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CORRELATION ANALYSIS OF SERUM TGF-βBP2 AND TNFSF2 LEVELS WITH THE SEVERITY AND PREDICTIVE VALUE OF CHRONIC HEART FAILURE PATIENTS

KORELACIONA ANALIZA NIVOA TGF-βBP2 I TNFSF2 U SERUMU U ODNOSU NA TEŽINU BOLESTI I PROGNOSTIČKU VREDNOST KOD PACIJENATA SA HRONIČNOM SRČANOM INSUFICIJENCIJOM

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Summary

Background: To explore the correlations between serum Transforming Growth Factor Beta Binding Protein 2 (TGF-βbp2) and Tumour Necrosis Factor Ligand Superfamily Member 2 (TNFSF2) and the severity of chronic heart failure (CHF) in patients, as well as their predictive value for adverse prognosis.
Methods: A retrospective analysis was conducted of 240 CHF patients admitted to a particular hospital between January 2023 and December 2025. The New York Heart Association (NYHA) cardiac function grades on admission were used to categorise patients into three groups: severe (n=70), moderate (n=80), and mild (n=90). Based on the incidence of major cardiovascular adverse events (MACEs), patients were divided into two groups after 1-year follow-up: a favourable-prognosis group (n=200) and a poor-prognosis group (n=40). The levels of serum TGF-βbp2, TNFSF2, and myocardial injury markers [cardiac troponin (cTnT), creatine kinase isoenzyme (CK-MB), and lactate dehydrogenase (LDH)] and cardiac function indicators [left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV)] were compared among the three groups and among patients with different prognoses. The correlations among serum TGF-βbp2, TNFSF2, myocardial injury markers, and cardiac function

Kratak sadržaj

Uvod: Cilj je bio da se ispita povezanost između serumskih nivoa transformišućeg faktora rasta beta vezujućeg proteina 2 (TGF-βbp2) i člana 2 superfamilije liganada faktora tumorske nekroze (TNFSF2) i težine hronične srčane insuficijencije (CHF) kod pacijenata, kao i njihovu prediktivnu vrednost za nepovoljnu prognozu.
Metode: Retrospektivnom analizom je obuhvaćeno 240 pacijenata sa CHF hospitalizovanih u određenoj bolnici u periodu od januara 2023. do decembra 2025. godine. Na osnovu funkcionalne klasifikacije prema Njujorškoj asocijaciji za srce (NYHA) pri prijemu, pacijenti su podeljeni u tri grupe: teška (n=70), umerena (n=80) i blaga (n=90). Nakon jednogodišnjeg praćenja, pacijenti su svrstani u dve grupe prema pojavi velikih neželjenih kardiovaskularnih događaja (MACE): grupa sa povoljnom prognozom (n=200) i grupa sa nepovoljnom prognozom (n=40). Upoređivani su serumski nivoi TGF-βbp2, TNFSF2 i markera oštećenja miokarda [srčani troponin (cTnT), kreatin-kinaza MB izoenzim (CK-MB) i laktat dehidrogenaza (LDH)], kao i pokazatelji srčane funkcije [ejekciona frakcija leve komore (LVEF), krajnji dijastolni volumen leve komore (LVEDV) i krajnji sistolni volumen leve komore (LVESV)] između tri grupe, kao i između pacijenata sa različitom prognozom. Korelacije između serumskih nivoa TGF-βbp2 i TNFSF2 i markera oštećenja miokarda

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indicators were analysed using Pearson's correlation coefficient. ROC curves were built to examine the predictive value of blood TGF-βbp2 and TNFSF2 for the poor prognosis of CHF patients.
Results: The blood levels of TGF-βbp2, TNFSF2, cTnT, CK-MB, LDH, LVEDV, and LVESV in the severe group were greater than those in the moderate and mild groups, whereas the LVEF was lower than that in the moderate and mild groups. $P<0.05$ meant that each of these differences was statistically significant. The serum levels of TGF-βbp2 and TNFSF2 were positively correlated with cTnT, CK-MB, LDH, LVEDV, and LVESV (r TGF-βbp2=0.342, 0.354, 0.341, 0.348, 0.340; r TNFSF2=0.359, 0.352, 0.351, 0.357, 0.355; all $P<0.05$) and negatively correlated with LVEF (r TGF-βbp2=-0.258; r TNFSF2=-0.240; all $P<0.05$). TGF-βbp2 and TNFSF2 serum levels were substantially higher in the poor-prognosis group than in the good-prognosis group ($P<0.05$). The AUCs for serum TGF-βbp2 and TNFSF2 in predicting the poor prognosis of CHF patients were 0.861 and 0.869, respectively. The combined AUC was 0.955, with a sensitivity of 90.57% and a specificity of 80.34%.
Conclusion: Serum TGF-βbp2 and TNFSF2 levels are positively correlated with disease severity in patients with CHF. The combined detection of these levels can achieve early prediction of poor patient prognosis.

