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Article

Serum Levels of Hcy, sST2 and CA-125 in CHF Patients and Their Correlation with Cardiac Function Classification

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Abstract

Background: The relationships between serum levels of homocysteine (Hcy), soluble stromelysin 2 (sST2), and tumor-associated cancer antigen 125 (CA-125) and heart failure requires further investigation. The aim of the present study was to evaluate the levels of Hcy, sST2 and CA-125 in patients with congestive heart failure and to correlate these with cardiac function, thereby providing a reference for the clinical diagnosis and treatment of heart failure. **Methods**: Seventy patients with chronic heart failure (CHF) diagnosed between August 2020 and July 2022 were classified into heart failure groups II (n = 25), III (n = 23) and IV (n = 22). Seventy individuals with normal physical examination results were selected as the healthy group. Serum Hcy, sST2 and CA-125 levels for all participants were evaluated and correlated with each other and with cardiac function classification. The diagnostic value of individual Hcy, sST2, CA-125 levels for CHF was evaluated, as well as a combination of these factors. **Results**: Hcy, sST2, and CA-125 levels were lower in the healthy group than in the heart failure group. Moreover, a progressive increase in Hcy, sST2, and CA-125 levels were observed in heart failure groups II, III, and IV. Individual Hcy, sST2 and CA-125 levels, as well as a combination of these factors, were significantly correlated with cardiac function classification ($p < 0.05$). Hcy, sST2 and CA-125 levels each showed diagnostic value for CHF, with the three combined having the best diagnostic value. **Conclusions**: Abnormally high levels of Hcy, sST2 and CA-125 occur in CHF patients and are positively correlated with cardiac function classification. Individual levels of these factors, and particularly a combination of the three, show good sensitivity and specificity for CHF diagnosis that could be widely used in clinical practice.

Keywords

chronic heart failure; cardiac function classification; HCY; sST2; CA-125; correlation

Introduction

Chronic heart failure (CHF) is mainly due to cardiac insufficiency caused by functional heart disease in the ventricle, as well as heart failure caused by continuous, long-term pressure load on the ventricle [1,2]. CHF is the final outcome for most heart diseases, with high morbidity and mortality rates [3,4]. The incidence of CHF in China is increasing continuously, and the incidence also increases with age [5]. The medical community has not reached a unified consensus regarding the pathogenesis of CHF, and this may be related to the role of myocardial damage. Once the diastolic and systolic functions of the heart are damaged, the venous return blood cannot be discharged from the heart. This leads to accumulation of blood flow in the venous system and insufficient perfusion of venous blood, resulting in cardiac circulatory disorders and CHF [6,7]. Cancer antigen 125 (CA-125) is a high-molecular glycoprotein derived from the endometrium, peritoneum, and ovary, and is important in the diagnosis of ovarian cancer, lung cancer and other diseases. Recent studies have found the serum CA125 level is closely related to the severity of congestive heart failure, with high levels present during CHF [8]. Homocysteine (Hcy) is a sulfhydryl-containing amino acid and an intermediate product of methionine metabolism. Hcy can directly damage vascular endothelial cells and functions, thereby increasing the risk of cardiovascular disease [9]. Soluble stromelysin 2 (sST2) is a cardiomyocyte A receptor protein that is secreted in response to changes in volume or pressure load, leading to myocardial remodeling and ventricular dysfunction and an increased risk of death [8]. Recent studies have shown that Hcy, CA-125, and sST2 may be new risk factors for heart failure, but further confirmation is needed [8,9]. These three biomarkers may show a correlation with heart failure. In the present study, the levels of serum Hcy, sST2, and CA-125 were evaluated in patients with congestive heart failure. Furthermore, their correlation with cardiac function was also investigated, thereby providing a reference for the clinical diagnosis and treatment of heart failure.

Table 1. Baseline data for the healthy and heart failure groups.

