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Rapid rule-out of suspected acute coronary syndrome in the Emergency Department by high-sensitivity cardiac troponin T levels at presentation

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Abstract

The reliability of initial high-sensitivity cardiac troponin T (hs-cTnT) under limit-of-detection in ruling-out short- and long-term acute coronary events in subjects for suspected non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is not definitely settled. In a retrospective chart review analysis, 1001 subjects with hs-cTnT ≤ 14 ng/L out of 4053 subjects with hs-cTnT measured at Emergency Department (ED) presentation were recruited. The main outcome measure is fatal or non-fatal myocardial infarction (MI) within 30 days; secondary outcomes are MI or major acute coronary events (MACE) as a combination of MI or re-hospitalization for unstable angina within 1 year. In subjects with hs-cTnT < 5 ng/L [32.6% of cases, mean age 63 years (interquartile range 23)], no cases (0%, NPV 100%) had MI within 30 days, 2 cases (0.6%, NPV 99.4%) MI at 1-year, and 11 cases (3.4%, NPV 96.6%) MACE at 1-year. Patients with hs-cTnT < 5 ng/L would have benefited from a shortened decision (9.30 h and 53% overnight ED stay saved). Hs-cTnT < 5 ng/L is confirmed as safe for patients and comfortable for physicians in ruling out MI or MACE both at short and long term, suggesting that a sizable number of patients can be rapidly discharged without unnecessary diagnostic tests and ED observation.

Keywords Undetectable high-sensitivity cardiac troponin T · Suspected non-ST-segment elevation acute coronary syndrome · Emergency department · Myocardial infarction

Introduction

In subjects with suspected acute coronary syndrome without persistent ST-segment elevation (NSTE-ACS), the availability of highly sensitive assays for the measurement of cardiac troponin (hs-cTn) has significantly improved the diagnostic accuracy of the diagnosis of myocardial infarction (MI).

For these subjects, the European Society of Cardiology proposes a diagnostic algorithm which indicates undetectable, i.e., below the assay-specific limit of detection, hs-cTn concentration at presentation as a useful tool to rule out MI [1], in particular when myocardial ischemia cannot be detected in the admission electrocardiogram (ECG) and time from symptom onset to presentation exceeds 3 h [2–12].

However, a comprehensive evaluation of subjects with suspected NSTE-ACS focuses not only on the rapid exclusion of MI as the index event, but also on a patient's safe disposition. In fact, the decision to discharge is based on the risk estimate of adverse cardiac events over a longer time period, typically 30 days [12–14].

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The high negative predictive value (NPV) of undetectable troponin for MI exclusion within the 30-day time-window might streamline the chest pain pathway, reducing the time spent in the ED and the hospital admission rate, without compromising patient safety.

We attempt to confirm the reliability of the combination of an ECG without signs of ischemia and undetectable high-sensitivity cardiac troponin T (hs-cTnT) at presentation to identify the clinical characteristics of the subjects who can benefit from this approach, and to calculate the potential time savings, unnecessary cardiac ECG recordings and hs-cTnT determinations associated with this strategy.

Methods

The hospital has a total capacity of 450 beds, the number of patients presenting to the adult ED being 47,500 during the study period. Patients who presented to the ED were identified from the district hospital registry. The ED of Forlì hospital is the only department where subjects with ACS are referred from the area; therefore, no case of suspected NSTE-ACS has expected to be lost in the study period. Catheterization laboratory performing percutaneous coronary interventions (PCI) is available on a 24-h basis 7 days a week. The hospital database is directly connected with the General Registry Office of the District.

In our setting, a dedicated pathway to evaluate subjects with suspected ACS has been in operation since 2003. At discretion of the attending physician, patients with baseline an ECG without signs of ischemia and hs-cTnT concentration below the 99th percentile (≤ 14 ng/L), are monitored and observed up to 12–24 h with serial 12-lead ECGs, and hs-cTnT determinations (3, 6 and eventually 12 h after presentation). Following a negative 12–24 h observation in ED and cardiology consult, second-line diagnostic tests are performed at the time of hospital discharge (exercise stress testing) or planned soon thereafter (mainly 99 m-Tc exercise myocardial scintigraphy or dobutamine stress-echocardiography).