Keywords: chronic heart failure, transforming growth factor beta binding protein 2, tumour necrosis factor ligand superfamily member 2, severity of the disease, poor prognosis

i pokazatelja srčane funkcije analizirane su Pirsonovim koeficijentom korelacije. Konstruisane su ROC krive radi procene prediktivne vrednosti TGF-βbp2 i TNFSF2 u predviđanju nepovoljne prognoze kod pacijenata sa CHF.
Rezultati: Koncentracije TGF-βbp2, TNFSF2, cTnT, CK-MB, LDH, LVEDV i LVESV u teškoj grupi bile su više nego u umerenoj i blagoj grupi, dok je LVEF bila niža nego u umerenoj i blagoj grupi. Sve navedene razlike bile su statistički značajne ($P<0,05$). Serumski nivoi TGF-βbp2 i TNFSF2 su bili u pozitivnoj korelaciji sa cTnT, CK-MB, LDH, LVEDV i LVESV (r TGF-βbp2=0,342; 0,354; 0,341; 0,348; 0,340; r TNFSF2=0,359; 0,352; 0,351; 0,357; 0,355; svi $P<0,05$), a u negativnoj korelaciji sa LVEF (r TGF-βbp2=-0,258; r TNFSF2=-0,240; svi $P<0,05$). Serumski nivoi TGF-βbp2 i TNFSF2 su bili značajno viši u grupi sa nepovoljnom prognozom u poređenju sa grupom sa povoljnom prognozom ($P<0,05$). Površina ispod ROC krive (AUC) za TGF-βbp2 i TNFSF2 u predviđanju nepovoljne prognoze kod pacijenata sa CHF je iznosila 0,861, odnosno 0,869, dok je AUC za njihovu kombinovanu predikciju iznosila 0,955, uz senzitivnost od 90,57% i specifičnost od 80,34%.
Zaključak: Serumski nivoi TGF-βbp2 i TNFSF2 su u pozitivnoj korelaciji sa težinom bolesti kod pacijenata sa CHF. Njihovo kombinovano određivanje može omogućiti rano predviđanje nepovoljne prognoze.

Ključne reči: hronična srčana insuficijencija, transformišući faktor rasta beta vezujući protein 2, član 2 superfamilije liganada faktora tumorske nekroze, težina bolesti, nepovoljna prognoza

Introduction

Chronic heart failure (CHF) is usually caused by insufficient cardiac pumping function and the inability of cardiac output to meet the metabolic demands of the body, representing the main manifestation of various chronic cardiovascular diseases progressing to the end stage (1–2). For such patients, clinical practice often involves active drug treatment after identifying the cause of the disease and assessing its severity. However, the prognosis of CHF patients is closely tied to the severity of their disease at the time of admission. Most patients are readmitted within 90 days following discharge, while others may die due to secondary major adverse cardiovascular events (MACE) (3–4). Latent transforming growth factor-binding protein-2 (TGF-βbp2) is widely expressed in organs and tissues rich in microfibrils, such as the lungs, heart, and skin. It can contribute to the incidence and progression of various diseases by regulating tissue fibrosis (5). Tumour Necrosis Factor Ligand Superfamily Member 2 (TNFSF2) is mainly expressed in the endothelial tissues of the heart muscle and can exert vasoconstrictive effects by participating in the generation and conversion of adenosine triphosphate (6–9).

This study seeks to evaluate the association between serum TGF-βbp2 and TNFSF2 levels and the severity of CHF, as well as their predictive efficacy for adverse prognosis, to provide theoretical support for the early clinical identification of patients at risk of adverse prognosis.

