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ORIGINAL ARTICLE

Diagnostic accuracy of troponin T measured ≥6h after symptom onset for ruling out myocardial infarction

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ABSTRACT

Objectives: Guidelines recommend a single high-sensitivity cardiac troponin T (hs-cTnT) ≤14 ng/L measured ≥6 h after chest pain onset combined with a GRACE score <140 and the patient being pain-free for ruling out myocardial infarction (MI). There is however little data on the performance of this strategy. We therefore aimed to evaluate the diagnostic accuracy of a hs-cTnT ≤14 ng/L measured ≥6 h after chest pain onset when combined with GRACE score or other clinical risk stratification tools. *Design*: This was a secondary analysis of a prospective observational study, which enrolled emergency department (ED) chest pain patients. The hs-cTnT strategy was combined with HEART, TIMI, EDACS, GRACE score and ED physician's overall assessment of patient history and ECG. The primary outcome was MI, and the secondary outcome was 30-day major adverse cardiac events (MACE). *Results*: All tested diagnostic strategies were shown to have a negative predictive value (NPV) ≥99.5% for ruling out MI. Using HEART, TIMI, EDACS or ECG + patient history also resulted in a NPV ≥98% for ruling out 30-day MACE. An isolated hs-cTnT ≤14 ng/L measured ≥6 h after chest pain onset and the combination with GRACE score both had a NPV <98% for ruling out 30-day MACE. *Conclusion*: A single hs-cTnT ≤14 ng/L obtained ≥6 h from chest pain onset, with and without GRACE score, reliably ruled out MI but did not perform well for ruling out 30-day MACE. These results question current guideline recommendations, and indicate that HEART, EDACS, TIMI, or ECG + patient history strategies should be the preferred risk stratification tools.

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Acute coronary syndrome; chest pain; diagnosis; myocardial infarction; sensitivity and specificity; unstable angina

Introduction

Chest pain is one of the most frequent reasons for visiting the emergency department (ED) accounting for 5–10% of all ED visits [1,2]. One of the primary concerns of ED physicians managing chest pain patients is to exclude acute coronary syndrome (ACS) i.e. myocardial infarction (MI) or unstable angina (UA). This usually includes serial troponin measurements, and in many cases admissions and stress testing [3–5], which causes a substantial health care burden and contributes to ED crowding [5,6]. Only about 14% of chest pain patients however turn out to have ACS [7], emphasizing that there is still room for significant improvement in the current management of these patients.

With the previous generation of troponins it has been shown that a troponin below the 99th percentile upper reference limit (URL) measured less than 6 h after symptom onset does not accurately rule out MI [8]. With the more recent high sensitivity troponins (hs-cTn), the European Society of Cardiology (ESC) guidelines however recommends a rule-out strategy utilizing a hs-cTn < URL measured at least 6 h from symptom onset and combined with a GRACE score <140 and the patient being pain-free [9]. Studies evaluating the performance of a single hs-cTnT or hs-cTnI measured ≥6 h after symptom onset have shown conflicting results, with most not being able to show that this approach is safe [10–12]. Most of these studies have however looked at hs-cTn in isolation. It is possible that the combination with a low GRACE score and the patient being pain-free might lower the pre-test probability such that this strategy would be safe.

Still, in real life practice most ED physicians do not use GRACE score in their evaluation of chest pain patients. More commonly, troponins are used in conjunction with physicians overall assessment of the patient history and the ECG, or a clinical score such as Thrombolysis in Myocardial Infarction (TIMI), Emergency Department Assessment of Chest Pain Score (EDACS) or HEART (History, ECG, Age, Risk factors, Troponin) [13–15]. There are however no studies so far that have evaluated the performance of a hs-cTnT below the 99th percentile URL (≤14 ng/L) measured ≥6 h after symptom onset when combined with either physician's overall assessment or

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Supplemental data for this article can be accessed here.

these clinical scores. It is also unclear whether 6 h is the most optimal time interval for a single hs-cTnT rule-out strategy.

Our primary aim was therefore to evaluate the diagnostic accuracy of a hs-cTnT ≤14 ng/L measured ≥6 h after chest pain onset when combined with GRACE score or other clinical risk stratification tools for predicting index visit MI and 30-day MACE.

Our secondary aim was to calculate the optimal time interval from symptom onset to hs-cTnT testing for a single troponin rule-out strategy.

