Validating the Manchester Acute Coronary Syndromes (MACS) and Troponin-only Manchester Acute Coronary Syndromes (T-MACS) rules for the prediction of acute myocardial infarction in patients presenting to the emergency department with chest pain

Jaimi H Greenslade,[1,2,3] Robert Nayer,[2] William Parsonage,[2,3,4] Shaela Doig,[1] Joanna Young,[5] John W Pickering,[5] Martin Than,[5,6] Christopher Hammett,[2,4] Louise Cullen[1,2,3]

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[1]Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia
[2]School of Medicine, University of Queensland, St Lucia, Queensland, Australia
[3]School of Public Health and Social Work,University of Technology, Brisbane, Australia
[4]Department of Cardiology, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia
[5]Department of Medicine, University of Otago, Christchurch, New Zealand
[6]Department of Emergency Medicine, Christchurch Hospital, Christchurch, New Zealand

Correspondence to
Dr Jaimi H Greenslade, Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Butterfield Street, Herston, QLD 4029, Australia; j.greenslade@uq.edu.au

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ABSTRACT

Background The Manchester Acute Coronary Syndromes (MACS) rule and the Troponin-only MACS (T-MACS) rule risk stratify patients with suspected acute coronary syndrome (ACS). This observational study sought to validate and compare the MACS and T-MACS rules for assessment of acute myocardial infarction (AMI).

Methods Prospectively collected data from twoEDs in Australia and New Zealand were analysed. Patients were assigned a probability of ACS based on the MACS and T-MACS rules, incorporating high-sensitivity troponin T, heart-type fatty acid-binding protein, ECG results and clinical symptoms. Patients were then deemed very low risk, low risk, intermediate or high risk if their MACS probability was less than 2%, between 2% and 5%, between 5% and 95% and greater than 95%, respectively. The primary endpoint was 30-day diagnosis of AMI. The secondary endpoint was 30-day major adverse cardiac event (MACE) including AMI, revascularisation or coronary stenosis (>70%). Sensitivity, specificity and predictive values were calculated to assess the accuracy of the MACS and T-MACS rules.

Results Of the 1244 patients, 114 (9.2%) were diagnosed with AMI and 163 (13.1%) with MACE. The MACS and T-MACS rules categorised 133 (10.7%) and 246 (19.8%) patients, respectively, as very low risk and potentially suitable for early discharge from the ED. There was one false negative case for both rules making sensitivity 99.1% (95.2%–100%).

Conclusions MACS and T-MACS accurately risk stratify very low risk patients. The T-MACS rule would allow for more patients to be discharged early. The potential for missed MACE events means that further outpatient testing for coronary artery disease may be required for patients identified as very low risk.

Key messages

What is already known on this subject?

- The Manchester Acute Coronary Syndromes (MACS) and Troponin-only MACS (T-MACS) rules accurately identify patients at low risk of acute myocardial infarction (AMI) in cohorts from the UK.

What this study adds?

- External validation of these rules using international cohorts is required.
- We have shown that the MACS and T-MACS rules provide accurate risk stratification for AMI in an Australasian cohort.
- The T-MACS rule allows more patients to be safely discharged than MACS.

INTRODUCTION

In 2007–2008, 5.5 million people presented to EDs in the USA with chest pain, yet less than one-quarter of these were diagnosed with acute coronary syndrome (ACS).[1] There is no single test with adequate sensitivity and specificity for diagnosis of ACS and so clinicians use a variety of clinical information to assess risk in this sizeable cohort.[2 3] Decision rules combining clinical features, ECG findings and novel biomarkers have been derived to improve risk stratification for patients with ACS. These rules have been limited by a number of factors including lack of specificity;[4] lack of guidance on the subsequent management of patients who require further assessment or admission; and reliance on rigid diagnostic cut-offs to dichotomise continuous variables (such as biomarker levels), potentially losing the richness of diagnostic information available.[4–6]

The Manchester ACS (MACS) rule[7] and Troponin-only MACS (T-MACS) rule[8] are clinical rules that were developed to overcome the limitations described above. The MACS rule incorporates high-sensitivity troponin T (hs-TnT), heart fatty acid-binding protein (h-FABP), ECG findings and clinical data. The T-MACS uses similar clinical data but excludes h-FABP as a variable in risk stratification. The MACS and T-MACS rules give the

probability that a patient will undergo a major adverse cardiac event (MACE) within 30 days.[7]

