Clinical application of high-sensitivity cardiac troponin T test in acute myocardial infarction diagnosis

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ABSTRACT. The aim of this study was to investigate the clinical application of a high-sensitivity cardiac troponin T (hs-cTnT) test in the diagnosis of acute myocardial infarction (AMI). Serum levels of hs-cTnT and cardiac troponin I (cTnI) were detected in 240 AMI patients and 200 healthy donors and used to plot receiver operating characteristic (ROC) curves. A clinically applicable diagnostic cut-off value of hs-cTnT was determined from the ROC curve and the diagnostic accuracy of hs-cTnT and cTnI levels in AMI were compared.The serum hs-cTnT levels in the AMI group were higher than 0.014 ng/mL (the 99th percentile of the healthy population), among which hs-cTnT levels in patients with ST-segment elevation myocardial infarction (STEMI) were higher than in patients with non-STEMI (NSTEMI). The area under the ROC curve (AUC) for hs-cTnT was significantly higher than for cTnI, and the detection combining hs-cTnT and creatine kinase isoenzyme (CK-MB) further increased the AUC. When 0.014 ng/mL was set as the cut-off value for hs-cTnT, the diagnostic sensitivity for AMI reached 100% but the specificity was only 45.5%. The diagnostic ability of hs-cTnT for AMI peaked at a cut-off value of 0.035 ng/mL, resulting in the highest Youden index (0.654) and sensitivity and specificity values of 91.8

and 74.9%, respectively. The diagnostic utility of the hs-cTnT test for AMI is superior to the traditional cTnI method. However, since hs-cTnT levels of non-AMI patients can be over the diagnostic cut-off value, further studies are necessary to define clinically applicable cut-off values of hs-cTnT.

Key words: High-sensitivity cardiac troponin T (hs-cTnT) test; Receiver operating characteristic curve (ROC curve); Diagnostic value; Acute myocardial infarction

INTRODUCTION

Acute myocardial infarction (AMI) is the myocardial necrosis caused by acute myocardial ischemia, which is the result of numerous factors such as coronary artery stenosis. AMI is an acute disease with a high mortality rate, causing death and disability worldwide. In recent years, there has been an upward trend in the morbidity of AMI, affecting people at an even younger age (Shen et al., 2013). High-sensitivity cardiac troponin T (hs-cTnT) tests can significantly improve early diagnosis of AMI for its higher sensitivity compared to the traditional detection of cardiac troponin I (cTnI). Hs-cTnT can be regarded as an independent index of prognosis and effect observation, which has now been gradually applied to clinical practice (Aldous et al., 2011; Than et al., 2012). The European Society of Cardiology (ESC) guidelines first recommended the hs-cTnT test as a rapid screening method for non-ST-segment elevation myocardial infarction (NSTEMI) patients in 2011 (Hamm et al., 2011). The 2012 publication, “The application of high-sensitivity cardiac troponin T in acute coronary syndrome: a consensus of Chinese experts” (Cardiovascular Science Branch of the Chinese Medical Association, Editorial Board of the Journal of Cardiovascular Diseases, 2012), also provided a detailed application scheme of the hs-cTnT test. This study aimed to observe changes in hs-cTnT levels in AMI patients and compare them with the traditionally measured cTnI levels. Appropriate cut-off diagnostic values of hs-cTnT applied to clinical practice were investigated, and its value in the diagnosis of AMI was also explored.

MATERIAL AND METHODS

General information

Two hundred and forty AMI patients visiting the Shandong Rizhao People’s Hospitalfrom July 2013 to March 2014 were selected, which included 132 patients with ST elevation myocardial infarction (STEMI) (89 males and 43 females; aged 44 to 73 years, average age 68.4 ± 12.3) and 108 patients with NSTEMI (76 males and 32 females; aged 44 to 74 years, average age 69.6 ± 13.1). The diagnostic criteria referred to the clinical practice guidelines of the ESC and American College of Cardiology (ACC) (Thygesen et al., 2007). The exclusion criteria included elevated non-ischemic cardiac troponin caused by chest pain over 12 h, malignant neoplasm, kidney failure and other renal diseases, heart failure, sepsis, pulmonary embolism, and pharmacological intervention. Two hundred healthy individuals who underwent physical examination in the same hospital during the same period were selected as normal control subjects (132 males and 68 females; aged 41 to 74 years, average age 67.5 ± 12.1). There were no significant differences in gender and age between the two groups ($P > 0.05$).

