

Original Article

Prognostic value of cystatin C in chronic heart failure in relation to creatinine

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Abstract: Objective: To investigate the prognostic value of cystatin-C (Cys-C) in chronic heart failure (CHF) in comparison to creatinine. Methods: A total of 221 patients with CHF during hospitalization from Jan. 2009 to Dec. 2011 were finally enrolled. Logistic regression models were used to examine the relationship of Cys-C and other known risk factors to incident heart failure. The area under the receiver operating characteristic curve was used to compare the performance of different risk factors in prognosis of CHF. Results: The mean age of the patients was 66.6 years, of which 59% patients (n = 131) were male. 18.6% patients (n = 41) died at the end of the follow up. Multivariate logistic regression showed age (OR = 1.11, 95% CI = 1.04-1.19), SBP (OR = 1.06, 95% CI = 1.01-1.10), LVEF (OR = 0.89, 95% CI = 0.82-0.95), Ig (BNP) (OR = 4.74, 95% CI = 1.77-12.69), creatinine (OR = 2.04, 95% CI = 1.03-4.08), Cys-C (OR = 2.97, 95% CI = 1.44-6.12) are the independent risk factors for prognosis of CHF. When compared with creatinine, Cys-C and Cys-C & Cr score showed a better performance of auROC (0.71 vs. 0.63, P = 0.249; 0.75 vs. 0.63, P = 0.001, respectively) in ROC analysis. Conclusion: Cys-C is a stronger predictor of the mortality of CHF patients than creatinine and it seems to be a promising risk marker and a more useful clinical tool for risk stratification of patients with CHF.

Keywords: Chronic heart failure, cystatin C, creatinine

Introduction

Understanding of the pathophysiology and new treatment have improved prognosis of chronic heart failure (CHF) in the last two decades [1, 2]. However, because CHF is a progressively debilitating condition and no treatment could stop its progression so far, it is still characterized by repeated hospitalizations and associated with poor long-term prognosis despite optimal use of modern therapies, only half of the patients can survive more than five years after diagnosis [3].

Accurate estimation of CHF risk and early initiation of primary preventive treatment is the most important way to prevent CHF morbidity and mortality. Previous studies have found that renal dysfunction, measured by creatinine or estimated glomerular filtration rate (GFR), is a strong predictor of mortality in the setting of CHF [4, 5]. For creatinine levels are influenced heavily by muscle mass, estimated GFR is recommended as the appropriate renal function

measure for clinicians [6]. However, traditional estimates of GFR which based on the serum creatinine levels may not be optimal in persons with normal creatinine levels [7]. In recent years, Cys-C (cystatin-c), a small 13 kDa cysteine protease inhibitor, has emerged to be a novel and interesting marker of the renal function as it does not appear to be dependent on age, gender, or body mass and it is believed to be almost exclusively dependent on the GFR [8].

Cys-C has predictive and prognostic value in cardiovascular disease including coronary heart disease (CHD) [9], acute heart failure (AHF) [3] and pulmonary heart disease (PHD) [10] had been revealed by previous studies. Recently Lee et al. published data from a meta-analysis involving 22509 high cardiovascular risk subjects suggesting that high Cys-C levels were independently linked to greater risk of CHF [11].

In this study, we wanted to assess the prognostic impact of Cys-C in a representative popula-

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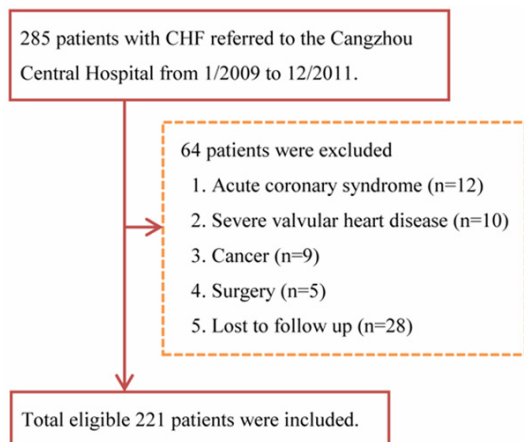


Figure 1. A flow diagram of study participants.

tion of patients with CHF and to examine its incremental value over creatinine, which was the conventional marker of renal function.

