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ORIGINAL RESEARCH

Cardiology

Multicenter analysis to assess risk of major adverse cardiac events in patients undergoing high-sensitivity troponin testing in the emergency department

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Abstract

Study hypothesis: Our objective was to evaluate 30-day major adverse cardiac events (MACE) in emergency department (ED) patients with normal high-sensitivity troponins (hs-trop). We hypothesized that MACE rates would be <1% in patients with (1) two normal troponins regardless of change in troponin (delta) and (2) index hs-trop below the limit of quantitation (LOQ) regardless of the institution modified HEART score.

Methods: This was a multicenter, retrospective, cohort study of adult patients who presented to 1 of 18 EDs between July 2020 and April 2021 with acute coronary syndrome as defined by an institutional-modified HEART score completed by their treating physician or midlevel, no evidence of ST-elevation myocardial infarction, and an index or serial gender-adjusted hs-trop within normal limits. The primary outcome was MACE within 30 days of index ED encounter. A detailed case review was then performed for those patients experiencing a MACE.

Results: Of the 9084 patients who had single or serial normal troponins, 31 (0.34%; confidence interval [CI] 0.23%–0.48%) experienced MACE. Of the 6140 patients with 2 normal hs-trop and a delta (change in troponin) <4, 27 patients (0.44%; CI 0.29%–0.64%) experienced MACE. Only 1 of the 69 patients with 2 normal hs-trop results but delta (change in troponin) ≥ 4 (1.45%; CI 0.04%–7.81%) suffered MACE. This patient was classified as non-low risk by our institutional HEART score. Of 7498 patients with an index hs-trop <LOQ, 14 (0.19%; CI 0.10%–0.31%) experienced MACE, with 57% ($N = 8$) deemed non-low risk by HEART score.

Conclusion: Patients with 2 normal hs-trop values in the ED are unlikely to suffer 30-day MACE. Although it remains unclear whether patients with delta (change in troponin) ≥4 despite normal troponins will have a 30-day MACE, this situation is rare. Additionally, a single index hs-trop <6 ng/L demonstrated a low risk for 30-day MACE independent of the institutional HEART score.

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1 | INTRODUCTION

1.1 | Background

Each year, 8 to 10 million patients present to an emergency department (ED) in the United States with complaints of chest pain, the majority of whom will subsequently undergo an acute coronary syndrome (ACS) work-up.[1] Up to 25% of these patients will eventually be admitted to the hospital despite 85% of them having benign, non-cardiac related chest pain.[1] This high rate of admission is driven by fear of misdiagnosing a patient as having non-cardiac chest pain when they are in fact suffering from ACS. Despite this high number of conservative admissions, approximately 1% of patients who present with unspecified chest pain and are subsequently discharged from the ED will go on to experience 30-day major adverse cardiac events (MACE).[2]

1.2 | Importance

Clinical decision rules have been developed to risk-stratify patients with chest pain and to guide ED disposition. One commonly used tool is the HEART score.[3–5] The last part of this score refers to the patient's troponin level. The traditional troponin I assay that had been used in the majority of US EDs has a sensitivity of 25%–65% at the time of ED presentation, with an increase to 59%–90% at 2 to 6 h after presentation.[6,7] Recently, newer high-sensitivity troponin I (hs-trop) assays have become available. Hs-trop assays have been shown to have a 1-h sensitivity of 96.7%–100% and negative predictive value of 99.1%–100% with in vitro testing.[8–11] Testing strategies with hs-trop have been shown to effectively identify patients at very low risk for 30-day MACE . Current strategies for hs-trop testing include single, serial, and delta (change in troponin). However, the optimal testing strategy remains unclear and the greatly improved sensitivity of hs-trop has prompted many clinicians to wonder if it is safe to discharge patients home after a normal index hs-trop regardless of HEART score.[12,13]

1.3 | Goals of this investigation

The objective of this study was to assess 30-day MACE in ED patients with normal hs-trop. We hypothesized that MACE rates would be <1% in patients with (1) 2 normal troponins regardless of delta (change in troponin) and (2) index hs-trop below the limit of quantitation (LOQ) regardless of the institutional HEART score.