Category	Healthy group (n = 70)	Heart failure group (n = 70)		
		Heart failure group II (n = 25)	Heart failure group III (n = 23)	Heart failure group IV (n = 22)
Age (years)	59.76 ± 8.77*	58.42 ± 9.23	58.59 ± 8.65	59.44 ± 8.48
Gender (male/female)	43/27*	14/11	13/10	12/10
Heart rate (beats/min)	77.27 ± 10.24*	76.51 ± 11.35	77.17 ± 10.52	76.83 ± 11.05
Hypertension				
No (n, %)	36 (51.43)	15 (60.00)	14 (60.87)	11 (50.00)
Yes (n, %)	34 (48.57)	10 (40.00)	9 (39.13)	11 (50.00)
Coronary heart disease				
No (n, %)	39 (55.71)	10 (40.00)	12 (52.17)	14 (63.64)
Yes (n, %)	31 (44.29)	15 (60.00)	11 (47.83)	8 (36.36)
Diabetes				
No (n, %)	33 (47.14)	15 (60.00)	8 (34.78)	11 (50.00)
Yes (n, %)	37 (52.86)	10 (40.00)	15 (65.22)	11 (50.00)
BMI (kg/m²)	25.87 ± 3.17*	26.95 ± 3.47	25.27 ± 3.22	26.85 ± 3.06
BUN (mmol/L)	6.35 ± 2.97*	7.44 ± 2.41	6.13 ± 3.04	6.47 ± 3.09
ALT (U/L)	23.42 ± 14.33*	23.50 ± 14.26	23.16 ± 14.24	22.82 ± 14.31
UA (μmol/L)	239.18 ± 64.24*	238.69 ± 65.76	235.60 ± 67.22	236.98 ± 67.37
TG (mmol/L)	1.64 ± 0.35*	1.59 ± 0.41	1.62 ± 0.27	1.59 ± 0.37
Cr (μmol/L)	48.92 ± 15.76*	49.96 ± 16.14	49.46 ± 13.25	50.35 ± 11.26
HDLC (mmol/L)	1.87 ± 0.23*	1.86 ± 0.34	1.84 ± 0.32	1.82 ± 0.29
LDLC (mmol/L)	2.29 ± 0.63*	2.37 ± 0.72	2.44 ± 0.75	2.51 ± 0.79

Values shown are (the $\bar{x}$ ± SD, except for hypertension, coronary heart disease and diabetes [n, (%)].

Note: * denotes compared to the heart failure group, * $p < 0.05$. BMI, body mass index; BUN, blood urea nitrogen; ALT, alanine aminotransferase; UA, uric acid; TG, triglycerides; Cr, creatinine; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol.

Materials and Methods

Baseline Data

Seventy CHF patients diagnosed from August 2020 to July 2022 were selected as the heart failure group. These were divided into heart failure group II (n = 25), heart failure group III (n = 23) and heart failure group IV (n = 22) according to classification criteria from the New York Heart Association (NYHA) [10]. Seventy healthy individuals with normal physical examination results were randomly selected as the control group. This study was approved by the Medical Ethics Committee of our hospital. The inclusion criteria were: (1) met the diagnostic criteria for CHF [11]; (2) complete clinical data was available, and individuals were informed about the research and signed the consent form; (3) no other malignant diseases; (4) no coagulation dysfunction. The exclusion criteria were: (1) abnormal neurological function, and unable to communicate normally; (2) suffering from liver function disease; (3) poor compliance and lack of cooperation; (4) unable to participate in the entire study.

Classification Method

The NYHA standard classification system was used here and is defined as follows. Heart failure grade II: patient has mild limitation of physical activity, is asymptomatic at rest, but general physical activity will result in excessive fatigue (asthma, palpitations and angina pectoris, etc.); Heart failure grade III: The patient's physical activity is significantly restricted, and although there are no symptoms at rest, general physical activity will result in excessive fatigue; Heart failure grade IV: The patient is unable to engage in any physical activity, the phenomenon of heart failure also occurs in the resting state, and the symptoms are aggravated after physical activity.

