Novel criteria for the Observe-Zone of the ESC 0/1h-hs-cTnT Algorithm

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Abstract (348 words)

Background: The non-ST elevation myocardial infarction (NSTEMI) guidelines of the European Society of Cardiology (ESC) recommend a 3h cardiac troponin determination in patients triaged to the observe-zone of the ESC 0/1h-algorithm; however, no specific cut-off for further triage is endorsed. Recently, a specific cut-off for 0/3h high-sensitivity cardiac troponin T (hs-cTnT) change (7ng/L) was proposed warranting external validation.

Methods: Patients presenting with acute chest discomfort to the emergency department were prospectively enrolled into an international multicenter diagnostic study. Final diagnoses were centrally adjudicated by two independent cardiologists applying the 4th universal definition of MI, based on complete cardiac work-up, cardiac imaging and serial hs-cTnT. Hs-cTnT concentrations were measured at presentation, after 1h and 3h. The objective was to externally validate the proposed cut-off, and if necessary, derive and internally as well as externally validate novel 0/3h-criteria for the observe-zone of the ESC 0/1h-hs-cTnT-algorithm in an independent multicenter cohort.

Results: Among 2076 eligible patients, application of the ESC 0/1h-hs-cTnT-algorithm triaged 1512 patients (72.8%) to either rule-out or rule-in of NSTEMI, remaining 564 patients (27.2%) in the observe-zone (adjudicated NSTEMI prevalence 120/564 patients, 21.3%). The suggested 0/3h-hs-cTnT-change of <7ng/L triaged 517 patients (91.7%) towards rule-out, resulting in a sensitivity of 33.3% (95%CI 25.5-42.2), missing 80 patients with NSTEMI, and ≥7ng/L triaged 47 patients towards rule-in (8.3%), resulting in a specificity of 98.4% (95%CI 96.8-99.2). Novel derived 0/3h-criteria for the observe-zone patients ruled-out NSTEMI with a 3h hs-cTnT concentration <15 ng/L and a 0/3h-hs-cTnT absolute change <4 ng/L, triaging 138 patients (25%) towards rule-out, resulting in a sensitivity of 99.2% (95%CI 96.0-99.9), missing 1 patient with NSTEMI. A 0/3h-hs-

cTnT absolute change ≥6 ng/L triaged 63 patients (11.2%) towards rule-in, resulting in a specificity of 98% (95%CI 96.2-98.9) Thereby, the novel 0/3h-criteria reduced the number of patients in the observe zone by 36%, and the number of T1MI by 50%. Findings were confirmed in both internal and external validation.

Conclusion: A combination of a 3h hs-cTnT concentration (<15 ng/L) and a 0/3h absolute change (<4 ng/L) is necessary to safely rule-out NSTEMI in patients remaining in the observe-zone of the ESC 0/1h-hs-cTnT-algorithm.

Clinical Trial Registration: ClinicalTrials.gov number, NCT00470587, https://clinicaltrials.gov/ct2/show/NCT00470587

Key words: Troponin, Rule-Out, ESC 0/1h-algorithm, Myocardial infarction, External Validation, Observe-zone

Clinical Perspective

What is new?

- The proposed 0/3h hs-cTnT change (<7 ng/L) criteria provided suboptimal safety for ruling-out NSTEMI in patients remaining in the observe-zone of the ESC 0/1h-algorithm, missing an unacceptable high number of NSTEMIs.
- Novel derived 0/3h-criteria combining a 3h hs-cTnT concentration <15 ng/L and a 0/3h absolute change cut-off <4 ng/L provided high safety for ruling-out NSTEMI in patients remaining in the observe-zone of the ESC 0/1h-hs-cTnT algorithm

What are the clinical implications?

- The previously proposed 0/3h hs-cTnT change <7 ng/L for ruling-out NSTEMI should not be implemented in routine clinical practice.
- The novel derived observe-zone 0/3h-criteria balances safety and efficacy well for further decision making (rule-out and rule-in of NSTEMI) in patients remaining in the observe-zone of the ESC 0/1h-hs-cTnT algorithm
- Internal validation of the novel observe-zone 0/3h-criteria and external validation in an independent international cohort showed robustness of performance metrics, further strengthening its possible clinical use.

Abbreviations

CAD – Coronary artery disease

CI - Confidence Interval

ED – Emergency department

ECG – Electrocardiogram

ESC – European Society of Cardiology

hs-cTn – High-sensitivity cardiac troponin

eGFR – Estimated glomerular filtration rate

IQR – Interquartile range

NSTEMI – Non ST Elevation Myocardial Infarction

NPV – Negative Predictive Value

PPV – Positive Predictive Value

ROC-AUC – Receiver operating characteristic curves – Area under the curve

STEMI – ST elevation myocardial infarction

T1MI – Type 1 myocardial infarction

T2MI – Type 2 myocardial infarction

Introduction

Annually, more than 10 million patients worldwide present to emergency departments (ED) with symptoms suggestive of acute myocardial infarction (AMI).[1] For the early triage of these patients, the European Society of Cardiology (ESC) 0/1h-algorithm is the most extensively validated algorithm, recommended by the current ESC non-ST elevation myocardial infarction (NSTEMI) guidelines with a Class I recommendation.[2–5] It combines very high safety for early rule-out and high accuracy for rule-in allowing definite triage in about 70 to 75% of patients using the 0h and 1h sample.[2,5,6] Major uncertainties remain regarding the most appropriate management of the 25-30% of patients remaining in the observe-zone.[5,7] While it has become clear that this is a heterogenous group with a considerable incidence of NSTEMI of about 20%, it is unknown how detailed clinical assessment, 12-lead ECG and high-sensitivity cardiac troponin (hs-cTn) at 3h can best be integrated to define the likelihood of NSTEMI and accordingly select the most appropriate management.[5,7]

In an effort to guide the management of patients in the observe-zone of the ESC 0/1h-hs-cTnT-algorithm, a small single-center pilot study including 154 patients in the observe-zone derived specific cut-offs for 0/3h-hs-cTnT-change to identify patients also eligible for early rule-out (<7ng/L) or early rule-in (≥7ng/L) of NSTEMI.[8] This study had a very low incidence of NSTEMI (2.1%) that was adjudicated using a conventional cardiac troponin assay with poor sensitivity rather than hs-cTn (potentially missing small NSTEMIs).[9] Thus, external validation and possible revision in a large multicenter study seems mandatory before this modification of the ESC 0/1h-hs-cTnT-algorithm could be considered for clinical use. To address this major gap in knowledge, we therefore aimed to: (i) externally validate the performance of the suggested cut-off for the observe-zone of the ESC 0/1h-hs-cTnT-algorithm in two large prospective multicenter diagnostic

studies, and (ii) if necessary, derive and internally as well as externally validate novel observe-zone 0/3-hour hs-cTnT criteria for the observe-zone of the ESC 0/1h-hs-cTnT-algorithm for further triaging patients towards rule-out and rule-in.

Methods

The data, code and study material that support the findings of this study are available from the corresponding author upon reasonable request.

Study design and population

Advantageous Predictors of Acute Coronary Syndromes Evaluation (APACE) is a prospective multicenter international diagnostic study (ClinicalTrials.gov registry, number NCT00470587),[2,7,10–12] recruiting adult patients presenting to the ED with symptoms suggestive of AMI (e.g., chest pain at rest or minimal exercise). For this analysis, patients were excluded if A) they presented with ST-elevation myocardial infarction (STEMI), B) the final diagnosis remained unclear even after final adjudication and had at least one elevated hs-cTn concentration, thereby possibly indicating MI, C) patients presenting with chest pain onset and maximum >12 hours, D) terminal kidney failure requiring dialysis, and E) patients with missing 0h, 1h or 3h measurements of hs-cTnT assay, as the suggested cut-off for the observe-zone of the ESC 0/1h-hs-cTnT-algorithm contains baseline (0h), 1h-, and 3h-hs-cTnT concentrations (**Figure I in the Supplement**).

