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Troponin-only Manchester Acute Coronary Syndromes (T-MACS) decision aid: single biomarker re-derivation and external validation in three cohorts

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ABSTRACT

Background The original Manchester Acute Coronary Syndromes model (MACS) ‘rules in’ and ‘rules out’ acute coronary syndromes (ACS) using high sensitivity cardiac troponin T (hs-cTnT) and heart-type fatty acid binding protein (H-FABP) measured at admission. The latter is not always available. We aimed to refine and validate MACS as Troponin-only Manchester Acute Coronary Syndromes (T-MACS), cutting down the biomarkers to just hs-cTnT.

Methods We present secondary analyses from four prospective diagnostic cohort studies including patients presenting to the ED with suspected ACS. Data were collected and hs-cTnT measured on arrival. The primary outcome was ACS, defined as prevalent acute myocardial infarction (AMI) or incident death, AMI or coronary revascularisation within 30 days. T-MACS was built in one cohort (derivation set) and validated in three external cohorts (validation set).

Results At the ‘rule out’ threshold, in the derivation set (n=703), T-MACS had 99.3% (95% CI 97.3% to 99.9%) negative predictive value (NPV) and 98.7% (95.3%–99.8%) sensitivity for ACS, ‘ruling out’ 37.7% patients (specificity 47.6%, positive predictive value (PPV) 34.0%). In the validation set (n=1459), T-MACS had 99.3% (98.3%–99.8%) NPV and 98.1% (95.2%–99.5%) sensitivity, ‘ruling out’ 40.4% (n=590) patients (specificity 47.0%, PPV 23.9%). T-MACS would ‘rule in’ 10.1% and 4.7% patients in the respective sets, of which 100.0% and 91.3% had ACS. C-statistics for the original and refined rules were similar (T-MACS 0.91 vs MACS 0.90 on validation).

Conclusions T-MACS could ‘rule out’ ACS in 40% of patients, while ‘ruling in’ 5% at highest risk using a single hs-cTnT measurement on arrival. As a clinical decision aid, T-MACS could therefore help to conserve healthcare resources.

BACKGROUND

A number of strategies have been proposed to ‘rule out’ acute coronary syndromes (ACS) in the ED using various combinations of the ECG, cardiac troponin and history. Several recent reports suggest that ACS could be ‘ruled out’ in some patients following a single blood test in the ED. For example, patients with high sensitivity cardiac troponin T (hs-cTnT) concentrations below the limit of detection (LoD) of the assay and no ECG ischaemia have very low probability of acute myocardial

Key messages

What is already known on this subject?

- The Manchester Acute Coronary Syndromes (MACS) model, which has been externally validated in two cohorts, could ‘rule out’ coronary syndromes following a single blood test, reducing unnecessary hospital admissions.
- The original model requires measurement of heart-type fatty acid binding protein (H-FABP), which some people may perceive as a barrier to implementation.

What this study adds?

- We refined MACS, producing a version that only requires measurement of high sensitivity troponin (and not H-FABP). On external validation in three cohorts, this refined version performed well, paving the way for further evaluation when the model is used in practice.

infarction (AMI) (the ‘LoD strategy’).^{1–3} We recently reported the derivation and external validation of the Manchester Acute Coronary Syndromes (MACS) decision aid. The decision aid uses a computer model to both ‘rule in’ and ‘rule out’ ACS by combining the presence or absence of six clinical features with two biomarkers measured on arrival: hs-cTnT and heart-type fatty acid binding protein (H-FABP).^{4–5} The components of the original MACS model and the method of calculation are displayed in [table 1](#). The absence of any clinical features and negative results of the biomarkers has been shown to have negative predictive values (NPVs) of 100%, 98.7% and 100% in three prior derivation/validation studies. The advantage of the computer decision aid is that it aims to ‘rule in’ ACS as well as ‘rule out’, which may help to make efficient use of inpatient resources. MACS has also been validated to predict AMI and major adverse cardiac events (MACE, which include AMI, death or coronary revascularisation) within 30 days.

A barrier to implementing MACS in practice is the need to run the H-FABP assay, which is not widely used.^{6–7} In the original analysis, H-FABP strongly predicted ACS independently of hs-cTnT, ECG ischaemia and other clinical information, thus



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Table 1 Predictors in the Manchester Acute Coronary Syndromes (MACS) model

Variable	Measurement scale
A. High sensitivity cardiac troponin T (ng/L)	Continuous
B. Heart-type fatty acid binding protein (ng/mL)	Continuous
C. ECG ischaemia	Dichotomous
D. Sweating observed by the treating clinician	Dichotomous
E. Vomiting in association with the presenting symptoms	Dichotomous
F. Systolic BP <100 mm Hg on arrival	Dichotomous
G. Worsening (or crescendo) angina	Dichotomous
H. Pain radiating to the right arm or shoulder	Dichotomous

*The MACS model estimates the probability (p) of acute coronary syndromes as follows (rounded values are presented): $p=1/(1+e^{-(0.068a+(0.17(b-0.28)/1.35)+1.75c+1.85d+1.72e+1.46f+0.92g+0.87h-4.83)})$.⁵ For dichotomous variables, a value of '1' is entered for 'yes' and '0' for 'no'. The constants presented here assume use of the Roche Diagnostics Elecsys hs-cTnT assay and the Randox Laboratories immunoturbidimetric H-FABP assay.

justifying its inclusion in the model. However, a re-derivation of MACS using cardiac troponin alone could enable more widespread clinical implementation without the expense of an additional assay.

