Patients discharged with elevated baseline high-sensitive cardiac troponin T from the emergency department

Christian Bjurmana*, Matteus Zywczykb, Soza Zangana, Sabin Salahuddinb, Martin Holzmannc,d, Tobias Carlsona and Ola Hammarstenb

aDepartment of Medicine, Sahlgrenska University Hospital at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; bDepartment of Clinical Chemistry and Transfusion Medicine, Sahlgrenska University Hospital at Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; cFunctional Area of Medicine, Karolinska University Hospital, Stockholm, Sweden; dDepartment of Internal Medicine, Solna, Karolinska Institutet, Stockholm, Sweden

ABSTRACT

Background: Elevated levels of high-sensitive cardiac troponin T (hs-cTnT) are linked to poor prognosis among emergency department (ED) patients.

Objective: Examine the effect of our ED risk assessment among patients with suspected acute coronary syndrome (ACS) and elevated baseline hs-cTnT levels.

Design: Observational cohort study of 16776 ED patients with chest pain or dyspnoea and a hs-cTnT sample analyzed at the time of the ED visit. Of these 1480 patients were sent home with elevated hs-cTnT levels (>14 ng/L).

Methods: Analysis of clinical and laboratory data from the local hospital and data from the National Board of Health and Welfare.

Results: Admitted patients had 11% and discharged patients had 1.2% 90-day mortality indicating effective risk assessment of patients with suspected ACS. However, if the suspected ACS patient presented with hs-cTnT between 14 and 22 ng/L, the 90-day mortality was 4.1% among discharged and 6.7% among admitted patients. Among discharged patients, an hs-cTnT level above 14 ng/L was a higher independent risk factor for 90-day mortality (HR 3.3, 95% CI 2.9–3.7, p < 0.001) than if the patient was triaged as a high-risk patient (HR 1.6, 95% CI 1.1–1.8, p < 0.001).

Conclusions: Our ED risk assessment was less effective among patients presenting with elevated hs-cTnT levels.

Introduction

Cardiac-specific troponins (cTn) are biomarkers that are primarily used when acute myocardial infarction (MI) is suspected (Thygesen et al. 2012). Several reports indicate that high-sensitive cTn (hs-cTn) assays and diagnostic cut-off points based on the 99th troponin percentile value in healthy patients improve diagnostic accuracy (Bandstein et al. 2014, Reichlin et al. 2015) and reduce hospital spending (Bjurman et al. 2017). However, the increased ability to exclude MI has been accompanied by an accumulation of patients presenting with hs-cTnT levels above the accepted cut-off point without MI (Hammarsten et al. 2012, Hammarsten et al. 2017) for which no consensus treatment exist.

It has been known for some time that elevated cTn levels are independent determinants of subsequent mortality and adverse outcomes among community dwellers (Ahmed et al. 2014), but even more so among patients in the emergency ward and hospitalized patients (Roos et al. 2017a). Patients with cTn elevations above the upper reference limit have a 5- to 10-fold higher risk of death or development of heart failure compared to patients without cTn elevations (Beatty et al. 2013, Roos et al. 2017a). The overall conclusion is that the prognosis among emergency department (ED) patients is highly cTn-level-dependent but the question is whether this risk is always included in the ED risk assessment.

One objective of ED risk assessment of patients with suspected ACS, such as chest pain, is to identify patients in need of admission and further intervention. Several reports indicate that this process is effective (Body et al. 2010, Body et al. 2014) and that patients sent home from the ED have a much better prognosis compared to patients that are admitted. Biomarkers like cTn and copeptin aids in this process, especially when the clinician suspicion of MI is moderate (Body et al. 2011, Maisel et al. 2013, Body et al. 2015). In this process, sometimes patients are sent home with elevated...
high-sensitive cardiac troponin T (hs-cTnT) levels (Roos et al. 2017b). However, since these patients have not been examined separately it is still unknown whether the ED risk assessment is capable of mitigating the elevated mortality linked to elevated hs-cTnT levels.

Here we have specifically examined patients discharged with hs-cTnT elevation according to the current cut-off point (14 ng/L) from the ED.

