Nilgun Isiksacan*, Ismail Biyik, Selcuk Opan, Fatma N.T. Caglar, Mehmet Erturk, Serkan Yazan, Pinar Kasapoglu, Dilay Karabulut, Nursel Kocamaz, Mehmet R. Yildirim, Omer F. Baycan, Begum Ozalp, Huseyin Karakurt and Ibrahim F. Akturk

Effect of age and gender differences on high-sensitive troponin T measurement in the diagnosis of acute myocardial infarction

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Abstract

Background: Cardiac troponins are the recommended markers for the detection of acute myocardial infarction (AMI). There is a controversy regarding their decision limits. In this study, our objective was to reveal the cut-off values of high-sensitive troponin T (hsTnT) for AMI diagnosis in our population and to examine the effect of age and gender on hsTnT cut-off values.

Methods: Patients who presented to the emergency department (ED) with chest pain were selected, and only those patients admitted during the first 3–6 h of symptom onset were included in the study.

Results: A total of 484 men and 182 women were included. A total of 355 (279 men/76 women) patients were diagnosed with AMI. The cut-off values of hsTnT were found to be 17 ng/L and 16 ng/L, for males and females, respectively. The cut-off values of hsTnT were detected to be significantly higher in men over 40 years of age (24 ng/L) than in men less than 40 years of age (10 ng/L).

Conclusions: The cut-off value for the hsTnT test for AMI was slightly lower in females than in males. The cut-off levels of hsTnT for the diagnosis of AMI were found to be significantly higher in men over 40 years of age than in men less than 40 years of age.

Keywords: acute myocardial infarction; cut-off; troponin.

Introduction

Cardiovascular diseases and acute myocardial infarction (AMI) constitute up to 32% of all deaths worldwide [1]. Biomarkers are important tools in the diagnosis, treatment and prognosis of heart diseases [2–4]. Cardiac troponin is a complex that consists of three subunits (T, I and C), is part of the contractile apparatus of the muscle and regulates the interaction of actin and myosin which play a critical role in the coordination of cardiac excitation-contraction coupling [5]. Following myocardial damage, there is rapid depletion of the cytoplasmic pool, and cardiac troponins are released into the circulation after breakdown of the contractile apparatus and therefore the measurement of their levels in serum is of great value in the early diagnosis of AMI [5, 6].

Monoclonal antibody-based assays can sufficiently differentiate the cardiac isoforms of troponin T and I from the skeletal isoforms because their amino acid sequences are different [5]. Cardiac troponin testing has been used in AMI diagnosis for about 25 years. Troponin I and T are superior to other markers of myocardial infarction because of their high sensitivity and specificity [2, 6]. Cardiac troponin T and I are the markers recommended by current guidelines for the detection of AMI and myocardial damage [2]. Specification of the decision limits in the measurement of high-sensitive troponins (hsTn) in AMI patients is of great importance. There is an ongoing controversy regarding their decision limits in the diagnosis of AMI. Age and gender differences in the measurement of hsTn levels have become a new focus of debate. Gore et al.

*Correspondence: Assoc. Prof., Nilgun Isiksacan, MD, Department of Biochemistry, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, 34000 Istanbul, Turkey, Phone: +905324944995, E-Mail: nisiksacan@gmail.com

Ismail Biyik: Department of Cardiology, Usak University, School of Medicine, Education and Research Hospital, Usak, Turkey

Selcuk Opan, Fatma N.T. Caglar, Dilay Karabulut and Ibrahim

F. Akturk: Department of Cardiology, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey

Mehmet Erturk, Serkan Yazan, Mehmet R. Yildirim, Omer F. Baycan, Begum Ozalp and Huseyin Karakurt: Department of Cardiology, Istanbul Mehmet Akif Ersoy Cardiology and Cardiovascular Surgery Education and Research Hospital, Istanbul, Turkey

Pinar Kasapoglu: Department of Biochemistry, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey

