External validation of a rapid algorithm using high-sensitivity troponin assay results for evaluating patients with suspected acute myocardial infarction

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ABSTRACT

Objective We sought to validate the clinical performance of a rapid assessment pathway incorporating the Siemens Atellica IM high sensitivity cardiac troponin I (hs-cTnI) assay in patients presenting to the emergency department (ED) with suspected acute myocardial infarction (AMI).

Methods This was a multicentre prospective observational study of adult ED patients presenting to five Australian hospitals between November 2020 and September 2021. Participants included those with symptoms of suspected AMI (without ST-segment elevation MI on presentation ECG). The Siemen's Atellica IM hs-cTnI laboratory-based assay was used to measure troponin concentrations at admission and after 2–3 hours and cardiologists adjudicated final diagnoses. The HighSTEACS diagnostic algorithm was evaluated, incorporating hs-cTnI concentrations at presentation and absolute changes within the first 2 to 3 hours. The primary outcome was index AMI, including type 1 or 2 non-ST segment elevation MI (NSTEMI) or ST-elevation MI (STEMI) following presentation. 30-day major adverse cardiac outcomes (including AMI, urgent revascularisation or cardiac death) were also reported. The trial was registered with the Australian and New Zealand Clinical Trials Registry.

Results 1994 patients were included. The average age was 56.2 years (SD=15.6), and 44.9% were women. 118 (5.9%) patients had confirmed index AMI. The 2-hour algorithm defined 61.3% of patients as low risk. Sensitivity was 99.1% (94.0%–99.9%) and negative predictive value was 99.9% (99.3%–100%). 24.4% of patients were deemed intermediate risk. When applying the parameters for high risk, 252 (14.3%) were identified, with a specificity of 91.5% (88.7%–93.6%) and a PPV of 42.0% (35.6–48.7%).

Conclusions A 2-hour algorithm based on the HighSTEACS strategy using the Siemens Atellica IM hs-cTnI laboratory-based assay enables safe and efficient risk assessment of emergency patients with suspected AMI.

Trial registration number ACTRN12621000053820.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior studies have evaluated high-sensitivity cardiac troponin (hs-cTn) assays, but a robust evaluation of each new hs-cTn assay and platform is needed to define safe and efficient methods for clinical use.

WHAT THIS STUDY ADDS

⇒ This is a validation of a clinical pathway incorporating the Siemens Atellica IM laboratory-based assay with cut-off values derived in the HighSTEACS study .

⇒ We demonstrated that a pathway incorporating the Siemen's Atellica IM assay can safely identify most patients as low risk for myocardial infarction (MI) and subsequent 30-day major adverse cardiac events.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The utilisation of this strategy may support efficient and early disposition planning for this large group of emergency patients.

INTRODUCTION

Acute chest pain comprises one of the most common reasons for visits to emergency departments (ED) throughout the world (5%–10% of all ED visits)[1 2] and early and safe discharge of patients at low risk for acute myocardial infarction (AMI) is essential. Using high-sensitivity cardiac troponin (hs-cTn) assay results leads to more efficient ED assessment for patients with suspected acute coronary syndrome (ACS) as these assays require shorter testing intervals than previous-generation assays.[3 4] For example, in patients with cTn concentrations near the limit of detection (LoD) on a single test at admission using a hs-cTn assay, the risk for AMI is extremely low, and these patients can be considered for early discharge without further serial troponin testing.[4 5]

Several algorithms have been developed and validated based on hs-cTn assays to enable early risk assessment for emergency patients with suspected ACS.[6–10] However, a robust evaluation of each new hs-cTn assay and platform is needed to define safe and efficient methods for clinical use and to support subsequent adoption into practice. This evaluation may focus on the accuracy of new assays

when included within existing algorithms or through modifying existing strategies.

The Siemens Atellica IM assay is a hs-cTnI assay designed for laboratory use. Although similar to the Siemens ADVIA Centaur hs-cTnI assay, this assay has its own metrics for use.[11] Early studies suggest that the Siemens Atellica IM hs-cTnI assay can be used to rapidly assess patients presenting to ED with suspected AMI.[12–15] Only two cohorts have been used to define the metrics for the clinical use of this assay, but the described strategies differ, and neither has been externally validated. Our current study aims to validate the clinical performance of a 2-hour algorithm that was derived by the HighSTEACS group that incorporates the Siemens Atellica IM hs-cTnI assay.[13] Our goal was to determine the safety and efficiency of this strategy for identifying index AMI and 30-day major adverse cardiac outcomes (MACE) in patients presenting to Eds with suspected ACS.

METHODS

Study design and population

The Suspected Acute Myocardial Infarction in Emergency (SAMIE) study recruited adult patients presenting to the ED with symptoms suggestive of an AMI but without ST elevation evident on their first ECG across five Australian hospitals. Hospitals included the Royal Brisbane and Women's Hospital (RBWH), Gold Coast University Hospital, Townsville Hospital, Logan Hospital and The Princess Alexandra Hospital. The prospective study design and population of the multicentred study have been described previously.[16] Data were collected between November 2020 and September 2021. The study was funded by the State-wide pathology provider (Pathology Queensland) who were implementing the Atellica IM assay as their standard laboratory-based assay. They funded this study to identify whether there was an evidence-based algorithm that allowed patients to be safely managed using the new assay. Patients were not involved in the design, conduct, reporting or dissemination plans of our research.

Consecutive eligible patients presenting to the ED within business hours (0730–1800), Monday to Friday, were approached and asked to participate. We have previously reported that the characteristics of patients presenting during and outside business hours do not significantly differ.[17] Patients were eligible for enrolment if they were ≥18 years old and were being investigated by their treating clinician for suspected ACS. Patients were excluded if they were transferred to the cardiac catheter laboratory without investigation in the ED, were transferred from another hospital, were previously enrolled in the trial within the past 30 days, were pregnant, were unable or unwilling to provide informed consent (eg, non-English speaking with no interpreter available) or where staff considered recruitment inappropriate (eg, patient receiving end of life care). Patients were excluded from the current analyses if they had delayed serial testing (≥6 hours after presentation), if the patient did not have a presentation Atellica IM hs-cTnI result, or if the patient had an initial ECG within the ED that was consistent with STEMI and were transferred to the cardiac catheter laboratory within 2 hours of presentation.

