Age-Specific 99th Percentile Cutoff of High-Sensitivity Cardiac Troponin T for Early Prediction of Non-ST-Segment Elevation Myocardial Infarction (NSTEMI) in Middle-Aged Patients

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Background: High-sensitivity cardiac troponin T (hs-cTnT) assay is used in the diagnosis and risk assessment of patients with symptoms of myocardial infarction. This study was undertaken to establish an age-specific 99th percentile cutoff value for hs-cTnT in Chinese population, and to evaluate its potential for early prediction of non-ST-segment elevation myocardial infarction (NSTEMI) in middle-aged patients. **Methods:** Troponin T levels in blood obtained from healthy Chinese adults were assayed using hs-cTnT. The distribution was plotted and 99th percentiles were determined by nonparametric statistics. Prediction performance at the conventional cutoff (14 ng/L) recommended by the Roche company was compared with the age-specific cutoff for NSTEMI in 100 middle-aged patients (40–60 years of age) with acute chest pain. **Results:** The 99th percentile for hs-

cTnT was 14 ng/L for patients ≥ 60 years of age and 11 ng/L for those < 60 . Fifty of the 100 patients were finally diagnosed with NSTEMI. The age-specific 99th percentile cutoff value of 11 ng/L identified a higher number of patients with NSTEMI than the conventional 14 ng/L cutoff (46 vs. 40 patients), although the difference was not statistically significant ($P = 0.084$). In addition, the sensitivity of hs-cTnT increased from 80 to 92% and the negative predictive values increased from 82.4 to 91.8%. **Conclusion:** Using 11 ng/L as a decision-making cutoff point for hs-cTnT facilitated earlier prediction of NSTEMI in middle-aged patients than the conventional 14 ng/L cutoff. Further studies are needed to confirm this finding in larger group of patients. J. Clin. Lab. Anal. 28:10–15, 2014. © 2013 Wiley Periodicals, Inc.

Key words: NSTEMI; hs-cTnT; cutoff value; early prediction

INTRODUCTION

Acute myocardial infarction (AMI), including non-ST elevation (NSTEMI) and ST elevation (STEMI) myocardial infarction, is currently the leading cause of death and morbidity in developed countries (1). Electrocardiography (ECG) and measurement of cardiac troponins are the mainstay of diagnosis, and complement clinical assessments in current AMI guidelines (2, 3). However, the absence of ST-segment elevation in NSTEMI means that its diagnosis is particularly dependent on the detection of positive cardiac markers (4). The high-sensitivity cardiac troponin T (hs-cTnT) assay, which has recently become available for use in clinical practice (5), allows early

diagnosis of NSTEMI in patients presented with acute coronary syndrome (6).

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In 2000, the American College of Cardiology and European Society of Cardiology (ACC/ESC) jointly recommended use of the 99th percentile of troponin T values from a reference control group and a coefficient of variation (CV) <10%, as cutoff limits for the diagnosis of MI (7,8). Most studies have subsequently used 14 ng/L as the 99th percentile cutoff value for hs-cTnT, and achieved a CV $\leq$ 10% at 13.5 ng/L (6,9). However, the level of the hs-cTnT in patients >60 years of age is reported to be higher than that in the middle-aged population <60 years of age (10), indicating the need for age-specific diagnostic cutoff points. In this study, we determined the 99th percentile for hs-cTnT in middle-aged and elderly cohorts within a Chinese reference population and evaluated the predictive performance of the age-specific cutoff for NSTEMI in middle-aged patients, presented with acute chest pain.

MATERIAL AND METHODS

Study Population

A total of 679 healthy subjects (mean age: 51.4 ± 15.7 years) presented at the Department of Physical Examination, Shanghai East Hospital, China between January 1 and August 31, 2011 were recruited in the study and formed the reference group. Subjects with diabetes mellitus, hypertension, known cardiac disease, known or treated hyperlipidemia, and those taking cardio-active medications such as beta blockers, calcium channel blockers, and ACE inhibitors were excluded from this population.

One hundred middle-aged subjects (age range: 40–60 years) presented with acute chest pain of less than 6-h duration at the Emergency Department of the Shanghai East Hospital between May and December 2011 formed the patient group. Patients requiring immediate or early percutaneous coronary intervention before a final diagnosis of NSTEMI could be made, were excluded from the study, as this procedure can induce postinterventional infarction or aggravate ongoing myocardial necrosis. Patients with significant kidney dysfunction (estimated glomerular filtration rate $<60 \text{ mL/min/1.73 m}^2$) were also excluded on entry, and patients diagnosed with STEMI were excluded at the time of diagnosis.

The study protocol was approved by the Research Ethics Committee of Shanghai East Hospital. Healthy subjects were recruited according to the National Committee for Clinical Laboratory Standards (11).

Clinical Assessments

All patients underwent detailed clinical assessments, including collection of previous medical history, 18-lead and bedside ECG monitoring, chest X-ray, and measurement

of cardiac biomarkers (hs-cTnT, creatine kinase (CK) MB, myoglobin).