**Clinical significance**

1. Elevated levels of high-sensitive cardiac troponin T (hs-cTnT) are linked to a poor prognosis, especially among emergency department (ED) patients.

2. Here we found that patients with slight hs-cTnT elevation had similar 90-day mortality among discharged and admitted patients.

3. Apparently, the risk assessment routines need to be adjusted to accommodate the very high risk linked to slightly elevated hs-cTnT at the ED.

**Material and methods**

**Study design and populations**

Patients seeking healthcare at the EDs at Sahlgrenska University Hospital (SU/Sahlgrenska) with a chief complaint of chest pain or dyspnoea and with at least one hs-cTnT sample ordered from the ED between 1 February 2012 and 30 September 2015 were included in the study. The collection of data was similar to a previous study from our hospital (Bjurman et al. 2017). Cohort 2 specified in Bjurman et al. (2017) is an overlapping dataset from the same hospital where the hs-cTnT sampling frequency and examinations are given. Additional data on examinations and lab tests, not part of this publication, are listed in Supplemental Table 1. The hs-cTnT sampling frequency can be found in Supplementary Table 2. The baseline level of hs-cTnT was the only hs-cTnT level used in the analysis in this study except for the analysis of change in the hs-cTnT level where also the highest hs-cTnT level during the hospital stay was used (Supplementary Table 2).

All patients with chest pain were triaged according to the 5 levels of the RETTS-A triage algorithm, a triage tool that combines vital signs and 43 categorized symptoms, such as dyspnoea and diaphoresis to prioritize patients to different levels of attendance (Widgren and Jourak 2011). High-risk priority levels ‘Red’ and ‘Orange’ are classified as potentially life-threatening, requiring medical attention immediately or within 20 min. Priority level ‘Yellow’ is classified as not life-threatening but in need of medical attention within 120 min. For priority levels ‘Green’ and ‘Blue’, no maximum time for medical attention is given. The ED did not have any point of care cTn analysis in use during the study period and all cTn evaluations were done using the hs-cTnT assay from the central laboratory. Risk scores (Chapman et al. 2018) and coronary CT and triple rule as recommended by ESC latest guidelines (Collet et al. 2021) were not in place at the time of the study. Patients with NSTEMI were diagnosed at the discretion of the attending clinician by reviewing available clinical and laboratory data collected during the hospital stay as described in Supplementary material in Bjurman et al. (2017).

A characterization of ED patients with chest pain or dyspnoea from the same region has been published before (Bjurman et al. 2017). Study data containing diagnoses and interventions and for each admission were retrieved from the hospital’s administrative database, and from the National Board of Health and Welfare’s National Patient Register, with information on hospital stays (Ludvigsson et al. 2011). Information on hs-cTnT levels was retrieved from the hospital’s laboratory database. Data entered in the local hospital database are used to allocate funds within the hospital, thus adding an economic incentive for the departments to keep these records complete. Entry of order time and patient identity in the laboratory database is a part of the test ordering procedure and is done automatically. It is not possible to obtain a test result from the central lab without a complete registration.

Patients with ST-elevation MI (STEMI) were typically not triaged at the ED and therefore not included in the study. Patients with temporary ID numbers making identity uncertain were excluded but no other exclusion criteria were used. For instance, also the patients with non-ST-elevation MI (NSTEMI) or with a later diagnosis of unstable angina pectoris (diagnoses I214 or I219) were included. Final diagnoses according to the ED visit were available for all admitted patients. We did not find any NSTEMI diagnosis recorded among the discharged patients. However, the working diagnosis among the discharged patients was incomplete and therefore not used. Therefore all patients with NSTEMI diagnosis were among the admitted. Among all study subjects there were 779 with NSTEMI diagnosis (4.8%) and 725 NSTEMI diagnoses (10%) among patients with a baseline hs-cTnT >14 ng/L. Previous diagnoses were retrieved from the Swedish National Board of Health and Welfare’s National Patient Register.

