

Machine learning to risk stratify chest pain patients with non-diagnostic electrocardiogram in an Asian emergency department

Ziwei Lin¹ MMed Emergency Medicine (Singapore), Tar Choon Aw² MMed Internal Medicine, Laurel Jackson³ MS, Cheryl Shumin Kow⁴ MBBS (Singapore), Gillian Murtagh³ MD, Siang Jin Terrance Chua⁵ FACC (USA), Arthur Mark Richards^{6,7} MBChB, Swee Han Lim⁸ FRCSEd (A&E)

ABSTRACT

Introduction: Elevated troponin, while essential for diagnosing myocardial infarction, can also be present in non-myocardial infarction conditions. The myocardial-ischaemic-injury-index (MI³) algorithm is a machine learning algorithm that considers age, sex and cardiac troponin I (TnI) results to risk-stratify patients for type 1 myocardial infarction.

Method: Patients aged ≥25 years who presented to the emergency department (ED) of Singapore General Hospital with symptoms suggestive of acute coronary syndrome with no diagnostic 12-lead electrocardiogram (ECG) changes were included. Participants had serial ECGs and high-sensitivity troponin assays performed at 0, 2 and 7 hours. The primary outcome was the adjudicated diagnosis of type 1 myocardial infarction at 30 days. We compared the performance of MI³ in predicting the primary outcome with the European Society of Cardiology (ESC) 0/2-hour algorithm as well as the 99th percentile upper reference limit (URL) for TnI.

Results: There were 1351 patients included (66.7% male, mean age 56 years), 902 (66.8%) of whom had only 0-hour troponin results and 449 (33.2%) with serial (both 0 and 2-hour) troponin results available. MI³ ruled out type 1 myocardial infarction with a higher sensitivity (98.9, 95% confidence interval [CI] 93.4–99.9%) and similar negative predictive value (NPV) 99.8% (95% CI 98.6–100%) as compared to the ESC strategy. The 99th percentile cut-off strategy had the lowest sensitivity, specificity, positive predictive value and NPV.

Conclusion: The MI³ algorithm was accurate in risk stratifying ED patients for myocardial infarction. The 99th percentile URL cut-off was the least accurate in ruling in and out myocardial infarction compared to the other strategies.

Ann Acad Med Singap 2025;54:219-26

Keywords: cardiology, emergency medicine, machine learning, myocardial infarction, troponin behaviour

CLINICAL IMPACT

What is New

- This study evaluates the performance of the myocardial-ischaemic-injury-index (MI³) algorithm, a machine learning algorithm, in risk stratifying chest pain patients in the emergency department for 30-day myocardial infarction, as compared to established risk stratification strategies.

Clinical Implications

- This study shows that MI³ is accurate in ruling in and out 30-day myocardial infarction as compared to existing strategies.
- Using the 99th percentile upper reference limit cut-off for troponin I for risk stratification is less accurate compared to other strategies.

INTRODUCTION

Risk stratification of patients presenting with chest pain poses a frequent, often difficult, challenge to the emergency physician. Cardiac biomarkers such as troponin are an important part of the evaluation of the patient suspected of having acute coronary syndrome (ACS). Serial readings are traditionally needed for troponin, given that the rise in troponin levels in older assays may not be apparent until

The Annals is an open access journal, allowing non-commercial use under CC BY-NC-SA 4.0.

¹ Department of Emergency Medicine, Sengkang General Hospital, Singapore

² Department of Laboratory Medicine, Changi General Hospital, Singapore

³ Core Diagnostics, Abbott Laboratories, Lake Forest, Illinois, US

⁴ Department of General Surgery, Singapore General Hospital, Singapore

⁵ Department of Cardiology, National Heart Centre Singapore, Singapore

⁶ Christchurch Heart Institute, Department of Medicine, University of Otago, Christchurch, New Zealand

⁷ Cardiovascular Research Institute, National University of Singapore, Singapore

⁸ Department of Emergency Medicine, Singapore General Hospital, Singapore

Correspondence: Professor Lim Swee Han, Department of Emergency Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

