in the 2016 ESC HF guidelines as HFrEF, HFmrEF, and HFpEF. Although sST2 and galectin-3 have been evaluated separately in these HF subtypes in previous studies, to our knowledge, this study is the first to examine ST2 and galectin-3 across all three HF subtypes simultaneously.

Galectin-3 and sST2 are novel biomarkers of inflammation and fibrosis that have been increasingly used in patients with HF in recent years. Because inflammation and fibrosis play a very important role in the natural history of HF, these biomarkers



	AUC	95 % CI	P
Soluble ST2	0.751	0.646-0.856	<0.001
Galectin-3	0.708	0.595-0.820	0.001

Figure 3. Receiver operating characteristic (ROC) curve analysis of soluble ST2 and galectin-3 levels for predicting heart failure with reduced ejection fraction (HFrEF).



	AUC	95 % CI	P
Soluble ST2	0.740	0.632-0.848	<0.001
Galectin-3	0.672	0.555-0.789	0.007

Figure 4. Receiver operating characteristic (ROC) curve analysis of soluble ST2 and galectin-3 levels for predicting heart failure with mildly reduced ejection fraction (HFmrEF).

provide valuable information in this patient population.[14] However, both biomarkers are influenced by general pathological processes such as fibrosis, programmed cell death, and inflammation in other parts of the body; therefore, they are not specific to the cardiovascular system.[15] While enrolling patients in our study, we excluded individuals with conditions such as acute infection, inflammatory or autoimmune diseases, malignancy, and renal or hepatic insufficiency to eliminate the effects of potential non-cardiac factors that may influence galectin-3 and sST2 levels. Therefore, we suggest that our results were not affected by these confounding factors.

In the 2016 ESC HF guidelines, HFmrEF was defined for the first time, and three HF subtypes were classified according to left ventricular EF: HFrEF, HFmrEF, and HFpEF.[16] There are conflicting results regarding this newly defined HFmrEF subtype. Some studies have shown an overlap between HFmrEF and the other two classes, whereas others have not demonstrated such a relationship.[17] The etiologic factors for HFrEF and HFpEF are well known. It has been reported that comorbid conditions, female sex, and obesity are more frequent in patients with HFpEF.[18] In our study, we also found that female sex and BMI were higher in patients with HFpEF compared to other HF subtypes. In addition, hypertension (HT) and diabetes mellitus (DM) were more common in these patients compared to those with HFrEF, although the difference did not reach statistical significance. These findings obtained in our study support the literature. Although the pathophysiological pathways in the HFrEF and HFpEF subtypes are relatively well understood, the pathophysiology of HFmrEF, a newer classification, has not yet been fully elucidated. Current evidence suggests that HFmrEF may result from progressive deterioration of left ventricular function in patients with HFpEF or, conversely, from improvement in left ventricular systolic function in patients with HFrEF.[17] However, it is also thought that HFmrEF may be a distinct condition from the other two HF subtypes. For these reasons, further studies are needed to better elucidate the pathogenesis of HFmrEF.

Numerous studies have investigated sST2 and galectin-3 levels in patients with HF. Most have shown that sST2 and galectin-3 levels are elevated and associated with poor prognostic outcomes in HF patients.[14,19-23] In addition, increased galectin-3 levels have been independently associated with an increased risk of developing HF in the general population.[24] Moreover, it has been reported that sST2, unlike NT-proBNP, is not affected by age, BMI, renal function, or HF etiology in patients with HFrEF and is superior to NT-proBNP in predicting one-year mortality in patients with HFpEF and HFrEF.[25,26]

Although sST2 and galectin-3 levels have been frequently examined in patients with HFrEF and HFpEF in previous studies, data regarding these parameters in patients with HFmrEF are very limited. Najjar et al.[27] examined sST2 levels in patients with HFrEF, HFpEF, and a control group. They found that sST2 levels were significantly higher in the HFrEF group compared with the HFpEF and control groups; however, they observed no difference between the HFpEF and control groups. In studies evaluating galectin-3, it was reported that galectin-3 levels were associated with the degree of diastolic dysfunction in patients with HFpEF.[28] In addition, a review by Rabkin et al.[29] examined the importance of growth differentiation factor-15 (GD-15), galectin-3, and sST2 in differentiating HFpEF from HFrEF. They concluded that these three biomarkers alone may not be sufficient for differentiation between HFpEF and HFrEF, but their combined use with BNP may be useful. To date, studies have primarily focused on patients with HFrEF and HFpEF, and HFmrEF patients have not been included in these studies. In our study, a control group was included in addition to all three HF subtypes, allowing for detailed comparisons.

