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Significance of High-Sensitivity Cardiac Troponin T in Hypertrophic Cardiomyopathy

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Objectives This study investigated the significance of the serum high-sensitivity cardiac troponin T (hs-cTnT) marker for prediction of adverse events in hypertrophic cardiomyopathy (HCM).

Background Although serum cardiac troponins as sensitive and specific markers of myocardial injury have become well-established diagnostic and prognostic markers in acute coronary syndrome, the usefulness of hs-cTnT for prediction of cardiovascular events in patients with HCM is unclear.

Methods We performed clinical evaluation, including measurements of hs-cTnT in 183 consecutive patients with HCM.

Results Of 183 HCM patients, 99 (54%) showed abnormal hs-cTnT values (>0.014 ng/ml). During a mean follow-up of 4.1 ± 2.0 years, 32 (32%) of the 99 patients in the abnormal hs-cTnT group, but only 6 (7%) of 84 patients with normal hs-cTnT values, experienced cardiovascular events: cardiovascular deaths, unplanned heart failure admissions, sustained ventricular tachycardia, embolic events, and progression to New York Heart Association functional class III or IV status (hazard ratio [HR]: 5.05, $p < 0.001$). Abnormal hs-cTnT value remained an independent predictor of these cardiovascular events after multivariate analysis (HR: 3.23, $p = 0.012$). Furthermore, in the abnormal hs-cTnT group, overall risk increased with an increase in hs-cTnT value (HR: 1.89/hs-cTnT 1 SD increase in the logarithmic scale, 95% confidence interval: 1.13 to 3.15; $p = 0.015$ [SD: 0.59]).

Conclusions In patients with HCM, an abnormal serum concentration of hs-cTnT is an independent predictor of adverse outcome, and a higher degree of abnormality in hs-cTnT value is associated with a greater risk of cardiovascular events. (J Am Coll Cardiol 2013;62:1252–9) © 2013 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with a broad spectrum of clinical presentations (1–3). The natural history of HCM varies from an asymptomatic and benign clinical course to sudden premature death. Several observations in community-based cohorts have shown that not only sudden death, but also heart failure and stroke related to HCM, were important adverse events (4–9). Although several clinical markers are accepted for risk stratification in patients with HCM, including previous cardiac arrest, family history of sudden death, syncope, degree of left ventricular (LV) wall thickness, basal outflow obstruction, and congestive symptoms, risk stratification in HCM is still not sufficient to identify patients at high risk for these morbid events (6,10–14).

Cardiac troponins, including cardiac troponin T and troponin I, as sensitive and specific markers of myocardial injury, are well-established diagnostic and prognostic markers in acute coronary syndrome. These troponins have been reported to predict adverse outcome in patients with heart failure even in the absence of coronary artery stenosis (15–17). However, the usefulness of high-sensitivity cardiac troponin T (hs-cTnT) for prediction of adverse clinical events in patients with HCM is unclear.

Methods

Patients. Patients were diagnosed as having HCM between 1982 and September 2010 at Kochi Medical School Hospital. In this study, we performed clinical evaluation, including measurements of hs-cTnT in 193 consecutive patients with HCM between October 2004 and September 2010. We excluded patients with evidence of coronary artery

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disease (8 patients with a history of percutaneous coronary intervention) and patients with renal failure (8 patients with serum creatinine ≥3 mg/dl). The final study population consisted of 183 patients.

The diagnosis of HCM was based on echocardiographic demonstration of unexplained LV hypertrophy (i.e., maximum LV wall thickness ≥15 mm) in the absence of systemic hypertension or other cardiac diseases (e.g., aortic stenosis or storage disease) that could produce hypertrophy of such magnitude (3). Informed consent was obtained from all patients or their parents in accordance with the guidelines of the Ethics Committee on Medical Research of Kochi Medical School.

Clinical evaluation. Evaluation of patients included medical history, clinical examination, 12-lead electrocardiography, and M-mode, 2-dimensional (2-D), and Doppler echocardiography. Maximum LV wall thickness was defined as the greatest thickness in any single segment. Left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) were measured from M-mode and 2-D images obtained from parasternal long-axis views, and fractional shortening (%FS = [LVEDD − LVESD]/LVEDD × 100) was calculated. LV outflow tract gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation.

For survival analysis, 3 modes of HCM-related death were defined: 1) sudden and unexpected death, in which collapse occurred in the absence of or <1 h from the onset of symptoms in patients who previously experienced a relatively stable or uneventful clinical course; 2) heart failure–related death, which was in the context of progressive cardiac decompensation ≥1 year before death, particularly if complicated by pulmonary edema or evolution to the end-stage phase; and 3) stroke-related death, which occurred as a result of probable or proven embolic stroke. Other morbid events included: 1) hospitalization for heart failure; 2) embolic stroke admission; 3) spontaneous sustained ventricular tachycardia (VT) associated with hemodynamic instability or appropriate implantable cardioverter-defibrillator (ICD) discharge; and 4) progression to New York Heart Association (NYHA) functional class III or IV status that required additional treatment. Data on survival and clinical status of patients were obtained during serial clinic visits or by direct communication with patients and their cardiologists for patients who were followed up at other institutions.