Email: lim.swee.han@singhealth.com.sg

Accepted: 4 December 2024

Published Online First: 17 April 2025

Published: 22 April 2025

hours after a cardiac event has commenced.¹ However, diagnostic protocols incorporating late generation, highly sensitive assays for cardiac troponin have decreased the time between serial troponin to a mere 1–2 hours.² A faster turnaround time of such patients without compromising patient safety and outcomes is welcomed, especially given the perennial problem of access block and overcrowding in the emergency department (ED). The European Society of Cardiology (ESC) currently recommends clinical pathways incorporating 0–2 or even 0–1 hour troponin results using high-sensitivity assays.³ The American Heart Association (AHA) also recommends the use of high-sensitivity troponin as the preferred biomarker for evaluating patients with chest pain, as well as the use of chest pain protocols incorporating troponin to guide disposition.⁴

Elevated circulating troponin, while a key part of the criteria for the diagnosis of myocardial infarction, is not specific for ACS and can also be seen in non-coronary cardiac injury and in circumstances such as renal disease. Hence, troponin results must be interpreted in clinical context. Clinical scores have been developed, to risk stratify patients for adverse events such as myocardial infarction or mortality, which incorporate age, cardiovascular risk factors and presentation history together with cardiac biomarker results. The accuracy of such risk scores may differ between populations. As myocardial infarction is a high-stakes diagnosis, a very high sensitivity and negative predictive value (NPV) are required for a risk score to be considered useful, as the consequences of misdiagnosis include increased patient morbidity and mortality. Pathways, which make use of troponin to rapidly diagnose myocardial infarction, should ideally have a positive predictive value (PPV) of more than 70%.^{5–7} The PPV of high-sensitivity troponin T in ruling in 30-day and 1-year major adverse cardiac events has been noted to plateau at about 70–80% with increasing troponin T cut-off values,⁸ similar to a plateau of more than 70% with increasing high-sensitivity troponin I (TnI) cut-offs for the diagnosis of myocardial infarction.⁹

In recent years, machine learning has been gaining recognition as a potential tool in healthcare to increase diagnostic accuracy. Organisations such as the ESC and AHA recognise the potential utility of machine learning and artificial intelligence in the evaluation of patients presenting with chest pain,¹⁰ which may allow an individualised approach to be taken in risk-stratifying patients for myocardial infarction.¹¹ The myocardial-ischaemic-injury-index (MI³) algorithm is a machine learning algorithm developed using gradient boosting that

integrates age, sex and cardiac TnI results (and the rate of change where serial results are available) to risk stratify patients for the outcome of type 1 myocardial infarction.¹² This algorithm has been shown to identify patients at low risk for index myocardial infarction, and has high sensitivity (97.8%) and NPV (99.7%)¹² with independent validation in European settings.^{13–15} The MI³ algorithm was chosen in our study as it has already been externally validated in other cohorts, and for its ease of use from a clinical standpoint as it only requires 3 objective variables which can be easily collected. Our study aims to evaluate the diagnostic accuracy of the MI³ algorithm for myocardial infarction within 30 days in an Asian population, and to compare its accuracy to existing standards of care such as the ESC 0/2-hour pathway³ and the 99th percentile upper reference limit (URL) for TnI.¹⁶

METHOD

Participants were recruited from March 2010 to April 2013 as part of a prospective observational study, which included patients aged 25 years and above who presented to the ED of Singapore General Hospital, a tertiary hospital in Singapore, with symptoms suggestive of ACS. The inclusion criteria included provision of informed written consent, and presenting symptoms consistent with suspected ACS. Patients who had an ED diagnosis of ST-elevation myocardial infarction (STEMI), a history of end-stage renal failure, those without cardiac troponin results and those lost to follow-up were excluded.

