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Increased plasma sestrin2 concentrations in patients with chronic heart failure and predicted the occurrence of major adverse cardiac events: A 36-month follow-up cohort study

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ABSTRACT

Background: Previous study had demonstrated that sestrin2 (Sesn2) expression was increased in human failing heart. Although, the circulating Sesn2 concentrations in patients with chronic heart failure (CHF) remains unknown. This study investigated plasma Sesn2 concentrations in patients with CHF and the role between Sesn2 and the occurrence of major adverse cardiac events.

Methods: A total of 80 control subjects and 220 CHF patients were enrolled and the Sesn2 concentrations of each sample were measured. Additionally, the occurrence of major adverse cardiac events in each CHF patient were followed prospectively for 36 months.

Results: Increased plasma Sesn2 concentrations were found in CHF patients and gradually increased from New York Heart Association (NYHA) functional class II to IV. The Sesn2 concentrations were positively correlated with N-terminal B-type natriuretic peptide (NT-pro BNP) but negatively correlated with left ventricular ejection fraction (LVEF) in CHF patients. The ROC curve suggested that Sesn2 had a certain value in predicting major adverse cardiac events during CHF patients, although, the predictive role of Sesn2 is not as good as NT-pro BNP. In addition, the multivariate Cox hazard analysis was performed after the CHF patients were divided into 3 groups (low, middle, and high) base on the plasma Sesn2 concentrations category, and the results showed that both high and middle Sesn2 concentrations increased the incidence of major adverse cardiac events when compared with low Sesn2 group. Furthermore, CHF patients with major adverse cardiac events showed higher Sesn2 concentrations when compared with CHF without major adverse cardiac events. The Kaplan-Meier analysis was performed after the CHF patients were divided into 2 groups according to the median Sesn2 concentrations and the results revealed that patients with high Sesn2 concentrations had a higher risk of major adverse cardiac events compared with those with low Sesn2.

Conclusions: Plasma Sesn2 concentrations were increased in CHF patients and positively correlated with the severity of CHF. Increased Sesn2 concentrations significantly increased the occurrence of major adverse cardiac events and suggested poor outcome in CHF patients.

1. Introduction

Numerous basic heart diseases, including abnormal heart structure and coronary artery disease, could result in the occurrence of chronic heart failure (CHF), which could further lead to the decline in activity tolerance and a variety of serious clinical complications. Among them, cardiac events are the most serious complications of CHF, many patients lose their lives without even having access to treatment [1–3]. Therefore, it is necessary to find some markers to predict the occurrence of cardiac events.

A total of 3 Sestrins (Sesns) members were discovered according to previous studies, including Sesn1, Sesn2, and Sesn3 [4–6]. Among them, Sesn2 is an important stress-induced protein and widely expressed in mammals [4,5]. Sesn2 could be secreted by numerous non-immune cells and immune cells, and the main sources are macrophages and T lymphocytes [7,8]. A variety of environmental stresses could promote Sesn2 secretion, the most important role should be stimulated by oxidative stress and the Sesn2 concentrations even indirectly reflect

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oxidative stress concentrations [6,9]. Sesn2 was also found to participated in diseases of multiple systems and play a protective role without exception via regulating apoptosis, toxicity, and oxidative stress [10–13].

Recent research also suggested that Sese2 was closely related to the progression and development of cardiovascular diseases via maintain the balance of oxidative stress, such as hypertension, cardiac ischemia reperfusion injury, cardiac fibrosis, and atrial fibrillation [14–17]. In addition, plasma Sesn2 concentrations were observed to increase in patients with coronary artery diseases, and positively correlated with Gensini score and oxidative stress concentrations [18]. Furthermore, increased Sesn2 expression was observed in human failing hearts and positively correlated with heart BNP and collagen concentrations [19]. However, the circulating Sesn2 concentrations in CHF patients and the role between Sesn2 concentrations and the occurrence of cardiac evens remains unknown.

