Association Between Cystatin C and Cardiac Function and Long-Term Prognosis in Patients with Chronic Heart Failure

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to investigate the association between cystatin C and cardiac function and long-term prognosis in patients with chronic heart failure (CHF).

Material/Methods: We selected 418 CHF patients admitted to our hospital as subjects. Patients were divided into 3 groups according to the cystatin C level (Quantile 1 group: 0.65–1.04 mg/L, Quantile 2 group: 1.05–1.35 mg/L, and Quantile 3 group: 1.36–7.84 mg/L), and patients were followed up for 5 years. We used odds ratio (OR) and 95% confidence interval (CI) to compare the results.

Results: The cystatin C and NT-ProBNP level in the cardiac function grade (NYHA) class IV group were higher than those in the class III group (P<0.05). Pearson correlation analysis showed that there was a positive correlation between cystatin C and NT-ProBNP $\log_{10}$ transform in CHF patients (r=0.411). During 5-year follow-up, 231 patients died and the 5-year all-cause mortality rate was 55.26% (231/418). There was a significant difference in 5-year all-cause mortality among the 3 groups (P for trend=0.010). After adjusting for potential confounders by multivariate regression analysis, the Quantile 2 group *vs.* Quantile 1 group were OR=0.83, 95% CI 0.51 to 1.35, P=0.448, and the Quantile 3 group *vs.* Quantile 1 group were OR=1.71, 95% CI. 1.04 to 2.82, P=0.034. Curve fitting showed that cystatin C was positively correlated with 5-year all-cause mortality in CHF patients.

Conclusions: Cystatin C was positively correlated with cardiac function and NT-ProBNP in CHF patients. Cystatin C could be used as a serological index to evaluate the long-term prognosis of CHF patients.

MeSH Keywords: **Cystatin C • Heart Failure • Mortality**

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Background

Chronic heart failure (CHF) [1–5] is a complex cardiovascular disease characterized by inability of the heart to meet the functional needs of the human body, resulting in progressive pump failure and fluid accumulation. At present, the number of CHF patients is increasing worldwide [6,7]. In this population, about 50% of CHF patients die within 5 years, significantly increasing the social and national medical economic burden [8–11]. Thus, it is necessary to further understand the pathophysiology and pathogenesis of CHF so as to adjust the treatment plan of clinicians in time.

Cystatin C is a protein composed of 120 amino acids. All human cells with nuclei (including DNA) produce cystatin C, and the concentration of cystatin C is almost entirely dependent on the glomerular filtration rate (GFR). Compared with the equation based on creatinine, it is equivalent or even superior in the estimation of GFR [12–14]. Therefore, cystatin C is an ideal endogenous marker for early prediction of renal function. In recent years, with the continuous development of medicine, researchers have found that cystatin C plays an important role in predicting new or worsening cardiovascular and cerebrovascular diseases [15,16]. A subgroup analysis from the PLATO [17] study showed a significant increase in cystatin C in patients with acute coronary syndrome (ACS), suggesting that cystatin C is associated with poor prognosis in ACS patients. In addition, a study of 3030 subjects found that cystatin C was associated with cognitive impairment in the elderly, even if potential confounding factors were adjusted [18]. At present, it is unclear whether there is a correlation between cystatin C level and 5-year all-cause mortality in CHF patients. The purpose of this study was to explore the relationship between serum cystatin C and the severity of cardiac function and long-term prognosis in patients with CHF.

Material and Methods

This retrospective cohort study enrolled CHF patients who were admitted to our hospital from July 2012 to July 2013. This study was conducted in accordance with the principles of the Helsinki Declaration, and all patient data are anonymous. Inclusion criteria were: 1) hospitalized patients meeting the heart failure criteria established by the European Heart Association in 2012 [19]; 2) older than 18 years old and less than 75 years old; 3) cardiac function grade (NYHA) ≥ class III; and 4) the language and communication skills of patients or their families can fully assist researchers in clinical follow-up. Exclusion criteria were: 1) patients with malignant tumors, such as colorectal cancer, esophageal cancer, gastric cancer, non-small cell lung cancer, or liver cancer; 2) patients with severe impairment of renal function; 3) complicated with autoimmune diseases (such as

systemic sclerosis, rheumatoid arthritis, or systemic lupus erythematosus) or hematological diseases; 4) patients with infection; and 5) patients with acute cerebrovascular disease, such as cerebral hemorrhage or cerebral infarction.

