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Derivation and validation of a high sensitivity troponin-T HEART pathway

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Background The HEART Pathway is widely used for chest pain risk stratification but has yet to be optimized for high sensitivity troponin T (hs-cTnT) assays.

Methods We conducted a secondary analysis of STOP-CP, a prospective cohort study enrolling adult ED patients with symptoms suggestive of acute coronary syndrome at 8 sites in the United States (US). Patients had a 0- and 1-hour hs-cTnT measured and a HEAR score completed. A derivation set consisting of 729 randomly selected participants was used to derive a hs-cTnT HEART Pathway with rule-out, observation, and rule-in groups for 30-day cardiac death or myocardial infarction (MI). Optimal baseline and 1-hour troponin cutoffs were selected using generalized cross validation to achieve a negative predictive value (NPV) >99% for rule out and positive predictive value (PPV) >60% or maximum Youden index for rule-in. Optimal 0-1-hour delta values were derived using generalized cross validation to maximize the NPV for the rule-out group and PPV for the rule-in group. The hs-cTnT HEART Pathway performance was validated in the remaining cohort (n = 723).

Results Among the 1452 patients, 30-day cardiac death or MI occurred in 12.7% (184/1452). Within the derivation cohort the optimal hs-cTnT HEART Pathway classified 36.5% (266/729) into the rule-out group, yielding a NPV of 99.2% (95% CI: 98.2-100) for 30-day cardiac death or MI. The rule-in group included 15.4% (112/729) with a PPV of 55.4% (95% CI: 46.2-64.6). In the validation cohort, the hs-cTnT HEART Pathway ruled-out 37.6% (272/723), of which 2 had 30-day cardiac death or MI, yielding a NPV of 99.3% (95% CI: 98.3-100). The rule-in group included 14.5% (105/723), yielding a PPV of 57.1% (95% CI: 47.7-66.6).

Conclusions A novel hs-cTnT HEART Pathway with serial 0- and 1-hour hs-cTnT measures has high NPV and moderate PPV for 30-day cardiac death or MI. (Am Heart J 2023;256:148–157.)

Each year, approximately 8 million patients with acute chest pain present to United States (US) emergency departments (EDs).[1] For the initial risk stratification of these patients, guidelines recommend use of structured risk assessments, such as the History, Electrocardiogram (ECG), Age, Risk factors, and Troponin Pathway (HEART Pathway).[2] The HEART Pathway is a well-validated clinical decision pathway that combines a modified HEART score with serial troponin measures.[3] Patients identified as low-risk by the HEART Pathway have a composite rate of death or myocardial infarction (MI) at 30 days of 0.4%, and its implementation has been associated with reduced hospitalizations, non-invasive and invasive cardiac testing, and hospital length of stay compared to usual care.[3]

High sensitivity cardiac troponin T and I measurements (hs-cTnT and hs-cTnI) can be successfully integrated into the HEART Pathway in place of contemporary troponin assays.[4] However, unlike pathways designed for use with hs-cTn assays, such as the 0/1-hour algorithm,[5] the HEART Pathway has yet to be optimized for use with hs-cTnT assays. Pathways designed for use with hs-cTnT typically utilize very low initial measures and a combination of initial cut points and delta values to exclude MI.[6]

Existing hs-cTnT clinical decision pathways, such as the hs-cTnT 0/1-hour algorithm, have limited data

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supporting their use in US ED populations. Recently, within a multisite US cohort, the hs-cTnT 0/1-hour algorithm was unable to achieve a sufficient negative predictive value (NPV) to exclude 30-day death or MI.[7] Thus, there is clinical need for a pathway optimized for use with hs-cTnT in the US ED population. The objective of this study was to derive and validate a modified HEART Pathway, which utilizes 0- and 1-hour serial hs-cTnT measures, incorporates delta values, and achieves high NPV for 30-day cardiac death or MI.

Methods

Study design

This is a pre-planned secondary analysis of the High-Sensitivity Cardiac Troponin T to Optimize Chest Pain Risk Stratification (STOP-CP) cohort. Prior to the study start, ethics approval was obtained from all relevant institutional review boards, and the study was registered at clinicaltrials.gov (NCT02984436).[7] The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization guidelines for Good Clinical Practice, and the Code of Federal Regulations 21, Part 50. Methods of the STOP-CP trial, a prospective observational cohort study of ED patients with suspected acute coronary syndrome (ACS) enrolled at 8 US EDs from 1/25/2017 to 09/06/2018, have been previously published.[7]

Study setting and population

Patients aged 21 years and older presenting to the ED with chest discomfort or other symptoms suggestive of ACS were prospectively enrolled. Exclusion criteria included ST-segment elevation MI at ED presentation, systolic blood pressure less than 90, a life expectancy less than 90 days, a non-cardiac illness requiring admission, lack of capacity to provide consent, inability to be contacted for follow-up, non-English speaking, pregnancy, and prior enrollment in the current study. See Figure 1 for flow diagram of study participants.