The Bottom Line

High-sensitivity troponins are increasingly being used to risk stratify patients presenting to emergency departments (EDs) with chest pain. In this multicenter, retrospective cohort of over 9000 patients with chest pain evaluated in EDs with normal initial or serial high-sensitivity troponins, the risk of 30-day major adverse cardiac event was 0.34% (95% confidence interval, 0.24%–0.48%). This helps inform decision-making regarding disposition of patients with normal high-sensitivity troponin testing.

2 | METHODS

2.1 | Study design and setting

This was a multicenter, retrospective, cohort study of patients who presented to 1 of 18 Atrium Health Greater Charlotte area EDs between July 27, 2020, and April 30, 2021. Physicians or midlevels who suspected ACS , either by history or physical examination, enrolled their patients into the Atrium-Health HEART Pathway by filling out an Atrium Health-modified HEART score (AH-HEART) (Table 1) and ordering high sensitivity troponin testing. Troponin testing was preformed using the Beckman Coulter hs-trop assay. Patients who presented with ECG changes indicating an ST-segment myocardial infarction (STEMI) were not enrolled in this pathway as it was hospital protocol to activate the cardiac catheterization lab as soon as a STEMI was identified.

A modified version of the legacy institutional HEART Score was implemented across [14] EDs within the health system 6 months before the initiation of this study to allow time for education of emergency medicine staff and to mitigate impact of COVID. The AH-HEART Pathway differed from the legacy institutional HEART score in that it offered detailed descriptors in the history and ECG sections to help reduce subjectivity in scores. Additionally, the history and troponin portions of the AH-HEART score are weighted to contribute a maximum of 4 points, whereas the highest value any section can contribute to the traditional HEART score is 2 points. Low risk was defined as a score of 0–3, moderate risk as a score of 4–6, and high risk as scores ≥7. AH-HEART scores used in this study were calculated by the physician or midlevel while caring for the patient in the ED.

2.2 | Selection of participants

The study population included adult patients (age ≥ 18 years) presenting to an Atrium Health's Greater Charlotte Region ED capable of using the AH-HEART score with (1) final or discharge diagnosis codes of chest pain other R07.89; chest pain unspecified R07.9; unstable angina- I20.0, I20.1, I20.8, I20.9; acute myocardial infarction (AMI) I21.9, I21.A1, I21.A9; acute ischemic heart disease I24.9; and non-STEMI (NSTEMI) I21.4; (2) initial hs-trop within normal limits, and (3) AH-HEART score calculated. Patients with a diagnosis for STEMI (I21.0, I21.01, I21.02, I21.09, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3) were excluded. The decision to follow up an initial troponin with a second or serial troponins was made by either the treating ED physician or the admitting physician. The Beckman Coulter hs-trop

assay was used with gender-specific cutoffs (hs-trop cutoff <12 ng/L for women and <20 ng/L for men) and an LOQ of <6 ng/L as per our hospital's guidelines. Additionally, a change in troponin (delta value) of <4 was considered a normal delta troponin. We included only patients who presented 6 months after our facilities began using the AH-HEART Pathway and hs-trop to allow for education and adoption of the new process and to mitigate the influence of COVID-19 on ED volume. This study adhered to the STROBE recommendations with inclusions and exclusions that can be referenced in Figure 1.

2.3 | Measurements and outcomes

Data on sociodemographic, comorbidities, and HEART score along with individual component scores were extracted from the electronic medical record (EMR) and enterprise data warehouse. The outcome of interest for the study was MACE at index visit and during the 30-day follow-up period. MACE was defined as a composite of death, myocardial infarction (MI), and revascularization (coronary artery bypass graft [CABG], stent placement, or other percutaneous coronary intervention [PCI]) during the index visit and the 30-day follow-up period. Data on MACE was determined by querying the EMR using *International Classification of Diseases, Tenth Revision* (ICD-10) codes and searching for study participants within several national registries including the National Cardiovascular Data Registry CathPCI registry, Chest Pain-MI registry and Society for Thoracic Surgeon—Adult Cardiac Surgery Database files, and Social Security Death Index (SSDI).