Patient information collection and treatment

Using our hospital information system (HIS), we collected data on patient demographic characteristics, complications, and clinical medication. The baseline characteristics of patients included sex, age, height, weight, leukocytes, hemoglobin, creatinine, uric acid, total cholesterol, low-density lipoprotein, high-density lipoprotein, homocysteine, cystatin C, fasting blood glucose, glycosylated hemoglobin, serum troponin I, NT-proBNP, disease history, and clinical medication history. Serological examination was performed within 24 h after admission, and the test process was completed by the Laboratory Department of our hospital. According to the actual situation of the patient, the drugs recommended in the 2012 European guidelines for heart failure were given for treatment. The main drugs included diuretics, β-blockers, angiotensin-converting enzyme inhibitor (ACEI), and angiotensin receptor antagonist (ARB).

Research outcome

This study was based on our hospital electronic medical records (including in-patient and outpatient systems) and 5-year all-cause mortality (including cardiovascular and non-cardiovascular deaths). Cardiovascular death events included cardiac arrest, cardiogenic shock, malignant arrhythmia, and acute attack of heart failure. The main outcome indicators were non-cardiovascular events, including gastrointestinal bleeding, multiple organ dysfunction syndrome, pulmonary heart disease, and pulmonary infection. We also used telephone interviews with the patient or the patient's family in detail to reconfirm the clinical outcome of the patient.

Statistical analysis

Patients were divided into 3 groups according to cystatin C level: Quantile 1 group: 0.65–1.04 mg/L, Quantile 2 group: 1.05–1.35 mg/L, and Quantile 3 group: 1.36–7.84 mg/L. Normally distributed measurement data are expressed by mean±standard deviation and LSD analysis of variance was used to compare between groups. Measurement data that were not normally distributed are expressed by median (quartile spacing) and the Kruskal-Wallis rank sum test was used to compare between groups. Count data are represented by the number of cases (%) and were compared between groups by chi-square test.

We used univariate analysis to explore the factors associated with 5-year all-cause mortality in CHF patients, and then adjusted the variables with significant differences in univariate
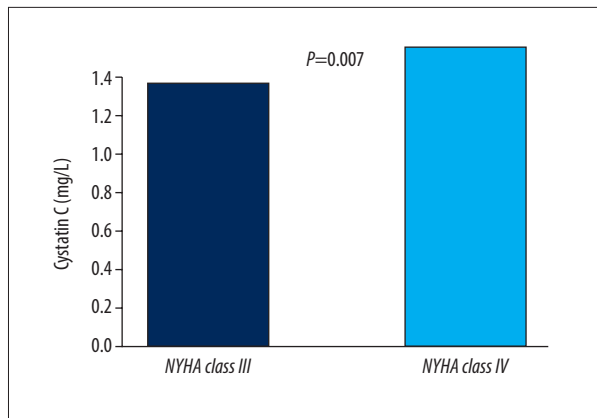
Figure 1. Comparison of cystatin C levels between 2 groups (NYHA III group and NYHA IV group).

analysis (P<0.05) into multivariate logistic regression analysis, and then observed the independent effect of cystatin C and 5-year all-cause mortality in CHF patients. Odds ratio (OR) and 95% confidence interval (CI) were used to compare the 5-year all-cause mortality among the 3 groups.

In addition, curve fitting was used to explore the relationship between cystatin C concentration and 5-year all-cause mortality in CHF patients. Considering the large value of NT-ProBNP, we converted NT-ProBNP to log10 (i.e., NT-ProBNP log10 transform). P value <0.05 was considered to be a statistically significant different. Data analyses were performed using the SPSS 22 statistical software package (IBM Corp., Armonk, NY, USA), R software 3.3.2 version (available at: *www.r-project.org*), GraphPad Prism 6 software, and EmpowerStats (*http://www.empowerstats.com*).