Data collection and sample handling

Patient management remained at the clinician's discretion, and the study's conduct did not alter usual care. Usual care at each site involved taking blood samples for measuring plasma hs-cTnI, serial ECG testing in all patients, and further testing for coronary artery disease, such as CT coronary angiography and/or functional testing for ischaemia when appropriate. Patients proceeded with standard care based on the results of the existing cTn assay (Beckman Coulter hs-cTnI). Research nurses collected data using a standardised case report form. Baseline characteristics, previous medical history and risk factors were gathered directly from the patient or their medical record. Patient sex was self-reported. Blood samples were taken per standard care at 0 and 2–3 hours, depending on the study site. At the same time, an additional 10 mL of blood for study samples was collected prospectively. In some cases, patients were discharged after a single cTn test. These individuals only had a single 0-hour study sample collected but were still included in the analysis.

In addition to ECG evaluation, risk determination according to usual care included patients defined as low risk (cTn values <2 ng/L), intermediate risk (two cTn values ≤99th sex-specific percentile (10 ng/L women, 20 ng/L men) or high risk (any value >sex-specific 99th%. Change metrics (deltas) were not part of usual risk assessment.

All study samples were sent to the local central laboratory initially. The local laboratory centrifuged the sample for 10 mins at 3000 g and sent this plasma sample at 4°C. Logan and PAH couriered, as soon as practical, to the Pathology Queensland laboratory at the RBWH for freezing. At the RBWH, GCUH and Townsville Hospital, the plasma was aliquoted and frozen to −80°C. All samples were frozen within 16 hours of initial collection. All frozen samples were transported to the RBWH and stored at −80°C before thawing and testing on the Atellica Platform using the Siemen's Atellica IM hs-c-TnI assay.

Thirty days after the initial presentation, research nurses conducted telephone follow-ups to determine whether the patient had further cardiac testing or admission to private hospitals within that period. State-wide databases were also investigated at 30 days to identify whether the patient had further hospital admissions or additional cTn testing. Where relevant, all additional investigations or admission reports were obtained.

Adjudication procedure

The primary outcome was index AMI (type 1 (T1MI) and type 2 (T2MI)) and included non-ST segment elevation myocardial infarction and STEMI that occurred after the presentation. Secondary outcomes included 30-day MACE incorporating T1MI, T2MI, cardiac death or unplanned revascularisation. AMI (T1MI and T2MI) was defined according to the fourth Universal Definition of Myocardial Infarction.[18] Cardiologist adjudication for AMI was conducted by a single cardiologist. A second cardiologist reviewed all instances of T2MI or those cases where the initial cardiologist requested a second review due to the complexity of the case. Events were adjudicated post hoc based on all available clinical data collected up to the time of patient follow-up (30 days). This included a review of the clinical record, ECGs, cTn results using the assay in clinical use at the time and all subsequent investigations from standard care but blinded to the Atellica IM hs-cTnI assay results. The hs-cTnI assay in clinical use in all sites was the Beckman Coulter Access 2, with the LoD being 2.3 ng/L and the 99th percentile upper reference limits being 11.6 ng/L and 19.8 ng/L for women and men, respectively. Local decisions for cut points were made, and in clinical practice, 10 ng/L for women and 20 ng/L for men were used.[11] The laboratory characteristics of the Beckman Coulter Access assay have previously been compared with the Atellica IM hs-cTnI assay.[19]