Data collection

Blood samples for hs-cTnT measurement were collected at baseline and 1 hour (plus or minus 30 minutes) in lithium heparin and ethylenediaminetetraacetic acid (EDTA) tubes. Following collection, samples were centrifuged for 10-15 minutes and maintained in storage at −70°C. Roche Diagnostics (Basel, Switzerland) hs-cTnT (generation 5 troponin T) concentrations were measured by a central laboratory (Clinical Core Research Laboratory, University of Maryland School of Medicine, Baltimore, MD) using the COBAS e 601 analyzer by personnel blinded to all other patient information. This assay has a measuring range of 3 ng/L to 10000 ng/L and a limit of quantification (LoQ) of 6 ng/L. Although the limit of blank has been reported to be 3 ng/L, results less than the LoQ are not reported in the US, per Food and Drug Administration specification. The assay has an overall 99th percentile upper reference limit (URL) of 19 ng/L in the US with a coefficient of variation of $<10\%$.[8]

Each patient had an ECG performed as part of routine clinical care, which was interpreted prospectively by the treating ED provider and recorded on the STOP-CP treating provider case report form. ECGs were defined as ischemic if they had new T-wave inversions or ST segment depressions greater than 1mm in at least 2 contiguous leads. Patients were considered to have known coronary artery disease (CAD) if they had history of prior MI, percutaneous coronary intervention, coronary artery bypass graft surgery, or a cardiac catheterization demonstrating coronary stenosis $\geq 70\%$. In addition, a modified History, ECG, Age, and Risk factor score (HEAR score), based on the HEART Pathway Implementation Study clinical decision support algorithm (Impathiq Inc., Raleigh, NC),[3] was collected prospectively from the treating ED provider.

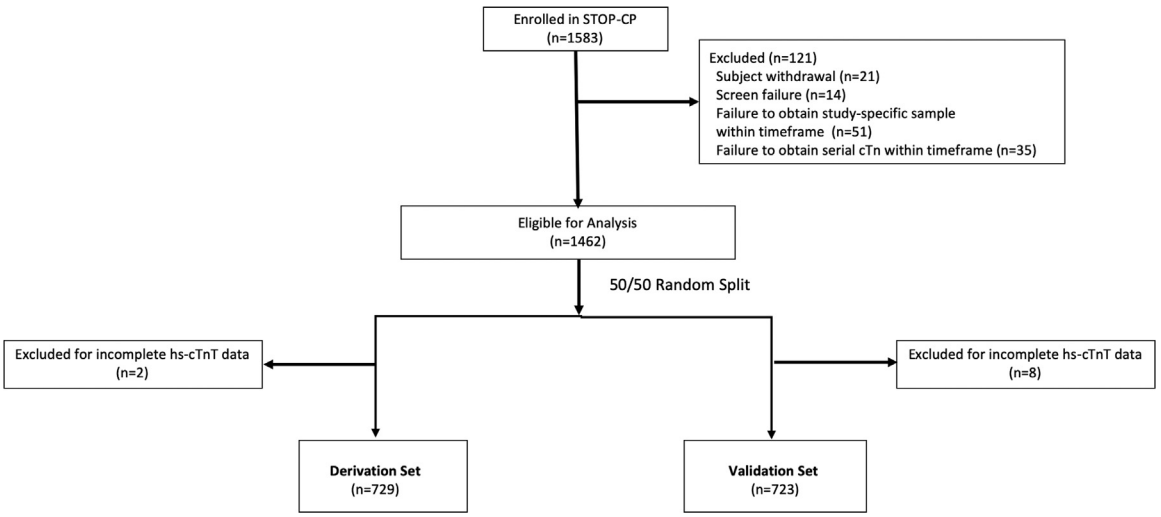
Outcomes

The primary outcome for this analysis was the composite of cardiac death or MI at 30-days, inclusive of index-visit events. Secondary outcomes included 30-day major adverse cardiac events (MACE: the composite of cardiac death, MI, or coronary revascularization) and index-visit MI. Thirty-day phone follow-up calls and medical record reviews were completed on all participants to identify outcomes. Patients with a clinical diagnosis of MI, an elevated local contemporary cTn, or death during the follow-up period were adjudicated by expert reviewers (MHV, MRM, JPS, JKM). Adjudicators classified deaths as cardiac or non-cardiac. Cardiac death was defined based on the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[9] Death from stroke was not considered a cardiac death. In cases where the cause of death could not be determined, the death was considered cardiovascular. To determine MI and MI type, adjudicators used the fourth Universal Definition of MI.[3] Adjudicators had access to all clinical data including the local clinical contemporary troponin assay results but were blinded to hs-cTnT results. All patients included in the analysis had serial contemporary troponin results available for adjudication. Any discrepancies between adjudicators were resolved through review by a third adjudicator. In the primary analysis the index-visit MI and composite 30-day cardiac death and MI outcomes included both type 1 and type 2 MI events. A sensitivity analysis was conducted, including only type 1 MI events for these outcomes.