Results

Comparison of cystatin C and NT-ProBNP in patients with different cardiac functions

CHF patients were divided into 2 groups according to cardiac function (III group and IV group). The differences between cystatin C and NT-ProBNP were compared between the 2 groups. The results showed that the concentration of cystatin C (1.54±0.99 mg/L *vs.* 1.35±0.76 mg/L, P=0.007) in the IV group was significantly higher than that of the III group, as shown in Figure 1. Similarly, the NT-ProBNP concentration [4143.00 (1934.00–9711.50) *vs.* 1629.00 (618.00–3875.00), P<0.001] was significantly higher in the IV group than that of the III group, as shown in Figure 2.
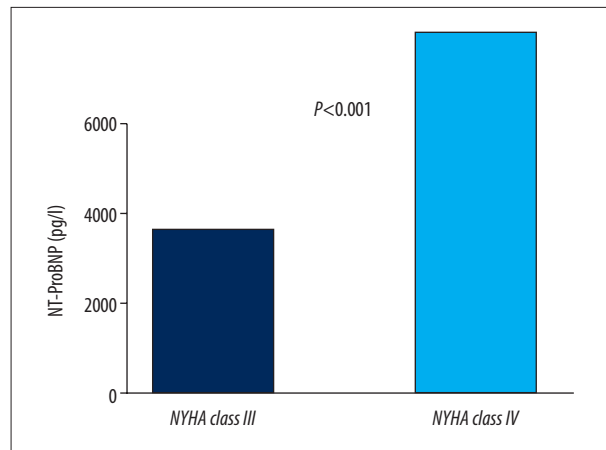

Figure 2. Comparison of NT-ProBNP levels between the 2 groups (NYHA III group and NYHA IV group).
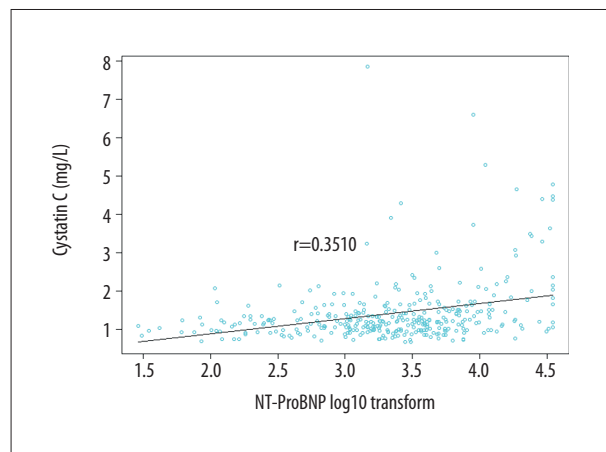

Figure 3. Pearson correlation analysis of cystatin C and NT-ProBNP log10 transform in CHF patients.

Pearson correlation analysis of cystatin C and NT-ProBNP

Considering the large value of NT-ProBNP, we performed a log10 transformation of NT-ProBNP and observed the correlation between cystatin C and NT-ProBNP. The results showed that the cystatin C and NT-ProBNP log10 transform were positively correlated in CHF patients, and the correlation coefficient was 0.411. This shows that the cystatin C concentration increased with the increase of NT-ProBNP log10 transform, as shown in Figure 3. The correlation between cystatin C and NT-ProBNP log10 transform in CHF patients with different cardiac functions was observed on the basis of subgroup analysis. The results showed that cystatin C and NT-ProBNP log10 transform were positively correlated in patients with NYHA class III, and the correlation coefficient was 0.4391. Similarly, in patients with NYHA class IV, cystatin C and NT-ProBNP log10 transform were also positively correlated, with a correlation coefficient of 0.3510, as shown in Figure 4.
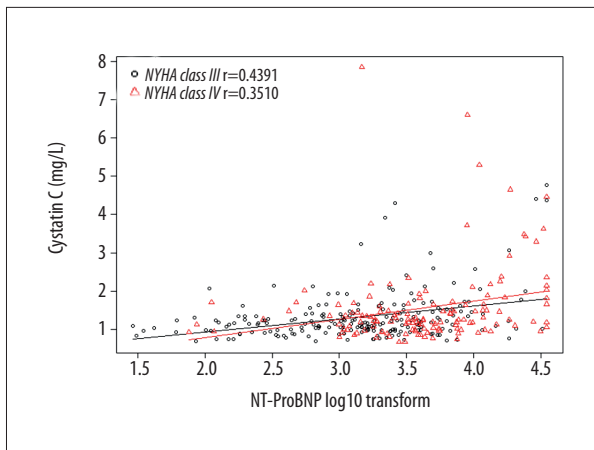
Figure 4. Pearson correlation analysis of cystatin C and NT-ProBNP log10 transform (subgroup analysis).