Method

Study design and participants

This was a secondary analysis of a prospective observational study and the methods have been described in detail previously [13]. Patients were enrolled from the ED at Skåne University Hospital in Lund during weekdays between 9 am and 9 pm from February 2013 to April 2014. We included patients ≥18 years who had a primary complaint of chest pain/discomfort of non-traumatic origin and had a hs-cTnT measured at ED-arrival (0 h). Patients were not enrolled if they had an ST-elevation myocardial infarction (STEMI), or if they could not provide informed consent. Patients were excluded if they had missing data needed for our analyses or if there was hemolysis with hemoglobin concentration >0.1 g/dl, H-index ≥100 (the manufacturer-recommended level) in the 0 h hs-cTnT sample as this can cause falsely low results. We also excluded patients with STEMI who were erroneously enrolled. This study was approved by the regional Ethical Review Board in Lund and all patients provided written informed consent.

Data collection

Clinical data, including time of chest pain onset, as well as the variables needed for calculating the different risk scores (Supplementary Appendix 1–3) were collected by research assistants using an electronic study questionnaire. The ED physician's assessment of the ECG as well as their assessment of the likelihood of ACS based on the patient history (very low, low, intermediate or high risk), was also prospectively collected. To avoid biased assessment no guidance was given on how to differentiate between the different risk groups.

Hs-cTnT samples were collected in lithium heparin tubes and analyzed with the Roche Cobas e602 (Roche Diagnostics, Basel, Switzerland). The assay has a limit of blank of 3 ng/L, a limit of detection of 5 ng/L and the coefficient of variation (CV) is <10% at the 99th percentile cut-off point of 14 ng/L [16].

Outcomes and adjudication process

The primary outcome was MI during the index visit. The secondary outcome was MACE within 30-days, including the index visit. MACE was defined as an adjudicated diagnosis of MI, UA, cardiac arrest, cardiogenic shock, ventricular arrhythmia or atrioventricular block requiring intervention, or death of a cardiac or unknown cause.

Events were adjudicated by two cardiologists, and in case of disagreement, by a third cardiologist. They were blinded to the data form with the collected clinical data including the data needed to calculate the different scores. A detailed account of the adjudication process has been provided previously [13]. For the adjudication process the cardiologists were provided with all available clinical information within 60 days from the index visit, including complete medical records, results of blood samples and radiologic investigations, ECGs, echocardiograms, stress tests, and coronary angiographies. Deaths and causes of death were obtained from medical records, the Swedish population registry and the national cause-of-death registry, and in order not to miss hospital visits outside our region, data for all admissions for in-hospital care in Sweden were also obtained from the National Patient Register [17,18].

The diagnosis of MI required a significant rise and/or fall of hs-cTnT levels with at least one value above the 99th percentile, combined with symptoms or signs of cardiac ischemia, in accordance with the universal definition [19]. As to not misclassify late presenters, a diagnosis of MI could also be made in patients with elevated hs-cTnT without a significant change on serial troponin measurements, if deemed to be the most likely diagnosis based on all available information [19,20].

The diagnosis of UA required normal or slightly elevated hs-cTnT levels without a significant rise or fall, *and* a history consistent with UA defined as rest angina, new-onset angina of Canadian Cardiovascular Society class ≥3, or increasing angina, *and* at least one of the following: stenosis ≥70% in a vessel on coronary angiography, positive stress test if no angiography was performed, or new ischemic ECG changes in patients managed without stress test or angiography. An UA diagnosis could also be adjudicated in patients who were discharged after MI was ruled out and were subsequently diagnosed with MI or suffered death of cardiac or unknown cause within 30 days from the index visit (Supplementary Appendix 4).

The other components of the 30-day MACE outcome were defined according to published standardized data definitions [21].

Index tests

The diagnostic accuracy of the following strategies for the primary and secondary outcome were evaluated:

1. Hs-cTnT ≤14 ng/L ≥6h after chest pain onset.
2. Hs-cTnT ≤14 ng/L ≥6h after chest pain onset and a non-ischemic ECG.
3. Hs-cTnT ≤14 ng/L ≥6h after chest pain onset, a non-ischemic ECG and a non-high risk patient history (intermediate, low, or very low risk) [13].

4. Hs-cTnT ≤14 ng/L ≥6h after chest pain onset, a non-ischemic ECG and a TIMI score ≤1 [15] (Supplementary Appendix 1).
5. Hs-cTnT ≤14 ng/L ≥6h after chest pain onset, a non-ischemic ECG and an EDACS score <16 [22] (Supplementary Appendix 2).
6. Hs-cTnT ≤14 ng/L ≥6h after chest pain onset and a HEART score ≤3 [14] (Supplementary Appendix 3).
7. Hs-cTnT ≤14 ng/L ≥6h after chest pain onset, a GRACE-score <140, and the patient being pain-free [23].

