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ORIGINAL RESEARCH

Suspected myocardial infarction in the emergency department: An evaluation of clinical thresholds for the Beckman Coulter Access hsTnI high-sensitivity cardiac troponin I assay

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Abstract

Objective: The primary objective was to determine rapid rule-out (RRO) criteria for the outcome of myocardial infarction (MI) using the Beckman Coulter Access high-sensitivity cardiac troponin I (hs-cTnI) assay. Secondary objectives were to explore cut-points for rapid rule-in (RRI) and amount of change at 3-h (3-h delta) indicative of MI.

Methods: A retrospective study included ED patients with suspected MI between June and September 2019. hs-cTnI levels were performed at baseline and after 3 h. The performance benchmark for RRO criteria was a negative predictive value (NPV) for MI with a lower 95% confidence limit >99%, and for RRI and 3-h delta cut-points was a positive predictive value (PPV) for MI >70%. Delta calculation required rising hs-cTnI levels, with at least one above the 99th percentile of the upper reference limit. Analyses utilised receiver operating characteristic (ROC) curves and contingency tables.

Results: Baseline hs-cTnI levels from 935 patients were available for RRO analyses. Of tested criteria, baseline hs-cTnI <6 ng/L (females) or <11 ng/L (males) plus symptom onset >2 h met the performance benchmark (NPV: 100% [95% confidence interval 99–100]). hs-cTnI levels were available for RRI and 3-h delta analyses from 935 and 52 patients, respectively. A 3-h delta cut-point >35 ng/L met the performance benchmark (PPV: 81% [95% confidence interval 58–95]) but no RRI cut-point did so.

Conclusions: For the Beckman Coulter Access hs-cTnI assay, RRO criteria of baseline hs-cTnI <6 ng/L (females) or <11 ng/L (males) plus symptom onset >2 h met our performance benchmark. A 3-h delta cut-point >35 ng/L met the performance benchmark, but poor precision means further adequately powered research is required.

Key findings

- Data on delta, RRO and RRI of MI for hs-cTnI levels from the Access hsTnI assay are limited.
- For the Access hsTnI assay, the present study identified potential RRO and 3-h delta cut-points but further adequately powered research is required.

Key words: *emergency department, high-sensitivity troponin I, myocardial infarction, patient safety, symptom assessment.*

Introduction

People with suspected myocardial infarction (MI) commonly present to the ED for assessment and management.[1] Due to the consequences of missing an acute MI, diagnostic pathways have traditionally been conservative,[2] but lengthy assessments can exacerbate ED crowding.[1–3] The development of high-sensitivity cardiac

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troponin I (hs-cTnI) assays, which detect cTnI elevations earlier than conventional assays, are an important advance in safely reducing time to MI confirmation or exclusion.[4–8] In recent years, research has supported the rapid rule-out (RRO) and rapid rule-in (RRI) of MI based on single baseline hs-cTnI levels, and reduction of initial between-test time intervals to 1 h.[6,9]

Our hospital upgraded from a conventional cTnI assay to the new Beckman Coulter Access hsTnI assay in 2020. To aid introduction, a trial pathway for the assessment of suspected MI was devised for evaluation. From June to September 2019, probable diagnoses and patient disposition under the trial pathway were compared with actual outcomes from routine care and the findings published.[10] Given the paucity of information on the Access hsTnI assay at the time, trial cut-points for RRO, RRI and significant interval change were inferred from general recommendations in the Fourth Universal Definition of Myocardial Infarction (2018).[6]

Since the conduct of our trial, the European Society of Cardiology (ESC) guideline for the management of acute coronary syndromes (2020) has been published.[9] This recommends the use of a 0/1-h assessment algorithm, including RRO and RRI.[9] The ESC suggest that a RRO cut-point should have a negative predictive value (NPV) for MI >99%, and that RRI and 1-h change cut-points should have a positive predictive value (PPV) for MI >70%.[8,9] For the Access hsTnI assay, a recent paper by Nestelberger *et al*. recommended cut-points of <4 ng/L for RRO, >50 ng/L for RRI and >15 ng/L for 1-h change.[8] These are included in the ESC guideline.[9] The ESC also recommends a third hs-cTnI level be done at 3 h for those with indeterminate 0/1-h results,[9] but a threshold for significant 3-h change has not been determined for the Access hsTnI assay. The objective of the present study was to use the hs-cTnI levels obtained in the original outcome study, to further evaluate potential cut-points for RRO and RRI, and to explore amounts of significant 3-h change.

