Performance of Novel High-Sensitivity Cardiac Troponin I Assays for 0/1-Hour and 0/2- to 3-Hour Evaluations for Acute Myocardial Infarction: Results From the HIGH-US Study

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Study objective: We determine the accuracy of high-sensitivity cardiac troponin I (hs-cTnI), European-derived, rapid, acute myocardial infarction, rule-out/rule-in algorithms applied to a US emergency department (ED) population.

Methods: Adults presenting to the ED with suspected acute myocardial infarction were included. Plasma samples collected at baseline and between 40 and 90 minutes and 2 and 3 hours later were analyzed in core laboratories using the Siemens Healthineers hs-cTnI assays. Acute myocardial infarction diagnosis was independently adjudicated. The sensitivity, specificity, and negative and positive predictive values for rapid acute myocardial infarction rule-out/rule-in using European algorithms and 30-day outcomes are reported.

Results: From 29 US medical centers, 2,113 subjects had complete data for the 0/1-hour algorithm analyses. With the Siemens Atellica Immunoassay hs-cTnI values, 1,065 patients (50.4%) were ruled out, with a negative predictive value of 99.7% and sensitivity of 98.7% (95% confidence interval 99.2% to 99.9% and 96.3% to 99.6%, respectively), whereas 265 patients (12.6%) were ruled in, having a positive predictive value of 69.4% and specificity of 95.7% (95% confidence interval 63.6% to 74.7% and 94.7% to 96.5%, respectively). The remaining 783 patients (37.1%) were classified as having continued evaluations, with an acute myocardial infarction incidence of 5.6% (95% confidence interval 4.2% to 7.5%). The overall 30-day risk of death or postdischarge acute myocardial infarction was very low in the ruled-out patients but was incrementally increased in the other groups (rule-out 0.2%; continued evaluations 2.1%; rule-in 4.8%). Equivalent results were observed in the 0/2- to 3-hour analyses and when both algorithms were applied to the hs-cTnI ADVIA Centaur measurements.

Conclusion: The European rapid rule-out/rule-in acute myocardial infarction algorithm hs-cTnI cut points can be harmonized with a demographically and risk-factor diverse US ED population. [Ann Emerg Med. 2020;76:1-13.]

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INTRODUCTION

Background

Accelerated diagnostic protocols with testing intervals as short as 1 hour and integrating high-sensitivity cardiac troponin (hs-cTn) assays to aid in the diagnosis of acute myocardial infarction have been incorporated into European guidelines and validated in cohorts from European countries and elsewhere.[1-5] hs-cTn Assays have been recently approved for use in the United States.[6] The differences between acute myocardial injury and acute myocardial infarction are highlighted in the recent "Fourth Universal Definition of Myocardial Infarction" document.[7] In our report, the diagnosis of myocardial injury was not considered by the adjudication committee; only the diagnosis of acute myocardial infarction was considered. In the United States, many clinicians view the introduction of hs-cTn assays for acute myocardial infarction diagnosis with trepidation. Lower acute myocardial infarction rates are reported in patients undergoing evaluation in US emergency departments (EDs) compared with other regions of the world.[8-10] This observation is also supported by recent publications from single-center urban academic medical centers.[11-13]

Editor's Capsule Summary

What is already known on this topic

Accelerated diagnostic protocols for acute myocardial infarction using high-sensitivity cardiac troponin (hs-cTn) assays have been developed and validated in European and Australasian populations.

What question this study addressed

What is the diagnostic accuracy of hs-cTn accelerated protocols for acute myocardial infarction in a US emergency department population?

What this study adds to our knowledge

In a US population, hs-cTn accelerated protocols have high sensitivity at the rule-out threshold and high specificity at the rule-in threshold used in European studies.

How this is relevant to clinical practice

hs-cTn Accelerated protocols are validated in the US population and can be used to guide practice if the reported sensitivity and specificity are considered acceptable.

Importance

It is unknown whether the high sensitivity and negative predictive value of hs-cTn assays with acceptable positive predictive value and specificity that were observed in European cohorts will be maintained in more diverse US populations.

Goals of This Investigation

The goal of the present study was to evaluate the performance of new high-sensitivity cardiac troponin I (hs-cTnI) assays from Siemens Healthineers on the Atellica Immunoassay Analyzer (Siemens Healthineers, Walpole, MA)[14] and the ADVIA Centaur XP (Siemens Healthineers) system[15] in the High-Sensitivity Cardiac Troponin I in the United States (HIGH-US) study. To evaluate harmonizing algorithms globally, we used the specific cut points from a rapid 0/1-hour and 0/2- to 3-hour rule-out/rule-in algorithm validated in a western European population[1] and assessed the negative and positive predictive value in a multicenter US population. We hypothesized that these hs-cTnI assays would demonstrate very high negative predictive values and acceptable positive predictive values, with baseline and interval testing in as little as 1 hour in US ED patients, despite anticipated demographic and risk-factor diversity compared with European and other cohorts outside the United States.

MATERIALS AND METHODS

Study Design and Setting

In the HIGH-US study, adults aged 22 years and older who presented to the ED with any suspected acute myocardial infarction prompting the clinical ordering of a cardiac troponin level test and who signed consent were prospectively enrolled in a Food and Drug Administration (FDA) 510(k) study. The EDs were located in 29 centers across the United States in both tertiary urban settings and community hospitals (Figure E1, available online at http://www.annemergmed.com). In accordance with recommendations from the FDA, there were no exclusion criteria for patients who could otherwise consent to participate.[16] Given the requirement for consent, enrollment generally took place during weekdays. The protocol was approved by either a central or local institutional review board and enrollment occurred between April 2015 and April 2016.

The points for sample collection for analysis included baseline ($\leq$90 minutes from the first clinical blood collection) and a target of 60 minutes ($\pm$15 minutes), and within 120 to 180 minutes after the baseline collection. Samples were collected in lithium heparin and serum blood tubes and sent to a laboratory for testing (Siemens Healthcare Diagnostics, Tarrytown, NY; Research & Development Institute, Calabasas, CA; Baylor Scott & White Healthcare Texas A&M Health Science Center, Temple, TX; University of Maryland, Baltimore, MD; or Minneapolis Medical Research Foundation, Minneapolis, MN), where measurements for hs-cTnI were performed on the Atellica Immunoassay Analyzer and ADVIA Centaur XP systems. The Atellica Immunoassay hs-cTn assay is a 3-site sandwich immunoassay that uses direct chemiluminescent technology and has a measuring range of 2.5 to 25,000 ng/L, a limit of detection of 1.6 ng/L, and limit of quantitation of 2.5 ng/L. The 10% coefficient of variation is found at 6 ng/L.