Evaluation of Serum Hcy, sST2 and CA-125

Peripheral venous blood (5 mL) was collected from all subjects in the fasting state and used to measure the serum levels of Hcy, sST2 and CA-125. Blood was centrifuged at 3000 r/min for 10 min to obtain the upper serum, which was then stored at –80 °C prior to testing. The Hcy level was measured by immunoassay using the 7600 automatic biochemical analyzer and kit (Hitachi, Tokyo, Japan). sST2 and CA-125 levels were measured by enzyme-linked immunosorbent assay (ELISA) method using the Cobas E411 automatic electrochemiluminescence immunoassay

Table 2. Hcy, sST2 and CA-125 levels in the healthy and heart failure groups ($\bar{x} \pm SD$).

Group	Number of cases	Hcy (μmol/L)	sST2 (ng/mL)	CA-125 (U/mL)
Healthy group	70	12.76 ± 4.02	33.05 ± 11.24	13.71 ± 5.26
Heart failure group	70	29.44 ± 9.34	84.79 ± 23.47	142.17 ± 7.85
t		7.541	8.224	7.134
p		<0.001	<0.001	<0.001

Hcy, homocysteine; sST2, soluble stromelysin 2; CA-125, cancer antigen 125.

Table 3. Hcy, sST2 and CA-125 levels in heart failure groups II, III and IV ($\bar{x} \pm SD$).

Group	Number of cases	Hcy (μmol/L)	sST2 (ng/mL)	CA-125 (U/mL)
Heart failure group II	25	19.50 ± 6.02	65.83 ± 17.47	61.35 ± 16.35
Heart failure group III	23	23.76 ± 7.68	78.62 ± 21.36	175.10 ± 25.91
Heart failure group IV	22	29.81 ± 8.79	85.17 ± 26.47	217.60 ± 32.54
t		9.881	8.243	10.949
p		<0.001	<0.001	<0.001

Table 4. Correlation analysis of Hcy, sST2 and CA-125 levels.

Category	sST2		CA-125	
	r	*p*	*r*	*p*
Hcy	0.674	<0.001	0.664	<0.001
sST2	-	-	0.717	<0.001

analyzer (Roche, Basel, Switzerland). ELISA kits were purchased from the Shanghai Institute of Enzyme-Linked Biology (Shanghai, China) and used according to the manufacturer's instructions. The study was approved by the medical ethics committee of the Nanning 10th People's Hospital (20200719), with no conflict of interest reported.

Serum Hcy, sST2 and CA-125

Serum HCY, sST2 and CA-125 levels were measured in the healthy group and in heart failure groups II, III and IV. They were then correlated with cardiac function classification, both individually and in combination. The diagnostic value of serum Hcy, sST2 and CA-125 levels for the detection for CHF was also assessed, both individually and combined.

Statistical Methods

SPSS 26.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Measurement data was expressed as the mean ± standard deviation ($\bar{x} \pm$ SD). The independent samples *t* test was used to compare data between groups, and the *F* test for multiple groups. Numerical data was expressed as a percentage (%) and analyzed by χ^2 test. Spearman analysis was used to evaluate the correlation between serum Hcy, sST2 and CA-125, as well as the correlation between each of these factors and cardiac function grade. The receiver operating characteristic (ROC) curve was used to estimate the diagnostic value of serum Hcy, sST2 and CA-125 levels for CHF. A *p*-value < 0.05 indicates statistical significance.

Results

Baseline Data

The healthy and heart failure groups showed no significant differences in any of the baseline data ($p > 0.05$), as seen in Table 1.

Hcy, sST2 and CA-125 Levels in the Healthy and Heart Failure Groups

The healthy group showed significantly lower Hcy, sST2 and CA-125 levels than the heart failure group (each $p < 0.001$; Table 2).

HCY, sST2 and CA-125 Levels in Heart Failure Groups II, III and IV

Significant differences in the levels of Hcy, sST2 and CA-125 were observed between heart failure groups II, III and IV (each $p < 0.0001$), as shown in Table 3.