Methods

Study design and setting

The original retrospective evaluation of the potential impact of a novel pathway for the assessment of ED patients with suspected MI[10] was conducted at Dandenong Hospital (annual ED census 69 000 patients), Melbourne, Australia. Data were collected on a consecutive series of eligible patients from 4 June 2019 to 20 September 2019. Study conduct was approved by the Monash Health Human Research Ethics Committee (RES-18-0000640A). The study complied with STROBE guidelines for observational studies.[11]

Study population

All adults (>18 years) presenting to ED who had cTnI levels obtained for suspected MI consented to inclusion. Relevant symptoms included acute (previous 6 h) chest, neck, jaw or arm pain, discomfort, or pressure without an apparent non-cardiac source.[2] People with ST-elevation MI (STEMI) on initial ECG, who were immediately transferred to the cardiac catheter laboratory, and those with a non-cardiac diagnosis made after initial assessment, were excluded.

Study procedure

During the original study period, all patients underwent routine care using an assessment pathway with cTnI levels from the conventional Beckman Coulter AccuTnI+3 assay. The conventional pathway included cTnI levels at baseline, 90 min, and 6 h. The trial pathway used hs-cTnI levels from the Access hsTnI assay, with sampling at baseline, 90 min, and 3 h (Fig. S1). ED clinicians drew serial samples as near 90 min, 3 h and 6 h as other duties allowed. The Access hsTnI assay was performed on each sample with cTnI requested for routine care but hs-cTnI levels were not available to treating clinicians. This ensured provision of routine care using the conventional pathway.

Actual diagnoses, disposition and outcomes, using the conventional cTnI assay and pathway, were recorded. These were compared with potential diagnoses, disposition and outcomes which would have occurred under the trial pathway. Potential diagnoses were made retrospectively by RM and AN, and were categorised as 'no myocardial injury', 'chronic myocardial injury', 'non-ischaemic acute myocardial injury' and 'acute MI'[6] (Fig. S2). Only these 'new' potential diagnoses, including for MI, are reported and used in the present study, and not the 'original' diagnoses made following routine care.[10] The 'new' acute MI diagnosis required rising hs-cTnI levels with at least one level above the 99th percentile of the upper reference limit (URL),[12] along with one or more of (i) symptoms of acute myocardial ischaemia; (ii) new ischaemic ECG changes; (iii) development of pathological Q waves; (iv) evidence for an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis.[6] Two remaining elements of MI definition,[6] demonstration of regional wall abnormality and falling cTnI levels, were not relevant for ED patients with symptom duration <6 h. The MI diagnosis did not require any pre-specified amount of hs-cTnI rise at any time-point, provided other criteria were present. MI was not further classified as type 1 or type 2.

Study objectives

The primary objective of this follow-up study was to identify RRO criteria which met the *a priori* performance benchmark of the NPV for the outcome of incident MI having a lower 95% confidence limit >99%.[9,13] Twelve criteria were evaluated, stemming from three different baseline hs-cTnI cut-points. These were <2 and <6 ng/L, which had previously been investigated,[14] and one novel approach of <6 ng/L for females or <11 ng/L for males. The latter equated with the mid-points of the sex-specific normal reference limits for the Access hsTnI assay.[12] Diagnostic performance for each of these three cut-points was examined in isolation, and with separate and

TABLE 1. *Patient characteristics for the whole population, and those who did or did not meet rapid rule-out (RRO) criteria*

