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Sensitivity of undetectable level of high-sensitivity troponin T at presentation in a large non-ST-segment elevation myocardial infarction cohort of early presenters

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ABSTRACT

Background: We aimed to evaluate the diagnostic sensitivity for myocardial infarction (MI) when using an undetectable level of high-sensitivity cardiac troponin T (hs-cTnT < 5 ng/L) at presentation combined with a non-ischemic electrocardiogram (ECG), to rule out MI in a non-ST-segment elevation MI (NSTEMI) cohort presenting ≤2 h from symptom onset. We also aimed to compare baseline characteristics and 30-day outcome in NSTEMI patients presenting with and without hs-cTnT < 5 ng/L.

Methods: All patients admitted to five centers in Sweden 2011–2015, after the introduction of hs-cTnT, who presented ≤2 h from symptom onset and received a final diagnosis of NSTEMI, were identified through the SWEDEHEART registry. These data and data of hs-cTnT levels were verified in the hospitals' medical records. The registry provided baseline and outcome data.

Results: Twenty-four (2.6%) of 911 NSTEMI patients presented with hs-cTnT < 5 ng/L. In patients presenting >1–≤2 h from symptom onset the sensitivity for MI when combining hs-cTnT and ECG was 99.4% (95% CI 98.4%–99.8%). In patients presenting ≤1 h, and in patients aged ≤65 years without prior MI, the sensitivity was insufficient. NSTEMI patients presenting with hs-cTnT < 5 ng/L were younger and had less often a prior MI. A total of 62.5 vs. 63.5% of the NSTEMI patients presenting with and without hs-cTnT < 5 ng/L underwent revascularization within 30 days and 4.5 and 3.2% died respectively.

Conclusions: Hs-cTnT < 5 ng/L at presentation combined with a non-ischemic ECG may be used to rule out MI in patients presenting as early as >1 h from symptom onset with a sufficient sensitivity.

1. Introduction

The introduction of high-sensitivity cardiac troponin (hs-cTn) assays in clinical routine has improved the assessment of chest pain patients considerably [1–3]. Low concentrations of troponin can be detected already within the first hours from symptom onset which enables a rule-in or rule-out of myocardial infarction (MI) with a high precision at an early stage [4–7]. As a consequence, several new hs-cTn algorithms for patients presenting to the emergency department (ED) with symptoms suggestive of an acute coronary syndrome (ACS) have been developed. One that has been successfully implemented in clinical routine is the use of an undetectable level of high-sensitivity cardiac troponin T (hs-cTnT) (i.e. <5 ng/L) at presentation to rule out MI, preferably

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CI, confidence interval; CCU, coronary care unit; ECG, electrocardiogram; ED, emergency department; ESC, European Society of Cardiology; hs-cTn, high-sensitivity cardiac troponin; hs-cTnT, high-sensitivity cardiac troponin T; IQR, interquartile range; LoD, limit of detection; MACE, major adverse cardiac event; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; SWEDEHEART registry, The Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies; TIMI score, Thrombolysis In Myocardial Infarction score.

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combined with a non-ischemic electrocardiogram (ECG) [8,9]. In a recent meta-analysis this combination was shown to have a diagnostic sensitivity for MI of 98.7% and the capacity to safely rule out MI without further testing in about 30% of chest pain patients presenting to the ED [10].

So far only a modest number of patients evaluated with the algorithm have been early presenters. A short time delay between symptom onset and presentation has been suggested to lower the algorithm sensitivity and to increase the risk that MI patients are missed [9–12]. It has been argued that patients that may be missed are at an overall low risk, but data supporting that is scarce and current guidelines from the European Society of Cardiology (ESC) recommend the algorithm in patients presenting >3 h from symptom onset [6]. Thereto, the number of MI patients that have been evaluated with the algorithm is still limited [13].