We additionally evaluated the negative predictive value (NPV) of hs-cTnT measured 1-12 h from chest pain onset for ruling out index visit MI, as to obtain the optimal time interval for hs-cTnT single troponin rule-out.

Statistical analyses

For descriptive data, mean ± SD and median with interquartile range (IQR) was used for continuous variables, and categorical variables were described with proportions. Sensitivity, specificity, NPV, and likelihood ratio (LR), with the corresponding 95% confidence intervals, were calculated for the rule-out strategies. The proportion of patients identified for rule-out with the different strategies was calculated based on the total study cohort.

We pre-specified that for a rule-out strategy to be deemed safe and clinically acceptable, it needed to have a NPV ≥99.5% for ruling out index visit MI [24].

Baseline characteristics were compared using Pearson's chi-square, independent t-test, and Mann-Whitney U test. Differences in efficacy between strategies utilizing different hs-cTnT time-intervals were calculated with McNemar's test.

Tests were two-tailed and a p-value of <.05 was considered significant. SPSS statistics (IBM, Armonk, New York) and Medcalc (MedCalc Software bvba, Ostend, Belgium) were used for all statistical analyses.

Results

A total of 1167 patients were enrolled in this study. Based on our exclusion criteria, 201 patients were excluded, with a total of 966 patients included in the final dataset. There were no large differences between included and excluded patients (Supplementary Appendix 5).

Baseline characteristics are presented in Table 1. Of the 966 study participants, 498 (51.6%) had a 0 h hs-cTnT measured ≥6 h after chest pain onset. Compared to those with a 0 h hs-cTnT measured <6 h after chest pain onset, they were more often female, less often had prior revascularization, and more often had a low risk score. A total of 117 patients in the overall study cohort were diagnosed with a 30-day MACE, of whom almost all were index visit MI ($n = 76$) or UA ($n = 38$), with the remaining events being death ($n = 3$). Those with a 0 h hs-cTnT measured ≥6 h after chest pain onset however less often had MI or 30-day MACE.

Diagnostic accuracy of rule-out strategies

The diagnostic accuracy of the different rule-out strategies for the primary outcome of index visit MI are shown in Table 2 and the corresponding 2x2 tables are shown in Supplementary Appendix 6. The strategy using an isolated hs-cTnT ≤14ng/L obtained ≥6 h after chest pain onset identified 38.5% of patients for rule-out with a NPV of 99.7% (95% CI: 98.5-100), missing one patient with MI. Of these 372 patients, 169 (45.4%) had a hs-cTnT <5 ng/L.

The addition of GRACE score <140 and the patient being pain-free, minimally increased the NPV to 100% (95% CI: 96.4-100), but resulted in only 10.5% of patients being identified for rule-out.

All seven rule-out strategies had a NPV ≥99.5% for ruling out MI, but the proportion of patients ruled out with the different strategies differed, with the lowest percentage seen using the GRACE score strategy and highest using hs-cTnT alone.

The diagnostic accuracy of the different rule-out strategies for the secondary outcome of 30-day MACE are shown in Table 3. For ruling out 30-day MACE, HEART, TIMI, EDACS and ECG + patient history strategies were all shown to have a NPV ≥98.0%. The hs-cTnT only strategy had a NPV of 97.0% (95% CI: 94.8-98.5), missing 11 patients with a 30-day MACE (1 MI, 10 UA) and the GRACE score strategy a NPV of 96.0% (95% CI: 90.2-98.9), missing 4 patients with UA.

When evaluating the diagnostic accuracy of the rule-out strategies for an outcome of 30-day MACE which also included urgent/emergency PCI/CABG, the results were almost identical (Supplementary Appendix 7).

As shown in Figure 1, only the strategies using HEART, TIMI, EDACS or ECG + a non-high risk patient history had both a NPV ≥99.5% for ruling out index visit MI, as well as a NPV ≥98.0% for ruling out 30-day MACE.

Optimal time-interval for Hs-cTnT single troponin rule-out

As shown in Figure 2 and Supplementary Appendix 8, a NPV ≥99.5% for MI was seen when the hs-cTnT sample was obtained ≥4 h after chest pain onset. This enabled 47.7% of patients to be identified for rule-out compared to 38.5% using the ≥6 h approach (95% CI for difference = 7.2 – 11.2%, $p < .001$).

