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Troponin limit of detection plus cardiac risk stratification scores to rule out acute myocardial infarction and 30-day major adverse cardiac events in ED patients

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Abstract

When screening for acute myocardial infarction (AMI), troponin levels below the 99th percentile, including those below the limit of detection (LOD), are considered normal. We hypothesized that a low-risk HEART Score (0–3) or ACS Pretest Probability Assessment <2% plus a single troponin below the LOD would rule out both AMI and 30-day major adverse cardiac events (MACE). We studied all patients who presented to a single academic ED and received a troponin I (Siemens Ultra Troponin I) from 9/1/13 to 11/13/13 (n=888). Demographic and clinical data were abstracted from the electronic medical record. Primary outcome was a final encounter diagnosis of MI. Secondary outcome was 30-day MACE, defined as composite of MI, revascularization, or death from a cardiac or uncertain etiology. Sensitivities of low-risk HEART score and ACS Pretest Probability <2% alone were 98% (95%CI 89–100%) and 96% (95%CI 86–100%) for AMI and 94% (95%CI 86–98%) and 95% (95%CI 88–99%), respectively, for 30-day MACE. When combined with troponin below the LOD, sensitivity for AMI was 100% (95%CI 93–100%; difference 2%, 95%CI −2% to 6%) for low-risk HEART Score and 100% (95%CI 93–100%; difference 4%, 95% CI −1.5 to 10%) for ACS Pretest Probability <2%. When combined with troponin below the LOD, sensitivity for 30-day MACE was 100% (95%CI 95–100%; difference 6%; 95%CI 1–12%) for low-risk HEART Score and 100% (95%CI 95–100%; difference 5%; 95%CI 0.2–10%) for ACS Pretest Probability <2%. Addition of a single troponin below the LOD to these scores improves sensitivity for 30-day MACE.

Keywords

Troponin; myocardial infarction; cardiac risk stratification

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Introduction

Chest pain is the second most common presenting symptom for emergency department (ED) visits in the United States, accounting for over six million ED visits annually.[1] While fewer than ten percent of patients with symptoms suggestive of acute cardiac ischemia are ultimately diagnosed with an acute myocardial infarction (AMI), a low but unacceptable number are discharged from the ED with a missed AMI.[2]

The American College of Cardiology Foundation and American Heart Association recommend screening for AMI with an electrocardiogram and serial troponin testing.[3] Troponin values below the 99th percentile of values in a healthy population are considered normal.[4] Many patients have a troponin level below the limit of detection (LOD) of troponin assays. However, the clinical significance of a troponin below the LOD as compared to a normal troponin levels in patients undergoing evaluation for AMI remains unknown.

Cardiac risk stratification systems help clinicians assess the risk of AMI and 30-day major adverse cardiac events (MACE) in patients presenting with chest pain.[5–9] The HEART score is one of the most widely used in the ED setting. This score uses elements of the patient's **H**istory, **E**lectrocardiogram, **A**ge, **R**isk factors, and **T**roponin to predict the risk of MACE within six weeks. Patients are divided into low, medium, or high risk categories.[5,6,9] The ACS Pretest Probability is less commonly used, but it is attractive for use in the ED because it can be calculated based on the patient's history alone, before laboratory findings are resulted. This tool quantifies the pre-test probability of coronary artery disease or a MACE within the next 45 days.[8]

Previous studies have evaluated the clinical utility of either risk scores[5,6,8,9] or troponin values alone.[10–12] In this investigation, we evaluated the sensitivity of low risk scores plus a single contemporary troponin level below the LOD for ruling out AMI and 30-day MACE.

Methods

Study design and ethics

We performed a retrospective cohort study at a single academic ED. This study was approved by our Institutional Review Board.