The 99th percentile upper reference limit for plasma was determined to be 34 ng/L for women (1,007 subjects), 53 ng/L for men (1,000 subjects), and 45 ng/L for combined sex (2,007 subjects).[13] Further details of additional sample collection, sample types, preanalytic handling, and testing have been previously published.[17] For study analyses, the nonsex-specific 99th percentile (45 ng/L) was used in the adjudication for acute myocardial infarction diagnosis.

Data Collection and Processing

Subject clinical characteristics; ECGs; all laboratory values, including site-specific contemporary troponin measurements (each site-specific assay and its 99th

percentile value were made available); other diagnostic or therapeutic cardiovascular procedures; final patient disposition (ED discharge, observation, or hospital admission); and all clinical information available during the 30 days after patient discharge were made available to each physician adjudicator. This included any initial narrative and discharge summary, with redaction of any final-site acute myocardial infarction diagnosis. At this study, standard-of-care guidelines in the United States and Europe recommended a baseline and a 3- to 6-hour troponin value for the evaluation of patients with symptoms suspicious for acute myocardial infarction.[18,19] During study enrollment, no FDA-approved hs-cTn assays were available.

The adjudication panel consisted of cardiologists and emergency physicians, with 5 physicians (at least 2 members of each specialty) assigned to each case. These individuals and the treating emergency physicians were blinded to the hs-cTnI results. Adjudicators determined acute myocardial infarction diagnosis (both type 1 and type 2) with the third universal definition of myocardial infarction.[20] No relative or absolute threshold was prespecified for a significant increase or decrease of cardiac troponin levels. Final diagnosis was determined by the majority adjudicator opinion.

Thirty-day adverse events are reported, including cardiac and all-cause mortality, nonfatal acute myocardial infarction, coronary revascularization, and heart failure hospitalization. Heart failure rehospitalization was included as an additional adverse event because this has been reported to be increased in patients admitted for possible acute coronary syndrome with a troponin value greater than the 99th percentile but without a definite acute coronary syndrome diagnosis established.[21] This information was collected by review of the subject's institutional medical records or through a telephone call with the patient or his or her relative or friend, or by contacting the subject's primary care physician or cardiologist. Death status was obtained by review of publicly available information, which included the Social Security Death Index and obituary searches (if all other methods failed).

Two algorithms were evaluated. Samples collected at baseline and 60 minutes created the 0/1-hour algorithm and samples collected at baseline and within 120 to 180 minutes created the 0/2- to 3-hour algorithm. To potentially harmonize global use of the hs-cTnI assays on the Atellica Immunoassay Analyzer and ADVIA Centaur systems, we used the same approach and cutoffs applied to similar algorithms developed in Europe.[1] These algorithms divide patients into 3 groups (rule-out, observe, and rule-in). Patient grouping is based on the absolute concentration of the initial sample and the change (Δ) between the first and second samples. Patients not meeting the criteria for rule-out or rule-in are assigned to an observation zone ("continued evaluations zone" in our analyses). We report the number of patients assigned to each category and the proportion of adjudicated acute myocardial infarctions in each group, along with their respective sensitivity, specificity, negative predictive value, and positive predictive value.[1]

Primary Data Analysis

Sample size determination is presented elsewhere.[17] All patients with acute ST-segment elevation acute myocardial infarction were excluded. The baseline patient characteristics of interest are summarized in Table 1 for the patients with a diagnosis of non–ST-segment elevation acute myocardial infarction (NSTEMI) versus NSTEMI, using frequencies (percentages) for categoric variables and medians (interquartile ranges) for numeric variables. The main analyses were descriptive and included 95% confidence intervals (CIs) as estimates of precision around the diagnostic parameters. Kaplan-Meier 30-day time-to-event curves were plotted for both algorithms according to group assignment for the composite outcome of all-cause mortality and postdischarge acute myocardial infarction. Statistical analyses were performed with SAS (version 9.4; SAS Institute, Inc., Cary, NC). All statistical analyses reported were initiated or confirmed by a statistician (G.J.) independent of the sponsor.

RESULTS

Our reported results are specifically those of the hs-cTnI assay using plasma on the Atellica Immunoassay Analyzer. No significant differences were found for the 0/1- and 0/2- to 3-hour algorithms when the Atellica Immunoassay Analyzer and the ADVIA Centaur XP system values and the plasma and serum measurements were compared (Figures E2 and E3 and Tables E1 and E2, available online at http://www.annemergmed.com).

Characteristics of Study Subjects

From April 2015 to April 2016, 2,505 patients were enrolled at the 29 US medical center EDs and 2,346 qualified (patients with ST-segment elevation acute myocardial infarction [35, or 0.01%] or who did not have a baseline hs-cTnI study result because of inadequate sample [124, or 5.0%] were excluded) from the primary analyses (Figure 1*A*). Two thousand one hundred thirteen subjects were eligible for the 0/1-hour analysis and 1,916 for the 0/2- to 3-hour analysis. The distribution of the Δ times for

Table 1. Patient characteristics included in the analysis of hs-cTnI on the Atellica Immunoassay Analyzer for lithium heparin samples at baseline.