Our primary objective was therefore to return to the derivation of the original MACS model, but using hs-cTnT as the only biomarker (Troponin-only Manchester Acute Coronary Syndromes (T-MACS)), and then to evaluate the model in three separate external cohort studies. A secondary objective was to compare the predictive characteristics of T-MACS with MACS and with the alternative 'LoD strategy'.

METHODS

Design and setting

In this work, we present secondary analyses from four prospective diagnostic cohort studies. The MACS model was rederived using data from the original study, which was undertaken at Manchester Royal Infirmary (January 2006 to February 2007). External validation was undertaken in three separate cohort studies as follows: validation cohort (1) took place at Stepping Hill Hospital, Stockport (April to July 2010); cohort study (2) was at Manchester Royal Infirmary (May 2011 to July 2013) and study (3) took place at Poole NHS Foundation Trust (July 2012 to August 2013), all of which are located in the UK. Several separate analyses have been published from these cohorts, as detailed in the online supplementary appendix. Ethical approval was obtained from the Research Ethics Committees separately for each study (references 05/Q1410/27, 09/H1014/74, 10/H1003/96 and 12/SW/0133) and all participants provided written informed consent.

Participants

In each study, we included patients who presented to the ED with a primary complaint of chest pain that the treating clinician suspected might be cardiac in nature and warranted investigation for a possible ACS. A detailed list of inclusion and exclusion criteria specific to each study is included in the online supplementary appendix. In summary, the only key difference in inclusion and exclusion criteria between cohorts is that patients with evidence of ECG ischaemia were excluded in validation study 3.

Data collection

In each study, data were collected prospectively using custom-designed case report forms. The initial ECG findings and systolic BP recording at the time of arrival in the ED were

considered. Because the model aims to support decisions at the point of arrival following a single blood test, serial recordings or measurements were not considered. ECGs were interpreted by the treating clinicians. We adopted this pragmatic approach because it is practising clinicians' interpretations that would be used to guide use of the model in practice.

Laboratory analyses

Serum samples were drawn at the time of arrival, stored at $\leq -70^{\circ}\text{C}$ and subsequently thawed for testing in batches. We analysed samples for hs-cTnT concentrations (Roche Diagnostics Elecsys, fifth generation, 99th percentile 14 ng/L, coefficient of variation <10% at 13 ng/L). To address a calibration shift affecting the initial batch of reagents used in validation study 1, samples were retested using an unaffected batch.⁸ Results from the unaffected batch are presented here. Other than in validation studies 2 and 3 (where hs-cTnT was used in clinical practice), samples were also tested for cTnT (Roche Diagnostics Elecsys, fourth generation, 99th percentile 10 ng/L, coefficient of variation <10% at 30 ng/L).

H-FABP concentrations were measured in serum samples drawn at the time of presentation to the ED, which are reported here to compare the accuracy of T-MACS with MACS. In the derivation study, H-FABP was evaluated in serum using the Cardiac Plus Array, Evidence Investigator, Randox Laboratories, County Antrim.⁴ In the validation studies, we used an automated immunoturbidimetric assay (Randox Laboratories), in which case the relevant coefficient for the MACS model was amended in accordance with a previous assay-specific validation.⁵

Follow-up

All participants underwent reference standard troponin testing at least 12 hours after peak symptoms (derivation study and validation studies 1 and 2) or at least 6 hours after presentation to the ED (validation study 3). Participants were also followed up by telephone, email, letter, home visit or in clinic after 30 days. We contacted the general practitioner for information if patients were persistently uncontactable.

Outcomes

The primary outcome was a diagnosis of ACS. In the absence of an accepted reference standard for unstable angina, patients were deemed to have ACS if they had either prevalent AMI or incident MACE within 30 days. MACE included incident AMI, death (from all causes) or coronary revascularisation. Secondary outcomes included the diagnosis of (prevalent) AMI alone and the identification of a coronary stenosis >50% of the luminal diameter of a major epicardial vessel, even if revascularisation did not take place.

The diagnosis of AMI was adjudicated at each study site by two independent investigators with reference to clinical data and any relevant investigation results blinded to the results of MACS and T-MACS. AMI was diagnosed if the patient developed a rise and/or fall of cardiac troponin with at least one value above the 99th percentile in conjunction with symptoms compatible with myocardial ischaemia.⁹ In line with the manufacturer's recommendations, we did not use sex-specific cut-points. Full details of the reference standards used in each study are shown in the online supplementary appendix.