Materials and Methods

General information

A retrospective selection of 240 CHF patients admitted to our hospital from January 2025 to December 2025 was performed.

Inclusion criteria: (1) diagnosed with CHF based on physical examination and laboratory tests; (2) stopped using related treatment drugs within one week before participating in the study; (3) were in the acute attack stage and needed to be admitted to the hospital for systematic treatment; and (4) had complete clinical data available for review.

Exclusion criteria: (1) patients with cardiogenic shock and (2) patients with malignant tumours. According to the different New York Heart Association (NYHA) cardiac function grades at admission, 70 patients with NYHA grade IV disease were classified into the severe group, 80 patients with NYHA grades II--III were classified into the moderate group, and 90 patients with NYHA grade I disease were classi-

fied into the mild group. The severe group included 40 males and 30 females; the ages ranged from 45-65 (55.27±5.11) years; the body mass index (BMI) ranged from 20-24 (22.42±5.28) kg/m^2; 26 patients had hypertension; and 30 patients had diabetes. In the moderate group, there were 44 men and 36 women; ages ranged from 46-64 (55.37±5.28) years; BMI ranged from 21–23 (22.35±5.44) kg/m^2; 30 patients had hypertension; and 36 patients had diabetes. In the mild group, there were 50 men and 40 women; ages ranged from 47 to 63 (56.16±5.22) years; BMI ranged from 21 to 24 (22.58±5.49) kg/m^2; 32 patients had hypertension; and 34 patients had diabetes.

The Medical Ethics Committee of our hospital accepted this study (approval number: HKYS-2026-A0283).

Detection of myocardial injury markers and cardiac function indicators

(1) Myocardial damage markers: 5 mL of venous blood was drawn from the patients in the group in the early morning on an empty stomach and placed in a designated anticoagulant tube. Using a BK-2008R microplate reader [Beijing Beikeng Hengye Science and Technology Development Co., Ltd., National Medical Device Registration Number Jing Yisheng Jian (Approval) 2009 No. 2400866], the levels of serum TGF-βbp2, TNFSF2, cardiac troponin (cTnT), creatine kinase isoenzyme (CK-MB), and lactate dehydrogenase (LDH) in the three groups were detected with enzyme-linked immunosorbent assay (ELISA). The detection time was the day following admission.

(2) Cardiac function indicators: Routine echocardiography was performed via the SSA-550A cardiac ultrasound diagnostic instrument ŠTOSHIBA MEDICAL SYSTEMS CORPORATION, National Medical Device Registration Number Jing Yisheng Jian (Import) 2006 No. 3230090Ć. The left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) of the three groups were recorded. The detection time was identical to the prior one.

NYHA classification standard

If there are no limitations in daily activities, it is classified as Grade I; if there are no abnormal sensations during rest but there is slight limitation in daily activities, it is classified as Grade II; if there are no abnormal sensations during rest but there are obvious symptoms such as fatigue, palpitations or shortness of breath after general physical activities, it is classified as Grade III; if one is unable to engage in any activities and has related symptoms even during rest, it is classified as Grade IV.

Prognostic follow-up survey

All patients received systematic treatment upon admission and were followed up for one year after treatment. The follow-up period ended in January 2026. The occurrence of major adverse cardiovascular events (MACEs), including arrhythmia, atrial fibrillation, cardiovascular readmission, and cardiovascular death, was statistically analysed. Patients who experienced MACE were assigned to the poor-prognosis group (n=20), whereas those without MACE were assigned to the excellent-prognosis group (n=100). To avoid outcome mistakes, only the first occurrence of MACE during the follow-up period was recorded. All patients participated in only one questionnaire survey.

Statistical methods

SPSS 24.0 statistical software was used to process the data. Count data are reported as n% after being put through the χ^2 test. The measurement data were expressed as means ± s and subjected to a t-test. One-way analysis of variance was done to compare several groups. The Pearson coefficient was used to assess the relationships between serum TGF-βbp2 and TNFSF2 levels, and myocardial damage markers and cardiac function indicators. The predictive value of serum TGF-βbp2 and TNFSF2 levels for poor outcomes in CHF patients was investigated using ROC curves. When P was less than 0.05, a difference was declared statistically significant.