The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. Written informed consent was obtained from all patients. The authors designed the study, gathered, and analyzed the data according to the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement[13] (**Table I in the Supplement**), vouched for the data and analysis, wrote the paper, and decided to submit it for publication. The routine clinical assessment has been described in detail previously.[2,10–12]

Adjudication of the final diagnosis

Adjudication of the final diagnosis was performed centrally at the core laboratory according to the fourth universal definition of MI (UDMI).[14] Two independent cardiologists reviewed all available medical records including cardiac imaging and serial hs-cTnT measurements. Two sets of data were used: First, all clinical data derived from routine clinical investigations including all available medical records – patient history, physical examination, results of laboratory testing including serial local (h)s-cTn, radiologic testing, ECG, echocardiography, cardiac exercise stress test, lesion severity and morphology at coronary angiography – pertaining to the patient from the time of ED presentation to 90-day follow-up. Second, study-specific assessments including detailed chest pain characteristics using 34 predefined criteria, serial hs-cTnT measurements obtained from study samples and clinical follow-up by telephone and mail. In situations of disagreement about the diagnosis, cases were reviewed and adjudicated in conjunction with a third cardiologist.

NSTEMI was defined and (hs-)cTn interpreted as recommended in current guidelines.[5,14–16] In brief, NSTEMI was diagnosed when there was evidence of myocardial necrosis in association with a clinical setting consistent with myocardial ischemia. Myocardial necrosis was diagnosed by at least one hs-cTn value above the 99th percentile together with a significant rise and/or fall. The criteria used to define a rise and/or fall in hs-cTn are described in detail in the **Methods section in the Supplement**. Patients with NSTEMI were further subdivided into type 1 MI (primary coronary events) and type 2 MI (ischemia due to increased demand or decreased supply, e.g., tachyarrhythmia or hypertensive crisis). All other patients were classified in the categories of unstable angina (UA), cardiac but non-coronary disease (e.g., heart failure,

perimyocarditis), non-cardiac chest pain and symptoms of unknown origin with normal levels of hs-cTnT.

Blood sampling and laboratory methods

Blood samples for determination of hs-cTnT were collected into heparin plasma and serum tubes at presentation to the ED and serially thereafter (at time points 1h, 2h, 3h and 6h after presentation). Serial sampling was discontinued when a patient was discharged or transferred to the catheterization laboratory for treatment (**Table II in the Supplement**). After centrifugation, samples were frozen at -80°C until assayed in a blinded fashion in a dedicated core laboratory. The Roche hs-cTnT assays used the Elecsys 2010 system (Roche Diagnostics, Rotkreuz, Switzerland), with a limit of detection (LoD) of 5ng/L, a 99th-percentile cut-off point of 14ng/L, and a coefficient of variation (CV) of less than 10% at 13ng/L. The estimated glomerular filtration rate was determined using the chronic kidney disease epidemiology collaboration formula.[17]

Follow-up and clinical endpoints

Patients were contacted 3, 12 and 24 months after discharge by telephone calls or in written form. Additionally, information regarding death during follow-up was obtained from the patient's hospital notes, the family physician's records and the national registry on mortality. The primary diagnostic endpoint was NSTEMI (type 1 and 2) at presentation to the ED.

External validation of the suggested 7ng/L cut-off for the observe-zone

The recently suggested approach for the observe-zone of the ESC 0/1h-hs-cTnT-algorithm is shown in **Figure II in the Supplement**.[8] Briefly, patients in the observe-

zone of the ESC 0/1h-hs-cTnT-algorithm were triaged using a 0/3h-hs-cTnT-change of <7ng/L for rule-out of NSTEMI and a 0/3h-hs-cTnT-change of ≥ 7ng/L for rule-in of NSTEMI.

Derivation and internal validation of a novel observe-zone 0/3h-hs-cTnT-criteria

The concept of the novel observe-zone 0/3h-hs-cTnT-criteria is comparable to the ESC 0/1h-hs-cTnT-algorithm, in which combination of a single cTn concentration (e.g., 3h) and the absolute change between the first and last cTn measurement (e.g., 0/3h delta) allows for further triaging into the rule-out, rule-in or observe-zone group.

The novel observe-zone criteria were developed in a derivation and validation design. All patients remaining in the observe-zone after applying the ESC 0/1h-hs-cTnT-algorithm were used for deriving the new cut-off values for triage. We assessed internal validity with a bootstrapping procedure (Bootstrap validation) for a realistic estimate of the performance of the alternative derived cut-offs in similar future patients, as recommended in the TRIPOD Guidelines.[13] The rationale for this derivation/internal validation strategy was two-fold. First, due to the relatively small sample size remaining in the observe-zone, a classical split-sample internal validation approach ("Data splitting") would have left 2 small sample size data sets, which might result in a non-representative validation sample. Second, the bootstrap validation approach uses all of the data to develop the prediction model (not making the sample size smaller) and provides a mechanism to account for model overfitting; thereby, quantifying optimism in the final prediction model. The bootstrap validation approach is described in detail in the **Methods section in the Supplement.** In brief, we tested multiple cut-off combinations (hs-cTnT 3h single measure cut-offs + hs-cTnT 0/3h absolute change cut-offs) in the whole sample and selected the optimal combination for rule-out (maximizing safety and

efficacy) and for rule-in (maximizing accuracy and efficacy) fulfilling the predefined performance targets (sensitivity and negative predictive value [NPV] >99% for rule-out; and specificity >95% and PPV >75% for rule-in, respectively). The tested cut-off combinations for rule-out ranged from 13 to 18 ng/L for 3h single hs-cTnT measurement and from 1 to 5 ng/L for hs-cTnT 0/3h absolute change. The tested cut-off combinations for rule-in ranged from 5 to 7 ng/L for hs-cTnT 0/3h absolute change. The apparent performance from the optimal selected combination strategy was calculated. To account for optimism, internal validation with a bootstrapping procedure was assessed. We repeated the entire cut-offs selection process in 1000 bootstrap samples drawn with replacement from the original sample. We determined the performance of the selected hs-cTnT cut-off strategy developed from each bootstrap sample in the bootstrap sample and in the original sample and calculated the difference, thereby accounting for optimism. This optimism was averaged among the 1000 repetitions and subtracted from the apparent performance obtained at the beginning (whole sample), obtaining the optimism-corrected estimate performance (internal validation). Performance measures included sensitivity, NPV, specificity, PPV and number of patients triaged to either rule-out or rule-in.

An optimism of the apparent performance of less or equal than 1% was predefined to be acceptable. If higher than 1%, then the cut-off strategy would be dismissed, albeit an apparent performance yielding a sensitivity and NPV>99%.

External validation of the novel observe-zone 0/3h-hs-cTnT-criteria

External validation of the novel observe-zone criteria was performed in an independent prospective international multicenter diagnostic study: *High-sensitivity cardiac Troponin T assay for RAPID rule-out of AMI* (TRAPID-AMI), recruiting patients with acute chest pain at 12 sites on 3 continents.[18] Two sensitivity analysis were performed to assess the

robustness of the findings (**Methods section in the Supplement**).

Statistical Analysis

Continuous variables are presented as medians (interquartile range [IQR]); categorical variables as numbers and percentages. Differences in baseline characteristics between patients with and without NSTEMI were assessed using the Mann-Whitney-U test or Kruskal-Wallis test for continuous variables when appropriate, and the Pearson Chi-square test for categorical variables. Confidence intervals of proportions were computed as appropriate.[19]

To study the performance of the suggested 7ng/L cut-off in our validation cohort, safety was assessed as the sensitivity and NPV of ruling-out index NSTEMI, accuracy as the specificity and PPV of ruling-in index NSTEMI, and efficacy was quantified by the proportion of patients triaged toward rule-out or rule-in of NSTEMI at 3 hours. The same performance measures were assessed for the novel observe-zone 0/3h-hs-cTnT-criteria for derivation (apparent performance) and bootstrap internal validation (optimism correction). Confidence intervals for apparent performance estimates were calculated using Wilsons method.[20] Confidence intervals for optimism corrected performance estimates were calculated with 500 repetitions to form an outer bootstrap loop to compute bootstrap nonparametric percentile confidence intervals, as previously recommended.[21] Subgroup analysis in early presenters for the observe-zone was performed to test the hypothesis that the prevalence of early presenters might be higher in the observe-zone.