Materials and methods

Patients

CHF is defined, clinically, as a syndrome in which patients have typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) and signs (e.g. elevated jugular venous pressure, pulmonary crackles, and displaced apex beat) resulting from an abnormality of cardiac structure or function, according to European Society of Cardiology guidelines [12]. 285 patients were diagnosed with CHF in the Cangzhou Central Hospital, from 1/2009 to 12/2011. Exclusion criteria were: acute coronary syndrome, severe valvular heart disease, cancer, surgery and patients who lost to follow up. Finally, total 221 eligible patients were included.

The start date of the follow up was the date of diagnosis of CHF. The endpoint of interest was death from any cause. All the patients were followed up for at least 3 years unless death. An informed consent was obtained from each patient included in the study, and the research protocol of the study was approved by the Ethics Committee of the Cangzhou Central Hospital.

Data collection

Clinical examination and data recording were conducted in the morning after an overnight fast and subjects were also instructed to refrain

from exercise during the day before their examination. Medical history and a health habit inventory were taken by a special doctor.

These included demographic characteristics (age, sex); traditional cardiovascular risk factors, such as body mass index, smoking (current versus past or never), systolic blood pressure and diastolic blood pressure, clinical disease (Diabetes, hypertension, previous myocardial infarction or cerebrovascular disease, which were adjudicated by a combination of self-report of physician diagnosis and review of medical records).

Standing height and body weight were measured without shoes or thick clothing. Blood pressure, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), was measured using a Riva-Rocci sphygmomanometer with the subject in a quiet environment and in a sitting position.

Fasting blood samples were obtained from each subject and were used for the analysis of biochemical measurements. Centralized analyze of NT-proBNP and creatinine was performed from blood samples obtained on admission. Plasma concentration of NT-proBNP was measured by microparticle enzyme immunoassay. Serum creatinine was analyzed using commercially available kits. Serum used for Cys-C detection was drawn in the morning and stored at -70°C . Cys-C was measured using the DakoCytomation immunoturbidimetric assay.

Echocardiography was assessed by 2 experienced imaging specialists who were blind to the study design. If the diagnose made by the 2 specialists were not in agreement or inconclusive, a third specialist was invited.

Statistical analysis

Continuous variables were summarized as mean \pm standard deviation (SD), and categorical variables were displayed as counts or percentages. Student-t test was used for continuous variables and χ^2 -test for categorical variables.

We used logistic regression model to examine the relationship of Cys-C and other known risk factors to incident heart failure in univariate and multivariable models. Creatinine and Cys-C

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Table 1. Baseline characteristics of patients with heart failure

	Total	Survival	Death	P-value
Male	131 (59%)	107 (59.11%)	24 (58.53%)	0.974
Age	66.6 ± 6.8	65.9 ± 6.2	69.9 ± 8.6	<0.001
BMI (kg/m ²)	20.9 ± 2.0	20.9 ± 1.9	20.6 ± 2.1	0.344
SBP (mmHg)	140.5 ± 11.1	139.5 ± 10.8	145.1 ± 11.0	0.003
DBP (mmHg)	80.8 ± 7.7	80.6 ± 7.1	81.5 ± 9.9	0.589
History of				
Diabetes	19 (8.6%)	14 (7.7%)	5 (12.2%)	0.425
Hypertension	82 (36.9%)	64 (35.4%)	18 (43.9%)	0.308
MI	23 (10.4%)	17 (9.4%)	6 (14.6%)	0.322
CBD	21 (9.5%)	17 (9.4%)	4 (9.8%)	0.943
Smoking	49 (22.1)	39 (21.6%)	10 (24.4%)	0.704
LVEF (%)	46.5 ± 6.7	47.4 ± 6.5	42.2 ± 5.5	<0.001
Lg(BNP)	2.5 ± 0.50	2.5 ± 0.5	2.8 ± 0.5	<0.001
Creatinine (μmol/L)	91.6 ± 25.0	88.2 ± 24.1	106.7 ± 23.3	<0.001
Cystatin C (mg/L)	1.2 ± 0.4	1.11 ± 0.3	1.5 ± 0.4	<0.001

Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; CBD, cerebrovascular disease; LVEF, left ventricular ejection fraction.