Statistical analysis

Refinement

Statistical analysis proceeded according to a prespecified statistical analysis plan. T-MACS was derived by including the seven variables in the original MACS model in a logistic regression

analysis, having removed H-FABP from the model. Two of the seven variables were on a continuous measurement scale: hs-cTnT concentration and systolic BP. We explored the appropriateness of assuming a linear relationship by examining the strength of association between each predictor variable and the outcome, using the raw variable, the squared variable and a discretised form (20 ordinal categories). We noted a sudden change in the prevalence of ACS at a systolic BP cut-off of 103 mm Hg (the bottom 20th) and therefore dichotomised this variable at 100 mm Hg, as in the original MACS model. As linearity appeared to hold for hs-cTnT, this was fitted as a continuous linear variable in the model.

We then examined whether other covariates had become important to the model by adding (as independent variables) those covariates that had been shown to be significant ($p < 0.05$) and reliable (Cohen's $\kappa > 0.6$ in a separately reported substudy of interobserver reliability) predictors of ACS in our original derivation study.⁴ Based on the refined model, we generated the predicted probability (p) of ACS for each individual patient. Using the same categorisation as for the original MACS rule, we classified patients into four risk groups based on this probability, as follows: very low risk ($p < 0.02$; ACS 'ruled out'); low risk ($0.02 < p < 0.05$; suitable to continue with serial cardiac troponin testing in a low dependency environment such as an ED observation ward); moderate risk ($0.05 < p < 0.95$; suitable for ongoing investigation including serial troponin sampling in a general ward such as an Acute Medical Unit) and high risk ($p \geq 0.95$; ACS 'ruled in'). Goodness of fit was evaluated by calculation of the Hosmer-Lemeshow statistic and by visual evaluation of a calibration plot.

Evaluation of diagnostic accuracy

The diagnostic accuracy of T-MACS was evaluated by calculating sensitivity, specificity, positive predictive value (PPV) and NPVs, positive and negative likelihood ratios and areas under the receiver operating characteristic curves (AUCs) for all cohorts, together with their respective 95% CIs. The AUC in the derivation (refinement) cohort was corrected for in-sample optimism by sample splitting with 10-fold cross-validation.

We pooled the data from each of the three validation studies (the 'validation set') for the primary analysis, although baseline characteristics are reported separately for each cohort and we undertook secondary analyses for each individual cohort.

Comparison with alternative strategies

We compared the diagnostic accuracy of T-MACS with MACS and to the 'LoD strategy' in the validation set. In the latter strategy, patients were considered 'ruled out' if they had initial hs-cTnT concentrations below 5 ng/L and no ECG ischaemia. The performance of MACS and T-MACS models were compared among patients who had sufficient data for applying the models.

Paired proportions (including sensitivities and specificities) were compared by McNemar's test. The AUCs for dependent receiver operating characteristic curves were compared by the method of De Long *et al*¹⁰ Independent proportions were compared with a χ^2 test (categorical data) or t-test (continuous data). As the proportion of missing data for each variable was very small (<3%), we ran a complete case analysis without imputation. Statistical analyses were completed using MedCalc V.13.1.3 (Mariakerke, Belgium) or SPSS V.23.0 (SPSS, Chicago, Illinois, USA).

Sample size

Sample size in the derivation study was determined in order to derive a clinical decision rule that would contain a maximum of 15 predictors. This required the inclusion of 150 patients with the primary outcome.¹¹ Estimating a 20% prevalence of ACS with 5% loss to follow-up would require 790 participants. Because the analyses were post hoc in the validation set, no formal sample size calculations that are directly relevant to this analysis were undertaken a priori.

RESULTS

A total of 804 participants were included in the derivation study, of which 703 had available blood samples and were included in this analysis. The validation set included a total of 1459 patients including 462 patients from the first validation study; 191 patients from the second validation study and 806 patients from the third (figure 1). In the derivation study, 157 (22.3%) patients had ACS including 130 (18.5%) with AMI on their initial presentation. In the validation set, a total of 212 (14.5%) patients had ACS, of whom 172 (11.8%) had AMI diagnosed on their initial admission. The baseline characteristics of participants in each study are summarised in table 2.

Refinement of the MACS model

All seven variables that were considered for inclusion in the refined model remained independent predictors of ACS, once H-FABP concentration had been removed. After entering these variables, considering additional variables with a stepwise approach identified no further independent predictors of ACS. We did not detect any significant interactions between variables. The refined MACS model thus estimated the probability (p) of ACS as follows (rounded values are presented):

$$p = \frac{1}{1 + e^{-(1.713E + 0.847A + 0.607R + 1.417V + 2.058S + 1.208H + 0.089T - 4.766)}}$$

Where E is ECG ischaemia; A is worsening or crescendo angina (defined as anginal pain with increasing frequency, occurring with less exertion or becoming more prolonged); R is pain radiation to the Right arm or shoulder; V is pain associated with Vomiting; S is Sweating observed; H is Hypotension (systolic BP <100 mm Hg) and T is hs-cTnT concentration on arrival. Calculation in clinical practice would be computer-based, tablet-based or smartphone-based. The Hosmer-Lemeshow statistic for the refined model was 0.144. A calibration plot is shown in the online supplementary appendix.

