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Sex-Specific Absolute Delta Thresholds for High-Sensitivity Cardiac Troponin T

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BACKGROUND: Sex differences in high-sensitivity cardiac troponin (hs-cTn) concentrations from healthy populations have led to the establishment of sex-specific upper reference limits for hs-cTn assays. This study assessed the performance of sex-specific delta (i.e., changes in concentrations) thresholds for the hs-cTnT assay for ruling in acute myocardial infarction (AMI) in different emergency department (ED) populations.

METHODS: This retrospective study consisted of 2 cohorts (Cohort 1 derivation and Cohort 2 validation). Cohort 1 consisted of 18 056 ED patients who had serial hs-cTnT measured using a 0-h/3-h algorithm at a US medical center, with Cohort 2 consisting of 1137 ED patients with 0-h/3-h sampling at a Canadian medical center. The primary outcome was AMI diagnosis with sex-specific deltas derived based on the Youden index and specificity estimates (i.e., ≥90%) in Cohort 1 and validated in Cohort 2.

RESULTS: In Cohort 1, 42% of all patients had 0-h hs-cTnT above the sex-specific 99th percentile. Males had higher 0-h hs-cTnT (median 17 ng/L) and absolute deltas (median 2 ng/L) than females (0-h median 11 ng/L, $P < 0.0001$; deltas median 1 ng/L, $P < 0.0001$) in non-AMI patients but not in patients with AMI. For ruling in AMI, the sex-specific delta thresholds based on 90% specificity (14 ng/L for males, 11 ng/L for females) performed best and resulted in 91% diagnostic accuracy in both males and females. The sex-specific delta thresholds yielding high specificity estimates were confirmed in the validation data set.

CONCLUSIONS: Sex-specific absolute delta thresholds can be used to rule in AMI and are robust across different study populations.

Introduction

The universal definition of myocardial infarction (MI) specifies that the detection of a rise and/or fall of a cardiac biomarker, preferably high-sensitivity cardiac troponin (hs-cTn), with at least 1 value above the 99th percentile of the upper reference limit (URL) is required for the diagnosis of acute MI (AMI) (1, 2). A changing pattern beyond an acceptable range (i.e., delta threshold) distinguishes between an acute and a chronic hs-cTn increase. The previous 2015 European Society of Cardiology (ESC) guideline recommended using a 0-h/3-h algorithm that did not list specific absolute delta thresholds for this timeframe (2). The 2020 ESC guideline has further promoted the 0-h/1-h and 0-h/2-h over the 0-h/3-h algorithm, while still not providing absolute deltas nor endorsing sex-specific URLs for the diagnosis of AMI (3). Open questions persist regarding the optimal absolute delta threshold when assessing serial sampling at 0-h/3-h and whether sex-specific delta thresholds improve the diagnosis of patients with possible AMI.

The observation that women tend to have atypical clinical presentations of AMI, which complicates recognition of symptoms (4, 5) and that women have significantly lower hs-cTn concentrations compared to men in presumably healthy populations (6–8) prompted the use of sex-specific cutoffs for the detection of myocardial injury (9–11). The current recommendations are to use the sex-specific 99th percentile URLs for hs-cTn to detect myocardial injury and aid in the diagnosis of MI (1, 12) with sex-specific single measurements to rule out AMI having also been investigated (13). Studies that evaluated the reclassification of AMI using sex-specific 99th percentiles have generated different messaging on its utility (14–24). However, an

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important data gap in the literature is the absence of interpreting sex-specific delta thresholds in this setting, as current algorithms and publications have used a common delta for both men and women (3, 25). Our objective in the study reported here was to evaluate and validate the use of sex-specific delta thresholds for hs-cTnT from samples collected 3 h apart in the emergency department (ED) for AMI diagnosis.

Methods

This retrospective study was approved by the University of Rochester Institutional Review Board for the derivation cohort (Cohort 1) with previous approval for the validation cohort (Cohort 2) by the Hamilton Integrated Research Ethics Board.

COHORT 1

The University of Rochester Medical Center implemented a 0-h/3-h hs-cTnT algorithm in May 2018. In this study, all patients presented to the ED with serial hs-cTnT testing between May 1, 2018 and October 30, 2019 (18-month period) at Strong Memorial Hospital were retrieved from the clinical laboratory information system. Only adult patients (≥18 years) were included. Results at presentation (0 h) of each encounter and its earliest sequential testing (3 h) were obtained for each patient. Further subsequent testing and the corresponding results (e.g., 6 h, 9 h) were not included in the final data set. In field situations of the ED setting, a small proportion of patients had a time interval between first and the earliest subsequent result deviating from 3 h (see Results section). Cases with a time interval over 10 h, possibly caused by nonreportable intervening results due to poor specimen integrity, were excluded.