All patients in whom the attending emergency physician requested serial hs-cTnT determination, with 1-st hs-cTnT concentration ≤ 14 ng/L, for suspected NSTE-ACS from 1 January to 31 December 2015 were eligible for the inclusion [15]. Archived laboratory data were retrieved to determine which patients had at least 2 hs-cTnT determinations. Presenting complaints and medical history of the study population are listed in Table 1. Subjects who attended the ED more than once during the study period were considered for analyses only on first admission.

Inclusion criteria were age > 18 years and the absence of signs of myocardial ischemia in an admission ECG. The clinical evaluation of the study population comprised a thorough assessment of risk factors for coronary artery disease (CAD), including gender, age, smoking habit, arterial hypertension, diabetes mellitus, hypercholesterolemia, history of CAD, and history of cerebrovascular accidents (CVA). The GRACE risk score [16] was considered in relation to initial hs-cTnT levels (Table 1).

Excluded were subjects with: a previous finding of left bundle branch block, STEMI at first ECG evaluation, definite NSTE-ACS following first ECG showing ischemic changes and hs-cTnT determination > 14 ng/L, subjects with single hs-cTnT determination for other reasons than suspected NSTE-ACS and ECG without signs of ischemia (Fig. 1). In the present analysis, subjects with an initial hs-cTnT ≤ 14 ng/L were categorized into 2 groups according to the initial hs-cTnT level: < 5 ng/L and 5–14 ng/L (Fig. 1). The ethics committee of the CEII AV Romagna—Forlì approved the study (3788/2016/O/OssN, June 15, 2016).

Two expert cardiologists (CB and FO), blinded to hs-cTnT results, were asked to review the ECGs recorded at admission to assess the presence of myocardial ischemia defined as [17]:

1. ST-segment elevation in two contiguous leads with cut points of ≥ 0.1 mV in all leads, except for leads V2–V3, where ≥ 0.2 mV in men ≥ 40 years of age and ≥ 0.25 mV in men < 40 years of age and ≥ 0.15 mV in women were applied, or
2. left bundle branch block that was considered new compared with previous ECGs (if available), or
3. significant ST-segment depression, defined as a horizontal or downsloping ST-segment ≥ 0.05 mV in two contiguous leads, or
4. T wave inversion ≥ 0.1 mV in two contiguous leads with prominent R wave or R/S ratio > 1. Disagreements were resolved by discussion.

Hs-cTnT was measured in the local laboratory using the Elecsys® Troponin T hs performed on Cobas 6000, e601 system (Roche Diagnostics GmbH, Mannheim, Germany) in plasma samples immediately after collection. This assay has a limit of detection of 5 ng/L, a limit of blank of 3 ng/L, a 99th percentile cutoff point of 14 ng/L, and a coefficient of variation of < 10% at 13 ng/L [18]. The assay performance was independently validated in our local response laboratory under routine working conditions, confirming that the coefficient of variation was 10% at 12.5 ng/L.

Due to the retrospective nature of the study, the time from symptom onset to blood sampling was available only in 721 subjects (72%), whereas the blood sampling time was calculated in all subjects as the time taken from arrival to ED to blood sample drawing. The turn-around time (TAT) of hs-c TnT determination was calculated as the total time taken from the sample to be processed within the laboratory from

Table 1 Baseline characteristics of patients visited in the ED for suspected NSTE-ACS, ECG without signs of ischemia, hs-cTnT at arrival below 99th percentile cutoff levels (≤ 14 ng/L)