At the time of study, as part of standard care, patients with chest pain or symptoms suggestive of ACS but with no diagnostic ECG changes underwent continuous cardiac monitoring and a standard 8-hour observation protocol in the emergency cardiac care unit of our ED. Serial 12-lead ECGs and serum cardiac troponin were obtained at 0, 2 and 7 hours. At the time of study, a high-sensitive serum troponin T assay (Elecsys Troponin T high sensitive, Roche Diagnostics, Basel, Switzerland) was used at the study institution as part of clinical care. Additional serum drawn for the study and frozen at -80 °C, was used in a high-sensitivity TnI assay (ARCHITECT STAT high-sensitivity TnI, Abbott Diagnostics, Chicago, IL, US) to generate results used in the MI³ analysis. Only the results from the samples obtained at 0 and 2 hours were used in the MI³ analysis. The 99th percentile for serum TnI for the ARCHITECT STAT assay was 17 ng/L for females and 35 ng/L for males.¹⁷

A standardised dataset on each participant was acquired. This included demographic variables, such as age and past medical history, current medications, presenting signs and symptoms, test results, all interventions and outcomes. Patients were followed up for a year via telephone and/or through assessing medical records.

The primary outcome for this analysis was myocardial infarction as defined by the third universal definition of myocardial infarction¹⁸ at 30 days. Outcomes were independently adjudicated by an emergency medicine attending physician and an attending cardiologist based on the case records, which included investigation results and data on troponin collected during the index visit and up to 1 year of follow-up. The TnI results used in the MI³ analysis were not available to adjudicators as it was not done as part of the patient's clinical visit. Where inter-reviewer differences with respect to adjudicated outcomes occurred, discussion was held between the 2 reviewers to reach consensus.

We compared the use of MI³ with (1) the ESC 0/2-hour algorithm and (2) using 99th percentile of TnI to see how they fared in predicting a diagnosis of myocardial infarction within 30 days.

The MI³ algorithm was evaluated both in patients with baseline samples only and in those with serial samples available. For serial samples, the algorithm developed originally by Than et al. was applied. Thresholds for serial scores were set to <1.6 ng/L for low risk, 1.6 to <49.7 ng/L for intermediate risk, and ≥49.7 ng/L for high risk, in line with prior reports on the use of MI³.^{12,13} As described in Than et al., 1.6 ng/L was the derived threshold for rule-out corresponding to sensitivity ≥99%, and 49.7 ng/L was the derived threshold for rule-in corresponding to PPV ≥75% in the development cohort. In the present analysis, the algorithm was further adapted to allow for prediction based on a single troponin value. For patients with baseline samples only, no data indicative of rate of change (delta) in circulating troponin were available. Thresholds for rule-in and rule-out were derived for the baseline score using a similar approach as that of the serial MI³ index score, with a threshold of <0.91 ng/L corresponding to low risk and ≥30.1 ng/L corresponding to high risk. Thus, a more conservative threshold for rule-out was used when only a single sample was available.

For the ESC 0/2-hour pathway, the cut-off for the low-risk group was defined as a baseline troponin result of <4, or baseline result of <6 with a delta change of <2.³ The high-risk group was defined as a baseline result of ≥64 or delta change of ≥15. When only a baseline sample was available, the delta change could not be evaluated, so only

the baseline result criteria were applied (baseline troponin <4 for rule-out and baseline result ≥64 for rule-in).

Statistical analysis

For MI³, which gives a quantitative score for risk of myocardial infarction, model performance was assessed by evaluating the area under the receiver-operating-characteristic curve (AUC). Confidence intervals (CIs) for AUC were calculated using the DeLong method. For both MI³ and ESC which provide risk categories, sensitivity and NPV were calculated for the low-risk group while specificity and PPV were calculated for the high-risk group. Predictive values were calculated using study prevalence. CIs for sensitivity, specificity and predictive values were calculated using the Wilson method. All statistical analyses were carried out using R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were described as proportions and continuous variables as mean with standard deviation (SD) or median with interquartile range as appropriate.

RESULTS

Our analysis included data from 1351 patients, 901 (66.7%) of whom were male, with a mean age of 55.8 years (SD 12.3). There were 902 patients (66.8%) with only baseline (0 hour) troponin available and 449 (33.2%) with serial (both 0 and 2 hour) troponin results available. In the full cohort, 7.0% (n=94) had the primary outcome of 30-day myocardial infarction. Among those with serial troponin results available, 4.5% (n=20) had 30-day myocardial infarction. Table 1 describes the characteristics of our study cohort. Table 2 compares the 3 risk stratification strategies (MI³, ESC 0/2-hour pathway and TnI 99th percentile as cut-offs). When serial troponin results were present, MI³ was able to identify a higher proportion of low-risk patients with comparable sensitivity and NPV to the ESC pathways. The 99th percentile strategy had the lowest sensitivity, specificity, NPV and PPV.