Statistical analysis

The 1462 patients in the STOP-CP cohort were randomly divided in half, resulting in final derivation ($n = 729$) and validation ($n = 723$) datasets after exclusions for incomplete hs-cTnT data (Figure 1). Patient

Figure 1



Study Flow Diagram.

demographics and 30-day death or MI rates were described overall and separately within the derivation and validation sets. The derivation set was used to develop a hs-cTnT HEART Pathway with rule-out, observation, and rule-in groups based on the primary outcome of 30-day cardiac death or MI. The modified hs-cTnT HEART Pathway was derived by determining optimal statistical cut-points within the general HEART Pathway framework. ECG (ischemic vs non-ischemic), known CAD (yes vs no), HEAR score, 0- and 1-hour serial hs-cTnT measures, and delta hs-cTnT values were included in the modified hs-cTnT HEART Pathway. A HEAR score cut-off of 5 was selected to optimize the rule-out proportion, while maintaining a negative predictive value (NPV) >99%. All of the hs-cTnT cutoffs that apply to both the 0- and 1-hour time points (0/1) were determined using the maximum of the 2 hs-cTnT values for each patient. Sex-specific hs-cTnT cut-points were not considered in this analysis due to sample size constraints when considering male and female patients separately.

The optimal 0-hour hs-cTnT cutoff for the rule-out group was selected using generalized cross validation (GCV) to maximize the specificity while keeping the NPV >99%. Patients with a non-ischemic ECG, no prior CAD, HEAR < 5 and 0-hour hs-cTnT ≥ 6 ng/L were then used to select an optimal 0/1-hour cutoff. The 0/1-hour cutoff was selected using GCV to maximize the specificity while keeping the NPV > 99%. The optimal 0-1-hour delta value for rule-out was selected using GCV to maximize the NPV.

For rule-in, patients who had a non-ischemic ECG, with no prior CAD, HEAR < 5, and whose 0- and 1-hour hs-cTnT did not meet rule-out criteria were used to find an optimal 0/1-hour cutoff and 0-1-hour delta cutoff. The 0/1-hour cutoff was selected using GCV to maximize the Youden index to optimize allocation to the observation vs rule-in groups and the 0-1-hour delta cutoff was selected using GCV to maximize the PPV. The 0-hour hs-cTnT cutoff used for rule-in was selected within the population that had an ischemic ECG, known CAD, or HEAR ≥ 5, where we used GCV to maximize the sensitivity while keeping the PPV > 60%.

The performance of the hs-cTnT HEART Pathway was then validated in the remaining patients (validation set). The efficacy (proportion ruled-out), sensitivity, specificity, NPV, PPV, and positive and negative likelihood ratios and corresponding 95% confidence intervals were calculated for the hs-cTnT HEART Pathway within the derivation and validation sets separately. Within the validation set, test characteristics were also calculated separately for patients with early (≤ 3 hours from arrival) vs late chest pain onset. Outcomes included 30-day cardiac death or MI (primary), 30-day MACE, and index-visit MI. As a sensitivity analysis, test characteristics were also calculated for 30-day cardiac death or type 1 MI and index-visit type 1 MI. Since the hs-cTnT HEART Pathway has 3 risk categories, specificity, PPV, and positive likelihood ratio (+LR) were calculated for rule-in (i.e., rule-in vs observation or rule-out) and sensitivity, NPV, and negative likelihood ratio (-LR) were calculated for rule-out (i.e., rule-in or observation vs rule-out).

Results

Among the 1452 patients included in the final derivation and validation sets, 46.3% (672/1452) were female and 37.0% (537/1452) were Black or African American