2. Methods and materials

2.1. Study population

The present study was a retrospective cohort study. Individuals ($n = 80$) who received a health check-up at the medical center and had been ruled out significant heart disease were enrolled as control subjects in this study, the significant heart diseases including coronary artery disease (CAD), systolic and diastolic dysfunction, valvular heart disease, or myocardial hypertrophy on echocardiography. Consecutive patients ($n = 220$) who were admitted for the treatment of worsening CHF, diagnosis and pathophysiological investigations, or for therapeutic evaluation of CHF were enrolled in this study. The diagnosis of CHF was made by an experienced cardiologist attending according to the history of dyspnea and symptoms of exercise intolerance followed by pulmonary congestion, pleural effusion, left ventricular (LV) enlargement by chest X-ray or echocardiography, and LV ejection fraction (LVEF) value according to previous literatures [20,21]. The exposure and observe outcomes of each groups are consistent. The blood samples were collected after all patients or their families provided informed consent. The process of blood sample collection and experiment were approved by the Medical Ethical Committee of the Shanxi Cardiovascular Hospital.

2.2. Measurement of plasma Sesn2 concentrations

The collection of blood samples from both control subjects and CHF patients was performed by an experienced nurse. After centrifuged for 20 min at 3000 $\times g$, the supernatant of each sample was collected and stored at $-80\,^{\circ}C$ until the beginning of the experiments. The plasma Sesn2 concentrations were detected using enzyme-linked immunosorbent assay (ELISA) kits (Cloud-clone crop, UAS) following the manufacturer's instructions.

2.3. Endpoints and follow-up

After receiving comprehensive treatment and before discharge, all the CHF patients were asked to return to our hospital for a re-examination once a month, if activity tolerance drops again or other conditions occur, even if not for a month. We also notify the CHF patients or their families using a telephone before 2–3 days of each follow-up time points. 2 attending physicians of the department of cardiology who did not known the Sesn2 results of CHF patients were responsible to record the occurrence of major adverse cardiac events of each CHF patient. The end point of follow-up is base on the occurrence of major adverse cardiac events, including death due to progressive HF, myocardial infarction, stroke and sudden cardiac death, and re-hospitalization for worsening HF. The follow-up period for these CHF patients was 36 (14, 36) months.

2.4. Statistical analyses

Continuous variables, including the plasma Sesn2 concentrations and data on most of clinical characteristics, were presented as the median (lower quartile to upper quartile) and compared by the Mann-Whitney U test. The categorical variables were expressed as counts (percentages). The correlations between NT-pro BNP, LVEF and plasma Sesn2 concentrations were analyzed by Spearman's correlation analysis. The diagnostic values of NT-pro BNP in CHF and Sesn2 in cardiac event of CHF patients were performed by Receiver Operating Characteristic (ROC) curve. To investigate whether Sesn2 was a significant predictor of cardiovascular events, Univariate and multivariate analyses with Cox proportional hazard regression were used. The Kaplan-Meier method and log rank test were used to compute and analyze the cumulative overall and event-free survival rates, respectively. A $P < .05$ was considered significant and was the threshold used to reject the null hypothesis.

3. Results

3.1. Comparison of clinical characteristics between control and CHF groups

The data of clinical characteristics were obtained from echocardiography results, laboratory results, and clinical course records. Importantly, increased age, heart rate (HR), fasting glucose (Glu), creatinine (CREA), C-reactive protein (CRP), N-terminal B-type natriuretic peptide (NT-pro BNP), and LV end-diastolic dimension (LVEDD) and reduced body mass index (BMI), total cholesterol (TC), high-density lipoprotein cholesterol (HDL−C), albumin, and LVEF were found in CHF group when compared to control group. No significant differences for other characteristics, including gender, smoking, blood pressure, total triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) were observed between the 2 groups. In addition, the etiology of CHF in different NYHA functional classes displayed no difference. The clinical data of all the patients are listed in Table 1.

3.2. Circulating Sesn2 concentrations in CHF patients

The Sesn2 concentrations were increased in CHF patients when compared with control group and gradually increased in the NYHA II, NYHA III and NYHA IV groups (Fig. 1A). In addition, according to the etiology of CHF, the CHF patients were respectively divided into dilated cardiomyopathy (DCM) group and non-DCM (NDCM) group, ischemic heart disease (IHD) group and non-IHD (NIHD) group, hypertensive heart disease (HHD) and non-HHD (NHHD) group. The results showed that there was no significant difference between DCM group and NDCM group, as well as IHD group and NIHD group, HHD group and NHHD group (Fig. 1B-D).

3.3. Circulating Sesn2 concentrations and CHF severity

To assess the role of Sesn2 and CHF severity, the correlation between NT-pro BNP, LVEF and Sesn2 concentrations were analyzed in CHF patients. The results showed that Sesn2 concentrations were positively correlated with NT-pro BNP but negatively correlated with LVEF (Fig. 2A and B).