Measurements of hs-cTnT. Peripheral venous blood samples were collected for measurements of biomarkers at the clinical evaluation. Plasma was separated by centrifugation at 3,500*g* for 15 min. Aliquots were stored at −80°. Serum hs-cTnT was measured by Elecsys Troponin T High Sensitive immunoassay (Roche Diagnostics Ltd., Rotkreuz, Switzerland). This hs-cTnT in our study conforms to guideline (universal definition of myocardial infarction) precision requirements: an increased value for cardiac troponin is defined as a measurement exceeding the 99th percentile of a normal reference population, and optimal precision (coefficient of variation) at the 99th percentile decision limit should be defined as ≤10% (18). The normal range of this troponin marker in an apparently healthy adult population is ≤0.014 ng/ml (99th percentile) (19,20). The limit of the blank of the hs-cTnT assay, that is, the smallest concentration of a measurement that can be reliably measured by an analytical procedure, is 0.003 ng/ml (19).

Statistical analysis. All data are expressed as mean ± SD or frequency (percentage). Comparisons of clinical characteristics between normal and abnormal hs-cTnT groups were assessed using Student's *t* test for normally distributed variables. Pearson's chi-square test was used for comparisons between categorical variables, and Fisher's exact test was used when expected frequency was <5. For statistical analysis as a continuous variable of hs-cTnT, logarithmic transformation was applied to serum hs-cTnT values to obtain normal distribution. Differences in means of continuous variable were assessed using Student's *t* test or 1-way analysis of variance. Pearson's correlation coefficient was used to study the relationship between hs-cTnT and echocardiographic data.

All cardiovascular events were the composite of HCM-related death and the previously described morbid events. Composite heart failure events included heart failure–related death, hospitalization for heart failure, and progression to NYHA functional class III or IV status. Arrhythmic events were the composite of sudden death, spontaneous sustained VT associated with hemodynamic instability, and appropriate ICD discharge. Cardiac events were defined as the composite of the previously mentioned heart failure events and arrhythmic events.

To determine the cutoff value of hs-cTnT for all cardiovascular events, a receiver-operating characteristic curve was constructed. Event-free estimates curves were calculated by the Kaplan-Meier method, and the log-rank test was used for comparison. Clinical characteristics were all first tested with univariate Cox proportional hazards analysis, and all variables with a value <0.05 were then taken forward to be considered for inclusion in the multivariate model. Predictors included in the multivariate analysis for all cardiovascular events were hs-cTnT, age, rhythm, NYHA functional class, left atrial diameter, and LVESD. Predictors in the multivariate model for cardiac events were hs-cTnT, age, rhythm, NYHA functional class, syncope, left atrial diameter, and LVESD. The model was constructed with

Abbreviations and Acronyms

CI = confidence interval
FS = fractional shortening
HCM = hypertrophic cardiomyopathy
HR = hazards ratio
hs-cTnT = high-sensitivity cardiac troponin T
ICD = implantable cardioverter-defibrillator
IDI = integrated discrimination improvement
LV = left ventricular
LVEDD = left ventricular end-diastolic diameter
LVESD = left ventricular end-systolic diameter
MRI = magnetic resonance imaging
NYHA = New York Heart Association
2-D = two-dimensional
VT = ventricular tachycardia

a forward selection procedure, with any variable that improved the likelihood ratio test statistic by an amount equivalent to $p < 0.05$ included. A Cox proportional hazards model was performed to estimate the hazard ratio (HR) for an abnormal hs-cTnT value and to estimate the effect on outcomes of the degree of increased hs-cTnT values. The predicted probability of having an event at 1, 2, and 3 years was calculated for each patient. This was done by obtaining the baseline survival from the Cox model for the cohort at each time point and calculating the increased risk associated with increased levels of hs-cTnT values. To test whether the serum hs-cTnT value was an independent predictor of risk, multivariate analysis was performed. Statistical analyses were performed with SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

Baseline characteristics. Clinical characteristics of the patients in the present study are shown in Table 1. Patients were from 13 to 88 years old (mean age: 61 ± 15 years), and 114 (62%) of the patients were males. Of the 183 patients, most patients were completely asymptomatic or mildly symptomatic at the time of troponin measurements; 108 (59%) were NYHA functional class I, 65 (36%) were NYHA class II, and only 5 (10%) were NYHA class III. No patients were treated with alcohol septal ablation or myectomy. Maximum LV wall thickness was 20.1 ± 4 mm, and 3 patients had wall thickness ≥30 mm. Twenty-five (14%) of the patients showed LV outflow tract obstruction (pressure gradient ≥30 mm Hg), and 28 (15%) of the patients had apical HCM. Forty-four (24%) of the patients had documentation of paroxysmal or chronic atrial fibrillation.