Characteristics	≤ 14 ng/L all cases, $N=1001$	< 5 ng/L, $N=326$	5–14 ng/L, $N=675$
Demographic			
Male	550 (54.9)	148 (45.4)#	402 (59.6)
Age, years[a]	63 ± 23	51 ± 15**	69 ± 18
Presenting complaint			
Chest pain	805 (80.4)	279 (85.6)[#]	526 (77.9)
Palpitations	141 (14.1)	47 (14.4)	94 (13.9)
Dyspnea	78 (7.8)	16 (4.9)	62 (9.2)
Syncope	36 (3.6)	5 (1.5)[#]	31 (4.6)
Other	57 (5.7)	14 (4.3)	43 (6.4)
Medical history			
Hypertension	584 (58.3)	130 (39.9)[#]	454 (67.3)
Hypercholesterolemia	438 (43.8)	118 (36.2)[#]	320 (47.4)
Smoking	347 (34.7)	126 (38.6)	221(32.7)
CAD	259 (25.9)	54 (16.6)[#]	205 (30.4)
Diabetes	152 (15.2)	35 (10.7)	117 (11.7)
CVA	111 (11.1)	19 (5.8)[#]	92 (13.6)
eGFR (ml/min/1.73 m^2)[a]	76.8 ± 17.3	84.2 ± 23.3**	75.3 ± 16.8
> 60	836 (83.6)	277 (85.0)	559 (82.8)
30–60	148 (14.8)	45 (13.8)	103 (15.3)
< 30	17 (1.7)	4 (1.2)	13 (1.9)
GRACE Score[a]	103 ± 28.0	84.2 ± 23.3**	112.3 ± 25.3
1–108	570 (56.9)	281 (86.2)[#]	289 (42.8)
109–140	334 (33.4)	42 (12.9)[#]	292 (43.3)
141–372	97 (9.7)	3 (0.9)[#]	94 (13.9)

Data are reported as number of cases and (percentage)

CAD history of coronary artery disease, *CVA* history of cerebral vascular accident, *eGFR* estimated glomerular filtration rate

[a]Variables described as mean ± standard deviation

[#]Fisher's exact test for categorical variables

**Student's t test for ordinal variables significant for $P<0.05$ comparing patients with hs-cTnT < 5 vs. 5–14 ng/L

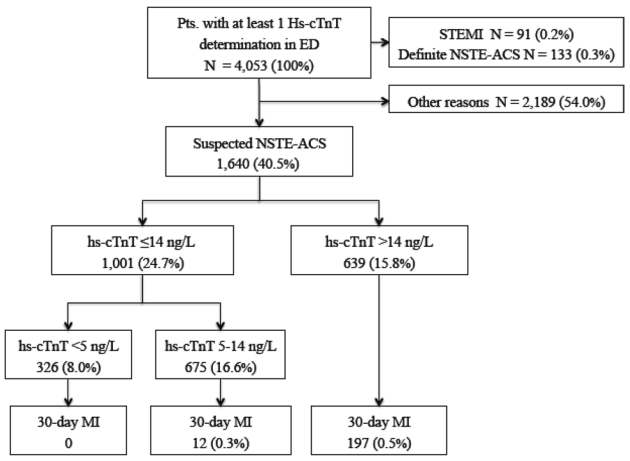

Fig. 1 Flow diagram showing the selection of patients and number of primary outcome measures in the different groups. Patients with hs-cTnT > 14 ng/L were excluded from the present analysis

arrival at the reception until a validated result. ED length of stay (LoS) was considered as the difference from patients' ED arrival time to final disposition (home discharge or hospital admission).

The estimated LoS (eLoS) was calculated as the total time from individual patients' ED arrival to the validated hs-cTnT laboratory result. ED overnight stay was considered as the ED stay for observation out of hours (from 20.00 to 8.00).

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [19]. Chronic kidney disease was defined as an eGFR of < 60 ml/min/1.73 m^2.

The occurrence of outcomes was assessed by a systematic search of death certificates and medical databases of our local health district. This approach allows the detection of all patients' presentations at our hospital. Two investigators (MA, BB) independently reviewed the clinical information including invasive and non-invasive investigations.