Participants

We included all adult patients (age 18 years and older) who presented to the ED and received at least two troponin I tests (Siemens Ultra Troponin I) from September 1, 2013 to November 13, 2013. We included only patients with two troponins resulted during their ED stay, because we wanted to study patients in whom clinicians felt serial troponins were indicated. We excluded patients who eloped from the ED prior to physician evaluation, patients for whom a final encounter diagnosis was not available, and patients with insufficient to calculate the HEART score or ACS Pretest Probability. For the 30-day MACE outcome, patients were excluded from the analysis if no follow up was available. Patients were not excluded based on chief complaint or past medical history.

Measurements

Data directly exported from the electronic medical record included patient age, race, ethnicity, date of ED visit, and troponin values. Additional data abstracted from the electronic health record by trained study team members included demographic and clinical characteristics, additional laboratory results, EGC results, final encounter diagnoses, and return visits within 30 days of the index visit. Electrocardiogram and serial troponin assays (Siemens Ultra Troponin I; 99th percentile defined as <0.04ng/ml; limit of detection defined as <0.01ng/ml) are part of the standard protocol for suspected acute coronary syndrome at the study hospital.

HEART scores[5,6] (Table 1a) and ACS Pretest Probability Assessment[8,13] (Table 1b) were calculated. HEART scores of 0–3 were considered low risk.[5] An ACS Pretest Probability cutpoint of less than two percent was chosen to represent “low risk” because the low-risk HEART score of 0–3 corresponds to less than two percent risk of 30-day MACE.[6]

Primary and secondary outcomes

The primary outcome was a final encounter diagnosis of AMI, defined as a diagnosis of ST elevation MI, non-ST segment elevation MI, or MI documented by the emergency medicine physician (for discharged patients) or the hospital discharge summary (for admitted patients). The secondary outcome was 30-day MACE, defined as MI, coronary revascularization, or death from a cardiac or uncertain etiology within 30 days from index presentation. Thirty-day outcomes were determined by electronic medial record review. Patients were considered alive with no MACE if they had a visit within the electronic medical record any time after 30 days that did not mention MACE within 30 days from index presentation.

Data abstraction

Standard methodology for retrospective chart review studies was followed.[14,15] Data abstractors were trained using a sample chart and used a standardized, electronic data collection form that included key definitions and instructions on where to locate information in the electronic health record. Questions regarding abstraction and coding were discussed electronically. The primary data abstractors were blinded to the study’s hypothesis. A second reviewer (faculty physician) independently abstracted the primary and secondary outcomes for 100 patients, including all patients with the primary outcome to assess inter-rater agreement. Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools.[16] REDCap is a secure, web-based application designed to support data capture for research studies, providing an intuitive interface for validated data entry; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to common statistical packages; and procedures for importing data from external sources.

Statistical Analysis

Descriptive statistics were performed. Cohen’s kappa coefficient was used to measure inter-rater agreement of the abstractors for the primary and secondary outcomes. Sensitivity and 95% confidence intervals (CI) were calculated for each of the following: low-risk HEART

score alone, ACS Pretest Probability Assessment <2% alone, and initial troponin below the LOD alone. Sensitivities and 95% CIs were also calculated for each risk score plus an initial troponin below the LOD. For the 30-day MACE outcome, patients were excluded from the main analysis if no follow up was available. We conducted a secondary analysis assuming all patients with missing 30-day follow up data had 30-day MACE. All analyses were performed using Stata version 14.2 (StataCorp, College Station, TX).

Results

Of the 919 adult patients who presented to the ED and received at least two troponin I tests, we excluded 31 patients for the following reasons: eloping prior to physician evaluation (n=1), no final encounter diagnosis (n=21), and insufficient data to calculate the HEART score or ACS Pretest Probability (n=9). We included 888 subjects with median age 62 (IQR 52–74) years. Nearly half (422; 48%) of subjects had an initial troponin below the LOD; 333 (38%) had a low-risk HEART Score, and 143 (16%) had an ACS Pretest Probability <2% (Table 2). Patients with and without 30-day follow up data available were similar (Table 2). Forty-nine (5.5%) subjects had an encounter diagnosis of AMI, and 80 (11%) had 30-day MACE. Two of the 422 patients with an initial troponin below the LOD had an encounter diagnosis of AMI. Both patients were admitted to the hospital for non-cardiac reasons (polysubstance overdose and sepsis) and were referred for outpatient cardiac evaluation upon hospital discharge.