Discussion

In this prospective observational study, we evaluated the diagnostic performance of a hs-cTnT ≤14ng/L obtained ≥6 h after chest pain onset combined with different risk stratification tools for ruling out MI and 30-day MACE. Our results showed that the ESC recommended strategy using GRACE score was safe for ruling out MI during the

Table 1. Baseline characteristics.

Characteristics	All patients ($n = 966$)	0h hs-cTn$T \geq 6$ h* ($n = 498$)	0h hs-cTn$T < 6$ h* ($n = 468$)	p-value**
Mean age, y	60.8 (17.3)	59.8 (17.6)	61.9 (16.8)	.07
Female gender, n (%)	438 (45.3)	251 (50.4)	187 (40.0)	.001
Medical history, n (%)				
Diabetes	138 (14.3)	70 (14.1)	68 (14.5)	.83
Hypertension	422 (43.7)	204 (41.0)	218 (46.6)	.08
COPD	71 (7.3)	35 (7.0)	36 (7.7)	.69
MI	196 (20.3)	92 (18.5)	104 (22.2)	.15
CABG or PCI	201 (20.8)	85 (17.1)	116 (24.8)	.03
Stroke/TIA	86 (8.9)	42 (8.4)	44 (9.4)	.60
Other risk factors, n (%)				
Family history of CAD***	230 (23.8)	128 (25.7)	102 (21.8)	.15
Current or previous smoker	549 (56.8)	277 (55.6)	272 (58.1)	.43
BMI $\geq$30, kg/m^2	208 (21.5)	107 (21.5)	101 (21.6)	.97
Prior medication, n (%)				
Acetylsalicylic acid	279 (28.9)	140 (28.1)	139 (29.7)	.59
Warfarin or NOAC	101 (10.5)	40 (8.0)	61 (13.0)	.01
Nitrates	230 (23.8)	98 (19.7)	132 (28.2)	.002
Statins	294 (30.4)	143 (28.7)	151 (32.3)	.23
Clinical findings				
Mean Systolic BP, mm Hg	145 (24)	144 (24)	146 (24)	.28
Mean Diastolic BP, mm Hg	85 (14)	84 (14)	85 (15)	.29
Mean heart rate, BPM	81 (17)	81 (16)	82 (19)	.24
Median 0h hs-cTnT, ng/L	7 (4-16)	6 (4-15)	8 (4-17)	.03
Risk stratification, n (%)				
Non-ischemic ECG	904 (93.6)	473 (95.0)	431 (92.1)	.07
History not high risk	826 (85.5)	442 (88.8)	384 (82.1)	.003
EDACS <16	584 (60.5)	326 (65.5)	258 (55.1)	.001
TIMI $\leq$1	486 (50.3)	264 (53.0)	222 (47.4)	.08
HEART $\leq$3	515 (53.3)	289 (58.0)	226 (48.3)	.002
GRACE <140 and pain-free	338 (35.0)	138 (27.7)	200 (42.7)	<.001
Final diagnosis, n (%)				
Index visit MI	76 (7.9)	30 (6.0)	46 (9.8)	.03
30-day MACE	117 (12.1)	48 (9.6)	69 (14.7)	.02

Values are presented as n (%), mean (SD), or median (IQR).
BMI: body mass index; BP: blood pressure; BPM: beats per minute; CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; EDACS: Emergency Department Assessment of Chest pain Score; GRACE: Global Registry of Acute Coronary Events; HEART: History, ECG, Age, Risk factors, Troponin; hs-cTnT: high sensitivity cardiac troponin T; IQR: interquartile range; MI: myocardial infarction; NOAC: novel oral anticoagulant; PCI: percutaneous coronary intervention; SD: standard deviation; TIA: transient ischemic attack; TIMI: Thrombolysis In Myocardial Infarction; y: years.
*0h hs-cTnT measured $\geq$6 h or <6 h after chest pain onset.
**For the comparison of those with a 0 h hs-cTnT $\geq$6 h after chest pain onset and those <6 h.
***Defined as close relative with MI, angina, or cardiac death before the age of 55 years.

Table 2. Diagnostic accuracy of rule-out strategies for an outcome of myocardial infarction.