MI³ in predicting the likelihood of myocardial infarction

Overall, the MI³ algorithm had an AUC of 0.936 (95% CI 0.906–0.966). MI³ was able to rule out myocardial infarction in the low-risk group with a sensitivity of 98.9% (95% CI 93.4–99.9%) and NPV of 99.8% (95% CI 98.6–100%), with only 1 of 448 (0.2%) participants in the low-risk group diagnosed with myocardial infarction. MI³ also performed well in ruling in myocardial infarction in the high-risk group (48 of 64, 75%) with a specificity of 98.7% (95% CI 97.9–99.2%) and a PPV of 75.0% (95% CI 62.3–84.6%).

Table 1. Baseline characteristics.

	Baseline only (n=902)	Serial sampling available (n=449)	Overall (n=1351)
Sex, no. (%)			
Female	295 (32.7)	155 (34.5)	450 (33.3)
Male	607 (67.3)	294 (65.5)	901 (66.7)
Race, no. (%)			
Chinese	570 (63.2)	273 (60.8)	843 (62.4)
Indian	166 (18.4)	96 (21.4)	262 (19.4)
Malay	120 (13.3)	60 (13.4)	180 (13.3)
Others	46 (5.1)	20 (4.5)	66 (4.9)
Hypertension, no. (%)	473 (52.4)	239 (53.2)	712 (52.7)
Diabetes, no. (%)	276 (30.6)	124 (27.6)	400 (29.6)
Ever smoker, no. (%)	258 (28.6)	120 (26.7)	378 (28.0)
History of myocardial infarction, no. (%)	106 (11.8)	43 (9.6)	149 (11.0)
Previous coronary artery bypass graft surgery, no. (%)	79 (8.8)	22 (4.9)	101 (7.5)
Previous coronary angioplasty, no. (%)	143 (15.9)	64 (14.3)	207 (15.3)
History of stroke or transient ischaemic attack, no. (%)	35 (3.9)	11 (2.4)	46 (3.4)

When considering only baseline troponin (n=1351), the MI³ algorithm had an AUC of 0.933 (95% CI 0.902–0.964). In this population, MI³ was able to rule out myocardial infarction with a sensitivity of 100% (95% CI 95.1–100%) and NPV of 100% (95% CI 96.0–100%). The baseline-only algorithm uses lower cut-offs for rule-out, resulting in a trade-off of a lower proportion being identified as low risk as compared to the overall cohort (115 of 1351 [8.5%] as compared to 448 of 1351 [33.2%] in the overall cohort). MI³ identified 57 patients (4.2%) as high risk in this cohort, with a specificity of 98.9% (95% CI 98.1–99.4%) and PPV of 75.4% (95% CI 62.0–85.5%).

For those with serial troponin (n=449), the MI³ algorithm had an AUC of 0.943 (95% CI 0.858–1.000). In this population, MI³ was able to identify a larger proportion of low-risk patients (n=367, 81.7%) with a sensitivity of 95.0% (95% CI 73.1–99.9%) and NPV of 99.7% (95% CI 98.2–100%). The proportion of identified high-risk patients (3.8%) was similar to the baseline troponin and overall cohort, with a specificity of 99.1% (95% CI 97.5–99.7%) and PPV of 76.5% (95% CI 49.8–92.2%).

Comparison with ESC 0/2-hour pathway

With the full cohort, the ESC 0/2-hour pathway identified 61.7% (n=833) as low-risk with a sensitivity of 94.7% (95% CI 87.5–98.0%) and NPV of 99.4% (95% CI 98.5–99.8%), and 8.3% (n=112) as high-risk with a specificity of 96.3% (95% CI 95.1–97.3%) and PPV of 58.9% (95% CI 49.2–68.0%). Comparatively, for those with serial troponin results (n=449), the pathway identified a higher proportion of those in the low-risk group (n=334, 74.4%) with a similar sensitivity (95.0%, 95% CI 73.1–99.7%) and NPV (99.7%, 95% CI 98.1–100.0%) as compared to the full cohort. The pathway identified 6.2% (n=28) as high risk in this cohort with serial troponin results with a specificity of 87.4% (95% CI 95.3–98.6%) and PPV of 60.7% (95% CI 40.7–77.9%).