Variable	Whole population ($n = 935$)	RRO criteria met ($n = 260$)	RRO criteria not met ($n = 675$)	Difference (95% CI)
Age, median years (IQR)	64 (52–76)	55 (47–64)	69 (55–79)	14 (10–17)
Male sex, *n* (%) [95% CI]	507 (54)	156 (60) [54–66]	351 (52) [48–56]	−8 [−15 to −1]
Low risk, *n* (%) [95% CI]	388 (42)	154 (59) [53–65]	234 (35) [31–38]	−24 [−32 to −18]
Admitted coronary care unit, *n* (%) [95% CI]	139 (15)	31 (12) [8–16]	108 (16) [13–19]	4 [−1 to 9]
Admitted general unit, *n* (%) [95% CI]	266 (28)	17 (7) [4–10]	249 (37) [33–41]	30 [26–35]
Discharged from ED, *n* (%) [95% CI]	530 (57)	212 (82) [76–86]	318 (47) [43–51]	−35 [−40 to −28]
Acute myocardial infarction, *n* (%) [95% CI]	87 (9)	0 (0) [0–1]	87 (13) [10–16]	13 [10–15]
Non-ischaemic acute myocardial injury, *n* (%) [95% CI]	24 (3)	1 (0.4) [0–2]	23 (3) [2–5]	3 [1–5]
Chronic myocardial injury, *n* (%) [95% CI]	163 (17)	2 (1) [0–3]	161 (24) [21–27]	23 [20–26]
No myocardial injury, *n* (%) [95% CI]	661 (71)	257 (99) [97–100]	404 (60) [56–64]	−39 [−35 to −43]

RRO criteria: hs-cTnI level <6 ng/L (females) or <11 ng/L (males) and symptom onset >2 h. The admissions and discharges are those which occurred following routine care under the conventional pathway; diagnostic categories are those retrospectively assigned under the trial pathway using the hs-cTnI levels. CI, confidence interval; IQR, interquartile range.

joint addition of (i) pre-test symptom onset (≤ or >2 h)[14] and (ii) risk stratification (low or non-low). Low risk was defined as an ED assessment of chest pain score (EDACS) <16 points plus a normal or unchanged ECG, with all others being non-low risk.[15]

Secondary objectives were to identify potential cut-points for RRI and the significant amount of change from baseline to 3 h ('3-h delta') indicative of incident MI. The literature-based *a priori* performance benchmark for these cut-points was defined as a PPV for MI >70%.[8,9]

Study materials and definitions

Full characteristics for the Access hsTnI assay are available in the manufacturer's information.[12] These include a Limit of Detection (LoD) of 2.3 ng/L, 20% and 10% coefficients of variation of 2.3 and 5.6 ng/L, respectively. The reporting range is 0–27 027 ng/L and the sex-specific 99th percentiles of the URL are 20 ng/L for males and 10 ng/L for females. The latter figure, which varies slightly from the manufacturer's recommendation,[12] is based on local research data.[16]

In different studies, RRO and RRI of MI may refer to either a combination of criteria from baseline and 1-h hs-cTnI levels,[8] or to baseline levels alone.[14] In the present study, only the baseline hs-cTnI levels were considered in both the RRO and RRI analyses.

The '3-h delta' refers to amount of change in the hs-cTnI level from baseline to 3 h. The '3-h' levels were those from samples drawn between 2 and 4 h from baseline. Both absolute and relative change was examined. Absolute change was calculated as the repeat hs-cTnI level minus the baseline hs-cTnI level, reported as change in ng/L. Relative change was calculated as (repeat hs-cTnI level minus baseline hs-cTnI level)/baseline hs-cTnI level, multiplied by 100, reported as percentage change. Inclusion for 'delta calculation' required serial hs-cTnI levels to be rising within the measuring range (2–27 027 ng/L), with at least one level being above the 99th percentile of the URL.

Statistical analysis

Baseline variables are described as median and interquartile range (IQR) or number and percentage. The discriminative ability for MI from baseline or change in serial hs-cTnI levels utilised ROC curve analysis and is reported as area under the curve (AUC). Diagnostic performance of identified cut-points utilised contingency table analysis.