Performance of the refined rule in the derivation set

In the derivation set, T-MACS gave an AUC of 0.94 after correction for in-sample optimism by cross-validation. The diagnostic performance for ACS and prevalent AMI is summarised in tables 3 and 4. In total, 37.7% (n=265) patients were classified as 'very low risk' and could have thus been 'ruled out' in the derivation study with a NPV of 99.3% (95% CI 97.3% to 99.9%) for ACS and 99.6% (97.9% to 100.0%) for AMI. Another 10.1% (n=71) patients were classified as 'high risk' (and thus 'ruled in') with a PPV of 100.0% (94.9% to 100.0%) for ACS and 97.2% (90.2% to 99.7%) for AMI.

Of the patients in the 'very low risk' group who had ACS, one (who presented to the ED within 1 hour of symptom onset, had an initial hs-cTnT concentration of 8 ng/L and no ECG ischaemia) had AMI (cTnT 2640 ng/L at 12 hours) and one underwent percutaneous coronary intervention within 30 days, although cTnT concentrations remained within the normal

Figure 1 Participant flow diagram. hs-cTnT, high sensitivity cardiac troponin T.

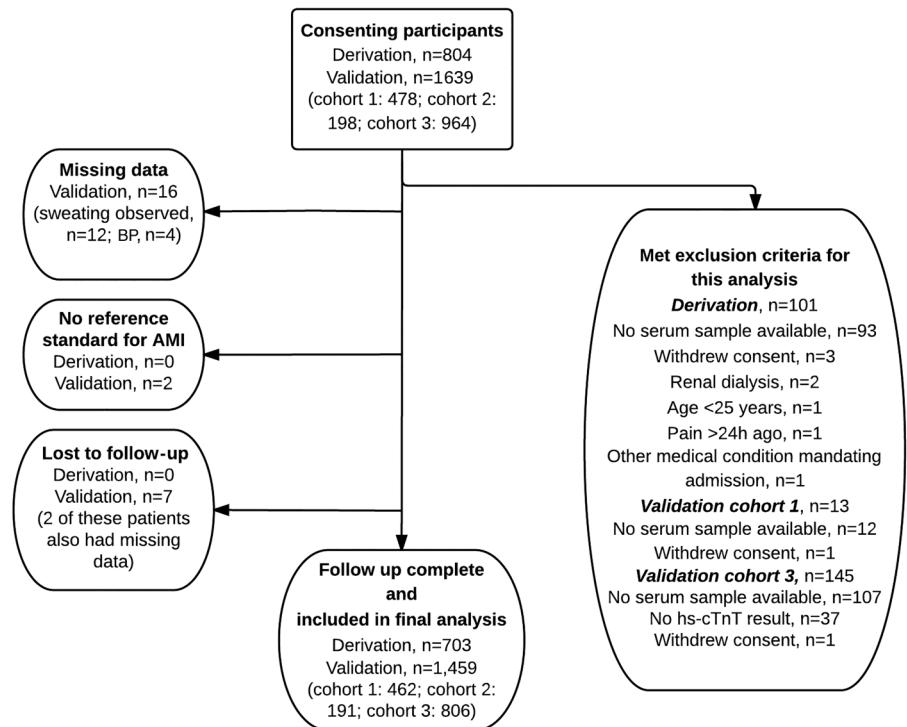


Table 2 Baseline characteristics of included patients stratified by individual cohort

	Derivation cohort (n=703)	Validation cohort 1 (n=462)	Validation cohort 2 (n=191)	Validation cohort 3 (n=806)
Age in years, mean (SD)	58.6 (14.3)	63.8 (15.6)	57.0 (14.7)	57.9 (13.1)
Men (%)	430 (61.2)	270 (58.4)	122 (63.9)	482 (59.8)
Previous angina (%)	221 (31.4)	185 (40.0)	54 (28.3)	210 (26.1)
Previous myocardial infarction (%)	167 (23.8)	138 (29.9)	54 (28.3)	177 (22.0)
Hypertension (%)	343 (48.8)	197 (42.6)	76 (39.8)	455 (56.5)
Hyperlipidaemia (%)	339 (48.2)	186 (40.3)	62 (32.5)	534 (66.3)
Diabetes mellitus (%)	125 (17.8)	80 (17.3)	27 (14.1)	137 (17.0)
Current smoking (%)	216 (30.7)	96 (20.8)	52 (27.2)	192 (23.8)
Previous coronary intervention (%)	140 (19.9)	101 (21.9)	43 (22.5)	158 (19.6)
Time from symptom onset to arrival in the ED (median, IQR)	2.5 (1.2–5.8)	3.4 (1.7–9.1)	3.2 (1.4–5.6)	2.3 (0.4–4.1)
Outcomes				
Number with AMI (%)	130 (18.5)	79 (17.1)	29 (15.2)	64 (7.9)
Number with ACS (%)	151 (21.5)	94 (20.3)	37 (19.4)	81 (10.0)
Number with death at 30 days (%)	5 (0.7)	6 (1.3)	3 (1.6)	1 (0.1)
Number with incident AMI at 30 days (%)	2 (0.3)	12 (2.6)	0 (0.0)	0 (0.0)
Number with coronary revascularisation at 30 days (%)	99 (14.1)	46 (10.0)	20 (10.5)	55 (6.8)
Number with coronary stenosis at 30 days (%)	111 (15.8)	55 (11.9)	30 (15.7)	91 (11.3)
Predictors in the T-MACS model				
Acute ECG ischaemia (%)	196 (27.9)	105 (22.7)	49 (25.7)	0 (0.0)
Worsening angina (%)	108 (15.4)	94 (20.3)	25 (13.1)	125 (15.5)
Patient reports vomiting in association with the chest pain (%)	47 (6.7)	33 (7.1)	10 (5.2)	35 (4.3)
Sweating observed (%)	82 (11.7)	25 (5.4)	13 (6.8)	27 (3.3)
Systolic BP <100 mm Hg (%)	23 (3.3)	17 (3.7)	6 (3.1)	27 (3.3)
hs-cTnT, median (IQR)	7.6 (<3–17.5)	9.8 (5.3–22.9)	4.0 (<3–16.0)	7.2 (4.6–11.9)
hs-cTnT >14 ng/L (%)	212 (30.2)	181 (39.2)	46 (24.1)	159 (19.7)
Pain radiating to right arm or shoulder (%)	69 (9.8)	59 (12.8)	24 (12.6)	93 (11.5)