After extraction of MACE from these preexisting registries, SSDI, and ICD-10 codes, a consensus of 2 reviewers who were unblinded to hs-trop and HEART score values (V.S., P.M.) adjudicated the type of MACE (death, cardiac arrest, PCI, left heart catheterization (L.H.C.), CABG, or NSTEMI). The reviewers were provided with participants' index and discharge records, records obtained from follow-up, and study definitions. Any disagreements were settled by consensus between the 2 reviewers or the involvement of a third unblinded reviewer (D.P.). If data regarding cause of death were not available during this chart review process it was noted in the addendum section. The Atrium Health Institutional Review Board (# 07-20-18E) approved collection and use of these data for study purposes.

2.4 | Analysis

All analyses were conducted using SAS Enterprise Guide 7.1 (Cary, NC; SAS Institute). Normal distribution of continuous variables was assessed by Shapiro–Wilk test. Baseline characteristics were summarized as frequencies and percentages for categorical variables and for continuous variables, means ± standard deviations or median and interquartile range for skewed variables were provided. Incidence of MACE rate for each stratum were calculated along with corresponding 95% exact binomial confidence intervals (CI) and negative predictive values.

3 | RESULTS

3.1 | Characteristics of study subjects

The 10,268 patients screened had an overall MACE rate of 0.87%. We included 9084 (88.5%) patients who had normal initial single or serial hs-trop values in the analysis (Figure 1). This population had a mean age of 51.3 (± 14.8) years, 56.3% were female, and 58.8% White. AH-HEART score classified 52.2% patients as low risk, 39.4% as moderate risk, and 8.4% as high risk. Table 2 provides patient demographics, AH-HEART score distribution, and insurance status.

3.2 | MACE rate

Of the 90,842 patients who had single or serial normal troponins, 31 (0.34%; CI 0.23%—0.48%) experienced MACE. Of those with MACE, 58% were ≥ 65 years, 61% male, 29% were low-risk AH-HEART score, and 45% were discharged home (Table 3). Table 4 demonstrates the distributions of both index and second hs-trop values along with the incidence of MACE with 95% CI for each strata of hs-trop values. Over half the patients (68.3%) included had at least 2 troponins. The majority (67.6%) had a delta (change in troponin) <4 with 27 of those patients with normal delta values having a MACE rate of 0.44% (95% CI 0.29%–0.64%). A much smaller number of patients (69) were found to have 2 hs-trop values within normal limits for gender but with a delta (change in troponin) ≥ 4. Only 1 of these patients experienced a MACE producing a MACE incidence rate of 1.64% (95% CI 0.29%–8.72%).

A majority of the patients (82.5%) with normal index troponin values were found to have an index troponin below LOQ. Fourteen of these patients experienced 30-day MACE (0.19%; 95% CI 0.10%–0.31%). Appendix 1 offers detailed descriptions of each of the 14 patients who had an index troponin <LOQ and suffered MACE. The most common adverse event was PCI, which occurred in seven patients. Three of the six patients who underwent PCI continued to have hs-trop values <6 ng/L during either their initial or repeat admissions but were deemed high risk for coronary artery disease prompting further investigation. Four patients were scheduled for an outpatient left heart catheterization after an ED follow-up visit with their cardiologist. Two patients suffered an NSTEMI on repeat presentation, one of whom underwent PCI, the other received a CABG.

Regarding mortality of those patients with index troponin <LOQ, 6 patients died, only 1 of whom was categorized as high risk. Three of the patients who died were classified as low risk; however, during chart review, we discovered the AH-HEART score for patient 9 was miscalculated as one of the patient's risk factors was not included. This should have been classified the patient as moderate risk.

Four of the 6 patients who died were transitioned to hospice or comfort care in response to non-cardiac related comorbidities at the end of their hospital admission. No definitive cause of death was identified for these patients. Social Security records for the other 2 patient deaths indicated they expired within 30 days of their index visit (EMR review was unable to provide further information regarding their deaths). One

TABLE 1 Atrium-Health modified HEART score.

