Measurement of High-Sensitivity Troponin T in Noncardiac Medical Intensive Care Unit Patients

Correlation to Mortality and Length of Stay

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ABSTRACT

Objectives: *To assess the frequency, magnitude, and prognostic significance of elevations in cardiac troponin T in noncardiac critically ill patients, including elevations at levels below the limit of detection of traditional assays.*

Methods: *Using a high-sensitivity assay, we measured troponin T (high-sensitivity troponin T [hsTnT]) in 451 unique patients within 12 hours of their admission to a noncardiac medical intensive care unit. Outcomes of patients, grouped by hsTnT level, were compared.*

Results: *Overall, 98% of the study patients had detectable levels of hsTnT (>3 ng/L), and 33% had levels above the diagnostic cutoff of a traditional fourth-generation cardiac troponin T assay. Patient groups with higher hsTnT levels had markedly higher rates of in-hospital mortality (P < .001) and longer stays in the hospital and intensive care unit (P < .01).*

Conclusions: *In noncardiac critically ill patients, cardiac troponin T elevations are common but often at levels undetectable by traditional assays. hsTnT elevations predict a more complex clinical course and an increased risk of death.*

Cardiac troponins are the most clinically useful biomarker of myocardial necrosis.[1,2] Release of cardiac troponins into the circulation is thought to result primarily or exclusively from irreversible myocyte death.[3] The general consensus regarding the upper limit of normal for troponin is the value representing the 99th percentile of a reference population of healthy individuals.[1-3] A diagnosis of acute myocardial infarction (AMI) can be made on the basis of an elevated troponin level (using the 99th percentile criterion) in combination with any one of several clinical or electrocardiographic findings or the use of serial troponin values showing the typical rise and fall pattern of troponin in the appropriate clinical context.[4]

Although conventional troponin assays cannot generally deliver the precision necessary to reliably measure at the 99th percentile, recently developed "high-sensitivity" troponin assays have become available and are used clinically in many developed countries.[3] Compared with earlier troponin assays, high-sensitivity troponin assays may be clinically advantageous, particularly with respect to early detection of myocardial infarction.[5-10] However, a notable caveat with respect to the use of high-sensitivity troponin assays is the clear expectation that with heightened sensitivity for myocardial necrosis comes a well-recognized reduction in specificity for AMI. Indeed, numerous conditions leading to myocardial injury may now be detected.

Previous reports using non–high-sensitivity assays have shown that critically ill patients may have elevated levels of cardiac troponins, even in the absence of overt cardiac pathology.[11-18] Although not specific for AMI, such prevalent troponin elevations are prognostically important.[11-14,16,17] However, these data are based nearly entirely on troponin measurements using previous-generation, less-sensitive

assays. Accordingly, the frequency, magnitude, and significance of cardiac troponin elevations using high-sensitivity assays have not been described. In this study, we evaluated high-sensitivity troponin T (hsTnT) levels in noncardiac patients in the medical intensive care unit (MICU) to better elucidate the frequency and significance of elevated hsTnT in critically ill patients.

Materials and Methods

Setting and Patient Population

The institutional review board approved all study procedures. This study was conducted at the Massachusetts General Hospital, a large (approximately 1,000-bed) tertiary care academic medical center in Boston, MA. We evaluated 451 unique patients from consecutive MICU admissions occurring over approximately 5 months. All patients admitted to the MICU during our study period were automatically enrolled. Patients were only excluded if they had already been evaluated during a previous MICU admission earlier in the study period. Patients admitted to MICU multiple times during the study period were only evaluated based on their hsTnT level on their first MICU admission and on outcome metrics associated with the hospital admission during which this first MICU admission occurred.

Sample Collection and Processing

Excess plasma samples (potassium ethylenediaminetetraacetic acid Vacutainer tubes [BD, Franklin Lakes, NJ]) collected within 12 hours of admission to the MICU were retrieved from the clinical laboratory and stored at –80°C for approximately 1.5 to 2 years while awaiting testing. hsTnT has been shown to be quite stable when stored at –70°C.[19] All specimens were tested together in batch mode using the Roche hsTnT troponin assay on a Roche/COBAS e411 platform (Roche Diagnostics, Indianapolis, IN). Detailed descriptions of this assay have been previously published.[10] Briefly, in accordance with the definition of high sensitivity, this assay has been demonstrated to achieve a coefficient of variation (CV) of 10% at 13 ng/L, which is below the upper reference limit of 14 ng/L (99th percentile of a healthy population).[10] At hsTnT concentrations higher than 30 ng/L, the CV of this assay has been demonstrated to be less than 5%. The limit of the blank of this assay is 3 ng/L, while the range from the limit of the blank to the 99th percentile is defined as 3 to 14 ng/L.[10] The approximate hsTnT equivalent to the upper limit of 30 ng/L on the fourth-generation cardiac troponin T assay is 50 ng/L.[10]