ACS, acute coronary syndromes; AMI, acute myocardial infarction; hs-cTnT, high sensitivity cardiac troponin T; T-MACS, Troponin-only Manchester Acute Coronary Syndromes.

Table 3 Diagnostic performance of the T-MACS model as a 'rule out' test (ie, 'very low risk' vs all other groups) in the derivation and validation cohorts

	Derivation set (n=703)		Validation study (n=1459)	
	For AMI	For ACS	For AMI	For ACS
Sensitivity	99.2 (95.8–100.0)	98.7 (95.3–99.8)	98.8 (95.9–99.9)	98.1 (95.2–99.5)
Specificity	46.1 (41.9–50.3)	47.6 (43.4–51.9)	45.7 (42.9–48.5)	47.0 (44.2–49.8)
Positive predictive value	29.5 (25.2–34.0)	34.0 (29.6–38.7)	19.6 (17.0–22.4)	23.9 (21.1–26.9)
Negative predictive value	99.6 (97.9–100.0)	99.3 (97.3–99.9)	99.7 (98.8–100.0)	99.3 (98.3–99.8)
Positive likelihood ratio	1.84 (1.70–1.99)	1.88 (1.74–2.05)	1.82 (1.73–1.92)	1.85 (1.75–1.96)
Negative likelihood ratio	0.02 (0.00–0.12)	0.03 (0.01–0.11)	0.03 (0.01–0.10)	0.04 (0.02–0.11)

ACS, acute coronary syndromes; AMI, acute myocardial infarction; T-MACS, Troponin-only Manchester Acute Coronary Syndromes.

range on serial sampling. No patients in the 'very low risk' group who had not already been diagnosed with ACS had detection of angiographic coronary stenosis >50% (the secondary outcome) within 30 days.

Performance in the validation set

In the validation set, T-MACS gave an AUC of 0.90. Again, diagnostic performance is summarised in tables 3 and 4. A total of 40.4% (n=590) patients would have been 'ruled out' by being classified as 'very low risk', with 99.3% NPV (95% CI 98.3% to 99.8%) for ACS and 99.7% (98.8%–100.0%) for AMI. Another 4.7% (n=69) patients would have had ACS 'ruled in' by being identified as 'high risk'. The PPV of T-MACS for 'ruling in' ACS was 84.0% (95% CI 73.7% to 91.5%). The performance of T-MACS in each individual cohort within the validation set is shown in the online supplementary appendix.

Four patients in the 'very low risk' group had ACS. Two of these patients had AMI. Of those one patient, who had chest pain in association with palpitations and an hs-cTnT concentration rising from 6 ng/L on arrival to 43 ng/L at 12 hours, was later diagnosed with paroxysmal supraventricular tachycardia. Thus it would appear that this patient had type 2 AMI. While contemporaneous knowledge of this would have excluded the patient from the study, the diagnosis of supraventricular tachycardia was not recognised until later and thus the patient was eligible for inclusion. The other patient with AMI had an hs-cTnT concentration of 6 ng/L rising to 18 ng/L at 6 hours. CT coronary angiography showed a moderate stenosis to the left anterior descending artery, but the patient did not undergo

coronary intervention. Two further patients in the 'very low risk' group had ACS, both of whom underwent symptom-induced coronary revascularisation within 30 days (4 and 8 days after presentation, respectively). A total of seven (1.2%) further patients in the 'very low risk group' developed the secondary outcome of angiographic stenosis detected within 30 days (without undergoing coronary intervention).

Paired comparison with the original MACS rule

A total of 1330 patients (187 with ACS including 150 with AMI) had H-FABP concentrations available and were included in the paired analysis. The AUC was 0.90 for MACS and 0.91 for T-MACS, giving an absolute difference of 0.01 (95% CI 0.00 to 0.02, p=0.06). The original MACS would have 'ruled out' ACS in 18.0% (n=239) patients, of whom none had ACS, compared with 40.5% (n=538) for T-MACS, of whom 3 (0.6%) had ACS. Thus, the sensitivity of MACS was 100.0% (95% CI 98.1% to 100.0%) compared with 98.4% (95% CI 95.4% to 99.7%) for T-MACS: absolute difference 1.6%, 95% CI = -0.7% to 1.6%, p=0.25. At this 'rule out' threshold, however, the specificity of MACS was 20.9% (95% CI 18.6% to 22.4%) compared with 46.8% (95% CI 43.9% to 49.8%) for T-MACS: absolute difference 25.9% (95% CI 25.3% to 25.9%, p<0.0001; table 5).