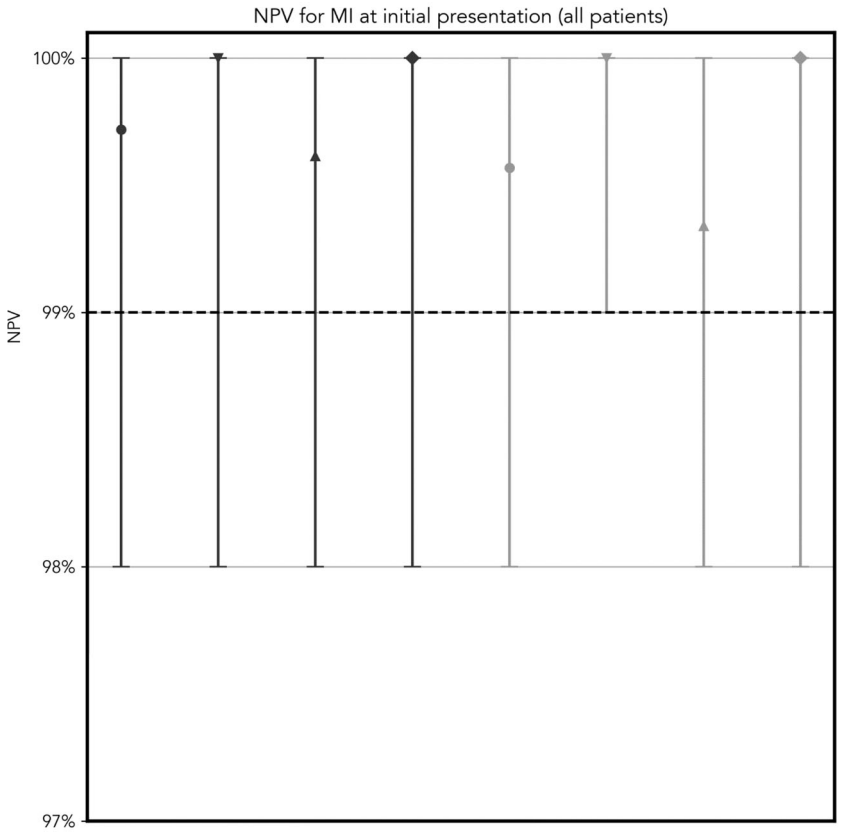

Figure 1. *Comparison of negative predictive values (NPVs) for incident myocardial infarction (MI) of the tested rapid rule-out (RRO) criteria. The figure displays the point estimate (symbol location) and corresponding 95% confidence interval of the NPV for each listed RRO tool in order from left to right. RPO tools: (●), cTnI >6 ng/L; (▼), cTnI >6 ng/L + duration >2 h; (▲), cTnI >6 ng/L + low risk; (◆), cTnI >6 ng/L + duration >2 h + low risk; (●), cTnI >6 ng/L (F), cTnI <11 ng/L (M); (▼), cTnI >6 ng/L (F), cTnI <11 ng/L (M) + duration >2 h; (▲), cTnI >6 ng/L (F), cTnI <11 ng/L (M) + low risk; (◆), cTnI >6 ng/L (F), cTnI <11 ng/L (M) + duration >2 h + low risk.*

Clinical characteristics, diagnosis, and disposition for patients who met identified RRO, RRI and 3-h delta criteria are described in Supporting Information. The original sample of 935 patients pertained to demonstration of a potential 30-day post-discharge major adverse cardiac event rate <1% and not for these additional investigations. Analysis was performed using Stata statistical software (Version 12; StataCorp, College Station, TX, USA).

Results

Baseline hs-cTnI levels for all 935 study patients were included in the RRO analyses. The three cut-points of <2, <6 and <6 ng/L (females) or <11 ng/L (males) identified 2, 42 and 55% of patients as being potentially suitable for early discharge. Of the 12 different RRO criteria examined, one met our *a priori* performance benchmark. This was for baseline hs-cTnI level <6 ng/L (females) or <11 ng/L (males) plus symptom onset >2 h (NPV 100%, 95% confidence interval [CI] 99–100), which identified 260/935 (28%) for potential early discharge. Characteristics of the total population, and for those who did or did not meet these criteria, are shown in Table 1. The RRO cohort were younger (55 [IQR 47–64] *vs* 69 [IQR 55–79] years), and more likely to be low-risk (59% [95% CI 53–65] *vs* 35% [95% CI 31–38]). NPVs for all criteria other than the small <2 ng/L groups are illustrated in Figure 1. Full details of diagnostic performance for all 12 tested RRO criteria are shown in Table S1.