Table 1. Patient characteristics

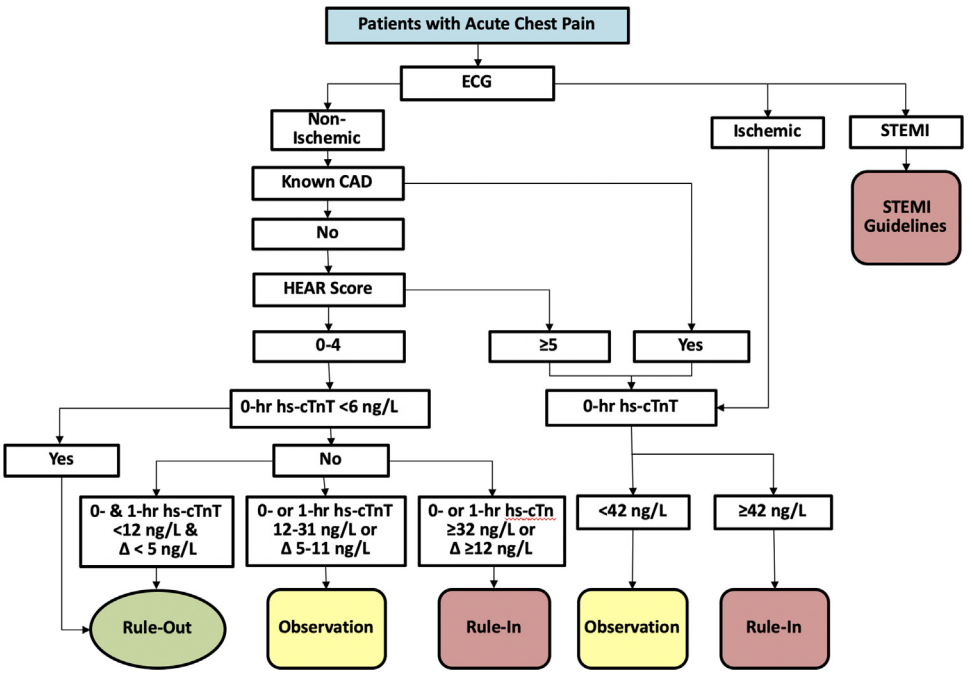
Patient characteristics	Derivation (n = 729)	Validation (n = 723)	Total (n = 1452)
Age (years), median (IQR)	58 (49-66)	58 (49-66)	58 (49-66)
Gender, n (%)			
Female	339 (46.5)	333 (46.1)	672 (46.3)
Race, n (%)			
American Indian/Alaska Native	9 (1.2)	14 (1.9)	23 (1.6)
Asian	6 (0.8)	6 (0.8)	12 (0.8)
Native Hawaiian	1 (0.1)	1 (0.1)	2 (0.1)
Black or African American	253 (34.7)	284 (39.3)	537 (37.0)
White	434 (59.5)	401 (55.5)	835 (57.5)
Other	19 (2.6)	16 (2.2)	35 (2.4)
Ethnicity, n (%)			
Hispanic or Latino	35 (4.8)	23 (3.2)	58 (4.0)
Not Hispanic or Latino	687 (94.2)	693 (95.8)	1,380 (95.0)
Unknown	7 (1.0)	7 (1.0)	14 (1.0)
Risk factors, n (%)			
Current or prior smoking	416 (57.1)	387 (53.6)	803 (55.3)
Current or prior cocaine use	87 (11.9)	80 (11.1)	167 (11.5)
Hypertension	464 (63.6)	485 (67.1)	949 (65.4)
Hyperlipidemia	354 (48.6)	357 (49.4)	711 (49.0)
Diabetes	215 (29.5)	196 (27.1)	411 (28.3)
Family history of coronary disease	329 (45.1)	338 (46.7)	667 (45.9)
BMI >30 (kg/m^2)	363 (49.8)	385 (53.3)	748 (51.5)
Prior coronary disease	187 (25.7)	170 (23.5)	357 (24.6)
Prior MI	182 (25.0)	172 (23.8)	354 (24.4)
Prior PCI	127 (17.4)	132 (18.3)	259 (17.8)
Prior CABG*	61 (8.4)	47 (6.5)	108 (7.4)
Prior cerebral vascular accident	97 (13.3)	88 (12.2)	185 (12.7)
Prior peripheral vascular disease	47 (6.4)	46 (6.4)	93 (6.4)
Prior end stage renal disease	46 (6.3)	32 (4.4)	78 (5.4)
Prior congestive heart failure	139 (19.1)	138 (19.1)	277 (19.1)
Chest pain at ED arrival, n (%)*	520 (71.4)	485 (67.5)	1,005 (69.5)
Chest pain onset, n (%)*			
≤ 3 Hours from arrival (early)	259 (35.5)	253 (35.0)	512 (35.3)
> 3 Hours from arrival (late)	467 (64.1)	465 (64.3)	932 (64.2)
Electrocardiogram at arrival, n (%)			
Ischemic	42 (5.8)	49 (6.8)	91 (6.3)
Non-ischemic	687 (94.2)	674 (93.2)	1361 (93.7)
HEAR score, median (IQR)	4 (3-5)	4 (3-5)	4 (3-5)
Initial study hs-cTnT sample (ng/L), median (IQR)	9 (5-20)	9 (5-22)	9 (5-21)
Creatinine at index visit (mg/dL), median (IQR)	0.81 (0.73-1.19)	0.82 (0.73-1.10)	0.82 (0.73-1.10)
30-day cardiac death or MI, n (%)	92 (12.6)	92 (12.7)	184 (12.7)
Cardiac death	4 (0.5)	0 (0)	4 (0.3)
MI	91 (12.5)	92 (12.7)	183 (12.6)
Type 1	40 (5.5)	32 (4.4)	72 (5.0)
Type 2	50 (6.9)	55 (7.6)	105 (7.2)
Missing	1 (0.1)	5 (0.7)	6 (0.4)
Index-visit MI, n (%)	86 (11.8)	82 (11.3)	168 (11.6)
Type 1	39 (5.3)	31 (4.3)	70 (4.8)
Type 2	46 (6.3)	46 (6.4)	92 (6.3)
Missing	1 (0.1)	5 (0.7)	6 (0.4)