As a 'rule in' tool ('high risk' vs 'not high risk') in the validation set, T-MACS 'ruled in' a smaller proportion of patients than the original MACS (4.4% vs 5.5%, difference 1.1% (95% CI 0.6% to 1.1%, p=0.0001). With MACS, 83.3% (n=60/72) patients in the 'high risk' group had ACS compared with 91.4% (n=53/58) with T-MACS.

Table 4 Proportion of patients with AMI and major adverse cardiac event (MACE) in each of the T-MACS risk groups (derivation and validation studies)

	Very low risk	Low risk	Moderate risk	High risk
Derivation study				
Total number of patients (%)	265 (37.7)	122 (17.4)	245 (34.9)	71 (10.1)
Number (%) with AMI	1 (0.4)	4 (3.3)	56 (22.9)	69 (97.2)
Number (%) with ACS	2 (0.8)	7 (5.7)	71 (47.0)	71 (100.0)
Validation study				
Total number of patients (%)	590 (40.4)	382 (26.2)	418 (28.6)	69 (4.7)
Number (%) with AMI	2 (0.3)	14 (3.7)	93 (22.2)	63 (91.3)
Number (%) with ACS	4 (0.7)	24 (6.3)	121 (28.9)	63 (91.3)

ACS, acute coronary syndromes; AMI, acute myocardial infarction; T-MACS, Troponin-only Manchester Acute Coronary Syndromes.

Paired comparison with the 'LoD strategy'

All 1459 patients in the validation set were included in this analysis. In total, 468 (32.1%) patients had hs-cTnT concentrations <5 ng/L and no ECG ischaemia. Of those patients, 4 (0.9%) had ACS (none of whom had AMI). The sensitivity of T-MACS and the LoD strategy for ACS was identical (98.1%, absolute difference 0.0%, 95% CI -2.2% to 2.2%, p=1.00), but T-MACS had greater specificity (47.0% vs 37.2%, absolute difference 9.8%, 95% CI 6.7% to 12.7%, p<0.0001). Thus, T-MACS would have 'ruled out' ACS in 40.4% (n=590) patients, compared with 32.1% (n=468) for the LoD strategy (see online supplementary table S5).

DISCUSSION

We have successfully re-derived and externally validated the MACS model as T-MACS. T-MACS can now be used more widely than MACS because it requires only the readily available

Table 5 Paired comparison of the sensitivity and specificity of the MACS and T-MACS models for ACS in the derivation and validation studies

	MACS	T-MACS	Absolute difference (95% CI), p value*
Derivation set			
Sensitivity	99.3 (96.4–100.0)	98.7 (95.3–99.8)	0.7% (–0.6 to 0.7), p=1.00
Specificity	45.2 (40.9–49.4)	47.6 (43.4–51.9)	2.8% (1.0 to 3.8), p=0.003
Validation set			
Sensitivity	100.0% (95% CI 98.1% to 100.0%)	98.4% (95.4%–99.7%)	1.6% (95% CI –0.7% to 1.6%), p=0.25
Specificity	20.9% (95% CI 18.6% to 22.4%)	46.8% (43.9%–49.8%)	25.9% (95% CI 25.3% to 25.9%), p<0.0001

*McNemar's test for paired proportions. N=698 in the derivation set and N=1331 in the validation set (5 patients in the derivation set and 131 in the validation set did not have an available sample for measurement of heart-type fatty acid binding protein concentration and were therefore not included in this analysis). This explains the minor differences in sensitivity and specificity compared with those reported in table 3.

ACS, acute coronary syndromes; T-MACS, Troponin-only Manchester Acute Coronary Syndromes.

hs-cTnT and not the less accessible H-FABP biomarker. Its use requires a computerised calculation but implementation advice and calculators are available on request from the lead author (RB). Examples of the output from a T-MACS calculator are demonstrated in the online supplementary material.

Although H-FABP was a strong predictor of ACS in our original study, its inclusion may present a barrier to clinical implementation at some centres, which has been highlighted in the literature.^{12 13} This new evidence suggests that a model using hs-cTnT as the only biomarker gives comparable sensitivity and greater specificity as a 'rule out' tool. Importantly, T-MACS would enable a greater proportion of patients to be 'ruled out' following a single blood test than either the original MACS model or the LoD strategy. Interestingly, we noted that both models had similar specificity in the derivation cohort. However, H-FABP was measured using a semi-automated ELISA in that cohort. We used an automated assay in the validation set, which is more relevant to clinical practice and may explain the lower specificity of the original MACS model in that cohort.