Rule-out strategy	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	LR (95% CI)	Proportion ruled-out, n (%)
Hs-cTnT[a]	96.7 (82.8-99.9)	79.3 (75.3-82.9)	99.7 (98.5-100)	0.04 (0.01-0.29)	372 (38.5)
Hs-cTnT[a] + ECG[b]	96.7 (82.8-99.9)	77.6 (73.5-81.3)	99.7 (98.5-100)	0.04 (0.01-0.30)	364 (37.7)
Hs-cTnT[a] + ECG[b] + Patient history[c]	100 (88.4-100)	73.7 (69.5-77.7)	100 (98.9-100)	0.00	345 (35.7)
Hs-cTnT[a] + ECG[b] + TIMI[d]	100 (88.4-100)	49.2 (44.5-53.8)	100 (98.4-100)	0.00	230 (23.8)
Hs-cTnT[a] + ECG[b] + EDACS|	96.7 (82.8-99.9)	59.8 (55.2-64.3)	99.6 (98.0-100)	0.06 (0.01-0.38)	281 (29.1)
Hs-cTnT[a] + HEART[e]	100 (88.4-100)	59.8 (55.2-64.3)	100 (98.7-100)	0.00	280 (29.0)
Hs-cTnT[a] + GRACE[f] + pain-free	100 (88.4-100)	21.6 (17.9-25.6)	100 (96.4-100)	0.00	101 (10.5)

Other abbreviations as in Table 1.
CI: confidence interval; NPV: negative predictive value; LR: likelihood ratio.
[a]Defined as high sensitivity cardiac troponin $T \leq 14$ ng/$L \geq 6$ h after symptom onset.
[b]Defined as ECG showing no signs of acute ischemia.
[c]Defined as patient history not assessed as high risk.
[d]Defined as TIMI score $\leq$1; |Defined as EDACS <16.
[e]Defined as HEART score $\leq$3.
[f]Defined as GRACE score <140.

Table 3. Diagnostic accuracy of rule-out strategies for an outcome of 30-day MACE.

Rule-out strategy	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	LR- (95% CI)	MACE missed n (UA/MI)
Hs-cTnT[a]	77.1 (62.7-88.0)	80.2 (76.2-83.8)	97.0 (94.8-98.5)	0.29 (0.17-0.48)	11 (10/1)
Hs-cTnT[a] + ECG[b]	79.2 (65.0-89.5)	78.7 (74.6-82.4)	97.3 (95.0-98.7)	0.26 (0.15-0.46)	10 (9/1)
Hs-cTnT[a] + ECG[b] + Patient history[c]	93.8 (82.8-98.7)	76.0 (71.8-79.9)	99.1 (97.5-99.8)	0.08 (0.03-0.25)	3 (3/0)
Hs-cTnT[a] + ECG[b] + TIMI[d]	97.9 (88.9-100)	50.9 (46.2-55.6)	99.6 (97.6-100)	0.04 (0.01-0.29)	1 (1/0)
Hs-cTnT[a] + ECG[b] + EDACS[e]	93.8 (82.8-98.7)	61.8 (57.1-66.3)	98.9 (96.9-99.8)	0.10 (0.03-0.30)	3 (2/1)
Hs-cTnT[a] + HEART[f]	100 (92.6-100)	62.2 (57.6-66.7)	100 (98.7-100)	0.00	0 (0/0)
Hs-cTnT[a] + GRACE[g] + pain-free	91.7 (80.0-97-7)	21.6 (17.8-25.7)	96.0 (90.2-98.9)	0.39 (0.15-1.0)	4 (4/0)

Other abbreviations as in Tables 1 and 2.
MACE: major adverse cardiac event; UA: unstable angina.
[a]Defined as high sensitivity cardiac troponin $T \leq 14$ ng/$L \geq 6$ h after symptom onset.
[b]Defined as ECG showing no signs of acute ischemia.
[c]Defined as patient history not assessed as high risk.
[d]Defined as TIMI score ≤ 1.
[e]Defined as EDACS < 16.
[f]Defined as HEART score ≤ 3.
[g]Defined as GRACE score < 140.

index visit, but not for ruling out 30-day MACE. It was also the most ineffective strategy, identifying only a small proportion of patients for rule-out, and did not provide a clinically relevant improvement compared to using hs-cTnT alone.

Although using a single hs-cTn ≥ 6 h after chest pain onset for rule-out has been recommended by the ESC guidelines since 2011 [25], only a few studies have evaluated its performance. Additionally, most of these studies have not incorporated GRACE score and the patient being pain-free, and none have previously combined this strategy with other risk stratification tools or evaluated its performance for a 30-day MACE outcome.