Patient Classification

All patients were classified into one of four functional categories based on their hsTnT level. The first category represents patients with undetectable hsTnT levels (<3 ng/L). The second category includes patients with hsTnT levels that are detectable but below the 99th percentile of a healthy reference population (≥3 but <14 ng/L). The third group includes patients with hsTnT concentrations of 14 ng/L or higher but less than 50 ng/L. The final group includes patients with hsTnT levels of 50 ng/L or higher (the equivalent of the upper reference limit on the fourth-generation assay). As noted, the assay CV is expected to be less than 5% for the final category, less than 10% for the third category, and more than 10% for most values within the second category.

Data Definition, Extraction, and Processing

Data were compiled and processed using Microsoft Excel 2003 and Microsoft Access 2003 software (Microsoft, Redmond, WA). The number of intensive care unit (ICU) days associated with each troponin result was taken as the number of days spent in the ICU during the current hospital admission, regardless of whether these days were distributed over multiple ICU admissions. Likewise, hospital days were calculated as total number of days per hospital admission. Classification of primary and secondary diagnoses was based primarily on coded diagnoses from the hospital electronic medical records, with chart review in selected cases. Three patients (<1%) were excluded from our analysis because of either data ambiguity (two cases) or insufficient specimen volume (one case).

Data Analysis and Statistics

Statistical analyses were performed primarily using the *R* statistical scripting language (www.R-project.org) with limited use of Microsoft Excel. Binomial confidence intervals (CIs) were calculated using the Wilson method as implemented in the *R*-binom package.[20] Jonckheere-Terpstra tests were performed using the *R* Clinfun package,[21] and Cochran-Armitage tests were performed using the *R* COIN package.[22] Graphs were generated using *R* and Microsoft Excel.

Results

Our final analysis included 448 patients consisting of 254 men and 194 women. They ranged in age from 20 to 96 years, with a median age of 62 years (interquartile range, 52-72 years).

Frequency and Magnitude of Troponin Elevation

Of the 448 cases, 439 (98%; 95% CI, 96%-99%) had detectable levels of hsTnT (>3 ng/L). The median troponin level was 33 ng/L. We classified patients by troponin level into four functional groups as described in the methods and shown in ❚Table 1❚. The majority (75%) of patients had hsTnT

levels above the 99th percentile of normal, and 33% had levels of 50 ng/L or higher.

Variation of hsTnT with Age and Gender

To test an association between hsTnT and age, we grouped patients by age into quartiles ❚Table 2❚. As shown, median hsTnT varied considerably with age, from 15 ng/L in patients aged 51 years or younger to 44 ng/L in those aged 73 years or older. This trend of increasing hsTnT with age was highly significant ($P < .001$, Jonckheere-Terpstra test, two-tailed). Likewise, male patients had a median hsTnT of 34 ng/L compared with 27 ng/L for female patients. However, the difference between male and female patients only trended toward statistical significance ($P = .17$, Mann Whitney U test, two-tailed).

Cardiac Troponin Levels Correlate with ICU and Hospital Length of Stay

❚Figure 1❚ shows the hospital length of stay and number of days spent in the ICU during the current admission grouped

❚Table 2❚
Association Between Age and hsTnT

| Age Range, y	No.	Median hsTnT (IQR), ng/L
≤51	112	15 (6-39)
52-62	113	27 (11-65)
63-72	115	37 (19-84)
≥73	108	44 (25-77)

hsTnT, high-sensitivity troponin T; IQR, interquartile range.