In our study, galectin-3 and sST2 levels were significantly higher in the HFrEF and HFmrEF subgroups compared to the control group, whereas they were similar between the HFpEF and control groups. In a recent study, sST2 and galectin-3 levels were evaluated in HFrEF, HfpEF, and control groups, and similar to our findings, sST2 and galectin-3 levels were significantly higher in the HFrEF group compared to the control group; however, no difference was observed between the HFpEF and control groups in terms of sST2 levels.[30] Unlike our study, that study found a significant difference between the control and HFpEF groups with respect to galectin-3 levels. However, in that study, the number of patients in the control (n = 30) and HFpEF (n = 172) groups were quite different, which may have affected the results. In addition, unlike our study, that study did not include patients with HFmrEF. In another recent study, galectin-3 and sST2 levels were analyzed in patients with atrial fibrillation (AF), HFmrEF, and HFpEF.[22] In the subgroup analysis of that study, unlike our study, HFmrEF (n = 16) and HFpEF (n = 71) patients were compared, and no significant difference was found between the two groups in terms of either biomarker. This may again be due to the insufficient number of patients in the HFmrEF group. The fact that a sufficient number of patients representing all three HF subtypes were examined in our study makes our findings stronger compared to previous studies. Considering that galectin-3 and sST2 reflect myocardial strain and fibrosis, our findings suggest that fibrosis is more prevalent in the HFmrEF and HFrEF groups than in the HFpEF group, and that HFmrEF patients are more similar to those with HFrEF. In addition, the fact that fibrosis was proven to be more common in HFrEF and HFmrEF patients than in HFpEF patients in previous studies also supports our findings.[31–33] Since sST2 and galectin-3 also indicate the risk of future HF development, our results suggest that the HF subgroup (HFmrEF) may potentially be included within the HFrEF group in the future. However, since we have not followed these patients for a long time, studies with longer follow-up periods are needed in this regard.

Another important finding of our study was that sST2 and galectin-3 levels were positively correlated with BNP and negatively correlated with LVEF. Similar to our findings, previous studies have reported positive correlations between these biomarkers and BNP, and negative correlations with LVEF.[27,30] Several mechanisms may explain the relationship between these two biomarkers and BNP and LVEF. BNP is released in response to myocardial tension and is elevated in patients with HF.[34] Given that sST2 and galectin-3 reflect fibrosis, myocardial tension, and stress, our findings are consistent with the literature. In addition, left ventricular EF was negatively correlated with these parameters, indicating that they were more elevated in patients with lower EF and more extensive fibrosis. These findings also partially explain why sST2 and galectin-3 levels may be higher in patients with HFmrEF than in those with HFpEF.

In our study, we also evaluated the areas under the curve of sST2 and galectin-3 levels using ROC analysis to predict HFmrEF. Compared to the control group, sST2 levels tended to have a higher AUC than galectin-3 levels for predicting HFmrEF (P = 0.098). Although this finding suggests that sST2 may be a better biomarker, particularly for predicting HFmrEF, it should be noted that the power of our study for galectin-3 was relatively lower than that for sST2. Further prospective studies with larger patient populations are needed to better elucidate the relationship among HFmrEF, sST2, and galectin-3.

Limitations of the Study

The relatively small number of patients is one of the main limitations of the present study. Second, the lack of long-term follow-up and prognostic assessment is another limitation. Third, performing cardiac magnetic resonance imaging (MRI) to provide visual evidence of fibrosis would have been useful. However, we could not perform cardiac MRI because it is not part of routine clinical evaluation. Assessment with cardiac MRI and analysis of the relationship between fibrosis level and sST2 and galectin-3 would have increased the clinical value of our study. Fourth, the inclusion of echocardiographic strain parameters could have further contributed to our findings. Fifth, we performed a post hoc power analysis. Although the power of our study was quite high for sST2, it was slightly lower for galectin-3. Finally, because only outpatients were analyzed in our study, our results cannot be generalized to patients presenting with acute decompensated heart failure.

Conclusion

sST2 and galectin-3 levels may help guide EF-based HF classification in patients with HF. These biomarkers were significantly higher in patients with HFrEF and HFmrEF, suggesting potential diagnostic value in identifying these subgroups. However, no significant differences were observed between HFpEF patients and the control group. To better establish the diagnostic significance of these biomarkers, validation in a larger patient population is required.

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