To further verify the central adjudication according to the 4th UDMI, patient characteristics, management, and outcome were compared among adjudicated NSTEMI patients missed by the suggested modification (false negatives) versus the correctly triaged NSTEMIs (true positives), as well as among adjudicated NSTEMI patients missed

by the suggested modification (false negatives) versus adjudicated non-NSTEMI patients (true negatives).

We performed binary logistic regression analysis to see whether a single hs-cTnT concentration at 0-, 1- or 3h, an absolute 0/3 or 1/3h change or their combination (single hs-cTnT measurement + an absolute change) provided the largest discrimination for diagnosing NSTEMI and would therefore be the preferred strategy for the new algorithm. Confidence Intervals of AUCs and p-values for comparison of AUCs were calculated according to DeLong.[22]

Four sensitivity analysis were performed to assess the robustness of our findings. First, we evaluated the diagnostic performance of the 7ng/L approach and the novel observe-zone 0/3h-hs-cTnT-criteria restricted to a primary outcome of type 1 NSTEMI. Second, we evaluated the diagnostic performance of the 7ng/L approach in patients stratified by evidence of myocardial ischemia on the ECG (defined as ST-segment depression or T-wave inversion). Third, the diagnostic performance of the novel observe-zone 0/3h-hs-cTnT-criteria were evaluated only in patients with available hs-cTnT measurements beyond 6-hours from ED presentation; and fourth, patients with an elevated hs-cTnT concentration, in whom the final adjudicated diagnosis was unclear were considered to have a type 1 NSTEMI. Power calculation is shown in **the Data Supplement (Methods section and Table III).**[13,23]

All hypothesis testing was two-tailed and p-values <0.05 were considered statistically significant. All statistical analyses were performed using Stata, version 16.1 (Stata Corp, College Station, TX, USA) and R, version 3.6.3 (R foundation for Statistical Computing).

Results

Patient characteristics

Among 2076 eligible patients with available baseline, 1-, and 3-hour hs-cTnT concentration, NSTEMI was the adjudicated final diagnosis in 431 (20.8%) patients (**Table IV in the Supplement**). After application of the ESC 0/1h-hs-cTnT-algorithm, 564 (27.2%) patients remained in the observe-zone; thus, eligible for external validation of the 7ng/L cut-off strategy and for derivation/validation of the novel observe-zone 0/3h-hs-cTnT-criteria (**Figure 1 and Table V in the Supplement**). Of these, 120 (21.3%) had NSTEMI (74 T1MI, 46 T2MI).

Among the observe-zone patients (n=564), median age was 74 years (IQR 65-81) and 25.4% were women (**Table 1**). NSTEMI and non-NSTEMI patients were comparable in many baseline characteristics. However, NSTEMI patients were younger (70 vs 75 years), more likely to present with typical chest pain characteristics (mid-chest pain location and pain radiation) or ischemic ECG changes (ST-segment depression or T-wave inversion). The incidence of early presenters in the observe-zone was lower versus the overall cohort (**Tables V and VI in the Supplement**). Hs-cTnT concentrations at 0-, and 3-hour were comparable in women versus men (**Table VII in the Supplement**).

External validation of the 7ng/L cutoff

After applying the suggested 0/3h-hs-cTnT-change of <7ng/L for rule-out of NSTEMI, 517 of the 564 patients in the observe-zone (91.7%) were triaged towards rule-out, resulting in a sensitivity of 33.3% (95%CI 25.5-42.2) and a NPV of 84.5% (95%CI 81.2-87.4), missing 80 patients with NSTEMI (66.7% of all NSTEMIs in the observe-zone, 47 T1MI and 33 T2MI). Using a 0/3h-hs-cTnT-change of ≥7ng/L, 47 patients in the observe-zone were triaged towards rule-in, of which 40 had an NSTEMI (27 T1MI, 13 T2MI),

resulting in a specificity of 98.4% (95% CI 96.8-99.2) and a PPV of 85.1% (95% CI, 72.3-92.6, **Figure 1**). Verification of the results of the central adjudication according to the 4th UDMI provided comparable characteristics, management, and outcome among adjudicated NSTEMI patients missed by the suggested modification (false negatives) versus the correctly triaged NSTEMIs (true positives, **Tables VIII-X in the Supplement and Figures III and IV in the Supplement**). It also documented important differences among NSTEMI patients missed by the suggested modification (false negatives) versus adjudicated non-NSTEMI patients (true negatives) in discharge medication, coronary revascularizations and outcomes (**Table XI in the Supplement** and **Figure V and VI in the Supplement**). Findings in a second external validation cohort (TRAPID-AMI) were comparable (**Figures VII-IX in the Supplement**).

Performance of single 0/3h hs-cTnT-change cut-off concentrations

Solely using lower 0/3h-hs-cTnT-change cut-offs for rule-out of patients in the observe-zone still resulted in missing a relevant number of patients with NSTEMI (**Figure 2A**). For rule-in, both ≥6ng/L and ≥7ng/L provided favorable performance as 0/3h-hs-cTnT-change cut-offs (**Figure X in the Supplement)**.

Performance of the hs-cTnT URL for triaging patients in the observe-zone

Solely using the URL (≤14 ng/L) for triaging patients in the observe-zone provided a sensitivity and NPV of 93.3% (95%CI 87.4-96.6) and 94.7% (95%CI 89.8-97.3) for rule-out, respectively and a specificity and PPV of 32.0% (95%CI 27.8-36.5) and 27.1% (95%CI 23.0-31.5) for rule-in, respectively (**Figure 2B**).

NPV and PPV for different hypothetical NSTEMI prevalence

Table XII in the Supplement shows the influence of different pretest probability (prevalence of NSTEMI) in the performance measure of NPV and PPV for the 0/3h-hs-cTnT-change of <7ng/L criterion. NPV did not reach the minimum of 99% in any hypothetical NSTEMI prevalence, not even with a 2% NSTEMI prevalence, indicating the need to develop an alternative approach.

Diagnostic accuracy of single hs-cTnT concentration, absolute changes and their combination

The diagnostic accuracy of single hs-cTnT measurements obtained at presentation, 1-, and 3-hours for diagnosing NSTEMI in observe-zone patients, quantified by the AUC, was 0.65 (0.59-0.70), 0.69 (0.64-0.74) and 0.76 (0.72-0.81), respectively. The AUC for hs-cTnT absolute changes 0/3h and 1/3h was 0.75 (0.70-0.81) and 0.84 (0.80-0.89), respectively. The largest discrimination was obtained when combining single hs-cTnT concentrations with absolute changes: baseline concentration and 0/3h-delta yielded an AUC of 0.87 (0.83-0.90) while 3h-concentration and 0/3h-delta yielded an AUC of 0.88 (0.85-0.91), **Table 2**. The combination of a 3h-concentration and 0/3h-delta value proved to be statistically significantly superior to the baseline concentration and 0/3h-delta (P=0.003), and therefore the preferred strategy (**Figure XI in the Supplement**).

Derivation and internal Validation of the novel observe-zone 0/3h-hs-cTnT-criteria

Optimal cut-off concentrations for the rule-out of NSTEMI were defined as a 3-hour hs-cTnT concentration <15 ng/L and a 0/3h-hs-cTnT absolute change <4 ng/L, triaging 138 patients (25%) towards rule-out, resulting in a sensitivity of 99.2% (95%CI 96.0-99.9) and a NPV of 99.3% (95%CI 95.4-99.9), **Table XIII in the Supplement**. Optimal cutoff criterion for the rule-in of NSTEMI was defined as a 0/3h-hs-cTnT absolute change ≥6

ng/L, triaging 63 patients (11.2%) towards rule-in, resulting in a specificity of 98% (95%CI 96.2-98.9) and a PPV of 85.7% (95%CI 75.0-92.3). Patients fulfilling neither of the above-mentioned criteria for rule-out or rule-in continued in the observe-zone (n=363, 64.4%). The optimism corrected (bootstrap internal validation) diagnostic performance for rule-out (sensitivity and NPV) and rule-in (specificity and PPV) was very high and comparable to the apparent (derivation) diagnostic performance (**Table 3** and **Figure 3)**. Overall, the ESC 0/1/3h-algorithm allowed a definite triage decision after 3h in 1713 of 2076 patients (82.5%; either rule-out or rule-in). Final adjudicated diagnosis among the 363 patients (17.5%) remaining in the observe-zone included NSTEMI (17.9%; 37 T1MI and 28 T2MI), unstable angina (24.5%), other cardiac disorders such as myocarditis, takotsubo syndrome, or acute heart failure (25.6%), and non-cardiac causes (32.0%).