Atrium Health modified HEART score		
History: select all that apply	☐ With radiation to both arms (4 pts) ☐ Similar to prior ischemia (4 pts) ☐ Change in pattern over prior 24 h (4 pts) ☐ Worse with exertion (4 pts) ☐ With radiation to neck or jaw (2 pts) ☐ Recent episode of similar chest pain (2 pt) ☐ With radiation to left arm (2 pts) ☐ With radiation to right arm (2 pts) ☐ Pressure, squeezing, crushing, or tightness (2 pts) ☐ Associated with diaphoresis (1 pt) ☐ Associated with dyspnea (1 pt) ☐ Symptoms of moderate suspicion (1 pt) ☐ Burning chest pain (1 pt) ☐ Pleuritic chest pain (0 pts) ☐ Positional chest pain (0 pts) ☐ Reproduceable chest pain (0 pts) ☐ None of the above (0 pts)	Total patients: (Max 4 pts)
ECG	☐ Normal (0 pts) ☐ No ECG changes compared to previous (0 pts) ☐ Non-specific repolarization abnormality not known to be old (1 pt) ☐ ST segment changes with Digoxin use (1 pt) ☐ LVH or BBB (right or left) not known to be old (1 pt) ☐ T wave changes (inversion or biphasic) without ST depression or elevation in 2 contiguous leads (1 pt) ☐ Non-specific ST changes horizontal/downsloping, ST depression <0.5 mm (1 pt) ☐ Non-specific ST changes upsloping ST depression 1 mm or less (1 pt) ☐ ST changes horizontal or downsloping, ST depression 0.5 mm or greater at the J-point in 2 two or more contiguous leads without BBB, LVH, or use of digoxin (2 pt) ☐ ST depression or elevation 1 mm or greater without BBB, STEMI criteria, deWinter criteria, possible posterior STEMI, or aVR sign (2 pts)	Total patients: (Max 2 pts)
Age	☐ Less than 45 years (0 pt) ☐ 45–64 years (1 pt) ☐ 65 years or greater (2 pts)	Total patients: (Max 2 pts)
Risk factors: select all that apply	☐ No risk factors (0 pt) ☐ Diabetes (1 pt) ☐ Hypertension (1 pt) ☐ Hyperlipidemia (1 pt) ☐ Smoking—past or recent history (1 pt) ☐ Obesity, BMI > 30 (1 pt) ☐ Parent or sibling with CVD before 65 (1 pt) ☐ Prior MI or known CAD (2 pts) ☐ Prior PCI/CABG (2 pts) ☐ Prior CVA/TIA (2 pts) ☐ Known PAD (2 pts)	Total paitents: (Max 2 pts)
Troponin	☐ hs-trop < 20 ng/L (0 pts) ☐ hs-trop 20–60 ng/L (1 pt) ☐ hs-trop > 60 ng/L (2 pts) ☐ Delta 1 hr greater than or equal to 4 ng/L (4 pts)	Total patients:: (Max 4 pts)
Total score		

Abbreviations: aVR, ; BBB, bundle-branch block; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CT, ; CVA, cerebrovascular accident; CVD, cardiovascular disease; hs-trop, high-sensitivity troponin; LVH, left ventricular hypertrophy; MI, myocardial infarction; PAD, peripheral artery disease; STEMI, ST-segment myocardial infarction; TIA, transient ischemic attack.