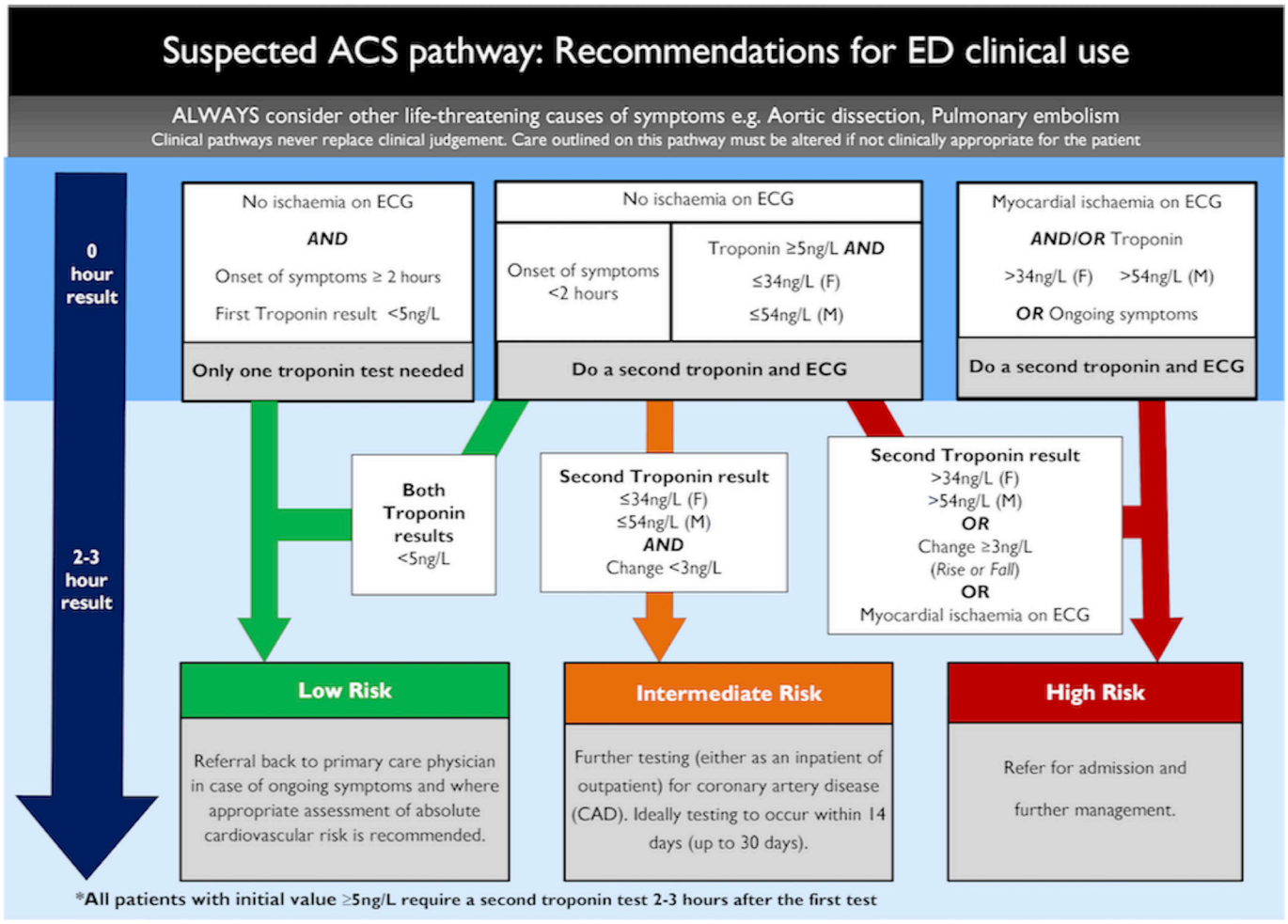

Figure 1 ACS pathway. ACS, acute coronary syndrome, ED, emergency department; F, female; M, male.

Investigational hs-cTnI procedure

cTn was measured using the Siemens Atellica IM hs-cTnI, a three-site sandwich immunoassay on a laboratory-based instrument with a 99th percentile of 38.6 ng/L and 53.5 ng/L for women and men, respectively.[11] The measurement was performed in a blinded fashion in a dedicated core laboratory. The LoD is 1.6 ng/L, and the limit of quantitation (coefficient of variation 20%) is 2.5 ng/L, with percentages of subjects with measurable values over the LoD of 75%.[20]

Algorithm development and validation

The algorithm evaluated was adapted from a pathway developed by the HighSTEACS group (figure 1). The low-risk category from the original algorithm was separated into low and intermediate risk to represent a three-tiered system of risk (high/intermediate/low) in the SAMIE cohort.[13] This algorithm incorporates both hs-cTnI levels and absolute hs-cTnI changes within the first 2 hours and time of symptom onset. For this study, all results were rounded to whole numbers.

Data analysis

We sought to recruit a minimum of 1890 patients for this study. This sample size was chosen as the proportion of patients with AMI was estimated to be approximately 10%, meaning that we would recruit about 189 patients with AMI. 189 AMI patients would allow for high sensitivity (98%) to be estimated with a prediction interval of 2% and an alpha of 0.05.

Baseline characteristics were reported as mean (SD), median (IQR) or n (%) as appropriate. Patients were categorised based on a modified HighSTEACs pathway. Patients were deemed low risk for AMI if their 0-hour hs-cTnI result was <5 ng/L and their symptom onset was >two hours before presentation. Patients were also considered low risk if they presented within 2 hours of symptom onset, but their 0-hour and 2-hour hs-cTnI results were both <5 ng/L (figure 1). Patients met high-risk criteria if they had either (1) a 0-hour or 2-hour hs-cTnI value >34 ng/L in women or >53 ng/L in men (or 2) an absolute change of ≥3 ng/L within the first 2–3 hours in patients who did not otherwise meet low-risk criteria. Patients who did not meet these criteria were classified as intermediate risk. Patients who met the criteria for intermediate risk at zero hours but did not have serial sampling performed were included in analyses focusing on zero hours only. These individuals were removed from the analyses requiring 2-hour results. There were no missing data for 0-hour index tests or index AMI diagnosis (the primary outcome variable). For the secondary outcome (30-day AMI), patients without evidence of an elevated troponin or cardiac investigation were presumed not to have a 30-day AMI.

For the low-risk and high-risk groups, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were reported for index AMI and 30-day MACE. For the primary analyses, estimates for the diagnostic accuracy statistics and 95% CIs were derived using multilevel logistic regression with hospital incorporated as a random effect. These analyses

Table 1 Baseline characteristics of patients

Characteristic	No index AMI (n=1876)	Index AMI (n=118)
Mean age (SD), years	55.6 (15.5)	66.3 (12.9)
Male sex	1016 (54.2%)	83 (70.3%)
Identifies as Indigenous	93 (5.0%)	2 (1.7%)
Presented with chest pain	1762 (93.9%)	114 (96.6%)
Patient history		
Prior AMI	315 (16.8%)	47 (39.8%)
Prior CABG	103 (5.5%)	14 (11.9%)
Prior Angioplasty	292 (15.6%)	37 (31.4%)
Prior CAD	429 (22.9%)	54 (45.8%)
Risk factors		
Hypertension	865 (46.1%)	76 (64.4%)
Diabetes	315 (16.8%)	36 (30.5%)
Dyslipidaemia	834 (44.5%)	76 (64.4%)
Family history of CAD	804 (42.9%)	43 (36.4%)
Smoking	421 (22.4%)	27 (22.9%)
Process data		
Presentation>2 hours after symptom onset	1426 (76.4%)	90 (76.9%)
Time from arrival to first troponin (hours)	0.6 (0.4-.1.0)	0.6 (0.4–0.8)
Time from first to second troponin (hours)	3.1 (2.8–3.3)	3.0 (2.9–3.3)
ED length of stay (hours)	3.7 (2.5–5.3)	4.4 (3.0–6.6)
Hospital Length of stay (hours)	6.3 (5.1–10.0)	73.8 (33.6–146.2)

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CAD, coronary artery disease; ED, emergency department.

adjust the statistical estimate for the clustering of patients within hospitals. Additional preplanned sensitivity analysis looks at the results by sex and age (<65 or ≥65 years). Data were analysed using Stata V.17.