Further triage of the observe-zone using ischemic ECG criteria

In patients still remaining in the observe-zone after applying the novel 0/3h-criteria, an ECG-based strategy exclusively for triaging patients towards rule-in was unable to reach the prespecified specificity >95% and PPV >75% (**Table XIV in the Supplement**). Of the 4 different ischemic ECG criteria evaluated, ST-segment depression seemed to be the best possible option for further reducing the observe-zone and identifying additional NSTEMI patients without reducing the overall 0/1/3h PPV <75% and specificity <95% (**Figure XII in the Supplement**). After using ST-segment depression as a 2nd step in the novel observe-zone 0/3h-criteria, overall, 84.3% of initial patients were triaged towards rule-out/in and 15.7% of patients remained in the observe-zone. Final adjudicated diagnosis among the 325 patients remaining in the observe-zone included NSTEMI (14.2%; 27 T1MI and 19 T2MI), unstable angina (24.9%), other cardiac disorders such as myocarditis, takotsubo syndrome, or acute heart failure (25.9%), and non-cardiac

causes (35%). Application of the ECG criterion (ST-segment depression) as the first step in patients remaining in the observe-zone of the ESC 0/1h-hs-cTnT-algorithm (before the novel 3-hour hs-cTnT-cut-offs) resulted in comparable diagnostic performance versus that obtained when the ECG criterion was applied after the novel 3-hour hs-cTnT-cut-offs (**Figure XIII in the Supplement**).

Sensitivity Analysis

In all four sensitivity analyses findings regarding diagnostic performance were consistent with the main analysis (**Results section in the Supplement**, **Figure XIV in the Supplement** and **Table XV in the Supplement**).

External validation cohort (TRAPID-AMI)

A total of 1010 patients were eligible for externally validating the novel observe-zone 0/3h-hs-cTnT-criteria (**Figure XV in the Supplement** and **Table XVI in the Supplement**). NSTEMI was the adjudicated final diagnosis in 168 (16.6%) patients. Distribution of adjudicated diagnoses was comparable to APACE (**Table XVII in the Supplement**). After application of the ESC 0/1h-hs-cTnT-algorithm, 243 (24.1%) patients remained in the observe-zone. These patients had a median age of 74 years (IQR 65-81), 28% were women, and 58 (23.9%) had an adjudicated diagnosis of NSTEMI (46 T1MI and 12 T2MI, **Table XVIII in the Supplement**).

External validation of the novel observe-zone 0/3h-hs-cTnT-criteria

In the external validation cohort, the performance of the novel observe-zone criteria was comparable to that in the main cohort, confirming a very high safety for rule-out (sensitivity 98.3% [95% CI, 90.9-99.7] and NPV 98.3% [95% CI, 97.7-99.4]), a high

accuracy for rule-in (specificity 95.7% [95% CI, 91.7-97.8] and PPV 78.4% [62.8-88.6]) and a good overall efficacy (147 of 1010 patients remained in the observe-zone [14.6%], **Figure 4 and Results section in the Supplement**). In both sensitivity analysis findings regarding diagnostic performance were consistent with the main analysis (**Results section in the Supplement** and **Figure XVI and XVII in the Supplement**).

Discussion

We performed a large prospective multicenter diagnostic study to externally validate the clinical performance of a suggested modification (7ng/L cutoff), and to derive/validate an alternative 0/3h-criteria for the observe-zone of the ESC 0/1h-hs-cTnT-algorithm. We report **five** major findings:

First, the sensitivity and NPV of the suggested 0/3h-hs-cTnT-change criteria (<7 ng/L) were unacceptably low (sensitivity 33.3%, NPV 84.5%) when using central adjudication by two independent cardiologists including serial sampling for hs-cTnT; thereby, allowing the accurate detection also of small NSTEMIs. In contrast, the 0/3h-hs-cTnT-change criteria of ≥7 ng/L performed well for rule-in of NSTEMI with a high specificity and PPV (98.4% and 85.1%). **Second**, 0/3h-hs-cTnT-changes lower than 7 ng/L (1 to 6) as single variables still resulted in a substantial number of missed NSTEMI. In addition, a 3h-hs-cTnT value below the URL (≤14 ng/L) as single criterion did not achieve high enough sensitivity (93.3%) nor NPV (94.7%). This is of particular importance given the prominent role of the URL at 3h as part of the ESC 0/3h-algorithm, and in full agreement with recent findings from other groups suggests that early rule-out pathways combining absolute concentrations with early changes should be preferred over early rule-out pathways relying on the 99th percentile alone in clinical practice. [5,24,25] In contrast, a strategy combining a single hs-cTnT measurement at 3h in combination with an absolute change criterion proved to have the highest discrimination for diagnosing NSTEMI in the observe-zone group. In a recent systematic review, this strategy has been shown to produce the highest rule-out rates with a very low risk of missed NSTEMI.[26] **Third**, using this strategy of combining a single hs-cTnT measurement at 3h (<15 ng/L) with a 0/3h-hs-cTnT absolute change criterion (<4 ng/L), we derived novel 0/3h-hs-cTnT-criteria for the observe-zone providing a sensitivity and NPV of 99.2% and 99.3%, respectively.

Triage towards rule-in was defined by an absolute change ≥6 ng/L within 3 hours, resulting in a specificity and PPV of 98.0% and 85.7%, respectively. Bootstrap internal validation confirmed these findings. The high safety of this approach is further highlighted by the fact that both type 1 and type 2 NSTEMI were included in this analysis. **Fourth**, adding ST-segment depression as a second or even first step (rule-in only) to the novel 0/3h-hs-cTnT-criteria allowed identification of additional NSTEMI patients while maintaining the overall PPV of 75% or higher. **Fifth**, external validation of the novel observe-zone 0/3h-hs-cTnT-criteria in an independent international diagnostic study confirmed the high safety for rule-out and high accuracy for rule-in observed in the derivation cohort.

The findings of this large multicenter diagnostic study extend and corroborate previous pilot data,[8] and have important and immediate clinical consequences. Three reasons seem mainly responsible for the major differences between the findings of the single-center pilot study and this multicenter study. First, in the derivation study a conventional cTn assay with poor sensitivity was used for the final diagnosis adjudication, invariably missing a relevant proportion of NSTEMIs.[9] Second, no validation was performed in the pilot study, with the consequent optimism of apparent estimates measures[13] further increasing the difference between the sensitivity and NPV between the pilot study and this study. Third, while the prevalence of NSTEMI in this study was comparable to other recent multicenter studies enrolling unselected patients with acute chest discomfort,[4,27–29] the prevalence of NSTEMI was unusually low in the pilot study (2%).[8] Even in institutions with an overall low AMI incidence in their ED chest pain patients, NSTEMI prevalence in the observe-zone will be invariably enriched, resulting in an unacceptable rate of missed NSTEMIs with the suggested 7ng/L cutoff. The implications are substantial as some institutions have already implemented the

suggested 0/3h absolute change cut-off of 7ng/L in their routine clinical practice (L. Kristin Newby, personal communication).