Patients are deemed very low risk, and eligible for immediate discharge, if their MACS/T-MACS probability is less than 2%. Patients are considered at low risk if their MACS/T-MACS probability is between 2% and 5%. It is recommended that such patients be admitted to a low dependency environment such as an ED observation unit. Patients are at moderate risk if their MACS/T-MACS probability is between 5% and 95%, and such patients should be admitted acutely to an inpatient ward. Patients are deemed high risk if their MACS/T-MACS probability is >95%, and these patients are referred to the coronary care unit or a high-dependency environment. In the MACS derivation study, 35% of the ED cohort was classified as very low risk, with a 30-day AMI prevalence of 0.0%.[7] In the T-MACS derivation study, 37.7% were classified as very low risk with an AMI prevalence of 0.7%.[8]

While initial research supports the utility of the MACS and T-MACS rules, further external validation is needed to ensure that these rules are accurate across different healthcare settings in different countries. This study sought to externally validate and compare the MACS and T-MACS rules for the assessment of ED patients with possible ACS.

METHODS

This is a secondary analysis of data prospectively collected during two studies. The data for the two studies were pooled as they both used the same inclusion and exclusion criteria, the same data definitions, the same method of data collection and were in regions with similar healthcare systems. The first study was a randomised trial conducted in New Zealand comparing standard assessment of chest pain to an accelerated diagnosis protocol using zero and 2-hour troponin testing in combination with the Thrombolysis in Myocardial Infarction (TIMI) score.[9] The second is the Brisbane cohort of the ADAPT trial.[10] This was a prospective observational study. The inclusion criterion for both of the studies was a presentation to the ED with at least 5 min of chest pain suggestive of ACS, as per the American Heart Association guidelines.[11] More general/atypical symptoms such as fatigue, nausea, vomiting, sweating and faintness in isolation were not used as inclusion criteria unless the treating clinician chose to investigate the patient for ACS.

Patients were excluded from both studies if there was a clear non-ACS cause for their symptoms, if they were unwilling or unable to provide informed consent (eg, suffering from dementia), if staff considered that recruitment was inappropriate (eg, terminal illness), if there were transferred from another hospital, were pregnant, were previously recruited to the study within the past 45 days or were unable or unwilling to be contacted after discharge. Patients were also excluded from this analysis if serum samples were not stored for delayed testing, or if they presented with ST segment elevation on their ECG. Recruitment for the Brisbane ADAPT trial occurred Monday to Friday between November 2007 and February 2011 during the hours of 08:00 and 17:00. Recruitment for the TIMI trial occurred between October 2010 and July 2012 between 08:00 and 20:00, 7 days per week. Research nurses completed recruitment for both studies. This study adhered to the TRIPOD checklist for reporting validation studies.

Index test

Data were collected from patient interviews in a standardised manner, and subsequently cross-checked with patient notes. All clinical data used to calculate the two rules were collected during the original data collection. Blood samples were taken on presentation (0 hours) and were frozen at −80°C. These samples were later analysed for h-FABP and hs-TnT. The h-FABP was analysed using Randox h-FABP immunoturbidimetric assay (Randox Laboratories Limited, County Antrim, UK). The 99th percentile of the h-FABP assay in a healthy population is 6.32 ng/mL, with a limit of detection of 3.49 ng/mL. The hs-TnT assay used for validating the rule was the Elecsys Troponin T-high sensitive assay (Roche Diagnostics, Penzberg, Germany). The hs-TnT assay has a limit of detection of 5 ng/L, 99th percentile of 14 ng/L and 10% coefficient of variation of 13 ng/L. After the hs-TnT assays had been tested for patients in the ADAPT study, the manufacturer indicated the reagent lots had used a suboptimally standardised calibration curve. The results were recalculated by the manufacturer with a restandardised calibration curve for the reagent kit. This revision was performed blind to the clinical endpoints, and the revised hs-TnT assay results were used for all analyses.