The aim of the study was to investigate the diagnostic sensitivity for MI when using an undetectable level of hs-cTnT at presentation, with and without information from the ECG, to rule out MI in a population restricted to non-ST-segment elevation MI (NSTEMI) patients presenting ≤2 h from symptom onset. The aim was also to compare baseline characteristics and outcome in NSTEMI patients who were and were not identified as an MI by the undetectable hs-cTnT at presentation algorithm.

2. Methods

2.1. Study design and setting

All patients admitted to five centers in Stockholm, Sweden January 1, 2011 to December 31, 2015, after the introduction of hs-cTnT, who presented ≤2 h from symptom onset and received a final diagnosis of NSTEMI were considered eligible for inclusion in this retrospective observational study. The participating centers were university or teaching hospitals with constant access to catheterization laboratories on site or nearby. A first selection was made in the Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART) registry [14,15]. Patients registered with an MI diagnosis classified as NSTEMI, type unknown or not classified and who had a reported delay of ≤2 h between symptom onset and presentation to the hospital were identified. In these patients, the hospitals' medical records were screened and the following inclusion criteria were applied: (1) presentation to the ED or a direct admittance to the coronary care unit (CCU) or catheterization laboratory without passing the ED, (2) documented time of presentation, (3) documented time of onset of the last episode of symptoms suggestive of ACS, (4) ≤2 h between symptom onset and presentation, (5) ≥2 samples of hs-cTnT obtained, including a first sample in the receiving unit and (6) a final diagnosis of NSTEMI. Patients were excluded if they had a cardiac arrest and/or cardiopulmonary resuscitation prior to presentation, an ST-segment elevation MI (STEMI) with a diagnostic ECG at presentation, or a type 2 MI or other secondary myocardial injury [16] (Fig. 1). The MI diagnoses used in the study were set by the clinicians and based on the Universal Definition of MI criteria [16,17]. The study was conducted according to the principles of the Declaration of Helsinki and approved by the Regional Ethical Review Board in Stockholm (approval number 2017-331/31).

2.2. Data collection

Baseline and presentation characteristics, medication, in- and out-of-hospital coronary angiographies, percutaneous coronary interventions (PCIs), coronary artery bypass grafting (CABG) and death data were retrieved from the SWEDEHEART registry. Data on presentation mode, time of presentation and of symptom onset and the sampling time and result of the baseline and peak hs-cTnT value obtained ≤24 h, were retrieved from the medical records. In case the information about the time of symptom onset was inconsistent, the earliest noted time was used. The troponin results used in the study were drawn and analyzed in routine clinical care at each center. The sampling time used in the study was the time that was automatically registered when the responsible nurse sent the electronic referral to the laboratory. All troponin analyses were performed with the Elecsys hs-cTnT assay (Roche Diagnostics, Basel, Switzerland). The assay has a limit of detection (LoD) of 5 ng/L, a 99th percentile of healthy controls of 14 ng/L and a coefficient of variation of <10% at or below the 99th percentile [4]. In patients presenting with an undetectable level of hs-cTnT (i.e. <5 ng/L), the admission ECG was classified by two independent cardiologists. In case of disagreement, a third cardiologist assessed the ECG. In patients presenting with a level of hs-cTnT at or above the LoD (i.e. ≥5 ng/L), the SWEDEHEART registry classification of the ECG was used. The ECG was classified into the categories presented in Table 2.

2.3. Outcome measures

The diagnostic sensitivity for MI when using an undetectable level of hs-cTnT at presentation to rule out MI was calculated separately in patients presenting ≤2 h, >1 h to ≤2 h and ≤ 1 h from symptom onset. The additive effect of a non-ischemic ECG, defined as an ECG with the absence of ST-segment elevation, ST-segment depression and T-wave inversion, was calculated. In an additive analysis, patients aged ≤65 years without prior MI were analyzed separately. Since only patients with NSTEMI (cases) were included, only sensitivity (not specificity, negative or positive predictive values) could be calculated. NSTEMI patients with and without a detectable level of hs-cTnT at presentation were compared regarding baseline characteristics and outcome. All patients were followed for 30 days regarding revascularization and death. Revascularization was defined as PCI or CABG. Death was defined as all-cause mortality. Data regarding reinfarction could not be retrieved.