Nursel Kocamaz: Department of Internal Medicine, Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey

reported that the usage of a standard cut-off value (14 ng/L) for the high-sensitive cardiac troponin T (hsTnT) assay may cause over-diagnosis of myocardial infarction, especially in elderly people and men [7]. Recently, Kimenai et al. showed that the cut-off values for hsTnT and hsTnI were lower in women than in men (hsTnT: 12 vs. 16 ng/L; hsTnI: 11 vs. 20 ng/L) and increased with age [8]. In their other study, they also suggested a downward adjustment of hsTn thresholds in women to reduce the under-diagnosis of AMI in women [9]. On the other hand, some authors report that present studies do not reveal an important clinical superiority of sex-specific hsTn 99th percentiles [10]. However, the 1-year mortality rate after AMI is higher in females than in males, and the proportion of undetectable incident myocardial infarction is also higher in women than in men [9]. Current guidelines have not yet recommended clear cut-off values and algorithms for women and the elderly in the diagnosis of AMI [9]. In the present study, our objective was to reveal the cut-off values of hsTnT for AMI diagnosis in our population and to examine whether there are age and gender differences for hsTnT cut-off values.

Subjects and methods

Study population

This observational study was conducted in tertiary education and research hospitals. We used inclusion and exclusion criteria similar to that used by Isiksacan et al. in the design of this study [4]. Patients presenting to the emergency department (ED) with chest pain were screened for inclusion. Patients who presented to the ED with chest pain were selected and only those patients admitted during the first 3–6 h of symptom onset were included in the study. Patients aged <18 years, with chest pain due to trauma or lasting <1 min, no chest pain, no electrocardiogram (ECG) or no troponin assay performed within 24 h of the index ED visit, an inability to communicate, hemodynamic instability, a definitive alternative diagnosis at the initial medical assessment and advanced chronic medical illness were excluded from this investigation [4]. Patients presenting after the first 6 h of the symptom onset were also excluded from the research. Informed consent forms were taken from all the study patients. Local Ethics Committee approval was obtained for the study protocol (2012/43). This study was performed in accordance with the Declaration of Helsinki, International Conference on Harmonization (ICH) and the Good Clinical Practice (GCP) guidelines.

Laboratory measurements

The measurement of hsTnT was performed using a high-sensitive troponin T assay kit (Roche High-Sensitive Troponin T, Hoffmann La Roche Diagnostics, Basel, Switzerland). Before the plasma was obtained, the venous blood samples were centrifuged for 10 min at 1500 rpm and the hsTnT assay was made via the electrochemiluminescence method (ECLIA) using a cobas e411 analyzer (Roche Diagnostics, Basel, Switzerland) [4]. Glucose, lipid profile and other biochemical parameters were measured from the serum samples by using cobas systems commercial kits (Roche Diagnostics Basel, Switzerland). Complete blood count (CBC) was taken from ethylenediaminetetraacetic acid (EDTA) whole blood samples using a BC 6800 auto analyzer (Mindray Medical International Limited, Shenzhen, China). For all the devices, internal quality controls were made at two levels.

Diagnosis of AMI

In this study, because it was aimed to determine the cut-off values of hsTnT according to age and sex in AMI patients, AMI diagnosis was made using AMI indicators outside of cardiac troponin values, and the coronary angiographic criteria of AMI were used as the basis in the diagnosis of AMI for the exclusion of other causes of myocardial injury [2, 11]. For the purpose of the study, a single hsTnT value taken in a time frame of 3–6 h after the onset of symptoms was included in the analysis [2, 11]. We used the methods of Isiksacan et al. for the diagnosis of AMI [4]. Clinical characteristics and symptoms of AMI such as chest pain, significant changes suggesting myocardial injury on an ECG such as ST elevation and depression, wall motion abnormalities in echocardiographic evaluation, and the recommended angiographic criteria for the diagnosis of AMI in previous studies were used. The angiographic criteria of AMI were accepted as culprit lesions, complex lesions consisting of plaque rupture and/or thrombus formation, and the evidence of plaque rupture or erosion in a coronary vessel [4, 12]. A recent total occlusion (dye stasis at the site) or a significant lesion that was generally filling defects indicating intracoronary thrombus or eccentric with abrupt shoulders, overhanging edges and ulcerations was defined as a complex lesion [4, 12]. Only significant lesions on the angiography (stenosis > 70% in diameter) in a coronary artery that complied with wall motion abnormalities in echocardiography or the new electrocardiographic changes and critical lesions in multi-vessel disease were accepted as culprit lesions [4, 12]. The

diagnosis of AMI according to the mentioned criteria was created by the comments of at least two cardiologists who were in agreement about the laboratory results.