Comparison of clinical data of 3 groups of patients (patients divided into 3 groups according to cystatin C level)

Age, leucocyte, hemoglobin, creatinine, uric acid, low-density lipoprotein, homocysteine, cardiac function classification, valvular heart disease, NT-proBNP, 5-year all-cause mortality, and history of hypertension in the 3 groups had statistical differences (all P<0.05). There was no significant difference in other baseline data of body weight, height, and sex among the 3 groups (all P>0.05). During the 5-year follow-up, 231 patients died, and the 5-year all-cause mortality rate was 55.26% (231/418). Among them, 70 patients died in Quantile 1 group, with a 5-year all-cause mortality rate of 51.09% (70/137); 68 patients died in Quantile 2 group, with a 5-year all-cause mortality rate of 48.92% (68/139); and 93 patients died in

Table 1. Comparison of clinical data of 3 groups.

Variables	Quantile 1		Quantile 2		Quantile 3		P for trend
N	137		139		142		
Height (cm)	160.86±8.04		161.65±8.30		161.31±8.54		0.735
Sex (n, %)							0.103
Female	71	(51.82%)	84	(60.43%)	91	(64.08%)	
Male	66	(48.18%)	55	(39.57%)	51	(35.92%)	
Cardiac function (n, %)							0.034
Class III	90	(65.69%)	90	(64.75%)	74	(52.11%)	
Class IV	47	(34.31%)	49	(35.25%)	68	(47.89%)	
Primary cardiomyopathy (n, %)							0.176
No	109	(79.56%)	104	(74.82%)	119	(83.80%)	
Yes	28	(20.44%)	35	(25.18%)	23	(16.20%)	
Valvular heart disease (n, %)							0.003
No	85	(62.04%)	106	(76.26%)	112	(78.87%)	
Yes	52	(37.96%)	33	(23.74%)	30	(21.13%)	
Coronary heart disease (n, %)							0.069
No	95	(69.34%)	81	(58.27%)	81	(57.04%)	
Yes	42	(30.66%)	58	(41.73%)	61	(42.96%)	
Hypertension (n, %)							0.018
No	129	(94.16%)	132	(94.96%)	123	(86.62%)	
Yes	8	(5.84%)	7	(5.04%)	19	(13.38%)	
Age (year)							<0.001
<45 year	32	(23.36%)	17	(12.23%)	8	(5.63%)	
45–65 year	72	(52.55%)	70	(50.36%)	49	(34.51%)	
≥65 year	33	(24.09%)	52	(37.41%)	85	(59.86%)	

Table 1 continued. Comparison of clinical data of 3 groups.

Variables	Quantile 1	Quantile 2	Quantile 3	P for trend
Weight (kg)				0.429
<50 kg	28 (21.88%)	23 (18.25%)	34 (26.98%)	
50–75 kg	86 (67.19%)	86 (68.25%)	74 (58.73%)	
≥75 kg	14 (10.94%)	17 (13.49%)	18 (14.29%)	
White blood cell (10^9/L)	8.28±3.53	8.57±3.96	8.38±3.76	0.811
Hemoglobin (g/L)	128.52±20.50	132.02±21.72	117.21±23.21	<0.001
Creatinine (umol/L)	77.80±19.30	92.59±20.74	171.87±138.40	<0.001
Uric acid (umol/L)	386.86±147.71	451.77±153.21	519.55±146.99	<0.001
Total cholesterol (mmol/L)	4.47±1.18	4.39±1.19	4.16±1.35	0.119
Low-density lipoprotein (mmol/L)	3.01±1.06	2.81±1.02	2.62±0.99	0.010
High-density lipoprotein (mmol/L)	1.24±0.45	1.19±0.44	1.14±0.53	0.215
Homocysteine (umol/L)	12.36±5.02	15.91±5.57	20.82±8.05	<0.001
Fasting blood sugar (umol/L)	5.63±2.80	5.41±1.57	6.11±2.78	0.072
Glycosylated hemoglobin (%)	6.43±1.77	6.30±1.07	6.40±1.62	0.872
Troponin I (μg/L)	0.02 (0.01–0.10)	0.05 (0.01–0.24)	0.06 (0.02–0.25)	0.861
NT-proBNP (pg/ml)	2072.00 (668.00–4322.50)	1799.00 (845.00–3926.00)	4354.00 (1473.00–10320.00)	<0.001
Beta blockers (yes, %)	88 (64.23%)	83 (59.71%)	89 (62.68%)	0.733
ACEI/ARB (yes, %)	74 (54.01%)	85 (61.15%)	75 (52.82%)	0.317
Diuretic (yes, %)	85 (62.50%)	81 (58.27%)	87 (61.27%)	0.761
5-year all-cause mortality (n, %)				0.010
No	67 (48.91%)	71 (51.08%)	49 (34.51%)	
Yes	70 (51.09%)	68 (48.92%)	93 (65.49%)	

