Original paper

The prognostic role of high-sensitivity cardiac troponin T over time in ischemic and non-ischemic heart failure

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Abstract

Introduction: High-sensitivity cardiac troponin T (hs-cTnT) as a prognostic biomarker can be detected in patients with heart failure (HF).

Aim: This study focuses on hs-cTnT to evaluate its prognostic role in ischemic heart failure (IHF) and non-ischemic heart failure (NIHF).

Material and methods: One hundred and sixty patients with HF were divided into IHF and NIHF groups. Hs-cTnT measured at baseline, 2–5 h, 6–24 h and 24 h–7 d after admission was analyzed by generalized estimating equations. Patients were followed up for 1 year at the endpoint events of re-hospitalization for HF and all-cause death that was tested by the Kaplan-Meier method and the Cox regression method.

Results: Hs-cTnT varied significantly over time, first increasing and then decreasing in IHF while showing a continuously elevated trend in NIHF. Patients with hs-cTnT levels > 0.014 ng/ml had a significantly higher re-hospitalization rate compared with those with hs-cTnT levels ≤ 0.014 ng/ml (23.7% vs. 7.0%, $p < 0.05$). Adjusted for age, New York Heart Association class, N-terminal pro-B-type natriuretic peptide, and left ventricular ejection fraction, baseline hs-cTnT was independently associated with re-hospitalization and all-cause death in HF ($p < 0.05$). Optimal hs-cTnT cut-off of 0.0275 ng/ml was derived to predict the re-hospitalization and death in IHF (AUC = 0.709, 95% CI: 0.561–0.856, sensitivity: 76.9%, specificity: 63.5%, $p < 0.05$).

Conclusions: Hs-cTnT varying over time is an important risk factor for the prognosis of patients with IHF and NIHF.

Key words: high-sensitivity cardiac troponin T, ischemic heart failure, non-ischemic heart failure, time, prognosis.

Summary

High-sensitivity cardiac troponin T (hs-cTnT) can be detected in patients with heart failure to predict the prognosis. The major finding of our study is that hs-cTnT changes over time with different trends between ischemic heart failure (IHF) and non-ischemic heart failure (NIHF), which could be an important risk factor for the prognosis of patients with IHF and NIHF.

Introduction

Heart failure (HF) is a rapidly growing public health issue with an estimated prevalence of 64.34 million individuals globally [1]. Estimation of prognosis for morbidity, disability and death helps patients, their families and clinicians decide on the appropriate type and timing of therapies and assists with planning of health and social services and resources [2]. Even if the clinical manifestations of the different types of HF are similar, the pathological mechanisms and clinical prognoses of ischemic heart failure (IHF) and non-ischemic heart failure (NIHF) are different. Early identification of precursors of HF is important for the diagnosis and treatment of HF [2–4].

Highly sensitive assays for measurement of cardiac troponin (hs-cTn) have been widely used in the diagnosis of myocardial infarction (MI) [5]. The prognostic role of hs-cTn is not only used for patients with MI but also for patients with HF [6–11]. Myocardial injury, an important pathophysiological mechanism of HF, is persistent when there is elevated hs-cTn in HF [12–14]. High-sensitivity cardiac troponin T (hs-cTnT), above the 99th percentile upper reference limit, is more sensitive and specific than cardiac troponin T in identifying myocardial injury

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at a much earlier time [5]. And hs-cTnT can be earlier detected than N-terminal pro-B-type natriuretic peptide (NT-proBNP) in minor myocardial injury, showing a more accurate evaluation of prognosis in HF [15, 16].

Aim

At present, there is no definite study on hs-cTnT between IHF and NIHF, and it is still not clear how to use hs-cTnT to predict the prognosis of IHF and NIHF. Therefore, this study focuses on hs-cTnT to evaluate its prognostic role between IHF and NIHF.