RESULTS

Patient characteristics

In total, 2022 patients with suspected ACS were recruited, with complete data available for analysis. Twenty-eight were excluded from the current analyses as they had no Atellica result, had an STEMI on presentation or had delayed troponin testing >6-hour post-ED presentation. This left 1994 (99%) patients. All patients were followed up using the statewide database and 81.9% were contacted by phone. The patient flow diagram is reported in online supplemental figure 1. Baseline characteristics are provided in table 1. Of 118 (5.9%) patients had index AMI, with 87 (4.4%) patients diagnosed with T1MI. 129 (6.5%) patients had a 30-day MACE. Hs-cTnI values were above the LoD in 65.7% (1310/1994) of patients using the institutional assay and 80.1% (1597/1994) using the investigational assay.

Figure 2 shows the performance of the algorithm. Overall 610 (30.6%) patients did not have serial samples. After a second troponin where necessary, the pathway identified 61.3% of patients as low risk. Most of these (894/1080; 82.8%) were classified based on a single result. One patient with an index myocardial infarction was missed giving an NPV of 99.9% (99.3%–100%) and sensitivity of 99.1% (94.0%–99.9%). Four additional MACEs at 30 days were missed using these criteria (figure 2). 252 (14.3%) patients were identified as high-risk after serial sampling. The high-risk criteria had a PPV for index MI of 42.0% (35.6%–48.7%) and specificity of 91.5% (88.7%–93.6%). Ninety-three (5.3%) patients were classified as high risk as their delta were ≥3 ng/L. Of these patients, 12 (12.9%) were diagnosed with index MI (see online supplemental table 1).

Of 960 patients (48.1%) were considered intermediate risk at zero hours (initial values >5 ng/L and ≤34 ng/L for women or ≤53 ng/L, respectively, or initial values <5 ng/L but taken within 2 hours of symptom onset). Of 231 (24.1%) of these patients

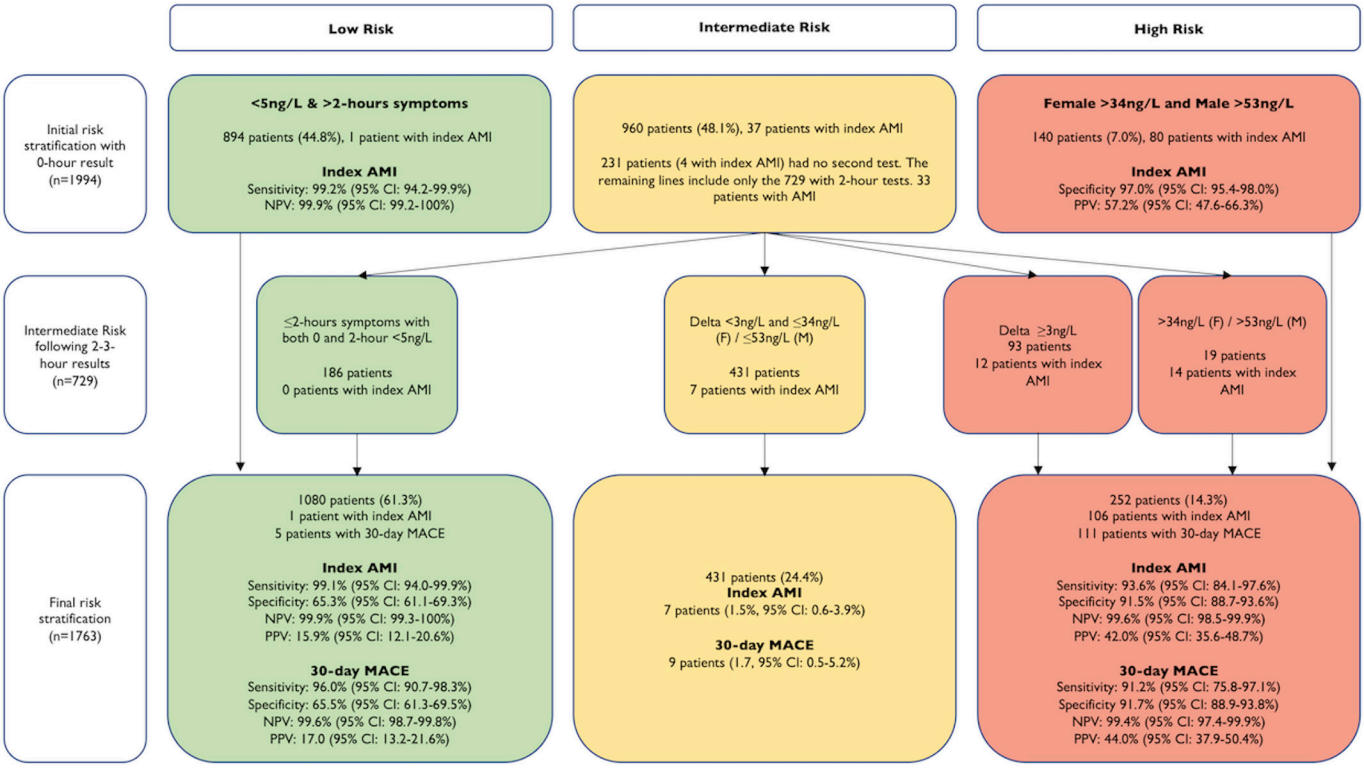

Figure 2 Performance of the algorithm. AMI, acute myocardial infarction; MACE, major adverse cardiac events.

did not have second samples stored. In this cohort of patients without second samples, four patients were diagnosed with index MI (1.7%, 95% CI 0.7 to 4.5). No further MACE was identified at 30 days. Of 431 (24.4%) patients were at intermediate risk for MACE following serial sampling. Of these intermediate-risk patients, seven (1.5%) were diagnosed with index MI and two additional with 30-day MACE.

Details of patients with missed index events in low-risk and intermediate-risk patients are outlined in online supplemental table 2. Predefined subgroup analyses by sex and age are shown in online supplemental tables 3,4. Of note, there were substantial sex differences in the PPV value based on sex-specific decision limits. Details of patients with elevated Atellica hs-cTnI values discordant with the clinical assay results are shown in online supplemental table 5.