Data reported to the National Board of Health and Welfare’s National Patient Register from 2010 were classified based on ICD codes. I50 was defined as heart failure, I48 as atrial fibrillation or flutter, J44 as COPD, and an ICD code beginning with ‘E1’ as diabetes. The diagnosis of ischaemic heart disease was not used in the study as we found that this diagnosis often was missing from the hospital records although the patient would qualify. The study was approved by the Ethics Committee at the University of Gothenburg, and the study protocol followed the ethical guidelines of the Declaration of Helsinki.

**Laboratory methods**

All laboratory analyses during the hospital stay were obtained from the local clinical chemistry database for each patient. Hs-cTnT was measured using the Elecsys® hs-cTnT immunoassay on a fully automated Modular® Analytics E170. The within-run, between-run and long-term coefficients of
variation (CV) have been published previously [15] and were <10%. During a few months of the study, Roche, the manufacturer of the hs-cTnT assay, made an error in the calibration routines, which resulted in a lower measured cTnT concentration, specifically around the 14 ng/L levels during the period January 2011 to May 2012. The local cTnT control based on pooled patient samples had a measured cTnT concentration of 15.8 ng/L in December 2009, when the hs-cTnT assay was introduced as a routine procedure. The same pooled sera gave a measured cTnT concentration of 12.1 ng/L in January 2011 and 17.9 ng/L after the introduction of the appropriate manufacturing routines at Roche in May 2012 (Hammarsten et al. 2013). After May 2012, we did not observe any significant drift of the hs-cTnT assay throughout the rest of the study period. The overall admission frequency was unchanged before and after May 2012 (55% vs 53%, p = 0.24) and the mortality among admitted and discharged at different baseline hs-cTnT levels remained unchanged if data before the recalibration were excluded (Supplementary Table 3). In addition, the linear correlation between hs-cTnT levels and mortality indicates that the difference in mortality would be the same if a patient presented during the short calibration error period. We therefore decided to include all data during the period in the analysis as we did in a previous report of a similar dataset (Bjurman et al. 2017).

Hs-cTnT values above the limit of quantification (LoQ) of 5 ng/L were reported to clinicians throughout the study. Risk scores were not used routinely by most physicians at the hospital and were therefore not included in the study protocol. The attending clinician made all the decisions about the number and the timing of the hs-cTnT sampling, based on clinical need. MDRD eGFR was calculated using the modified MDRD equation (Levey et al. 1999).

**Statistical analyses and calculations**

Multivariate Cox regression analyses for factors known to result in elevation of hs-cTnT levels and generally available in all patients were used to evaluate associations between total mortality (until 31 December 2015) and independent variables, presented in Table 4. Hazard ratios (HR) with 95% confidence intervals (CIs) were collected from these analyses. Medians were compared using median tests and means using independent samples t-tests. Dichotomous values were compared using exact tests with MonteCarlo estimates. Statistical analyses were performed using SPSS version 24. The moving window was calculated using hs-cTnT levels sorted in descending order and forming hs-cTnT ranges (windows) that contained 30 deaths within 90 days of the ED visit for discharged patients and 100 deaths within 90 days for patients who were admitted. In each hs-cTnT-level-window, the median hs-cTnT level and 90-day mortality were calculated. The use of a specific number of deaths within the hs-cTnT ranges resulted in a more stable trend compared with other ways to determine the hs-cTnT ranges in the moving window analysis. For discharged patients, median hs-cTnT levels within 7–37 ng/L contained enough deaths and patients to allow analysis. For admitted patients, the median hs-cTnT levels within 8–407 ng/L contained enough deaths and patients to allow analysis (Supplementary Figure 1). The trend was approximately linear for hs-cTnT levels between 6–22 ng/L for both discharged ($R^2 = 0.98$) and admitted ($R^2 = 0.99$). Linear regression was used to calculate 95% CIs within the linear range, using Medcalc 14, and plotted (Figure 1). All probabilities were used to two-tailed, and p-values <0.05 were regarded as significant.