Material and methods

Study population

Patients were enrolled from Beijing Tsinghua Changgung Hospital between November 2016 and December 2018. The study was approved by the Beijing Tsinghua Changgung Hospital Research Ethics Committee. The diagnosis of HF was based on typical symptoms and signs according to the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF [2]. The IHF group was made up of patients with obstructive coronary heart diseases whose coronary stenosis was more than 50% evaluated by coronary angiography (CAG) or coronary computed tomography (CCT). The NIHF group was chosen from patients with non-obstructive coronary heart disease, including atrial fibrillation, hypertension, dilated cardiomyopathy, and valvular heart disease, that had been previously definitely diagnosed. The exclusion criteria were acute myocardial infarction, radiofrequency ablation, and/or pacemaker implantation within 1 month, acute pulmonary embolism, chronic kidney disease (estimated glomerular filtration rate (eGFR) < 30 ml/min/173 m^2), sepsis, rhabdomyolysis, acute cerebral infarction, and acute cerebral hemorrhage.

Study protocol

According to the primary cause of HF, patients were divided into two groups: an IHF group and a NIHF group. Baseline data including gender, age, body mass index (BMI), blood pressure (BP), heart rate (HR), and other data were recorded. Peripheral blood samples for measuring serum levels of hs-cTnT, NT-proBNP and other indexes were compared between the two groups. Then the ventricular and atrial function and dimensions were evaluated by echocardiography. Patients were telephoned or seen in outpatient clinics at different time points (1, 6, 12 months after discharge), and their endpoint events were re-hospitalization for HF and all-cause death.

Measurement of hs-cTnT

Blood samples for assays of hs-cTnT were taken from peripheral veins at different times when the patients were admitted to the hospital, 2–5 h, 6–24 h, and 24 h–7 days

after admission. All the blood samples were stored at room temperature (25°C) and centrifuged at 3000 rpm for 20 min. Hs-cTnT assay was based on electrochemiluminescence technology (Elecsys 2010, cobas e411, Roche Diagnostics). This assay had the lower limit detection of 0.001 ng/ml, coefficient variation of < 10% at a limit of 0.013 ng/ml. In the present study, elevated hs-cTnT was defined as > 0.014 ng/ml.

Statistical analysis

All data were analyzed and processed using SPSS20 statistical software. Continuous and categorical variables were reported as mean ± standard deviation (SD) and number (*n*) (%) respectively, and tested by the *t*-test and χ^2 test between two groups where appropriate. Hs-cTnT and NT-proBNP were reported as median and tested by the Mann-Whitney U test. The levels of hs-cTnT over time and with different New York Heart Association (NYHA) class were analyzed by generalized estimating equations. The rate of re-hospitalization and all-cause death were calculated with the Kaplan-Meier method and the Cox regression method. A receiver operating characteristic (ROC) curve was used to analyze the role of hs-cTnT in predicting the endpoints in HF according to the Youden index.

Results

Baseline characteristics

Baseline characteristics of 65 patients with IHF and 95 patients with NIHF are displayed in Table I. Patients with NIHF had a higher heart rate (HR) and lower complication rate of hyperlipidemia compared to patients with IHF (*p* < 0.05). Patients with IHF were mostly in NYHA class II–III while patients with NIHF were mainly in NYHA III–IV (*p* < 0.05). Through echocardiography, patients with NIHF had a larger left atrial dimension (LA) and right ventricular dimension (RV) (*p* < 0.05).

Variation of hs-cTnT levels

The variation of hs-cTnT levels over time is shown in Figure 1. With the passage of time, hs-cTnT first increased and then decreased in the IHF group, but showed a continuously elevated trend in the NIHF group. The level of hs-cTnT varied statistically significantly over time, but membership of the IHF or NIHF group showed no effect on this level. Patients with different NYHA classes had various levels of baseline hs-cTnT (Table II). It seemed that the higher the NYHA class in patients was, the higher was the baseline hs-cTnT.