Patients were assessed for coexisting diseases, hypertension was defined as active treatment with antihypertensive agents or as systolic blood pressure 140 mmHg and/or diastolic blood pressure 90 mmHg. Hypercholesterolemia was defined by the presence of direct or calculated low-density lipoprotein cholesterol $\geq 160 \text{ mg/dL}$ in a fasting or nonfasting sample, total cholesterol $\geq 200 \text{ mg/dL}$, or use of statin medication. Diabetic subjects were defined as those receiving treatment with insulin or hypoglycemic agents. The diagnosis of NSTEMI was adjudicated by two independent cardiologists according to the ACC/American Heart Association guidelines (12).

Hs-cTnT Assay

Hs-cTnT concentrations were measured at the time of emergency department presentation in 100 patients with acute chest pain of less than 6-h duration. Follow-up measurements were made 6 and 12 h after the onset of chest pain.

Blood samples were centrifuged immediately after collection and the serum was stored at -80°C until analysis. Plasma concentrations of hs-cTnT in healthy subjects and patients were analyzed using Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany) according to the instructions of the manufacturer.

Statistical Analysis

Statistical analysis was performed using the SPSS version 13.0 software. The results were expressed as means and standard deviations ($\pm$ SD), medians (with interquartile range), or as numbers and percentages, as appropriate. The 99th percentile reference limits were determined using nonparametric analysis and comparison of hs-TnT concentration between groups was performed using Mann-Whitney test. Differences in categorical variables were analyzed using Chi-square or Fisher's exact tests. Two-tailed values of $P < 0.05$ were considered statistically significant.

RESULTS

Distribution of Hs-cTnT Values in the Healthy Chinese Population

Concentrations of hs-cTnT were measured in 679 healthy Chinese subjects (374 men and 305 women) between 18 and 89 years of age. With all results from the reference samples included, the hs-cTnT concentration ranged from 3 to 18 ng/L (median, 3; interquartile range, 3–4 ng/L). Majority of subjects (72.0%) had values no higher than 3 ng/L (Fig. 1). The 99th percentile cutoff

Fig. 1. The hs-cTnT concentration ranged from 3 to 18 ng/L (median, 3; interquartile range, 3–4 ng/L).

value for hs-cTnT obtained using all reference data was 12.2 ng/L.

The 99th Percentiles for Hs-cTnT by Age in the Healthy Chinese Population

The reference population was divided into cohorts <60 and ≥60 years of age. As shown in Figure 2, the 99th percentile for hs-cTnT in cohort ≥60 was 14 ng/L, which was comparable with the value recommended in the Cobase™ cTnT fourth-generation assay (Roche Diagnostics). For the cohort <60 years of age, the 99th percentile was 11 ng/L, which was significantly lower than conventional cutoff (14 ng/L). Statistically significantly higher hs-cTnT values were seen in men (median: 3 and 4) than in women (median: 3 and 3) in both cohorts <60 years of age (Fig. 2A) and ≥60 years of age (Fig. 2B).

Patient Characteristics

Of the 100 patients recruited in the study, 50 patients were finally diagnosed as NSTEMI according to current ESC/ACC guidelines (12). The other 50 patients were excluded from NSTEMI and finally diagnosed with myocar-

dial bridge syndrome, aortic dissection, angina pectoris, or other conditions. Baseline characteristics of the study population are listed in Table 1. Patients with NSTEMI had the same time delays from onset of symptoms to hospital admission ($P = 0.98$) but significantly higher baseline hs-cTnT concentrations ($P < 0.001$) than patients who did not have NSTEMI.

The Predictive Performance of Age-Specific Hs-cTnT

Figure 3 shows changes in hs-cTnT concentrations from admission to the 6-h followup. Among the 50 patients with evolving NSTEMI, 40 had a baseline hs-cTnT concentration ≥14 ng/L, six had concentrations between 11 and 14 ng/L, and only four had hs-cTnT concentrations <11 ng/L (Fig. 3). Among the 50 patients excluded from NSTEMI, 45 had baseline hs-cTnT concentrations <11 ng/L. Only three had hs-cTnT concentrations ≥14 ng/L and two had concentrations between 11 and 14 ng/L on admission. These five patients who had hs-cTnT concentrations >1 ng/L included three patients with aortic dissection, one with arrhythmia, and one with angina pectoris.

Fig. 2. (A) Data from cohort <60 years of age presented by gender. P for comparison between men and women. (B) Data from cohort ≥ 60 years of age presented by gender. P for comparison between men and women.