2.4. Statistical analyses

Sensitivity was calculated as the number of MI patients identified by the algorithm divided by the number of patients with MI and the exact Clopper-Pearson 95% confidence interval (CI) for the observed proportion was calculated. Patients presenting with an undetectable level of hs-cTnT, i.e. those not identified as an MI by the undetectable hs-cTnT at presentation algorithm, were compared with patients presenting with a level of hs-cTnT at or above the LoD, i.e. those identified as an MI by this algorithm. Categorical variables are presented as numbers and percentages and comparisons were made with the chi-square test or the Fisher's exact test when appropriate. Continuous data are presented as medians with interquartile ranges (IQR) and the Mann-Whitney *U* test was used for comparisons. All statistical analyses were performed using IBM SPSS Statistics version 23, Armonk, North Castle, NY or MedCalc version 18.2.1, MedCalc Software, Ostend, Belgium.

3. Results

3.1. Diagnostic sensitivity for MI

In total, 911 NSTEMI patients presented to the hospital ≤2 h from symptom onset, met the inclusion criteria and were included in the study. Out of these, 24 (2.6%) patients presented with an undetectable level of hs-cTnT. The diagnostic sensitivity for MI when using an undetectable level of hs-cTnT at presentation to rule out MI is presented in Table 1. The sensitivity was highest in patients presenting >1 h to ≤2 h from symptom onset (98.5% (95% CI 97.2%–99.3%)). In the subgroup of patients aged ≤65 years without prior MI presenting >1 h to ≤2 h, the sensitivity was 96.9% (95% CI 93.5%–98.9%). In all patients presenting ≤1 h, the sensitivity was 94.6% (95% CI 91.0%–97.0%) and in patients aged ≤65 years without prior MI presenting ≤1 h, the sensitivity was as low as 86.0% (95% CI 76.9%–92.6%).

The diagnostic sensitivity for MI improved when analysis of ECG was added to the algorithm. In all patients presenting >1 h to ≤2 h the sensitivity increased to 99.4% (95% CI 98.4%–99.8%) and in patients aged ≤65 years with no prior MI the sensitivity increased to 98.5% (95% CI 95.6%–99.7%). In all patients presenting ≤1 h, the sensitivity increased to 95.7% (95% CI 92.5%–97.8%) and in patients aged ≤65 years without prior MI, the sensitivity increased to 89.5% (95% CI 81.1%–95.1%) when the admission ECG was taken into account.

3.2. Comparison between NSTEMI patients with and without a detectable level of hs-cTnT at presentation

Compared to NSTEMI patients with a level of hs-cTnT at or above the LoD (i.e. those identified as an MI by the undetectable hs-cTnT at presentation algorithm), patients presenting with an undetectable level of hs-cTnT were younger (median age 56 vs. 69 years), to a comparable extent male (70.8 vs. 68.9%) and had less often a history of diabetes mellitus and prior MI (Table 2). A majority of the patients in both groups stated chest pain as their chief complaint. A total of 62.5% of the patients presenting with an undetectable level of hs-cTnT had a non-ischemic admission ECG, compared to 42.6% of the patients presenting with a level of hs-cTnT at or above the LoD ($p = 0.052$). Patients with an undetectable baseline level of hs-cTnT more often presented within the first hour from symptom onset (58.3 vs. 27.4%)