AMI diagnosis was obtained from the Chest Pain–MI Registry from the Department of Cardiology at the University of Rochester Medical Center. The Chest Pain–MI Registry recorded all subjects diagnosed with type I AMI at Strong Memorial Hospital, compliant to institutional guidelines. It was maintained independently of this study to provide feedback on the care and outcomes of patients with possible acute coronary syndrome. Matching of the Chest Pain–MI Registry to the ED hs-cTnT database required the exact match of patient name, date of birth, and date of hs-cTnT test. Therefore, only index AMI (i.e., no inpatient AMI) was included in the final data set. All patients included in the registry had a qualifying diagnosis on discharge and were evaluated by more than 1 cardiologist who reviewed all available clinical information. The exclusion criteria of the registry included transfer patients with a time interval from outside facility to arrival over 24 h, non-ST-segment elevation myocardial infarction (NSTEMI) occurring beyond 24 h of arrival and type II AMI. The diagnostic criteria of AMI require the detection of a dynamic cardiac troponin with at least 1 value above the 99th percentile URL and at least 1 of the following: symptoms of acute myocardial ischemia; new or presumed new significant ST-segment elevation consistent with AMI [for ST-segment elevation myocardial infarction (STEMI)] or new ischemic electrocardiogram changes (for NSTEMI); development of pathological Q waves; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemia etiology; and/or identification of an intracoronary thrombus or plaque rupture/erosion by angiography including intracoronary imaging (1). For Cohort 1, sex-specific 99th percentile URL was adopted with the delta threshold for dynamic change not rigidly applied, although 20% was usually used in agreement with the universal definition of myocardial infarction (1). Further subsequent testing at 6 h and 9 h or longer were pursued to aid diagnosis when needed.

COHORT 2

The details of Cohort 2 have been previously published (NCT01994577) (25–27). Briefly, adult patients presenting with symptoms suggestive of acute coronary syndrome in the city of Hamilton, Ontario, Canada, were prospectively enrolled if the ED physician ordered cardiac troponin. Patients were excluded if they were transferred from another hospital; symptoms were nonacute coronary syndrome; or they had chest trauma, cardiac surgery, or manipulation within 1 month of presentation; a pulmonary embolus or MI (STEMI or NSTEMI) confirmed within the previous month; known active cancer or noncardiac fatal illness; sepsis; ventricular fibrillation or sustained ventricular tachycardia; or STEMI at presentation. Two serial samples, collected in dipotassium ethylenediaminetetraacetic acid vacutainers and centrifuged prior to testing the plasma, were tested for both cardiac troponin I (cTnI) and hs-cTnT. An ED physician led an adjudication panel, whose members were blinded to the hs-cTnT results. The AMI diagnosis was based on the cTnI (μg/L) assay (Abbott ARCHITECT i2000s) with a cTnI concentration of >0.03 μg/L (>99th percentile URL) and a rise/fall pattern (delta ≥0.03 μg/L for concentrations <0.10 μg/L or proportional changes of ≥20% for concentrations ≥0.10 μg/L) or new ST-segment elevation or depression indicative of ischemia, new left bundle branch block, coronary artery intervention, or pathologic findings of an acute MI within 7 days after ED presentation. The median time [interquartile range (IQR)] between the 2 samples was 3.03 h (2.97–3.17).

LABORATORY MEASUREMENTS

Testing in both cohorts was performed on fresh samples (i.e., not frozen). In Cohort 1 the hs-cTnT assay was performed on Roche Cobas 602 with Elecsys Troponin T Gen 5 STAT reagent (distributed in the United States by Roche Diagnostics). The lower reporting limit is the limit of quantification at 6 ng/L as approved by the US Food and Drug Administration. For the purpose of data analysis, results reported as <6 ng/L were replaced as 5 ng/L. The 99th percentile URL published by the manufacturer's package insert is 22 ng/L for males, 14 ng/L for females, and 19 ng/L for both males and females (28). The assay imprecision measured by the coefficient of variation (CV) is 2.6% at 16 ng/L and 2.1% at 98 ng/L at the performing laboratory. The details of testing for hs-cTnT in Cohort 2 have been previously published (29). In brief, the hs-cTnT assay was performed on Roche Modular E170 platform, with CVs of 2.3% at approximately 30 ng/L and 2.1% at approximately 2253 ng/L. The lower reporting limit is the limit of blank at 3 ng/L. For the creatinine assay and estimated glomerular filtration rate, the Chronic Kidney Disease–Epidemiology Collaboration creatinine equation was used in both cohorts with creatinine measured on Roche Cobas 502/702 in Cohort 1 and the Abbott ARCHITECT analyzer in Cohort 2.