Methods

Collection and management of specimens

Venous blood (4 mL) was collected from AMI patients upon their hospital visit and 4 mL fasting venous blood of healthy controls was obtained, followed by centrifugation at 3000 *g* for 10 min. The serum was isolated and frozen.

Instruments and reagents

The COBAS E601 electro-chemiluminescence immunity analyzer (Roche Group，Switzerland) was used for hs-cTnT detection, with the Roche original ELISA kits as the reagents. The upper limit of the hs-cTnT reference range (the 99th percentile of the healthy population) was 0.014 ng/mL and this was used in the instructions for the analyzer. The DXI800 chemiluminescence immunity analyzer (Beckman Coulter Inc., South Kraemer Boulevard Brea, CA, USA) was employed for cTnI detection, with original ELISA kits as the reagents. The upper limit of the cTnI reference range was 0.04 ng/mL and this was used in the instructions for the analyzer. The Hitachi 7600 automatic biochemistry analyzer (Beijing Strong Biotechnologies Inc., China) was employed for the creatine kinase isoenzyme (CK-MB) test. All the instruments and experiments were managed by professional staff. Internal quality control was carried out every day for the duration of the project, and all measurements were made after quality control was completed.

Statistical analysis

Data analysis was performed using the SPSS17.0 (Chicago, IL, USA) software. First, the normality test was conducted for measured data. The normal distributions of the data are reported as means ± standard deviation (means ± SD) and the Student *t*-test was used to compare differences of the same index between two groups. The data of abnormal distribution are reported by median ($X_{50\%}$) and interquartile range ($X_{25\%}$-$X_{75\%}$), and the Wilcoxon rank sum test was applied to compare differences between the two groups. $P < 0.05$ was considered to be statistically significant. Receiver operating characteristic (ROC) curves were plotted and statistical indexes, such as area under the curve (AUC), Youden index, sensitivity and specificity, were calculated.

RESULTS

Serum levels of hs-cTnT, cTnI and CK-MB

Serum hs-cTnT, cTnI and CK-MB levels in each group (AMI and control) and the related analyses are shown in Table 1.

Diagnostic accuracy of measuring hs-cTnT and cTnI in AMI

The diagnostic accuracy of serum hs-cTnT, which was detected immediately upon the patients' arrival at the hospital, and traditional cTnI were evaluated by the ROC curve. AUC values for hs-cTnT and traditional cTnI were 0.905 (95%CI = 0.841-0.969) and 0.793 (95%CI = 0.705-

0.880), respectively. Thus, the diagnostic accuracy of hs-cTnT for AMI was superior to traditional cTnI (P < 0.05; Figure 1).

Table 1. Serum hs-cTnT, cTnI, and CK-MB levels in each group.

Groups	hs-cTnT (ng/mL)	cTnI (ng/mL)	CK-MB (U/L)
AMI group	0.593 (0.019-10.240)△	0.51 (0.22-11.08)△	99 (35-226)△
STEMI group	0.785 (0.0281-2.650)▲	0.71 (0.05-11.79)▲	136 (54-265)▲
NSTEMI group	0.201 (0.010-6.370)	0.18 (0.03-5.87)	56 (21-158)
Control group	0.006 (0.002-0.012)	0.02 (0.01-0.03)	13 (3-22)

△Compared with control group, P < 0.05; ▲compared with NSTEMI group, P < 0.05.