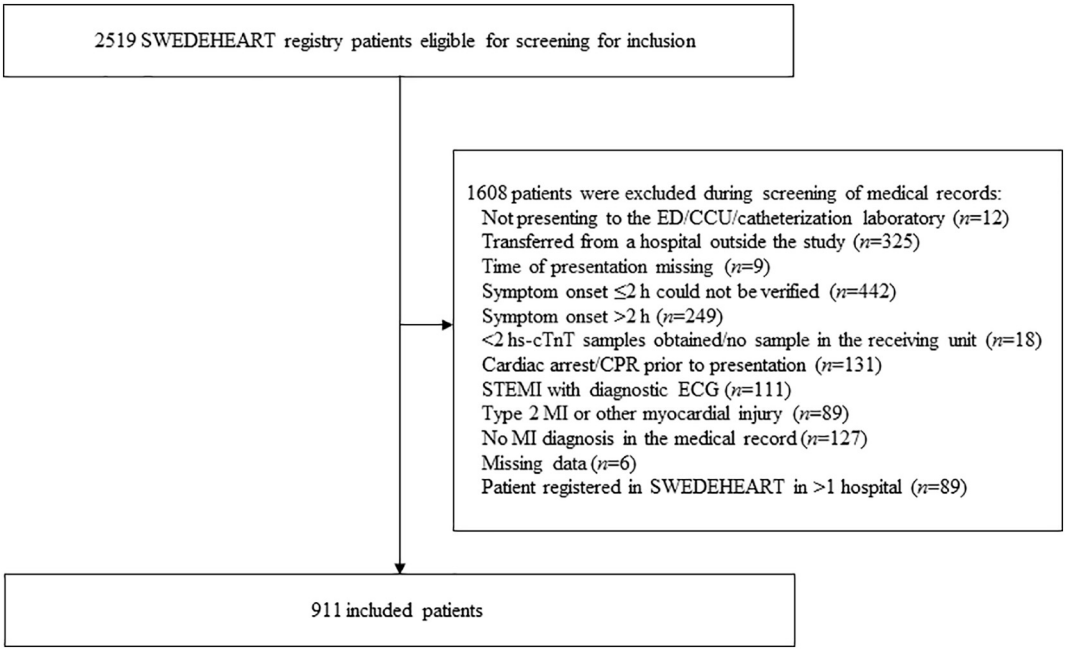

Fig. 1. Selection of the study group of NSTEMI patients presenting ≤ 2 h from symptom onset. A first selection was made in SWEDEHEART registry. Patients registered with an MI diagnosis classified as NSTEMI, type unknown or not classified and who had a reported delay of ≤2 h between symptom onset and presentation to the hospital were identified and the medical records were screened for inclusion. CCU = coronary care unit; CPR = cardiopulmonary resuscitation; ECG = electrocardiogram; ED = emergency department; h = hours; hs-cTnT = high-sensitivity cardiac troponin T; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; SWEDEHEART registry = The Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies registry.

but the median time from presentation to the first hs-cTnT sample obtained was comparable (10 vs. 14 min).

When comparing NSTEMI patients who presented with an undetectable level of hs-cTnT to those who presented with a level at or above the LoD, no difference was seen regarding the peak level of hs-cTnT recorded during the first 24 h of hospitalization (median 182 vs. 200 ng/L) (Table 3). There was no statistically significantly difference in the proportion of coronary angiographies (95.8 vs. 79.7%), revascularization (62.5 vs. 63.2%) or death (4.2 vs. 1.6%) before discharge. The patients in the two groups were to a similar extent discharged with acetylsalicylic acid, P2Y12 inhibitors, beta blockers and lipid lowering drugs as secondary prevention medication. At the end of the 30-day follow-up, a total of 95.8% and 62.5% of the patients who presented with an undetectable level of hs-cTnT had undergone coronary angiography and revascularization respectively, compared to 80.3% and 63.5% respectively of those who presented with a level at or above the LoD. The 30-day cumulative incidence of death was 4.5 and 3.2% respectively.