Re-hospitalization rate for heart failure and all-cause mortality

During the follow-up, 28 patients with baseline hs-cTnT levels > 0.014 ng/ml were re-hospitalized for HF and

Table I. Comparison of baseline characteristics between IHF and NIHF

Parameter	IHF (65)	NIHF (95)	*P*-value
Female, *n* (%)	32 (49.2)	53 (55.8)	0.294
Age [years]	71.32 ±11.227	69.14 ±15.158	0.324
BMI [kg/m²]	25.32 ±3.87	24.94 ±4.5	0.574
SBP [mm Hg]	128 ±16	123 ±20	0.105
DBP [mm Hg]	69 ±16	73 ±14	0.059
HR [beats/s]	78 ±13	87 ±19	0.002
Smoker, *n* (%)	14 (21.5)	23 (24.2)	0.207
Etiology, *n* (%):			
Angina pectoris	35 (63.6)		
Old myocardial infarction	30 (36.4)		
Atrial fibrillation		79 (83.2)	
Dilated cardiomyopathy		16 (16.8)	
Hypertension		59 (62.1)	
Valvular heart disease		31 (32.6)	
NYHA class, *n* (%):			
NYHA II	32 (49.2)	29 (30.5)	0.018
NYHA III	23 (35.4)	35 (36.8)	0.018
NYHA IV	10 (15.4)	31 (32.6)	0.018
Medical history, *n* (%):			
Diabetes mellitus	34 (52.3)	35 (36.8)	0.643
Cerebral infarction	12 (18.5)	12 (12.6)	0.656
Hyperlipidemia	34 (52.3)	13 (13.7)	0.000
Laboratory indicators:			
NT-proBNP [pg/ml]	3562 (1368–11313)	2464 (1577–8328)	0.003
eGFR [ml/min/1.73 m²]	68.81 ±22.68	73.80 ±25.18	0.208
HDL-C [mmol/l]	0.97 ±0.29	0.99 ±0.32	0.666
LDL-C [mmol/l]	2.27 ±0.90	2.34 ±0.84	0.629
TC [mmol/l]	3.80 ±0.96	3.93 ±1.00	0.413
HbA$_{1c}$ (%)	7.21 ±2.07	6.21 ±1.10	0.001
Ultrasonic cardiogram indicators:			
LVEF (%)	49.8 ±14.2	50.4 ±12.5	0.764
LA [mm]	38 ±10	47 ±10	0.000
LVEDD [mm]	53 ±8	55 ±11	0.353
LVESD [mm]	35 ±10	38 ±13	0.164
RV [mm]	22 ±3	24 ±5	0.001
IVS [mm]	10 ±1	10 ±2	0.585

ACEI – angiotensin-converting enzyme inhibitor, ARB – angiotensin receptor blocker, BMI – body mass index, DBP – diastolic blood pressure, eGFR – estimated glomerular filtration rate, HDL-C – high-density lipoprotein cholesterol, HR – heart rate, LDL-C – low-density lipoprotein cholesterol, IVS – interventricular septum, LA – left atrial dimension, LVEDD – left ventricular end diastolic dimension, LVEF – left ventricular ejection fraction, LVESD – left ventricular end systolic dimension, NT-proBNP – N-terminal pro-brain natriuretic peptide, NYHA – New York Heart Association, RV – right ventricular diameter, SBP – systolic blood pressure, TC – total cholesterol.

3 patients with baseline hs-cTnT levels ≤ 0.014 ng/ml; 10 patients were re-hospitalized for HF in the IHF group and 21 patients in the NIHF group. The Kaplan-Meier method showed that patients with a baseline hs-cTnT level > 0.014 ng/ml had a significantly higher re-hospitalization rate compared with those with baseline hs-cTnT levels ≤ 0.014 ng/ml (23.7% vs. 7.0%, *p* < 0.05) (Figure 2 A). But the re-hospitalization rate for HF was not statistically different between IHF and NIHF groups (Figure 2 A). Moreover, 4 patients with baseline hs-cTnT level > 0.014 ng/ml died of all causes; 2 patients with IHF and 2 pa-

tients with NIHF died. The Kaplan-Meier method showed no statistically significant difference between patients with baseline hs-cTnT levels > 0.014 ng/ml and patients with baseline hs-cTnT levels ≤ 0.014 ng/ml, or between IHF and NIHF (Figure 2 B).