When considering only baseline results with the ESC pathway (n=1351), 58.1% (n=785) were identified as low risk with a sensitivity of 95.7% (95% CI 88.8–98.6%) and NPV of 99.5% (98.6–99.8%). Thus, while the sensitivity and NPV of the ESC pathway with only baseline troponin was similar to that of those with serial troponin results,

Table 2. Accuracy of risk stratification strategies for 30-day acute myocardial infarction.

Risk stratification strategy	Area under the curve	Proportion stratified to low risk	Proportion stratified to intermediate risk	Proportion stratified to high risk	Sensitivity (95% CI)	Negative predictive value (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)
ESC 0/2-hour algorithm for full cohort (n=1351)	0.955 (0.913–0.977)	61.7%	30.1%	8.3%	94.7% (87.5–98.0%)	99.4% (98.5–99.8%)	96.3% (95.1–97.3%)	58.9% (49.2–68.0%)
ESC 0/2-hour algorithm for baseline troponin (n=1351)	0.962 (0.921–0.981)	58.1%	34.3%	7.6%	95.7% (88.8–98.6%)	99.5% (98.6–99.8%)	96.6% (95.4–97.5%)	58.3% (48.1–67.8%)
ESC 0/2-hour algorithm for serial troponin (n=449)	0.962 (842–0.992)	74.4%	19.4%	6.2%	95.0% (73.1–99.7%)	99.7% (98.1–100%)	97.4% (95.3–98.6%)	60.7% (40.7–77.9%)
MI ³ for full cohort (n=1351)	0.936 (0.906–0.966)	33.2%	62.1%	4.7%	98.9 (93.4–99.9%)	99.8% (98.6–100%)	98.7% (97.9–99.2%)	75.0% (62.0–84.6%)
MI ³ for baseline troponin (n=1351)	0.933 (0.902–0.964)	8.5%	87.3%	4.2%	100% (95.1–100%)	100% (96.0–100%)	98.9% (98.1–99.4%)	75.4% (62.0–85.5%)
MI ³ for serial troponin (n=449)	0.943 (0.858–1.00)	81.7%	14.5%	3.8%	95.0% (73.1–99.7%)	99.7% (98.2–100%)	99.1% (97.5–99.7%)	76.5% (49.8–92.2%)
Abbott ARCHITECT STAT troponin I 99th percentile cut-off (n=1351)	0.845 (0.786–0.892)	88.6%	Not applicable	11.4%	75.5% (65.4–83.6%)	98.1% (97.1–98.7%)	93.4% (91.8–94.7%)	46.1% (38.1–54.3%)

CI: confidence interval; ESC: European Society of Cardiology; MI³: myocardial-ischaemic-injury-index

the proportion of identified low-risk patients was less in those with only baseline troponin. A total of 103 patients (7.6%) were identified as high risk with a specificity of 96.6% (95.4–97.5%) and PPV of 58.3% (95% CI 48.1–67.8%).

Comparison with 99th percentile for serum troponin

Using the sex-specific 99th percentile for baseline troponin as a cut-off, 1197 (88.6%) were identified as low risk with a sensitivity of 75.5% (95% CI 65.4–83.6%) and NPV of 98.1% (95% CI 97.1–98.7%). Using the cut-off as a rule-in, 154 (11.4%) were identified as high risk with a specificity of 93.4% (95% CI 91.8–94.7%) and PPV of 46.1% (38.1–54.3%).