Correlation of Hcy, sST2 and CA-125 Levels

Spearman correlation analysis showed that Hcy levels were positively correlated with those of sST2 ($r = 0.674$, $p < 0.001$) and CA-125 ($r = 0.664$, $p < 0.001$). The sST2 level was also positively correlated with that of CA-125 ($r = 0.717$, $p < 0.001$), as shown in Table 4 and Figs. 1,2,3.

Correlation of Hcy, sST2 and CA-125 Levels with Cardiac Function Classification

Hcy, sST2 and CA-125 levels were positively correlated with cardiac function classification ($r = 0.755$, $r = 747$, $r = 724$, respectively; each $p < 0.001$), as shown in Table 5 and Fig. 4,5,6.

Table 5. Correlation between Hcy, sST2 and CA-125 levels and cardiac function classification.

Category	Hcy		sST2		CA-125	
	r	*p*	*r*	*p*	*r*	*p*
Cardiac function classification	0.755	<0.001	0.747	<0.001	0.724	<0.001

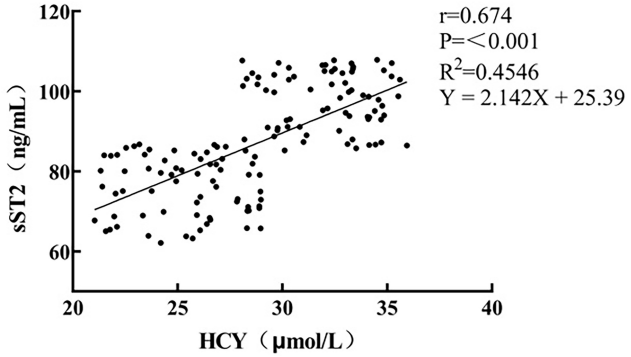

Fig. 1. Correlation between Hcy and sST2 levels.

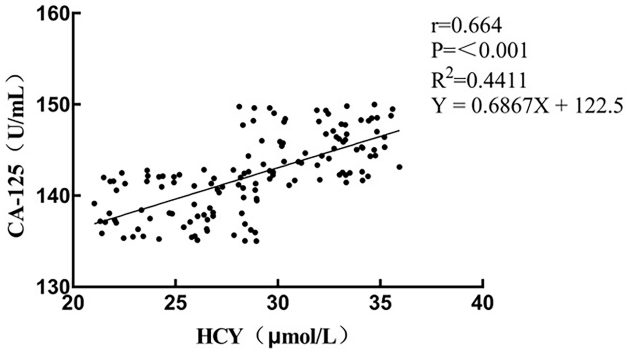

Fig. 2. Correlation between Hcy and CA-125 levels.

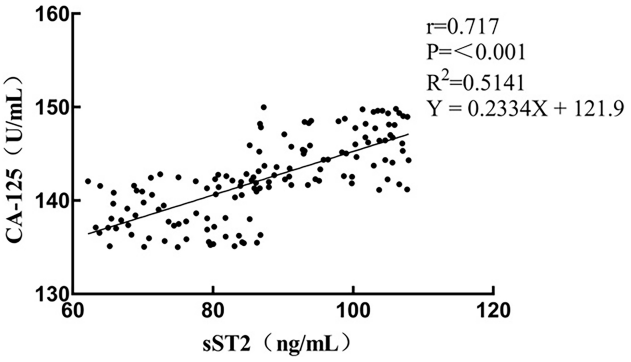

Fig. 3. Correlation between sST2 and CA-125 levels.

Diagnostic Value of Hcy, sST2, CA-125 for the Detection of CHF

Individual Hcy, sST2, and CA-125 levels, as well as the three levels combined, showed significant diagnostic value for the detection of CHF, with sensitivities of 81.69%, 81.33%, 79.89%, and 93.56%, respectively, and specificities of 80.13%, 77.87%, 74.76%, and 89.01%, respectively.