The MACS and T-MACS probabilities were calculated using the formulae in box 1. The included variables are ischaemic ECG, diaphoresis, vomiting, blood pressure, medical history of angina, radiating pain and biomarkers (presentation hs-TnT and h-FABP for MACS or presentation hs-TnT alone for T-MACS). The original MACS rule used worsening of angina. This data point was available for the ADAPT cohort, but not for the New Zealand TIMI cohort. As such, prior angina was used as a surrogate measure within both cohorts as it was assumed that patients with a history of angina were presenting to ED due to worsening of their anginal symptoms. The original rule also used sweating observed by the clinician. We did not have physician observed sweating and so patient-reported sweating (verified by the research nurse) was used as a surrogate. In line with recommendations outlined in the MACS rule derivation study,[7] patients were considered very low risk if their MACS/T-MACS probability was less than 2%. Patients were considered low risk

Box 1 Manchester Acute Coronary Syndrome (MACS) and Troponin-only Manchester Acute Coronary Syndrome (T-MACS) rule formulas

$$\text{MACS} = \frac{1}{1+e^{(0.068*\text{hs-TnT}+(0.17*\frac{\text{H-FABP}-0.2844}{1.3520})+1.75E+1.85S+1.72V+1.46H+0.92A+0.87R-4.83)}}$$

$$\text{TMACS} = \frac{1}{1+e^{-((0.089*\text{hs-TnT})+1.713E+0.847A+0.607R+1.417V+2.058S+1.208H-4.766)}}$$

where

- E=0 if the ECG is not diagnostic of ischaemia and 1 if the ECG is diagnostic of ischaemia
- S=0 if no sweating is observed and 1 if sweating is observed
- V=0 if no vomiting and 1 if the patient is vomiting
- H=0 if the systolic blood pressure (SBP) is ≥100 mm Hg and 1 if SBP <100 mm Hg
- A=0 if the patient does not have a worsening of previous angina and 1 if the patient has a worsening of previous angina
- R=0 if the pain does not radiate to the arm or shoulder and 1 if the pain does radiate to the right arm or shoulder
- Note: Heart fatty acid-binding protein and high-sensitivity troponin T are measured on presentation.

if their MACS/T-MACS probability was between 2%and 5%, and moderate risk if their MACS/T-MACS probability was between 5% and 95%. Patients were deemed high risk if their MACS/T-MACS probability was >95%.

Outcome

The primary outcome was AMI at 30 days including ST-segment myocardial infarction (STEMI), non-STEMI (NSTEMI) or emergency revascularisation. The secondary outcome was major adverse cardiac events (MACE) at 30 days. MACE was defined as per the original MACS rule derivation[7] and included acute myocardial infarction (AMI), all-cause mortality, revascularisation or significant (>70%) angiographic coronary stenosis that was not known to be old. The information required for 30-day endpoint adjudication was obtained from patient notes, hospital databases and directly from the patient. Research nurses conducted telephone follow-up to determine whether patients had any cardiac events, investigations or contact with any healthcare providers during the 30-day period after presentation to ED. All follow-up information was verified through contact with the healthcare provider, and original copies of medical records and cardiac investigation results were obtained. Hospital records were also searched to determine whether the patient had represented or undergone further investigation and a search of the national death registry was performed to identify vital status.

Outcomes were adjudicated independently by local cardiologists using predefined standardised reporting guidelines. Cardiologists had knowledge of the clinical record, ECG and troponin results from standard care. The troponin assays used in standard care were different from those that were used to categorise patients for the index test and were different across different sites. The troponin assay used in standard care at the Royal Brisbane and Women's Hospital was the Beckman Coulter second-generation AccuTnI (Beckman Coulter, Chaska, Minnesota, USA). The standard of care troponin assay used in the New Zealand cohort was the Architect c-TnI assay (Abbott Diagnostics, Illinois, USA). Both of these assays are sensitive, not highly sensitive troponin assays. A second cardiologist conducted a blind review of all ACS cases and 10% of non-ACS cases. In cases of disagreement, endpoints were agreed by consensus of the two cardiologists and an ED physician. Consensus was achieved for all endpoints.

Diagnosis of AMI was made according to international guidelines. Patients were required to have symptoms compatible with myocardial ischaemia, evidence of myocardial necrosis and evidence of ischaemia (at least one of ECG changes or imaging results including exercise tolerance testing, myocardial perfusion scan, stress echocardiography, CT coronary angiography (CTCA) or coronary angiography during catheterisation).[12] Necrosis was diagnosed based on a rise or fall of cardiac troponin concentration with at least one value above the 99th percentile of the normal reference range, at a level of assay imprecision near to 10%. If the troponin was greater than the reference range but no rise or fall was recorded, other causes of raised troponin were considered. If no alternative cause for the troponin rise was apparent and if the clinical presentation was suggestive of ACS, an adjudicated diagnosis of AMI was made.

Data analysis

The MACS rule has a reported sensitivity of >98%,[7 13] and the baseline probability of ACS in the cohort was estimated to be 15%. Using the sample size calculation described by Jones *et al*,[14] 1260 participants were required to detect this sensitivity with CIs of ±2% with an alpha of 0.05%.