Table 2. Logistic regression analysis for patients with heart failure

Variables	Univariate			Multivariable		
	OR	95% CI	P-value	OR	95% CI	P-value
Male	0.98	0.49-1.94	0.946	0.93	0.39-2.29	0.901
Age	1.07	1.01-1.12	0.012	1.11	1.04-1.19	0.003
SBP	1.05	1.02-1.09	0.004	1.06	1.01-1.10	0.012
DBP	1.02	0.97-1.06	0.504	1.00	0.95-1.06	0.906
History of						
Diabetes	1.66	0.56-4.89	0.361	1.33	0.34-5.27	0.682
Hypertension	1.43	0.72-2.85	0.308	1.26	0.51-3.12	0.616
MI	1.66	0.61-4.49	0.324	1.82	0.47-6.41	0.389
CBD	1.04	0.33-3.28	0.943	0.59	0.13-2.60	0.485
Smoking	1.75	0.53-2.60	0.692	0.82	0.28-2.38	0.716
LVEF	0.84	0.78-0.90	<0.001	0.89	0.82-0.95	0.001
Lg (BNP)	5.44	2.46-12.04	<0.001	4.74	1.77-12.69	0.002
Cr	2.51	1.26-6.00	0.009	2.04	1.03-4.08	0.041
Cystatin C	3.92	1.88-8.19	0.002	2.97	1.44-6.12	0.008

Note: Note: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial infarction; CBD, cerebrovascular disease; LVEF, left ventricular ejection fraction.

were transformed to dichotomous variable for a better clinic understand and application (creatinine ≥ 90 μmol/L defined as high level and Cys-C ≥ 1.2 mg/L defined as high level). Multivariable model was adjusted for included sex, age, SBP, DBP, diabetes, hypertension, myocardial infarction, cerebrovascular disease, smoking, left ventricular ejection fraction, BNP, Creatinine and Cys-C.

To assess differences in prognosis efficiency between the creatinine and Cys-C, area under the receiver operating characteristic curve (auROC), which is a measure of discrimination, was calculated. The 3-year mortality was used to evaluate diagnostic performance of scoring systems for patients with CHF. Furthermore, the standard index of validity, such as Youden index, sensitivity, specificity was calculated according to the ROC results.

Results

Study population

A total of 285 patients with CHF during hospitalization from Jan 2009 to Dec 2011 were enrolled. The diagnosis of CHF had to be confirmed during hospital stay. After exclusion of those who did not meet the inclusive criteria (**Figure 1**), 221 patients were finally included. Information of all cases about baseline characteristics was collected from the medical records. The mean age of the patients was 66.6 years, of which 59% patients (n = 131) were male. 18.6% patients (n = 41) died at the end of the follow up. The mean serum Cys-C, creatinine, lg(BNP) and LEVF in death group were 1.5 ± 0.4 mg/L, 106.7 ± 23.3 μmol/L, 2.8 ± 0.5, significantly higher than those in survival ones. Patients who died had a lower LEVF (42.2 ± 5.5% vs. 47.4 ± 6.5%, P<0.001). There seemed a higher prevalence of clinical disease or smoking in patients who died, but not statistically significant (**Table 1**).

Risk factors analysis for 3-years mortality

Cr and Cys-C were transformed into dichotomous variables. Univariate logistic regression

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Table 3. ROC analysis of creatinine and cystatin c on 3-years mortality of patients with heart failure

Values	auROC	95% CI	P*	P#	Youden	Cut-off	Sensitivity	Specificity
Creatinine	0.63	0.57-0.70	0.002	Ref	0.23	105	45.2%	77.8%
Cystatin c	0.71	0.65-0.76	<0.001	0.249	0.40	1.31	59.5%	80.6%
Cr & Cys C	0.75	0.69-0.81	<0.001	0.001	0.43	5.99	66.7%	76.7%

Note: Value of (Cr & Cys C) = 0.027*creatinine + 2.68* cystatin c. P*, compared with 0.5; P#, compared with auROC of creatinine.