Data representation: mean±standard deviation or median (interquartile range) or number (%). Cystatin C: Quantile 1: 0.65–1.04 mg/L; Quantile 2: 1.05–1.35 mg/L; Quantile 3: 1.36–7.84 mg/L.
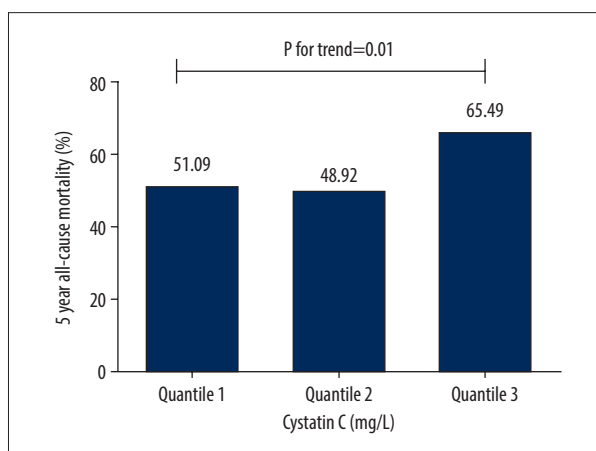

Figure 5. Comparison of 5-year all-cause mortality in 3 groups of patients. (Quantile 1: 0.65–1.04 mg/L; Quantile 2: 1.05–1.35 mg/L; Quantile 3: 1.36–7.84 mg/L).

Quantile 3 group, with a 5-year all-cause mortality rate of 65.49% (93/142). The 5-year all-cause mortality rate among the 3 groups was significantly different (P for trend=0.010), as shown in Table 1 and Figure 5.

Univariate analysis of 5-year all-cause mortality in CHF patients

Univariate analysis showed that sex (OR=0.57, 95% CI: 0.38 to 0.84), cardiac function grade (OR=3.86, 95% CI: 2.51 to 5.94),

Table 2. Univariate analysis of 5-year all-cause mortality in CHF patients.