4. Discussion

Previous studies, examining the diagnostic performance of the undetectable hs-cTnT at presentation algorithm have included chest pain patients of which a small proportion has been early presenters with MI. This has resulted in uncertainty regarding the safety of using the algorithm in early presenters. This is so far the largest sensitivity study in early presenters with a final diagnosis of NSTEMI. The main findings were the following: An undetectable level of hs-cTnT at presentation alone did not result in an acceptable sensitivity for MI in patients presenting within 2 h from symptom onset. The combination of an undetectable level of hs-cTnT at presentation and a non-ischemic ECG resulted in a satisfying diagnostic sensitivity of 99.4% (95% CI 98.4%–99.8%) in patients presenting in the second hour (i.e. >1 h to ≤2 h) from symptom onset, which is a new finding. However, in all patients presenting within the first hour (i.e. ≤1 h) from symptom onset, as well as in the subgroup of patients aged ≤65 years with no history of MI, independently of symptom onset, the diagnostic sensitivity for MI

Table 1
Diagnostic sensitivity for myocardial infarction. Sensitivity for MI when using an undetectable level of hs-cTnT at presentation, with and without information from the ECG, to rule out MI in a NSTEMI population presenting ≤2 h from symptom onset.

	Presentation ≤ 1 h from symptom onset	Presentation > 1- ≤ 2 h from symptom onset	Presentation ≤ 2 h from symptom onset
Sensitivity (95% CI) (n/t) for hs-cTnT at presentation			
All patients ($n = 911$)	94.6 (91.0–97.0) (243/257)	98.5 (97.2–99.3) (644/654)	97.4 (96.1–98.3) (887/911)
Patients ≤65 years, no prior MI ($n = 282$)	86.0 (76.9–92.6) (74/86)	96.9 (93.5–98.9) (190/196)	93.6 (90.1–96.2) (264/282)
Sensitivity (95% CI) (n/t) for hs-cTnT and ECG[a] at presentation			
All patients ($n = 911$)	95.7 (92.5–97.8) (246/257)	99.4 (98.4–99.8) (650/654)	98.4 (97.3–99-1) (896/911)
Patients ≤65 years, no prior MI ($n = 282$)	89.5 (81.1–95.1) (77/86)	98.5 (95.6–99.7) (193/196)	95.7 (92.7–97.8) (270/282)

CI = confidence interval; d = denominator; ECG = electrocardiogram; hs-cTnT = high-sensitivity cardiac troponin T; MI = myocardial infarction; n = nominator; NSTEMI = non-ST-segment elevation myocardial infarction.

[a] Normal ST-T-findings were defined as the absence of an ST-segment elevation >1 mm (>2 mm in lead V2-V3), of an ST-segment depression >1 mm in two leads and of a T-wave inversion >1 mm.

Table 2
Baseline characteristics. All patients with a final diagnosis of NSTEMI who presented ≤2 h from symptom onset ($n = 911$).