STATISTICAL ANALYSIS

Continuous variables were expressed as medians and 25th and 75th percentiles (IQR) due to data skewness. The absolute delta change was calculated as the absolute difference between 0-h and 3-h hs-cTnT results. Comparisons between groups were analyzed by the nonparametric Mann–Whitney U test at the 2-tailed 0.05 significance level. The 2015 0-h/3-h ESC algorithm was also assessed in this study (30), with the percentage change calculated as the absolute delta value divided by the 0 h hs-cTnT concentration. An empirical ROC analysis was conducted to assess diagnostic sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for different delta thresholds with the Youden index calculated (31, 32). To summarize the performance of classifiers' overall thresholds, area under the ROC curve (AUC) was computed using numerical integration and associated CIs were constructed using a large sample normal approximation. For the performance of the 2015 ESC 0-h/3-h algorithm (30), sex-specific 99th percentiles were used, and the ROC analysis was repeated. The deltas for males and females from the best Youden index and those that yielded specificities ≥90% (33, 34) were obtained from Cohort 1 and assessed in Cohort 2. The optimal delta thresholds were decided based on percentage accuracy comparing decisions from the delta thresholds to true diagnoses. Statistical analysis was performed using the computing environment R (R Development Core Team, 2005) and GraphPad Prism 7.

Results

In Cohort 1, there were 18 056 adult ED presentations with 0-h and 3-h hs-cTnT results (Table 1), 9524 (52.7%) of which were male and 8532 (47.3%) of which were female. AMI was diagnosed in 533 cases (2.9%, 95% CI: 2.7%–3.2%), among which 433 (81.2%) were patients with NSTEMI (291 males, 142 females) and 100 (18.8%) were patients with STEMI (71 males, 29 females). Coronary angiography was performed in 85.2% of the cases diagnosed with AMI. The 0-h/3-h endorsed sampling protocol yielded the following estimates: 58.2% of all cases had a time interval between sequential testing within 3 h ± 15 min; 90.4%, within 3 h ± 1 h; and 98.5%, within 6 h.

Over 40% (41.8% male, 42.3% female) of all patients had a 0-h hs-cTnT concentration above the sex-specific 99th percentile. The median 0-h hs-cTnT concentration was 17 ng/L (IQR 9–42 ng/L) for male patients and 11 ng/L (IQR 5–26 ng/L) for female patients ($P < 0.0001$) (Fig. 1, A). In patients without an AMI diagnosis, the median concentrations were the same as what was observed for the overall group ($P < 0.0001$ between the sexes) (Fig. 1, B). However, in patients diagnosed with AMI, there was no difference in the 0 h hs-cTnT concentrations between men (median 68.5 ng/L, IQR 33–191 ng/L) and women (median 64 ng/L, IQR 26–194 ng/L) ($P = 0.45$). Since NSTEMI constituted most AMI cases (80.4%), we analyzed the NSTEMI group separately and also observed no difference in 0-h hs-cTnT concentrations between the sexes ($P = 0.09$) (Fig. 1, C and D).

Determining sex-specific deltas identified that men had a higher absolute delta value than women in the non-AMI group (Fig. 2). The median absolute delta value was 2 ng/L (IQR 1–5 ng/L) in males and 1 ng/L (IQR 1–3 ng/L) in females ($P < 0.0001$) in the entire population, as well as in patients without an AMI diagnosis ($P < 0.0001$). In patients with AMI, the median deltas were similar between the sexes (male median 75.5 ng/L, IQR 23–304 ng/L vs female median 71 ng/L, IQR 24–190 ng/L, $P = 0.18$). Lower median deltas, but again no difference between sexes, were observed in patients with NSTEMI (male median 56 ng/L, IQR 20–169.5 ng/L vs female median 53.5 ng/L, IQR 18.5–134 ng/L, $P = 0.46$).