Variables	OR	95% CI	P value
Age (year)	1.01	(0.99, 1.02)	0.2116
Sex (Male *vs.* Female)	0.57	(0.38, 0.84)	0.0051
Coronary heart disease (yes *vs.* no)	0.85	(0.57, 1.26)	0.4220
Hypertension (yes *vs.* no)	0.90	(0.45, 1.82)	0.7764
Valvular heart disease (yes *vs.* no)	0.97	(0.63, 1.50)	0.9031
Primary cardiomyopathy (yes *vs.* no)	1.09	(0.68, 1.76)	0.7199
Cardiac function (class IV *vs.* class III)	3.86	(2.51, 5.94)	<0.0001
Height (cm)	1.01	(0.98, 1.03)	0.6682
Weight (kg)	0.98	(0.96, 0.99)	0.0042
White blood cell (10^9/L)	1.04	(0.99, 1.10)	0.1354
Hemoglobin (g/L)	1.00	(0.99, 1.01)	0.5357
Creatinine (umol/L)	1.01	(1.00, 1.02)	0.0026
Uric acid (umol/L)	1.00	(1.00, 1.00)	0.0837
Total cholesterol (mmol/L)	0.96	(0.82, 1.13)	0.6053
Low-density lipoprotein (mmol/L)	1.02	(0.84, 1.24)	0.8550
High-density lipoprotein (mmol/L)	0.79	(0.51, 1.20)	0.2639
Homocysteine (umol/l)	1.00	(0.97, 1.03)	0.8355
Fasting blood sugar (umol/L)	1.06	(0.97, 1.16)	0.1762
Glycosylated hemoglobin (%)	1.00	(0.83, 1.20)	0.9929
Troponin I (µg/L)	0.99	(0.96, 1.02)	0.4208
NT-proBNP (pg/ml)	1.00	(0.96, 1.02)	0.4208
Beta blockers (yes *vs.* no)	0.50	(0.33, 0.75)	0.0008
ACEI/ARB (yes *vs.* no)	0.75	(0.51, 1.11)	0.1475
Age			
<45 year	Reference	Reference	Reference
45–65 year	0.77	(0.43, 1.40)	0.3967
≥65 year	1.23	(0.67, 2.26)	0.5023
Cystatin C			
Quantile 1	Reference	Reference	Reference
Quantile 2	0.92	(0.57, 1.47)	0.7180
Quantile 3	1.82	(1.12, 2.94)	0.0151

Data representation: OR (95% CI) P value. Cystatin C: Quantile 1: 0.65–1.04 mg/L; Quantile 2: 1.05–1.35 mg/L; Quantile 3: 1.36–7.84 mg/L.

Table 3. Multivariate logistic regression analysis of 5-year all-cause mortality in serum cystatin C and CHF patients.

Cystatin C	5-year all-cause mortality		
	OR	95% CI	P value
Non-adjusted			
Quantile 1	Reference	Reference	Reference
Quantile 2	0.92	(0.57, 1.47)	0.718
Quantile 3	1.82	(1.12, 2.94)	0.015
Adjust			
Quantile 1	Reference	Reference	Reference
Quantile 2	0.83	(0.51, 1.35)	0.448
Quantile 3	1.71	(1.04, 2.82)	0.034

Data representation: OR (95% CI) P value. Cystatin C: Quantile 1: 0.65–1.04 mg/L; Quantile 2: 1.05–1.35 mg/L; Quantile 3: 1.36–7.84 mg/L. The adjustment factors included sex, weight, cardiac function classification, and beta blockers.

body weight (OR=0.98, 95% CI: 0.96 to 0.99), creatinine (OR=1.01, 95% CI: 1.00 to 1.02), beta blockers (OR=0.50, 95% CI: 0.33 to 0.75), and cystatin C (Quantile 2 group *vs.* Quantile 1 group: OR=0.90, 95% CI: 0.00 to 1.02; Quantile 3 group *vs.* Quantile 1: OR=1.82, 95% CI: 1.12 to 2.94, respectively) were significantly correlated with 5-year all-cause mortality in CHF patients. Other factors, such as age, coronary heart disease, hypertension, valvular heart disease, primary cardiomyopathy, height, weight, and white blood cells, had no significant association with 5-year all-cause mortality in CHF patients (all P>0.05), as shown in Table 2.

Multivariate logistic regression analysis of 5-year all-cause mortality in cystatin C and CHF patients

We used cystatin C as an independent variable, 5-year all-cause mortality in CHF patients as a dependent variable, and variables (sex, body weight, cardiac function grading, creatinine, and beta blockers) selected from univariate analysis as covariate variables to adjust in multivariate logistic regression, and then observed the independent effect of cystatin C on 5-year all-cause mortality. The results showed that Quantile 2 group *vs.* Quantile 1 group was (OR=0.83, 95% CI 0.51 to 1.35), and Quantile 3 group *vs.* Quantile 1 group was (OR=1.71, 95% CI 1.04 to 2.82), which indicated that the 5-year mortality of CHF patients increased with the increase of cystatin C, as shown in Table 3.