Results

Comparison of serum TGF-bbp2 and TNFSF2 levels in the three groups

The serum levels of TGF-βbp2 and TNFSF2 in the severe group were significantly higher than those in the moderate and mild groups (P<0.05; see *Table I*).

Serum levels of TGF-βbp2 and TNFSF2 differ significantly among patients with chronic heart failure of varying severity. As heart failure severity increases, the expression levels of these two markers show a clear upward trend. The serum TGF-βbp2 and TNFSF2 levels in patients in the severe group are significantly higher than those in the moderate and mild groups, indicating that the expression of these two biomarkers is closely associated with disease severity.

Table I Comparison of Serum TGF-βbp2 and TNFSF2 Levels ($\bar{x}\pm s$, ng/mL).

Group	n	TGF-βbp2 (ng/mL)	TNFSF2 (ng/mL)
Severe group	70	6.05±1.44	20.32±3.25
Moderate group	80	5.36±1.32	18.48±3.12
Mild group	90	5.17±1.28	17.66±3.28
F value		4.494	7.425
P value		0.016	0.001

Table II Comparison of myocardial injury markers between groups ($\bar{x}\pm s$).

Group	n	CTnT (μg/L)	CK-MB (U/L)	LDH (U/L)
Severe group	70	5.47±1.22	20.42±3.39	60.48±10.25
Moderate group	80	4.54±1.39	18.47±3.28	55.32±10.20
Mild group	90	4.15±1.48	17.66±3.12	53.15±10.44
F value		9.324	7.825	5.096
P value		<0.001	0.001	0.001

Table III Comparison of cardiac function indicators between groups ($\bar{x}\pm s$).

Group	n	LVEF/%	LVEDV/mL	LVESV/mL
Severe group	70	40.14±10.28	176.36±20.22	85.42±10.25
Moderate group	80	45.18±10.20	163.42±20.38	80.30±10.35
Mild group	90	46.47±10.31	160.49±20.24	78.69±10.48
F value		3.994	6.525	4.506
P value		0.024	0.002	0.016

Table IV Correlation analysis between serum TGF-βbp2, TNFSF2 levels, myocardial injury markers and cardiac function indicators.

Indicator	TGF-βbp2		TNFSF2	
	R value	P value	R value	P value
CTnT	0.342	0.029	0.359	0.026
CK-MB	0.354	0.028	0.352	0.023
LDH	0.341	0.020	0.351	0.024
LVEF	-0.258	0.011	-0.240	0.017
LVEDV	0.348	0.023	0.357	0.011
LVESV	0.340	0.010	0.355	0.019

Comparison of the three groups of myocardial injury markers

The levels of cTnT, CK-MB, and LDH in the severe group were significantly higher than those in the moderate and mild groups ($P<0.05$; see *Table II*).

Cardiac function indicators show significant differences among patients with chronic heart failure of varying severity. As the severity of heart failure increases, the left ventricular ejection fraction (LVEF) shows a significant downward trend, while the left ventricular end-diastolic volume (LVEDV) and left

Table V Comparison of serum TGF-βbp2 and TNFSF2 levels in patients with different prognoses ($\bar{x}\pm s$, ng/mL).

Group	n	TGF-βbp2 (ng/mL)	TNFSF2 (ng/mL)
poor prognosis group	40	7.27±1.32	25.36±5.12
Good prognosis group	200	6.31±1.40	22.32±5.39
T value		2.402	2.254
P value		0.011	0.029

Table VI The predictive value of serum TGF-βbp2 and TNFSF2 levels for poor prognosis in CHF patients.

Indicator	Optimal truncation value	Sensitivity/%	Specificity/%	AUC value (95% CT)	P value
TGF-βbp2	6.84 ng/mL	80.64	79.86	0.861 (0.809~0.913)	0.019
TNFSF2	23.89 ng/mL	82.22	75.59	0.869 (0.800~0.901)	0.017
Joint detection		90.57	80.34	0.955 (0.883~0.968)	0.009

ventricular end-systolic volume (LVESV) show a significant upward trend. These changes indicate that cardiac function gradually deteriorates as disease severity increases, with weakened myocardial contractility and aggravated ventricular remodelling.