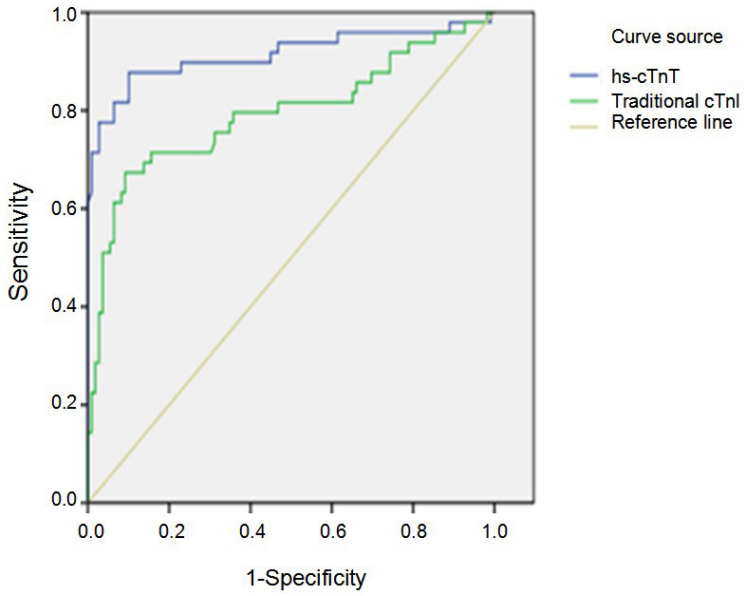

Figure 1. ROC curve of hs-cTnT and cTnI to the diagnosis of AMI. Sensitivity versus specificity is shown with hs-cTnT (blue), traditional cTnI (green) and reference (yellow) curves.

Analysis of the improved diagnostic value of hs-cTnT combined with CK-MB levels in AMI

The AUC of hs-cTnT combined with CK-MB levels was 0.954 (95%CI = 0.915-0.993), which was higher than that of hs-cTnT alone (Z = 2.098, P < 0.05; Figure 2).

Analysis of diagnostic cut-off value of hs-cTnT in AMI

Statistics analysis was carried out with the ROC curve compared to the diagnosis of AMI. For the cut-off values of 0.014, 0.020, 0.025, 0.030, 0.035, 0.040, 0.045, 0.050, 0.060, or 0.100 ng/mL, the corresponding sensitivity, specificity and Youden index of hs-cTnT were determined and are shown in Table 2. According to the results, as the cut-off value increased, the sensitivity

showed a downward trend and the specificity showed an upward trend. Taking both specificity and sensitivity into consideration, hs-cTnT had the most powerful diagnostic capability at a cut-off value of 0.035 ng/mL, corresponding to the highest Youden index (0.654) and sensitivity and specificity values of 91.8 and 74.9%, respectively.

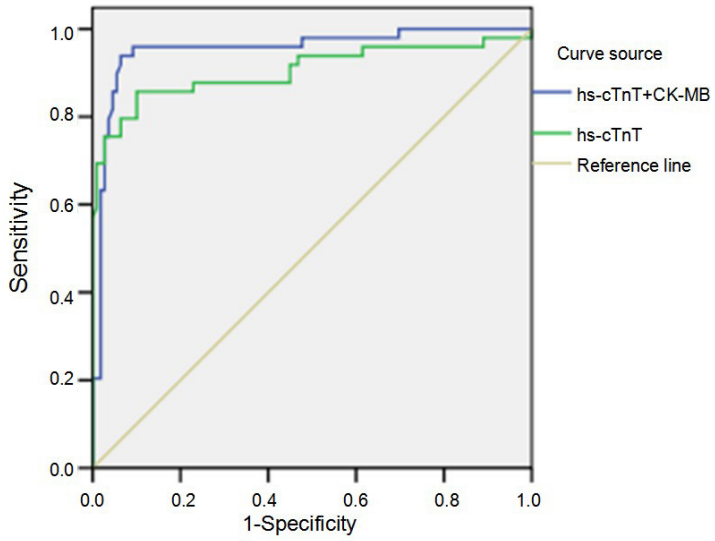

Figure 2. ROC curve of hs-cTnT combined with CK-MB levels to the diagnosis of AMI. Sensitivity versus specificity is shown with hs-cTnT + CK-MB (blue), hs-cTnT (green) and reference (yellow) curves.

Table 2. Statistical analysis of diagnostic cut-off value of hs-cTnT to AMI (%).

Cut-off value (ng/mL)	Sensitivity	Specificity	Youden index
0.014	100.0	45.5	44.8
0.020	97.2	53.4	52.7
0.025	95.4	62.1	57.8
0.030	92.6	66.8	62.5
0.035	91.8	74.9	65.4
0.040	88.7	75.3	61.3
0.045	85.6	76.9	57.9
0.050	81.3	78.6	55.2
0.060	75.6	81.7	51.6
0.100	67.4	92.1	43.4