Adjusted for age, NYHA class, NT-proBNP, and LVEF, Cox regression analysis showed that baseline hs-cTnT was independently related to re-hospitalization and all-cause death between IHF and NIHF (*p* < 0.05). Additionally, the cut-off of hs-cTnT (0.0275 ng/ml) was determined by the receiver operating characteristic (ROC)
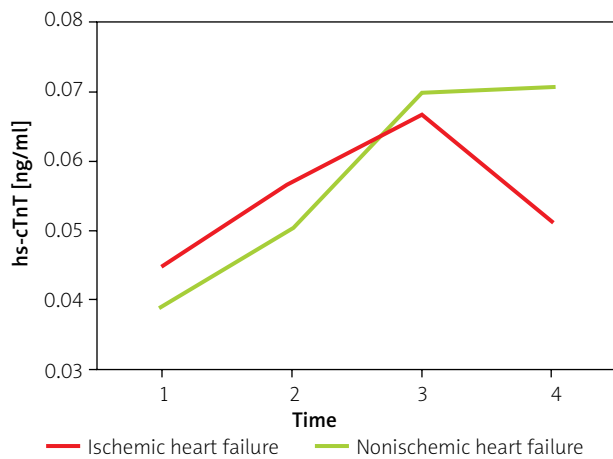
Figure 1. Variation of hs-cTnT at different times between ischemic heart failure and non-ischemic heart failure

hs-cTnT – high-sensitivity cardiac troponin T, time 1 – admission, time 2 – 2–5 h after admission, time 3 – 6–24 h after admission, time 4 – 24 h – 7 days after admission.

Table II. Baseline hs-cTnT with different NYHA classification

NYHA	Medium	95% Wald CI	
		Lower limit	Upper limit
II	0.050	0.031	0.068
III	0.049	0.034	0.064
IV	0.088	0.055	0.120

Baseline hs-cTnT – hs-cTnT at time of admission, NYHA – New York Heart Association.

analysis to predict the composite endpoints in IHF (AUC = 0.709, 95% CI: 0.561–0.856, sensitivity: 76.9%, specificity: 63.5%, $p < 0.05$) (Figure 3), and the AUC showed no significant difference in NIHF.

Discussion

This study demonstrated that the hs-cTnT levels over time showed an increasing trend in NIHF while first increasing and then decreasing in IHF. Adjusted for age, NYHA class, NT-proBNP, and LVEF, baseline hs-cTnT was independently related to re-hospitalization and all-cause death between IHF and NIHF. Furthermore, the optimal hs-cTnT cut-off of 0.0275 ng/ml was derived to predict the re-hospitalization rate for HF and all-cause death in IHF. Hs-cTnT was found to be an important biomarker to evaluate the re-hospitalization rate for HF and all-cause death in patients with HF.

Whatever the primary disease of HF was, myocardial injury actually existed and affected the functions and outcomes of HF [17–21]. Therefore, myocardial injury resulted in increased hs-cTnT levels in both IHF and NIHF patients. Ischemic myocardial injury could directly cause myocardial cell necrosis, and also could promote the release of growth factors that cause proliferation of the extracellular matrix and remodeling of myocardial tissues [22]. In addition, the direct effects of ischemic factors and the interaction of multiple factors may lead to higher hs-cTnT levels in IHF than those in NIHF. As functional and structural mechanisms can affect the physiological function of myocardial ischemia, the assessments of functional ischemia, including coronary flow reserve (CFR), cardiac magnetic resonance (CMRI), fractional flow reserve (FFR), index of microvascular reserve (IMR), positron emission tomography (PET), and single photon emission computed tomography (SPECT) [23], were essential to patients with HF. It is necessary to perform future studies that can assess the relation between functional ischemia of the myocardium and the dynamics of hs-cTnT in patients with HF.