3.4. Diagnostic value of Sesn2 in CHF and predictive value in major adverse cardiac events

The results of ROC curve showed that the area under the curve (AUC) of Sesn2 for predicting positive outcome of CHF was 0.802 (95% CI: 0.751 to 0.853, $P < .001$; Fig. 3A). While the AUC of NT-pro BNP for predicting positive outcome of CHF was 1.00 (Fig. 3A). These results suggested that diagnostic value of Sesn2 in CHF was not as well as NT-pro BNP (Fig. 3A). While the AUC of Sesn2 for predicting positive

Table 1
Information of Clinical Characteristics in control and CHF group.

Characteristics	Control	CHF			
		Total	NYHA II	NAHY III	NYHA IV
Age (years)	53 (42, 61)	63 (57, 74) *	63 (56, 74) *	63 (57, 74) *	63 (57, 73) *
Male (n, %)	42 (52.5%)	116 (52.7%)	36 (54.6%)	49 (54.4%)	31 (48.4%)
Smoking (n, %)	24 (30.0%)	67 (30.5%)	21 (31.8%)	26 (28.9%)	20 (31.3)
BMI (Kg/m^2)	25.7 (22.7, 27.4)	23.7 (21.7, 25.6) *	24.1 (22.1, 26.4) *	23.7 (21.7, 25.6) *	23.4 (20.9, 25.2) *
HR (bpm)	72 (67, 75)	74 (68, 83) *	69 (63, 77) #	76 (68, 74) *,§	78 (72, 94) *,#,§
SBP (mmHg)	125 (117, 135)	122 (109, 131)	119 (108, 131)	121 (108, 130) *	125 (114, 136)
DBP (mmHg)	77 (69, 83)	75 (67, 84)	76 (67, 85)	77 (67, 82)	75 (70, 84)
TC (mmol/l)	4.5 (3.9, 4.7)	4.1 (3.1, 4.6) *	3.9 (2.9, 4.6) *	4.1 (3.1, 4.6) *	4.1 (3.2, 4.7)
TG (mmol/l)	1.1 (0.9, 1.4)	1.0 (0.9, 1.4)	1.1 (0.9, 1.4)	1.0 (0.9, 1.5)	1.0 (0.7, 1.5)
HDL-C (mmol/l)	1.2 (1.0, 1.4)	0.9 (0.8, 1.2)*	0.9 (0.8, 1.1)*	1.0 (0.8, 1.1)*	1.0 (0.8, 1.3)*,§
LDL-C (mmol/l)	2.3 (1.7, 2.7)	2.1 (1.6, 2.6)	2.2 (1.6, 2.6)	2.1 (1.6, 2.6)	2.0 (1.6, 2.4) *
Glu (mmol/l)	5.3 (4.8, 5.9)	6.2 (5.1, 7.8)*	6.4 (5.2, 8.1) *	6.1 (4.9, 7.3) *	6.3 (5.2, 8.1) *,§
Albumin (g/l)	45 (41, 48)	39 (35, 42) *	40 (37, 43) *	40 (35, 43) *	36 (33, 39)*,#,§,†
CREA (μmol/l)	74 (66, 83)	86 (69, 111) *	86 (62, 112) *	85 (65, 112)	90 (73, 109) *
CRP (mg/l)	0.6 (0.3, 1.1)	6.3 (3.2, 18.3) *	6.7 (3.7, 15.0) *	6.4 (2.6, 22.5) *	6.0 (3.2, 19.6) *
BNP (pg/ml)	85 (69, 105)	2420 (1728, 3504) *	1826 (1418, 2406)*,#	2294 (1643,3171)*,§	3568 (2637, 4388)*,#,§,†
LVEF (%)	61 (57, 66)	38 (32, 42) *	40 (37, 43)*,#	37 (32, 41)*,§	36 (30, 41)*,#,§
LVEDD (mm)	47 (45, 50)	58 (55, 64) *	57 (53, 61)*,#	60 (54, 65)*,§	60 (57, 64)*,§
DCM (n, %)	–	50 (22.7%)	12 (18.2%)	24 (26.7%)	14 (21.9%)
IHD (n, %)	–	66 (30.0%)	19 (28.8%)	25 (27.8%)	22 (34.4%)
HHD (n, %)	–	50 (22.7%)	16 (24.2%)	21 (23.3%)	13 (20.3%)
Others (n, %)	–	54 (24.5%)	19 (28.8%)	20 (22.2%)	15 (23.4%)
Medications, n(%)					
ACEI/ARB	0 (0%)	168 (76.4%)*	48 (72.7%)*	77 (85.6%)*	43 (67.2%)*,†
β blockers	10 (12.5%)	151 (68.6%)*	52 (78.8%)*	72 (80.0%)*	27 (42.2%)*,#,§,†
Diuretics	1 (0.5%)	171 (77.7%)*	38 (57.6%)*,#	74 (82.2%)*,§	59 (92.2%) *,#,§
Digitalis	0 (0%)	140 (63.6%)*	21 (31.8%)*,#	66 (73.3%)*,§	53 (82.8%) *,#,§
Spironolactone	0 (0%)	171 (77.7%)*	38 (57.6%)*,#	74 (82.2%)*,§	59 (92.2%) *,#,§
Aspirin	21 (26.3%)	130 (59.1%)*	34 (51.5%)*	58 (64.4%)*	38 (59.4%)*
Statin	17 (21.3%)	128 (58.2%)*	34 (51.5%)*	55 (61.1%)*	39 (60.9%)*