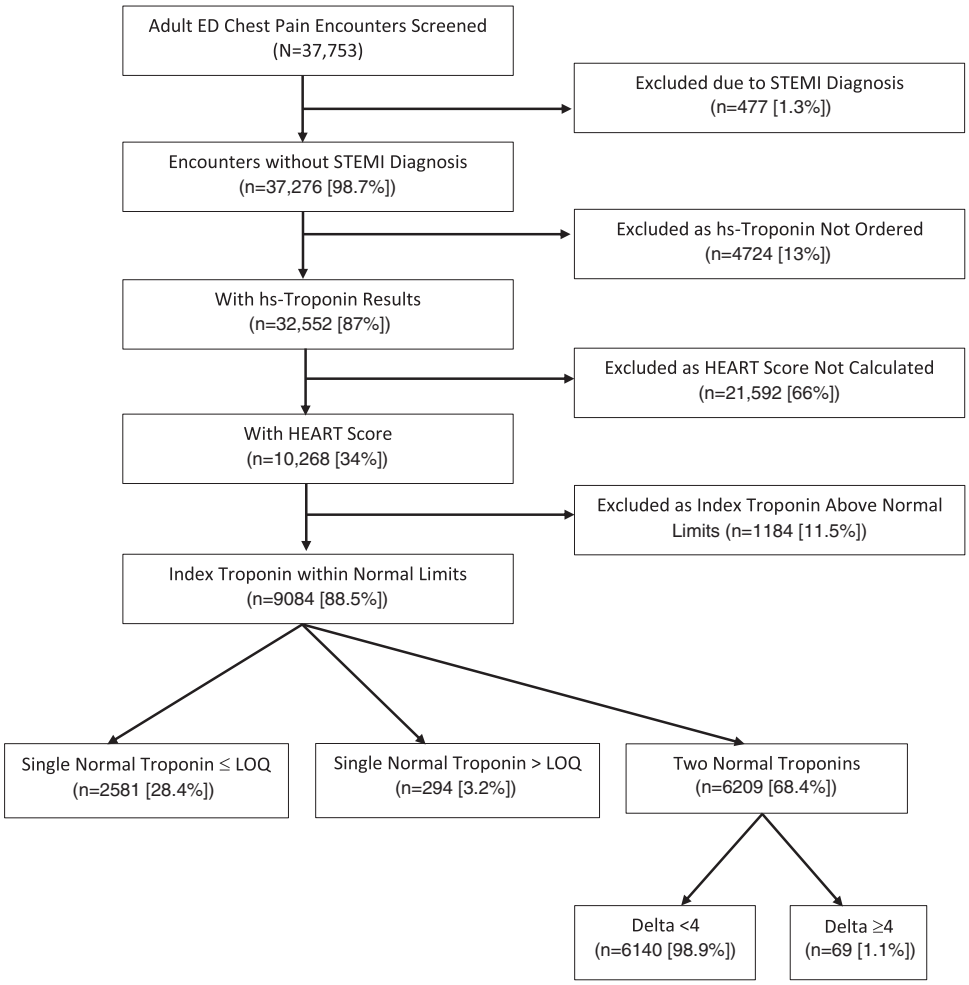

FIGURE 1 Flow diagram of patient inclusions and exclusions.
Abbreviations: ED, emergency department; LOQ, limit of quantitation; STEMI, ST-segment myocardial infarction.

of the 2 patients had a low-risk AH-HEART score and history of intravenous drug use. The other was diagnosed with pneumonia on index visit with an AH-HEART Score of 4 and was treated for urinary retention on his second visit with a computed tomography angiogram of the chest incidentally noting an aortic diverticulum. He was discharged home and did not follow up again within our hospital system before his death.

4 | LIMITATIONS

A major limitation of this study was that data entry into the EMR was dependent on the emergency medicine staff using the AH-HEART score at the time of the evaluation. There were instances during the data collection period when an hs-trop was obtained for the suspicion of ACS and an AH-HEART score was not completed, potentially resulting in a selection bias in our patient population. The monthly systemwide average usage rate since implementing the AH-HEART Pathway during the study period was 34%. This low incidence of use may have introduced spectrum bias into our study by selecting only patients who were deemed to be less sick by the treating team. It was possible physicians felt the need to fill out an AH-HEART score only when they were on the fence about admission whereas patients whose presentations were highly concerning for ACS were quickly admitted without entering the AH-HEART Pathway. This would have inadvertently selected for a healthier patient population. Launch of this new pathway preceding COVID pandemic in 2020 led to barriers in more rapid adoption of the AH-HEART Pathway, however, poststudy current adherence is 75%.

Another limitation was that MACE may have occurred in patients who followed up at a facility located outside the Atrium Health network. Atrium Health covers a geographic region that is primarily served by only 2 large health systems and thus, our evaluation of patient return to initial organization has historically been above 90%. An additional limitation was that this study was retrospective and performed within a single healthcare system within a single geographic region and thus, results may not be generalizable. There were no adjustments made for within-site correlations for each of the 18 EDs. Physicians and midlevels across the 18 EDs received that same education

TABLE 2 Study patients demographics and Atrium Health-HEART score distribution (*N* = 9084).