Data were analysed using Stata version 14 (StataCorp, Texas, USA). Baseline characteristics of the sample were reported by 30-day AMI status. Patients were placed in risk categories according to the MACS rule and T-MACS rule formulas, and the number of patients and the event rates in each risk category were reported. The diagnostic accuracy of the MACS and T-MACS rule for identifying patients at very low risk of AMI and MACE was calculated using sensitivity, specificity, positive and negative predictive values (PPV and NPV). The sensitivity, specificity and predictive values also were reported for those classified as high risk (vs all other risk categories) for AMI and MACE. Exact binomial CIs were reported. Sensitivity and specificity for the MACS and T-MACS rules were compared using the McNemar's test for paired data.

Discrimination for the overall score was assessed using receiver operating characteristic (ROC) curve analysis. The area under the curve for each ROC curve (AUROC) was computed using a non-parametric method, and AUROC pairs were compared using the algorithm suggested by DeLong, DeLong and Clarke-Pearson.[15] The Hosmer-Lemeshow (H-L) statistic was used to assess model calibration. Predicted and actual probabilities of AMI were compared across 10 deciles of risk, and a calibration graph of observed versus expected probabilities was provided. If the model calibrates well, the plot of expected versus actual AMI will not substantially deviate from the 45° line of perfect fit. To provide further detail about the prediction of AMI in the current cohort, AMI was regressed on each of the MACS rule variables. The logistic model was tested in 1000 bootstrap samples, and the proportion of samples in which the lower CI for each variable exceeded one was reported.

A sensitivity analysis was also performed using the Brisbane cohort only. This analysis examined whether modifying the MACS and T-MACS rules by including prior angina rather than worsening of angina altered the accuracy of the rule. Data were also reported on number of patients categorised into each risk group by the MACS and T-MACS rule when using worsening or prior angina. Cohen's Kappa was calculated to compare agreement between rules when worsening or prior angina was used. The sensitivity and specificity of the MACS and T-MACS rules using the original formulas were compared with that using prior angina.

RESULT

One thousand seven hundred and fifteen patients were enrolled in the two studies. Four hundred seventy-one patients were excluded as they did not have blood stored for measurement of biomarkers, or they presented to the ED with STEMI. The final sample included 1244 patients (figure 1). The mean age was 57.0 years (SD=14.6), and 764 (61.41%) were male. Of these, 114 (9.16%) were diagnosed with AMI and 163 (13.1%) with MACE. Baseline characteristics by AMI are shown in table 1. Patients with AMI were older, were more likely to have risk factors and were more likely to have a cardiac history than patients without AMI. The baseline characteristics in our cohort were similar to the derivation samples of MACS and T-MACS but our cohort did have a slightly lower prevalence of AMI and a lower proportion of patients with prior AMI (20.1% vs 23.8%), prior angina (27.9% vs 31.5%) and diabetes (13.8% vs 17.8%). We had similar rates of coronary intervention (19.9% vs 20%) to the MACS[7] and T-MACS[8] derivation samples and a higher proportion of smokers (39.3% vs 30.7%).

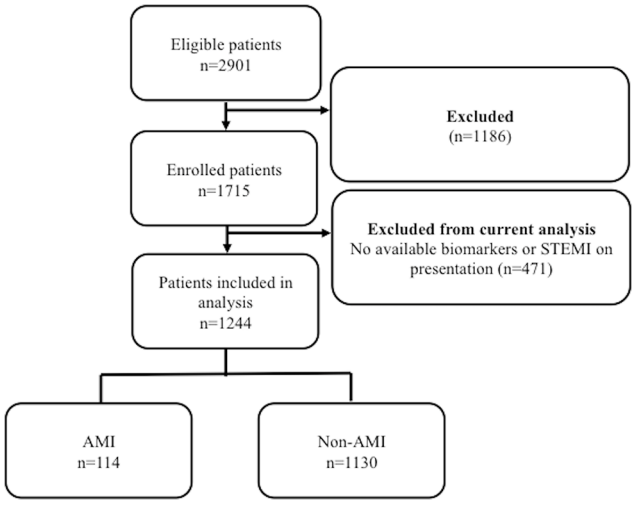

Figure 1 Participant flow. AMI, acute myocardial infarction; STEMI, ST-segment myocardial infarction.