Patient Characteristics	All Patients (n=2,346)	AMI (n=278)	Non-AMI (n=2,068)
Age, median (IQR), y	56 (48–65)	60 (54–70)	56 (47–64)
Male sex, No. (%)	1,313 (56.0)	179 (64.4)	1,134 (54.8)
Race, No. (%)			
White	1,313 (56.0)	155 (55.8)	1,158 (56.0)
Black	939 (40.0)	109 (39.2)	830 (40.1)
Other or multiple	94 (3.9)	14 (5.0)	80 (3.8)
Ethnicity, No. (%)			
Hispanic or Latino	190 (8.2)	19 (6.9)	171 (8.3)
Not Hispanic or Latino	2,136 (91.8)	257 (93.1)	1,879 (91.7)
Symptom onset to first blood draw, h	7.5 (3.6–28.0)	6.0 (3.4–19.9)	7.7 (3.6–29.2)
Early presenter (first draw ≤3 h of onset), No. (%)	423 (18.0)	55 (19.8)	368 (17.8)
Risk factors, No. (%)			
Hypertension	1,626 (69.5)	220 (79.7)	1,406 (68.1)
Dyslipidemia	904 (40.1)	122 (45.7)	782 (39.3)
Diabetes	687 (29.4)	103 (37.2)	584 (28.4)
Current smoker	633 (27.0)	99 (35.6)	534 (25.8)
Former smoker	725 (30.9)	93 (33.5)	632 (30.6)
Never smoked	988 (42.1)	86 (30.9)	902 (43.6)
History, No. (%)			
Coronary artery disease	876 (37.9)	146 (52.9)	730 (35.8)
Previous MI	473 (21.0)	89 (33.5)	384 (19.4)
Previous revascularization	656 (28.6)	122 (40.5)	534 (26.5)
Peripheral artery disease	97 (4.4)	19 (7.3)	78 (4.0)
Previous stroke	240 (10.9)	39 (14.7)	205 (10.4)
Renal dialysis	77 (3.3)	11 (4.0)	66 (3.2)
Heart failure	471 (20.4)	73 (26.9)	398 (19.5)
ECG findings, No. (%)			
Left bundle branch block	65 (2.8)	11 (4.0)	54 (2.6)
ST-segment depression ≥0.5 mm	138 (5.9)	47 (16.9)	91 (4.4)
T-wave inversion, No. (%)	277 (11.8)	64 (23.0)	213(10.3)
Normal ECG result	730 (31.2)	40 (14.4)	690 (33.5)
Body mass index, kg/m^2	29.7 (25.7–34.7)	29.5 (25.8–34.6)	29.8 (25.7–34.7)
Creatinine, mg/dL	0.91 (0.78–1.14)	1.03 (0.86–1.49)	0.90 (0.77–1.12)
CKD-EPI eGFR, mL/min per 1.73 m^2	85.6 (66.5–101.3)	73.6 (52.9–91.4)	87.0 (69.0–102.2)
CKD-EPI eGFR intervals, No. (%)			
<30	140 (6.2)	30 (10.8)	114 (5.6)
≥30 and <60	309 (13.3)	57 (20.6)	252 (12.3)
≥60 and <90	864 (37.2)	113 (40.8)	751 (36.7)
≥90	1,007 (43.3)	77 (27.8)	930 (45.4)

blood samples obtained at both the 1-hour and 2- to 3-hour times is shown in Figure 1*B*. The sample distribution was 40 to 90 minutes for the 1-hour point, and all analyzed samples were between 2 and 3 hours for the 2- to 3-hour point. The mean time from ED presentation to the first hs-cTnI blood samplings for the 2,113 patients analyzed for the 0/1-hour algorithm and the 1,926 individuals for the 0/2- to 3-hour algorithm were 98.4 minutes (SD 52.9 minutes) and 97.8 minutes (SD 53.1 minutes), respectively. To put this into context, the mean time from ED presentation to first standard-of-care blood draw was 56.1 minutes (SD 48.9 minutes) and 55.5 minutes (SD

Table 1. Continued.

Patient Characteristics	All Patients (n=2,346)	AMI (n=278)	Non-AMI (n=2,068)
Long-term medication, No. (%)			
Aspirin	1,300 (56.1)	200 (72.7)	1,100 (53.9)
Anticoagulant	254 (10.9)	35 (12.7)	219 (10.7)
β-Blocker	974 (41.9)	151 (54.5)	823 (40.1)
Statin	1,019 (43.8)	151 (54.7)	868 (42.3)
ACE inhibitor	912 (39.3)	143 (51.6)	769 (37.7)
Calcium channel blocker	494 (21.3)	68 (24.7)	426 (20.9)
Nitroglycerin	552 (23.7)	83 (30.0)	469 (22.9)

AMI, Acute myocardial infarction; *IQR*, interquartile range; *MI*, myocardial infarction; *CKD-EPI eGFR*, chronic kidney disease epidemiology collaboration estimated glomerular filtration rate; *ACE*, angiotensin-converting enzyme.
Numeric data are presented as median (interquartile range); categoric, as frequency (percentage). Patients with a normal ECG result are defined as those with sinus rhythm, normal QRS interval, normal ST segment, and normal T wave.

48.7 minutes) for the 0/1- and 0/2- to 3-hour algorithm subjects, respectively. The duration of symptoms from symptom onset to ED presentation was less than 3 hours for 851 (36.6%) of the 2,346 baseline patients. Within the overall set of 2,344 enrolled patients, 374 (16.0%) had 1 standard-of-care troponin value reported, 937 (40.0%) had 2, and 1,033 (44.1%) had 3 or more.

The clinical characteristics and initial ECG findings for patients with a baseline hs-cTnI sample draw are shown in Table 1. There were 278 subjects (11.8%) adjudicated with an NSTEMI, with 166 judged to be a type 1 and 101 a type 2, and 11 with an undetermined acute myocardial infarction type. The median age of the study population was 56 years (interquartile range 48 to 65 years), with 40% women and 40% blacks. Patients with a diagnosis of acute myocardial infarction were older, were men, and had more cardiac risk factors, known coronary artery disease, worse renal function, and more abnormal ECG findings compared with those without an acute myocardial infarction. ST-segment depression was present in 16.9% of acute myocardial infarction patients.