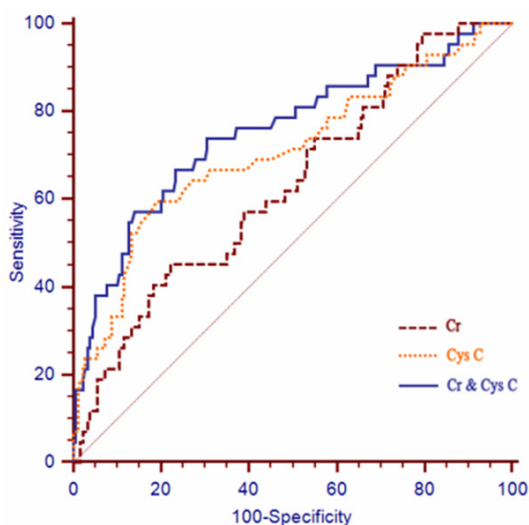


Figure 2. ROC analysis of Cys-C, Cr and Cr & Cys-C score on 3-years mortality of patients with chronic heart failure.

showed that age (OR = 1.07, 95% CI = 1.01-1.12), SBP (OR = 1.05, 95% CI = 1.02-1.09), LVEF (OR = 0.84, 95% CI = 0.78-0.90), lg(BNP) (OR = 5.44, 95% CI = 2.46-12.04), Cr (OR = 2.51, 95% CI = 1.26-6.00) and Cys-C (OR = 3.92, 95% CI = 1.88-8.19) were significantly associated with mortality (all $P < 0.05$). Then, all variables were entered into the multivariate logistic regression analyses. As **Table 2** has presented, age (OR = 1.11, 95% CI = 1.04-1.19), SBP (OR = 1.06, 95% CI = 1.01-1.10), LVEF (OR = 0.89, 95% CI = 0.82-0.95), lg(BNP) (OR = 4.74, 95% CI = 1.77-12.69), creatinine (OR = 2.04, 95% CI = 1.03-4.08), Cys-C (OR = 2.97, 95% CI = 1.44-6.12) were found to be the independent risk factors. The result may indicated Cys-C was more relevant to the mortality of CHF than Cr.

ROC analysis of Cr and Cys-C for 3-years mortality

Table 3 shows the ability of the Cr and Cys-C to predict 3-years mortality risk in patients with

CHF. The performance of the Cys-C was higher than Cr, with an auROC of 0.71 (95% CI: 0.65-0.76), but not statistically significant. When using a best cut-off value of 105 for the Cr, the sensitivity was 45.2%, the specificity was 77.8% and a cut-off value of 1.31 for the Cys-C, the sensitivity was 59.5%, the specificity was 80.6%. Then, we combined Cr and Cys-C to make a Cr & Cys-C score (Cr & Cys-C score = 0.027*creatinine + 2.68* Cys-c), of which the coefficients were calculated by the multivariate logistic regression with just Cr and Cys-C included. The score had an auROC of 0.75 (95% CI: 0.69-0.81), significantly higher than that of the Cr ($P = 0.001$). When we had a cut-off value of 5.99 for this score, the sensitivity was 66.7%, the specificity was 76.7%. Cr & Cys-C score had a better performance than Cr or Cys-C alone (**Figure 2**).

Discussion

In this study, we found Cys-C was a strong predictor of mortality in patients hospitalized for CHF. This finding was consistent across age and gender groups, and remained significant even after adjustment for other prognostic factors. What's more, we found that Cys C was a stronger marker than creatinine to predict 3-years mortality risk in patients with CHF. Besides, a further improve in risk stratification was observed when Cys C and creatinine were combined.

It has been widely accepted that renal dysfunction is one of the strongest risk factors for mortality in ambulatory CHF patients [13]. In patients hospitalized for CHF, impaired renal function is associated with a significant increased risk of mortality as well as higher rehospitalization rates. Reliable identification of renal dysfunction is a key issue in identifying patients of CHF at risk of death. However, the primary clinical tool to measure renal function, the serum creatinine level, is affected by factors unrelated to renal function, such as sex,

age, race, and lean muscle mass and is insensitive for the detection of moderate reductions in renal function [14]. Creatinine-based equation to estimate the GFR has been derived to compensate for these nonrenal influences on the relationship between creatinine and GFR, but its precision is unclear, particularly in patients with reduced muscle mass [15].