	N	%
AH-HEART sore		
Low risk (0–3)	4,740	52.2%
Moderate risk (4–6)	3,577	39.4%
High risk (≥7)	767	8.4%
Age, years, mean(± SD)	51.3(± 14.8)	
Sex		
Female	5113	56.3%
Male	3971	43.7%
Race		
White	5340	58.8%
Black	3197	35.2%
Asian	103	1.1%
Native American	71	0.8%
Others	373	4.1%
Ethnicity		
Hispanic	669	7.4%
Non-Hispanic	8293	91.3%
Not specified	122	1.3%
Risk factors		
Current smoking	1474	16.2%
Hypertension	3475	38.3%
Hyperlipidemia	1903	20.9%
Diabetes mellitus	1343	14.8%
BMI > 30 kg/m	4092	45.0%
Previous coronary disease	525	5.8%
Previous MI	160	1.8%
Previous cerebral vascular disease	114	1.3%
Peripheral arterial disease	101	1.1%
Insurance status		
Private	3897	42.9%
Medicare	1997	22.0%
Medicaid	1756	19.3%
Other	1434	15.8%

Abbreviations: AH, Atrium Health; BMI, body mass index; MI, myocardial infarction.

TABLE 3 Demographics, AH-HEART score, and disposition for patients who experienced major adverse cardiac events (*N* = 31).

	N	%
Age		
<65 years	13	41.9%
≥65 years	18	58.1%
Gender		
Male	19	61.3%
Female	12	38.7%
AH-HEART score		
Low risk (0–3)	9	29.0%
Moderate risk (4–6)	17	54.8%
High risk (>7)	5	16.1%
Disposition		
Discharged	14	45.2%
Observation	12	38.7%
Inpatient admission	5	16.1%

Abbreviation: AH, Atrium Health.

regarding hs-trop testing and the AH-HEART Pathway at deployment. MACE events across sites were reviewed to assess if any sites had higher event rate compared to another and we found no differences by sites.

Without a comparison group, it was also difficult to assess if there was an actual reduction in the number of MACE events occurring in a similar time period during use of first-generation troponins. It was possible that physicians faced with a new diagnostic test ordered a hs-trop on a patient whom they would not have with previous first-generation tests and hence artificially diluting our event rate. However, the additional requirement of AH-HEART score use does imply that the ordering team did have some suspicion of ACS before ordering a hs-trop.

Although reviewers were not involved in selecting patients who suffered MACE, they were not blind to hs-trop results while reviewing selected charts, which may have also introduced bias. Finally, the inter-rater reliability of the AH-HEART score is unknown and may lead to limitations in the reproducibility of risk stratification. The AH-HEART Score has not been validated externally and we have not published the internal validation study on the testing characteristics of the AH-HEART Score.

5 | DISCUSSION

This study demonstrated a <1% MACE rate in the 9084 ED patients who presented with suspicion for ACS and were entered into the AH-HEART Pathway with normal single or serial hs-trop values. Important subcategories of patients within this population included those with 2 normal hs-trop regardless of delta (change in troponin) and those with index hs-trop below the LOQ regardless of AH-HEART score. The MACE rates for these patients were 0.45% (95% CI: 0.30%–0.65%) and 0.19% (95% CI 0.10%–0.31%) respectively.

Prior studies have demonstrated testing and disposition strategies whereby patients with normal troponins were safely managed on an outpatient basis.[12,13,15,16] Our study further affirms the low incidence of MACE for patients with normal hs-trop and strengthens support for a discharge strategy when single or serial hs-trop are normal. Evidence is mounting that normal hs-trop values, even for patients who are moderate-risk by HEART score, result in a MACE <1%

TABLE 4 Major adverse cardiac events rates by AH-HEART score distribution and troponin values.