Outcome measures were separately adjudicated by two cardiologists (BC, OF) with all clinical, laboratory (including subsequent hs-cTnT results obtained at physician discretion), ECG-graphic, and imaging (echocardiography, cardiac stress testing, lesion severity and morphology at coronary angiography) data available for review, but blinded to initial laboratory results. Any discrepancies were resolved by the adjudication of a third independent reviewer (MG).

Myocardial infarction was adjudicated according to the third universal MI definition [17], which requires the biochemical evidence of myocardial injury (at least one hs-cTnT concentration above the 99th percentile with a rising or falling pattern, i.e., change in concentration exceeding 50% when baseline level was below the 99th percentile, and 20% in comparison with the previous sample when it was elevated [20] associated with evidence of myocardial ischemia (ischemic symptoms, ECG changes or imaging evidence). Patients were retrospectively classified as having type 1 or type 2 MI, or acute myocardial injury [17]. Type 1 MI was defined as myocardial injury in subjects with clinical presentation typical for acute coronary syndrome and evidence of myocardial ischemia as detected by available investigations. Type 2 MI was considered in patients with symptoms or signs of myocardial ischemia due to imbalance of oxygen supply (e.g., tachydysrhythmia, hypotension, or anemia) associated with myocardial injury. Acute myocardial injury was defined as evidence of injury in the absence of any clinical feature of ischemia. Only patients with type 1 MI as the index event or during follow-up were considered for this analysis.

The primary outcome measure is the combination of fatal or non-fatal MI at 30-days. Secondary outcome measures are otherwise considered the combination of fatal or non-fatal MI at 1 year, or major acute coronary events (MACE), i.e., the combination of fatal, non-fatal MI and re-hospitalization for unplanned coronary revascularization for unstable angina (UA) at 1-year follow-up. [21] In the absence of accepted standards for the diagnosis of UA, we considered as UA all subsequent admissions to the ED for suspected NSTE-ACS, in the absence of biochemical evidence of myocardial injury, followed by percutaneous coronary intervention during the index admission, i.e., unplanned coronary revascularization.

Fatal MI was defined as any death due to MI recorded during the follow-up.

Data are reported as mean, standard deviation, number of cases, percent with 95% confidence intervals. Fisher's exact test for categorical variables and Student *t* test for continuous variables were used to compare variables between groups.

We investigated the independent predictors of hs-cTnT < 5 ng/L by multivariable logistic regression analysis; the variables considered for the analysis were: age, gender, hypercholesterolemia, smoking, diabetes mellitus, history of coronary artery disease (CAD), history of cerebral vascular accident (CVA), eGFR and GRACE risk score. The negative predictive values (NPV) were also calculated. In subjects with initial hs-cTnT < 5 ng/L, a sensitivity analysis of the NPV based on independent predictors selected by the logistic model was performed.

Comparison of the cumulative risk of fatal or non-fatal MI at 1 year between groups was tested by Chi Square log rank Mantel–Cox test in a Kaplan–Meier survival analysis.

Statistical analyses were performed by the SPSS/PC+ statistical package (20.0 edition) and MedCalc (17.8 version). Two-tailed P values < 0.05 were considered statistically significant.

Results

A total of 4053 subjects with at least 1 hs-cTnT determination at ED arrival were considered for a chart review analysis. Ninety one (0.2%) subjects with STEMI and 133 (0.3%) subjects with definite NSTE-ACS were excluded.

Another group of 2189 (54.0%) subjects in whom hs-cTnT determination was performed for other reasons (391 tachydysrhythmia, 376 heart failure, 55 pulmonary embolism, 272 pneumonia, 57 CKD, 462 muscoloscheletal, 203 dyspepsia, 183 syncope, 122 trauma, 49 gastrointestinal disease, 136 other) was also excluded. Finally, 639 (15.8%) subjects, who had suspected NSTE-ACS and initial hs-cTnT concentration > 14 ng/L, were excluded from the analysis (Fig. 1).