Recently, the use of serum creatinine or creatinine-based GFR to assess renal function has been challenged by novel markers, particularly Cys C, which emerged to be a more reliable index of GFR [16]. Cys C is a small serine protease inhibitor that is secreted by almost all active functional cells in the body [11]. Because of its small molecular weight at 13 kDa, Cys C is freely filtered by the renal glomerulus and then metabolized by the proximal tubule [17]. Therefore, levels of Cys C in serum are mainly dependent on glomerular filtration rate (GFR). In addition, Cys C seems not to be affected by diet, age, body mass index (BMI), or gender, leading to the suggestion that it would be the preferred endogenous marker of renal function [18, 19]. Compared with the creatinine based measurements, the addition of Cys C measurements in calculating the eGFR could significantly improve the risk classification for end-stage renal disease and cardiovascular disease [20, 21]. Cys C allows detection of minor changes in renal function [22] and recent study conducted by Shlipak et al. also suggested that eGFR equations that based on the measurement of Cys C can detect increased risks of adverse outcomes that are not detected with creatinine-based calculation of the GFR [6].

As a marker of renal function, Cys C is also a predictive and prognostic marker for CVD. Shlipak et al. and Sarnak et al. showed that for each quartile of Cys-C concentration there was a stepwise increase in the risk of developing HF independently of other risk factors [23, 24]. Besides, in acute HF, Lassus et al. demonstrated a significantly increased mortality rate with each tertile of Cys-C [3]. Several studies have suggested that Cys C is superior to serum creatinine or creatinine-based eGFR for prediction of cardiovascular mortality among elderly persons and among persons with known CHD [9]. In our study, we found that Cys-C could enable stratification of patients with CHF according to risk of death, and may help in directing intensified treatment efforts to high-risk groups.

However, whether the association between Cys-C with mortality of CHF patients is caused by its correlation with GFR or by other mechanisms is still unknown. Studies up to now cannot exclude the possibility that circulating Cys-C levels either have directly harmful effects in CHF patients or reflect another pathologic process distinct from renal function. Koenig et al. showed that in patients without kidney disease, elevated levels of serum Cys-C was still a predictor of outcome in CHF patients and suggested that the predictive and prognostic effects of Cys-C was not related to renal function [25].

The pathogenesis of CHF involves substantial proteolysis of cardiovascular extracellular matrix, composed predominantly of fibrillar collagen I and III [26]. Several families of proteolytic enzymes participate in the process, including cysteinyl cathepsins (Cats), serine proteases (SP), and matrix metalloproteinases (MMP). As a protease inhibitor, Cys-C plays an important role in regulation of these proteolytic enzymes extracellularly [27]. Recently, Xie et al. demonstrated that the elevation of Cys C in doxorubicin treatment induced cardiomyopathy mice correlated with an inhibition of cathepsin B (CTB), accumulation of collagen I, collagen III, and fibronectin in the ischemic area of the myocardium. What's more, they found that overexpression of Cys C gene or treating fibroblasts with purified Cys C protein could finally lead to inhibition of CTB activity and accumulation of the ECM proteins [28]. These results showed that circulating Cys-C participated in the progression of CHF by regulating the degradation or accumulation of the ECM proteins besides its correlation with GFR [26, 28].

This study has certain important limitations. First, the sample size of participants with CHF was small and all patients were from a single-center cohort. These limited the power to conduct subgroup analyses by gender, race or other factors. Second, we presumed the link between high Cys-C concentrations and poor CHF outcome was compromised renal function. We could not exclude the possibility that plasma Cys-C levels either have directly harmful effects or reflect another pathologic process other than renal function.

In this study, we demonstrated that Cys-C, as an alternative measure of kidney function, was a stronger predictor of the mortality of CHF

patients than creatinine. Cys-C seems to be a promising risk marker and a more useful clinical tool for risk stratification of patients with CHF. Further studies are needed to assess the applicability of Cys-C in directing treatment and as a risk marker during follow-up in patients with CHF.

Disclosure of conflict of interest

None.

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