The delta value did not increase as 0-h hs-cTnT increased above the 99th percentile in patients with AMI. A scatter plot of the 2 values in the entire cohort failed to reveal a clear positive correlation in either patients with STEMI or NSTEMI (Fig. 3); however, patients

Table 1. Basic profiles of the Cohorts 1 and 2 study populations.

	Cohort 1			Cohort 2		
	Male	Female	Total	Male	Female	Total
Cases, n (%)	9524 (52.7)	8532 (47.3)	18 056	535 (47.1)	602 (52.9)	1137
Age (years) mean, (range)	62.7 (18.1–102.6)	63.8 (18.2–105.8)	63.7 (18.1–105.8)	64.1 (18–99)	69.0 (20–95)	66.7 (18–99)
Creatinine (mg/dL), median (range)	1.06 (0.06–22.1)	0.83 (0.07–30.5)	0.96 (0.06–30.5)	0.97 (0.44–8.86)	0.83 (0.50–9.68)	0.88 (0.44–9.68)
eGFR[a] (mL/min/ 1.73m^2), median (range)	75 (0.1–328)	75 (1–189)	75 (0.1–328)	82 (5–145)	72 (4–134)	77 (4–145)
0-h hs-cTnT <6 ng/L, n (%)	1297 (13.6)	2376 (27.9)	3673 (20.3)	84 (15.7)	164 (27.2)	248 (21.8)
0-h hs-cTnT >99th sex-specific percentile, n (%)	3978 (41.8)	3602 (42.3)	7580 (42.0)	181 (33.8)	256 (42.5)	438 (38.4)
AMI, n (%)	362 (3.8)	171 (2)	533 (3)	69 (12.9)	64 (10.6)	133 (11.7)

[a]Estimated glomerular filtration rate.

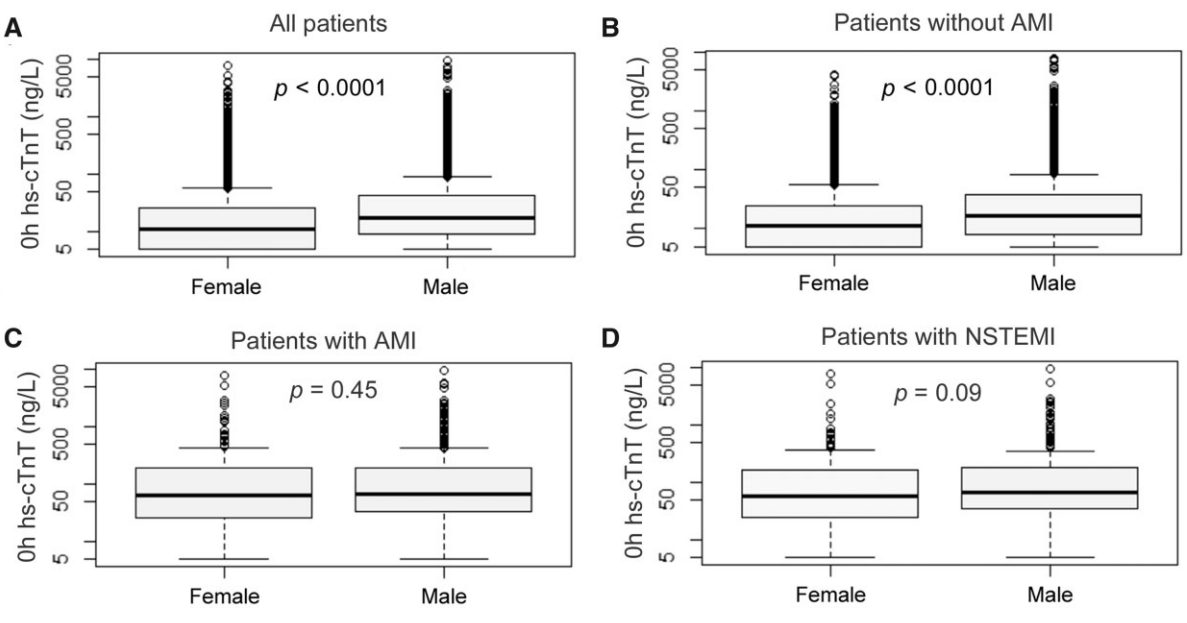

Fig. 1. Comparison of 0-h hs-cTnT results between male and female in all patients (A), patients without AMI (B), patients with AMI (C), and patients with NSTEMI (D) by nonparametric Mann-Whitney U test.

with STEMI showed higher delta values than patients with NSTEMI. Both groups exhibited a weak positive correlation between delta values and 0-h hs-cTnT concentrations only at high 0-h hs-cTnT concentrations above approximately 300 ng/L. This trend remained the same for both male and female patients (Fig. 3, C).