Sensitivities of low-risk HEART score and ACS Pretest Probability <2% alone were 98% (49/50; 95%CI 89–100%) and 96% (48/50; 95%CI 86–100%) for AMI and 94% (75/80; 95%CI 86–98%) and 95% (76/80; 95%CI 88–99%), respectively, for 30-day MACE. When combined with troponin below the LOD, sensitivity for AMI was 100% (50/50; 95%CI 93–100%; difference 2%, 95%CI −2% to 6%) for low-risk HEART Score and 100% (50/50; 95%CI 93–100%; difference 4%, 95% CI −1.5 to 10%) for ACS Pretest Probability <2% (Table 3). When combined with troponin below the LOD, sensitivity for 30-day MACE was 100% (80/80; 95%CI 95–100%; difference 6%; 95%CI 1–12%) for low-risk HEART Score and 100% (80/80; 95%CI 95–100%; difference 5%; 95%CI 0.2–10%) for ACS Pretest Probability <2% (Table 4). The Appendix shows sensitivities and specificities for 30-day MACE when all patients missing 30-day follow up were assumed to have MACE.

Overall, 296 patients (33%) were discharged home from the ED, 38 (4.3%) were observed in the chest pain observation unit, and 538 (61%) were admitted or transferred (Table 2). Of the 242 patients with a low-risk HEART score and an initial troponin below the LOD, 148 (61%) were ultimately discharged home.

The kappa coefficients were 0.90 and 0.89 for AMI and 30-day MACE, respectively, indicating excellent inter-rater reliability of the abstractors for the primary and secondary outcomes.

Discussion

In our population, patients with an initial troponin I value below the LOD and a low-risk HEART Score or ACS Pretest Probability <2% had no AMIs or 30-day MACE. The addition

of a single troponin I value below the LOD to these scoring systems is practical, as a troponin level is routinely ordered in the evaluation of patients with suspected acute coronary syndrome. Availability of online calculators and increasing use of decision support within the electronic medical record facilitates calculation of these risk scores in a busy clinical environment.[17,18]

In our ED and several others, serial troponin measurements are drawn three hours apart for patients with concern for acute coronary syndrome, in accordance with current guidelines.[3,19] This practice requires extended ED evaluations and contributes to ED crowding. The ability to safely discharge patients following a single troponin below the LOD may shorten ED length of stay for these patients, ease overall ED crowding, and save costs for hospitals.[20,21] In our dataset, 17% (148/888; 95% CI 14–19%) of patients with a low-risk HEART score and initial troponin below the LOD were discharged from the ED, suggesting that 17% of our ED population that currently undergoes evaluation with serial troponin testing might be safely discharged after a single troponin.

One reason for the guideline recommendation for serial troponins is that troponin may not be detectable until two to four hours after infarction begins.[3] Thus, our results should be interpreted with caution in patients whose chest pain began shortly before the initial laboratory draw. Similarly, guidelines caution that troponin values alone should not be used to rule out AMI.[3] The two patients with initial troponin below the LOD and AMI were both admitted to the hospital for non-cardiac reasons. Despite their final diagnosis of AMI, these patients are not the primary targets of ED screening to rule out AMI. Future studies should evaluate whether a troponin below the LOD alone is sufficient to rule out AMI in patients without alternate reasons for hospital admission.