DISCUSSION

This large multicentre trial is the first external validation of the HighSTEACS strategy using the Atellica IM hs-cTnI assay, using the laboratory-based instrument. This study validates the previously published assay-specific metrics and can provide confidence to clinicians and pathology specialists about values for clinical implementation. While the original HighSTEACS pathway classified individuals as either low or high risk, this study used a three-tiered risk assessment strategy to enable accurate, rapid risk assessment for emergency patients with suspected AMI. This aligns with the European Society of Cardiology's recommended three-tiered strategy that supports disposition planning for most patients at early time points.[6] The proportions of patients in each risk category are similar to those found with other reported assay strategies.[6]

The HighSTEACS strategy enabled a large proportion of patients (~61%) to be identified as low risk of AMI, with nearly two-thirds of these identified using only a single troponin test. The proportion of patients with AMI in the low-risk group was much lower than the generally accepted miss rate of 1%, supporting safe discharge without the need for additional objective testing for symptomatic underlying coronary artery disease.[21] The troponin-only strategies recommended by ESC do not explicitly outline requirements for further testing in low-risk patients. Recent research has noted that for low-risk patients, applying the No Objective Testing rule[22] would allow approximately one-third of the cohort to be discharged with no further testing.[23 24] However, the combination of the 0/1-hour ESC strategy with the NOT rule is a conservative approach that was safe for ruling out MACE, including unstable angina pectoris for up to 1 year. The simple strategy that we tested only focused on ruling out AMI and enabled a larger proportion of patients to be safely discharged without additional testing than when the NOT rule is combined with the 0/1 ESC strategy or the HEART pathway alone.[23 24]

This study identified only a small proportion of high-risk patients (14%), but the cohort's index AMI event rate was substantial (prevalence of AMI 42.1%). Early disposition planning for further urgent investigation and cardiac management is indicated for this high-risk cohort. The significance of identifying patients at higher risk for AMI with small changes (≥3 ng/L) in hs-cTnI over 2 to 3 hours corroborated the HighSTEACS findings.[13] This highlights the importance for clinicians not to overlook a small change in early serial cTnI values. Our strategy also includes recommendations for an intermediate-risk cohort, requiring additional investigation for coronary artery disease burden, with a prevalence of AMI of 1.5%. A recommended strategy based on these data is suggested in figure 1. This strategy adopts a pragmatic approach that combines hs-cTnI data with the time of onset of symptoms and ECG data. For the patients deemed at intermediate risk for MACE following serial sampling (24.4%), further evaluation is required. Index AMI event rates (1.5%) were higher than that deemed generally acceptable.[21]

Although hs-cTn assays may be similar, performance differences using different platforms mandate evaluation of each assay using the instruments for clinical use. The Siemens ADVIA Centaur hs-cTn I assay (with 99% for women and men 40 ng/L and 58 ng/L, respectively) has been assessed in the high-STEACS algorithm, finding a higher proportion of low-risk patients (74%) with lower sensitivity (93.7%).[25] The differences to our study findings may relate to the different performance of the hs-cTnI assay on the different laboratory instruments.

Our paper has several strengths. First, this study incorporated a 2 to 3-hour serial testing time to reflect real-life ED management. Many strategies suggest a fixed second sampling time (eg, 1-hour, 2-hour or 3-hour samples), but in clinical practice, tests are taken near, but not strictly at the recommended time. As such, we have evaluated the performance of the hs-cTnI testing as it is used in clinical practice. Second, we increased generalisability by utilising patients across five study sites. Third, cardiologists independently adjudicated the diagnosis in those patients with an elevated troponin on either the Beckman or Atellica assay but used the Beckman assay with sex-specific thresholds as the reference standard. Our approach ensures that our observations are generalisable and relevant for clinical practice across different healthcare settings using this assay; however, other hs-cTnI or hs-cTnT assays require evaluation.

Several limitations are worthy of consideration. The results were obtained from a prospective diagnostic study and evaluation with the application of the recommended algorithm in clinical care is needed. The values reported are specific to this assay and should not be used with other hs-cTn assays. The diagnosis of acute myocardial injury or infarction was dependent on the finding of an elevated troponin value. As adjudication was based on the assay in clinical use, the outcomes reported for the investigational assay could at best be equal to, but never better than, this assay. The recommended strategy used previously determined assay thresholds, and not the manufacturers reported 99th percentiles. The fourthuniversal definition of myocardial infarction (UDMI) requires that diagnosis of AMI is based on the 99th percentile. The metrics within the strategy described are for risk assessment only. The original HighSTEACS study and this study utilised stored samples. The impact of a difference in sample type cannot be defined. Not all intermediate-risk patients had serial troponin testing. Removing this cohort would reduce the overall number of participants and inflate the percentage of low-risk patients. Many of the individuals with a single troponin were those who had an initial Beckman Coulter result of ≤2. A Bland-Altman plot for those individuals is provided in online supplemental figure 2 and shows a mean difference between the Siemens and Beckmans assays of −0.84 with limits of agreement being −8.3 to 6.6. Not all patients were able to be contacted by phone at 30 days. The likelihood that this was due to patients' death is exceedingly low, given the overall mortality rate of 0.1% (2/1994 patients), which is comparable to events in other similar ED studies. Trained cardiologists performed the adjudication using the fourth universal definition of myocardial infarction. However, misclassification cannot be excluded,

especially in patients with atypical clinical features and only minor biomarker changes. The strategy tested only used cTn results. The addition of clinical criteria (eg, ongoing chest discomfort and ECG criteria) in the recommended strategy will alter the proportions of patients within each risk group. Evaluation of the strategy after implementation would help to define this. The trial was observational in nature, and evaluation of the true impact on patient care and health service impact with the implementation of this strategy is required and is underway (ACTRN12622001474741). This was an ED-based study, and further evaluation is required prior to use in other settings, such as inpatient wards.

Translation of this modified HighSTEACS strategy incorporating the Siemens Atellica IM hs-cTnI assay for clinical use in the emergency setting should occur as this approach is accurate for the diagnosis of AMI and safe. The impact on clinical care and health services requires evaluation.