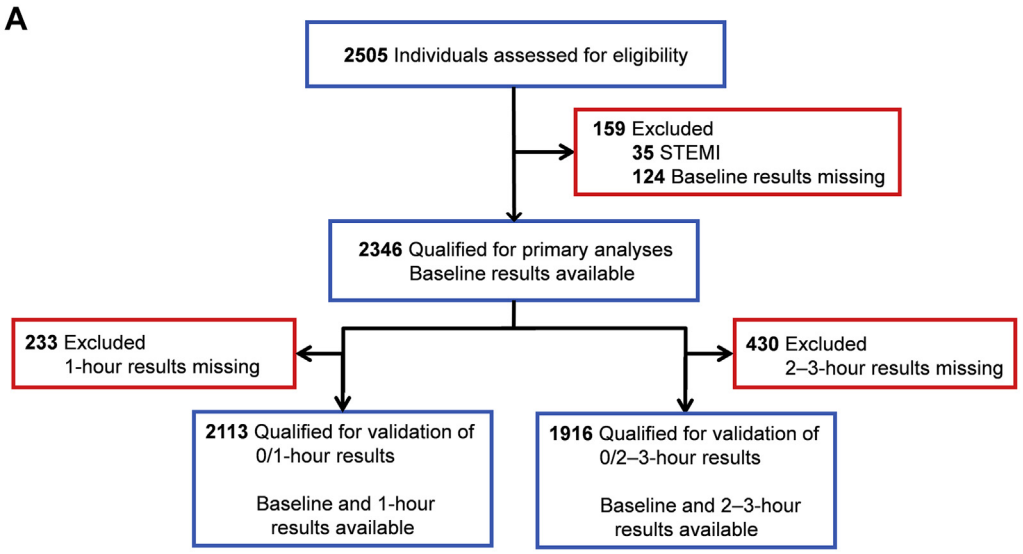
Main Results

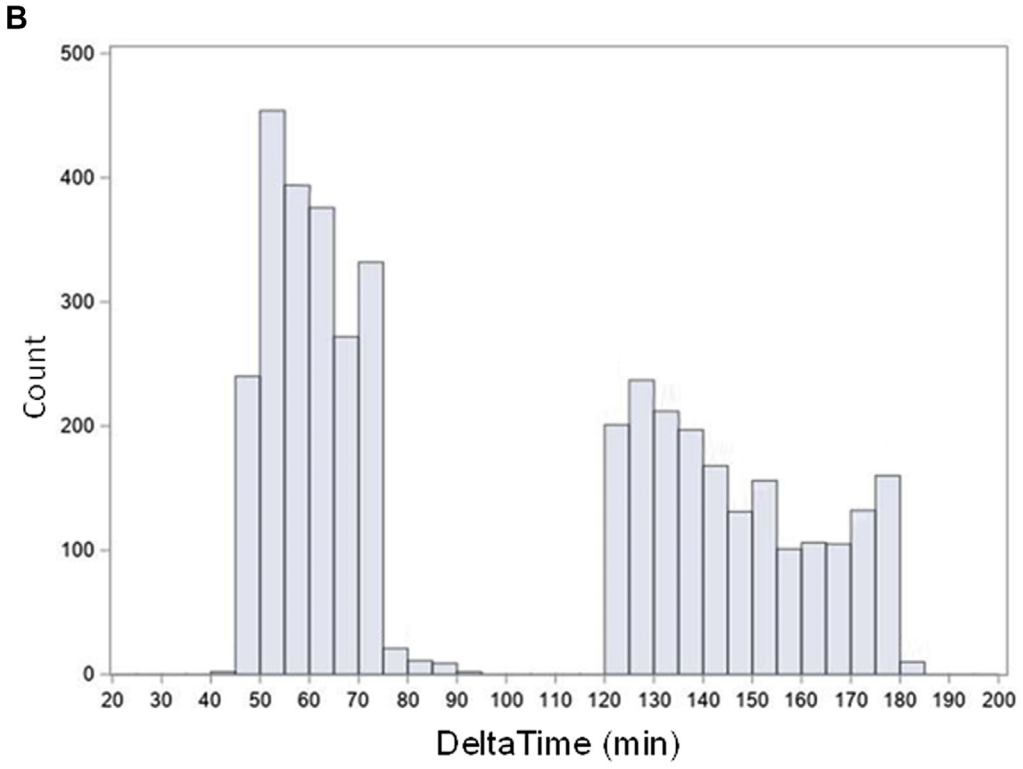
The complete rule-out/rule-in analyses based on the hs-cTnI algorithm cut points chosen are reported in Table 2. However, the main results are shown as have been reported to date in other hs-cTn studies, focusing on the rule-out negative predictive values and sensitivities and rule-in positive predictive values and specificities for each algorithm studied.

The 0/1-hour rule-out/rule-in acute myocardial infarction algorithm ruled out 714 patients (33.8%) according to an initial hs-cTnI value less than 3 ng/L. The 1-hour Δ (baseline value <6 ng/L and a 1-hour Δ hs-cTnI value <3 ng/L) ruled out an additional 351 individuals (16.6%). Overall, 1,065 patients (50.4%) with clinically suspected acute myocardial infarction were ruled out within the first hour of evaluation, with a negative predictive value of 99.7% and a sensitivity of 98.7% (95% CI 99.2% to 99.9% and 96.3% to 99.7%, respectively) (Figure 2*A*). Three patients with an adjudicated acute myocardial infarction were missed. Two of these were admitted to the hospital for further evaluation (one type 1, one type 2), whereas one (type 1) was discharged from the ED after a nuclear cardiac stress test and a cardiology consultation.

The 0/1-hour acute myocardial infarction rule-in protocol (initial hs-cTnI value ≥120 ng/L) identified 210 patients (9.9%) and inclusion of a Δ 1-hour hs-cTnI greater than or equal to 12 ng/L identified an additional 55 subjects (2.6%) (Figure 2*A*). Within 1 hour (40 to 90 minutes), 265 patients (12.5%) were ruled in with a positive predictive value of 69.4% and a specificity of 95.7% (95% CI 63.5% to 74.9% and 94.7% to 96.6%, respectively). The remaining 783 patients (37.1%) not meeting any of these baselines and 1-hour Δ hs-cTnI values were assigned to the continued evaluations group.

The 0/2- to 3-hour algorithm results are shown in Figure 2*B*. Acute myocardial infarction was ruled out with an initial hs-cTnI value (<3 ng/L) in 612 patients (31.9%) and a baseline value less than 8 ng/L and a Δ 2- to 3-hour hs-cTnI value less than 7 ng/L in an additional 454 individuals (23.7%). Overall, 1,066 patients (55.6%) with clinically suspected acute myocardial infarction were ruled out within the first 2 to 3 hours of evaluation, with a negative predictive value of 99.8% and a sensitivity of 99.1% (95% CI 99.3% to 100.0% and 96.8% to 99.9%, respectively). Two patients with an adjudicated acute myocardial infarction were missed with this algorithm. Both patients were admitted to the hospital (one was the same patient missed with the 0/1-hour algorithm).





