Use of High-Sensitivity Troponin Assays Predicts Mortality in Patients With Normal Conventional Troponin Assays on Admission — Insights From a Meta-Analysis

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ABSTRACT

Background: Use of high-sensitivity troponin (hs-Tn) assays can detect small levels of myocardial damage previously undetectable with conventional troponin (c-Tn) assays. However, prognostic utility of these hs-Tn assays in prediction of mortality remains unclear in the presence of nonelevated c-Tn levels on admission. A systematic review and meta-analysis was performed to assess mortality risk of patients with hs-Tn elevations in the setting of normal c-Tn levels.

Hypothesis: Patients with hs-Tn elevations with normal c-Tn levels on admission blood samples, drawn to rule out acute coronary syndrome (ACS), have a higher mortality risk than those without hs-Tn or c-Tn elevations.

Methods: A search was made of the PubMed, CENTRAL, EMBASE, CINAHL, EBSCO, and Web of Science databases. Studies evaluating patients with suspected ACS that reported mortality rates for those with elevated hs-Tn levels but normal c-Tn levels on admission were included. A random-effects model was used to pool event rates, and data were reported in odds ratios (95% confidence interval).

Results: Four studies (N = 2033, mean age 64–75 years, 49%–70% male) revealed that nearly 32% of suspected ACS patients with normal c-Tn levels on admission had elevated hs-Tn levels. Elevated hs-Tn levels conferred a significantly higher risk of all-cause mortality vs normal hs-Tn levels (odds ratio: 4.35, 95% confidence interval: 2.81–6.73, $P < 0.01$), with negligible heterogeneity ($I^2 = 0\%$).

Conclusions: Elevation of hs-Tn levels predicted a higher risk of mortality in patients with suspected ACS and may aid in the early identification of higher-risk patients in this setting. Future studies are needed to investigate further optimal management strategies.

Introduction

Cardiac troponin (Tn) is the current biomarker of choice in the diagnosis and risk stratification of patients with

suspected acute coronary syndrome (ACS).^{1,2} The latest generation of high-sensitivity troponin assays (hs-Tn) can improve the early diagnosis of acute myocardial infarction (MI) due to its high accuracy at lowered thresholds for detecting myocardial necrosis as compared with the conventional Tn assays (c-Tn).^{3,4} Although the improved diagnostic performance of hs-Tn over c-Tn has been established in several studies,^{5,6} the prognostic utility and the clinical relevance of detecting small levels of myocardial damage previously undetectable with c-Tn assays remain controversial. Available studies^{7,8} are limited by sample size to consistently show a significant impact of using hs-Tn instead of c-Tn assays in terms of clinical outcomes.

Hence, we performed a meta-analysis and systematic review of the available literature to determine the prognostic value of elevated hs-Tn levels in patients with suspected ACS and normal c-Tn levels on admission.

Methods

Data Sources and Searches

This review was carried out per Cochrane metrics⁸ and reported in accordance with the Meta-analysis

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Figure 1. Flow diagram of the search strategy. Abbreviations: cTrop, conventional troponin levels; hsTrop, high-sensitivity troponin levels.

of Observational Studies in Epidemiology (MOOSE) guidelines for systematic reviews and meta-analyses of observational studies.⁹ A comprehensive search of the Medline, EMBASE, Cochrane CENTRAL, CINAHL, EBSCO, and Web of Science databases from January 1, 1966, to December 15, 2012, was carried out to identify published studies that met our study-selection criteria. Reference lists of appropriate review articles and of the original retrieved studies were searched to identify studies potentially missed by the database searches (Figure 1).

Study Selection

Two authors (SC and JK) reviewed titles, abstracts, and full-text articles. Any discrepancy about study inclusion was resolved by discussion among all authors. Inclusion criteria for the studies were (1) adult population admitted for suspected ACS; (2) published in English language; (3) had both hs-Tn and c-Tn levels drawn on admission; (4) the hs-Tn assay used met standard guideline definition (ie, detection threshold was below the upper reference limit of normal for >99th percentile of the healthy population with a <10% coefficient of variation at the 99th percentile limit¹; and (5) mortality data were available for ≥30 days of follow-up.