The Siemens Ultra Troponin I is a contemporary troponin assay similar to those currently used in most hospitals in the United States. The United States Food and Drug Administration recently approved a fifth-generation (“high sensitivity”) troponin T assay (Roche Elecsys® hs-cTnT) which may provide increased sensitivity for rapidly ruling out AMI in ED patients undergoing evaluation for acute coronary syndrome.[10,11] Future studies should evaluate the use of this fifth-generation troponin T assay both alone and in combination with established cardiac risk stratification scores for ruling out AMI in a United States population.

The study has several limitations. First, it was conducted at a single center, and thus may not be generalizable to other populations. Second, despite sampling nearly 900 patients, only 5.5% had AMI. A larger sample size would allow for tighter confidence intervals, and allow for more definitive conclusions. Third, HEART scores and ACS Pretest Probability Assessment were calculated retrospectively. While most elements in these scores are routinely recorded in clinical documentation, our calculations were limited to the data in the electronic medical record. Finally, 30-day follow up was not available for 151 (17%) of patients. However, patients with and without 30-day follow up had similar characteristics (Table 2).

Conclusion

In this single center study, patients with an initial troponin I value below the LOD and a low-risk HEART Score or ACS Pretest Probability 2% had no AMIs or 30-day MACE. Addition of a single troponin below the LOD to these scores improves sensitivity for 30-day MACE.

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Appendix. Comparison of test characteristics for 30-day composite outcome assuming MACE for all patients with missing 30-day followup

	Sensitivity (%, 95% CI)	Difference (%, 95% CI)	Specificity (%, 95% CI)	Difference (%, 95% CI)	Positive LR (LR, 95% CI)	Negative LR (LR, 95% CI)
HEART Score 0–3	70% (64–76%)	--	40% (36–44%)	--	1.17 (1.06–1.30)	0.74 (0.60–0.93)
ACS Pretest Probability <2%	86% (81–90%)	--	17% (14–20%)	--	1.04 (0.97–1.10)	0.82 (0.57–1.18)
Troponin below LOD	59% (52–65%)	--	50% (46–54%)	--	1.17 (1.03–1.34)	0.83 (0.70–0.98)
HEART Score 0–3 + Troponin below LOD	78% (72–83%)	7% (4–11%)	29% (26–33%)	11% (9–14%)	1.09 (1.00–1.19)	0.78 (0.60–1.02)
ACS Pretest Probability <2% + Troponin below LOD	91% (86–94%)	5% (2–8%)	13% (10–16%)	4% (3–6%)	1.04 (0.99–1.10)	0.71 (0.45–1.12)

CI = Confidence interval; LR = Likelihood ration; LOD = Limit of detection

Table 1a

HEART Score

Variable	Score
History	
Highly suspicious	2
Moderately suspicious	1
Slightly suspicious	0
Electrocardiogram	
Significant ST-depression	2
Non-specific repolarization disturbance	1
Normal	0
Age	
≥ 65	2
45–64	1
< 45	0
Risk Factors	
≥ 3 or history of atherosclerotic disease	2
1–2 risk factors	1
No known risk factors	0
Troponin	
> 3 times the normal limit	2
1–3 times the normal limit	1
≤ normal limit	0

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Table 1b

ACS Pretest Probability Assessment Variables

Age
Gender
Race
Chest pain with palpation
Personal history of CAD
Diaphoresis
ECG ST depression > 0.5mm
T-wave inversion > 0.5mm

CAD = Coronary artery disease; ECG = Electrocardiogram

Crit Pathw Cardiol. Author manuscript; available in PMC 2018 December 01.