Statistical analysis

Statistical analyses were performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium, <http://www.medcalc.org>). Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median and maximum). The Mann-Whitney U test was used to compare two independent variables with no normal distribution. The chi-square (χ^2) test (or Fisher's exact test in appropriate conditions) was used to examine the relationship between the categorical variables. Sensitivity and specificity calculations were done to examine the power of the applied diagnostic tests. Statistical significance level was determined as $p=0.05$.

Results

In total, 666 candidates (484 men and 182 women) were included in this study; 355 patients received a diagnosis of AMI and were treated. Clinical characteristics and laboratory results of patients with and without AMI are presented in Table 1. In patients with AMI, the mean age, presence of diabetes and hypertension, white blood cell count, troponin T levels, and interestingly, the ratio of no-smoking were significantly higher than those in patients without AMI. Triglyceride and high-density lipoprotein (HDL) cholesterol levels were significantly lower in patients with AMI. A total of 76 (21%) women and 279 (79%) men were in the AMI group and the ratio of women was significantly lower in this group. There was a significant difference between men and women in terms of hsTnT dispersion according to gender in the study ($p<0.05$). The mean troponin T values for women were measured as 290 ± 900 ng/L (median: 10 min-max (3–6410)), and the mean troponin T values for men were measured as 760 ± 2070 ng/L median: 20 min-max (0–13760). According to receiver operating characteristics (ROC) curve analysis, the cut-off values for hsTnT in AMI were 16 ng/L for women and 17 ng/L for men (Table 2). According to age differentiation, the cut-off values for hsTnT in AMI were 10 ng/L for patients <40 years and 17 ng/L for patients ≥ 40 years (Table 3). According to gender and age differentiation, cut-off values of 16 ng/L were found for

Table 1: Clinical characteristics and laboratory results of patients with and without AMI.

	Mean $\pm$ SD Median (Min-Max)		p-Value
	Without AMI (n=311)	With AMI (n=355)	
Age, years	47.9 $\pm$ 13.7 47 (17–86)	58.3 $\pm$ 12.6 57 (24–89)	<0.001^a
Triglyceride, mg/dL	187.9 $\pm$ 119.3 155 (14–764)	158.5 $\pm$ 143.3 114 (29–981)	<0.001^a
LDL, mg/dL	125.9 $\pm$ 36.6 124 (33–242)	128.6 $\pm$ 40.7 131 (12.1–246)	0.152 ^a
HDL, mg/dL	44.6 $\pm$ 13 43 (23–114)	41.2 $\pm$ 9.9 40 (21–74)	0.003^a
Total cholesterol, mg/dL	190.1 $\pm$ 41.9 186 (94–326)	197.5 $\pm$ 49.9 192.5 (66–488)	0.061 ^a
Creatinine, mg/dL	0.89 $\pm$ 0.4 0.9 (0.5–8)	0.91 $\pm$ 0.5 0.8 (0.3–8.4)	0.112 ^a
White blood cells ($\times 10^9$ /L)	8.5 $\pm$ 2.4 8.1 (3.04–20.5)	12.5 $\pm$ 3.3 12.2 (4.6–21.6)	<0.001^a
Platelets	258.7 $\pm$ 62.8 257 (33–465)	255.9 $\pm$ 70.3 244 (108–537)	0.216 ^a
HsTnT, ng/L	14 $\pm$ 50 4 (1–69)	1250 $\pm$ 2480 190 (0–13,800)	<0.001^a
Gender, n (%)			
Female	106 (34.1)	76 (21.4)	<0.001^b
Male	205 (65.9)	279 (78.6)	
CABG, n (%)			
No	283 (94.6)	150 (94.9)	1.00 ^c
Yes	16 (5.4)	8 (5.1)	
Smoking, n (%)			
No	110 (37.8)	149 (42.6)	<0.001^b
Yes	114 (39.2)	163 (46.6)	
Ex-smoker	67 (23.0)	38 (10.9)	
Diabetes, n (%)			
No	261 (87.9)	277 (78.2)	0.001^b
Yes	36 (12.1)	77 (21.8)	
Hypertension, n (%)			
No	169 (73.2)	221 (64.8)	0.035^b
Yes	62 (26.8)	120 (35.2)	
Pain type, n (%)			
Atypical	260 (83.6)	14 (5.5)	<0.001^c
Typical	51 (16.4)	242 (94.5)	
ECG, n (%)			
Normal	277 (89.1)	24 (6.8)	<0.001^c
Non ST Elevation	31 (10.0)	24 (6.8)	
Complex ST Elevation	2 (0.6)	6 (1.7)	
CAG, n (%)			
Yes	126 (91.3)	4 (1.6)	<0.001^c
No	12 (8.7)	246 (98.4)	