The MACS and T-MACS rules classified 133 and 246 patients as very low risk, respectively (table 2). Of these low-risk patients, one was diagnosed with AMI. The patient missed by both MACS and T-MACS was a 56-year old man with a h-FABP of 2.0 ng/mL and hs-TnT of 8.2 ng/L. This patient presented 24 hours after first onset of symptoms, had an elevated troponin result using the Beckman AccuTnI sensitive troponin I assay on presentation (0.09 mcg/L) and underwent angiography and percutaneous coronary intervention for NSTEMI. The MACS and T-MACS probabilities for this patient were 1.69% and 1.73%, respectively. The 2-hour hs-TnT value for this patient was 9.85 ng/L, a value which would have resulted in a T-MACS (but not MACS) probability >2%. In total, there were three patients with very low-risk MACS who met MACE criteria. Apart from the one individual with AMI, the remaining two patients were classified as MACE following an angiogram showing stenosis >70%. One of these patients underwent revascularisation and both were diagnosed with unstable angina pectoris. Six patients with very low risk T-MACS met the MACE criteria. One of these had AMI and the remaining five had an angiogram with stenosis >70%. Four of these patients went on to have revascularisation during their admission. All were diagnosed with unstable angina pectoris.

Table 1 Patient characteristics

Characteristic	Non-AMI (n=1130)	AMI (n=114)	p
Age	55.9 (14.3)	68.7 (12.5)	<0.01
Male gender	683 (60.4)	81 (71.1)	0.03
Risk factors			
Hypertension	486 (43.0)	70 (61.4)	<0.01
Dyslipidaemia	509 (45.0)	62 (54.4)	0.06
Diabetes	144 (12.7)	28 (24.6)	<0.01
Family history	575 (50.9)	65 (57.0)	0.21
Current or recent smoking	435 (38.5)	54 (47.4)	0.07
Prior history			
AMI	209 (18.5)	41 (36.0)	<0.01
Angina	302 (26.7)	45 (39.5)	<0.01
CHF	51 (4.5)	7 (6.1)	0.43
CABG	74 (6.5)	13 (11.4)	0.05
Angioplasty	183 (16.2)	26 (22.8)	0.07

AMI, acute myocardial infarction; CABG, coronary artery bypass graft; CHF, congestive heart failure.

The sensitivity and specificity of the MACS very low risk category was 99.1% (95% CI: 95.2% to 100%) and 11.7% (95% CI: 9.9% to 13.7%) respectively for AMI (table 3). For T-MACS, sensitivity was similar at 99.1% (95% CI: 95.2% to 100%, p=1.0), but specificity was slightly higher at 21.7% (95% CI: 19.3% to 24.2%, p<0.01). For high-risk patients, the T-MACS rule had specificity of 98.4% (95% CI: 97.5% to 99.1%), which was higher than the specificity of the MACS rule at 97.6% (95% CI: 96.5% to 98.4%, p=0.01).

The area under the curve (AUC) for MACS (0.88, 95% CI: 0.84 to 0.92) was similar to that of T-MACS (0.89, 95% CI: 0.86 to 0.93) for AMI (p=0.09). Calibration plots comparing observed and expected AMI are presented in figure 2. Visual inspection reveals that both MACS and T-MACS overestimated AMI rates at all predicted probabilities. The H-L χ^2 was significant for both MACS (p<0.001) and T-MACS (p<0.001) indicating lack of model fit. To provide further explanation for the poor calibration, AMI was regressed on each of the variables specified within the MACS rule. Patients with outlying hs-TnT values (>100) were excluded from the logistic regression model. These patients (n=43) were poorly predicted (large regression residuals), had undue influence on the model coefficients, and resulted in a breach of the linearity of logit assumption for hs-TnT. Removal of such patients was deemed clinically relevant as they would be deemed high risk on presentation and referred to cardiology or general medicine, rather than undergoing detailed risk stratification in the ED.

The results of the logistic regression are provided in online supplementary table 1. The AUC for the predictive model was 0.91 (95% CI: 0.88 to 0.95), and the model provided a good fit to the data (H-L χ^2, p=0.21). Increasing levels of hs-TnT and an ischaemia ECG were associated with increased odds of AMI in 100% and 87% of bootstrapped samples, respectively. Radiation of pain to the arms or shoulder emerged as a predictor in 60% of samples. All remaining predictors emerged in less than 30% of the bootstrapped sample. Increasing levels of h-FABP were associated with increased risk of AMI in only 0.3% of samples.