Serum hs-cTnT ranged from 0.003 to 0.140 ng/ml. Associations of hs-cTnT with age, maximum LV wall thickness, LV size, %FS, and left atrial diameter in patients with HCM are shown in Table 2. Serum hs-cTnT did not have strong correlations with age, maximum LV wall thickness, and left atrial diameter, but did have significant correlations with these characteristics. Table 3 shows the hs-cTnT values with respect to clinical characteristics. Serum hs-cTnT values were higher in patients with atrial fibrillation than in those with sinus rhythm. Higher hs-cTnT levels were also observed in patients with LV systolic dysfunction than in those without LV systolic dysfunction. Among the 173 HCM patients without LV systolic dysfunction, serum hs-cTnT values were significantly lower in patients with apical HCM than in patients with other subtypes of HCM. Serum hs-cTnT was significantly higher with respect to progressive severity of heart failure symptoms, as judged by NYHA functional class.

We divided the patients into 2 groups by hs-cTnT values: a normal hs-cTnT group (hs-cTnT ≤0.014 ng/ml) and an abnormal hs-cTnT group (>0.014 ng/ml) (Table 1). The percentage of patients with atrial fibrillation in the abnormal hs-cTnT group was higher than that in the normal hs-cTnT group. More patients with abnormal hs-cTnT values experienced significant dyspnea (NYHA functional class III).

Table 1 Serum Hs-cTnT and Baseline Characteristics in 183 HCM Patients

	Total (n = 183)	Normal hs-cTnT (n = 84) (≤0.014 ng/ml)	Abnormal hs-cTnT (n = 99) (>0.014 ng/ml)	p Value
Age, yrs	61.2 ± 15.3	58.1 ± 14.4	63.9 ± 15.5	0.010
Male	114 (62%)	47 (56%)	67 (68%)	0.103
Serum hs-cTnT*, ng/ml	0.015 ± 0.008	0.007 ± 0.004	0.025 ± 0.018	<0.001
Atrial fibrillation	44 (24%)	8 (10%)	36 (36%)	<0.001
NYHA functional class				0.022
I or II	173 (95%)	83 (99%)	90 (91%)	
III	10 (5%)	1 (1%)	9 (9%)	
Risk factors for SCD				
Wall thickness ≥30 mm	3 (2%)	0 (0%)	3 (3%)	0.251
Rest LVOTO ≥30 mm Hg	25 (14%)	11 (13%)	14 (14%)	0.837
Family history of SCD	31 (17%)	12 (14%)	19 (19%)	0.378
Syncope	23 (13%)	6 (7%)	17 (17%)	0.041
Sustained VT/VF	3 (2%)	0 (0%)	3 (3%)	0.251
Echocardiographic data				
Maximum LV wall thickness, mm	20.1 ± 4.0	18.9 ± 2.9	21.1 ± 4.6	<0.001
IVS, mm	15.6 ± 4.4	14.1 ± 3.6	16.8 ± 4.6	<0.001
PW, mm	10.9 ± 1.9	10.4 ± 1.5	11.4 ± 2.1	<0.001
LV end-diastolic diameter, mm	45.5 ± 6.2	45.5 ± 5.4	45.5 ± 6.9	0.999
LV end-systolic diameter, mm	26.8 ± 7.0	26.2 ± 5.5	27.2 ± 8.0	0.334
Fractional shortening, %	42.0 ± 9.1	43.0 ± 7.6	41.0 ± 10.2	0.126
Left atrial diameter, mm	44.3 ± 7.3	42.2 ± 6.1	46.1 ± 7.8	<0.001

Values are mean ± SD or n (%). *Data are shown as median ± quartile.

HCM = hypertrophic cardiomyopathy; hs-cTnT = high-sensitivity cardiac troponin T; IVS = interventricular wall thickness; LV = left ventricular; LVOTO = left ventricular outflow tract obstruction; NYHA = New York Heart Association functional class; PW = posterior wall thickness; SCD = sudden cardiac death; VT/VF = ventricular tachycardia/ventricular fibrillation.

Table 2 Correlations Between Hs-cTnT and Echocardiographic Data in 183 HCM Patients

	r Value	p Value
Age	0.252	0.001
Maximum LV wall thickness	0.341	<0.001
LV end-diastolic diameter	0.061	0.409
LV end-systolic diameter	0.131	0.078
Fractional shortening	0.138	0.063
Left atrial diameter	0.414	<0.001

Abbreviations as in Table 1.