DISCUSSION

Machine learning has gained traction in recent years and has been studied in medicine as a potential tool in clinical medicine for the diagnosis of critical conditions such as myocardial infarction^{19,20} and in predicting myocardial infarction-related mortality.²¹ MI³ could accurately risk stratify patients for myocardial infarction^{12,22} and has been validated in other populations.^{13,14} Our study further demonstrates MI³'s accuracy in predicting the risk of myocardial infarction in an Asian cohort, showing its consistent performance in different populations. While several risk scores for chest pain have been validated and used in clinical practice, some scores use components that are subjective. For example, the history component in the HEART score²³ requires clinicians to score the patient's history as either slightly, moderately or highly suspicious, which introduces subjectivity as different clinicians may have varying thresholds in interpreting the patients' presenting history. Other scores may also have numerous components, which may make it difficult to use in day-to-day practice. MI³ only uses age, sex and troponin results, making it an objective and practical strategy as it only requires 3 variables and does not require any subjective interpretation. Moreover, rather than classifying patients into discrete risk categories, MI³ provides an objective assessment of the patient's probability of myocardial infarction on a scale of 0 to 100, which allows flexibility for different cut-offs to be established according to the setting for which it is being adapted.

In comparison to established risk stratification strategies, such as the ESC 0/2-hour pathway, MI³ was able to identify a larger proportion of patients at low risk for type 1 myocardial infarction within 30 days with higher sensitivity and similar NPV, making it an accurate tool in identifying which patients can be discharged from the ED. Chest pain is a common presentation in the ED and constitutes about 5% of all ED visits.²⁴ The MI³

algorithm allows for patients to be assessed expediently, stratifying their risk within 1–2 hours of presentation, potentially increasing ED throughput and decreasing ED overcrowding. ED overcrowding is associated with negative effects such as increased risk of adverse outcomes, rate of medical errors and hospital-acquired infections.²⁵ Ruling out a larger proportion of low-risk individuals among those who present with chest pain may also potentially reduce healthcare costs, as these patients can be discharged directly from the ED, avoiding unnecessary admissions. In Singapore, the personnel cost for admissions for chest pain unrelated to a coronary event was estimated to be SGD416 per case of chest pain,²⁶ while the median hospital bill for the diagnosis code of chest pain ranged from SGD484 to SGD4677 in public hospitals and SGD5673 to SGD10,496 in private hospitals.²⁷ Reducing the number of admissions for chest pain for those at low risk may lead to cost savings for both the patient and the healthcare system. Future economic evaluations can be done to determine the extent of cost savings.

In the original study, MI³ was able to rule out 69.4% of the cohort as low risk of 30-day myocardial infarction with a sensitivity of 96.6% (95% CI 95.3–97.8%) and an NPV of 99.5% (95% CI 99.3–99.7%).¹² In our cohort, the sensitivity of MI³ for those with serial troponin results for 30-day myocardial infarction was slightly lower at 95.0% (95% CI 73.1–99.7%). This may be due to differences in prevalences of comorbidities in our population, for example, the higher prevalence of diabetes mellitus in our cohort (29.6%) compared to the original study's cohort (14.6% in training set, 18.7% in testing set).¹² Our cohort also had a lower proportion of those with previous myocardial infarction (11.0%) compared to the original study (21.1% in training set, 20.0% in testing set).¹² Moreover, while MI³ was derived from an international cohort, the training and testing cohorts were noted to be from Europe, New Zealand, Australia and the US.¹² It is likely that Asians may still be underrepresented as compared to our predominantly Asian cohort, and it remains unclear to which extent ethnicity may affect baseline troponin results.^{28,29}

The original MI³ requires 2 troponin readings—a baseline reading and one at 2 hours after the first sample is taken. However, in clinical practice, there may be instances where only a single troponin is used, such as when the patient presents long after the onset of symptoms. In our study cohort, MI³ was shown to have high sensitivity (100%, 95% CI 95.1–100%) and NPV (100%, 95% CI 96.0–100%) when considering only baseline troponin, but the proportion of those considered low risk was much smaller than when serial troponins were available

(8.5% versus 81.7%). Further studies may be required to see how MI³ can be modified to increase its utility with single troponin readings.