by hsTnT level. As shown (Figure 1A), median length of hospital stay ranged from 5 days in patients with hsTnT levels below detection (<3 ng/L) to 11 days in patients with hsTnT levels of 50 ng/L or higher. This trend of increasing length of stay with increased hsTnT (by hsTnT group) was statistically significant ($P < .01$, Jonckheere-Terpstra test, two-tailed). Because hospital stay ends at patient death, the data may be biased by inpatient mortality. Accordingly, we reanalyzed the length of stay by hsTnT group for only those patients who

❚Table 1❚
Classification of Patients by Functional hsTnT Level and Frequency of hsTnT Elevations

Functional Significance of Group	hsTnT, ng/L	No. of Patients	Percentage of Patients (95% CI)
Below the limit of the blank on the hsTnT assay	<3	9	2 (1-4)
Detectable on the hsTnT assay but below the 99th percentile of a healthy reference population (3-14 ng/L)	3-<14	105	23 (20-28)
Above the 99th percentile but below the upper reference limit at our hospital using a 4th-generation cardiac troponin T assay	14-<50	184	41 (37-46)
Above the reference limit on our hospital's 4th-generation cardiac troponin T assay	≥50	150	33 (29-38)

CI, confidence interval; hsTnT, high-sensitivity troponin T.
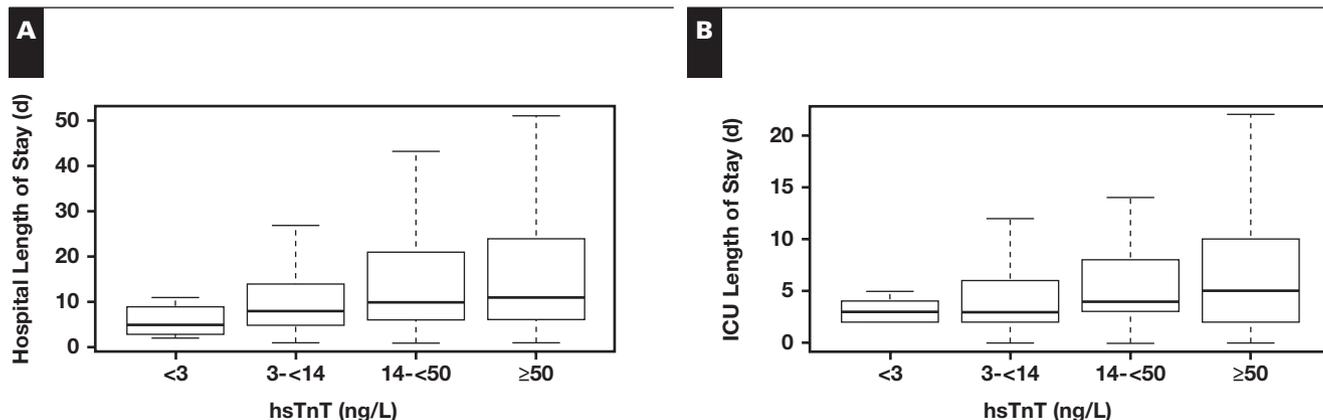
❚Figure 1❚ Association between high-sensitivity troponin T (hsTnT) level and hospital or intensive care unit (ICU) length of stay. Box plots show the association between hospital length of stay (**A**) or ICU length of stay (during current admission, **B**) and hsTnT level, with patients grouped by hsTnT into four different functional categories as defined in the "Materials and Methods" section and Table 1. Dark horizontal lines show the median number of days, boxes represent interquartile ranges (middle 50%), and whiskers represent the range (excluding those values that lie more than 1.5 times the interquartile range from the outside of each box).

were alive at discharge (although mean and median lengths of stay were still more in patients who died). In the patients who lived, median length of stay was 5, 9, 10, and 12 days for patients with hsTnT levels of less than 3 ng/L, 3 to less than 14 ng/L, 14 to less than 50 ng/L, and 50 ng/L or more, respectively. This increase was again statistically significant ($P < .001$, Jonckheere-Terpstra test, two-tailed).

Similarly, median number of days each patient spent in the ICU during the current admission also increased with increasing hsTnT, from a median of 3 days for patients with hsTnT less than 3 ng/L or 3 to less than 14 ng/L to 5 days for patients with an hsTnT level of 50 ng/L or more (Figure 1B). The increase in ICU days based on hsTnT group was statistically significant ($P < .01$, Jonckheere-Terpstra test, two-tailed). Analogous to hospital length of stay, ICU length of stay is affected by patient death. Therefore, we evaluated ICU length of stay subgrouped for the patients who lived. Median ICU days for patients who were alive at discharge was 3 days for patients with hsTnT less than 3 ng/L or 3 to less than 14 ng/L and 4 days in the groups of patients with hsTnT levels of 14 to less than 50 ng/L or 50 ng/L or more ($P < .001$, Jonckheere-Terpstra test, two-tailed).