The insufficient performance of <7ng/L cutoff for the triage towards rule-out led us to derive and validate alternative 0/3h-hs-cTnT-criteria for the observe-zone of the ESC 0/1h-hs-cTnT-algorithm. A strategy of combining a single hs-cTnT measurement at 3h (<15ng/L) in combination with an absolute change criterion (<4ng/L) provided very high sensitivity and NPV for the triage of a substantial number of additional observe-zone patients towards rule-out. Triage towards rule-in using an absolute change ≥6 ng/L within 3 hours as a single criterion resulted in high specificity and PPV. After addition of ST-segment depression as the second step, or even first step, in the novel observe-zone criteria, overall, 85% of patients were triaged towards rule-out or rule-in by the ESC 0/1h-hs-cTnT-algorithm complemented with the novel observe-zone 0/3h-hs-cTnT-criteria, with only 15% of patients remaining in the observe-zone. While it is clear that ECG information should be included, the optimal sequence in which ECG criteria as well as 0h-, 1h-, and possibly even 3h-hs-cTnT concentrations should be applied in real-world clinical practice in acute chest pain patients who are hemodynamically stable and in whom STEMI has been ruled out, is a matter of ongoing debate.

It is important to highlight that the novel 0/3h-hs-cTnT-criteria should be exclusively applied to patients remaining in the observe-zone of the ESC 0/1h-hs-cTnT-algorithm. Future studies deriving and validating optimal cut-offs for the observe-zone of other hs-cTnI assays are warranted.

To the best of our knowledge, no other triage strategy has been able to achieve such a low percentage of patients remaining in the observe-zone, while maintaining excellent safety for rule-out and high accuracy for rule-in.[10,24,25,30–33] Rapid rule-out and/or rule-in of NSTEMI in an additional proportion of patients by the observe-zone

criteria provide important medical value. First, a substantial number of patients in the observe-zone with NSTEMI were correctly identified. Among 120 (74 T1MI) patients with NSTEMI in the observe-zone of the ESC 0/1h-hs-cTnT-algorithm, 55 (37 T1MI) were correctly and rapidly identified by the novel observe-zone criteria. This represents a 50% relative reduction of T1MI remaining in the observe-zone. Second, some, but definitely not all patients triaged towards rule-out of NSTEMI in the observe-zone, might also be appropriate candidates for out-patient management. Detailed clinical assessment including the actual working diagnosis in the ED and patient preference will have to determine whether in-hospital or outpatient management would be preferable. Particularly in case outpatient management is selected, very close follow-up is mandatory as comorbidities and long-term risk of death in patients in the observe-zone are substantially higher versus patients triaged towards rule-out within the ESC 0/1h-algorithm (rule-out zone).[7,10,34]

We wish to emphasize that 15% of the overall patient population will remain in the observe-zone even after the application of the novel 0/3h-hs-cTnT-criteria. Given the high prevalence of NSTEMI and unstable angina in the remaining observe-zone patients, invasive and non-invasive coronary imaging will be warranted and central to the diagnostic work-up in the majority of these patients. The role of formal risk scores or clinical criteria for further risk stratification in those patients is unknown and should be an area of future research.[5]

The data of this study suggest that the proposed addition of the novel observe-zone 0/3h-hs-cTnT-criteria further improve the effectiveness and thereby attractiveness for clinical practice of the ESC 0/1h-hs-cTnT-algorithm. The new criteria will not impact the remainder of the pathway and will aid physicians when interpreting the 3h value. Likely, future studies will need to: first, identify hurdles for a safe and effective

implementation; second, identify strategies to overcome them including IT-based decision support systems (e.g., visual display green, orange and red of the triage zone); and third, verify the necessary analytical precision on the local laboratory platform.[35]

Several limitations merit consideration when interpreting these findings. First, this study was conducted in patients presenting to the ED. Therefore, we cannot comment on the performance of the novel 0/3h-criteria in other clinical settings. Second, although we used a very stringent methodology to adjudicate NSTEMI including central adjudication by experienced cardiologists using cardiac imaging and serial measurements of hs-cTn, we may still have misclassified a small number of patients.[14] Third, central adjudication according to the 4th UDMI is the mandatory state of the art methodology to be applied in a diagnostic study. However, it will invariably create an inclusion bias towards the criteria listed as mandatory within the 4th UDMI and thereby may also influence the cut-offs of derived algorithms. Fourth, not all patients in APACE had a 3-hour sample possibly introducing some selection bias for this analysis (e.g., adjudicated final diagnosis of NSTEMI was 16.9% in patients without 3-hour sample vs 20.8% in patients with 3-hour sample, and therefore eligible for this analysis). As a result, calculated sensitivities of the evaluated algorithms would not have been affected, however prevalence dependent measures like NPV would likely be slightly higher. Fifth, although not all patients in the observe-zone had measurements 6-hours from presentation, the sensitivity analysis confirmed the main findings. Sixth, late-presenters defined as chest pain onset and maximum beyond 12 hours were excluded. Future studies need to investigate possible algorithms for late presenters remaining in the observe-zone of the ESC 0/1h-hs-cTnT-algorithm.[36]

In conclusion, using a single 0/3h absolute change cut-off of 7ng/L, suggested in a pilot-study, does not allow safe rule-out of NSTEMI for patients remaining in the

observe-zone of the ESC 0/1h-hs-cTnT-algorithm. In contrast, the novel alternative observe-zone 0/3h-criteria combining a 3h hs-cTnT concentration with 0/3h absolute change criteria balanced safety and efficacy well.

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Supplemental Materials

Expanded Methods

Supplemental Results

Supplemental Figures I-XVII

Supplemental Tables I-XVIII

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Tables

Table 1. Characteristics of Patients triaged to the Observe-Zone

	All Patients (n=564)	No AMI (n=444)	AMI (n=120)	*P* Value
Age, y	74.0 (65.0, 81.0)	75.0 (67.0, 81.0)	70.0 (59.0, 79.0)	<0.001
Female	143 (25.4%)	118 (26.6%)	25 (20.8%)	0.20
Primary symptom, n (%)				
Pain location mid chest	382 (69.5%)	291 (66.9%)	91 (79.1%)	0.01
Radiation	301 (53.4%)	221 (49.8%)	80 (66.7%)	<0.001
Dyspnea	294 (52.9%)	239 (54.7%)	55 (46.2%)	0.10
Nausea	82 (15.6%)	68 (16.3%)	14 (12.8%)	0.38
Time since pain started	5.0 (2.5, 11.0)	5.0 (2.5, 11.7)	5.0 (2.0, 11.0)	0.47
Early presenters (≤2h)	126 (22.3%)	95 (21.4%)	31 (25.8%)	0.30
History, n (%)				
Coronary artery disease	311 (55.1%)	247 (55.6%)	64 (53.3%)	0.65
Previous MI	227 (40.2%)	175 (39.4%)	52 (43.3%)	0.44
Previous revascularization	262 (46.5%)	208 (46.8%)	54 (45.0%)	0.72
Peripheral Artery Disease	50 (8.9%)	34 (7.7%)	16 (13.3%)	0.05
Previous Stroke	42 (7.4%)	36 (8.1%)	6 (5.0%)	0.25
Cardiovascular risk factors, n (%)				
Hypertension	473 (83.9%)	380 (85.6%)	93 (77.5%)	0.03
Hypercholesterolemia	378 (67.0%)	303 (68.2%)	75 (62.5%)	0.24
Diabetes mellitus	164 (29.1%)	125 (28.2%)	39 (32.5%)	0.35
Current smoking	71 (12.6%)	48 (10.8%)	23 (19.2%)	0.01
ECG findings, n (%)				
Left Bundle-Branch Block	45 (8.0%)	38 (8.6%)	7 (5.8%)	0.33
Right Bundle-Branch Block	26 (4.6%)	21 (4.7%)	5 (4.2%)	0.79
ST-segment depression	56 (9.9%)	26 (5.9%)	30 (25.0%)	<0.001
T-wave inversion	87 (15.4%)	57 (12.8%)	30 (25.0%)	0.001
Laboratory findings				
eGFR,	71.7 (56.4, 88.2)	70.7 (54.8, 85.8)	74.0 (62.3, 93.7)	0.011
Chronic medication on admission, n (%)				
Antiplatelet therapy	334 (59.2%)	266 (59.9%)	68 (56.7%)	0.52
Oral anticoagulation	123 (21.8%)	104 (23.4%)	19 (15.8%)	0.07
Beta-blocker	314 (55.7%)	245 (55.2%)	69 (57.5%)	0.65
Statin	320 (56.7%)	257 (57.9%)	63 (52.5%)	0.29
ACEIs/ARBs	361 (64.0%)	286 (64.4%)	75 (62.5%)	0.70
Calcium antagonists	152 (27.0%)	123 (27.7%)	29 (24.2%)	0.44
Nitrates	93 (16.5%)	73 (16.4%)	20 (16.7%)	0.95

ECG stands for electrocardiogram; eGFR, estimated Glomerular Filtration Rate; ACEIs, Angiotensin-converting enzyme 2; and ARBs, Angiotensin II receptor blockers.