Curve fitting of 5-year all-cause mortality in CHF patients and cystatin C patients

We used curve fitting to explore the 5-year all-cause mortality of serum cystatin C and CHF patients. The results showed that the 5-year all-cause mortality of CHF patients increased with the increase of cystatin C concentration. There was a
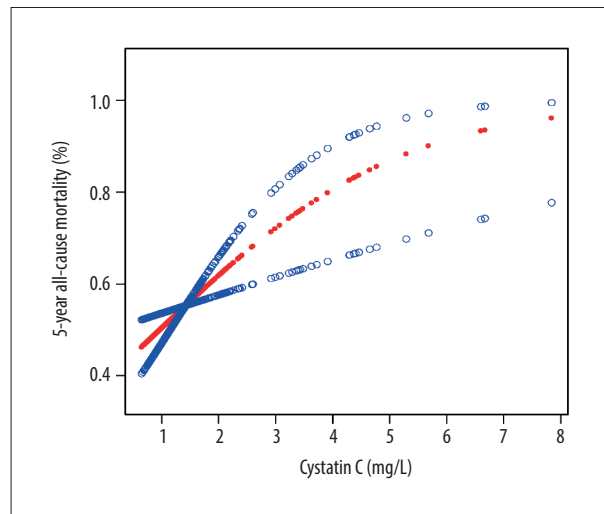

Figure 6. The relationship between cystatin C and 5-year all-cause mortality in CHF patients.

rising trend, and this trend had a nonlinear positive correlation, as shown in Figure 6.

Discussion

Cystatin C is a member of the cysteine protease inhibitor (CPI) family, which is mainly composed of 122 amino acids and has a molecular weight of about 13.3 KD [20,21]. Cystatin C is closely related to traditional inflammatory markers and is an independent predictor of adverse prognosis in patients with acute cerebrovascular diseases. Cystatin C can even be used to predict the area of cerebral infarction and the total amount of intracranial hemorrhage in patients with cerebral apoplexy [22,23]. A cohort study including 245 patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) found that elevated

cystatin C was significantly associated with all-cause mortality and incidence of secondary myocardial infarction in NSTE-ACS patients [24]. In another population-based cohort study, a prospective follow-up of 3075 community-living elderly people found that elevated cystatin C could be a marker of cognitive impairment in the elderly population [25]. A retrospective cohort study in Korea included 322 patients with type 2 diabetes, showing that cystatin C increased with the increase of albuminuria concentration, and reached the highest level in patients with macroalbuminuria (P <0.001) [26]. A meta-analysis of 19 studies involving 3336 patients showed that the threshold value of acute kidney injury (AKI) predicted by cystatin C level was 27.7 (95% CI, 12.8–55.8), sensitivity and specificity were 0.86 and 0.82, respectively, and the corresponding area under the receiver operating characteristic curve surface was 0.87 (95% CI, 0.81–0.99) [27]. Interestingly, a representative large-scale HIV infection study conducted in multiple centers also showed that nephropathy characterized by elevated cystatin C levels appears to be an important risk factor for mortality among HIV-infected people [28]. However, at present, most of the clinical evaluation of renal function depends on serum creatinine clearance rate, and a large part of the risk of death may not be recognized early.

In this study, we found that worse cardiac function classification was associated with higher levels of cystatin C and NT-ProBNP in CHF patients. Pearson correlation analysis indicated that there was a significant correlation between cystatin C and NT-ProBNP (r=0.411). In addition, multivariate regression analysis showed that elevated baseline cystatin C level was still a risk factor for 5-year all-cause mortality in CHF patients. The results of this study are similar to those of previous research. The Tromsø Study, conducted in Norway [29], followed up 2 852 men and 3153 women for 12 years. The results showed that cystatin C was not significantly associated with lethal or non-lethal myocardial infarction and ischemic stroke, but could be used as an independent predictor of all-cause mortality. A meta-analysis of 9 studies that included 38 854 people showed that [30] elevated cystatin C was independently associated with higher cardiovascular and all-cause mortality risk. A cohort study explored whether cystatin C could be used as an accurate serum marker for judging GFR and prognosis in CHF patients, finding that cystatin C was an independent predictor of adverse outcomes (HR=2.27, 95% CI 1.12–4.63) compared with GFR. In addition, a retrospective cohort study followed up 189 patients with chronic kidney disease (CKD) for an average of 36.55 months and divided them into 3 equal groups according to cystatin C levels, showing that cardiovascular mortality in CKD patients increased with cystatin C levels [31].