The absolute delta threshold outperformed the percentage delta threshold. ROC analyses based on absolute delta values in men and women separately yielded an AUC (95% CI) of 0.948 (0.932–0.964) for men and 0.953 (0.930–0.975) for women. For the percentage delta change, the AUC (95% CI) were 0.877 (0.857–

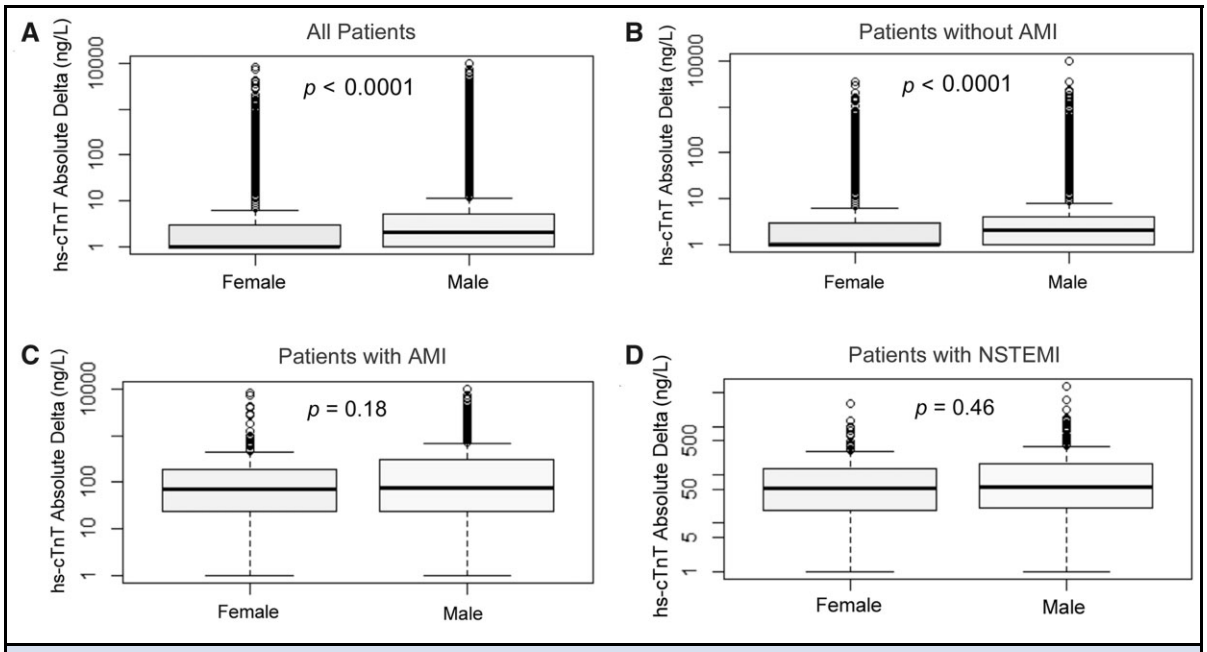

Fig. 2. Comparison of absolute delta hs-cTnT changes between male and female in all patients (A), patients without AMI (B), patients with AMI (C), and patients with NSTEMI (D) by nonparametric Mann–Whitney U test.