In the present analysis, we considered only 1001 subjects out of 4053 (24.7%) subjects with suspected NSTE-ACS, an ECG without signs of ischemia and an initial troponin level ≤ 14 ng/L; in this group, MI occurred in 12 patients: in 7 patients MI was the index event and in 5 patients MI occurred during the follow-up (30 day MI rate 1.2%) (Fig. 1).

As a consequence, disease prevalence of MI in whole group of 1640 subjects with suspected NSTE-ACS is 12.7% (209 cases).

Subjects with hs-cTnT < 5 ng/L were 326 (32.6%) (Table 1): they are younger and more frequently females than subjects with hs-cTnT 5–14 ng/L. Chest pain is the most frequent complaint (80.4% of cases) without differences between groups. Time from symptoms onset to ED arrival was available in only 72% of subjects ($n = 721$). The percentage of subjects presenting within 2 h is low in both groups (11% and 13%, respectively). The eGFR is 76.8 ± 17.3 ml/min/1.73 m^2 with 14.8% of subjects with values between 30 and 60 and only 2% with values < 30 ml/min/1.73 m^2; no differences are found between the categories. Comorbidities are less represented in subjects with hs-cTnT < 5 ng/L. For example, the GRACE risk score is lower in patients with hs-cTnT < 5 ng/l than in those with hs-cTnT 5–14 ng/L (84.2 ± 32.3 vs. 112 ± 25.3 points; P < 0.001) (Table 1).

Among the main characteristics of the patients, independent predictors of hs-cTnT < 5 ng/L are: age below the median (Wald 77.2), female gender (Wald 66.2) and low-risk GRACE score (Wald 11.2).

Initial hs-cTnT sampling time is 1.38 ± 1.30 h with 71% of subjects within 2 h from arrival and 15.6% of cases over 3 h. The TAT is 0.54 ± 0.15 h without differences in relation to initial hs-cTnT levels. The ED stay in the study population is 13.36 ± 8.23 h, without differences between groups. In patients with hs-cTnT < 5 ng/L, the eLoS is 2.34 ± 1.49 h (Table 2). At the end of the chest pain pathway, 97 subjects (9.7%) were hospitalized; the admission rate is significantly different between groups being 2.5% in subjects with hs-cTnT < 5 ng/L and 13.2% in those with hs-cTnT 5–14 ng/L; $P = 0.017$. In subjects with hs-cTnT < 5 ng/L, an overnight stay would have been avoided in 173 out of 326 (53%) cases if they were discharged at the time of availability of hs-cTnT result.

Table 2 Time series analysis in subjects with different hs-cTnT concentration in the study population

	≤14 ng/L all cases; $N = 1001$	<5 ng/L; $N = 326$	5–14 ng/L; $N = 675$
Sampling time	01.38 ± 1.30	1.36 ± 1.26	1.39 ± 1.32
TAT	0.54 ± 0.15	0.57 ± 0.18	0.54 ± 0.16
LoS	13.36 ± 8.32	12.05 ± 7.10	14.01 ± 8.36
eLoS	2.34 ± 1.49	2.30 ± 1.13	2.36 ± 1.65

Data are reported as mean ± standard deviation. Sampling time (h) is considered as the total time from arrival to the Emergency Department to blood sample drawing. TAT (turn around time) as the time from blood sampling to the availability of the validated laboratory result to the clinician. ED length of stay (LoS) is calculated from patient ED arrival to the final disposition (discharge or admission). eLoS is the hypothetical ED length of stay estimated from the patient's ED arrival to the available and validated result of initial hs-cTnT determination. Fisher's exact test significant for $P < 0.05$ comparing patients with hs-cTnT < 5 vs. 5–14 ng/L: no differences were observed

At 30-day follow-up, no subjects out of 326 with hs-cTnT < 5 ng/L had MI (NPV 100%); in the group of 675 subjects (67.4%) with hs-cTnT 5–14 ng/L, the primary outcome measure occurred in 12 subjects (1.8%); the NPV is 98.2% (Table 3).