The mechanism underlying the association between cystatin C and poor prognosis in CHF patients is unclear. At present, there are 4 main possible mechanisms. (1) Ventricular remodeling: this pathophysiological change is the most direct basis for the increase in all-cause mortality caused by cystatin C. Previous studies have shown that structural changes in the heart include destruction and injury of cardiomyocytes and changes in myocardial extracellular matrix. The disorder of myocardial collagen production is one of the fundamental causes of remodeling of cardiac extracellular matrix. Cystatin C can selectively inhibit the activity of cystine protease, reduce degradation of elastic fibers in cardiomyocytes, and increase destruction of myocardial collagen fibers, resulting in changes in cardiac structure and function [32–34]. (2) Atherosclerotic: Cystatin C is an inhibitor of cathepsin family cysteinase (including elastase and collagenase) and plays an important role in atherosclerosis. Cysteinase degrades elastin and collagen, which are 2 important components of the extracellular matrix of the vessel wall. Therefore, cystatin C may play an important role in matrix remodeling in the development of heart failure. Previous studies have shown that cystatin C can indirectly act on arterial vascular smooth muscle cells to produce amyloid-like substances, resulting in the increase of blood lipids and the production of fiber cap [35]. However, the experiments in animals did not test the hypothesis that elevated cystatin C concentrations were associated with an increased incidence of cardiovascular disease or heart failure. After several weeks of atherogenic diet intervention, the atherosclerotic plaques in apolipoproteins E deficient mice deficient in cystatin C were larger than those in cystatin C mice, suggesting that cystatin C may have a protective effect in atherosclerotic plaques. Part of the reason for this apparent paradox may be related to other inflammatory markers in subjects with elevated cystatin C concentrations. (3) Oxidative stress: studies in CKD patients have shown that cystatin C increases with the increase of oxidative stress index *in vivo*. It is speculated that cystatin C is also involved in oxidative stress reaction *in vivo* to promote cardiomyocyte injury and autophagy [36,37]. (4) Inflammatory response: a number of studies have reported a relationship between inflammatory markers and serum cystatin C levels. In most of these studies, cross-sectional analysis showed a moderate correlation that remained significant even after the estimated GFR had been corrected. Therefore, it is assumed that cystatin C is not only a marker of glomerular filtration, but also a marker of inflammation, especially endothelial wall stress and atherosclerosis. Inflammation is involved in the occurrence and development of heart failure. A study published in the Chinese Medical Journal showed that there was a positive correlation between cystatin C and inflammatory markers, and speculated that cystatin C could be used as a new type of inflammatory marker. It also plays an important role in pathophysiological changes in heart failure [38]. However, these studies did not measure GFR by the clearance rate of iodocarbamate, so the observed results may still be related to the reduced clearance rate of cystatin C.

This study has the following limitations. First, we did not collect data to distinguish between heart failure that retains left ventricular function and heart failure that does not retain left ventricular function (given that the hospital did not submit all data on cardiac ultrasound to the PACE system from July 2012 to July 2013, there was no obvious record in the course of the disease). Therefore, we were not able to obtain the ejection fraction of the included patients for further analysis. According to the literature, cystatin C is positively correlated with systolic blood pressure, and we suggest that cystatin C has a stronger correlation with diastolic heart failure caused by hypertensive cardiomyopathy. Second, as a retrospective cohort study, we could not rule out the effects of residual or unmeasured confounding factors on our results. In addition, the risk of selective bias and retrospective bias are inevitable shortcomings in retrospective studies, because the definition of symptoms or diseases may change, but also have a certain impact on the results. Third, the end event observed in this study is all-cause mortality, but we could not identify which major cardiovascular events contributed to all-cause mortality, so as to carry out further follow-up analysis. On the other hand, the study has the following advantages. We collected covariates to control the influence of residual confounding factors. We also used multivariate logistic regression analysis to adjust the confounding variables. Finally, we had a relatively long follow-up time. To the best of our knowledge, this is the first study to assess the relationship between baseline serum cystatin C and 5-year all-cause mortality in patients with heart failure.

Conclusions

Cystatin C level is positively correlated with the severity of cardiac function and NT-ProBNP level in CHF patients, and could be used as a predictive indicator of long-term prognosis in CHF patients.

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