Table 2. Diagnostic accuracy of single hs-cTnT concentration, absolute changes and their combination during serial sampling in Observe-Zone Patients

Time Point of hs-cTnT	ROC AUC (95% CI)
Presentation (0h)	0.65 (0.59-0.70)
After 1h	0.69 (0.64-0.74)
After 3h	0.76 (0.72-0.81)
Delta 1/3h	0.75 (0.70-0.81)
Delta 0/3h	0.84 (0.80-0.89)
Presentation and delta 0/3h	0.87 (0.83-0.90)
Presentation and delta 1/3h	0.79 (0.74-0.84)
3h and delta 0/3h	0.88 (0.85-0.91)
3h and delta 1/3h	0.82 (0.78-0.86)

Delta values refer to the absolute change between the level of hs-cTnT at baseline and after 3h or at 1h and after 3h (delta 0/3h and delta 1/3h, respectively). Hs-cTnT refers to high-sensitivity cardiac troponin T; ROC, receiver-operating characteristic curve; AUC, area under the curve.

Table 3. Apparent and Optimism Corrected performance of the novel proposed 0/3h strategy for the observe-zone of the ESC 0/1h-hs-cTnT-algorithm

Rule-Out criteria: hsTnT 3h <15 ng/L and 0/3h absolute change <4 ng/L		
Performance measure	**Derivation**	**Bootstrap internal validation**
Sensitivity	99.2% (95.4-99.9)	98.2% (98.0-99.6)
NPV	99.3% (96.0-99.9)	98.5% (98.2-99.7)
Number Rule Out	138 (119-158.9)	138.3 (98.9-181)
Missed NSTEMI	1 (0.2-5.5)	2.2 (0.5-2.3)

Rule-in criteria: 0/3h absolute change ≥6 ng/L		
Performance measure	**Derivation**	**Bootstrap internal validation**
Specificity	98.0% (96.2-98.9)	97.9% (96.7-99.5)
PPV	85.7% (75.0-92.3)	84.8% (76.6-95.4)
Number Rule In	63 (49.8-79.2)	62.8 (37.0-77.2)
Detected NSTEMI	54 (43.7-64.7)	53.4 (31.5-65.8)

Derivation (apparent) and bootstrap internal validation (optimism corrected) performance point estimates and 95% confidence intervals for the novel proposed 3h rule-out and rule-in criteria. NPV indicates negative predictive value; PPV, positive predictive value; NSTEMI, non-ST elevation myocardial infarction; and hs-cTnT, high-sensitivity cardiac Troponin T.

Figure legends

Figure 1. External Validation of the suggested 0/3h-hs-cTnT-change criteria (7 ng/L).

The algorithm displays patient flow and diagnostic performance for the ESC 0/1h-hs-cTnT-algorithm and the suggested 0/3h-hs-cTnT-change criteria. Sens indicates sensitivity; Spec, specificity; NPV, negative predictive value; PPV, positive predictive value; and NSTEMI, non-ST elevation myocardial infarction; Δ, delta.

*****Patients with a chest pain onset<3h can't be directly rule-out with a 0h hs-cTnT value.

Figure 2. Diagnostic Performance and patients rule-out for different single strategies.

Diagnostic Performance and number of patients ruled-out stratified by presence or absence of NSTEMI according to each 0/3h-hs-cTnT absolute change cut-offs from Δ <7ng/L until Δ <1ng/L (**A**), and patient flow and diagnostic performance when using the URL (≤14 ng/L) for triaging observe-zone patients towards rule-out and rule-in (**B**). hs-cTnT indicates high-sensitivity cardiac Troponin T; NPV, negative predictive value; and NSTEMI, non-ST elevation myocardial infarction; Δ, delta.

Figure 3. Performance of the novel derived observe-zone 0/3-hs-cTnT-criteria.

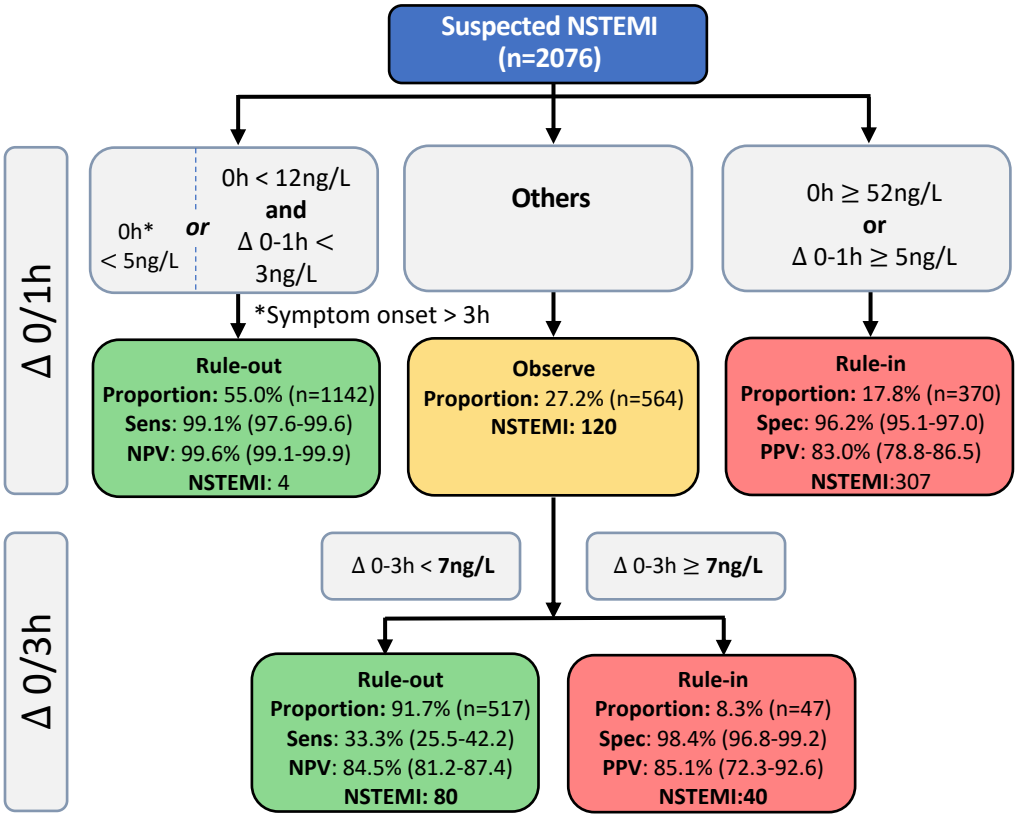
The algorithm displays patient flow and diagnostic performance for the ESC 0/1h-hs-cTnT-algorithm and the novel alternative observe-zone 0/3h-criteria which combines a 3h hs-cTnT concentration with a 0/3h absolute change criterion. Sens indicates sensitivity; Spec, specificity; NPV, negative predictive value; PPV, positive predictive value; and NSTEMI, non-ST elevation myocardial infarction; Δ, delta.