*Missing responses for Prior CABG (n = 1), Chest Pain at ED Arrival (n=6), and Chest Pain Onset (n = 8).SD, standard deviation; BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; ED, emergency department; IQR, interquartile range.

with a median age of 58 (IQR: 49-66) years. In this cohort, 30-day cardiac death or MI occurred in 12.7% (184/1452). Demographics and rates of 30-day cardiac death or MI were similar in the derivation and validation sets (Table 1).

Optimal hs-cTnT cut points for the HEART Pathway are summarized in Figure 2. For patients with a non-ischemic ECG, no prior CAD, and a HEAR score <5, the optimal 0-hour hs-cTnT cut point to rule-out 30-day cardiac death or MI was 6 ng/L (the LoQ). For patients with a 0-hour hs-cTnT ≥ 6 ng/L, the optimal hs-cTnT measures at 0- and 1-hour and delta value to exclude cardiac death or MI at 30-days were <12 ng/L and <5 ng/L, respectively. Among patients with an ischemic ECG, known CAD, or a HEAR score ≥ 5, the optimal 0-hour hs-cTnT cut point to rule-in 30-day cardiac death or MI was ≥ 42 ng/L. Among

Figure 2



The Modified hs-cTnT HEART Pathway.

patients with a non-ischemic ECG, no known CAD, and HEAR score <5, the optimal hs-cTnT measures at 0- or 1-hour and delta value to rule-in cardiac death or MI at 30-days were ≥ 32 ng/L and ≥ 12 ng/L respectively.

Within the derivation cohort, the optimal hs-cTnT HEART Pathway classified 36.5% (266/729) into the rule-out group. Among these patients, 30-day cardiac death or MI occurred in 0.8% (2/266) yielding a NPV of 99.2% (95% CI: 98.2-100) and –LR of 0.05 (95% CI: 0.01-0.21). The observation group included 48.2% (351/729), of which 8.0% (28/351) had 30-day cardiac death or MI. The optimal hs-cTnT HEART Pathway classified 15.4% (112/729) into the rule-in group. Among these patients, 55.4% (62/112) had 30-day cardiac death or MI, resulting in a PPV of 55.4% (95% CI: 46.2-64.6) and a + LR of 8.59 (95% CI: 6.35-11.61). Results from the derivation cohort are summarized in Figure 3.

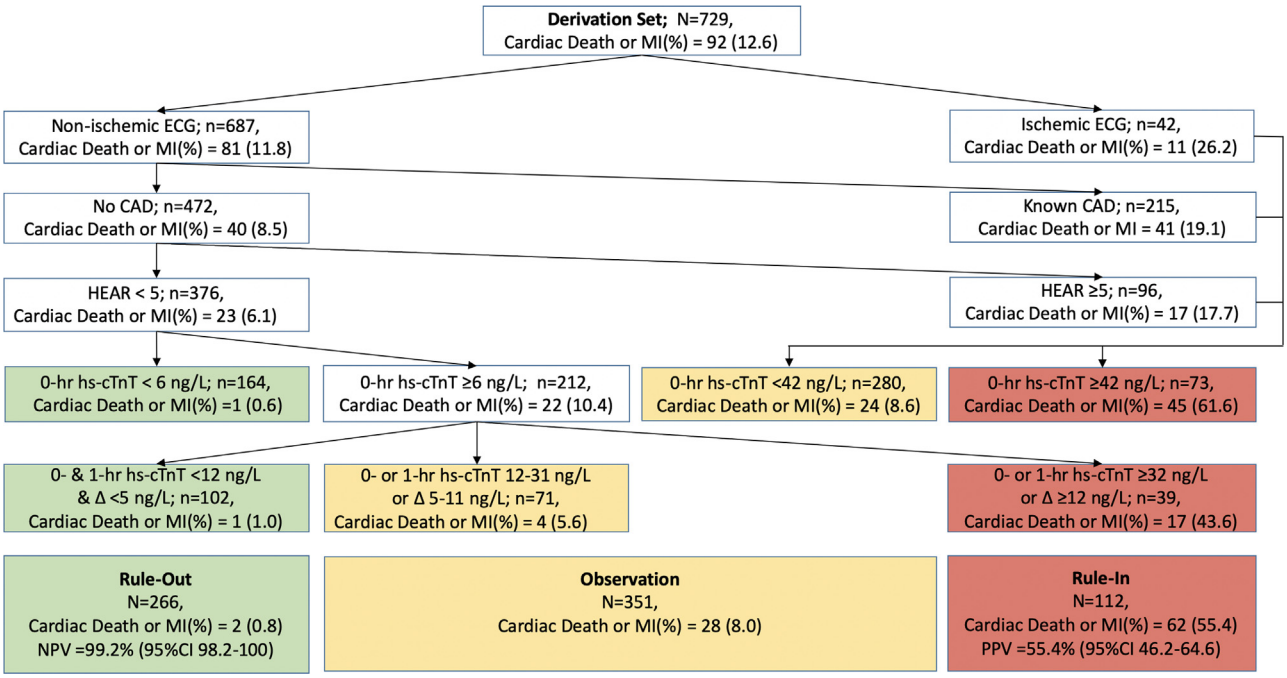
In the validation cohort, the hs-cTnT HEART Pathway ruled-out 37.6% (272/723). Among these patients, 0.7% (2/272) had 30-day death or MI, yielding a NPV of 99.3% (95% CI: 98.3-100) and –LR of 0.05 (95% CI: 0.01-0.20). The observation group had 47.9% (346/723), among which 30-day death or MI occurred in 8.7% (95%CI 5.9-12.1). The hs-cTnT HEART Pathway classified 14.5% (105/723) of patients into the rule-in group, with a PPV of 57.1% (95% CI: 47.7-66.6) and + LR of 9.14 (95% CI: 6.65-12.58). Results from the validation cohort are summarized in Figure 4.