^aMann-Whitney U; ^bKi-Kare; ^cFisher's Exact. SD, standard deviation; Min-Max, minimum-maximum values; LDL, low-density lipoprotein; CABG, coronary artery bypass grafting. $p\leq 0.05$ Values are considered as statistically significant and are indicated in bold.

women ≥ 40 years and of 24 ng/L for men ≥ 40 years. In patients with AMI, there were no women <40 years of age (Table 4).

Table 2: Receiver operating curve analysis according to gender differentiation.

		AUC	p-Value	Cut-off	Sensitivity	%95 lower CI	%95 Upper CI	Specificity	%95 Lower CI	%95 Upper CI
Female	HsTnT	0.944	<0.001	16	82.89	72.5	90.6	93.33	86.7	97.3
Male	HsTnT	0.931	<0.001	17	85.61	80.9	89.5	86.14	80.6	90.6

AUC, area under the curve; CI, confidence interval.

Table 3: Receiver operating curve analysis according to age differentiation.

		AUC	p-Value	Cut-off	Sensitivity	%95 Lower CI	%95 Upper CI	Specificity	%95 Lower CI	%95 Upper CI
<40 years	HsTnT	0.959	<0.001	10	88	68.8	97.5	92.45	85.7	96.7
≥40 years	HsTnT	0.926	<0.001	17	85.41	81.1	89.0	85.57	79.9	90.1

AUC, area under the curve; CI, confidence interval.

Table 4: Receiver operating curve analysis according to age and gender differentiation.

		AUC	p-Value	Cut-off	Sensitivity	%95 lower CI	%95 upper CI	Specificity	%95 lower CI	%95 upper CI
<40 years										
Female	HsTnT	–	–	–	–	–	–	–	–	–
Male	HsTnT	0.950	<0.001	10	88	68.8	97.5	89.61	80.6	95.4
≥40 years										
Female	HsTnT	0.931	<0.001	16	82.89	72.5	90.6	90.79	80.3	95.3
Male	HsTnT	0.922	<0.001	24	81.03	75.6	85.7	88.8	81.9	93.7

AUC, area under the curve; CI, confidence interval.

Discussion

The present study revealed that hsTnT levels were slightly lower in women than in men among patients diagnosed with AMI, and the cut-off levels of hsTnT were higher in patients ≥40 years compared with those under 40 years, and the cut-off values for hsTnT were significantly lower in female patients ≥40 years compared to male patients ≥40 years. The criteria for the universal definition of AMI diagnosis are predominantly focused on hsTn levels. While the hsTn tests indicate a significant difference in the cut-off values in men when compared to women, there is no consensus statement on the application of age- and gender-specific diagnostic and prognostic decision limits. It is argued that the cut-off values accounted for hsTnT in the AMI test may be different according to the age and the sex of the patients. Cardiac troponin T is a larger protein and stays longer in blood circulation than cardiac troponin I, but the two biomarkers have been accepted to be theoretically equivalent for the detection of AMI [13]. Both the troponins are degraded, and troponin I is also modified in the blood stream. Therefore, the detectability in the blood depends on the binding site of the monoclonal antibodies used in the single assays [14].