*****Patients with a chest pain onset<3h can't be directly rule-out with a 0h hs-cTnT value.

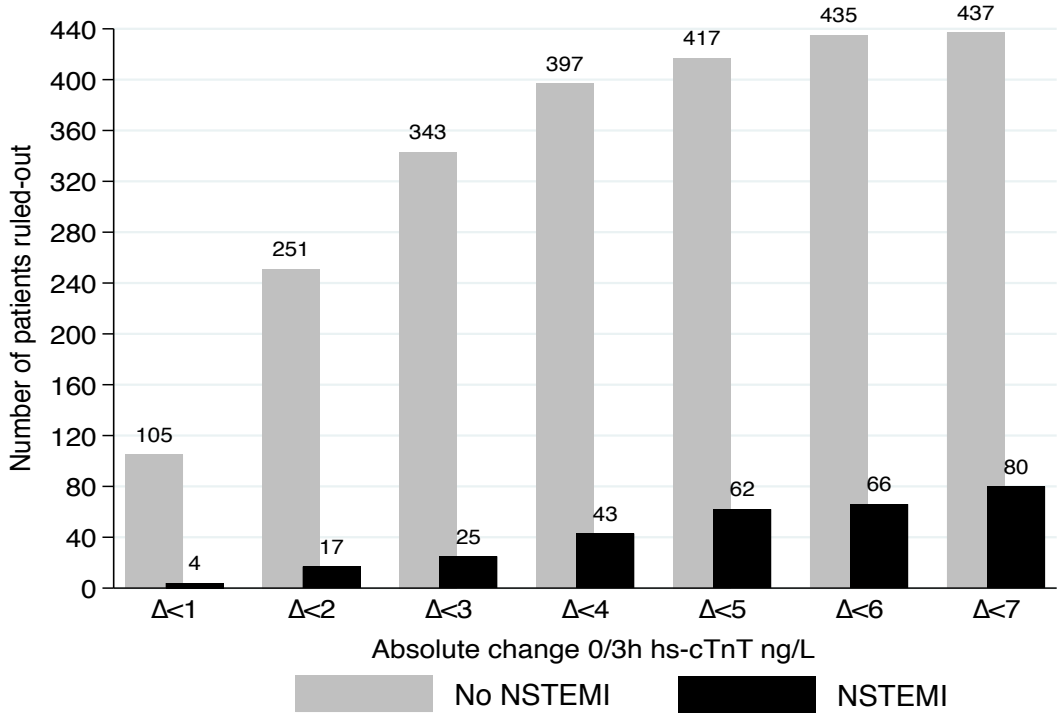
Figure 4. External validation in the TRAPID-AMI cohort of the novel derived observe-zone 0/3h-hs-cTnT-criteria.

The algorithm displays patient flow and diagnostic performance for the ESC 0/1h-hs-cTnT-algorithm and the novel observe-zone 0/3h-criteria which combines a 3h hs-cTnT concentration with a 0/3h absolute change criterion. 3h values were estimated by calculating the mean between the 2h and 5/6h hs-cTnT measurements. Sens indicates sensitivity; Spec, specificity; NPV, negative predictive value; PPV, positive predictive value; and NSTEMI, non-ST elevation myocardial infarction; Δ, delta.

*****Patients with a chest pain onset<3h can't be directly rule-out with a 0h hs-cTnT value.

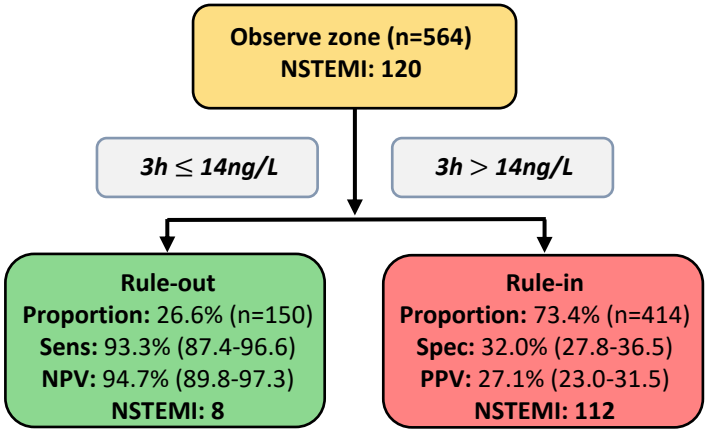

Suspected NSTEMI
(n=2076)
Δ 0/1h
0h* < 5ng/L
or
0h < 12ng/L and Δ 0-1h < 3ng/L
Others
0h ≥ 52ng/L or Δ 0-1h ≥ 5ng/L
*Symptom onset > 3h
Rule-out
Proportion: 55.0% (n=1142)
Sens: 99.1% (97.6-99.6)
NPV: 99.6% (99.1-99.9)
NSTEMI: 4
Observe
Proportion: 27.2% (n=564)
NSTEMI: 120
Rule-in
Proportion: 17.8% (n=370)
Spec: 96.2% (95.1-97.0)
PPV: 83.0% (78.8-86.5)
NSTEMI:307
Δ 0/3h
Δ 0-3h < 7ng/L
Δ 0-3h ≥ 7ng/L
Rule-out
Proportion: 91.7% (n=517)
Sens: 33.3% (25.5-42.2)
NPV: 84.5% (81.2-87.4)
NSTEMI: 80
Rule-in
Proportion: 8.3% (n=47)
Spec: 98.4% (96.8-99.2)
PPV: 85.1% (72.3-92.6)
NSTEMI:40