Matrix	Time Point Delta	n	Mean (min)	Median (min)
Li-Hep	Delta 0/1 h	2113	59.0	59.0
Li-Hep	Delta 0/2–3 h	1916	145.3	142.0

Figure 1. Analysis flow chart for enrolled patients and blood sampling draw time distributions (Atellica Immunoassay Analyzer). *A*, Flow chart. *B*, Blood sample draw time distribution.

The 0/2- to 3-hour rule-in algorithm using an initial hs-cTnI value greater than or equal to 120 ng/L identified 199 patients (10.4%) with acute myocardial infarction, and inclusion of a 2- to 3-hour Δ hs-cTnI greater than or equal to 20 ng/L identified an additional 55 (2.9%). Overall, 254 patients (13.3%) were ruled in within the first 2 to 3 hours of evaluation, with a positive predictive value of 69.7% and a specificity of 95.5% (95% CI 63.6% to 75.3% and 94.4% to 96.4%, respectively). The remaining 596 patients (31.1%) not meeting any of the baseline or Δ hs-cTnI

Table 2. Complete hs-cTnI rule-out/rule-in algorithm analyses.

Algorithm	Threshold	Sensitivity 95% CI n/N	Specificity 95% CI n/N	PPV 95% CI n/N	NPV 95% CI n/N
0/1 h	Rule-out	0.987	0.564	0.218	0.997
		0.963–0.997	0.541–0.587	0.193–0.244	0.992–0.999
		228/231	1,062/1,882	228/1,048	1,062/1,065
	Rule-in	0.797	0.957	0.694	0.975
		0.739–0.847	0.947–0.966	0.635–0.749	0.966–0.981
		184/231	1,801/1,882	184/265	1,801/1,848
0/2–3 h	Rule-out	0.991	0.628	0.258	0.998
		0.968–0.999	0.604–0.651	0.228–0.288	0.993–1.000
		219/221	1,064/1,695	219/850	1,064/1,066
	Rule-in	0.801	0.955	0.697	0.974
		0.742–0.852	0.943–0.964	0.636–0.753	0.965–0.981
		177/221	1,618/1,695	177/254	1,618/1,662

PPV, Positive predictive value; *NPV*, negative predictive value.

cutoff values were assigned to the continued evaluations group. The negative predictive values, sensitivities, positive predictive values, and specificities of the rule-out/rule-in of NSTEMI for the 0/1- and the 0/2- to 3-hour algorithms were not different (P=.55 to .98).

We evaluated several relevant clinical subgroups in regard to the interpretation of hs-cTnI results in the setting of using a rapid rule-out/rule-in ED protocol for patients presenting with suspected acute myocardial infarction. No demographic or clinical characteristic significantly influenced the negative predictive value of either the 0/1-hour or 0/2- to 3-hour algorithms (Figure 3). Furthermore, no negative predictive value point estimate was less than 99.4%. In contrast, the positive predictive value for the diagnosis of acute myocardial infarction was significantly reduced for blacks and patients with a history of heart failure or chronic kidney disease for both algorithms.

In the full cohort (n=2,346), 30-day outcomes were available for 2,335 patients (99.5%), with 24 (1.0%) with all-cause mortality, 12 (0.5%) with postdischarge acute myocardial infarction, 32 (1.4%) with postdischarge coronary revascularization, and 50 (2.1%) with a heart failure hospitalization. We report the Kaplan-Meier 30-day cumulative events for all-cause death/acute myocardial infarction according to the 0/1-hour and 0/2- to 3-hour algorithm group assignments. With the 0/1-hour algorithm, these rates were extremely low for patients in the rule-out group (2, or 0.2%; 95% CI 0.0% to 0.7%) and significantly increased for those assigned to continued evaluations (16, or 2.1%; 95% CI 1.2% to 3.3%) and the rule-in groups (13, or 4.9%; 95% CI 2.6% to 8.2%) (Figure 4*A*). Similar differentiation was observed in accordance with the 3-group assignment using the 0/2- to 3-hour algorithm (Figure 4*B*). The expanded composite endpoints of all-cause mortality, acute myocardial infarction, revascularization, and heart failure are shown in Figure E4*A* and *B* (available online at http://www.annemergmed.com) for the 0/1-hour and 0/2- to 3-hour algorithms, respectively. The expanded composite outcome was significantly higher across group assignment for both algorithms.

LIMITATIONS

First, although the HIGH-US study was designed to be inclusive of a broad demographic, we cannot say with confidence that these results apply to nonblack or nonwhite races because relatively few of these patients were enrolled. Second, if hs-cTnI and not a variety of contemporary troponin assays had been used to adjudicate for acute myocardial infarction diagnosis, the positive predictive value and number of ruled-in acute myocardial infarctions of the algorithms may have been higher. The adjudicated reclassification of acute myocardial infarction or myocardial injury and its clinical significance with an hs-cTnI assay is evolving. It has recently been reported to occur in 17% of patients but without an increase in acute myocardial infarction or cardiovascular death within 1 year.[22] Third, we have shown that the 0/1-hour algorithm maintained a greater than 99% negative predictive value for patients (423, 18.0%) who had symptom onset less than or equal to 3 hours from the initial hs-cTnI blood draw. Given that the time from ED presentation to hs-cTnI sampling had a mean of approximately 98 minutes (approximately 45 minutes after the standard-of-care blood collections), this indicates that many enrolled patients had symptoms onset of less than 2 hours before ED presentation. Although our