Results of echocardiography showed that interventricular septal wall, posterior wall, and maximum LV wall thicknesses were greater, and left atrial diameter was larger in patients with abnormal hs-cTnT levels than in patients with normal hs-cTnT levels. There were more syncope patients in the abnormal hs-cTnT group, and all of the patients with wall thickness ≥30 mm and all of the patients with a history of sustained VT belonged to the abnormal hs-cTnT group.

Measurements of hs-cTnT and adverse cardiovascular events. The mean follow-up of the patient cohort was 4.1 ± 2.0 years. There were 9 cardiovascular deaths, including sudden death in 4 patients, heart failure death in 3 patients, and embolic stroke death in 2 patients, all of which occurred in the abnormal hs-cTnT group (Table 4, Fig. 1A). A receiver-operating characteristic curve of hs-cTnT level to predict all cardiovascular events showed that the best cutoff value of this marker was 0.014 ng/ml, and the area under the curve was 0.77 (Fig. 2); this cutoff level was the same as the normal range in a healthy adult population. Overall, 38 (21%) of the 183 patients had cardiovascular events (the composite of HCM-related death and the morbid events including embolic stroke): 32 (32%) of the 99 patients in the abnormal hs-cTnT group, but only 6 (7%) of the 84 patients in the normal hs-cTnT group (HR: 5.05, 95% confidence interval [CI]: 2.11 to 12.09, $p < 0.001$) (Table 4, Fig. 1B). Abnormal concentration of hs-cTnT predicted all cardiovascular events with a sensitivity of 84%, specificity of 54%, positive predictive value of 32%, negative predictive value of 93%, and accuracy of 60%. In the normal hs-cTnT group, no patient with levels <0.006 ng/ml experienced any cardiovascular events. Similarly, 29 (16%) of the 183 patients had cardiac events (cardiovascular events excluding embolic stroke death or admission): 27 (27%) of the 99 patients in the abnormal hs-cTnT group, but only 2 (2%) of the 84 patients in the normal hs-cTnT group (HR: 12.56, 95% CI: 2.99 to 52.82, $p < 0.001$) (Table 4, Fig. 1C) (sensitivity of 93%, specificity of 53%, positive predictive value of 27%, negative predictive value of 98%, and accuracy of 60%). In the normal hs-cTnT group, no patient with levels <0.011 ng/ml experienced cardiac events. In 2 patients with cardiac events, 1 patient with hs-cTnT 0.011 ng/ml underwent hospitalization for heart failure, and another patient with hs-cTnT 0.014 ng/ml had hospitalization for heart failure before ICD discharge. Furthermore, patients with abnormal hs-cTnT values had significantly more frequent heart failure events. In contrast, frequency of arrhythmic events in the abnormal hs-cTnT group was not significantly higher than that in the normal hs-cTnT group, as shown in Table 4. Multivariate analysis showed that abnormal hs-cTnT value was an independent predictor of all cardiovascular events (HR: 3.23, 95% CI: 1.29 to 8.10,

Table 3 Serum Hs-cTnT Values in 183 HCM Patients With Respect to Clinical Characteristics

	Serum hs-cTnT (ng/ml)	p Value
Sex, (n = 183)		
Male (n = 114)	0.016 ± 0.009	
		0.140
Female (n = 69)	0.014 ± 0.007	
Atrial fibrillation (n = 183)		
Present (n = 44)	0.023 ± 0.017	
		<0.001
Absent (n = 139)	0.013 ± 0.006	
LV systolic dysfunction (n = 183)		
Present (n = 10)	0.030 ± 0.021	
		0.012
Absent (n = 173)	0.015 ± 0.007	
Subtypes in HCM without LV systolic dysfunction, (n = 173)		
HCM with obstruction,* (n = 33)	0.018 ± 0.010	
HCM without obstruction (n = 112)	0.016 ± 0.009	0.001
Apical HCM (n = 28)	0.008 ± 0.005	
NYHA functional class (n = 183)		
I (n = 108)	0.015 ± 0.007	
II (n = 65)	0.016 ± 0.010	<0.001
III (n = 10)	0.055 ± 0.036	

Values are median ± quartile. *HCM with obstruction includes LV outflow obstruction and midventricular obstruction.
Abbreviations as in Table 1.