For RRI of MI, ROC curve analysis showed that baseline hs-cTnI levels alone had excellent discrimination for MI presence, with ROC-AUC 0.90 (95% CI 0.87–0.93) (Fig. S3). A cut-point of 150 ng/L yielded greatest total agreement (91%), with sensitivity and PPV for detection of MI of 53% (95% CI 42–64) and 48% (95% CI 38–59), respectively. A cut-point of 650 ng/L maximised PPV at 63% (95% CI 45–76), with sensitivity 25% (95% CI 17–36). Clinical details of patients meeting the >150 ng/L and >650 ng/L cut-points are available in Figure S4.

Of all 935 patients, 923 (99%) and 234 (25%) had second and third hs-cTnI levels performed. Between-test intervals approximated pathway-designated times of 90 min, 3 h or 6 h, with third tests being done about 3 h after second tests (Fig. 2). Of the 923 patients who had a second test, 213 (23%) were done at 3 h (median time 165 min [IQR 135–195]). Of these, 52 (24%) patients, including 19 of 87 (22%) diagnosed with MI, met criteria for delta calculation (Fig. 2).

For the 3-h delta subgroup, the ROC-AUCs for absolute and relative change were 0.94 (95% CI 0.87–1.0) and 0.90 (95% CI 0.80–0.99), respectively (Fig. S3). For absolute change, the highest total diagnostic agreement (88%) was for an increase in hs-cTnI by >35 ng/L from baseline to 3 h. For relative change, the highest total diagnostic agreement (88%) was for an increase in the hs-cTnI level by >50% from baseline to 3 h. For the contingency table analyses, cell counts for the absolute and relative change cut-points were identical. The sensitivity and PPV for MI for both were 89% (95% CI 67–99) and 81% (95% CI 58–95) (Table 2). Clinical details of the two different 'false negative patients' are also shown.