Before the advent of high-sensitivity troponin, the 99th percentile URL was commonly used as the cut-off for conventional troponin. However, with high-sensitivity assays, the interpretation of troponin has changed, and international guidelines now recommend the interpretation of high-sensitivity troponin according to the time of draw (whether baseline or serial readings taken 1–2 hours later) and consider the delta change.³ The 99th percentile URL has been used as a cut-off in clinical practice,^{16,30} but our findings reinforce the concept that this is less accurate for risk stratification of myocardial infarction regardless of whether it is used as a rule-in or rule-out strategy. Institutions should thus reconsider the use of the 99th percentile URL as a cut-off for risk stratifying patients with chest pain in clinical practice.

Limitations

The use of a machine learning algorithm may enhance clinical decision-making. It should not be used indiscriminately and requires interpretation of the algorithm-generated risk stratification in the full clinical context. In that sense, machine learning is not a panacea for all diagnostic dilemmas. Physicians will still need to rule out other dangerous causes of chest pain, such as pulmonary embolism and aortic dissection, before applying the MI³ algorithm to patients to risk stratify those with possible cardiac chest pain.

MI³ has also only been validated for use with high-sensitivity TnI. Not all centres use high-sensitivity TnI, some may use troponin T and others may not have access to high-sensitivity assays, which will limit the utility of MI³. In facilities which do not have access to laboratory testing with fast turnaround times, such as in primary care settings, MI³ may not be as beneficial. With the emergence of point-of-care troponin testing,³¹ this may eventually be overcome if MI³ is validated for these tests.

The MI³ algorithm also requires a baseline and serial reading. Clinicians may not always deem serial troponin readings to be necessary if the patient presents much later than symptom onset. As MI³ currently requires 2 sets of troponin results, it may not be useful in this group of patients.

CONCLUSION

The MI³ algorithm has shown to be accurate in risk stratifying ED patients for myocardial infarction when compared to current standard of care algorithms, such as the ESC 0/2-hour algorithm.

The 99th percentile reference range was shown to be less accurate in ruling in and out myocardial infarction as compared to MI³ and the ESC 0/2-hour algorithm.

Ethics statement

This study was approved by the SingHealth Centralised Institutional Review Board (2017/2130).

Declaration

This study was supported by Abbott Laboratories' research grant for the retrieval of frozen serum and analysis of high-sensitivity troponin I. Abbott Laboratories also provided support with statistical analysis. Ms Laurel Jackson and Dr Gillian Murtagh are full-time employees and shareholders of Abbott Laboratories. Prof Arthur Mark Richards has received support in kind for troponin assays included in his research programme from both Roche Diagnostics and Abbott Laboratories. He has also received advisory board fees and research grants from Roche Diagnostics.

REFERENCES

1. Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2011;32:2999-3054.
2. Sandoval Y, Apple FS, Mahler SA, et al. High-Sensitivity Cardiac Troponin and the 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guidelines for the Evaluation and Diagnosis of Acute Chest Pain. *Circulation* 2022;146:569-81.
3. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;42:1289-367.
4. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;144:e368-454.
5. Boeddinghaus J, Twerenbold R, Nestelberger T, et al. Clinical Validation of a Novel High-Sensitivity Cardiac Troponin I Assay for Early Diagnosis of Acute Myocardial Infarction. *Clin Chem* 2018;64:1347-60.
6. Twerenbold R, Neumann JT, Sorensen NA, et al. Prospective Validation of the 0/1-h Algorithm for Early Diagnosis of Myocardial Infarction. *J Am Coll Cardiol* 2018;72:620-32.
7. Twerenbold R, Badertscher P, Boeddinghaus J, et al. 0/1-Hour Triage Algorithm for Myocardial Infarction in Patients With Renal Dysfunction. *Circulation* 2018;137:436-51.
8. Lin Z, Lim SH, Yap QV, et al. Comparing conventional and high sensitivity troponin T measurements in identifying adverse cardiac events in patients admitted to an Asian emergency department chest pain observation unit. *Int J Cardiol Heart Vasc* 2021;34:100758.
9. Sandoval Y, Nowak R, deFilippi CR, et al. Myocardial Infarction Risk Stratification With a Single Measurement of High-Sensitivity Troponin I. *J Am Coll Cardiol* 2019;74:271-82.