BMI: body mass index; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: total triglycerides; HDL−C: high-density lipoprotein cholesterol; HDL−C: low-density lipoprotein cholesterol; Glu: fasting glucose; CREA: creatinine; CRP: C-reactive protein; BNP: N-terminal B-type natriuretic peptide; LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic dimension; DCM: dilated cardiomyopathy; IHD: ischemic heart disease; HHD: hypertensive heart disease; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

* $p < .05$ vs. Control group.
# $p < .05$ vs. Total CHF group.
§ $p < .05$ vs. NYHA II group.
† $p < .05$ vs. NYHA III group.

outcome of cardiac event was 0.737 (95% CI: 0.670 to 0.803, $P < .001$; Fig. 3B), the optimal plasma Sesn2 cutoff point for predicting positive outcome of cardiac event was 1.76 ng/ml with a sensitivity of 64.4%, and a specificity of 73.3%.

3.5. Association between plasma Sesn2 concentrations and major adverse cardiac events

Depending on whether the CHF patients had major adverse cardiac events during the follow-up, the CHF patients were further divided into cardiac event (−) and event (+) groups. Compared with event (−) group, higher NT-pro BNP concentrations and NYHA IV patients and lower NYHA II patients were observed in event (+) group, on differences of other clinical characteristics were found between the 2 groups. The clinical data of these 2 groups are listed in Table 2. The plasma Sesn2 concentrations were increased in cardiac event (−) group, and further increased in cardiac event (+) group. In addition, according to the Sesn2 concentrations category, the CHF patients were divided into three groups (T1: low Sesn2 group; T2: middle Sesn2 group; T3: high Sesn2 group). The results of Multivariate Cox hazard analysis showed that plasma Sesn2 concentrations were independently associated with major adverse cardiac events after adjustment for age, smoking, BMI, Glu, albumin, CRP, BT-pro BNP, LVEF and LVEDD (T2: hazard ratio 4.7, 95% CI 1.9 to 10.4, $p < .001$; T3: hazard ratio 6.1, 95% CI 3.2 to 15.2, $p < .001$; Fig. 4B). The P value and 95% CI of each group are list as Table 3. The CHF patients were also divided into a high Sesn2 group and a low Sesn2 group base on the median plasma Sesn2 concentrations (15.71 ng/ml). Kaplan-Meier analysis revealed that the CHF patients with high plasma Sesn2 concentrations had a higher risk of major adverse cardiac events compared to those with low plasma Sesn2 concentrations (log-rank test $p < .0001$, Fig. 5).

4. Discussion

We found that the circulating Sesn2 concentrations were increased in the CHF patients, the NYHA classification, rather than the etiologies of CHF, could affect the plasma Sesn2 concentrations. In addition, the Sensn2 concentrations were positively correlated with NT-proBNP concentrations, but negatively correlated with LVEF in CHF patients. Furthermore, Sesn2 were significantly increased in CHF patients with major adverse cardiac events when compared with CHF patients without major adverse cardiac events, and had a certain predicting value of major adverse cardiac events in CHF patients, increased plasma Sesn2 concentrations suggested higher rates of major adverse cardiac events and poorer prognosis.