DISCUSSION

People who visit a hospital for chest pain account for 5-10% of all patients admitted to the emergency room (Nawar et al., 2007). Therefore, how to accurately identify and diagnose AMI among all patients with chest pain so as to provide timely treatment is critical to improve prognosis and reduce mortality. The diagnosis of AMI has predominantly relied on electrocardiogram (EKG), symptoms of myocardial ischemia and serum enzyme changes (e.g., CK-MB). However, the early symptoms of some AMI patients, especially NSTEMI patients, are not always clear and changes

in EKG can be ambiguous, leading to difficulty in differential diagnosis. cTnT is a specific marker reflecting the injury of cardiomyocytes, which can be detected even when there is only a small region of necrosis. Considering its superiority, cTnT has recently become the gold standard of AMI diagnosis, displacing CK-MB and myohemoglobin. In 2007, the National Academy of Clinical Biochemistry (NACB) also recommended cTnT as the preferred biomarker for AMI diagnosis in the practice guidelines for the biochemical markers of acute coronary syndrome (ACS) (Morrow et al., 2007), and claimed that the coefficient of variation (CV) of the 99th percentile of the upper reference range of cTnT should be less than 10%. The traditional cTnI test is not likely to meet the requirements of these guidelines due to its methodology limitation, which is why it is not widely used in clinical practice. With the development of new detection techniques and updated methods, hs-cTnT can meet the requirements of these guidelines due to its higher sensitivity and specificity compared to the traditional cTnI test, and dramatically improve the early diagnosis of AMI (Aldous et al., 2011; Than et al., 2012). This study used a ROC curve to analyze hs-cTnT and cTnI levels compared to AMI diagnosis, and the results showed that the AUC for hs-cTnT was 0.905, which is significantly higher than that of cTnI (0.793). According to the diagnostic criteria of Swets (1988), ROC curves are more accurate when the AUC is between 0.7-0.9 and an AUC>0.9 indicates a high accuracy. Therefore, our results show that the diagnosis value of hs-cTnT for AMI is superior compared to cTnI. The AUC was increased from 0.905 to 0.954 by combining hs-cTnT with CK-MB serum levels, further improving the diagnostic accuracy of AMI. In addition, hs-cTnT was helpful for early risk stratification and prognosis evaluation of AMI. Keller et al. (2009) compared the results of hs-cTnT and cTnI and found that patients would have poorer outcomes within 30 days if the hs-cTnT value was higher compared to control. Studies have shown that application of the hs-cTnT value can identify more risks of recurrence and death of myocardial infarction within 1 year (Mills et al., 2012). A study on 4513 cases of non-ST elevation ACS showed that cases where hs-cTnT is higher than control have a three times higher risk of death and myocardial infarction than cases with normal hs-cTnT levels (Bonaca et al., 2010).

However, while hs-cTnT improves the diagnosis of AMI, the levels of hs-cTnT in many non-AMI patients may also exceed the upper reference range. Yang et al. (2014) found that plasma hs-cTnT was increased in patients with pulmonary embolism, chronic kidney disease, pneumonia, or patent ductus arteriosus in preterm infants to different degrees. At present, 0.014 ng/mL (the 99th percentile of the healthy population) provided by companies is often used by domestic laboratories as the upper reference range of hs-cTnT. Our study showed that a cut-off value of 0.014 ng/mL results in a diagnostic sensitivity of 100% but the specificity was just 45.5%. In this study, hs-cTnT levels of the patients in the AMI group were all higher than 0.014 ng/mL, suggesting that AMI could be excluded by a negative value of hs-cTnT but could also result in the positive diagnosis of non-AMI patients. Therefore, differential diagnosis should be carried out carefully during clinical practice. Specificity increases with a rise in cut-off value but occurs at the cost of sensitivity. This study also revealed that a cut-off value of 0.1 ng/mL could improve specificity to 92.1% but the sensitivity was only 67.4%. When taking both specificity and sensitivity into account, hs-cTnT had the most powerful diagnostic capability at a cut-off value of 0.035 ng/mL, which corresponded to the highest Youden index (0.654) with sensitivity and specificity values of 91.8 and 74.9%, respectively. Thus, the cut-off value of 0.035 ng/mL was more applicable in clinical practice because early over-medication of some patients due to a higher sensitivity will be avoided.

Although the clinical value of the hs-cTnT test in terms of AMI diagnosis is recognized by a number of scholars, there are few related clinical studies. Various problems in detection and clinical

application of hs-cTnT remain to be solved, including how to choose cut-off diagnostic values, the influence of physiological variation of cTnT in individuals, the influence of different hs-cTnT monitoring time points upon AMI diagnosis, differential diagnosis upon slight hs-cTnT increase, and the value of hs-cTnT levels in risk stratification, prognosis evaluation and clinical guide of the patients. These issues require further evaluation in order to mainstream the clinical use of hs-cTnT in the diagnosis of AMI.

Conflicts of interest

The authors declare no conflict of interest.

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