Table 4 Cardiovascular Events in 183 Patients With Normal hs-cTnT Values and With Abnormal Hs-cTnT Values (Univariate Analysis)

Total (n = 183)	Normal hs-cTnT (n = 84) (≤0.014 ng/ml)	Abnormal hs-cTnT (n = 99) (>0.014 ng/ml)	Hazard Ratio	95% CI	p Value
All cardiovascular events	6	32	5.05	2.11–12.09	<0.001
Cardiovascular deaths	0	9	NA	—	—
Cardiac events	2*	27†	12.56	2.99–52.82	<0.001
Heart failure events	2	24	11.16	2.64–47.21	0.001
Arrhythmic events	1	7	5.81	0.72–47.30	0.100

*One patient had both a heart failure event and an arrhythmic event. †Four patients had both heart failure events and arrhythmic events.
CI = confidence interval; other abbreviation as in Table 1.

p = 0.012). Other variables that were found to be independently associated with all cardiovascular events were NYHA functional class and left atrial diameter. For reclassification analysis, integrated discrimination improvement (IDI) was used to access the improvement between models with and without hs-cTnT, and IDI was 0.033 (p = 0.056). Similarly, abnormal hs-cTnT value and NYHA functional class also remained independent predictors of cardiac events (HR: 10.84, 95% CI: 2.53 to 46.39, p = 0.001).

In the abnormal hs-cTnT group, the overall risk of cardiovascular events increased with an increase in the hs-cTnT value (Fig. 3). After logarithmic transformation of serum hs-cTnT values as a continuous variable, HR was 1.89/hs-cTnT 1 SD increase in the logarithmic scale (95% CI: 1.13 to 3.15, p = 0.015 [SD: 0.59]). When groups were allocated according to the degree of abnormality in hs-cTnT value (lower abnormal hs-cTnT: 0.015 to 0.018 ng/ml, n = 32; middle abnormal hs-cTnT: 0.019 to 0.030 ng/ml, n = 32; and upper abnormal hs-cTnT: 0.031 to 0.140 ng/ml, n = 35), clinical course was significantly worse in patients with higher hs-cTnT values (Figs. 4A and 4B). Table 5 shows the significant predictors of cardiovascular or cardiac events after multivariate analysis: frequency of morbid events seemed to increase with higher hs-cTnT values.

As a continuous variable of hs-cTnT, this biomarker was also significantly associated with all cardiovascular events in both univariate and multivariate Cox proportional hazards regression analyses, and the odds ratios were 2.66 (95% CI: 1.86 to 3.80) and 1.59 (95% CI: 1.08 to 2.33), respectively. Similarly, the continuous variable of this troponin marker was significantly associated with cardiac events, and the odds ratios in univariate and multivariate analyses were 2.99 (95% CI: 1.99 to 4.49) and 1.97 (95% CI: 1.29 to 3.03), respectively.

Discussion

There is little information on the utility of troponins as prognostic markers in HCM. The main findings of this study are that an abnormal hs-cTnT value itself and the degree of abnormality in hs-cTnT value are associated with a greater risk of adverse cardiovascular events. This biomarker seems to be useful as an additive monitoring parameter in patients with HCM.

HCM is characterized by a heterogeneous clinical course ranging from asymptomatic status with normal life expectancy to severe heart failure, stroke caused by atrial fibrillation, and sudden cardiac death (1–3). Although sudden death is the most catastrophic event, a significant proportion of patients with HCM in a regional cohort largely free of referral bias had heart failure and embolic complications (4–9). In this study, during a follow-up of 4.1 ± 2 years, HCM-related deaths occurred in 9 patients (including sudden death in 4 patients). The annual mortality rate in the present study was 1.2% (0.5% for sudden death), which is in accordance with previously reported data obtained from community-based cohorts for HCM (4–8). Several risk factors for sudden cardiac death, including degree of LV hypertrophy, family history of sudden death, and unexplained syncope, have been established by tertiary institutes (1–3,10,11). In addition, advanced age and the presence of atrial fibrillation, basal outflow obstruction, and congestive symptoms were found to be clinically important predictors of HCM mortality or stroke (5,8,12–14). However, risk stratification in HCM is still limited because the positive predictive values of these clinical markers for adverse events were not high, and this difficulty in prediction is thought to be due to markedly diverse heterogeneity of clinical phenotypes in HCM.

In the present study, we divided the patients into 2 groups by hs-cTnT values. The cutoff value was defined as 0.014 ng/ml because the normal range is ≤0.014 ng/ml (99th percentile) in the system for measuring hs-cTnT, and this cutoff value of 0.014 ng/ml was also determined by a receiver-operating characteristic curve of hs-cTnT to predict all cardiovascular events. Assessment of the relationships of serum hs-cTnT levels with baseline clinical characteristics showed that abnormal hs-cTnT value was associated with findings supporting clinical deterioration in HCM, including presence of atrial fibrillation, severity of heart failure symptoms as judged by NYHA functional class, prevalence of syncope, greater wall thickness, and larger left atrial diameter. Moreno et al. (21) recently reported in their cross-sectional HCM study that clinical variables correlated with hs-cTnT and showed that increased hs-cTnT serum levels were associated with different conditions related to the severity of disease; hs-cTnT was increased in patients with severe dyspnea, and hs-cTnT was positively correlated with maximum LV wall thickness.