There has been a major confusion about their cut-off levels in the diagnosis of AMI. On the necessity of age- and sex-specific predictive values, discussions and investigations have begun and are continued. The authors have stated that the troponin cut-off concentrations should be identified via ROC curve analysis and not determined on the 99th percentile of a healthy population in this situation [13]. In a previous study, Shoaibi et al. reported that the sensitivity of the test was higher when the baseline troponin was measured after 2 h of symptom onset, and did not observe a significant gender difference in the conventional cardiac troponin I assay sensitivity and specificity [5]. In an Asian cohort, Aw et al. detected higher 99th percentile upper reference limit (URL) values in men and individuals over 50 years and lower 99th percentile URL values in women and in apparently healthy individuals [15]. In an Italian population study, Franzini et al. studied the 99th percentile URL values of hsTnT using the same commercial method as in our study, and they found lower URL values in young individuals and women compared with men and elderly individuals [16]. In a large American cohort, Gore et al. found that the 99th percentile URL values for hsTnT were higher in men and increased with age, and in the light of these results, the

use of the standard 14 ng/L cut-off value for hsTnT may lead to under-diagnosis of AMI in women and young individuals and over-diagnosis of AMI in men and the elderly [7]. Our results are consistent with the mentioned reports. Eggers et al. investigated hsTnI levels in an elderly population and found higher levels of hsTnI depending on the chosen level and significantly higher levels in men than in women. They also reported that there was no major difference in the predictive capacity of single vs. sex-specific cut-off values after multivariate adjustments [17]. Slagman et al. investigated two commonly used commercial hsTnT and hsTnI assays in patients with non ST elevation myocardial infarction (NSTEMI), and they found lower troponin levels, lower sensitivity and negative predictive values in women compared to men [18]. The diagnosis of AMI was more often made in men than in women, and men had higher troponin levels than the women in their study [18]. Their findings support our results. On the other hand, Balmelli et al. compared the area under the ROC curves in the diagnosis of NSTEMI with conventional and hsTnT assays, and they did not reveal significant gender difference [19]. Their result is conflicting with ours, but different cut-off values were not investigated in their study. In a large-scale population study, Omland et al. found that hsTnI is associated with cardiovascular death, and there is higher relative risk in women than in men, and the prognostic role of hsTnI is stronger in women than in men in the general population [20]. Mueller-Hennessen et al. compared the generally used standard hsTnT cut-off (14 ng/L) with age (28 ng/L for ≥ 65 years) and gender-specific cut-off values (90 ng/L for women, 15.5 ng/L for men) in AMI patients [21]. In their study, the use of age- and gender-specific cut-off values reduced AMI diagnosis in elderly patients (>65 years) and men but increased in women. The end-point outcomes did not change with the use of age- and gender-specific cut-off values compared with the standard cut-off value [21]. The use of these age and gender cut-off values may cause over-diagnosis of AMI in women and may lead to unnecessary interventions and medications. This point of view may be in contrast to the general belief of under-diagnosis of AMI in women. Kimenai et al. reported different 99th percentile URLs of hsTnT and hsTnI influenced by gender [8]. URLs were higher in men than in women (16 vs. 12 ng/L for hsTnT and 20 vs. 11 ng/L for hsTnI, respectively) [8]. The present study does have several shortcomings. The relatively small sample size of our study was the most important limitation. There were no women under 40 years of age with AMI. To measure a cut-off value for these patients would have been better. Long-term follow-up data were not adequately collected, and it would have been better to reveal the clinical and prognostic importance of the results. The diagnosis of

AMI was constituted via clinical findings, electrocardiography, echocardiography and coronary angiography [12]. The use of tools showing the loss of myocardial viability such as positron emission tomography and thallium scintigraphy would have been better. Despite the shortcomings mentioned, our results are important and valuable in terms of shedding light on the situation in our country and contributing to this issue in the international literature. As a result, in the light of the studies in the literature, it seems necessary for each community to set its own 99th percentile URLs according to sex and age groups. This approach may prevent the risks of under-diagnosis of AMI in women and young patients, over-diagnosis in the elderly, and unnecessary medications and interventions.

The results of this study indicate that hsTnT levels in women with AMI are lower than those in men. The cut-off value for the hsTnT test in the diagnosis of AMI was slightly lower in women than in men. The cut-off values for hsTnT in AMI were significantly lower in patients <40 years than in patients ≥ 40 years. Together with gender and age differentiation, the cut-off values were found to be significantly lower in women ≥ 40 years of age than in men ≥ 40 years of age. However, it seems that adequate scale studies are necessary for each community to set its own 99th percentile URLs according to sex and age groups in the definite diagnosis of AMI.

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