Participants

Our population of interest was adults admitted for clinically suspected ACS (patients with retrosternal discomfort/chest pain/equivalent clinical features) with normal c-Tn levels on admission, who had hs-Tn levels drawn at the same time as well.

Data Extraction and Quality Assessment

Data were extracted independently by 2 authors (S.C., J.K.). When multiple publications were available from a single cohort, we extracted data from the publication that provided the largest sample size to maximize power. We formally assessed the quality of the studies included in the review, using the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria for studies that report diagnostic test results.¹⁰ Exact numbers of events were extracted, and in studies where the exact number of events was not available, exact values were calculated from percentages and rounded off to the next-highest integer.

Statistical Analysis

Among the study population with normal c-Tn levels, we pooled the studies to compare the mortality risk at 30 days or longer between patients with elevated vs normal hs-Tn levels. Event rates were pooled using a random effects model (DerSimonian and Laird) to obtain a conservative estimate that accounts for potential heterogeneity between studies, and the results were reported as odds ratio (OR) and 95% confidence interval (CI).

Potential publication bias was assessed with the Egger test.¹¹ Sensitivity analyses were performed by calculating the pooled estimate adding each individual study at a time, to evaluate if a single study contributed significantly to the overall outcome.

Given the variability in the length of follow-up between the trials, we also conducted adjusted analyses that accounted for differential length of follow-up. Thus, we calculated patient-years of follow-up for each study by multiplying the study sample size with the full duration of follow-up of the study to obtain event rates.¹² We considered rates, rather than number of events, because they incorporate the duration of the studies, which was variable. Rate ratios were then estimated from the event rates and the accompanying 95% CIs, assuming a constant rate of events for the individual studies. Analyses were carried out using Review Manager (RevMan) v5.1 in accordance with the *Cochrane Handbook for Systematic Reviews*.⁸

Results

We included 4 studies (N = 2033) of suspected ACS patients with normal c-Tn levels on admission^{8,13,14} or within 48 hours of admission¹⁵ that satisfied the inclusion criteria (Table 1). All included reports met QUADAS-2 criteria for quality of diagnostic test studies (see Supporting Table in the online version of this article). The mean age of the study population ranged from 64 to 75 years, 50% to 70% of which were male, with a range of follow-up of 1 month to 2 years (total = 2636 person-years of follow-up). In this study population, 642 (31.6%) patients had elevated hs-Tn levels and 1391 patients had normal hs-Tn levels on admission. The mortality rate of the elevated hs-Tn cohort was 9.7%, whereas the mortality rate of the normal hs-Tn cohort was 2.5%. In addition to mortality, there was 1 study that reported rates of recurrent MI after discharge,¹³ and 1 additional study that reported combined rates of death and recurrent MI,¹⁵ all of which showed higher adverse-event rates for the elevated vs the nonelevated hs-Tn cohort (Table 2). The heterogeneity of

Table 1. Characteristics of Included Studies

Author	Year of Publication	Mean Age, y	Male, %	hs-Tn Assay Studied, ng/L			Limit of Detection for Assay
				99% URL	10% CV		
Hochholzer et al ¹³	2011	75	61	14	13		5
Lindahl et al ¹⁵	2010	69	58	14	13		3
Schreiber ⁷	2012	67	49.2	8	0.8		0.1
Weber et al ¹⁴	2011	64	69.6	14	13		1

Abbreviations: CV, coefficient of variation; hs-Tn, high-sensitivity troponin; NA, not available (in primary publication referenced); URL, upper reference limit.

these combined outcomes precluded further pooling of data beyond descriptive purposes.