The expression of Sesn2, an important antioxidant protein, has been demonstrated to increase in different microenvironment and a variety of diseases. In earlier studies, ox-LDL and angiotensin II were reported to time- and dose- dependently increased Sesn2 expression in RAW264.7 cells and human umbilical vein endothelial cells, respectively [22,23]. In another study, Ding et al. reported that glucose starvation could induce sesn2 secretion in H1299 cells [24]. In

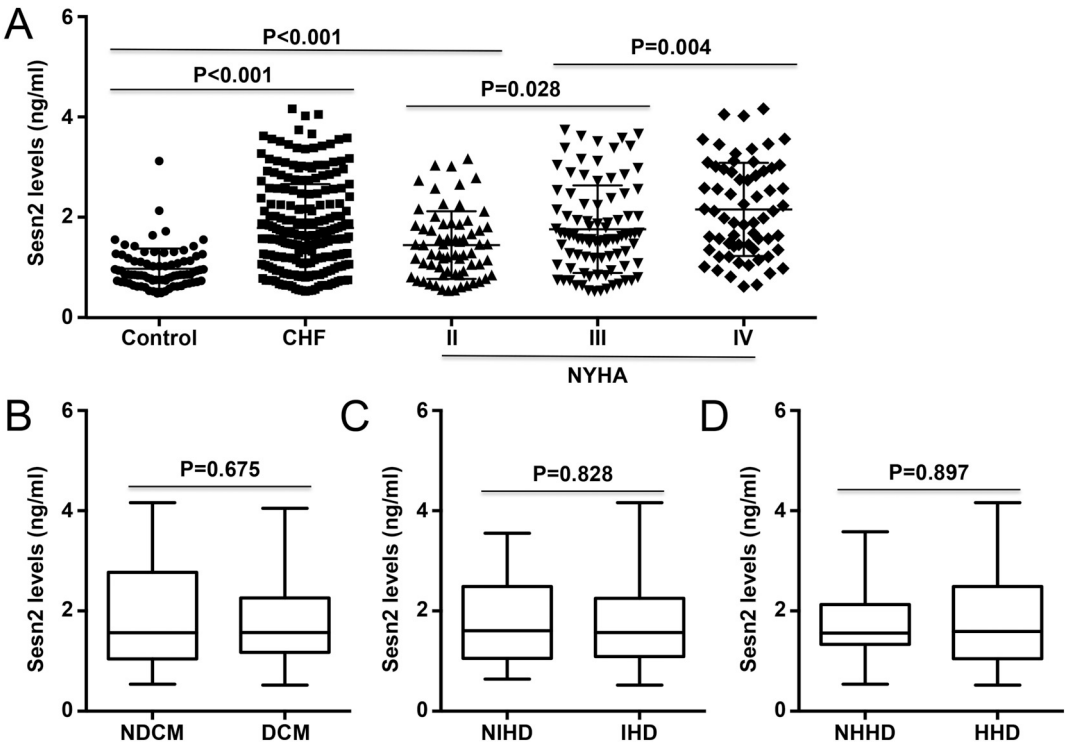

Fig. 1. Plasma Sesn2 concentrations in CHF patients. (A). The Sesn2 concentrations in control subjects (n = 80), CHF (n = 220), NYHA II (n = 66), NYHA III (n = 90), and NYHA IV (n = 64) groups were measured. Sesn2 concentrations in NDCM (n = 170) and DCM (n = 50) group (B), NIHD (n = 154) and IHD (n = 66) group (C), NHHD (n = 170) and HHD (n = 50) group (D).

addition, rotenone dose-dependently increased the sesn2 protein expression in Mes 23.5 cells, increased the dose of rotenone did not affect the Sesn2 concentrations [25]. In animal study, higher Sesn2 mRNA concentrations were found in rat failing hearts which induced by both myocardial infarction and doxorubicin [26]. In clinical experiments, Sesn2 concentrations were also observed to increase in both intestine and left atrium respectively isolated from patients with ulcerative colitis and atrial fibrillation [27,28]. Furthermore, the plasma Sesn2 concentrations were also increased in patients with coronary artery disease and positively correlated with the Gensini score [29]. In the present study, we detected plasma Sesn2 concentrations in CHF patients and found that the Sesn2 concentrations were gradually increased according to the severity of CHF. These results may suggest that Sesn2 is involved in CHF, while the mechanisms remain unclear and more researches are needed to be clarified it.