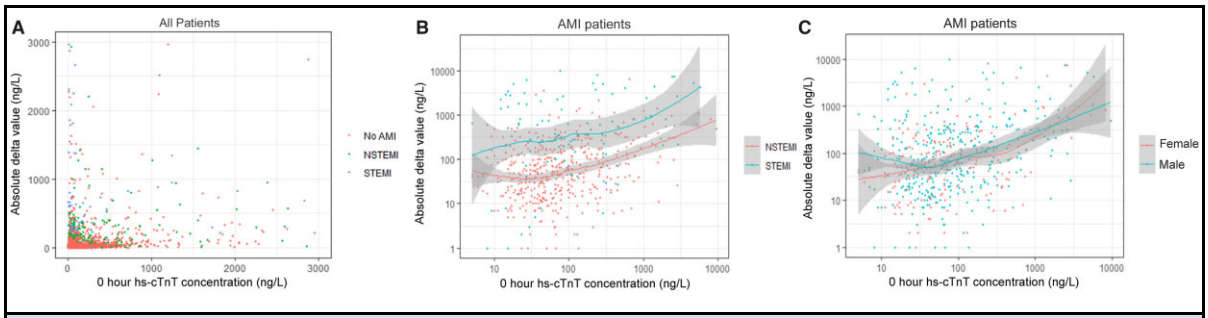

Fig. 3. Relationship between absolute delta changes and 0-h hs-cTnT concentrations in all patients in linear scales (A) and in patients with AMI in log scales with locally weighted scatterplot smoothing curve and 95% CIs grouped by STEMI and NSTEMI (B) and by male and female (C).

0.896) for men and 0.875 (0.848–0.902) for women (Fig. 4). For the performance of the ESC 0-h/3-h algorithm in Cohort 1, the AUC (95% CI) were 0.858 (0.834–0.883) for men and 0.851 (0.815–0.887) for women.

As shown in Table 2, the ROC-based delta threshold for men was 10 ng/L (Youden index 0.7915) with sensitivity of 91.7% (95% CI 88.9%–94.6%), specificity of 87.4% (95% CI 86.8%–88.1%), PPV of 23.6%, and NPV of 99.6%. In contrast, in women, the ROC-based delta threshold was 7 ng/L (Youden index 0.7923) with a sensitivity of 92.4% (95% CI 88.4%–96.4%), specificity of 86.8% (95% CI 86.1%–87.6%), PPV of 13.5%, and NPV of 99.8%. The ESC 0-h/3-h algorithm resulted in a sensitivity of 79.8% (95% CI 74.0%–83.4%) in males and 80.1% (95% CI 72.9–86.2%) in females and a specificity of 91.6% (95% CI 91.0%–92.1%) in males and 90.1% (95% CI 88.4%–96.4%) in females. For a specificity of ≥90% (i.e., lower confidence limit is ≥90.0%), a delta threshold of 14 ng/L for men and 11 ng/L for women was obtained, which yielded a sensitivity of 87.0% (95% CI 83.6%–90.5%) for men and 85.4% (95% CI 80.1%–90.7%) for women.

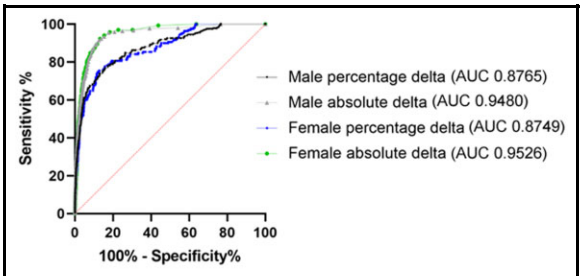

Fig. 4. ROC and AUC of percentage delta and absolute delta change to predict acute myocardial infarction in male and female patients.

ROC analysis in all patients (males and females combined) resulted in an AUC of 0.951 (95% CI 0.938–0.964) and an ROC-based general absolute delta threshold of 7 ng/L (Youden index 0.7916), which coincided with the female ROC-based delta threshold (Table 2). For a 90% specificity estimate, a general delta threshold of 12 ng/L was derived, yielding a sensitivity of 87.8% (95% CI 85.0%–90.6%). When using sex-specific 99th percentiles, there were 3 male patients in Cohort 1 with an AMI diagnosis, and they had delta changes of 7 or 8 ng/L, but neither 0-h nor 3-h hs-cTnT results exceeded the 99th percentile (0-h hs-cTnT range 9–14 ng/L, 3-h hs-cTnT range 16–22 ng/L). However, these male patients all

Table 2. Performance of absolute delta thresholds by ROC analysis for ruling in acute myocardial infarction in the Cohort 1 study population.