Pooled analyses of these 4 studies^{8,13–15} showed that elevated hs-Tn levels in patients with normal c-Tn levels on admission were associated with a significantly higher risk of all-cause mortality (OR: 4.35, 95% CI: 2.81–6.73, $P < 0.01$; Figure 2) without evidence of significant heterogeneity ($I^2 = 0\%$), despite differential periods of follow-up. The Egger test showed no significant publication bias ($P = 0.42$). Sensitivity analyses including inspection of individual study weights in their contribution toward the overall pooled estimate failed to identify any single study as an outlier or significant contributor by itself (Figure 3). In the analysis adjusted for differential follow-up in the individual studies, we found the overall effect on mortality to be similar to our unadjusted analysis (rate ratio: 4.35, 95% CI: 1.85–10.23, $P < 0.01$).

Discussion

Although hs-Tn assays have been shown to be diagnostically superior to c-Tn assays^{16,17} and have been increasingly adopted in clinical practices, several head-to-head studies that compared the prognostic utility of c-Tn vs hs-Tn assays in the setting of ACS have yielded inconclusive results.^{8,15} Our current systematic review identified approximately 2000 patients (4 cohorts) that may fill this literature gap and showed that nearly one-third of the patients with clinically

suspected ACS and normal c-Tn levels on admission had elevated hs-Tn levels. Despite normal c-Tn levels on admission, elevated hs-Tn levels predicted a higher risk of mortality after hospital discharge in these patients, independent of the follow-up period, which ranged from 30 days to 2 years.

In a recent study of consecutive patients presenting to an emergency department (ED),¹⁸ hs-Tn elevation in the absence of elevated c-Tn was not an independent predictor of ED readmissions and mortality from all causes. Their study differed from ours in some significant aspects. First, theirs was an “all-comers” study of 2384 consecutive ED patients, whereas we restricted our focus to patients with clinically suspected ACS with normal c-Tn levels on admission who had hs-Tn levels drawn at the same time as well. Second, the baseline variables differed among the populations of the 2 studies. For example, although in the Hammerer-Lercher et al study¹⁸ the mean age for the whole study population was 60 years, the subgroup with chest pain (and, thus, most likely to have ACS) had a mean age of 55.7 years; whereas in our study, the overall mean age was 68.75 years—thus, by age itself, the population of our study was at higher risk of ACS. These differences indicate that our results should be considered to be pertinent to the population we studied (patients with clinically suspected ACS on admission) and may need further research before they could be attempted to be extrapolated to the general population.

Patients with suspected ACS and elevated Tn levels have worse clinical outcomes compared with their counterparts with nonelevated Tn levels, using either c-Tn^{19–21} or hs-Tn assays.¹⁷ Previous studies using the c-Tn assays have also suggested that the degree of Tn elevation independently correlates with infarct size and worse clinical outcomes.^{22,23} The caveat with the above literature is that at least some, if not the majority, utilize peak Tn levels as opposed to admission or <48-hour troponin levels in our study. Based on admission levels in the cohort of patients with suspected ACS, we demonstrated that even a small increase in hs-Tn levels, at a level that previously would have been undetectable or deemed normal by c-Tn assays, is associated with a >4-fold increase in the rate of death.

Prior studies utilizing c-Tn assays have shown that patients with Tn elevations are more likely to have more significant and complex coronary anatomy and thrombus

Table 2. Outcome and Follow-up Duration of Included Studies

Study	Follow-up Period, d	hs-Tn (+) and c-Tn (–)			hs-Tn (–) and c-Tn (–)		
		No. of Patients	Death	Adverse Events	No. of Patients	Death	Adverse Events
Hochholzer ¹³	720	207	12.9%	8%, recurrent MI	735	3.2%	3.0%, recurrent MI
Lindahl ¹⁵	360 for death; 30 for adverse events	231	10.4%	7.9%, recurrent MI and death	340	2.7%	2.3%, recurrent MI and death
Schreiber ⁷	30	24	4.17%	NA	167	0%	NA
Weber ¹⁴	180	180	7.2%	NA	149	2.0%	NA
Total	1290	642	9.7%	—	1391	2.5%	—

Abbreviations: c-Tn, conventional troponin levels; hs-Tn, high-sensitivity troponin levels; MI, myocardial infarction; NA, not available (in primary publication referenced).