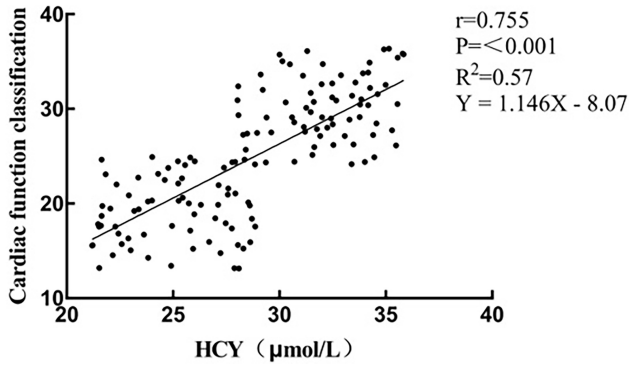

Fig. 4. Correlation between Hcy level and cardiac function classification.

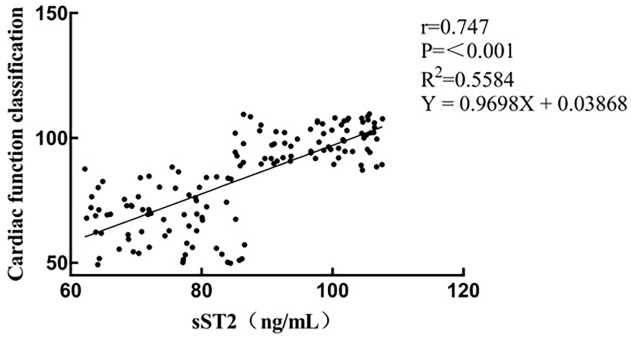

Fig. 5. Correlation between sST2 level and cardiac function classification.

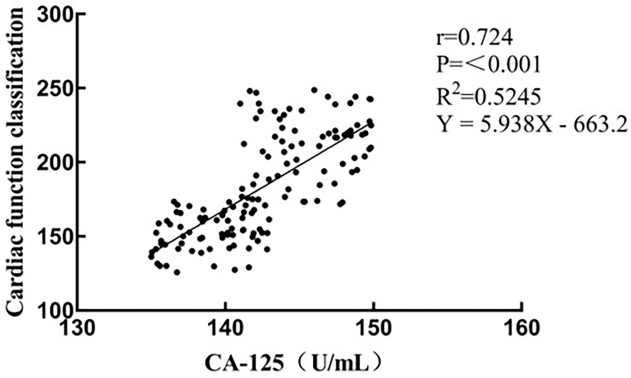

Fig. 6. Correlation between CA-125 level and cardiac function classification.

The combination of all three biomarkers showed the best sensitivity and specificity for the detection of CHF (Table 6 and Fig. 7).

Table 6. Diagnostic values of Hcy, sST2 and CA-125 individually and in combination for the detection of CHF.

Index	95% CI	*p*	Sensitivity (%)	Specificity (%)	Area under the curve	Cutoff value
Hcy (μmol/L)	0.724~0.875	<0.001	81.69	80.13	0.800	17.32
sST2 (ng/mL)	0.701~0.860	<0.001	81.33	77.87	0.780	53.88
CA-125 (U/mL)	0.637~0.814	<0.001	79.89	74.76	0.725	100.54
Combined	0.847~0.961	<0.001	93.56	89.01	0.904	52.48

CHF, chronic heart failure.

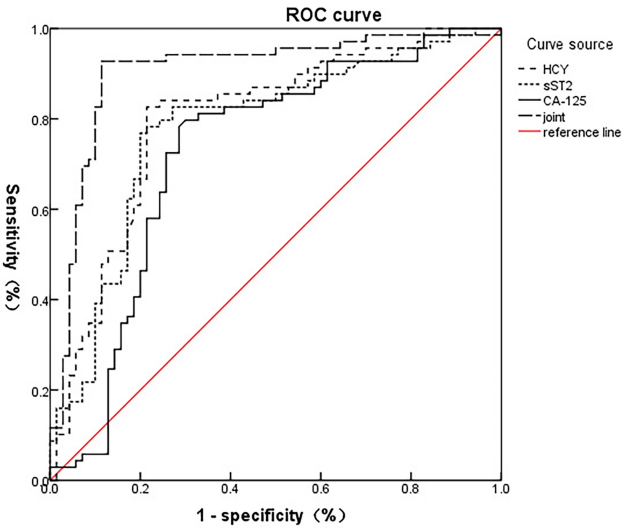

Fig. 7. ROC chart for individual Hcy, sST2 and CA-125 levels and a combination of all three for the detection of CHF.