When considering only index-visit MIs as the outcome to evaluate diagnostic performance, results were similar to those described for 30-day cardiac death or MI. Performance characteristics of the hs-cTnT HEART Pathway for the derivation and validation cohorts for the outcomes of 30-day cardiac death or MI, 30-day MACE and index-visit MI are reported in Table 2. Sensitivity analyses of performance characteristics considering only type 1 MIs in the outcomes (i.e., 30-day cardiac death or type 1 MI and index-visit type 1 MI) are presented in Supplemental Table 1 and performance characteristics for early vs late onset of chest pain in the validation cohort are presented in Supplemental Table 2.

Discussion

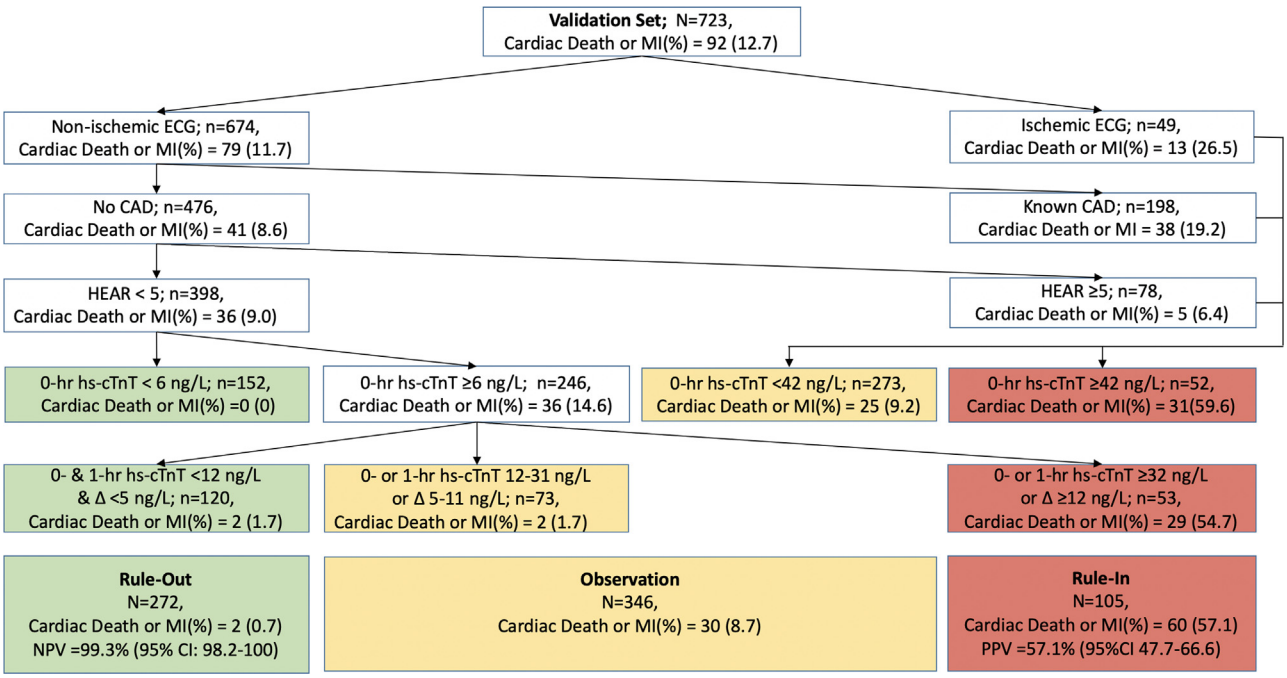
In this pre-planned secondary analysis of the STOP-CP cohort, we derived and validated a modified hs-cTnT HEART Pathway within a multisite US ED population of patients with possible ACS. The hs-cTnT HEART Pathway combines a non-ischemic ECG, no prior CAD, a modified HEAR score <5, and a single measure <LoQ or serial 0- and 1-hour measures <12 ng/L with an absolute delta <5 ng/L to achieve high NPV for 30-day cardiac death or MI while ruling-out a significant proportion of patients. In addition, to enhance PPV for 30-day cardiac death or MI, our novel pathway utilizes a rule-in strategy that includes cut points above the 99th percentile URL.