**Results**

**Effect of the emergency department risk assessment on the study cohort**

Patients with suspected acute coronary syndrome (ACS) were identified based on a primary complaint of chest pain or dyspnea and at least one hs-cTnT analyzed at the time of the visit to our ED. As expected, compared with patients who were admitted ($n = 8870$), discharged patients ($n = 7906$) were younger, had lower hs-cTnT levels, and fewer comorbidities (Table 1). Compared with admitted patients, discharged patients had only one-tenth of the 90-day mortality (1.2% vs 11%), indicating an overall effective ED triage (Table 2, Figure 2(A)). The efficiency of the ED triage was similar when patients with suspected ACS with different risks, based on age and lactate levels (Bou Chebl et al. 2017), were compared (Table 2). Among discharged patients in our study, any level detectable of hs-cTnT (>5 ng/L) resulted in increased 90-day mortality.

**Effect of the emergency department triage on patients with elevated baseline hs-cTnT levels**

In the study cohort, we identified 7237 patients (43%) with a baseline hs-cTnT level above 14 ng/L, the cut-off point used...
for the hs-cTnT analysis in the study cohort (Table 3). Among these, 1480 patients were discharged from the ED. An hs-cTnT level above 14 ng/L was the strongest risk factor for the 90-day mortality among discharged patients (HR 4.4, 95% CI 3.5–5.4, \( p < 0.001 \)) and a stronger risk factor compared with the triage level (HR 1.2; 95% CI 1.1–1.6, \( p = 0.003 \)), also after adjustment for factors known to increase hs-cTnT levels (Table 4) (Thygesen et al. 2019). As expected, the baseline hs-cTnT level was lower among discharged patients. The baseline hs-cTnT level had a linear correlation with the 90-day mortality in both admitted and discharged patients with the range of 6–22 ng/L (Figure 1) but levelled out at higher levels (Supplementary Figure 1).

The difference in 90-day mortality between discharged and admitted patients was 10-fold among all patients (1.2% vs 11%), 3-fold among patients with a baseline hs-cTnT > 14 ng/L (4.8% vs 15%) and only 1.6-fold (4.1% vs 6.7%) among patients with a baseline hs-cTnT level between 6–22 ng/L (Table 5, Figure 2).

**Discussion**

We conclude that our medical ED risk assessment was less effective if the patient with suspected ACS presented with slightly elevated hs-cTnT levels. This observation points to a potential problem with clinical routines when hs-cTnT levels are elevated.

One factor that may influence how we handle patients with hs-cTnT elevations is that these patients are often old and have several comorbidities, like heart failure, kidney disease, lung disease or cancer (Mair et al. 2018a), where many emergency physicians often are of the opinion that an elevated hs-cTnT level adds little to the overall prognostic evaluation which is not consistent with current knowledge (Roos et al. 2017b). In addition, patients with hs-cTnT elevations are often admitted to overcome an acute situation, such as worsening of heart failure, infection or exacerbation of lung disease. The underlying condition that results in a stable hs-cTnT elevation is often not targeted during the admission, in part, because we do not know the pathophysiological mechanisms behind stable hs-cTnT elevations (Hammarsten et al. 2018, Mair et al. 2018b).

However, recent studies show that the risk associated with hs-cTnT elevations has been underestimated in population studies. Compared to the general population, the risk for death at a given hs-cTnT level is much higher in hospitalized patients, the group that is most frequently subjected to hs-cTnT sampling (Roos et al. 2017a). Among hospitalized patients with chest pain but no MI or other acute conditions, any detectable level of hs-cTnT is associated with an increased risk of death and adverse cardiovascular outcomes. Mortality are close to ten-fold higher in patients with hs-cTnT levels around 50 ng/L, compared with similar patients with low hs-cTnT levels. However, minor elevations are also of importance. Already at an hs-cTnT level of 5–9 ng/L; that is, below the 99th upper reference value of 14 ng/L, there is a doubled risk of death after adjustment for confounders. The increased risk is even more pronounced among younger patients with hs-cTnT elevations (Roos et al. 2017a).