Discussion

Despite constant advances in science and technology, as well as in the treatment methods and medical equipment used for CHF, there has been no reduction in the morbidity and mortality from this disease. Hence there is a need to further improve the early detection and diagnosis of CHF, thereby allowing preventive treatment measures [12,13]. Currently, the commonly used clinical diagnostic markers are B-type brain natriuretic peptide and N-terminal B-type brain natriuretic peptide. However, these markers have a short half-life, their concentration in human blood is unstable, and inter-individual variation is quite large. Therefore, the currently used diagnostic tests are not ideal [14,15]. In the present work we evaluated the concentrations of Hcy, sST2 and CA-125 in CHF patients and correlated these with the classification of cardiac function, thereby allowing an assessment of their diagnostic value. The levels of Hcy, sST2 and CA-125 were found to be significantly higher in the heart failure group than in the healthy group. Moreover, the levels of these markers increased progressively in heart failure groups II, III, and IV. Emdin *et al.* [16] reached similar conclusions to the current work. Together, these findings indicate that Hcy, sST2 and CA-125 levels continue to increase with the development of CVD and may be explained as follows. Hcy is an intermediate product of methionine metabolism, which is an independent risk factor for CVD. The Hcy level increases significantly during the development of CHF, such that a higher degree of heart failure correlates with a higher Hcy level. Although the level of sST2 is also higher, it is not affected by factors such as age, gender or renal function, and is thus a single threshold marker of heart failure. At the same time, the emergence of CVD increases stimulation of the pericardium, leading to increased secretion of CA-125 by the epithelial cells.

The current study found that individual Hcy, sST2 and CA-125 levels, as well as the three combined, were positively correlated with cardiac function classification, indicating they were independent risk factors for CHF. A possible explanation for this is that the pathogenesis of CHF can lead to vitamin B deficiency in the body. The more severe the disease, the more serious the vitamin B deficiency. Essential metabolic co-factors such as vitamin B are reflected in the Hcy level, and the lack of such factors will reduce the Hcy response, causing its concentration in the body to increase. Studies have also shown that an increased level of sST2 will also accelerate the development of heart failure, thereby increasing the risk of death. Moreover, the secretion by pericardial mesothelial cells increases after cardiac function is impaired, resulting in increased production of CA-125 [17,18]. A previous study showed that Hcy, sST2 and CA-125 have diagnostic value for CHF [19]. The present study confirmed that the serum levels of each of these factors has diagnostic value for CHF, and that the three combined have the best diagnostic value. These results suggest that Hcy, sST2 and CA-125 levels can be used as auxiliary indicators for the evaluation of patients with CHF.

Conclusions

Increased concentrations of Hcy, sST2 and CA-125 are found in CHF, and are positively correlated with each other. Furthermore, the Hcy, sST2 and CA-125 levels increased with higher stages of cardiac function classification, thus showing a positive correlation with the disease. The evaluation of all three biomarkers provides high diagnostic value for CHF and can be used as a basis for clinical diagnosis. However, the number of subjects investigated here was small, and the results may have some bias.

Therefore, it is necessary to study larger research cohorts and to conduct more in-depth investigation, thus allowing for more accurate clinical diagnosis and treatment of CHF.

Availability of Data and Materials

The simulation experiment data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

WM: Conceptualization, Methodology, Writing—original draft, Project administration. PZ: Data curation, Visualization, Writing—review & editing. HH: Formal analysis, Writing—review & editing, Supervision, Project administration. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

The study was approved to be implemented after review by the medical ethics committee of Nanning 10th People's Hospital (20200719). All patients were informed about the research and signed the consent form.

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Conflict of Interest

The authors declare no conflict of interest.

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