In an earlier study, Wang et al. reported that the Sesn2, but not Sesn1 and Sesn3, was increased in human failing hearts, and the Sesn2 mRNA were positively related with heart BNP mRNA concentrations [26]. While in the present study, the circulating Sesn2 concentrations were also increased in patients with CHF, and positive correlation between Sesn2 and NT-pro BNP were observed. Our results were consistent with previous conclusions. Although the authors also reported that the Sesn2 were also increased in failing heart because of DCM, but not ischemic cardiomyopathy. No changes of Sesn2 concentrations in DCM were observed in our study, these parts of results seemed to contradict previous reports. The first possible season was the sample size of DCM was only 18 in that study, the sample size was too small to guarantee the accuracy of the conclusion. The others season was the heart samples were collected from the patients who suffered end-stage CHF and received a heart transplant, these patients tend to be associated with other complications which may affect the results.

Progression from a normal heart to chronic heart failure is a complex and long process, multiple pathological processes and injury factors were confirmed to be involved, including inflammatory response,

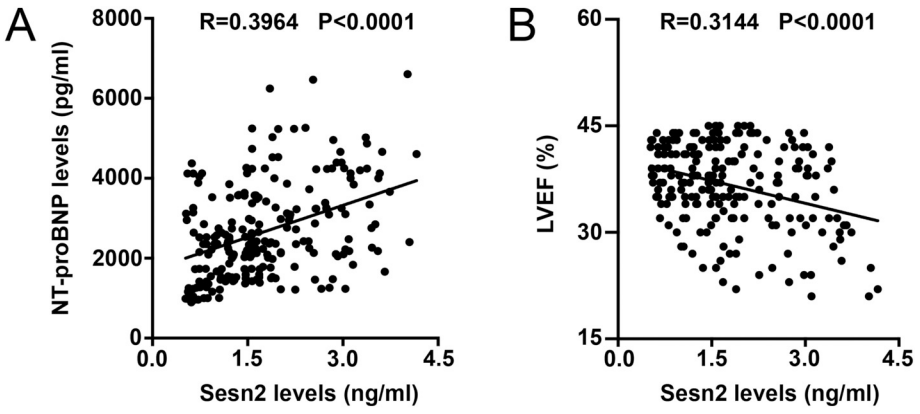

Fig. 2. Correlation between Sesn2 and the CHF severity. The correlation between NT-pro BNP (A), and LVEF (B) were analyzed by Spearman's correlation analysis.

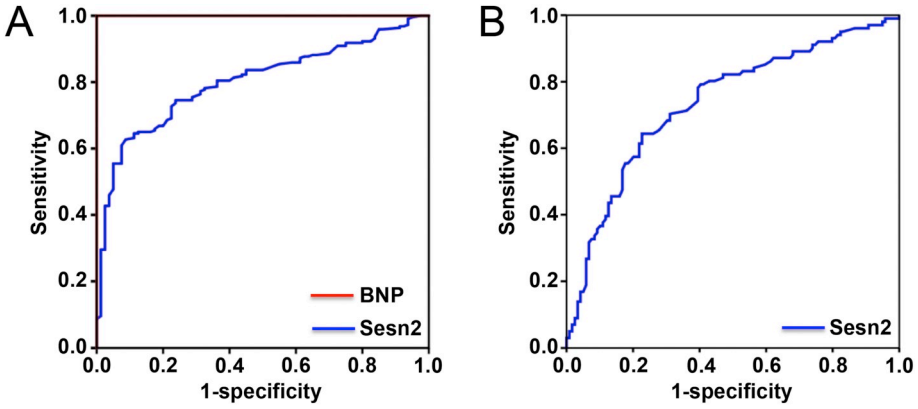

Fig. 3. The diagnostic value of plasma Sesn2 in CHF and major adverse cardiac events. (A) ROC curve of NT-pro BNP and Sesn2 for predicting the diagnostic value of CHF. (B) ROC curve of plasma Sesn2 for predicting the diagnostic value of major adverse cardiac events in CHF patients.

Table 2
Comparison of CHF patients without and with cardiac events.