The sensitivity analyses for the Brisbane cohort are provided in online supplementary tables 2 and 3. There was very high agreement between categories of risk for the MACS rule when using prior angina (our modification) or worsening angina (as per the original rule) (κ=0.94, p<0.01). There was also high agreement for the T-MACS rule using prior angina or worsening angina (κ=0.94, p<0.01). Both rules missed one patient with an AMI (the same patient as previously described) in the very low risk category. For the very low risk MACS rules, sensitivity was the same using worsening or prior angina (97.8%, 95% CI: 88.5 to 99.9, p=1.0) but specificity was slightly higher using worsening (14.5%, 95% CI: 12.1% to 17.3%) compared with prior angina (13.3%, 95% CI: 11.0 to 16.0, p=0.01). Similarly, for T-MACS very low risk, sensitivity was the same using the worsening or prior angina (97.8%, 95% CI: 88.5 to 99.9, p=1.0) and specificity was slightly higher using the worsening (25.4%, 95% CI: 22.3% to 28.7%) compared with prior angina (23.0%, 95% CI: 20.0% to 26.2%, p<0.01). For high risk, there were no differences between sensitivity or specificity using worsening or prior angina within the MACS and T-MACS rules.

DISCUSSION

The MACS and T-MACS rules effectively risk stratify patients presenting with chest pain. Both rules identified a group of patients with a very low rate of ACS (<1%) who could be

Table 2 Risk categories for MACS and T-MACS by outcome

Risk category	MACS		T-MACS	
	Total N=1244 n (%)	AMI N=114 n, % of patients in category (95% CI)	Total N=1244 n (%)	AMI N=114 n, % of patients in category (95% CI)
Very low risk	133 (10.7)	1, 0.8 (0.2% to 4.1%)	246 (19.8)	1, 0.4 (0.0% to 2.2%)
Low risk	200 (16.1)	3, 1.5 (0.3% to 4.3%)	181 (14.6)	5, 2.8 (0.9% to 6.3%)
Moderate risk	828 (66.6)	54, 6.5 (4.9% to 8.4%)	750 (60.3)	59, 7.9 (6.0% to 10.0%)
High risk	83 (6.7)	56, 67.5 (56.3% to 77.4%)	67 (5.4)	49, 73.1 (60.9% to 83.2%)
	Total N=1244 n (%)	MACE N=163 n, % of patients in category (95% CI)	Total N=1244 n (%)	MACE N=163 n, % of patients in category (95% CI)
Very low risk	133 (10.7)	3, 2.3 (0.5% to 6.5%)	246, (19.8)	6, 2.4 (0.9% to 5.2%)
Low risk	200 (16.1)	9, 4.5 (2.1% to 8.4%)	181, (14.6)	12, 6.6 (3.5% to 11.3%)
Moderate risk	828 (66.6)	93, 11.2 (9.2% to 13.6%)	750, (60.3)	94, 12.5 (10.2% to 15.0%)
High risk	83 (6.7)	58, 69.9 (58.8% to 79.5%)	67 (5.4)	51, 76.1 (64.1% to 85.7%)

AMI, acute myocardial infarction; MACE, major adverse cardiac event; MACS, Manchester Acute Coronary Syndrome; T-MACS, Troponin-only Manchester Acute Coronary Syndrome.

discharged from the ED after a single blood draw. They also identify individuals at high risk of AMI who require referral to cardiology. Compared with the MACS rule, the T-MACS allowed more patients to be ruled out without compromising patient safety.

In line with previous research,[7 13 16] we found that the MACS very low risk category has high sensitivity for ruling out AMI. This is advantageous as it suggests that a group of patients could be safely discharged soon after presentation to the ED with chest pain. However, we found that the MACS rule had lower specificity than the derivation study (11.7% vs 43.7%). It also categorised a lower percentage of patients as very low risk (10.7%) than the derivation study (35.5%)[7] and a previous external validation study with similar AMI prevalence to ours (17%).[16] The rule may identify fewer low risk patients than other rules designed to be of use on presentation.[17 18] For instance, the use of a single high-sensitivity troponin T below the limit of detection (LOD) would have ruled out 30.4% of patients with a sensitivity of 98.2% in