T-MACS has the added advantage of risk-stratifying the patients who cannot be 'ruled out', pending further investigation, such that patients in the 'high risk group' can be considered to have ACS 'ruled in' with high PPV. This is particularly important given concerns about the high prevalence of elevated hs-cTnT concentrations among patients presenting to the ED who do not have ACS.¹⁴ Emergency physicians need an effective 'rule out' tool and a tool that will determine which patients can have ACS immediately confirmed. This would help to ensure appropriate, selective and judicious use of high dependency and specialist resources and would potentially enable early treatment to be targeted to those who stand to benefit while minimising unnecessary risk (pending further investigation) to lower risk patients. It should be noted, however, that T-MACS is intended to be assistive rather than directive and should therefore be used alongside (rather than instead of) clinical judgement in any individual clinical scenario.

Interestingly, the coefficients in the original MACS meant that no patient with an hs-cTnT concentration >14 ng/L (the 99th percentile) could have ACS 'ruled out'. In T-MACS, the absence of H-FABP caused an adjustment such that the effective hs-cTnT threshold is lower. With T-MACS, patients will only be 'ruled out' if each of the features incorporated in the model is absent and if the hs-cTnT concentration is <10 ng/L, which was 40% of the cohort. Thus, T-MACS presents another novel way of using hs-cTnT concentrations below the 99th percentile to achieve early 'rule out', building on previous work evaluating the 'LoD rule out' and 1-hour strategies.^{3 15} While this feature does mean that T-MACS could be used as a simple checklist ('rule out' only if each feature is absent) without affecting sensitivity and NPV, the

granularity of the model presented allows for superior overall risk stratification and has potentially important advantages for clinicians and patients, which are potential avenues for future research.

Limitations

We should note that validation cohort 3 (Poole) excluded patients with evidence of ECG ischaemia. MACS and T-MACS are designed to risk-stratify 'all comers' with suspected cardiac chest pain. This difference in inclusion criteria may therefore account for the smaller proportion of patients in the 'high risk' group and the lower PPV of being 'high risk' in that cohort.

In addition, the T-MACS rule incorporates hs-cTnT concentrations, which relates to a single commercially available high sensitivity troponin assay. Performance may be different with other troponin assays and this should be a focus for future work. Lastly, it is possible that decisions to undertake coronary angiography were influenced by elements of the MACS and T-MACS models (eg, ECG ischaemia or hs-cTnT concentration in validation cohort 3, the only cohort in which hs-cTnT was used in routine practice during the study period). This could have influenced the observed incidence of this outcome in different MACS rule risk groups and is a potential limitation of all observational research in this field.

Future directions

MACS and T-MACS show great promise to reduce the number of unnecessary hospital admissions for patients who present to EDs with chest pain. At present, chest pain is the most common reason for emergency hospital admission, accounting for over a quarter of a million hospital admissions each year in England and Wales alone.¹⁶ If 40% of those patients can be safely discharged immediately from the ED following a single blood test, the cost savings for health services will be substantial and this is likely to have a large impact on the current challenges we face with ED and hospital overcrowding.¹⁷ Following on from this work, external validation in other cohorts will help to ensure that our findings can be generalised to other settings. Our findings also pave the way for evaluation of the impact of clinical implementation, such as in the context of a randomised controlled trial.

It is important to note that there are other emerging alternatives that could potentially achieve a similar reduction in unnecessary hospital admissions for these patients. Some strategies rely on serial troponin testing over 1–2 hours^{15 18 19} while others, such as the History, Electrocardiogram, Age, Risk Factors, Troponin (HEART) score or Triage Rule-out Using high-Sensitivity Troponin protocol, could be used to discharge patients after a single troponin test.^{13 20–22} There is growing evidence to support the single test LoD rule out strategy.^{1–3} All of

these strategies have relative advantages and disadvantages. Single test strategies such as the T-MACS rule have the advantage of facilitating rapid decisions soon after patients arrive in the ED with minimal inconvenience for patients and no requirement for serial blood sampling.

It is, of course, possible that the optimal diagnostic pathway will require a combination of a single test strategy (which will 'rule in' and 'rule out' ACS in a proportion of patients) followed by serial sampling over 1–3 hours for patients who remain in the 'observational zone' (which equates to the T-MACS 'low' and 'moderate' risk groups). At each time point, fewer patients will remain in the observational zone until all patients have either had ACS 'ruled out' or 'ruled in'. Such a strategy may make the most efficient use of healthcare resources and make the most substantial contribution to unburdening overcrowded EDs and hospitals, but will require further evaluation in clinical practice.

Finally, it will be important to determine the acceptable risk of missed ACS for a rule out strategy in practice. Clearly, no strategy could ever achieve perfect sensitivity and NPV. Even with an observed NPV of 100.0%, the lower bound of the 95% CI will always extend below that. Our work suggests that the post-test probability of ACS in the T-MACS 'very low risk' group is <1%, which may be considered acceptable. It is important to recognise, however, that the sensitivity is 98.8% and thus 1.2% of patients with ACS would not be identified. An international survey demonstrated that emergency physicians are relatively risk averse, with only 40% accepting a 1% risk of MACE within 30 days (and thus a 99% NPV).²³ However, strategies may be cost-effective at a much lower threshold and patients may be willing to accept greater degrees of risk.²⁴ The use of the T-MACS model to facilitate shared decision making, which has been shown to be effective in this patient group, is an avenue worthy of future evaluation.