Table 2

Patient Characteristics

Characteristics	Overall n=888 N (%)	30-day Follow up n=737 N (%)	No 30-day Follow up n=151 N (%)
Demographic characteristics			
Age *	62 (52, 74)	63 (53–74)	59 (48–70)
Male sex	460 (52%)		
Race/ethnicity			
White, non-Hispanic	266 (30%)	222 (30%)	44 (29%)
White, Hispanic	95 (11%)	78 (11%)	17 (11%)
Black	119 (13%)	106 (14%)	13 (9%)
Asian	54 (6%)	47 (6%)	7 (5%)
Other	57 (6%)	43 (6%)	14 (9%)
Unreported	297 (33%)	241 (33%)	56 (37%)
Clinical characteristics			
Chief complaint of chest pain	309 (35%)	250 (34%)	59 (39%)
Prior MI	243 (28%)	217 (29%)	26 (17%)
Diabetes	329 (37%)	279 (38%)	50 (33%)
Tobacco use	246 (28%)	197 (27%)	49 (32%)
Troponin below LOD	422 (48%)	336 (46%)	86 (57%)
Risk Categories			
Low Risk HEART score (0–3)	333 (38%)	269 (36%)	64 (42%)
Low Risk HEART score (0–3) and troponin below LOD	242 (27%)	190 (26%)	52 (34%)
ACS Pre-test Probability <2%	143 (16%)	115 (16%)	28 (19%)
ACS Pre-test Probability <2% and troponin below LOD	105 (12%)	84 (11%)	21 (14%)
ED Disposition			
Discharge home	296 (33%)	237 (32%)	59 (39%)
Observation unit	38 (4.2%)	27 (4%)	11 (7%)
Admission/transfer	538 (61%)	457 (62%)	81 (54%)
Missing	16 (1.8%)	16 (2%)	0 (0%)

Crit Pathw Cardiol. Author manuscript; available in PMC 2018 December 01.

* Presented as median (Q1, Q3)

MI = Myocardial infarction; LOD = Limit of detection; ED = Emergency department

Table 3

Comparison of test characteristics for acute myocardial infarction.

	Sensitivity (%, 95% CI)	Difference (%, 95% CI)	Specificity (%, 95% CI)	Difference (%, 95% CI)	Positive LR (LR, 95% CI)	Negative LR (LR, 95% CI)
HEART Score 0–3	98% (89–100%)	--	40% (36–43%)	--	1.62 (1.52–1.74)	0.05 (0.01–0.35)
ACS Pretest Probability <2%	96% (86–100%)	--	17% (14–20%)	--	1.15 (1.08–1.23)	0.24 (0.06–0.93)
Troponin below LOD	96% (87–100%)	--	50% (47–54%)	--	1.92 (1.76–2.10)	0.08 (0.02–0.31)
HEART Score 0–3 + Troponin below LOD	100% (93–100%)	2% (−2 to 6%)	29% (26–32%)	11% (9–13%)	1.41 (1.35–1.47)	0.00
ACS Pretest Probability <2% + Troponin below LOD	100% (93–100%)	4% (−2 to 10%)	13% (10–15%)	4% (3–6%)	1.14 (1.11–1.17)	0.00

CI = Confidence interval; LR = Likelihood ration; LOD = Limit of detection

Table 4

Comparison of test characteristics for 30-day composite outcome.

	Sensitivity (%, 95% CI)	Difference (%, 95% CI)	Specificity (%, 95% CI)	Difference (%, 95% CI)	Positive LR (LR, 95% CI)	Negative LR (LR, 95% CI)
HEART Score 0–3	94% (86–98%)	--	40% (36–44%)	--	1.57 (1.44–1.71)	0.16 (0.07–0.37)
ACS Pretest Probability <2%	95% (88–99%)	--	17% (14–20%)	--	1.14 (1.08–1.21)	0.30 (0.11–0.78)
Troponin below LOD	89% (80–95%)	--	50% (46–54%)	--	1.77 (1.58–1.97)	0.23 (0.12–0.42)
HEART Score 0–3 + Troponin below LOD	100% (96–100%)	6% (1–12%)	29% (65–33%)	11% (9–14%)	1.41 (1.34–1.48)	0.00
ACS Pretest Probability <2% + Troponin below LOD	100% (96–100%)	5% (0.1–10%)	13% (10–16%)	4% (3–6%)	1.15 (1.11–1.18)	0.00

CI = Confidence interval; LR = Likelihood ration; LOD = Limit of detection