Among previous studies, those evaluating a single hs-cTnI ≥ 6 h have yielded NPVs ranging between 96.1-100% for ruling out MI, with large variations depending on the study cohort, the hs-cTnI assay used, and whether combined with GRACE score or not [10–12]. With hs-cTnT, Wildi *et al.* have shown that the hs-cTnT and GRACE score strategy yields a NPV of 99.8% for ruling out MI [12]. Our results are in line with those of Wildi *et al.* showing that this strategy has a sufficient NPV for ruling out MI. Our results however further show that this strategy does not perform adequately for ruling out 30-day MACE with a NPV that is likely not acceptable by most ED physicians [26].

All missed events were MI and UA, and it has previously been reported that the test threshold for ACS is about 2%. This means that among patients who have a probability of having ACS $<2\%$, additional testing is more likely to be harmful than beneficial [27]. Optimally, a rule-out strategy should therefore have a NPV $>98\%$ for an outcome including MI and UA, while most consider that the NPV for MI alone should be $\geq 99.5\%$ [24].

In our cohort, hs-cTnT in combination with HEART, EDACS, TIMI as well as ECG + patient history fulfilled these safety thresholds for both outcomes, and all four strategies had a LR ≤ 0.1.

Both the GRACE score and TIMI score were initially developed as a mean of risk stratifying patients with confirmed ACS, and not unselected ED chest pain patients [28,29]. They were thereby not derived for diagnosing ACS, and consequently do not incorporate aspects of the chest pain history. Although TIMI score-based strategies have been shown to perform well in the ED setting [15,30], such data for the GRACE score is lacking. It has furthermore been shown to perform inferiorly to other scores such as TIMI, HEART and EDACS for predicting 30-day MACE [31–33]. TIMI, HEART, EDACS and ECG + patient history strategies have however consistently been shown to perform well in this regard, both in observational studies as well as randomized controlled trials [13,15,34,35].

Our results confirm these findings, and thereby question the current ESC recommendation of using GRACE score as a risk stratification tool in the ED in combination with $a \geq 6$ h hs-cTn. The fact that HEART, TIMI, EDACS and ECG + patient history strategies are more commonly used in real clinical practice as means of risk stratification [36,37] further emphasizes that they should be the preferred recommended risk stratification tools. Which one of these four to use is more a matter of preference with each having their strength and limitations with regards to subjective components, safety, and efficacy.

Due to the poor performance of hs-cTn obtained ≥ 6 after chest pain onset in studies using hs-cTnI [10,11], concerns have been raised regarding the safety of this strategy, and the ESC biomarker group has also advised caution with