CONCLUSIONS

With a single blood test at the time of arrival in the ED, T-MACS identifies 40% of patients as being at 'very low risk'. These patients have <1% probability of ACS, which may be considered to 'rule out' the diagnosis. Similarly, T-MACS can 'rule in' ACS in approximately 5% of patients with high PPV. Future work should focus on evaluation of the impact of T-MACS when used in practice, particularly when combined with serial troponin sampling over 1–3 hours and in conjunction with shared decision making.

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REFERENCES

- 1 Body R, Carley S, McDowell G, *et al*. Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay. *J Am Coll Cardiol* 2011;58:1332–9.
- 2 Body R, Burrows G, Carley S, *et al*. High-sensitivity cardiac troponin t concentrations below the limit of detection to exclude acute myocardial infarction: a prospective evaluation. *Clin Chem* 2015;61:983–9.
- 3 Bandstein N, Ljung R, Johansson M, *et al*. Undetectable high-sensitivity cardiac troponin T level in the Emergency Department and risk of myocardial infarction. *J Am Coll Cardiol* 2014;63:2569–78.
- 4 Body R, Carley S, McDowell G, *et al*. The Manchester Acute Coronary Syndromes (MACS) decision rule for suspected cardiac chest pain: derivation and external validation. *Heart* 2014;100:1462–8.
- 5 Body R, Burrows G, Carley S, *et al*. The Manchester Acute Coronary Syndromes (MACS) decision rule: validation with a new automated assay for heart-type fatty acid binding protein. *Emerg Med J* 2015;32:769–74.
- 6 Radecki R. The unusable Manchester chest pain instrument. *Emergency Medicine Literature of Note*. 2014 (cited 31 March 2015). <http://www.emlitofnote.com/2014/05/the-unusable-manchester-chest-pain.html>
- 7 Davidson C, Datta D. MACS CDR. RCEM FOAMed Network. 2015 (cited 31 March 2015). <http://www.cemfoamed.co.uk/portfolio/macs-cdr/>
- 8 Apple FS, Jaffe AS. Clinical implications of a recent adjustment to the high-sensitivity cardiac troponin T assay: user beware. *Clin Chem* 2012;58:1599–600.
- 9 Thygesen K, Alpert JS, Jaffe AS, *et al*. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012;60:1581–98.
- 10 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988;44:837–45.
- 11 Stiell IG, Wells GA. Methodologic standards for the development of clinical decision rules in emergency medicine. *Ann Emerg Med* 1999;33:437–47.

- 12 Brace-McDonnell SJ, Laing S. When is low-risk chest pain acceptable risk chest pain? *Heart* 2014;100:1402–3.
- 13 Carlton EW, Cullen L, Than M, *et al.* A novel diagnostic protocol to identify patients suitable for discharge after a single high-sensitivity troponin. *Heart* 2015;101:1041–6.
- 14 Vafaie M, Biener M, Mueller M, *et al.* Analytically false or true positive elevations of high sensitivity cardiac troponin: a systematic approach. *Heart* 2014;100:508–14.
- 15 Mueller C, Giannitsis E, Christ M, *et al.* Multicenter evaluation of a 0-hour/1-hour algorithm in the diagnosis of myocardial infarction with high-sensitivity cardiac troponin T. *Ann Emerg Med.* 2016;68:76–87.e4.
- 16 The Health and Social Care Information Centre. Hospital Episode Statistics, Admitted Patient Care—England, 2012-13: Primary diagnosis, 3 characters table. (cited 25 November 2013). <http://www.hesonline.nhs.uk>
- 17 Iacobucci G. Waits for emergency care are worst for 10 years, figures show. *BMJ* 2015;350:h66.
- 18 Than M, Cullen L, Aldous S, *et al.* 2-Hour accelerated diagnostic protocol to assess patients with chest pain symptoms using contemporary troponins as the only biomarker: the ADAPT trial. *J Am Coll Cardiol* 2012;59:2091–8.
- 19 Than M, Flaws D, Sanders S, *et al.* Development and validation of the Emergency Department Assessment of Chest pain Score and 2 h accelerated diagnostic protocol. *Emerg Med Australas* 2014;26:34–44.
- 20 Backus BE, Six AJ, Kelder JC, *et al.* Chest pain in the Emergency Room: a multicentre validation of the HEART score. *Crit Pathw Cardiol* 2010;9:164–9.
- 21 Backus BE, Six AJ, Kelder JC, *et al.* A prospective validation of the HEART score for chest pain patients at the emergency department. *Int J Cardiol* 2013;168:2153–8.
- 22 Six AJ, Cullen L, Backus BE, *et al.* The HEART score for the assessment of patients with chest pain in the emergency department: a multinational validation study. *Crit Pathw Cardiol* 2013;12:121–6.
- 23 Than M, Herbert M, Flaws D, *et al.* What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department? *Int J Cardiol* 2013;166:752–4.
- 24 Hess EP, Knoedler MA, Shah ND, *et al.* The chest pain choice decision aid: a randomized trial. *Circ Cardiovasc Qual Outcomes* 2012;5:251–9.