At 1 year, an MI occurred in 2 subjects (0.6%) with hs-cTnT < 5 ng/L and in 26 cases (3.9%) with hs-cTnT 5–14 ng/L (NPV 99.4% vs. 96.1%, respectively; $P = 0.002$). MACE are recorded in 11/326 subjects (3.4%) with hs-cTnT < 5 ng/L and in 54 subjects (8.0%) with hs-cTnT 5–14 ng/L (NPV 96.6% vs. 92.0%, respectively; $P = 0.006$) (Table 3).

The cumulative risk of MI at 1 year is significantly different between groups (Chi square log rank Mantel–Cox test $P = 0.004$; Fig. 2).

When stratified by independent predictors of hs-cTnT < 5 ng/L, the NPV for 1 year MI was is confirmed to be 100% in subjects under the median age (63 years) and in those with low-risk GRACE score (Table 4).

Discussion

The study provides further evidence that patients presenting to the ED for symptoms suspected for NSTE-ACS, with an ECG without signs of ischemia and initial hs-cTnT concentration < 5 ng/L, may be safely discharged without unfavorable outcomes at short- and long-term follow-up. This finding would streamline the ED chest pain pathway, sparing

Table 3 Negative predictive value of different hs-c-TnT thresholds at presentation under the 99th percentile in the prediction of outcome measures

Outcome measures	<5 ng/L all cases ($N = 326$)	5–14 ng/L ($N = 675$)
30 days		
Fatal or non-fatal MI		
No. of cases (% with 95% CI)	0	12 (1.8%; 1.0–3.0%)
NPV	100%	98.2% (98.1–98.3%)
1-year		
Fatal or non-fatal MI		
No. of cases (% with 95% CI)	2 (0.6%; 0.1–2.0%)[#]	26 (3.9%; 2.6–5.5%)
NPV	99.4% (97.7–99.8%)	96.1% (95.7–96.5%)
MACE		
No. of cases (% with 95% CI)	11 (3.4%; 1.8–5.7%)[#]	54 (8.0%; 6.1–10.2%)
NPV	96.6% (94.3–98.0%)	92.0% (91.1–92.8%)

Data reported as number of cases and percentage with 95% confidence intervals

NPV negative predictive value, *MI* myocardial infarction, *MACE* major acute coronary events as combination of fatal MI, non-fatal MI or re-hospitalization for unplanned percutaneous coronary intervention

[#]Fisher's exact test significant for $P < 0.05$ comparing patients with hs-cTnT < 5 vs. 5–14 ng/L

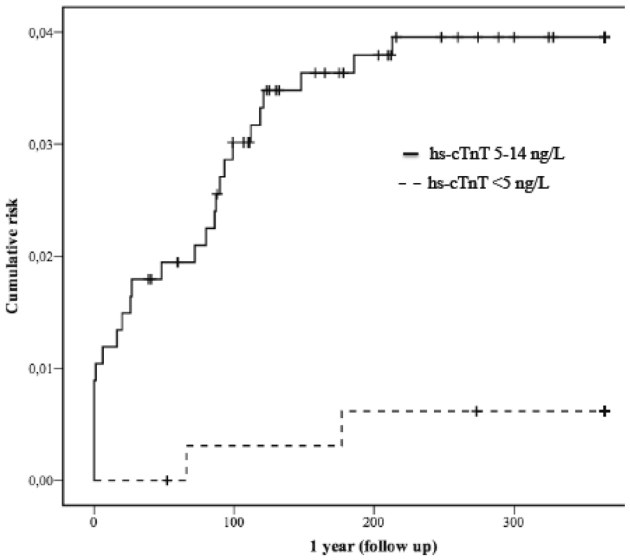

Fig. 2 Cumulative risk over time as a result of Kaplan–Meier analysis in subjects with initial high-sensitivity cardiac troponin t (hs-cTnT) at different concentrations. The results are reported as the cumulative risk of fatal or non-fatal MI in subjects with initial hs-cTnT 5–14 ng/L (upper panel) and < 5 ng/L (lower panel) (*P* for significance = 0.004)