	Number of patients (%)	Number of MACE	Strata specific incidence of MACE (95% CI)
Patients included in the study	9,084	31	0.34% (CI 0.24%–0.48%)
Single normal troponin > LOQ	294 (3.2%)	1	0.34% (CI 0.01%–1.9%)
Low risk (0–3)	151	1	0.66 % (CI 0.02%–3.6%)
Moderate risk (4–6)	118	0	–
High risk (> = 7)	25	0	–
Single normal troponin < LOQ	2,581 (28.4%)	2	0.08% (CI 0.02%–0.28%)
Low risk (0–3)	2,162	1	0.05% (CI 0.01%–0.26%)
Moderate risk (4–6)	380	0	–
High Risk (> = 7)	39	1	2.56% (CI 0.45%–13.18%)
Two normal troponins	6,209 (68.3%)	28	0.45% (CI 0.30%–0.65%)
Low risk (0–3)	2,427	7	0.29% (CI 0.12%–0.59%)
Moderate risk (4–6)	3,079	17	0.55% (CI 0.32%–0.88%)
High risk (> 7)	703	4	0.57% (CI 0.16%–1.45%)
Index troponin < LOQ	7498 (82.5%)	14	0.19% (CI 0.10%–0.31%)
Low risk (0–3)	4,312	6	0.14% (CI 0.06%–0.30%)
Moderate risk (4–6)	2,745	7	0.26% (CI 0.12%–0.53%)
High risk (> 7)	441	1	0.23% (CI 0.04%–1.27%)
Delta value < 4	6140 (67.6%)	27	0.44% (CI 0.29%–0.64%)
Low risk (0–3)	2,427	7	0.29% (CI 0.14%–0.59%)
Moderate risk (4–6)	3,071	17	0.55% (CI 0.35%–0.88%)
High risk (>7)	642	3	0.47% (CI 0.16%–1.36%)
Delta value ≥4	69 (0.8%)	1	1.45% (CI 0.04%–7.81%)
Low risk (0–3)	0	0	–
Moderate risk (4–6)	8	0	–
High risk (> 7)	61	1	1.64% (CI 0.29%–8.72%)

Abbreviations: AH, Atrium Health; CI, confidence interval; LOQ, limit of quantitation; MACE, major adverse cardiac events.

and are amendable to outpatient pathways as opposed to hospital admissions.[1,17,18] Our results further strengthen support that when hs-trop is normal, the 30-day MACE rate is <1% and thus these patients may warrant consideration of outpatient management. However, consideration of the clinical context, including historical features such as known coronary artery disease or abnormal ECG findings, remains imperative and a normal hs-trop should not drive management in isolation.

In reference to the delta troponin, the change in hs-trop may represent an AMI, noting that thresholds differ based on assay used.[19] This has led to the question of what to do with patients who have 2 normal troponins but a delta (change in troponin) ≥4. To our knowledge, this was the first study to assess this ED population; however, we encourage caution and individualized consideration given the low number of patients fitting this clinical situation.

Prior studies have also demonstrated that patients with index hs-trop <LOQ had low incidence of MACE.[12,14,15,20,21] Our study demonstrated low MACE incidence of 0.19% for patients with index hs-trop <LOQ despite only 42% ($N = 6$) of these patients being deemed low risk by the AH-HEART Score. Despite the risk that reproducibility of the AH-HEART score and correct use may be challenging, as has been observed in other studies, given the low MACE incidence in the population with initial hs-trop <LOQ, there is the potential for safe outpatient management.[22] However, these findings do not negate the importance of the clinical context inclusive of history, comorbidities, and ECG findings. Although the clinical aspects of care are imbedded in the HEART to include historical and ECG features, integration into HEART score is an important strategy. As hospital and ED capacity become further constrained, development of novel and safe outpatient management strategies for patients beyond the low-risk categories is imperative.

In conclusion, our study suggests patients presenting with 2 normal troponins with a delta (change in troponin) <4 or an index hs-trop <LOQ have a low incidence of 30-day MACE within our hospital system regardless of their AH-HEART score. Future studies should further explore the delineation of high-risk clinical features in patients with normal hs-trop that may allow for safe outpatient evaluation.

AUTHOR CONTRIBUTIONS

Victoria Serven , Gabriel Rivera-Camacho, Tyler Siekmann, and David Pearson conceived the study and designed the trial. David Pearson obtained research funding. Victoria Serven, David Pearson, Kamala Swayampakala, Gabriel Rivera-Camacho, and Tyler Siekmann supervised the conduct of the trial and data collection. David Pearson and Santosh Rao undertook recruitment of participating centers. Kamala Swayampakala and Christy Lesassier managed the data including quality control. Kamala Swayampakala and Matthew Sullivan provided statistical advice on study design and analyzed the data. David Pearson chaired oversight. Victoria Serven drafted the manuscript. All authors contributed substantially to its revision. Victoria Serven takes responsibility for the paper as a whole.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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