Val-HeFT and GISSI-HF studies found that the hs-cTnT levels over time present a decreasing trend in HF [24]. But there was lack of classification of etiology with HF
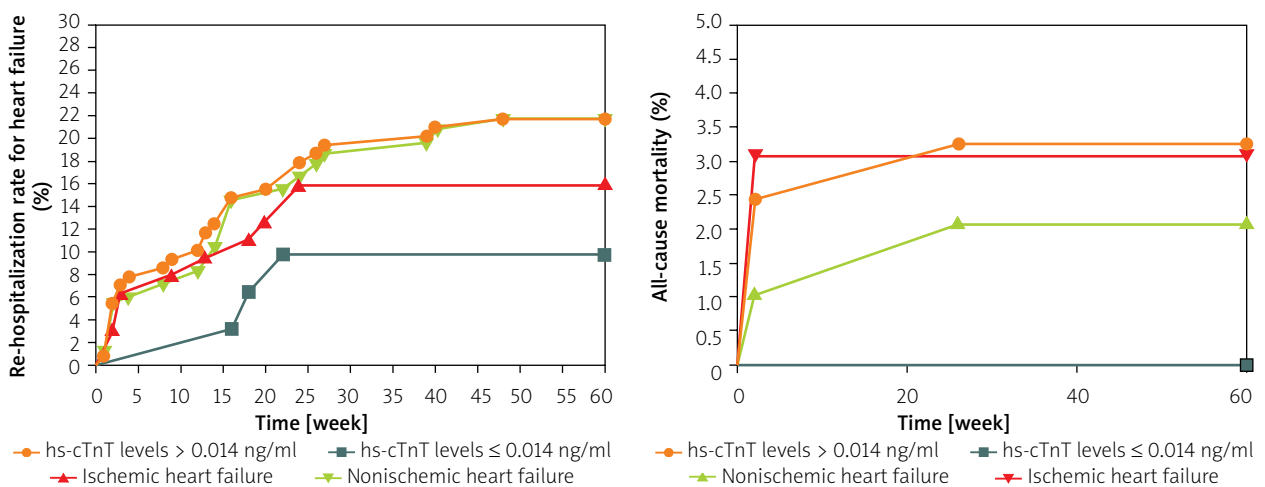

Figure 2. A – Re-hospitalization rate for heart failure in different groups. **B** – All-cause mortality in different groups
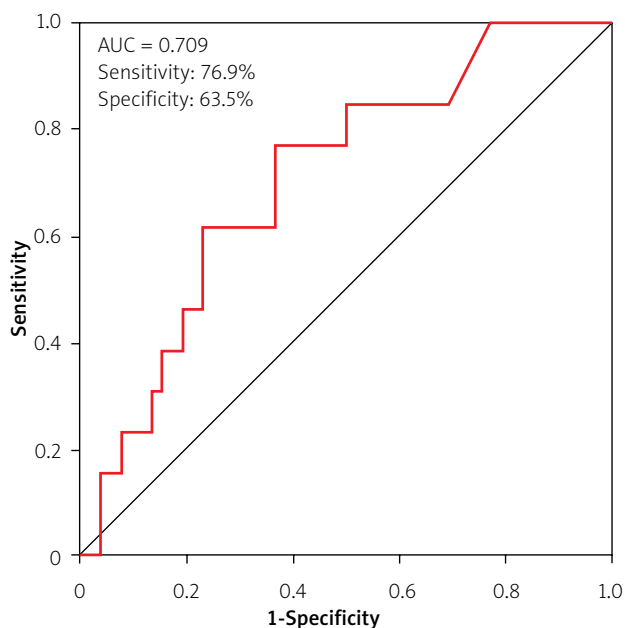
Figure 3. ROC curve for hs-cTnT to predict the composite endpoints in ischemic heart failure