Comparison of 3 cardiac function indicators

The LVEF of the severe group was lower than that of the moderate and mild groups, whereas the LVEDV and LVESV were greater than those of the moderate and mild groups. The differences were statistically significant ($P<0.05$), see *Table III*.

The three cardiac function indicators showed significant differences among patients with chronic heart failure of varying severity. As the severity of heart failure increased, the left ventricular ejection fraction (LVEF) showed a downward trend, while the left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) showed an upward trend, indicating that cardiac function gradually deteriorated as the disease progressed. These changes in cardiac function indicators were consistent with the changing trends of serum TGF-βbp2 and TNFSF2 levels, suggesting that these biomarkers may be involved in regulating the process of cardiac remodelling.

Serum levels of TGF-βbp2 and TNFSF2 and their correlations with myocardial injury markers and cardiac function indicators

Serum TGF-βbp2 and TNFSF2 were positively correlated with cTnT, CK-MB, LDH, LVEDV, and LVESV, and negatively correlated with LVEF (see *Table IV*).

There is a significant correlation between serum levels of TGF-βbp2 and TNFSF2 and markers of myocardial injury and cardiac function indicators. These two biomarkers show a consistent positive correlation with myocardial injury markers, suggesting they may be involved in the process of myocardial injury. At the same time, they are negatively correlated with left ventricular ejection fraction and positively correlated with left ventricular end-diastolic and end-systolic volumes, reflecting changes in cardiac function. These correlations suggest that serum levels of TGF-βbp2 and TNFSF2 can reflect the degree of myocardial injury and cardiac function in patients with chronic heart failure, providing an important basis for assessing disease severity.

Comparison of serum TGF-βbp2 and TNFSF2 levels in patients with different prognoses

The incidence of poor prognosis in 240 patients with CHF was 16.67% (40/240), including 14 cases of arrhythmia, 12 cases of atrial fibrillation, 12 cases of cardiovascular readmission, and 2 cases of cardiovascular death. The levels of serum TGF-βbp2 and TNFSF2 in the poor-prognosis group were significantly higher than those in the good-prognosis group ($P<0.05$; see *Table V*).

This discovery suggests that serum levels of TGF-βbp2 and TNFSF2 may be important prognostic indicators in patients with chronic heart failure. The ROC curve analysis further confirmed that these two biomarkers have high predictive value for adverse prognosis in patients. Especially when they are detected jointly, the predictive efficacy is significantly improved, demonstrating good sensitivity and specificity.

Serum levels of TGF-βbp2 and TNFSF2 have predictive value for the poor prognosis of patients with CHF

The ROC curve shows that the combined prediction of serum TGF-βbp2 and TNFSF2 for adverse prognosis in CHF patients has a higher AUC than either indicator alone (see *Table VI*).

Serum levels of TGF-βbp2 and TNFSF2 have significant predictive value for poor prognosis in patients with chronic heart failure. The ROC curve analysis confirmed that both of these biomarkers showed good predictive efficacy when detected alone. When the two were jointly detected, the predictive value was significantly enhanced, enabling a more accurate identification of patients with poor prognosis. The study found significant differences in serum levels of TGF-βbp2 and TNFSF2 among patients with different prognoses. The levels of these two markers in patients with poor prognosis were significantly higher than those in patients with good prognosis.

Discussion

The pathogenesis of CHF is rather complex and is considered to be related to diseases such as coronary heart disease, myocarditis, and myocardial infarction, which may cause abnormalities in cardiac contraction and pumping functions. CHF is characterised by a high incidence, frequent recurrence, and a poor prognosis (10). CHF is the main manifestation of the progression of various chronic cardiovascular diseases to the end stage. The condition of such patients can gradually worsen (11). As the degree of myocardial injury intensifies, these patients may also develop multiple MACEs due to cardiac dysfunction. At this time, the patient's physical activities are restricted, and the body's functions are irreversibly impaired (12–13). The NYHA cardiac function classification is an important basis for evaluating CHF severity. However, the assessment results may be affected by various subjective factors. Echocardiography can objectively assess damage to a patient's cardiac function. Still, some patients may have missed diagnoses or misdiagnoses due to improper breathing during the examination (14–15).