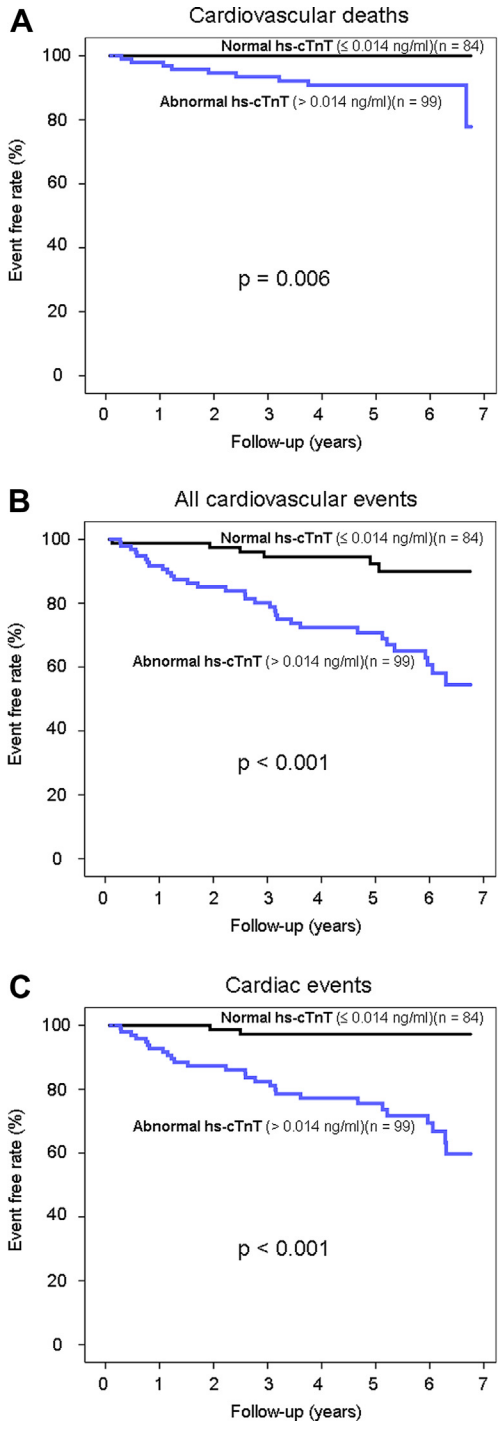

Figure 1 **Freedom from CV deaths, All CV Events, and Cardiac Events**

(A) Kaplan-Meier unadjusted estimates of freedom from cardiovascular (CV) deaths in 183 hypertrophic cardiomyopathy HCM patients according to normal (≤0.014 ng/ml) and abnormal (>0.014 ng/ml) values of hs-cTnT. **(B)** Kaplan-Meier unadjusted estimates of freedom from all CV events in 183 HCM patients according to the normal (≤0.014 ng/ml) and abnormal (>0.014 ng/ml) values of hs-cTnT. **(C)** Kaplan-Meier unadjusted estimates of freedom from cardiac events in 183 HCM patients according to normal (≤0.014 ng/ml) and abnormal (>0.014 ng/ml) values of hs-cTnT. Hs-cTnT = high-sensitivity cardiac troponin T.

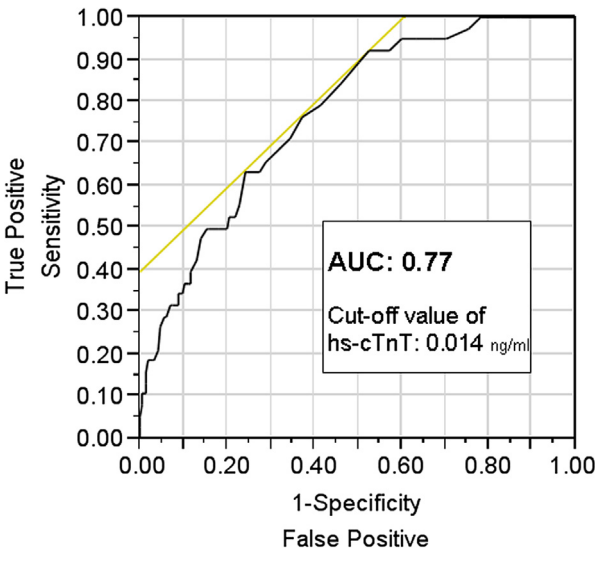

Figure 2 **A Receiver-Operating Characteristic Curve of hs-cTnT to Predict All Cardiovascular Events**

AUC = 0.77. Cutoff value of hs-cTnT = 0.014 ng/ml. AUC = area under the curve; other abbreviations as in Figure 1.