Figure 3



Flow Diagram for Derivation Set.

Figure 4



Flow Diagram for Validation Set.

Table 2. Test characteristics for 30-day cardiac death or MI, 30-day MACE, and index-visit MI for risk stratification strategies using the hs-cTnT heart pathway in the derivation and validation sets

Outcome	Efficacy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	+LR (95% CI)	-LR (95% CI)
30-Day cardiac death or MI							
Derivation	36.5 (33.0-40.1)	97.8 (94.8-100)	92.1 (90.1-94.2)	55.4 (46.2-64.6)	99.2 (98.2-100)	8.59 (6.35-11.61)	0.05 (0.01-0.21)
Validation	37.6 (34.1-41.3)	97.8 (94.9-100)	92.9 (90.9-94.9)	57.1 (47.7-66.6)	99.3 (98.3-100)	9.14 (6.65-12.58)	0.05 (0.01-0.20)
30-Day MACE							
Derivation	36.5 (33.0-40.1)	96.1 (92.4-99.9)	92.3 (90.2-94.4)	57.1 (48.0-66.3)	98.5 (97.0-100)	8.10 (5.94-11.06)	0.09 (0.04-0.24)
Validation	37.6 (34.1-41.3)	98.1 (95.5-100)	92.9 (90.8-94.9)	58.1 (48.7-67.5)	99.3 (98.3-100)	8.16 (5.88-11.33)	0.04 (0.01-0.17)
Index-visit MI							
Derivation	36.5 (33.0-40.1)	97.7 (94.4-100)	92.1 (90.0-94.2)	54.5 (45.2-63.7)	99.3 (98.2-100)	8.94 (6.65-12.02)	0.06 (0.01-0.22)
Validation	37.6 (34.1-41.3)	98.8 (96.4-100)	92.4 (90.3-94.4)	53.3 (43.8-62.9)	99.6 (98.9-100)	8.94 (6.57-12.14)	0.03 (0.004-0.20)

We previously demonstrated that hs-cTnT and hs-cTnI could be successfully integrated into the HEART Pathway in place of contemporary troponin assays.[4] However, in this prior analysis hs-cTn assays were incorporated using sex-specific URLs, and we did not evaluate the performance of single low cut-points or absolute deltas. Multiple studies have demonstrated that cut-points below the 99th percentile URL and the use of absolute deltas improve rule-out performance compared to the URL.[10-12] Furthermore, the improved performance of hs-cTn assays relative to contemporary assays allows for more rapid serial sampling than the 0- and 3-hour measures used in the original HEART Pathway.[6] Thus, our newly derived and validated modified hs-cTnT HEART Pathway has been updated to include hs-cTn best practices. These features are similar to those included in other hs-cTn algorithms, such as the 0/1-hour algorithm.[5] However, unlike the 0/1-hour algorithm, the hs-cTnT HEART Pathway includes a validated risk score to incorporate key clinical variables, such as the patient's history, age, cardiovascular risk factors, and ECG findings.