Table 3 Diagnostic accuracy of MACS and T-MACS

	Sensitivity, n (95% CI)	Specificity, n (95% CI)	PPV, n (95% CI)	NPV, n (95% CI)
AMI				
MACS rule very low risk	**99.1% (95.2% to 100%)**	11.7% (9.9% to 13.7%)	10.2% (8.5% to 12.1%)	**99.2 (95.9% to 100%)**
MACS rule high risk	49.1% (39.6% to 58.7%)	**97.6% (96.5% to 98.4%)**	**67.5% (56.3% to 77.4%)**	95% (93.6% to 96.2%)
T-MACS very low risk	**99.1% (95.2% to 100%)**	21.7% (19.3% to 24.2%)	11.3% (9.4% to 13.5%)	**99.6% (97.8% to 100%)**
T-MACS high risk	43.0% (33.7% to 52.6%)	**98.4% (97.5% to 99.1%)**	**73.1% (60.9% to 83.2%)**	94.5 (93.0% to 95.7%)
MACE				
MACS rule very low risk	**98.2% (94.7% to 99.6%)**	12.0% (10.1% to 14.1%)	14.4% (12.4% to 16.6%)	**97.7% (93.5% to 99.5%)**
MACS rule high risk	35.6% (28.3% to 43.4%)	**97.7% (96.6% to 98.5%)**	**69.9% (58.8% to 79.5%)**	91% (89.2% to 92.5%)
T-MACS very low risk	**96.3% (92.2% to 98.6%)**	22.2% (19.8% to 24.8%)	15.7% (13.5% to 18.1%)	**97.6% (94.8% to 99.1%)**
T-MACS high risk	31.3% (24.3% to 39.0%)	**98.5% (97.6% to 99.2%)**	**76.1% (64.1% to 85.7%)**	90.5% (88.7% to 92.1%)

AMI, acute myocardial infarction; MACE, major adverse cardiac event; MACS, Manchester Acute Coronary Syndrome; T-MACS, Troponin-only Manchester Acute Coronary Syndrome. Bolded values represent the most relevant statistic for each category.

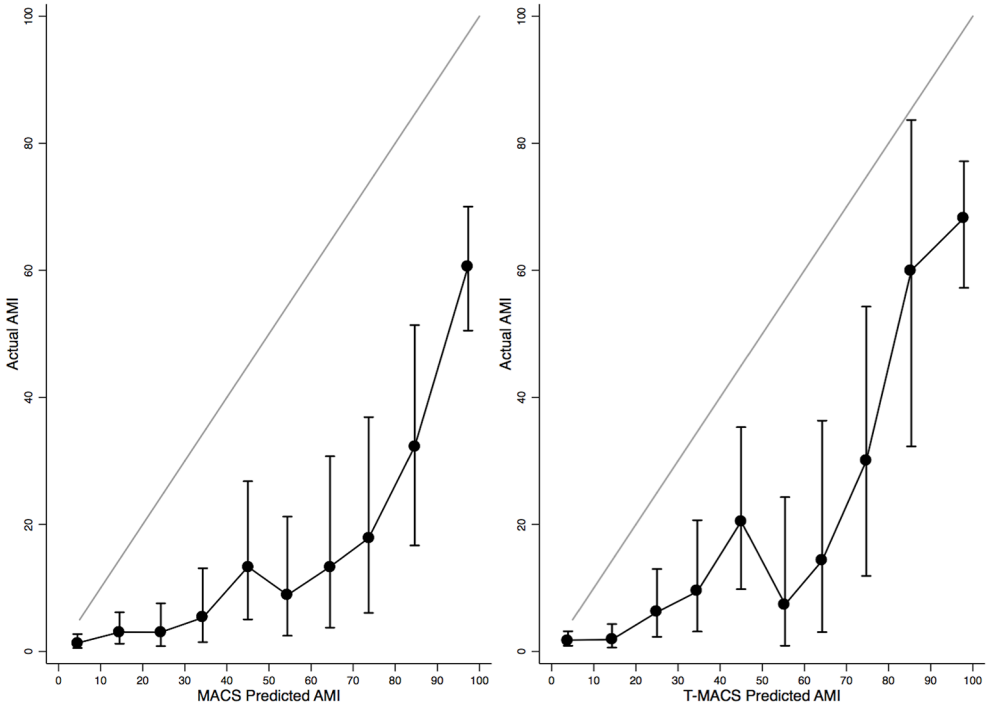

Figure 2 Calibration plots for the Manchester Acute Coronary Syndrome (MACS) and Troponin-only Manchester ACS (T-MACS) rules. AMI, acute myocardial infarction.

our cohort, a pattern of results that differed in the original MACS validation cohort, where only 20% of patients would have been ruled out using the LOD. Regardless of these cohort differences, the utility of the MACS rule may be in providing accurate risk stratification for the entire spectrum of chest pain patients. The provision of an estimated probability of AMI along with clear guidelines for categorising patients into low-risk, moderate-risk and high-risk categories, with associated disposition decision, may improve efficiency and accuracy of disposition decisions.