For the prediction of cardiovascular outcome, patients with abnormal hs-cTnT values had significantly more frequent adverse events, and abnormal hs-cTnT and NYHA functional class were independent predictors of both cardiovascular and cardiac events. Furthermore, the risk of adverse cardiovascular events seemed to be greater with an increase in the degree of abnormality in hs-cTnT values. These results were predominantly driven by the development of heart failure. Kawahara et al. (17) reported that a high concentration of hs-cTnT was an independent prognostic predictor in heart failure patients with nonischemic dilated cardiomyopathy. Our study findings showed that the serum hs-cTnT marker was also useful to manage patients with HCM. In contrast, for arrhythmic events, abnormal hs-cTnT did not reach statistical significance probably because of the small number of these events in this study. All of the patients with a history of sustained VT had abnormal values of hs-cTnT, and 88% (7 of 8 patients) of the arrhythmic events that occurred during follow-up were in the abnormal hs-cTnT group.

Although the mechanisms of myocyte injury and release of hs-cTnT in HCM remain unresolved, we speculate that they may be caused by relative myocardial ischemia resulting from an imbalance between inappropriate hypertrophy of the myocardium and insufficient coronary arterial supply. Petersen et al. (22) reported that patients with HCM showed a reduced myocardial perfusion reserve, as assessed by magnetic resonance imaging (MRI), that was in proportion to the magnitude of hypertrophy. Furthermore, they found that the decreased prevalence of myocardial fibrosis as assessed by delayed contrast-enhanced MRI was accompanied by an increased hyperemic myocardial blood

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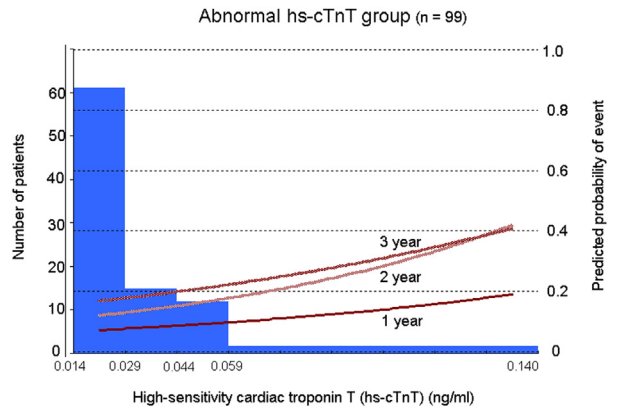

Figure 3 **Probability of All CV Events on the Basis of Annual Risk and Degree of Abnormality in hs-cTnT Value in 99 HCM Patients With Abnormal hs-cTnT Values**

Predicted probability of all CV events at 1, 2, and 3 years on the basis of the degree of abnormality in hs-cTnT value, plotted against the X-axis on the **right**. The **bar charts** represent the number of the patients with this concentration of hs-cTnT, plotted on the X-axis on the **left**. Abbreviations as in Figure 1.

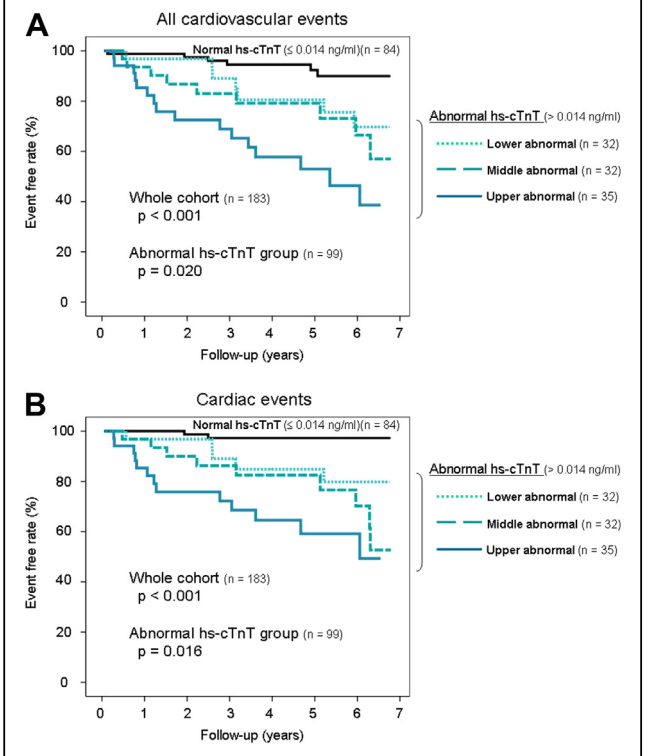

Figure 4 **All CV and Cardiac Event-Free Rates Allocated According to the Degree of Abnormality in hs-cTnT Value**