Concentrations of hs-cTnT significantly increased (ranged from 303 to 4,770 ng/L) at the 6-h followup in six of the eight patients (two excluded from NSTEMI and six with NSTEMI) with a baseline hs-cTnT between 11 and 14 ng/L (data not shown). These patients were finally diagnosed with NSTEMI. The other two patients achieved hs-cTnT concentrations of 19 and 181 ng/L and were diagnosed with aortic dissection and arrhythmia, respectively (Fig. 3). Using the age-specific 99th percentile cutoff value of 11 ng/L at the time of emergency department presentation identified a higher number of patients with NSTEMI (46 patients) than the conventional 99th

TABLE 1. Clinical Characteristics

Characteristic	NSTEMI		P -value
	Yes ($n = 50$)	No ($n = 50$)	
Male, n	40	24	0.02
Mean age ($\pm$ SD), (years)	54.4 ± 4.4	51.7 ± 7.4	0.03
Hypertension, n (%)	22 (44%)	24 (48%)	0.84
Diabetes, n (%)	6 (12%)	7 (14%)	1.00
Hypercholesterolemia, n (%)	7 (14%)	5 (10%)	0.76
Current smoking, N (%)	26 (52%)	24 (48%)	0.84
Median (IQ range) time from onset of symptoms (h)	5 (3; 6)	6 (3; 6)	0.98
Median (IQ range) baseline hs-cTnT concentration (ng/L)	80 (18; 379)	3 (3; 5)	<0.001
Medical history			
Myocardial infarction, n (%)	5 (10%)	3 (6%)	0.71
Heart failure, n (%)	3 (6%)	2 (4%)	1.00
PCI/CABG, n (%)	4 (8%)	3 (6%)	1.00
Ischemic stroke, n (%)	2 (4%)	2 (4%)	1.00

IQ, interquartile range; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

percentile cutoff (40 patients), although the difference was not statistically significant ($P = 0.084$).

The sensitivity of hs-cTnT increased from 80 to 92% and the negative predictive values increased from 82.4 to 91.8% based on the 11 ng/L decision cutoff as the reference point. The positive predictive value was 90.2% with the 11 ng/L cutoff and 93% with the 14 ng/L cutoff. Corresponding values for the negative predictive value were 91.8 and 82.4%, respectively.

DISCUSSION

Previous studies indicate that slight increases in hs-cTnT are observed in up to 22% of the healthy population 70 years of age or older (13, 14). Koerbin et al. studied 104 healthy subjects and found the 99th percentile of hs-cTnT was 10.5 ng/L in men and 5.6 ng/L for women <60 years (9). The 99th percentiles in men and women >60 years of age were 13.1 and 11.7 ng/L, respectively (7).

In the present study, we determined the 99th percentile for hs-cTnT for different age cohorts in a Chinese population. We observed a significant difference in the 99th percentile cutoff value between subjects <60 years of age (11 ng/L) and those >60 years of age (14 ng/L). We then compared the prediction performance of the age-specific (11 ng/L) and conventional hs-cTnT cutoff values (14 ng/L) for NSTEMI in the middle-aged patients. We showed that six out of eight patients with a baseline hs-cTnT concentration between 11 and 14 ng/L were diagnosed with NSTEMI on the basis of results obtained 6 h after admission, suggesting that close attention should

Fig. 3. All patients included were divided according to their hs-cTnT concentration (<11 ng/L, ≥11 ng/L and ≤14 ng/L or >14 ng/L) at baseline and 6-h followup. AT, arrhythmia; AP, angina pectoris; AD, aortic dissection. Others include patients with chest pain finally diagnosed with symptoms due to myocardial bridge, coronary heart disease, cervical spondylosis, autonomic nerve disorder, gallbladder, or cardiac syndrome.

be paid to this subpopulation. However, compared with the conventional 99th percentile cutoff (94% specificity), the age-specific cutoff resulted in a relatively low specificity of 90%. Previous studies have shown that subjects with vascular and respiratory disorders as well as those with diseases related to infections also have elevated cardiac troponin (cTn) concentrations (15–20). Concentrations of cTn at presentation have shown to increase in up to 18% of patients with acute aortic dissection and the resulting misdiagnosis is reportedly associated with a three- to fourfold increased risk of delay in hospital diagnosis (17). In our study, hs-cTnT concentrations were above 11 ng/L in all of the three patients with aortic dissection and in two of them, the concentrations were

above 14 ng/L. Therefore, the use of hs-cTnT for diagnosing NSTEMI should be undertaken with caution in patients with other suspected cardiac diseases, especially aortic dissection. Another limitation to our study was the significant difference between the 99th percentile in men and women <60 years of age. The relatively small sample size in the present study only enabled meaningful analysis of a single variable to be estimated. Further studies with larger populations will be required to assess the dual influence of age and gender on 99th percentile values.

In conclusion, we established 11 ng/L as the 99th cutoff value for hs-cTnT in Chinese middle-aged population. The use of the age-specific 99th percentile cutoff value at the time of emergency department presentation identified a higher number of patients with NSTEMI than the conventional 99th percentile cutoff. Based on these preliminary findings, 11 ng/L should be further investigated as a decision cutoff point for hs-cTnT in middle-aged patients with NSTEMI.

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CONFLICT OF INTEREST

There is no conflict of interest.

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