Characteristics	Cardiac event (−)	Cardiac event (+)	P value
Age (years)	63 (56, 74)	63 (58, 74)	0.525
Male (n, %)	66 (55.5%)	50 (49.5%)	0.417
Smoking (n, %)	36 (30.3%)	31 (30.7%)	0.999
BMI (Kg/m^2)	24.1 (21.8, 26.2)	23.6 (21.6, 25.4)	0.192
HR (bpm)	74 (67, 83)	73 (68, 84)	0.990
SBP (mmHg)	122 (109, 131)	121 (109, 132)	0.715
DBP (mmHg)	75 (67, 84)	75 (70, 84)	0.594
TC (mmol/l)	3.9 (3.1, 4.6)	4.1 (3.1, 4.6)	0.528
TG (mmol/l)	1.0 (0.9, 1.4)	1.1 (0.8, 1.9)	0.252
HDL-C (mmol/l)	0.9 (0.8, 1.2)	1.0 (0.8, 1.2)	0.980
LDL-C (mmol/l)	2.1 (1.5, 2.6)	2.1 (1.6, 2.5)	0.867
Glu (mmol/l)	6.2 (5.1, 7.5)	6.3 (5.1, 8.1)	0.912
Albumin (g/l)	38.8 (34.4, 42.3)	39.1 (35.3, 42.4)	0.480
CREA (μmol/l)	85 (66, 108)	88 (73, 124)	0.190
CRP (mg/l)	6.6 (2.8, 18.3)	6.1 (3.3, 18.6)	0.852
BNP (pg/ml)	2351 (1524, 3259)	2524 (2072, 3925)	0.015
LVEF (%)	38 (35, 42)	37 (32, 42)	0.098
LVEDD (mm)	58 (54, 63)	58 (56, 64)	0.213
NYHA FC, II/III/IV	48/44/27	18/46/37	< 0.001/0.217/0.026
DCM (n, %)	29 (24.4%)	21 (20.8%)	0.629
IHD (n, %)	34 (28.6%)	32 (31.7%)	0.869
HHD (n, %)	29 (24.4%)	21 (20.8%)	0.629
Others (n, %)	27 (22.7%)	27 (26.7%)	0.531
Medications (n, %)			
ACEI/ARB	92 (77.3%)	76 (75.2%)	0.752
β blockers	78 (65.5%)	73 (75.2%)	0.310
Diuretics	90 (75.6%)	81 (80.2%)	0.516
Digitalis	70 (58.8%)	70 (69.3%)	0.123
Spironolactone	90 (75.6%)	81 (80.2%)	0.516
Aspirin	76 (63.9%)	54 (54.5%)	0.131
Statin	76 (63.9%)	52 (51.5%)	0.075

NYHA FC: New York Heart Association functional class.

mitochondrial dysfunction, abnormal energy metabolism, excessive autophagy and apoptosis of cardiac cells [30–32]. Oxidative is another important reason of CHF, because myocardial cells have poor tolerance to oxidative stress, and may easily lead to damage of myocardial cells and decrease of cardiac function [33]. Sesn2 is an important antioxidant protein, which could be secreted by a variety seasons, including oxidative stress, DNA damage, hypoxia, and most important is oxidative stress, Sesn2 can even indirectly reflect the concentrations of oxidative stress in the body [6,9]. The increased Sesn2 concentrations in our study also suggested that oxidative stress was closely related to CHF, although the predictive value of Sesn2 in CHF is not as good as NT-pro BNP.

Besides the occurrence of CHF, oxidative stress has also been demonstrated to be closely related to major adverse cardiac events, and reduction of oxidative stress concentrations significantly decreased the occurrence of major adverse cardiac events [34]. In our present study, we firstly found that the occurrence of major adverse cardiac events can be predicted to some extent. To further analyze the special role of Sesn2 on major adverse cardiac events, the Sesn2 concentrations in CHF patients with or without major adverse cardiac events, as well as the effect of Sesn2 on the incidence of major adverse cardiac events were investigated. The results exhibited that CHF patients with major adverse cardiac events had higher Sesn2 concentrations when compared without major adverse cardiac events, and the middle and higher groups respectively increased the incidence of major adverse cardiac events for 3.7-fold and 5.1-fold when compared with the low Sesn2 group. In addition, as an antioxidant protein, higher Sesn2 group surprisingly had worse outcome than the lower Sesn2 group. According to the above description that the oxidative stress concentrations was the most important reason for Sesn2 secretion, we suspected that Sesn2 compensatory increase in the oxidative stress environment of CHF, although increased oxidative stress concentrations still dominated, and increased sesn2 concentrations were not sufficient to counter it, leading to a false impression which higher Sesn2 increased the occurrence of major adverse cardiac events in CHF patients. Oxidative stress play the dominant role in Sesn2 expression [9], and Sen2 expression was positively correlated with of oxidative stress concentrations although it is an antioxidant protein [7]. One possible reason of Sesn2 increased in CHF patients and further elevates in CHF patients with major adverse cardiac events is that Sesn2 may be only involved in cellular responses to different stress conditions and is able to maintain redox homeostasis and Sestrin2 induction may be as a compensatory response under stressful conditions [35]. Just like BNP is increased in CHF and BNP was demonstrated to alleviate the symptoms of chronic heart failure due to dilated veins and diuretic action.