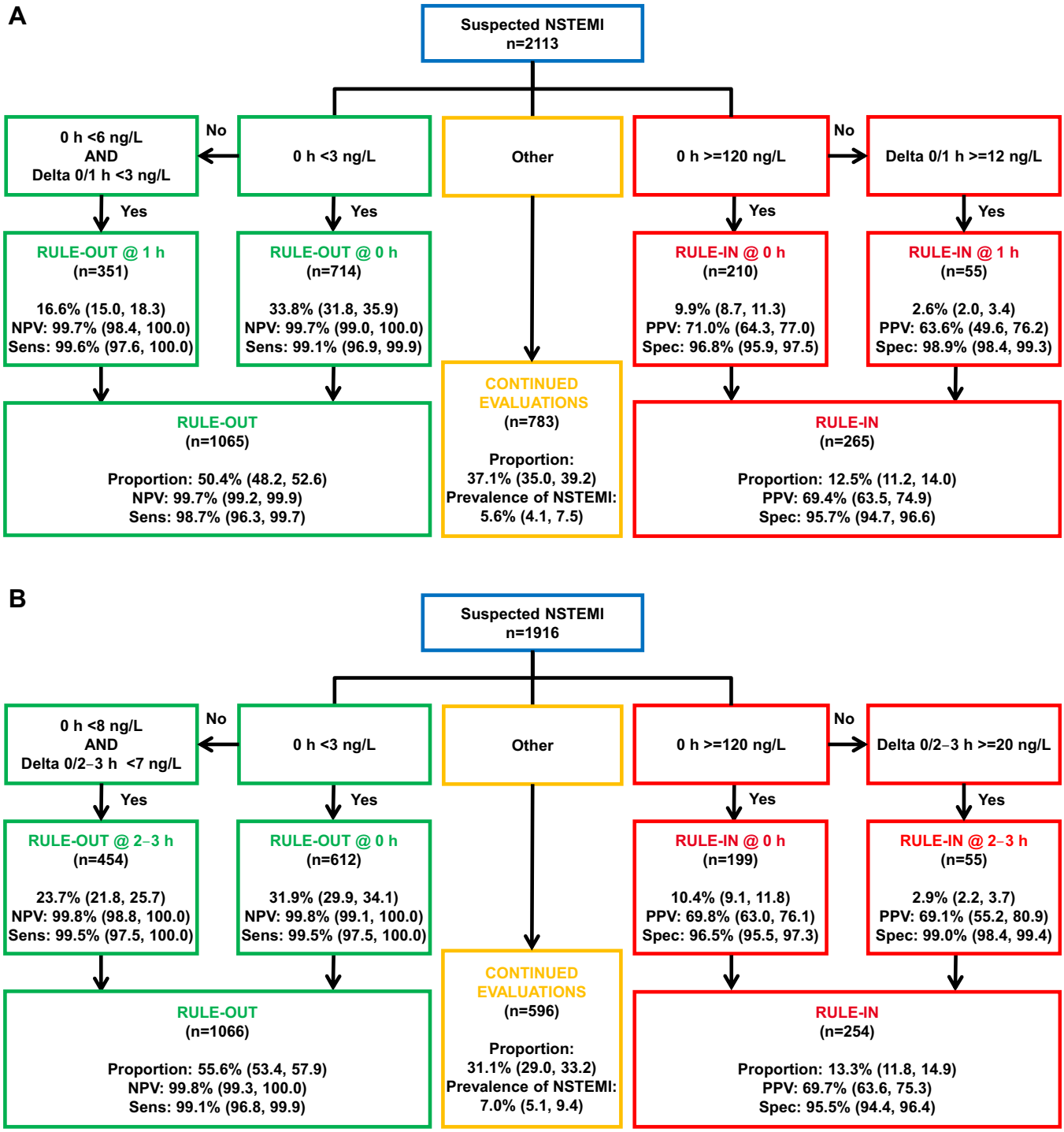


Figure 2. Clinical performance of the hs-cTnI assay on the Atellica Immunoassay Analyzer with 0/1-hour and 0/2- to 3-hour algorithms in a US population for lithium heparin samples. *A*, 0/1-Hour algorithm. *B*, 0/2- To 3-hour algorithm. Δ 0/2- To 3-hour=absolute change in assay result between baseline (0 hour) and 2 to 3 hours (120 to 180 minutes). Sample type was lithium heparin. All parenthetic elements=95% exact confidence levels. *Sens*, Sensitivity; *Spec*, specificity.

data suggest that most early presenters (≤3 hours of symptoms before ED presentation) can be effectively ruled out with the 0/1-hour algorithm, the CIs are wide, with a negative predictive value as low as 98%. We agree with the recommendations that patients presenting to the ED within 3 hours of onset of symptoms complete both points for either algorithm.[5] Fourth, there was a possible time blood-draw bias, increasing both the negative and positive

A

A			RO	Obs	RI	NPV (%)	PPV (%)
Symptom Onset	≤3 hours Prior	No NSTEMI	193	134	9		
		NSTEMI	0	7	39	100%	81.3%
	>3 hours Prior	No NSTEMI	869	605	72		
		NSTEMI	3	37	145	99.7%	66.8%
Sex	Female	No NSTEMI	561	257	29		
		NSTEMI	3	15	66	99.5%	69.5%
	Male	No NSTEMI	501	482	52		
		NSTEMI	0	29	118	100%	69.4%
Race	White	No NSTEMI	656	390	34		
		NSTEMI	2	21	109	99.7%	76.2%
	Black	No NSTEMI	367	321	43		
		NSTEMI	1	21	63	99.7%	59.4%
Age	<65	No NSTEMI	888	471	61		
		NSTEMI	2	20	117	99.8%	65.7%
	≥65	No NSTEMI	174	268	20		
		NSTEMI	1	24	67	99.4%	77.0%
History of CAD	No	No NSTEMI	760	376	37		
		NSTEMI	2	11	91	99.7%	71.1%
	Yes	No NSTEMI	284	353	44		
		NSTEMI	1	33	91	99.6%	67.4%
History of Heart Failure	No	No NSTEMI	952	488	44		
		NSTEMI	3	24	135	99.7%	75.4%
	Yes	No NSTEMI	94	243	33		
		NSTEMI	0	18	44	100%	57.1%
Renal Function	GFR<60	No NSTEMI	77	219	39		
		NSTEMI	0	18	51	100.%	56.7%
	GFR≤60	No NSTEMI	974	515	42		
		NSTEMI	3	26	132	99.7%	75.9%