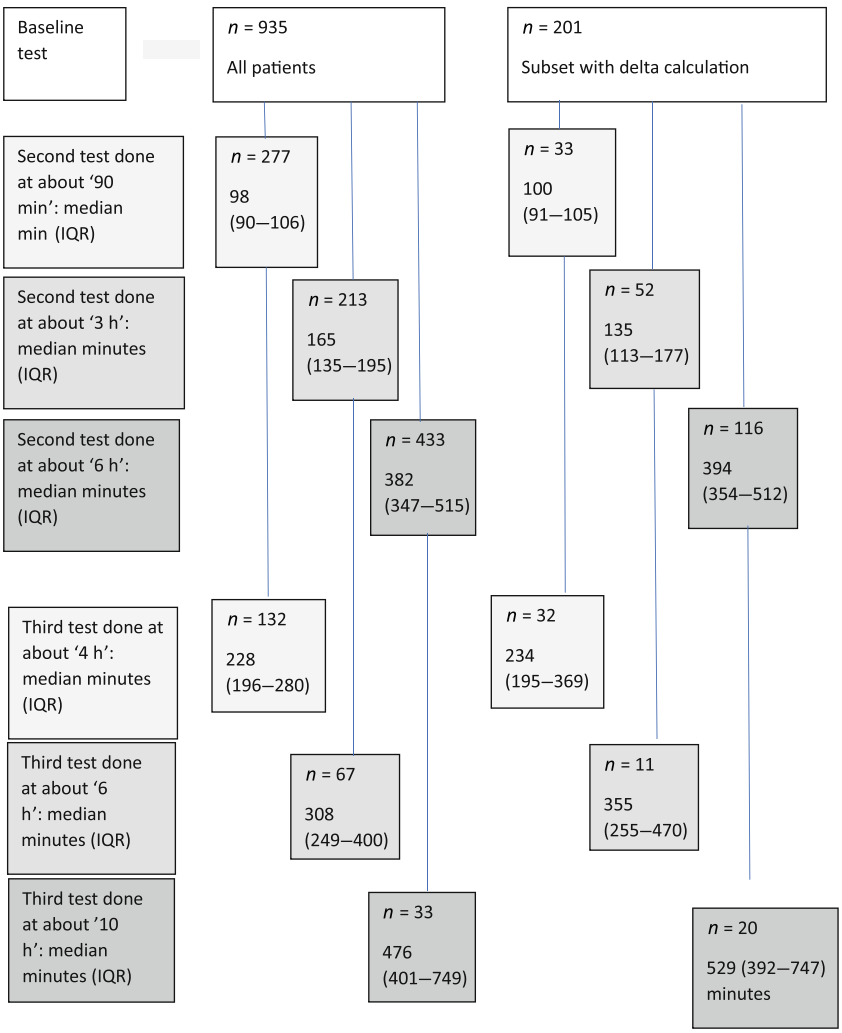

Figure 2. *Times from baseline to serial tests: total population and delta calculation subgroup. Delta calculation required an increased second hs-cTnI level within the measuring range (0–27 000 ng/L) with at least one level being above the 99th percentile of the upper reference limit. IQR, interquartile range.*

Discussion

The present study found that for RRO of MI, criteria of <6 ng/L (females) or <11 ng/L (males) plus symptom onset >2 h satisfied our *a priori* performance benchmark and identified 28% of the population for potential early discharge. Early RRO research with hs-cTnI assays set cut-points at the assay LoD.[17,18] Most reported NPV >99% but 95% CIs were wide.[17,18] Reported population capture rates vary between 19% and 60%, presumably due to sampling differences. Influence of symptom duration and risk stratification has been examined with variable results.[18,19]

Recent studies by Nestelberger *et al.*[8] and Greenslade *et al.*[14] investigated RRO for the Access hsTnI assay. RRO criteria of <2 or <4 ng/L plus symptom onset >3 h, yielded NPV with lower 95% confidence limits >99% and captured about 30% of the population. These studies informed the 'very low' RRO cut-point of <4 ng/L recommended for the Access hsTnI assay in the ESC 0/1-h algorithm.[9] As neither of these studies[8,14] considered sex-specific rule-out thresholds, it seemed reasonable to evaluate cut-points set at the sex-specific 50th centile values. The use of sex-specific URLs for MI rule-in is seen as beneficial, especially for women,[20] but their use at lower levels for rule-out has not previously been studied. This approach performed well but required incorporation of symptom duration to meet our *a priori* benchmark. Since diagnostic performance is impacted by MI prevalence, cut-points will not perform identically in different populations. In the present study, the MI rate was 9%, while for the Greenslade *et al.* and Nestelberger *et al.* populations it was 5% and 14%, respectively.[8,14] Consequently, EDs should monitor the performance of adopted RRO cut-points in their own populations.

For RRI of MI from a single baseline hs-cTnI level, no cut-point satisfied our *a priori* benchmark.[8] The PPV for MI of evaluated RRI tools has ranged from 38% to 73%.[8,21] Authors have cautioned against low cut-points due to concerns about overwhelming cardiology referral services and generating unnecessary admissions for cardiac investigations.[22,23] A reasonable approach may be that immediate referral to cardiology is reasonable for initial hs-cTnI levels >150 ng/L if patient symptoms and/or ECG changes suggest type 1 MI. This probably reflects current ED practice.