CONCLUSION

Using the laboratory-based Atellica IM hs cTnI assay within a HighSTEACS pathway format to evaluate emergency patients with suspected ACS can safely identify most patients as low risk for MI and subsequent 30-day major adverse cardiac events. The utilisation of this strategy may support efficient and early disposition planning for this large group of emergency patients.

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Contributors The authors confirm their contribution to the paper as follows: study conception and design: LC, JHG, LS, MT, FA and WP; data collection: LS, IR, NG, MKB and EM; analysis and interpretation of results: JHG, LC, MT, FA, WP; draft manuscript preparation: LC, JHG, FA, WP. All authors reviewed the results and approved the final version of the manuscript. LC is guarantor.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Royal Brisbane and Women's Hospital Human Research Ethics Committee, LNR/2020/QRBW/65773. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

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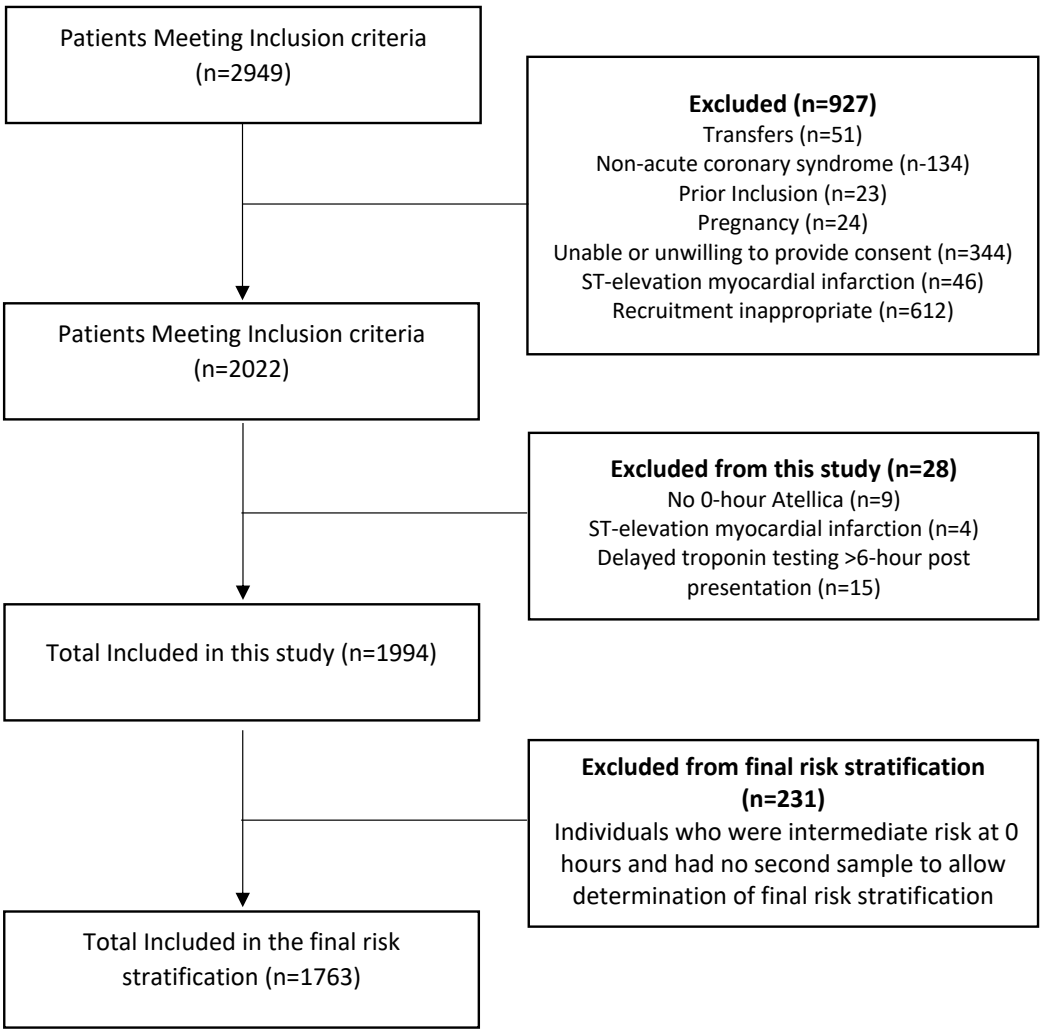
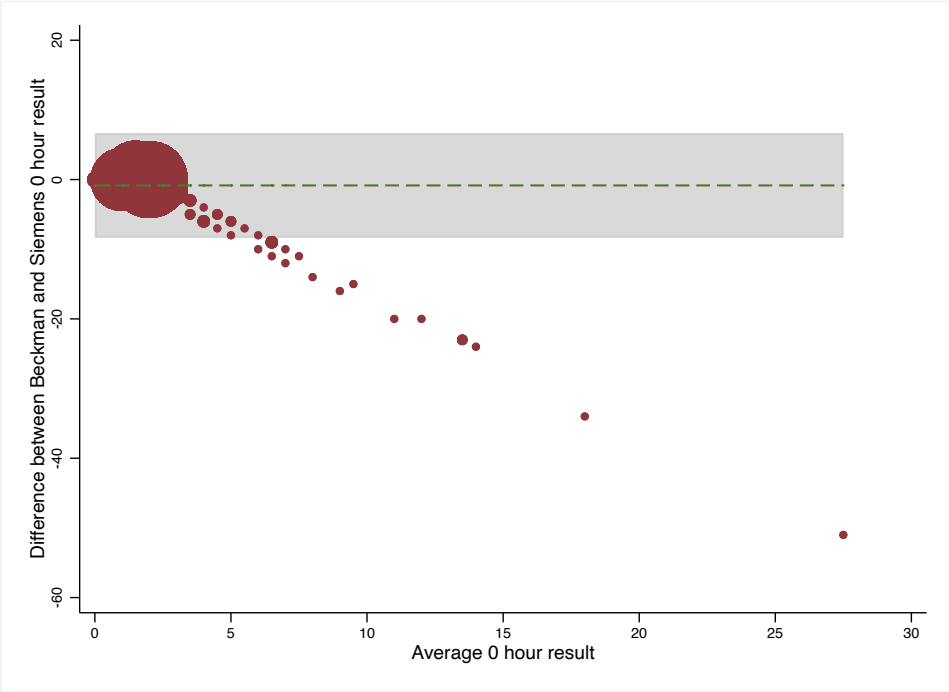
Supplementary Material