	Patients presenting with hs-cTnT ≥ 5 ng/L ($n = 887$)	Patients presenting with hs-cTnT < 5 ng/L ($n = 24$)	p
Demography			
Age	69 (59–79) [880]	56 (52–63) [23]	0.000
Female	276 (31.1)	7 (29.2)	0.839
Risk factors			
Current smoking	172 (21.2) [812]	6 (26.1) [23]	0.605
BMI	27 (24–30) [867]	27 (25–29) [22]	0.836
Hypertension	454 (51.4) [883]	9 (37.5)	0.178
Diabetes mellitus	222 (25.1) [886]	1 (4.2)	0.019
Prior cardiovascular disease			
Prior myocardial infarction	321 (36.4) [881]	3 (12.5)	0.016
Prior PCI	231 (26.3) [879]	4 (16.7)	0.290
Prior CABG	125 (14.1) [884]	0 (0.0)	0.063
Known LVEF <0.50	101 (11.9) [852]	0 (0.0) [23]	0.097
Prior stroke (not including TIA)	68 (7.7) [885]	1 (4.2)	1.000
Presentation characteristics			
Chief complaint of chest pain	823 (92.8)	24 (100.0)	0.405
Admittance to the CCU or catheterization laboratory without passing the ED	35 (3.9)	0 (0.0)	1.000
Heart rate	76 (67–93)	74 (64–95)	0.522
Systolic blood pressure	150 (135–170)	148 (121–170)	0.296
Diastolic blood pressure	86 (76–96) [750]	85 (70–99) [22]	0.578
Pulmonary rales	86 (9.7) [883]	0 (0.0)	0.157
Admission ECG			
Sinus rhythm	778 (88.2) [882]	23 (95.8)	0.346
Atrial fibrillation/flutter	83 (9.4) [882]	1 (4.2)	0.718
BBB	218 (24.8) [879]	0 (0)	0.005
ST-segment elevation[a]	35 (4.0) [875]	1 (4.2)	1.000
ST-segment depression[a]	229 (26.2) [875]	6 (25.0)	0.897
T-wave inversion[a]	93 (10.6) [875]	3 (12.5)	0.735
ST-T normal[b]	373 (42.6) [875]	15 (62.5)	0.052
Time delay			
Presentation ≤1 h from symptom onset	243 (27.4)	14 (58.3)	0.001
Onset of symptoms to 1st troponin (min)	97 (74–120)	67 (40–100)	0.000
Presentation to 1st troponin (min)	14 (7–28)	10 (5–16)	0.069
Troponin results			
Median hs-cTnT at presentation (ng/L)	32 (17–66)	<5 (<5- < 5)	0.000
Mean hs-cTnT at presentation (ng/L)[c]	88 (5–7860)	<5 (<5- < 5)	0.000

Data are presented as median (IQR) or *n* (%) if not indicated otherwise. In case of missing values, the total numbers are expressed within the brackets.
BBB = bundle branch block; BMI = body mass index; CABG = coronary artery bypass grafting; CCU = coronary care unit; ECG = electrocardiogram; ED = emergency department; hs-cTnT = high-sensitivity cardiac troponin T; IQR = interquartile range; LVEF = left ventricular ejection fraction; min = minutes; ng/L = nanogram/l; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIA = transitory ischemic attack.

[a] ST-segment elevation was defined as an ST-segment elevation >1 mm (>2 mm in lead V2-V3), ST-segment depression as an ST-segment depression >1 mm in two leads and T-wave inversion as a T-wave inversion >1 mm. Patients with a previously known or non-persistent ST-segment elevation were not assessed as having an ongoing STEMI and all patients had a final diagnosis of NSTEMI. More than one of these criteria could be fulfilled in one ECG.

[b] Defined as the absence of an ST-segment elevation >1 mm (>2 mm in lead V2-V3), of an ST-segment depression >1 mm in two leads and of a T-wave inversion >1 mm.

[c] Mean (minimum and maximum range).

was insufficient. Further, NSTEMI patients with an undetectable level of hs-cTnT at presentation were younger but had a similar need for revascularization and 30-day outcome as NSTEMI patients with a detectable level of hs-cTnT at presentation.

There is no general recommendation for the sensitivity for MI of a diagnostic test even though a sensitivity at or above 99% is often the aim among clinicians. In a survey performed among one thousand ED physicians, about 40% of the participants were willing to accept a miss-rate of a major adverse cardiac event (MACE) of 1% and 55% a miss-rate of 0.5% [18]. Prior studies have reported a varying but decreased diagnostic sensitivity for MI when applying the undetectable level of hs-cTnT at presentation algorithm [11] combined with a non-ischemic ECG [9,10,19] in early presenters. These studies have suggested a time delay of 2 or 3 h between symptom onset and presentation in order to apply the algorithm. However, the number of early presenters with MI overall and MI with an undetectable level of hs-cTnT at presentation, was low when compared to our study. Our large study cohort enabled a more detailed analysis of the early presenters with NSTEMI, including the possibility to further divide the study population according to time delay from onset of symptoms which may explain the fact that we found a sufficient sensitivity in the second hour from symptom onset. Nevertheless, we found an insufficient diagnostic sensitivity in patients presenting within the first hour from symptom onset even when combining an undetectable level of hs-cTnT with a non-ischemic ECG to rule out MI (95.7% (95% CI 92.5%–97.8%)). We consider this due to the fact that the time interval is too short to expect a rise in hs-cTnT and the current recommendation is to perform serial testing in these patients in order to detect an early alteration of hs-cTnT levels [6,7,20].