Table 4 Negative predictive value of initial hs-cTnT < 5 ng/L for fatal or non-fatal MI at 1 year, stratified by predictor variables selected in the logistic model

Characteristics	True negative	False negative	Negative predictive value (95% CI)
Gender			
Male	147	1	99.3% (97.3–99.8%)
Female	177	1	99.4% (97.8–99.9%)
Age (years)			
> 63	58	2	96.7% (95.8–97.3%)
≤ 63	266	0	100%
Grace Score			
≤ 108	281	0	100%
> 108	43	2	95.6% (94.2%–96.6%)

Data reported as number of cases, negative predictive value as percentage with 95% confidence intervals

unnecessary examinations and reducing ED hours of observation in a sizable number of patients.

The strategy to rapidly rule out fatal and non-fatal MI in subjects with suspected NSTE-ACS and undetectable hs-cTn levels has been widely proposed by several studies [4, 13, 14, 22–27] and later confirmed in the case of hs-cTnT in a recent meta-analysis that includes 9241 participants from 11 studies: the pooled NPV is 99.3% (95% CI 97.3–99.8%), ranging from 96.5 to 100% [28]. Our results, obtained in an all-comers population presenting to a community hospital (at a variance with the cited studies that were conducted in academic centers), are in keeping with these findings (NPV 100%) confirming also that more than 30% of subjects with initial hs-cTnT below the 99th percentile might be rapidly discharged after clinical evaluation, an ECG and single-sample troponin determination. The ability to rule out MI without serial testing may became a paradigm-changing innovation with important implications in terms of ED efficiency and diagnostic accuracy.

The reliability of this approach was also confirmed in the presence of a different prevalence of subjects with an undetectable troponin, which is 32.6% in our study, but ranges from 6% in the ADAPT study [29] to 60.8% in one large retrospective study [14]. This may depend on different patient characteristics: the median age in our study is 51 years, with males accounting for 45.4% of cases, median age ranging from 47 [14] to 56 years [22] and the prevalence of males from 47% [22] to 53% [14]. Further differences might also be explained by underlying comorbidities, namely diabetes mellitus, 10.7% in our study vs. 4.7% [14] and 12% [22], and history of coronary disease, which is 16.6% in our series and in 4.0% [14] and 12% [22] in previous studies. The triage code assignment and the decision to perform the initial blood sampling by a nurse, as part of a nurse-initiated pathway, might further influence the prevalence of subjects with undetectable troponin by including very low-risk cases. We are reassured that in our study this has not happened, because all subjects were considered for the chest pain pathway only following the clinical evaluation by the attending emergency physician. This reinforces the assumption that in our analysis only patients with really suspected NSTE-ACS are included and explains the time interval from patient presentation to blood sampling.

There are concerns regarding the robustness of undetectable hs-cTn as the sole indicator for MI exclusion. In our study, independent predictors of undetectable hs-Tn are: younger age (below the median), female gender and low-risk GRACE score. It is unknown whether the NPV would be so high in non-low-risk patients. In fact, given the low number of events recorded, we are not able to ascertain whether the NPV would remain high in elderly, male and intermediate or high-risk GRACE score subjects.

In the US, the limit of quantification of the hs-cTnT assay has been set by the FDA at 6 ng/L, since at this concentration, the precision of the assay is considered acceptable (CV 20%). This cutoff value has been recently proposed in a retrospective study [30], being 40% of ED subjects with chest pain below the limit of detection. At 30 days, the single troponin assay has an NPV of 99.9% (95% CI 99.8–100) [30]. We reanalyzed our data using hs-cTnT < 6 ng/L as the cutoff for MI rule out, but the NPV is still confirmed at 100%.