patients in testing hs-cTnT over time. In our study, hs-cTnT levels were tested over time between IHF and NIHF, showing first increasing and then decreasing levels in IHF but a continually increasing trend in NIHF. We took samples from peripheral veins for assays of hs-cTnT when the patients were admitted to the hospital, 2–5 h, 6–24 h, and 24 h–7 days. But in those two studies, hs-cTnT was measured at randomization and after 3 months (GISSI-HF) or 4 months of follow-up (Val-HeFT) [24]. First of all, the different test time may contribute to the difference in hs-cTnT levels over time. There were also some reasons for the discrepancy, including the pathological processes of IHF and NIHF, and the treatment strategies for various causes of HF. Time and other factors could act individually and interact to influence hs-cTnT levels. Therefore, a large amount of research data is needed to analyze further the changing trends of hs-cTnT over time in IHF and NIHF.

de Antonio *et al.* found that the hs-cTnT levels were directly related to the severity of HF [25]. The greater the severity of HF was, the higher were the hs-cTnT levels. In our study, with increasing NYHA class, the hs-cTnT levels displayed an upward trend. With the deterioration of disease, the cardiac systolic and diastolic functions decreased, causing myocardial fibers' fibrosis and activation of the sympathetic nervous system and renin–angiotensin–aldosterone system. Those changes promoted myocardial remodeling and myocardial injury marked by increased hs-cTnT. Because the degree of myocardial injury was different at the different levels of cardiac function, hs-cTnT levels may also vary with the cause and degree of myocardial injury.

Figald *et al.* reported that hs-cTnT was associated with re-hospitalization for HF and mortality in HF, which was a predictive indicator of cardiovascular events [6, 26, 27]. Yan *et al.* reported that adjusted for age, sex, and classical cardiovascular risk factors, hs-cTnI could be an independent factor for the prognosis of HF, and optimal hs-cTnI cutoff values of 0.0026 ng/ml for women and 0.0042 ng/ml for men were derived for selecting individuals at risk [28]. In our study, hs-cTnT was independently related to re-hospitalization rate for HF and all-cause mortality by the Kaplan-Meier method and Cox regression method. And an optimal hs-cTnT cut-off of 0.0275 ng/ml for IHF was derived to predict the composite endpoints. But the ROC curve was not significant for hs-cTnT to predict the composite endpoints in NIHF. Moreover, the effect of hs-cTnT on cardiovascular events between IHF and NIHF was not reported in the previous literature. Definitely, hs-cTnT representing myocardial injury was an indicator of re-hospitalization and death in HF patients. More studies should be focused on the prognostic role of hs-cTnT in NIHF and explore the difference in hs-cTnT between IHF and NIHF to treat early and improve prognosis in HF.

We mainly aimed to determine the prognostic role of hs-cTnT between IHF and NIHF; therefore, the HF patients included were only those in whom HF was caused by ischemic heart disease or non-ischemic heart disease; we eliminated those with mixed heart disease. Due to the strict selection criteria, the amount of data in the study is relatively small and may not fully reflect the value of hs-cTnT. In our study, myocardial ischemia was evaluated by CAG or CCT, which was used for the assessment of macrovascular coronaries but not sufficiently for cardiac microcirculation and functional ischemia. In addition, although sepsis and chronic renal insufficiency were excluded in this study, it is not clear whether general infection and transient renal insufficiency may interfere with the results of this study. The follow-up time was relatively short as it has not yet reached 3–5 years. Therefore, this study cannot fully reflect the long-term prognoses of patients with HF.

Conclusions

Hs-cTnT varied significantly over time, showing an increasing trend in NIHF while first increasing and then decreasing in IHF. Hs-cTnT was independently related to re-hospitalization rate for HF and all-cause mortality in patients with HF, which could play an important role in prognosis of HF.

Acknowledgments

Conflict of interest

The authors declare no conflict of interest.

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