95 98 99 100

50 60 70 80 90 100

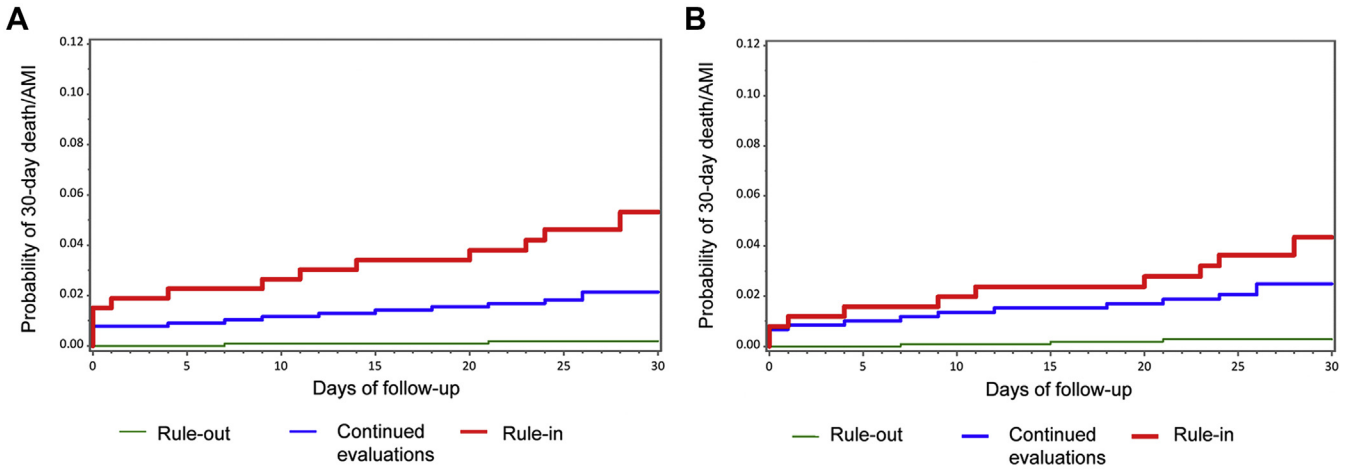
B

A			RO	Obs	RI	NPV (%)	PPV (%)
Symptom Onset	≤3 hours Prior	No NSTEMI	203	103	13		
		NSTEMI	0	4	40	100%	75.5%
	>3 hours Prior	No NSTEMI	861	451	64		
		NSTEMI	2	38	137	99.8%	68.2%
Sex	Female	No NSTEMI	531	180	28		
		NSTEMI	2	8	63	99.6 %	69.2%
	Male	No NSTEMI	533	374	49		
		NSTEMI	0	34	114	100%	69.9%
Race	White	No NSTEMI	672	280	34		
		NSTEMI	2	20	105	99.7%	75.5%
	Black	No NSTEMI	349	251	39		
		NSTEMI	0	22	60	100%	60.6%
Age	<65	No NSTEMI	872	345	50		
		NSTEMI	2	20	113	99.8%	69.3%
	≥65	No NSTEMI	192	209	27		
		NSTEMI	0	22	64	100%	70.3%
History of CAD	No	No NSTEMI	730	279	33		
		NSTEMI	0	12	85	100%	72.0%
	Yes	No NSTEMI	315	269	43		
		NSTEMI	2	30	90	99.4%	67.7%
History of Heart Failure	No	No NSTEMI	943	341	43		
		NSTEMI	2	22	129	99.8 %	75.0%
	Yes	No NSTEMI	106	207	30		
		NSTEMI	0	18	44	100%	59.5%
Renal Function	GFR<60	No NSTEMI	85	187	35		
		NSTEMI	1	20	45	98.8%	56.3%
	GFR≤60	No NSTEMI	968	364	42		
		NSTEMI	1	22	131	99.9%	75.7%

95 98 99 100

50 60 70 80 90 100

Figure 3. hs-cTnI Results on the Atellica Immunoassay Analyzer for 0/1-hour and 0/2- to 3-hour algorithms: negative and positive predictive value by subgroup. *A*, 0/1-Hour algorithm. *B*, 0/2- To 3-hour algorithm.



Number at risk, 0/1-hour algorithm			
	Rule Out	Continued Evaluations	Rule In
At zero days	1060	779	265
At 30 days	1058	763	252

Number at risk, 0/2-3-hour algorithm			
	Rule Out	Continued Evaluations	Rule In
At zero days	1062	592	253
At 30 days	1059	578	243

Figure 4. Kaplan-Meier 30-day outcome curves for the hs-cTnI assay on the Atellica Immunoassay Analyzer according to 0/1-hour and 0/2- to 3-hour algorithms.

predictive values in the study, because the hs-cTnI specimens were drawn approximately 40 minutes after the standard-of-care blood samples were obtained (for both algorithms) because written informed consent was required before any patient could be enrolled. Fifth, 16.0% of enrolled patients had only a single standard-of-care troponin value determined, most likely because of presentation with prolonged symptoms, so it may have been possible that some of these individuals would have had a different adjudicated acute myocardial infarction diagnosis if additional standard-of-care troponin levels had been obtained. Sixth, patient enrollments were not sequential chronologically at any site (no site had research coordinators available continuously) and enrollment periods varied at each participating site. Whether the results might have been different if sequential patient enrollment had been accomplished is not known. Seventh, 5% of enrolled patients did not have an adequate baseline blood sample drawn, thus potentially leading to a bias for patients when blood collection was challenging. Eighth, we were not able to obtain 30-day follow-up for 11 patients (0.5%). It may have been that a few of these patients had an adverse outcome that we could not determine, but most likely this would have minimally changed our results and discussion.

In our study, all the "missed" acute myocardial infarction patients, using either the 0/1-hour (3 patients) or 0/2- to 3-hour (2 patients) algorithms, were either admitted to the hospital for further evaluations or had a cardiology consultation and provocative testing completed before ED discharge. This reinforces the importance of using these hs-cTnI algorithms in conjunction with clinical judgment.