Figure 2. Risk of mortality in patients with negative conventional but elevated high-sensitivity troponins on admission blood sample. Abbreviations: CI, confidence interval; cTrop, conventional troponin levels; hsTrop, high-sensitivity troponin levels; M-H, Mantel-Haenszel.

Figure 3. Sensitivity analysis of the risk of mortality in patients with negative conventional but elevated high-sensitivity troponins on admission using the cumulative meta-analysis method. Abbreviations: CI, confidence interval; DL, DerSimonian-Laird.

burden with resultant increased risk of recurrent MI, depressed left ventricular function, and death.^{24,25} Although this has not been shown using hs-Tn assays, we speculate a similar mechanism for worse prognostic outcomes in this population. This speculation is supported by 2 of the studies (Table 2) included in this analysis that showed significantly higher rates of recurrent MI in patients who have elevated hs-Tn levels.

In view of our results, there are certain clinical implications of the use of hs-Tn assays in the evaluation of patients with suspected ACS. One implication is a possible higher frequency of MI diagnosis, given the ability to detect minor myocardial damage at lower detection thresholds. Mills and colleagues showed a 47% increase in the diagnosis of MI using hs-Tn assays and a lower threshold for the diagnosis of MI.²⁶ In our study, we also showed that nearly one-third of suspected ACS patients with normal c-Tn levels on admission would have elevated hs-Tn levels that would meet the 99th-percentile threshold for MI diagnosis recommended by current guidelines.^{1,2} However, this increase in MI diagnosis may pose a challenge in management of these patients, given that the current risk-stratification algorithms and risk scores, such as the commonly used Global Registry of Acute Coronary Events (GRACE) and Thrombolysis in Myocardial Infarction (TIMI) risk scores,^{27,28} were developed using the c-Tn assays. Thus, it is not clear now how the hs-Tn assays would fit into or change these risk-classification schemes and affect management.

Another implication is the earlier detection of myocardial damage, which will affect triage decisions and influence choices for management. Patients with suspected ACS, in the absence of ischemic changes in electrocardiograms, are a particularly challenging group of patients from a diagnostic standpoint. With the utilization of hs-Tn assays, early identification of high risk will affect choices

for medical and invasive therapies. Potential benefits of early risk stratification with hs-Tn assays may include targeting early invasive treatment,^{29,30} utilization of early adjunctive medical therapy (eg, low-molecular-weight heparin, upstream IIb/IIIa inhibition),^{31–34} and decisions about early discharge. However, the optimal management of these patients with Tn elevations previously undetectable with older assays will need to be further studied.

Our study has limitations. First, most studies reported outcomes based on Tn (c-Tn and hs-Tn) levels at the time of admission; thus, we could not determine the change in the mortality risk if additional Tn levels were to be drawn and utilized. We also could not determine whether knowledge of hs-Tn levels by clinicians would have resulted in changes in clinical management that would have subsequently modified patients' outcomes. However, such changes in practice patterns and clinical outcomes have previously been noted when abnormal levels of hs-Tn were reported to clinicians, leading to more aggressive management strategies and improved clinical outcomes including mortality.³⁵ Given the observational nature of the included studies, the possibility of confounding and alternative explanations for our findings would exist and should be validated in future randomized studies that would also investigate potential management strategies. Finally, studies have distinct periods of follow-up; however, the lack of significant heterogeneity in our results and the consistency of our findings in the adjusted analysis support the robustness of the results.

Conclusion

Nearly one-third of suspected ACS patients with normal c-Tn levels on admission had elevated hs-Tn levels. Elevation of hs-Tn levels in these patients were associated with a

4-fold higher risk of all-cause mortality. Future studies are needed to investigate optimal management strategies for these higher-risk patients.

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