Cardiac Troponin Levels Predict Risk of Death

❚Figure 2❚ depicts the number of patients who were alive at discharge from the hospital and those who died before discharge grouped by troponin level (using the groups defined in Table 1.) These data indicate that mortality increased significantly with hsTnT levels, ranging from 0% (0-30%, 95% CI) in patients with undetectable hsTnT levels to 31% (24%-39%,
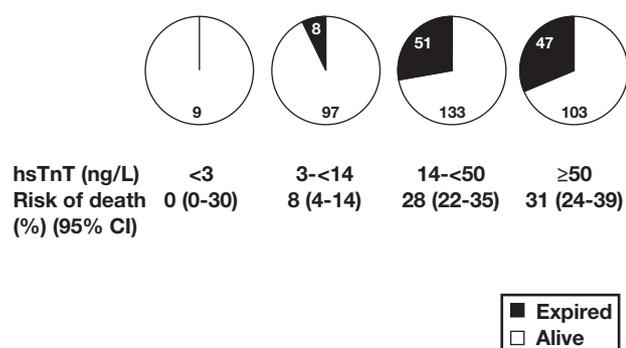

hsTnT (ng/L)	<3	3-<14	14-<50	≥50
Risk of death (%) (95% CI)	0 (0-30)	8 (4-14)	28 (22-35)	31 (24-39)

■ Expired
□ Alive

❚Figure 2❚ Association between high-sensitivity troponin T (hsTnT) level and in-hospital mortality. The relationship between in-hospital mortality (on the current admission) and hsTnT level is shown, with patients grouped by hsTnT into different functional categories as defined in the "Materials and Methods" section and Table 1. Risk of death represents the percentage of patients in each group who died before hospital discharge. Pie charts illustrate the number of patients in each hsTnT group who were alive at discharge and the number who died in the hospital. CI, confidence interval.

95% CI) in patients with levels of 50 ng/L or more ($P < .001$, Cochran-Armitage test).

Evaluation of Patients Without Diagnosed Cardiac Pathology

This study was designed to evaluate patients without a primary cardiac diagnosis because it included only patients in the MICU. Nearly all patients with critical cardiac illness at our hospital are admitted to a separate cardiac intensive care unit. Nonetheless, to confirm that patients did not have primary cardiac pathology, we retrospectively reviewed patient medical records to determine primary and secondary diagnosis. We found that only 10 patients (2%) had a primary cardiac diagnosis (seven had heart failure and three had other cardiac pathology, but none had AMI). Nonetheless, nearly all patients had multiple medical problems; of the 438 patients without a cardiac primary diagnosis, 202 (46%) had at least one cardiac-related secondary diagnosis. Thus, to help exclude the possibility of confounding from patients with secondary cardiac pathology, we looked at survival and length of stay for the 236 patients without primary or secondary cardiac diagnoses ❚Table 3❚, which was consistent for the group as a whole in terms of hsTnT associated with mortality, hospital length of stay, and ICU length of stay.

Discussion

In this study, we showed that cardiac troponin T is elevated above the limit of the blank in most MICU patients (98%) within 12 hours of admission when measured using a high-sensitivity assay. In 75% of patients the elevation was above the 99th percentile hsTnT cutoff, and in 33% the level was above the concentration that is equivalent to the cutoff for AMI with our current non–high-sensitivity method. Elevations of hsTnT were associated with increased mortality and with hospital and ICU length of stay. Furthermore, the mortality rate increased progressively with increasing hsTnT level. The mortality rate for patients with an undetectable hsTnT was 0%, whereas those with an hsTnT of 50 ng/L or more had a mortality rate of 31%.