(A) CV event-free rate: normal hs-cTnT value: ≤0.014 ng/ml, lower abnormal hs-cTnT value: 0.015 to 0.018 ng/ml; middle abnormal hs-cTnT value: 0.019 to 0.030 ng/ml; upper abnormal hs-cTnT value: 0.031 to 0.140 ng/ml. **(B)** Cardiac event-free rate: normal hs-cTnT value: ≤0.014 ng/ml; lower abnormal hs-cTnT value: 0.015 to 0.018 ng/ml; middle abnormal hs-cTnT value: 0.019 to 0.030 ng/ml; upper abnormal hs-cTnT value: 0.031 to 0.140 ng/ml. Abbreviation as in Figure 1.

flow. This observation suggests a pathophysiological link between repetitive hypoperfusion during stress and development of myocardial fibrosis. Recently, the presence of late gadolinium enhancement in MRI has been reported to be associated with arrhythmic events and heart failure symptoms in HCM patients, and the presence of this fibrosis indicated by MRI seems to be a novel marker for identifying those at risk of progressive disease (23–28). Although we did not evaluate the presence and extent of fibrosis using late gadolinium-enhanced MRI, Moreno et al. reported that hs-cTnT levels were raised in HCM patients with gadolinium enhancement in cardiac MRI (21). From these findings, the serum hs-cTnT marker may reflect microvessel ischemia and subsequent fibrosis in HCM.

Study limitations. First, this was a single-center study, and it was not prospective. Second, our study cohort differed from tertiary center cohorts in which referral patterns were skewed toward patients perceived to be at high risk. The present study was a community-based cohort and included less high-risk patients than those in major referral centers. That is, prevalence of HCM with obstruction was low, and only a few patients experienced arrhythmic events during follow-up in our study. Therefore, it remains unclear whether the hs-cTnT marker in HCM patients at high risk, particularly for sudden death, was useful. Third, the size of our population was small, and the study was not designed with a priori calculations with respect to sample size or statistical power. As such, the findings need to be confirmed in larger and prospectively designed studies. Fourth, this biomarker was originally introduced clinically for earlier diagnosis of acute myocardial infarction, and we did not perform angiograms in all patients. However, the 183 enrolled patients in this study did not show any evidence of

Table 5 **Multivariate Analysis of All Cardiovascular Events or Cardiac Events**

	Hazard Ratio	95% CI	p Value
All cardiovascular events			
Lower abnormal hs-cTnT	2.94	0.98–8.84	0.055
Middle abnormal hs-cTnT	3.06	1.02–9.13	0.046
Upper abnormal hs-cTnT	3.67	1.31–10.25	0.013
NYHA class II	4.34	1.96–9.59	<0.001
NYHA class III	22.78	7.50–69.18	<0.001
Left atrial diameter	1.08	1.03–1.13	0.001
c Statistics	0.84	0.78–0.91	
Cardiac events			
Lower abnormal hs-cTnT	7.47	1.44–38.65	0.017
Middle abnormal hs-cTnT	13.74	2.92–64.59	<0.001
Upper abnormal hs-cTnT	12.14	2.56–57.49	0.001
NYHA class II	5.30	2.03–13.86	<0.001
NYHA class III	57.18	16.48–198.41	<0.001
c Statistics	0.86	0.79–0.93	

Abbreviations as in Tables 1 and 4.

ischemic heart disease, and coronary artery obstruction was denied by angiograms in 55 patients or thallium-201 myocardial scintigrams in 17 patients. All 38 patients who had extremely high hs-cTnT values (>0.10 ng/ml) and who presented with LV systolic dysfunction or had cardiac events (the composite of the heart failure events and arrhythmic events) were examined by either angiography or thallium-201 myocardial scintigraphy, and no one had coronary artery obstruction. Therefore, we believe that coronary artery disease was not related to their clinical deteriorations in the present study. Fifth, the reasonable cutoff value might depend on various situations, such as different cohorts (tertiary center cohorts vs. community-based cohorts) or different outcomes (arrhythmic events vs. heart failure events). Furthermore, it might be better to use sex-specific cutoff values, but we were unable to use different cutoff levels for distinction between sexes because of the small study cohort. Finally, we did not have serial measurements of hs-cTnT in this study, and we had no data on whether there were any interventions to reduce the concentrations of this biomarker, which might have led to improved outcome in patients with HCM.

Conclusions

In patients with HCM, an abnormal serum concentration of hs-cTnT is an independent predictor of adverse outcome, and a higher degree of abnormality in hs-cTnT values is associated with a greater risk of cardiovascular events.

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Key Words: biomarker ■ high-sensitivity cardiac troponin T ■ hypertrophic cardiomyopathy ■ prognosis.