In summary, we found that circulating Sesn2 concentrations were increased in CHF patients and positively correlated with the CHF severity. Additionally, Sesn2 is valuable for predicting major adverse cardiac events in patients with CHF, although it is less useful than BNP in predicting the occurrence of CHF. Furthermore, CHF with high Sesn2 group exhibited higher incidence and worse prognosis. Although, the present study had certain limitations. First, Sesn2 could be involved in diseases via promoting the expression of various antioxidant proteins, and the downstream proteins of sesn2 were not detected in this study. In addition, all the patients came from the same center, more samples from different centers should be included in this study.

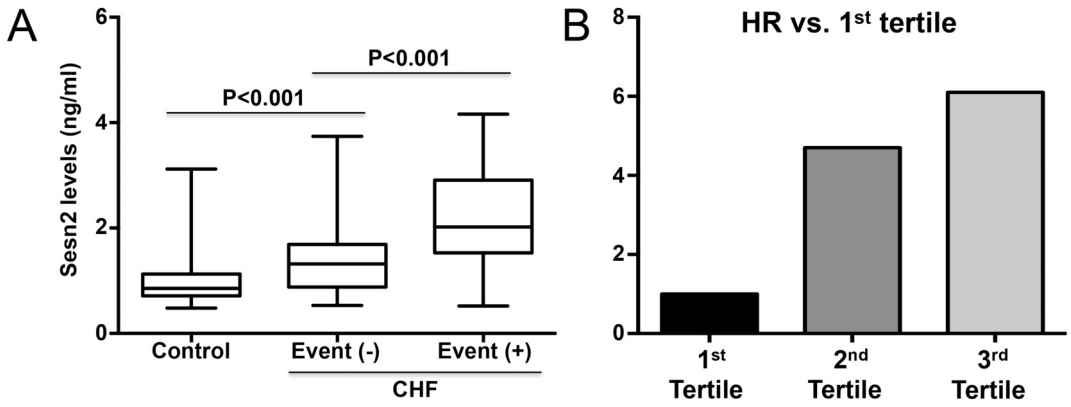

Fig. 4. Association between plasma Sesn2 concentrations and major adverse cardiac events. (A). Plasma Sesn2 concentrations in CHF patients with (n = 101) and without (n = 119) major adverse cardiac events were measured. (B). Hazard ratio of the tertiles of plasma Sesn2 concentrations for major adverse cardiac events.

Table 3
Association between Sesn2 and the occurrence of cardiac events was assessed by univariate and multivariate analyses.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Low	1	Reference	Reference	1	Reference	Reference
Middle	5.4	2.6 to 11.9	< 0.001	4.7	1.9 to 10.4	< 0.001
High	6.9	1.7 to 17.1	< 0.001	6.1	3.2 to 15.2	< 0.001

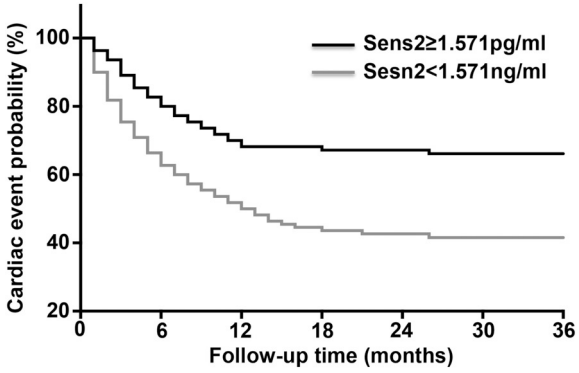

Fig. 5. Kaplan-Meier curve for adverse major adverse cardiac events according to low and high plasma Sesn2 concentrations. N = 110 for each group. P values are from the log-rank test.

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