Supplementary Figure 1: Patient flow diagram



Supplementary Figure 2: Bland Altman Plot comparing 0-hour Siemens Atellica and Beckman Coulter assays for patients with a 0-hour Beckman result ≤2



Supplementary Table 1: Details for the 12 patients with index MI who met high-risk criteria based on delta ≥3

0- and 2-hour Atellica IM values (ng/L)	Delta (ng/L)	Outcome
21 and 24	3	T1 MI
35 and 31	4	T2 MI
11 and 15	4	T2 MI
27 and 31	4	T2 MI
21 and 17	4	T1 MI
42 and 37	5	T1 MI
18 and 24	6	T1 MI
9 and 18	9	T2 MI
16 and 29	13	T1 MI
9 and 31	22	T1 MI
14 and 36	22	T2 MI
8 and 45	37	T2 MI

T1MI, Type 1 Myocardial infarction; T2MI, Type 2 Myocardial infarction

Supplementary Table 2: Patients with AMI who were deemed low or intermediate risk using the Atellica algorithm

0- and 2-hour Atellica values (ng/L)	0- and 2-hour Institutional values (ng/L)[a,b]	Adjudicated outcome	Details
2 and 3	28 and 28	T1MI	Chest pain. Diabetes, hypertension. Unremarkable echocardiogram. CTCA and subsequent ICA showed 3 vessel CAD (chronic total occlusion to mid-LAD with collaterals and mid-RCA with collaterals. 50% occlusion to proximal LCx). The treating team discharged with a diagnosis was non-cardiac pain and minimal ischemia on interval DSE. Medical management.
34 and 36	26 and 29	T1MI	Chest pain, dyspnoea and diaphoresis. Evolving T wave changes. Admitted. Angiography non-obstructive, ectatic coronary disease.
5 and 5	7 and 12	T1MI	Chest pain. Declined further investigation. Admitted 2 weeks later with cholelithiasis, dilated bile ducts and abnormal liver function tests. Normal ECG.
26 and 28	19 and 21	T1MI	Typical ischemic chest pain. Admitted. Not investigated further for CAD. Treating team discharge diagnosis 'diastolic dysfunction'.
14 and 16	9 and 14	T2MI	Atypical chest pain in context of acute exacerbation of inflammatory arthritis (CRP 68). Investigated for pulmonary embolism. Coronary calcification noted on CTPA. No investigation for CAD.
30 and 30	25 and 24	T1MI	Chest pain. Complex diabetes mellitus, hypertension, chronic kidney disease. New non-specific T wave changes on ECG. Admitted. Previous documented CAD. No further investigations. Treating team discharged with diagnosis of 'High risk atypical chest pain'
39 and 39	51 and 47	T1MI and revascularisation	Chest pain and dyspnoea at rest. hypertension, smoker, dyslipidaemia. ECG – minor ST segment changes. Angiography showed severe LMCA disease. Urgent CABG
25 and 27	21 and 22	T1MI and revascularisation	Chest pain. Typical presentation. ECG – progressive inferior T wave inversion. Previous CABG and recent PCI to RCA graft. Treating team diagnosed with UAP. PCI to in-stent restenosis RCA graft.

T1MI, Type 1 myocardial infarction; T2MI, type 2 myocardial infarction; CTCA, CT coronary angiography; ICA, invasive coronary angiography; CAD, coronary artery disease; LAD, left anterior descending; RCA, right coronary artery; LCx, left circumflex; ECG, electrocardiogram; CTPA, CT pulmonary angiography; LMCA, left main coronary artery; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; UAP=unstable angina pectoris.

[a] Underlined values are elevated values according to assay in clinical use

[b] Additional troponin values and other clinical information was used in the adjudication process

Supplementary Table 3. Results by sex

Final risk stratification **Females (n=808[a])**	**LOW Risk** **566 patients (70.0%)** 0 (0%) with index AMI 0 (0%) with 30-day MACE **Index AMI** Sensitivity: 100% (89.4-100%) Specificity 73.0% (69.8-76.1%) NPV: 100% (99.4-100%) PPV: 13.6% (9.6-18.6%) **30-day MACE** Sensitivity: 100% (89.7-100%) Specificity 73.1% (69.9-76.2%) NPV: 100% (99.4-100%) PPV: 14% (9.9-19.1%)	**INTERMEDIATE Risk** **139 patients (17.2%)** Prevalence of index AMI - 3 patients (2.2%) Prevalence of 30-day MACE – 3 patients (2.2%)	**HIGH risk** **103 patients (12.7%)** 30 (29.1%) with index AMI 31 (30.1%) with 30-day MACE **Index AMI** Sensitivity: 90.9% (75.7-98.1%) Specificity 90.6% (88.3-92.5%) NPV: 99.6% (98.8-99.9%) PPV: 29.1% (20.6-38.9%) **30-day MACE** Sensitivity: 91.2% (76.3-98.1%) Specificity 90.7% (88.4-92.7%) NPV: 99.6% (98.8-99.9%) PPV: 30.1% (21.5-39.9%)
Final risk stratification **Males (n=955[b])**	**LOW Risk** **514 patients (53.8%)** 1 (0.2%) with index AMI 5 (1.0%) with 30-day MACE **Index AMI** Sensitivity: 98.8% (93.3-100%) Specificity 58.7% (55.3-62.0%) NPV: 99.8% (98.9-100%) PPV: 18.1% (14.7 22.1%) **30-day MACE** Sensitivity: 94.5% (87.6-98.2%) Specificity 58.9% (55.5-62.2%) NPV: 99.0% (97.7-99.7%) PPV: 19.5% (15.9-23.5%)	**INTERMEDIATE Risk** **292 patients (30.6%)** Prevalence of index AMI - 4 patients (1.4%) Prevalence of 30-day MACE – 6 patients (2.1%)	**HIGH risk** **149 patients (15.6%)** 76 (51.0%) with index AMI 80 (53.7%) with 30-day MACE **Index AMI** Sensitivity: 93.8% (86.2-98.0%) Specificity 91.6% (89.6-93.4%) NPV: 99.4% (98.6-99.8%) PPV: 51.0% (42.7-59.3%) **30-day MACE** Sensitivity: 87.9% (79.4-93.8%) Specificity 92.0% (90.0-93.7%) NPV: 98.6% (97.6-99.3%) PPV: 53.7% (45.3-61.9%)