DISCUSSION

Several hs-cTn assays are now approved by the FDA for use in the United States to aid in the diagnosis of acute myocardial infarction, and more are expected in the near term. To our knowledge, this is the first US-based multicenter prospective study to report the efficacy of rapid hs-cTn algorithms in a US ED population representative of the diversity and heterogeneity of the intended use population. However, the percentage of blacks enrolled (40%) was higher than the 17% to 19% black composition of the overall US population. Our findings identify that rapid diagnostic algorithms incorporating the Siemens Healthineers hs-cTnI assays measured across multiple instruments are associated with an excellent negative predictive value but with only a moderate positive predictive value. Our findings are comparable to those in European-based cohorts using the same assays, allowing international harmonization of results and providing future opportunities to easily translate findings despite differences in the demographics of the populations being tested.

In our rapid assessment for acute myocardial infarction algorithms, we have replaced the previous "observe" zone nomenclature with a "continued evaluation" one because we believe that this better reflects how these patients are

assessed. They were not simply observed, but rather the emergency physician would in many cases order more laboratory tests (including additional troponin measurements), ECGs, and imaging tests or would assign patients to observation status or admit them to the hospital in an attempt to safely clarify the diagnosis for each patient.

Reports from outside the United States indicate that these newer high-sensitivity assays can be used for rapidly (1 or 2 hours after ED presentation) ruling out and ruling in acute myocardial infarction.[1,2,23] The selection of individuals enrolled in these non-US studies is often associated with a prevalence of acute myocardial infarction that can be much higher than that reported in US-based studies.[5,6,11-13] Within the United States, cardiac troponin measurements are widely applied to patients presenting to the ED with any suspected acute myocardial infarction and are inclusive of a broad demographic that uses the ED for a variety of conditions in urban, suburban, and rural settings.[8] Compared with a recent international study from Europe and South America,[5] the HIGH-US study had 8% more women and 44% more nonwhites. Additionally, the prevalence of traditional cardiac risk factors was greater than in European cohorts, with 69.5% hypertensive patients, 39.4% diabetic patients, and 19.6% of patients with chronic kidney diseases in the HIGH-US study versus 51%, 13%, and 6%, respectively, in the European study. Findings from previous US-based single-center and multicenter reports of another FDA-approved hs-cTn assay show high negative predictive values, but in contrast to that of international cohorts, much lower positive predictive values.[6,11,12] We report high negative predictive values (using hs-cTnI values below the 99th percentile) but a positive predictive value that was comparable to that of European cohorts tested with the same assays and algorithms. These findings remain robust even across subgroup analyses of sex and patients presenting early in their symptom course.

We show that black race, presence of renal disease, and history of heart failure were associated with a lower acute myocardial infarction positive predictive value. European cohorts have also shown that renal disease similarly decreases the positive predictive value of hs-cTn testing for acute myocardial infarction.[24,25] The proportion of black participants was higher in this study compared with another US-based multicenter study of an alternative hs-cTn that showed a much lower positive predictive value.[8] The explanation does not appear to be related to differences in clinical features of the tested population. Potentially, there are unique characteristics to the hs-cTnI assays tested in this study that may make them more specific for differentiating acute versus chronic injury compared with other hs-cTn assays.[26] Although we were able to demonstrate harmonization in a prospective US-based study with European-derived rapid algorithms, it should not be assumed that this is applicable to other hs-cTn assays without assay-specific supporting evidence.

The precise timing of cTn blood draws in patients at 1, 2, or 3 hours after presentation to a busy ED will depend on patient volumes and staffing. We have reported the actual sample draw distributions at 1 hour after the baseline blood sampling and within the 2- to 3-hour redraw window. Additionally, because there was no significant difference in the negative or positive predictive value for either of the algorithms to rule out or rule in acute myocardial infarction, the emergency physician has time between patient presentation and for up to 3 hours later in which the evaluations of patients are equally effective.

A recent report[27] from the HIGH-US study has detailed the utility of the use of a single optimized baseline hs-cTnI value of less than 5 ng/L to identify almost half of ED patients with suspected acute myocardial infarction as low risk both at presentation for acute myocardial infarction and for the 30-day outcomes of death or acute myocardial infarction. However, there was some concern[28] that the time differences between the standard-of-care troponin blood draw and the hs-cTnI research sample (always later by research design) might have inappropriately favored the hs-cTnI values in the results reported. Our 0/1-hour algorithm identified 50.4% of patients as not having had an acute myocardial infarction, whereas the 0/2- to 3-hour one identified 55.6% of these patients, with similar negative predictive values and sensitivities, and both our algorithms were equally effective in predicting similar 30-day adverse outcomes compared with the use of a single optimized value, as has been recently reported.[27] The use of either a 0/1- or 2- to 3-hour algorithm further minimizes any possible bias for time of draw for the hs-cTnI compared with the standard-of-care measurements.

The 30-day follow-up rates (data missing for only 11 patients [0.5%]) for all-cause death and acute myocardial infarction for patients assigned to the rule-out groups with the hs-cTnI values alone confirm that these event rates are acceptably low for patients to be discharged from the ED with routine follow-up if no other acute disease is diagnosed. This was independent of any ECG findings or the use of any clinical risk-stratification tools before patient discharge. Recent clinical reports support the concept that in the era of hs-cTn, the value itself can be used for 30-day predictions for death and acute myocardial infarction.[29,30] However, the rates of these adverse events for patients with the higher cTnI values observed in the continued evaluations and rule-in zones are high enough that increased caution is needed before any early ED discharge.

Furthermore, when the 30-day outcomes of postdischarge revascularization and heart failure admission were added to death and acute myocardial infarction, adverse event rates in the rule-out, continued observations, and rule-in zones approximately doubled.

The accuracy for the early rule-out or rule-in of acute myocardial infarction with either a 0/1-hour or 0/2- to 3-hour novel hs-cTnI algorithm in a diverse US-based ED population is similar to that reported in comparable previous non-US studies, allowing a harmonization of these algorithms internationally. US ED patients can be equivalently evaluated with either a 0/1-hour or 0/2- to 3-hour algorithm. The rule-out zone hs-cTnI cut points of these algorithms additionally accurately predict the extremely low-prevalence 30-day outcomes of all-cause mortality and acute myocardial infarction, regardless of any ECG changes or the use of any clinical risk-stratification tools. The rapid rule-in of acute myocardial infarction with hs-cTnI assays requires more studies in the United States to improve the positive predictive values and specificities.

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