We found that the diagnostic sensitivity for MI was notably lower in patients aged ≤65 years without prior MI, even in patients presenting in the second hour from symptom onset (98.5% (95% CI 95.6%–99.7%)). This is important since these patients might be considered as low-risk patients suitable for discharge when presenting to the ED. Since elderly patients in general are more likely to have a baseline level of hs-cTnT at or above the LoD [9,19,21,22], they are also at a lower risk to be missed by the undetectable hs-cTnT at presentation algorithm. A prior study compared the diagnostic sensitivity for MI in younger (<70 years) and elderly (≥70 years) patients using an undetectable level of hs-cTnT at presentation to rule out MI [22]. They found no difference in sensitivity between these two age cohorts, but none of the patients in the study had a false negative result. This was probably due to a low number of NSTEMI patients (i.e. 70), in our study only 24 out of 911 NSTEMI

Table 3
In-hospital and 30-day outcome. All patients with a final diagnosis of NSTEMI who presented ≤2 h from symptom onset ($n = 911$).

	Patients presenting with hs-cTnT ≥ 5 ng/L ($n = 887$)	Patients presenting with hs-cTnT < 5 ng/L ($n = 24$)	p
In-hospital outcome			
Peak hs-cTnT ≤24 h (ng/L)	200 (81–541)	182 (26–359)	0.072
Coronary angiography	707 (79.7)	23 (95.8)	0.065
Revascularization[a]	561 (63.2)	15 (62.5)	0.940
Death	14 (1.6) [886]	1 (4.2)	0.332
Medication at discharge			
Acetylsalicylic acid	815 (92.4) [882]	23 (95.8)	1.000
P2Y12 inhibitors	724 (82.1) [882]	21 (87.5)	0.786
Oral anticoagulants	115 (13.0) [882]	0 (0.0)	0.061
Beta blockers	799 (90.6) [882]	23 (95.8)	0.718
ACE inhibitors/ARBs	641 (72.8) [881]	16 (66.7)	0.509
Lipid lowering therapy	783 (88.9) [881]	23 (95.8)	0.504
30-day outcome			
Coronary angiography	712 (80.3)	23 (95.8)	0.065
Revascularization[a]	563 (63.5)	15 (62.5)	0.922
Death	28 (3.2) [864]	1 (4.5) [22]	0.523

Data are presented as median (IQR) or *n* (%). In case of missing values, the total numbers are expressed within the brackets.
ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; hs-cTnT = high-sensitivity cardiac troponin T; IQR = interquartile range; ng/L = nanogram/l; NSTEMI = non-ST-segment elevation myocardial infarction.
[a] Defined as percutaneous coronary intervention or coronary artery bypass grafting.

patients had an undetectable level of hs-cTnT at presentation. Two other studies have indicated an increased sensitivity for MI or a MACE when combining an undetectable level of hs-cTnT at presentation and a non-ischemic ECG with age < 65 years [9], or with a non-high risk history (including younger patients and patients who less often had a history of MI) [23]. The difference in study results might partly be explained by the fact that we only included patients presenting within 2 h from symptom onset in our study, while the other studies weren't restricted to early presenters. Since a very short time interval between symptom onset and presentation increases the risk of a false negative hs-cTnT result, later presenters with an undetectable baseline level of hs-cTnT are less likely to have an MI compared to those presenting early with an undetectable hs-cTnT level. A pooled analysis of chest pain patients presenting <3 h from symptom onset resulted in a diagnostic sensitivity for MI above 99% when combining an undetectable level of hs-cTnT at presentation with a Thrombolysis In Myocardial Infarction (TIMI) score of 0 points (i.e. age < 65 years) in order to rule out MI [24]. Again, this study group contained substantially fewer patients with a final diagnosis of NSTEMI, as well as fewer patients with a false negative result, when compared to our study.