AMI, acute myocardial infarction; MACE, major adverse cardiac events

[a]There were missing samples for 87 females, including two (2.3%) with index AMI and two (2.3%) with 30-day MACE (2.3%).
[b]There were missing samples for 144 males, two (1.4%) with index AMI and two (1.4%) with 30-day MACE.

Supplementary Table 4. Results by age

Final risk stratification **<65 years (n=1257[a])**	**LOW Risk** **893 patients (71.0%)** 1 (0.1%) with index AMI 3 (0.3%) with 30-day MACE **Index AMI** Sensitivity: 98.1% (89.7-100%) Specificity 74.0% (71.5-76.6%) NPV: 99.9% (99.4-100%) PPV: 14.0% (10.6-18.0%) **30-day MACE** Sensitivity: 94.9% (85.9-98.9%) Specificity 74.3% (71.7-76.7%) NPV: 99.7% (99.0-99.9%) PPV: 15.4% (11.8-19.5%)	**INTERMEDIATE Risk** **240 patients (19.1%)** Prevalence of index AMI - 2 patients (0.8%) Prevalence of 30-day MACE – 4 patients (1.7%)	**HIGH risk** **124 patients (9.9%)** 49 (39.5%) with index AMI 52 (41.9%) with 30-day MACE **Index AMI** Sensitivity: 94.2% (84.1-98.8%) Specificity 93.8% (92.3-95.1%) NPV: 99.7% (99.2-99.9%) PPV: 39.5% (30.9-48.7%) **30-day MACE** Sensitivity: 88.1% (77.1-95.1%) Specificity 94.0% (92.5-95.3%) NPV: 99.4% (98.7-99.8%) PPV: 41.9% (33.1-51.1%)
Final risk stratification **Sex ≥65 (n=506[b])**	**LOW Risk** **187 patients (37.0%)** 0 (0%) with index AMI 2 (1.1%) with 30-day MACE **Index AMI** Sensitivity: 100% (94.2-100%) Specificity 42.1% (37.5-46.9%) NPV: 100% (98.0-100%) PPV: 19.4% (15.2 -24.2%) **30-day MACE** Sensitivity: 97.0% (89.5-99.6%) Specificity 42.0% (37.4-46.8%) NPV: 98.9% (96.2-99.9%) PPV: 20.1% (15.8 -24.9%)	**INTERMEDIATE Risk** **191 patients (37.7%)** Prevalence of Index AMI - 5 patients (2.6%) Prevalence of 30-day MACE – 5 patients (2.6%)	**HIGH risk** **128 patients (25.3%)** 57 (44.5%) with index AMI 59 (46.1%) with 30-day MACE **Index AMI** Sensitivity: 91.9% (82.2-97.3%) Specificity 84.0% (80.3-87.3%) NPV: 98.7% (96.9-99.6%) PPV: 44.5% (35.7-53.6%) **30-day MACE** Sensitivity: 89.4% (79.4-95.6%) Specificity 84.3% (80.6-87.6%) NPV: 98.1% (96.2-99.3%) PPV: 46.1% (37.2-55.1%)

AMI, acute myocardial infarction; MACE, major adverse cardiac events.

[a]There were missing second samples for 143 patients <65 years, including two (1.4%) with index AMI and two (1.4%) with 30-day MACE.
[b]There were missing second samples for 88 patients≥65: 88 patients, including two (2.3%) with index AMI and two (2.3%) with 30-day MACE.

Supplementary Table 5: Clinical outcomes for patients with discordant elevated results from the investigational assay and normal values using the clinical assay[a].

0- and 2-hour Atellica IM values (ng/L)	0- and 2-hour Institutional values[b] (ng/L)	Adjudicated diagnosis[c]
40 and 35	4 and 3	Probably non-cardiac pain despite recent NSTEMI in July
65 and 64	8 and 7	Musculoskeletal pain
60 and 61	15 and 15	Post infarct angina (NSTEMI 4/52 earlier)
47 and 44	6 and 5	Non-cardiac pain
44 and 43	6 and 7	Angina
105 and 97	6 and 5	Musculoskeletal pain
37 and 36	9 and 8	Non-cardiac pain
280 and 261	11 and 9	Non-cardiac pain
55 and 61	3 and 4	Non-cardiac pain with an Incidental finding of mesenteric atherosclerosis
69 and 63	5 and 5	Dyspepsia
53	2	Non-cardiac
125	8	Other cardiac Atrial flutter (atypical). Stable CAD
90	9	Non-cardiac. Syncope (probably not cardiogenic). Hypertension
38	4 and 4	Non-cardiac pain. Frequent ventricular ectopy
66	9	Other cardiac. Atrial fibrillation
50	4 and 4	Non-cardiac pain
4 and 72	4	Non cardiac pain

NSTEMI, non-ST segment myocardial infarction; CAD, coronary artery disease

[a] The institutional assay: Beckman Coulter hs-cTnI

[b] This table only includes patients who had either 1) serial troponin results available on the Atellica and institutional assay (n=10), 2) an elevated Atellica on presentation, normal investigational assay on presentation and no serial Atellica performed (n=6), or serial Atellica results with no serial investigational assay (n=1)

[c] No patient had a diagnosis of myocardial injury or AMI as the institutional assay was used for adjudication of results.