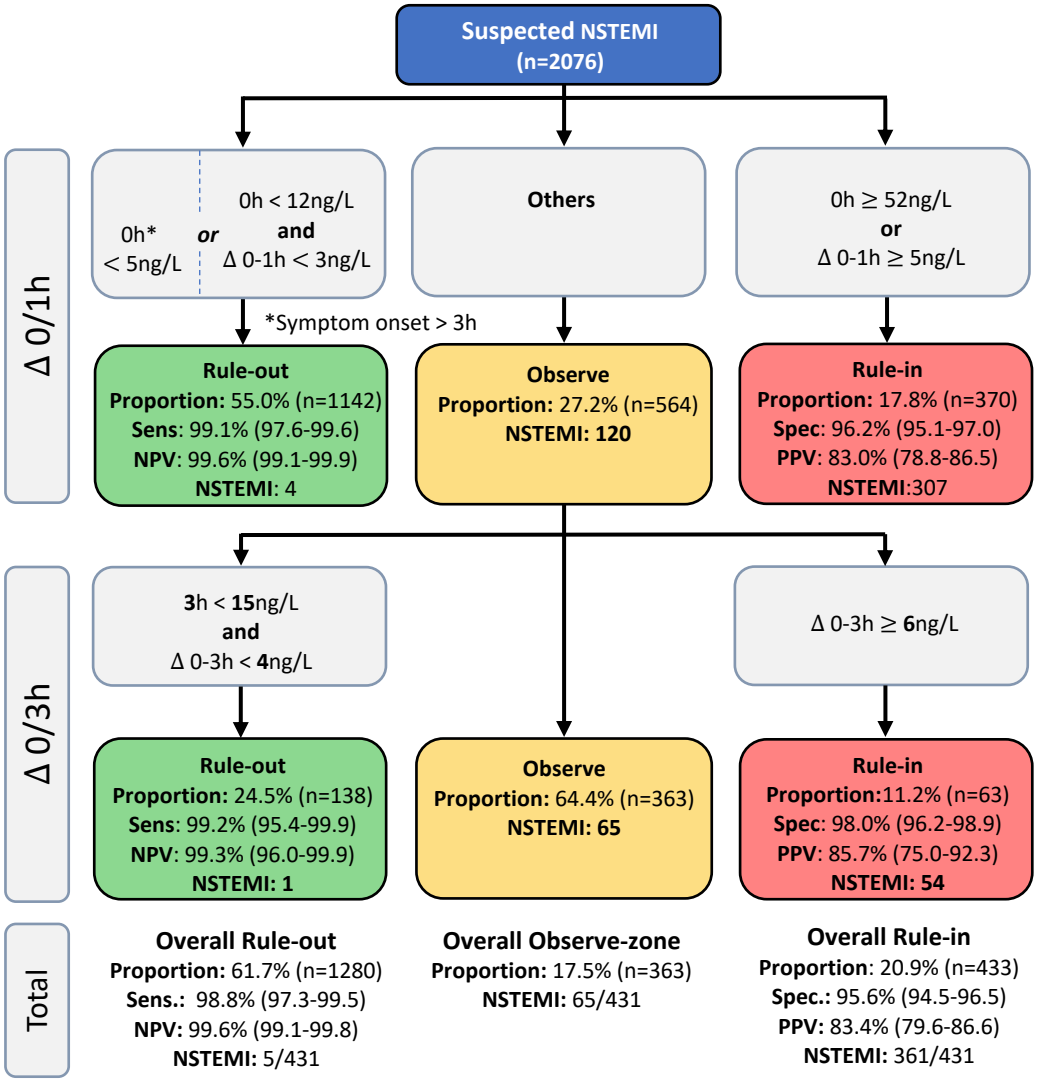
A

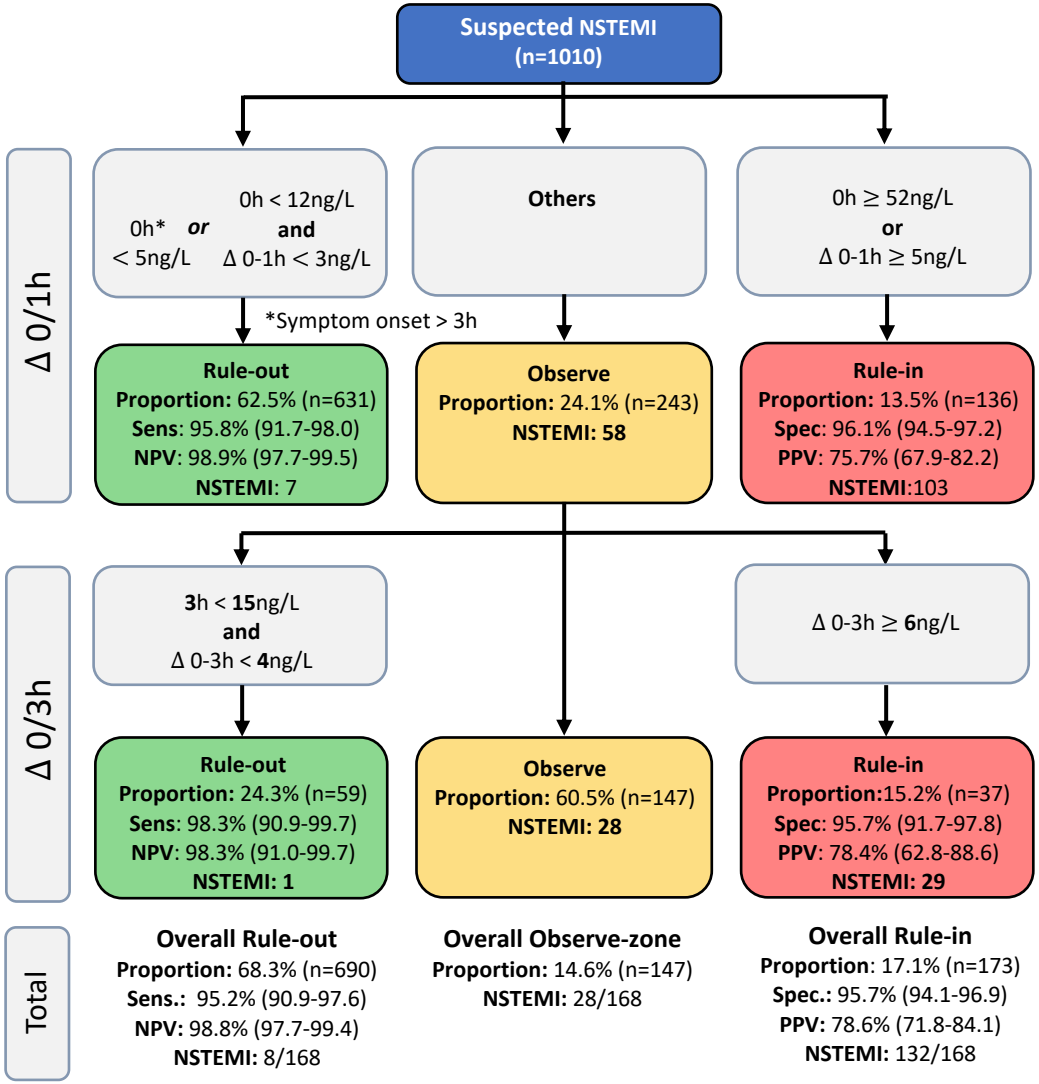


Absolute change 0/3h hs-cTnT (ng/L)	<1	<2	<3	<4	<5	<6	<7
Sensitivity	96.7 (91.7-98.7)	85.8 (78.5-91.0)	79.2 (71.1-85.5)	64.2 (55.3-72.2)	48.3 (39.6-57.2)	45 (36.4-53.9)	33.3 (25.2-42.2)
NPV	96.3 (90.9-98.6)	93.7 (90.1-96.0)	93.2 (90.2-95.4)	90.2 (87.1-92.7)	87.1 (83.8-89.8)	86.8 (83.6-89.5)	84.5 (81.2-87.4)

B




Suspected NSTEMI
(n=2076)
Δ 0/1h
0h*
< 5ng/L
or
0h < 12ng/L
and
Δ 0-1h < 3ng/L
Others
0h ≥ 52ng/L
or
Δ 0-1h ≥ 5ng/L
*Symptom onset > 3h
Rule-out
Proportion: 55.0% (n=1142)
Sens: 99.1% (97.6-99.6)
NPV: 99.6% (99.1-99.9)
NSTEMI: 4
Observe
Proportion: 27.2% (n=564)
NSTEMI: 120
Rule-in
Proportion: 17.8% (n=370)
Spec: 96.2% (95.1-97.0)
PPV: 83.0% (78.8-86.5)
NSTEMI:307
Δ 0/3h
3h < 15ng/L
and
Δ 0-3h < 4ng/L
Δ 0-3h ≥ 6ng/L
Rule-out
Proportion: 24.5% (n=138)
Sens: 99.2% (95.4-99.9)
NPV: 99.3% (96.0-99.9)
NSTEMI: 1
Observe
Proportion: 64.4% (n=363)
NSTEMI: 65
Rule-in
Proportion:11.2% (n=63)
Spec: 98.0% (96.2-98.9)
PPV: 85.7% (75.0-92.3)
NSTEMI: 54
Total
Overall Rule-out
Proportion: 61.7% (n=1280)
Sens.: 98.8% (97.3-99.5)
NPV: 99.6% (99.1-99.8)
NSTEMI: 5/431
Overall Observe-zone
Proportion: 17.5% (n=363)
NSTEMI: 65/431
Overall Rule-in
Proportion: 20.9% (n=433)
Spec.: 95.6% (94.5-96.5)
PPV: 83.4% (79.6-86.6)
NSTEMI: 361/431


Suspected NSTEMI
(n=1010)
Δ 0/1h
0h* < 5ng/L or 0h < 12ng/L and Δ 0-1h < 3ng/L
Others
0h ≥ 52ng/L or Δ 0-1h ≥ 5ng/L
*Symptom onset > 3h
Rule-out
Proportion: 62.5% (n=631)
Sens: 95.8% (91.7-98.0)
NPV: 98.9% (97.7-99.5)
NSTEMI: 7
Observe
Proportion: 24.1% (n=243)
NSTEMI: 58
Rule-in
Proportion: 13.5% (n=136)
Spec: 96.1% (94.5-97.2)
PPV: 75.7% (67.9-82.2)
NSTEMI:103
Δ 0/3h
3h < 15ng/L and Δ 0-3h < 4ng/L
Δ 0-3h ≥ 6ng/L
Rule-out
Proportion: 24.3% (n=59)
Sens: 98.3% (90.9-99.7)
NPV: 98.3% (91.0-99.7)
NSTEMI: 1
Observe
Proportion: 60.5% (n=147)
NSTEMI: 28
Rule-in
Proportion:15.2% (n=37)
Spec: 95.7% (91.7-97.8)
PPV: 78.4% (62.8-88.6)
NSTEMI: 29
Total
Overall Rule-out
Proportion: 68.3% (n=690)
Sens.: 95.2% (90.9-97.6)
NPV: 98.8% (97.7-99.4)
NSTEMI: 8/168
Overall Observe-zone
Proportion: 14.6% (n=147)
NSTEMI: 28/168
Overall Rule-in
Proportion: 17.1% (n=173)
Spec.: 95.7% (94.1-96.9)
PPV: 78.6% (71.8-84.1)
NSTEMI: 132/168