We find that patients with slight hs-cTnT elevation had similar 90-day mortality among discharged and admitted patients. This indicates that the ED process likely underestimates the prognostic implications of hs-cTnT elevations. Possibly, discharged patients with stable hs-cTnT elevations that is judged not to be due to MI or other acute conditions could be referred to a follow-up with hs-cTnT resampling a week or so after the initial ED visit as we have suggested in previous studies (Bjurman et al. 2013). For instance, we have shown that 95% of patients with MI have a 2-week hs-cTnT change exceeding 400%. Follow-up and resampling with a long-term hs-cTnT analysis could therefore complement the ED triage to exclude acute myocardial injury (Bjurman et al. 2013). In this respect, it is important to note that we only examined the level of the baseline hs-cTnT sample in this study. To exclude ongoing myocardial damage one must

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**Table 1. Characteristics of patients with chest pain or dyspnoea as the principal complaint in the emergency department, analyzed with hs-cTnT.**

| Male (%) | Discharged (n = 7906) | Admitted (n = 8870) | All (n = 16776) | p-Value |
| --- | --- | --- | --- | --- |
| Age (years) [median and interquartile range] | 62 (52–72) | 74 (63–83) | 68 (57–79) | < 0.001 |
| Laboratory data | 11.9 (40) | 68.8 (338) | 42 (249) | < 0.001 |
| hs-cTnT > 14 (%) | 19 | 43 | < 0.001 |
| MDRD eGFR (mL/min/1.73 m2) [median and interquartile range] | 84 (71–100) | 73 (53–92) | 79 (61–96) | < 0.001 |

**Table 2. 90-day mortality in relation to risk factors.**

| Outcome | Discharged | Admitted | Fold differencea |
| --- | --- | --- | --- |
| All | 1.2% | 11% | 9 |
| >65 years | 2.1% | 14% | 7 |
| <65 years | 0.6% | 3.2% | 5 |
| Lactate > 2.2 | 2.6% | 19% | 7 |
| Lactate < 2.2 | 1.0% | 8.2% | 8 |

*aAll differences \( p < 0.01 \).
resample and examine the short-term hs-cTnT change. In our dataset, this was only done in 62% of all patients with chest pain or dyspnoea. To provide a normal range of hs-cTnT change in discharged chest pain or dyspnoea patients we are currently investigating this group with a 2-week follow-up.

This study has several limitations. It was a service evaluation of retrospective data and therefore does not include information about smoking habits and some other important risk factors for coronary artery disease. Echocardiography was not part of the predischarge evaluation although it is recommended in suspected acute coronary syndrome by the European Society of Cardiology recommendations (Collet et al. 2021). The final diagnosis was not available for all patients that were discharged. In addition, there was a drift in the hs-cTnT assay calibration, resulting in an underestimation of the hs-cTnT levels, during four of the study months. The exact changes in assay performance during this time have been published (Hammarsten et al. 2013). It is unclear whether this affected the clinical judgement in some cases.

Figure 2. Kaplan–Meier plots of all patients (A), only patients with a baseline hs-cTnT level above 14 ng/L (B). Patients with a baseline hs-cTnT between 14 and 22 ng/L (C) was chosen to compare admitted and discharged patients with similar levels of hs-cTnT. In the comparisons in A and B, the median hs-cTnT was higher among admitted patients. Admitted patients are shown with solid lines and discharged patients with dotted lines.

Table 3. Characteristics of patients with chest pain or dyspnoea as the principal complaint in the emergency department, with hs-cTnT above 14 ng/L.

|                  | Discharged (n = 1480) | Admitted (n = 5757) | All (n = 7237) | p-Value |
|------------------|-----------------------|---------------------|---------------|--------|
| Male (%)         | 57                    | 57                  | 57            | 0.79   |
| Age (years) [median and interquartile range] | 77 (68–85)            | 78 (69–85)          | 78 (69–85)   | 1.0    |
| Laboratory data  |                       |                     |               |        |
| hs-cTnT (ng/L) [mean and SD] | 36 (88)              | 102 (416)           | 88 (374)     | <0.001 |
| hS-cTnT (ng/L) [median and interquartile range] | 22 (17–32)          | 34 (22–64)          | 30 (20–55)   | <0.001 |
| MDRD eGFR (mL/min/1.73 m²) [median and interquartile range] | 68 (51–89)          | 64 (46–84)          | 65 (47–85)   | <0.001 |
| Comorbidity      |                       |                     |               |        |
| COPD* (%)        | 5.4                   | 9.0                 | 8.3           | <0.001 |
| Diabetes* (%)    | 7.8                   | 6.3                 | 6.6           | 0.035  |
| Atrial fibrillation or atrial flutter* (%) | 11                    | 13                  | 12           | 0.10   |
| Heart failure* (%) | 8.8                  | 17                  | 15           | <0.001 |
| Outcome          |                       |                     |               |        |
| 90-day mortality (%) | 4.8                 | 15                  | 13           | <0.001 |
| Return to ED within 30 days (%) | 23                    | 16                  | 17           | <0.001 |
| Return to ED and admitted within 30 days (%) | 9.8                   | 14                  | 13           | <0.001 |