The T-MACS rule also had high sensitivity for ruling out AMI but had lower specificity (21.7% vs 47.6%) and categorised a lower percentage of patients as very low risk (19.8% vs 40%) than the derivation study.[8] T-MACS categorised nearly double the number of patients as very low risk in comparison with the MACS rule (10.7%). This is in line with previous research suggesting that h-FABP may have limited independent value over a high-sensitivity troponin assay[19] and in line with the finding of our study that h-FABP was not a reliable predictor of AMI. The improved identification of very low risk patients in combination with the cost reduction of not requiring the h-FABP assay means that the T-MACS rule represents an improvement on the original MACS rule. This finding is important for practising clinicians who do not have access to h-FABP.

There are several potential reasons why the specificity and proportion of patients ruled out in our study was lower compared with previous research. First, the performance of a predictive model is typically lower when based on a sample outside of the population from which it was derived.[20] Second, the slightly different definitions of some of the patient history variables may have reduced the number of patients ruled out. Specificity was slightly lower when using prior angina rather than worsening of angina as outlined in the previous rule. Further, the derivation studies for MACS and T-MACS assessed sweating observed by the treating clinician, while our study included patient reported sweating verified by a research nurse. If patients reported sweating that was not deemed relevant by a treating clinician, this may have reduced the proportion of patients deemed low risk.

One notable feature of the MACS and T-MACS rules is that they provide a predicted probability of AMI. This prediction may provide clinicians with additional information when making decisions about patient assessment and discharge. In our cohort, both the MACS and T-MACS scores overestimated the probability of AMI. Such overestimation is likely to have occurred because these scores were developed in a cohort with an AMI rate almost double ours (18.5%) and with slightly higher proportion of patients with risk factors for AMI. Moreover, in contrast to the original derivation studies for MACS and T-MACS, we found that several of the clinical variables did not emerge as reliable predictors of AMI in our cohort, including vomiting, previous angina and sweating. This suggests that while the risk categories of MACS and T-MACS display good utility for risk stratification, the absolute risk of AMI should not be used in clinical care without recalibration to the sample of interest. Further calibration of the MACS and T-MACS rules in a large multicentre cohort may help to provide more generalisable data on the exact probability of AMI.

When using the published thresholds for the very-low risk group, neither the MACS nor T-MACS rule identified all patients with MACE. Thus, the value for these rules may be in rapidly ruling out AMI before referring patients for early inpatient provocative testing, referral to a chest pain clinic or referral to a general practitioner for outpatient objective testing. Given the large number of ED patients presenting with chest pain, rapid identification of a group of very low risk patients would help improve patient flow and reduce pressure on EDs, where overcrowding is associated with increased mortality risk.[21]

Limitations and future research

This is an analysis of previously collected data. Data on worsening of angina were not collected in both study cohorts and

so the formulas were modified by using previous history of angina as a substitute for worsening angina. The sensitivity of the test does not appear to be affected by the use of a history of angina and it may be possible to use history as a substitute in the case of missing data. This was an observational study and, as such, a significant proportion of low risk patients had further investigations for coronary artery disease. Further assessment of the MACS and T-MACS rule in an intervention trial is recommended. Approximately one-quarter of the patients enrolled in the original studies were excluded from this analysis as they did not have bloods stored for assessment of biomarkers or because they met the criteria for STEMI on admission to the ED. This may have affected the results of this study.

Conclusions

Both the MACS and T-MACS rules are effective for risk stratifying patients with chest pain using only a single blood draw on arrival to the ED. Patients deemed very low risk by these rules have a low rate for AMI but do require additional testing to rule out broader MACE events. The T-MACS rule identifies more very low risk patients than the MACS rule without compromising safety.

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Validating the Manchester Acute Coronary Syndromes (MACS) and Troponin-only Manchester Acute Coronary Syndromes (T-MACS) rules for the prediction of acute myocardial infarction in patients presenting to the emergency department with chest pain

Jaimi H Greenslade, Robert Nayer, William Parsonage, Shaela Doig, Joanna Young, John W Pickering, Martin Than, Christopher Hammett and Louise Cullen

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