As would be expected, our current fourth-generation troponin assay would have reported abnormal results in one-third of the 439 patients with detectable levels of hsTnT found on the high-sensitivity assay. This difference between assays is of substantial clinical relevance, as we demonstrate that even troponin elevations too small to be detected with the fourth-generation assay predict considerably poorer prognosis and increased length of stay. These findings expand on similar findings of prior studies that show that cardiac troponin elevations detected on traditional troponin assays are common in critically ill patients and are associated with poorer

■Table 3■
Frequency of hsTnT Elevations and Associated Mortality and Length of Stay After Excluding Patients With Primary or Secondary Cardiac Diagnoses

Variable	hsTnT Categorization				
	<3 ng/L	3-<14 ng/L	14-<50 ng/L	≥50 ng/L	*P*
Patients in category who died	0	5	25	19	
Total no. of patients in category	8	69	96	63	
% of Patients in category who died	0	7	26	30	<.01[a]
Median hospital length of stay for patients in category, d	6	8	12	12	<.001[b]
Median ICU length of stay for patients in category, d	2.5	3	4	6	<.001[b]

hsTnT, high-sensitivity troponin T; ICU, medical intensive care unit.
[a] Cochran-Armitage test.
[b] Jonckheere-Terpstra test, two-tailed.

prognosis.[11-16] In particular, our findings show that even small elevations in cardiac troponin T below the levels quantifiable by non–high-sensitivity cardiac troponin T assays have prognostic significance.

Earlier studies of hsTnT in acute chest pain evaluation suggest that the enhanced sensitivity of hsTnT assays is worth the trade-off of modest reduction in specificity among a medically complex group of subjects without manifest cardiac diagnoses. However, our results indicate that a substantial percentage of patients have significant myocardial necrosis in the absence of obvious acute coronary syndrome. These results are not entirely unexpected; prior studies using non-hsTnT assays have shown that critically ill patients frequently have troponin elevations.[11-18]

Prior studies have focused on conventional cardiac troponin T methods, but to our knowledge this is the first study to demonstrate the frequency and prognostic significance of hsTnT elevations in critically ill patients without primary cardiac diagnoses or clinical suspicion for AMI. The finding that measurable hsTnT was present in 98% of subjects (which contrasts with the expected ~70% in community-based subjects), along with substantial percentages above the 99th percentile for a normal population, indicates that the hsTnT assay detects a substantial amount of cardiac injury that was previously unsuspected.

The implications of our results are significant, but the clinical applications of these findings demand further research and consideration. For example, our results suggest that clinicians should be aware of the highly prevalent nature of cardiac injury in critically ill patients, including those not suspected to have AMI. The extent to which undiagnosed coronary artery disease is responsible for this cardiac injury is uncertain. However, prior studies have shown detectable hsTnT in 25%[23] to more than 50%[24] of individuals in a general community-based population, with hsTnT levels increasing among subgroups of patients with cardiac risk factors, electrocardiographic abnormalities, or other evidence of cardiac pathology.[23,24] hsTnT elevations above the limit of detection and above the 99th percentile are much more frequent in critically ill patients in our study than in these community-based populations. Nonetheless, given these community-based data, preexisting, undiagnosed coronary artery disease likely contributed to at least some of the hsTnT elevations observed in our study as well. Likewise, the therapeutic implications of an hsTnT elevation in a critically ill patient not suspected to have AMI is not well defined; however, individualizing care for such patients in an attempt to mitigate myocardial injury seems justifiable. Lastly, beyond its diagnostic potential, hsTnT may be useful for at least some critically ill patients as a predictor of prognosis, mortality, and length of stay.

The main limitation of this study is that it does not address whether the elevations in troponin serve as an independent predictor of mortality and length of stay after controlling for clinical condition and known clinical comorbidities. It is possible that troponin elevations simply serve as a marker of underlying illness that is of sufficient severity to result in prolonged hospitalization or death. We plan to address this consideration in a subsequent study. In addition, this study does not address the role of patient factors besides age and gender in influencing hsTnT level; patient factors including comorbidities and renal function may be addressed in subsequent studies. Regardless, hsTnT levels may prove useful as an objective and quantitative marker of illness severity and risk of poor outcomes. Another caveat is that our study only evaluated short-term outcomes. Finally, this study only addressed hsTnT levels on initial MICU admission; future studies evaluating changes in hsTnT levels over time in critically ill patients may also prove informative.

The findings of our study have important implications for future research. For example, additional research into the mechanistic basis for these troponin elevations may be informative in helping to better translate the findings of this study to clinical practice. Elucidating the mechanism of these elevations may also help improve our understanding of cardiac pathophysiology.

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