*Based on reported ICD codes from 1 January 2010.

Table 4. Hazard ratio for mortality after adjustment for factors known to elevate hs-cTnT levels in Cox regression.

| Cox regressions | Discharged | p-Value | Admitted | p-Value | All | p-Value |
|-----------------|------------|---------|----------|---------|-----|---------|
| Hs-cTnT (>14 vs ≤14 ng/L) | 4.4 (3.5–5.4) | <0.001 | 3.0 (2.6–3.4) | <0.001 | 4.0 (3.6–4.4) | <0.001 |
| Triage colour (red or orange vs others) | 1.2 (1.1–1.6) | 0.003 | 1.6 (1.5–1.8) | <0.001 | 1.8 (1.6–1.9) | <0.001 |
| Age (years)** | 1.6 (1.5–1.8) | <0.001 | 1.6 (1.6–1.7) | <0.001 | 1.7 (1.6–1.7) | <0.001 |
| MDRD eGFR (<60 vs ≥60 mL/min/1.73 m²) | 1.04 (0.84–1.3) | 0.73 | 1.3 (1.2–1.4) | <0.001 | 1.3 (1.2–1.4) | <0.001 |
| Sex (male vs female) | 1.4 (1.2–1.7) | <0.001 | 1.2 (1.1–1.3) | <0.001 | 1.2 (1.2–1.3) | <0.001 |

**Quartiles: <58 years; 58–68 years; 69–79 years; >79 years.
The local triage routines were not fully calibrated against the management of grey-zone patients proposed by 2020 ESC guidelines (Collet et al. 2021), or strategies that incorporate coronary CT or triple rule-out CT. Possibly this could have improved the poor outcome seen among discharged patients with hs-cTnT evaluations.

We only evaluated 90-day mortality that might not be representative for death due to preventable cardiovascular or other diseases. In addition, we did not have data on the cause of death.

In summary, we find that our ED risk assessment was less efficient when patients present with slight hs-cTnT elevations. Risk assessments at our ED may still be relevant regarding acute treatable conditions, but inadequate regarding chronic conditions. Possibly a structured follow-up for ED patients that present with slight hs-cTnT elevation should be developed.

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Ethical approval
The study was approved by the Ethics Committee at the University of Gothenburg, and the study protocol followed the ethical guidelines of the 1975 Declaration of Helsinki.

Author contributions
Christian Bjurman, Matteus Zywczyk, Max Petzold, Martin Holzmann, Soza Zangana and Ola Hammarsten have contributed significantly to the conception and design of the manuscript and the interpretation of data, to the drafting of the article, and to the revisions for important intellectual content and the final approval of the version to be published. Christian Bjurman, Matteus Zywczyk, Soza Zangana and Max Petzold have also worked on the acquisition and analysis of data.

Disclosure statement
No potential conflict of interest was reported by the author(s).

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Table 5. 90-day mortality in relation to baseline hs-cTnT level and admission (ng/L).

| hs-cTnT | Discharged | Admitted | Fold difference | p-Value |
|---------|------------|----------|-----------------|---------|
| <7.5    | 0.2%       | 1.6%     | 6.8             | <0.001  |
| 7.5–14  | 0.6%       | 4.0%     | 6.3             | <0.001  |
| >14–22  | 4.1%       | 6.7%     | 1.6             | 0.015   |
| >22     | 5.5%       | 18.5%    | 3.4             | <0.001  |

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