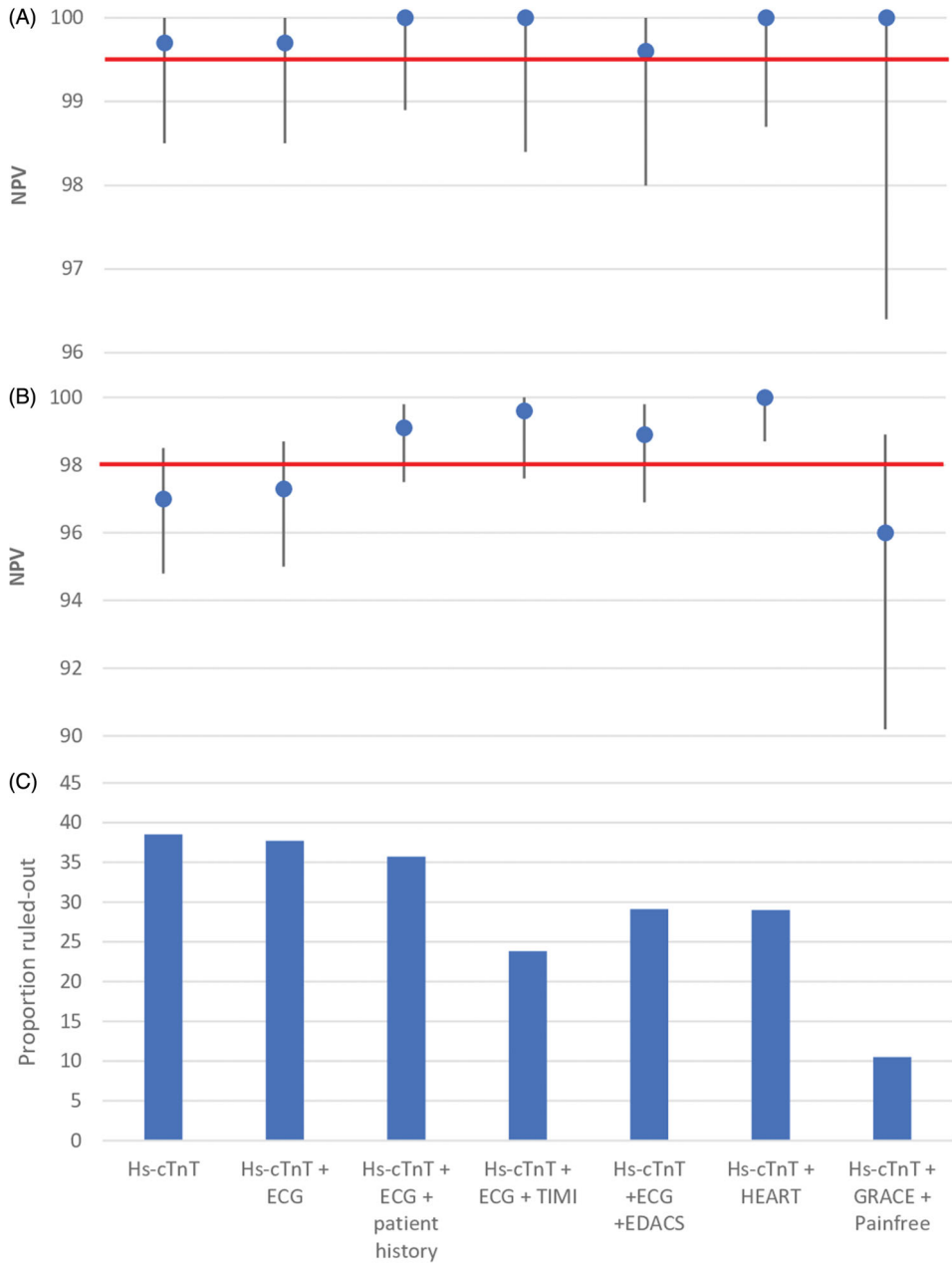

Figure 1. Negative predictive value of rule-out strategies for (A) MI (B) 30-day MACE and (C) proportion ruled-out with the different strategies. The red lines delineate the lowest acceptable NPVs. Abbreviations as in Tables 1–3.

using this approach [38]. Our results however show that the limitations perhaps may be overcome by combining this strategy with an appropriate risk stratification tool. This could enable a rapid safe rule-out, with the potential to reduce ED length of stay. We would however not recommend this strategy in cases where there are difficulties in obtaining an accurate time of chest pain onset.

We could further show that a single hs-cTnT obtained ≥4 h after chest pain onset was sufficiently safe for ruling out MI. It is therefore perhaps possible to lower current recommendations of a 6 h limit, which could increase the proportion of patients identified for single hs-cTnT rule-out. This should however only be seen as hypothesis generating, and these results would need to be validated in other settings before clinical implementation.

The purpose of this study was to evaluate a rule-out method for identifying patients for safe discharge. Among those not identified for rule-out with this strategy, still only a minority will have a 30-day MACE. In these patients, the addition of a second hs-cTnT as part of a 0 h/1h, 0 h/2h, or a 0 h/3h strategy will further identify a large proportion for safe discharge [9,13,15,30,35,39–41].

The use of a 0 h/1h algorithm is currently also recommended by the ESC guidelines. This approach includes a single hs-cTn rule-out strategy using a hs-cTnT <5 ng/L. We believe the ≥6 h hs-cTnT strategy complements this