A streamlined chest pain pathway would be appreciated by emergency physicians, especially in low-risk subjects:

it should be time saving, with unnecessary hospital admissions, without hazards in terms of unfavorable outcome at short and long-term follow-up. In our study, the admission-to-hospital rate is 9.7%, being only 2.5% (8 cases out of 326) subjects with hs-cTnT < 5 ng/L, and 13.2% (89 out of 675) in those with hs-cTnT 5–14 ng/L. This figure sounds different from previous studies in which hospital to admission rate ranges from 22 [14] to 61% [22], suggesting that chest pain pathways are very different in the disposition decision.

An important finding of our study is that the strategy of discharge at the time of the hs-cTnT laboratory result would have saved up to 9.30 h per patient, avoiding overnight stays in the ED by over 50% of cases. This is in keeping with a recent study in which the accelerated decision based on initial hs-cTnT < 5 ng/L saved 6.2 h in ED stay, avoiding 7.5% of short stay unit admissions and 25% of admissions to a cardiac ward; such results were obtained without the occurrence of ACS at 30 days [31].

There is concern with respect to the accuracy of the final decision to rapidly discharge a patient after a single troponin determination when subjects present within 2 h from symptoms onset [27]. Unfortunately, we do not have data of sufficient quality to address this important issue. In fact, time from symptom onset to ED arrival was available in only 72% of cases and, similarly to other studies [22], only a few cases (around 10%) present at less than 2 h. We, however, measured in 100% of patients the sampling time, i.e., the time between ED arrival and blood sampling: in our series it was 1.38 h, a time interval similar that observed in the TRAPID study [32]. This reassures that the time interval between symptom onset and blood sampling is in the vast majority of patients higher than 2 h.

This study has limitations. First: this is a retrospective chart review analysis examining the clinical characteristics and the outcome of subjects presenting to our ED, who had hs-cTnT measured as part of routine practice: the present method might increase the risk of missing patients with the outcomes of interest. This approach has limited the collection of important variables such as the time of symptom onset, thus making inaccurate the calculation of the time from symptom onset to ED arrival in 28% of patients. On the other hand, such approach made possible the inclusion of consecutive patients, avoiding non-random selection or exclusions due to missing data. Therefore, this study documents the clinical value of hs-cTnT when assayed in the local rapid response laboratory.

Second: we are exposed to a beta-type error having included only 1001 cases. As previously suggested [22, 26, 33], an NPV of 99.5%, for an α error of 0.05 and with a power of 92% to test the null hypothesis, would have required the enrollment of approximately 3500 subjects.

Third: the analysis was based on a single centre cohort, which may limit the generalisability of the results.

Fourth: the high level of NPV of undetectable hs-cTnT for safe rule out of MI could have been overestimated, since NPV decreases when the disease prevalence increases; in this case sensitivity, which is independent from disease prevalence, should be used. In our study, disease prevalence is 12.7%, a value fairly below the threshold affecting the NPV [34]. In addition, in our series, the false-negative rate of undetectable hs-cTnT of 0% reassures us that the results would not have changed if we had used sensitivity instead of NPV.

In summary, our study provides further evidence that in subjects with symptoms suspected for NSTE-ACS, a rapid rule out of MI, based on a streamlined pathway (i.e., rapid discharge based on single hs-cTnT concentration < 5 ng/L, and a negative ECG in subjects with low-risk profile), may be considered safe for patients and comfortable for physicians. This strategy should lighten the burden of chest pain pathway in the ED, i.e., serial controls, hours of observation, overnight stays, and inappropriate cardiac testings without hazards of unfavorable outcomes.

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Author contributions AF and MG had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the results. All authors were involved in the study concept and design and statistical analyses. MC, BB, AM, SS and BC were responsible for collection, management, analyses and interpretation of the data. AF and MG conducted the statistical analyses and drafted the manuscript. All authors contributed substantially to its revision and agree to be accountable for all the aspects of the work. FO, ASJ and RD supervised the study. AF takes responsibility for the paper as a whole.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

Statement of human and animal rights The authors declare that all contents in this study are in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent This is a retrospective study and for this type of study formal consent is not required.

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