Delta cutoff (ng/L)	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Youden	PPV	NPV
Male	0.9480 (0.9320–0.9640)					
14		87.0 (83.6–90.5)	90.7 (90.1–91.3)	0.7770	26.9	99.4
13		87.6 (84.2–91.0)	90.1 (89.5–90.7)	0.7765	25.8	99.4
12		89.2 (86.0–92.4)	89.4 (88.7–90.0)	0.7861	24.8	99.5
11		90.1 (87.0–93.1)	88.5 (87.8–89.1)	0.7855	23.6	99.5
10		91.7 (88.9–94.6)	87.4 (86.8–88.1)	0.7915	22.3	99.6
9		92.5 (89.8–95.2)	86.2 (85.5–86.9)	0.7878	20.9	99.6
8		93.6 (91.1–96.2)	84.6 (83.9–85.4)	0.7828	19.3	99.7
7		95.9 (93.8–97.9)	82.2 (81.4–83.0)	0.7806	17.5	99.8
6		96.1 (94.1–98.1)	79.2 (78.4–80.0)	0.7532	15.4	99.8
Female	0.9526 (0.9303–0.9749)					
12		84.8 (79.4–90.2)	91.5 (90.9–92.1)	0.7627	16.9	99.7
11		85.4 (80.1–90.7)	91.0 (90.4–91.6)	0.7640	16.3	99.7
10		86.5 (81.4–91.7)	90.3 (89.7–91.0)	0.7690	15.5	99.7
9		87.7 (82.8–92.6)	89.5 (88.8–90.1)	0.7719	14.6	99.7
8		89.5 (84.9–94.1)	88.3 (87.6–89.0)	0.7775	13.5	99.8
7		92.4 (88.4–96.4)	86.8 (86.1–87.6)	0.7923	12.5	99.8
6		94.2 (90.6–97.7)	84.6 (83.8–85.4)	0.7876	11.1	99.9
Male and female combined	0.9506 (0.9378–0.9635)					
13		86.7 (83.8–89.6)	91.0 (90.6–91.4)	0.7766	22.6	99.6
12		87.8 (85.0–90.6)	90.4 (90.0–90.8)	0.7818	21.7	99.6
11		88.6 (85.9–91.3)	89.7 (89.2–90.1)	0.7825	20.7	99.6
10		90.1 (87.5–92.6)	88.8 (88.4–89.3)	0.7888	19.6	99.7
9		91.0 (88.6–93.4)	87.8 (87.3–88.3)	0.7878	18.4	99.7
8		92.3 (90.0–94.6)	86.4 (85.9–86.9)	0.7868	17.0	99.7
7		94.7 (92.9–96.6)	84.4 (83.9–85.0)	0.7916	15.6	99.8
6		95.5 (93.7–97.3)	81.8 (81.2–82.3)	0.7727	13.7	99.8

had a subsequent hs-cTnT concentration >22 ng/L at a later time point in the ED.

Further comparison of the diagnostic agreement with true diagnosis produced by different absolute delta thresholds are shown in Supplemental Table 1 in the online Data Supplement. Sex-specific delta thresholds yielded higher overall diagnostic accuracy than general delta thresholds, especially in male patients. The ROC-based delta threshold (≥10 ng/L in males, ≥7 ng/L in females) resulted in a diagnostic agreement of 87%, while the delta thresholds based on 90% specificity (≥14 ng/L in males, ≥11 ng/L in females) reached a diagnostic agreement of 91%, in both males and females. In contrast, the ROC-based general delta threshold (≥7 ng/L) provided a diagnostic agreement of 85% (83% in males, 87% in females), and the 90% specificity-based general delta threshold (≥12 ng/L) produced a diagnostic agreement of 90% (89% in males, 91% in females).

The derived sex-specific absolute delta thresholds from Cohort 1 were then evaluated in Cohort 2 (see Supplemental Table 2). Threshold analysis in Cohort 2, males and females, separately and combined, reproduced the ROC-derived delta threshold of 7 ng/L by Youden index (0.55) in females and in all patients. In females, this resulted in a sensitivity of 60.0% (95% CI 44.8%–75.2%), specificity of 94.8% (95% CI 92.7%–96.9%), PPV of 51.1%, and NPV of 96.3%. In male patients, a higher absolute delta was needed (9 ng/L, Youden index 0.54) to achieve comparable specificity of 94.9% (95% CI 92.7%–97.2%), a sensitivity of 58.7% (95% CI 44.5%–72.9%), specificity PPV of 58.7%, and NPV of 94.9%. For delta thresholds derived from 90% specificity benchmark in Cohort 1, 11 ng/L for females in Cohort 2 resulted in a sensitivity of 52.5% (95% CI 37.0%–68.0%), specificity of 98.6% (95% CI 97.6%–99.7%), PPV of 77.8%, and NPV of 95.8%; while 14 ng/L for males in Cohort 2 reached comparable performance with a sensitivity of 50.0% (95% CI 35.6%–64.5%), specificity of 98.4% (95% CI 97.1%–99.7%), PPV of 79.3%, and NPV of 94.1%.