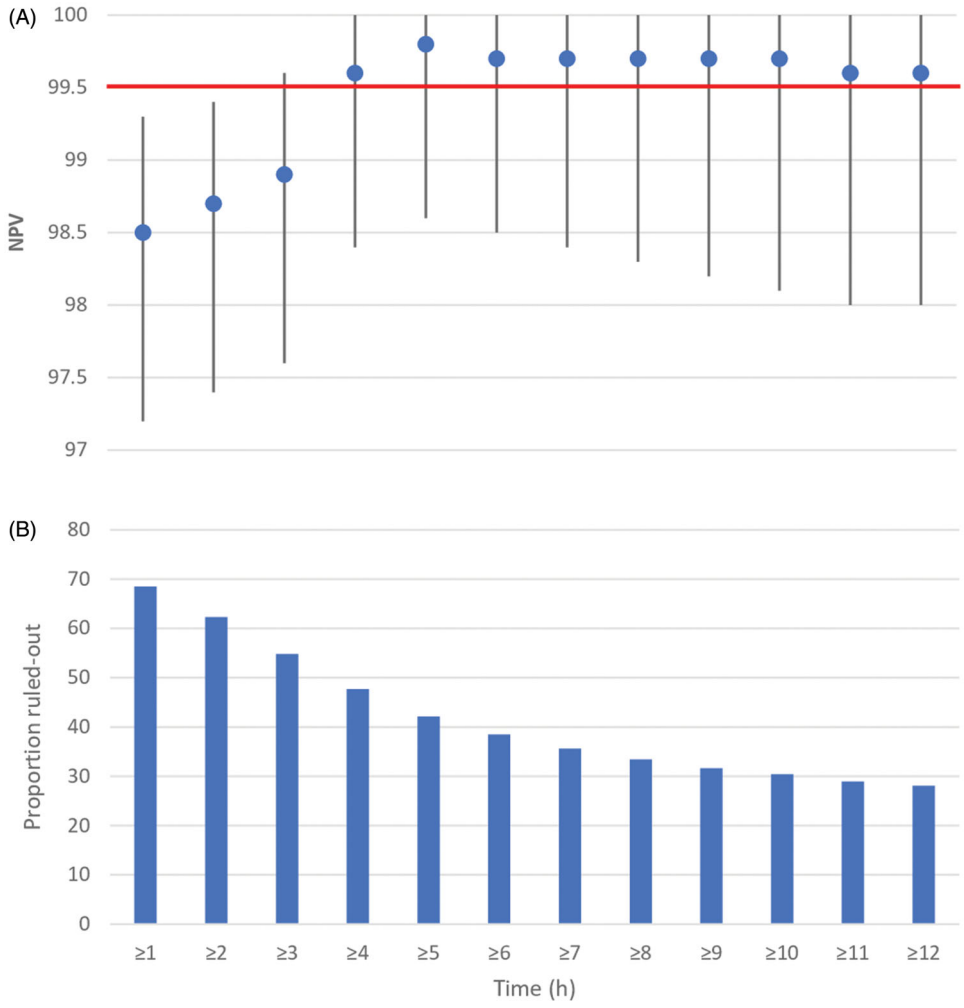

Figure 2. (A) Negative predictive value and (B) proportion of patients ruled-out with a hs-cTnT ≤14 ng/l based on time of chest pain onset to 0 h hs-cTnT measurement for an outcome of index visit MI. Abbreviations as in Table 1.

algorithm as about 55% of those identified by the ≥6 h strategy had a hs-cTnT ≥5 ng/L and would not have otherwise been identified for a single hs-cTnT rule-out. This indicates that this strategy could be incorporated into the ESC 0 h/1h algorithm as to potentially enable an even more rapid assessment by increasing the proportion of patients eligible for single hs-cTnT rule-out.

Limitations

Patients were included in a tertiary care university hospital and the results might not be generalizable to other settings with different ACS prevalence. Our MACE/ACS prevalence was however similar to the average ED rate reported in a recent systematic review [7]. Nevertheless, our results should be validated in other settings, and the NPVs will likely be lower in settings with a higher MACE/ACS prevalence and higher in settings with a lower prevalence.

We did not include patients during all hours of the day and during weekends why there may be some selection bias. We have however previously shown that patients who were not enrolled were similar to the included patients with regard to age, sex and MI prevalence [13]. Our MI and UA prevalence was also similar to what was seen in a previous study with 24 h patient inclusion at our ED [42], which indicates that the present sample likely is representative of our ED chest pain population.

We excluded patients with missing data, which may also have led to selection bias. There were however no large differences between those included and excluded why this likely only had a small impact on our results if any.

Our results were obtained using Roche hs-cTnT, and they do not necessarily apply to hs-cTnI assays, especially since studies using hs-cTnI assays have shown lower NPVs with ≥6 h hs-cTn strategies [10–12].

Patient data were collected by research assistants and not by the ED physicians, which would have more accurately reflected real life clinical practice. This is however common practice in ED research.

Conclusion

A single hs-cTnT ≤14ng/L obtained ≥6 h from chest pain onset, with and without GRACE score, reliably ruled out MI

but did not perform well for ruling out 30-day MACE. These results question current guideline recommendations, and indicate that HEART, EDACS, TIMI, or ECG + patient history strategies should be the preferred risk stratification tools.

Additionally, in this cohort a single hs-cTnT ≤14 ng/L obtained ≥4 h from chest pain onset could safely rule out MI, and if validated, could enable lowering the current 6 h recommendation.

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Disclosure statement

No potential conflict of interest was reported by the authors.

Author contributions

All authors have read and approved the final manuscript and meet the criteria for authorship as established by the ICMJE.

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