There is considerable debate regarding whether risk scores and other clinical variables, such as ECG interpretation, are additive to the risk prediction of hs-cTn pathways. The 0/1-hour algorithm, which does not include any clinical variables beyond hs-cTn, is well validated for ruling-out MI, particularly in Europe, and is recommended by European Society of Cardiology.[5,13] A prior study, by the team that derived the 0/1-hour algorithm, demonstrated that the addition of a HEART score to the 0/1-hour algorithm decreased efficacy (the proportion ruled-out) without a meaningful improvement in safety.[14] Similarly, a study by the High-STEACS investigators showed that risk scores decreased the efficacy of the High-STEACS hs-cTnI pathway without improving NPV for cardiac death or MI. However, in this same analysis the HEART score significantly improved the NPV of the 0/1-hour algorithm for cardiac death or MI from 97.9% to 99.7%.[15] Furthermore, other studies have demonstrated improvement in the detection of MACE events with the addition of a risk score or other clinical history and non-ischemic ECG to the 0/1-hour algorithm.[16,17]

These results are consistent with our primary analysis of the STOP-CP cohort, in which the 0/1-hour algorithm was unable to achieve a NPV >99% for 30-day cardiac death or MI or 30-day MACE unless it was combined with a HEART score.[7] Based on these findings, we suggested that in a US population of patients with symptoms concerning for ACS, hs-cTnT strategies should be used in combination with a HEART score. However, the HEART score was designed for use with contemporary troponin assays and has several limitations compared to the HEART Pathway. First, the HEART score incorporates a single troponin measure. Although rare, patients with an elevated troponin level can have a low-risk score. Second, the HEART score can be low-risk in patients with acute ischemic changes on ECG or known CAD. The HEART Pathway uses serial troponin measurements and prioritizes troponin elevation, ischemic ECG changes, and prior CAD; patients with any of these are considered non-low-risk regardless of score. Finally, the HEART score has subjective criteria and is manually calculated, which decrease its reproducibility and reliability.[18,19] The HEART Pathway decision support algorithm (Impathiq Inc., Raleigh, NC) replaces subjective components of the HEART score with objective binary questions and uses an algorithm to determine each HEAR score component. Given these advantages relative to the HEART score, a modified version of the HEART Pathway optimized for use with hs-cTnT is needed.

A key difference between our novel hs-cTnT HEART Pathway and the original HEART Pathway is the use of a HEAR score cut-off of <5 scores for low-risk rather than <4 traditionally used to designate low-risk. The improved analytical sensitivity of the hs-cTnT assay allows using a higher HEAR score cut point to improve efficacy (rule-out proportion), while maintaining a NPV >99% for 30-day cardiac death or MI. Thus, in the validation cohort, the hs-cTnT HEART Pathway ruled-out 37.6% of patients. For context, in our primary STOP-CP analysis we reported an efficacy of 30.8% for the combination of the HEART score with the 0/1-hour algorithm,[7] and the original HEART Pathway reported efficacy of 30.7%[3].

Our study has limitations. Although our study was conducted across 8 US EDs, our sites were urban academic medical centers. Thus, our results may not be generalizable to all US ED settings. In addition, use of the HEART Pathway decision support algorithm (Impathiq Inc., Raleigh, NC) in this study may limit generalizability as many sites use the traditional HEART score calculation instead of the Impathiq tool. Furthermore, our cohort had a higher cardiac event rate than has been reported in many prior US studies.[20,21] While our lost to follow-up rate was small (<4%), we were unable to contact all patients in the cohort, which may have caused misclassification and underestimation of MACE. However, a sensitivity analysis imputing events based on patient variables did not change results.[7] In addition, while point estimates for NPV reached the goal of >99% in the derivation and validation cohorts, the lower bound of the 95% CIs did not exceed the benchmark of 99%. Furthermore, in the early presenter subgroup, the point estimate for NPV for 30-day cardiac death and MI was 98.9%. This study utilized only the Roche hs-cTnT assay, and results cannot be extrapolated to other hs-cTn assays. Optimal sex-specific hs-cTnT cut points were not evaluated in this analysis due to sample size constraints, which could limit the use of this pathway. However, our use of the LoQ and absolute delta values likely mitigates risk of sex disparities in hs-cTnT HEART Pathway diagnostic performance. Finally, the hs-cTnT HEART Pathway was derived and validated within equal splits of the STOP-CP cohort. External validation in a separate prospective multisite cohort is needed.

Conclusions

A modified hs-cTnT HEART Pathway was derived and validated within a multisite US ED cohort of patients with possible ACS. This novel clinical decision pathway leverages the enhanced analytical sensitivity of the Roche hs-cTnT assay to achieve high NPV for 30-day cardiac death or MI, while simultaneously ruling-out a significant proportion of patients. It does so by combining a non-ischemic ECG, no prior CAD, and a modified HEAR score <5 with a single measure <LoQ or serial 0- and 1-hour measures <12 ng/L with an absolute delta <5 ng/L. In addition, it achieves moderate PPV for 30-day cardiac death or MI, by using a hs-cTnT cut point above the URL. Given that many US EDs currently use hs-cTnT based on the 0/1-hour algorithm, the original HEART Pathway, or HEART score, the development of an optimized hs-cTnT HEART Pathway has the potential to improve care of ED patients with possible ACS. External validation and comparison of the hs-cTnT HEART Pathway to other hs-cTnT clinical decision pathways are needed.

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Disclosures

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Supplementary materials

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