Our results indicate that admitted NSTEMI patients with and without a detectable level of hs-cTnT at presentation have a similar 30-day outcome. The peak levels of hs-cTnT and the incidence of revascularization were comparable. The incidence of coronary angiography in our study was comparable to that among Swedish NSTEMI patients in general during this period [25]. In a prior study, the question of whether an MI diagnosis in patients presenting with an undetectable level of hs-cTnT would do more harm than benefit due to a limited myocardial damage and the risk of a PCI-related MI, was raised [19]. Our conclusion is that NSTEMI patients presenting with an undetectable level of hs-cTnT benefit from being identified.

The present study has some limitations. Since this is a retrospective study it may be difficult to set the exact time of symptom onset and of drawing of blood samples. Thus, these time points may deviate somewhat from the actual ones. However, the sampling was automatically registered when the electronic referral was sent to the laboratory and, therefore, the deviation should be small. The relatively high exclusion rate due to uncertainty regarding symptom onset and time from symptom onset to presentation might be explained by the difficulties retrieving exact information retrospectively. We included only cases with MI, thus we could calculate sensitivity but no other measurement of diagnostic performance such as specificity, negative and positive predictive value. However, the aim was to examine the safety of the algorithm and sensitivity is then considered the most important measurement. The possible benefit of a clinical risk score combined with the rule-out algorithm was not evaluated in this study. Even though our study included a large cohort of NSTEMI patients, only 24 of them presented with an undetectable level of hs-cTnT. Only admitted patients were included in the study and some MI patients with an undetectable level of-hs-cTnT might have been sent home from the ED. If these MI patients presented again, they would then present with a detectable level of hs-cTnT, which falsely may have increased the calculated diagnostic sensitivity for MI in our study. Type 2 MI was an exclusion criterion of the study. Since the MI diagnoses used in the study were set by the clinicians (not centrally adjudicated) and all patients didn't undergo coronary angiography, it is possible that some MIs were incorrectly classified. However, the validity of MI diagnoses set in routine clinical care in Sweden has been reported to be high [26]. The time relation between the peak value of hs-cTnT and the coronary angiography was not documented. However, all patients were considered to have type 1 MI before coronary angiography. We were unable to provide data on reinfarction during the first 30 days after hospital discharge. Such information is not recorded in the SWEDEHEART registry and can neither be obtained from the Swedish Patient Registry as this registry only contains reinfarction occurring 30 days after the index hospitalization. A larger population should have been needed in order to compare differences in mortality between the groups.

5. Conclusions and clinical implications

We found that an undetectable level of hs-cTnT at presentation combined with a non-ischemic ECG may be used to rule out MI in patients presenting as early as in the second hour from symptom onset with a sufficient sensitivity, which is notably earlier than the 3 hour delay recommended by the ESC guidelines [6]. However, patients aged ≤65 years without a history of MI should be assessed with great caution due to the risk of a false negative result. Further, admitted NSTEMI patients with an undetectable level of hs-cTnT at presentation were younger but had a similar 30-day outcome when compared to NSTEMI patients presenting with a detectable level of hs-cTnT.

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Conflicts of interest

BL has received research support from Fiomi diagnostics and bioMérieux and has served as consultant for Fiomi Diagnostics, bioMérieux, Roche Diagnostics, Philips, Thermo-Fischer.

KME has received honoraria from Abbott Laboratories and has served as a consultant for Abbott Laboratories and Fiomi Diagnostics. The remaining authors have no industry relationships to declare.

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