High-Sensitivity Cardiac Troponin I for Predicting Death in a Female Emergency Department Population

To the Editor:

The Third Universal Definition of Myocardial Infarction has indicated that “sex-dependent values may be recommended for high-sensitivity troponin assays” (1). This statement is supported by several reference-interval studies that reported that women had lower concentrations and 99th percentile cutoffs with the high-sensitivity assays than men (2, 3). Despite these findings, it is unclear whether this information—gained only from the use of high-sensitivity assays—would be important for diagnostic or prognostic purposes in the female population. Presently, only Roche Diagnostics’ high-sensitivity cardiac troponin T (hs-cTnT)1 assay and Abbott Diagnostics’ high-sensitivity cardiac troponin I (hs-cTnI) assay have been approved by regulatory bodies. These assays are in clinical use throughout the world (outside the US). Roche has discontinued the fourth-generation cTnT assay in jurisdictions where the hs-cTnT assay has achieved regulatory approval; therefore, prospective comparisons of the readjusted hs-cTnT assay (in 2012) and the fourth-generation assay for assessing sex-specific clinical performance are no longer possible in many regions. Nevertheless, studies that assess both high-sensitivity and sensitive cTnI assays with respect to health outcomes in the female population are essential if sex-specific cutoffs are to be used. To this end, we performed a large prospective observational study of emergency department (ED) patients to assess whether an incremental benefit for predicting hospital death for women at presentation (compared with men) exists when a high-sensitivity cardiac troponin assay is used, vs. a sensitive cardiac troponin assay.

After ethics approval was obtained, every adult patient who presented to the ED at the Hamilton General Hospital and Juravinski Hospital and had a cTnI test (ARCHITECT STAT TnI; Abbott Diagnostics) and results over a period of 3 months also had the same sample measured with a hs-cTnI assay (ARCHITECT STAT hsTnI; Abbott Diagnostics), with the result blinded to the treating physician. During the study, commercial QC materials and the same patient pool material were also measured with both the cTnI and hs-cTnI assays on 3 different platforms. As expected, the imprecision (CV) values of the results for the pools were greater for the cTnI assay than for the hs-cTnI assay (CV for the cTnI assay 12% for the ci16200#1 cTnI pool (n = 197; mean = 43.2 ng/L); 17% for the ci16200#1 cTnI pool (n = 197; mean = 0.032 μg/L) vs. 4.8% for the hs-cTnI pool (n = 147; mean = 41.0 ng/L). After completion of the study, medical records were reviewed for all patient encounters in the ED (i.e., a new encounter of the same patient would be recorded if troponin measurements in the ED were 3 days apart) to ascertain if death occurred in the ED or after admission to the hospital from the ED (i.e., hospital death). For the present study, we carried out nonparametric analyses with the Mann–Whitney U-test (StatsDirect v.2.7.9; StatsDirect Ltd.) and ROC curve analyses [95% CIs calculated via the binomial exact method (MedCalc v.1.12; MedCalc Software)] with the ED-presentation cTnI and hs-cTnI results only for the ED encounters for which an ED disposition was recorded (i.e., 61 patient visits were not assessed because the patients left after receiving medical advice, after being seen, or after being triaged but not seen, or because the field was missing).

cTnI was measured at presentation for 3206 ED visits, with hs-cTnI detectable [limit of detection (LoD) > 1.2 ng/L] (2) in 93.3% (95% CI, 92.6%–94.0%) of EDTA-containing plasma samples [2552 samples (49%) from female patients]. The female population was older than the male population: a median of 73 years (interquartile range (IQR), 58–83 years) for females and 67 years (IQR, 54–79 years) for males (P = 0.001). There was no difference in the prevalence of hospital death between females (4.6%; 95% CI, 3.8%–5.5%) and males (5.2%; 95% CI, 4.5%–6.2%; P = 0.305), nor was there a difference between the sexes in the performance of the cTnI assay, as assessed by ROC curve analysis for death [area under the ROC curve (AUC) for females, 0.766 (95% CI, 0.749–0.782); AUC for males, 0.741 (95% CI, 0.724–0.757)]. With respect to the hs-cTnI assay, ROC curve analysis yielded a significantly higher AUC for women (0.793; 95% CI, 0.777–0.809) than for men (0.748; 95% CI, 0.731–0.764) (Fig. 1). Further analysis revealed no difference in hs-cTnI concentration between females with a hospital death (median, 35 ng/L; IQR, 12–92 ng/L) and males with a hospital death (median, 33 ng/L; IQR, 14–102 ng/L; P = 0.795). hs-cTnI concentrations in patients without the outcome, however, were significantly lower in the female population (median, 6 ng/L; IQR,

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1 Nonstandard abbreviations: hs-cTnT, high-sensitivity cardiac troponin T (assay); hs-cTnI, high-sensitivity cardiac troponin I (assay); ED, emergency department; LoD, limit of detection; IQR, interquartile range; AUC, area under the ROC curve.
Lowest reported hs-cTnI 99th (adult male) cTnI assay, with a cutoff of 69% (81 of 117 patients) with the cTnI assay, compared with only (110 of 117 patients) with the hs-cTnI assay, achieved a CV value of 2%–48%; CV, 9%)

The lowest reported 99th percentile that represents a 25% increase (95% CI, 2%–48%; P = 0.036) in the rate of predicting death when the hs-cTnI assay is used at this cutoff, compared with use of the LoD for the current sensitive cTnI assay. Lowering the hs-cTnI cutoff to a concentration corresponding to a 20% CV (2.0 ng/L) (5) or the LoD (1.2 ng/L) identified all 117 deaths in the female population.

These findings suggest that the increased analytical sensitivity of the hs-cTnI assay may be especially useful for the female population. A limitation to the present analysis is the limited clinical information and the incomplete information about cause of death; however, the large observational study assessing hs-cTnI performance in predicting death in the female population at ED presentation is noteworthy. Another limitation to consider is that this cohort of patients who underwent troponin testing represents approximately one-third of all ED visits (n = 15,282) during this period and most likely represents a higher-risk cohort, with >85% of the deaths occurring after admission to the hospital. Additional studies are nevertheless required to assess which cutoff is the most appropriate for the female population; however, these data are the first to demonstrate the added benefit of high-sensitivity assays for the female population.

**References**


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