10. American Heart Association. Artificial intelligence may speed heart attack diagnosis and treatment 2023. <https://newsroom.heart.org/news/artificial-intelligence-may-speed-heart-attack-diagnosis-and-treatment>. Accessed 1 November 2024.
11. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. *Eur Heart J* 2023;44:3720-826.
12. Than MP, Pickering JW, Sandoval Y, et al. Machine Learning to Predict the Likelihood of Acute Myocardial Infarction. *Circulation* 2019;140:899-909.
13. Doudesis D, Lee KK, Yang J, et al. Validation of the myocardial-ischaemic-injury-index machine learning algorithm to guide the diagnosis of myocardial infarction in a heterogenous population: a prespecified exploratory analysis. *Lancet Digit Health* 2022;4:e300-8.
14. Lopez Ayala P, Boeddinghaus J, Nestelberger T, et al. External validation of the myocardial-ischemic-injury-index: a machine learning algorithm for the early diagnosis of myocardial infarction. *Eur Heart J* 2023;44(Supplement_2):ehad655.145.
15. Lopez-Ayala P, Boeddinghaus J, Nestelberger T, et al. External validation of the myocardial-ischaemic-injury-index machine learning algorithm for the early diagnosis of myocardial infarction: a multicentre cohort study. *Lancet Digit Health* 2024;6:e480-8.
16. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *Circulation* 2018;138:e618-51.
17. Abbott Diagnostics. ARCHITECT STAT High Sensitive Troponin-I H03755/R01. <https://www.corelaboratory.abbott/us/en/offerings/segments/cardiac/troponin.html>. Accessed 17 August 2023.
18. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Glob Heart* 2012;7:275-95.
19. Al-Zaiti SS, Martin-Gill C, Zegre-Hemsey JK, et al. Machine learning for ECG diagnosis and risk stratification of occlusion myocardial infarction. *Nat Med* 2023;29:1804-13.
20. Doudesis D, Lee KK, Boeddinghaus J, et al. Machine learning for diagnosis of myocardial infarction using cardiac troponin concentrations. *Nat Med* 2023;29:1201-10.
21. Oliveira M, Seringa J, Pinto FJ, et al. Machine learning prediction of mortality in Acute Myocardial Infarction. *BMC Med Inform Decis Mak* 2023;23:70.
22. McCord J, Gibbs J, Hudson M, et al. Machine Learning to Assess for Acute Myocardial Infarction Within 30 Minutes. *Crit Pathw Cardiol* 2022;21:67-72.
23. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the HEART score. *Neth Heart J*. 2008;16:191-6.
24. National Center for Health Statistics. National Hospital Ambulatory Medical Care Survey: 2021 Emergency Department Summary Tables. Updated 11 October 2023. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2021-nhamcs-ed-web-tables-508.pdf. Accessed 4 November 2024.
25. Sartini M, Carbone A, Demartini A, et al. Overcrowding in Emergency Department: Causes, Consequences, and Solutions-A Narrative Review. *Healthcare (Basel)*. 2022;10:1625.
26. Goh OQM, Xin X, Lim WT, et al. Economic Evaluation of Novel Models of Care for Patients With Acute Medical Problems. *JAMA Netw Open* 2023;6:e2334936.
27. Ministry of Health, Singapore. F74Z - Chest Pain 2024. Updated 4 November 2024. <https://www.moh.gov.sg/managing-expenses/bills-and-fee-benchmarks/cost-financing/drg-f74z-bill-information>. Accessed 4 November 2024.
28. Lee DJW, Aw T-C. Population differences and high-sensitivity troponin values: a narrative review. *J Lab Precis Med* 2023;8.
29. Kalaria TR, Harris N, Sensi H, et al. High-sensitivity cardiac troponin I: is ethnicity relevant? *J Clin Pathol* 2021;74:709-11.
30. Neumann JT, Sorensen NA, Schwemer T, et al. Diagnosis of Myocardial Infarction Using a High-Sensitivity Troponin I 1-Hour Algorithm. *JAMA Cardiol* 2016;1:397-404.
31. Cullen L, Collinson PO, Giannitsis E. Point-of-care testing with high-sensitivity cardiac troponin assays: the challenges and opportunities. *Emerg Med J* 2022;39:861-6.