The ESC algorithm for the assessment of suspected MI recommends a 1-h delta cut-point of 15 ng/L for the Access hsTnI assay,[8,9] but evidence for 3-h delta was lacking. Our cut-points of >35 ng/L or >50% have promising point estimates for sensitivity and PPV, but poor precision means confirmation from adequately powered studies is required. Relative and absolute change performed similarly in this sample, although most recommendations favour use of the latter.[9,24]

While our potential 3-h delta cut-point of >35 ng/L appears consistent with the Nestelberger *et al.* 1-h cut-point of >15 ng/L,[8] the impact of sampling differences on between-study comparisons is uncertain. Nestelberger *et al.* enrolled only stable patients with suspected type 1 MI and

TABLE 2. *Diagnostic performance for acute myocardial infarction of absolute and relative 3-h delta, with characteristics of the two 'false negative' patients*

		MI diagnosis			
		Yes	No	Total	Diagnostic performance
3-h delta, >35 ng/L (or >50% – results identical)	Yes	17	4	21	Sensitivity for detection of MI, *n* (%) [95% CI] 17/19 (89) [67–99]
	No	2	29	31	Positive predictive value for MI, *n* (%) [95% CI] 17/21 (81) [58–95]
Total		19	33	52	Negative predictive value for MI, *n* (%) [95% CI] 29/31 (94) [79–99]

Study number	Age/sex	Baseline hs-cTnI level	Serial hs-cTnI level	Delta change (ng/L)	Delta change (%)	Disposition	Primary clinical problem(s)
Characteristics of the two MI patients with absolute change <35 ng/L							
681	78 years Female	18 ng/L	47 ng/L	29 ng/L	161%	General unit	Chronic airways disease/asthma
908	79 years Female	9 ng/L	27 ng/L	18 ng/L	200%	CCU	Rapid atrial fibrillation
Characteristics of the two MI patients with relative delta change <50%							
362	78 years Female	812	933	121	15	General unit	Syncope/fall/trauma
80	77 years Female	753	931	178	24	CCU	Type 1 MI

CI, confidence interval; MI, myocardial infarction.

no concurrent acute conditions.[8] Our relatively heterogenous sample included suspected MI in the setting of other primary complaints. Physicians must remember that recommended delta cut-points are only aids to decision-making for their local populations. Change in the hs-cTnI level is just a first step towards an MI diagnosis, which still requires the presence of supportive clinical, ECG or imaging findings.[6] Accepting this caveat, a proposed flowchart of how the findings from the present study might be combined with the ESC recommendations[9] is available in Figure S5.

Limitations

Our sample size was dictated by the original study.[10] Small numbers in the 3-h delta subgroup mean these findings are hypothesis-generating only. Also, actual between-test intervals only approximated the desired 90, 180 and 360-min sampling times, which reflects scheduling difficulties in ED practice.

Our population will differ from those for which similar pathways are used elsewhere. The implications of this have been discussed. Diagnosis allocation, including MI, can be subjective and inter-rater reliability is unknown. This may impact cut-point performance to some degree.

Conclusions

For the Beckman Coulter Access hsTnI assay, criteria for RRO of MI of hs-cTnI levels <6 ng/L (females) or <11 ng/L (males) plus symptom onset >2 h prior to blood collection satisfied our performance benchmark. For RRI of MI, identified cut-points did not meet performance benchmarks. The 3-h delta cut-point requires further adequately powered research.

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Author contributions

RM and ZL originally conceived the study with contributions from LC, AN and LK. ZL, RM and LS were responsible for data acquisition and entry. RM and AN were responsible for clinical outcome allocations. RM and LS performed the data analysis. RM and LC drafted the manuscript with ongoing contributions from ZL, LK, AN and LS. RM takes responsibility for the manuscript as a whole.

Competing interests

LC has received research funding, consulting fees and/or honorarium from Beckman Coulter, Siemens Healthineers and Abbott Diagnostics.

Data availability statement

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

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site:

Figure S1. Assessment pathway for suspected myocardial infarction using the Access hsTnI assay.
Figure S2. Diagnostic conclusions based on hs-cTnI levels. Reproduced with permission of the ACRE project, Clinical Excellence Queensland.
Figure S3. ROC curves for detection of myocardial infarction from the baseline hs-cTnI level alone, and from absolute and relative change at 3-h for those meeting delta calculation criteria.
Figure S4. Diagnosis and disposition of patients with initial hs-cTnI levels >150 and >650 ng/L.
Figure S5. Assessment of suspected myocardial infarction in the ED with recommended delta, rapid rule-out and rapid rule-in criteria.
Table S1. Diagnostic performance for defined rapid rule-out tools.