Discussion

This study explored sex-specific delta thresholds for ruling in AMI (type I). The findings of this study may be helpful for hospitals using the 0-h/3-h protocol for hs-cTnT testing, since it now provides sex-specific absolute deltas to enhance sex-specific AMI classification further. The current sex-specific hs-cTn cutoffs are based on the sex-specific 99th percentile, of which men have substantially higher concentrations than women in healthy populations (35, 36). In our large ED patient population, male patients without AMI presented with significantly higher 0 h hs-cTnT and absolute delta changes than female patients without AMI, indicating that a sex-specific delta threshold may improve the specificity, especially in the male population.

The importance of hs-cTn dynamic changes to differentiate acute from chronic cardiac conditions was emphasized by the high incidence of ED patients presenting with initial hs-cTnT above the 99th percentile URL (nearly 40% of the population from Cohorts 1 and 2). The findings from this study, consistent with previous reports (37, 38), show that absolute deltas are superior to percentage deltas. Both the delta cutoffs derived by the Youden index or 90% specificity benchmark yielded higher sensitivities than the ESC 0-h/3-h algorithm. Sex-specific delta thresholds perform better than general delta thresholds by providing higher specificity and diagnostic accuracy, especially in males, with the delta thresholds based on 90% specificity (≥14 ng/L in males, ≥11 ng/L in females) producing the highest overall diagnostic accuracy (91%) in both males and females. Cohort 2 confirmed that sex-specific delta thresholds yield higher specificity in males. In Cohort 2, 14 ng/L in males and 11 ng/L in females achieved a specificity >90% and a PPV >75%, both of which have been proposed as AMI rule-in performance criteria for hs-cTn algorithms (39). It has also been shown that patient selection affects specificity estimates for serial hs-cTn testing algorithms (39). Given the different number and composition of subjects and the different inclusion criteria of these 2 study populations, the same optimal sex-specific delta thresholds derived from both cohorts proved the robustness of these thresholds.

Currently available algorithms to predict AMI diagnosis include the Calculation of Myocardial Infarction Risk Probabilities to Manage Patients with Suspicion of Myocardial Infarction (25), which was based on delta changes of serial hs-cTn measurements. However, it did not incorporate sex differences, nor did the studies evaluated with this algorithm use sex-specific 99th percentiles to identify myocardial injury. Other clinical risk score calculations such as the Global Registry of Acute Coronary Events score also do not consider the dynamic changes of hs-cTn or the sex differences (40).

LIMITATIONS

Cohort 1 included ED patients who had serial hs-cTnT testing with symptoms that may be atypical for acute coronary syndrome, including syncope, trauma, and cardiac arrhythmia, among others. This may explain, at least in part, the low PPV observed in this cohort. Furthermore, Cohort 1 only included type I AMI, which may further contribute to its low PPV compared to Cohort 2 and the study by Mueller et al. in which types I and II AMI were not differentiated (38). The angiography rate in our patients with AMI was 85.2%,

which was comparable to other studies in ED populations (37). For patients without angiography, we cannot exclude the possibility that some patients with type II MI or unstable angina were diagnosed as type I AMI, or vice versa. In addition, there could be a small number of patients who had type I AMI but were not diagnosed and included in the registry. This could occur in situations such as patient requested to be transferred to another hospital before a final diagnosis was made or patient did not elect to receive any care. Together, these features may cause a slight underestimation of the AMI rate and the hs-cTnT assay sensitivity. However, considering the large number of subjects in Cohort 1 (18 056), such variations will have a negligible effect on the results reported here.

Conclusions

Sex-specific absolute delta thresholds increase specificity and diagnostic accuracy, especially in male patients. Delta thresholds of $\geq$14 ng/L in males and $\geq$11 ng/L in females are optimal for ruling in AMI using a hs-cTnT 0-h/3-h algorithm. Further study is needed to assess whether the sex-specific thresholds impact outcomes in male and female patients with AMI.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online.

Nonstandard Abbreviations: hs-cTnT, high-sensitivity cardiac troponin T; URL, upper reference limit; AMI, acute myocardial infarction; ED, emergency department; ESC, European Society of Cardiology; STEMI, ST-segment elevation myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

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