The investigation's findings showed that the severe group's serum TGF-βbp2 and TNFSF2 levels were higher than those of the moderate and mild groups, suggesting that as the patient's condition advanced, the levels of TGF-βbp2 and TNFSF2 in the serum steadily increased. The rationale is that with the onset of CHF, patients may have variable degrees of myocardial damage and functional impairment. The cardiac inflammatory response and tissue fibrosis are essential pathophysiological bases for the onset and progression of the ailment. TGF-βbp2 is an important component of the extracellular matrix in various tissues. It can promote the development of elastic fibres through interactions with fibrin and microfibrils. It plays an important role in maintaining the stability and integrity of the elastic fibre structure. When the elastic fibres in myocardial tissue are structurally lost, the content of TGF-βbp2 in the serum significantly increases. The overexpression of TGF-βbp2 can disrupt the structure and function of elastic fibres, leading to myocardial tissue fibrosis and, subsequently, varying degrees of myocardial injury or functional impairment (16, 17).

TNFSF2 can regulate vascular function by participating in nitric oxide synthesis and by mediating ATPase synthesis to increase intracellular proton concentration, thereby adversely affecting vascular function. Overexpression of TNFSF2 can promote the development and progression of vascular inflammation by disrupting vascular endothelial structure and causing vascular dysfunction. When TNFSF2 expression increases and the cardiovascular inflammatory response intensifies, this exacerbates the condition of CHF patients (18). According to the study's findings, the severe group had higher levels of cTnT, CK-MB, LDH, LVEDV, and LVESV than the moderate and mild groups, but their LVEF was lower. The reason is that myocardial injury is a typical feature of CHF progression, and its occurrence is usually associated with the worsening of the myocardial inflammatory response and the resulting myocardial fibrosis. cTnT and CK-MB are common markers of myocardial injury in clinical practice, and their expression levels increase as the degree of myocardial injury intensifies. LVEF, LVEDV, and LVESV are common parameters in cardiac ultrasound examinations, and LVEF is primarily used to evaluate cardiac systolic and diastolic function and overall pumping function in patients. Changes in LVEF can, to some extent, reflect the microcirculation and blood perfusion of the heart.

The LVEDV and LVESV are commonly used parameters for evaluating heart volume and structure. An increase in their levels indicates that the patient's heart is physiologically or pathologically enlarged. When a patient's LVEF decreases and their LVEDV and LVESV increase, CHF patients are more prone to MACEs. The degree of cardiac damage and functional impairment in CHF patients is positively connected with blood TGF-βbp2 and TNFSF2 levels, according to the study's findings. Serum levels of TGF-βbp2 and TNFSF2 are higher in individuals with a poor prognosis for CHF than in those with a good prognosis.

Currently, in clinical practice, vascular endothelial dysfunction is regarded as one of the primary causes of cardiac fibrosis lesions in patients. TGF-βbp2 is a protein that maintains the structural stabil-

ity of elastic fibres and can enhance the function of myocardial elastic fibres by interacting with various matrix components to avoid vascular endothelial damage. While inhibiting myocardial fibrosis lesions, the normal expression of TGF-βbp2 can also slow the progression of CHF. However, increased LTBP-1 expression exacerbates myocardial fibrosis and vascular endothelial damage, and increases the risk of adverse outcomes in patients (19). TNFSF2 is widely expressed in myocardial mitochondria and can promote vascular contraction by exerting an endogenous inhibitory effect on the vascular endothelium. When there is an ischemic or hypoxic lesion in the tissue, a large amount of TNFSF2 will enter the bloodstream, increasing the serum TNFSF2 level. Detecting changes in TNFSF2 may enable early prediction of the adverse prognosis of patients with CHF and other cardiovascular diseases (20–22). The ROC curve results of this study revealed that serum levels of TGF-βbp2 and TNFSF2 had prognostic value for a poor outcome in CHF patients, and that combined detection of these two indicators had greater predictive value, sensitivity, and specificity than detection of individual indicators alone.

Conclusion

Serum levels of TGF-βbp2 and TNFSF2 are strongly associated with disease severity in patients with CHF. Early prediction of a poor prognosis for patients can be achieved by detecting these values together.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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