Diagnostic Accuracy of Clinical Pathways for Suspected Acute Myocardial Infarction in the Out-of-Hospital Environment

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Study objective: Chest pain is one of the most common reasons for emergency ambulance calls. Patients are routinely transported to the hospital to prevent acute myocardial infarction (AMI). We evaluated the diagnostic accuracy of clinical pathways in the out-of-hospital environment. The Troponin-only Manchester Acute Coronary Syndromes decision aid and History, ECG, Age, Risk Factors, Troponin score require cardiac troponin (cTn) measurement, whereas the History and ECG-only Manchester Acute Coronary Syndromes decision aid and History, ECG, Age, Risk Factors score do not.

Methods: We conducted a prospective diagnostic accuracy study at 4 ambulance services and 12 emergency departments between February 2019 and March 2020. We included patients who received an emergency ambulance response in whom paramedics suspected AMI. Paramedics recorded the data required to calculate each decision aid and took venous blood samples in the out-of-hospital environment. Samples were tested using a point-of-care cTn assay (Roche cobas h232) within 4 hours. The target condition was a diagnosis of type 1 AMI, adjudicated by 2 investigators.

Results: Of 817 included participants, 104 (12.8%) had AMI. Setting the cutoff at the lowest risk group, Troponin-only Manchester Acute Coronary Syndromes had 98.3% sensitivity (95% confidence interval 91.1% to 100%) and 25.5% specificity (21.4% to 29.8%) for type 1 AMI. History, ECG, Age, Risk Factors, Troponin had 86.4% sensitivity (75.0% to 98.4%) and 42.2% specificity (37.5% to 47.0%); History and ECG-only Manchester Acute Coronary Syndromes had 100% sensitivity (96.4% to 100%) and 3.1% specificity (1.9% to 4.7%), whereas History, ECG, Age, Risk Factors had 95.1% sensitivity (88.9% to 98.4%) and 12.1% specificity (9.8% to 14.8%).

Conclusion: With point-of-care cTn testing, decision aids can identify patients at a low risk of type 1 AMI in the out-of-hospital environment. When used alongside clinical judgment, and with appropriate training, such tools may usefully enhance out-of-hospital risk stratification. [Ann Emerg Med. 2023;■:1-11.]

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BACKGROUND

Chest pain is the one of the most common reasons for emergency medical service calls, accounting for up to 2,000 calls per day in England.[1] When assessing patients with chest pain, paramedics must consider the possibility of several serious diagnoses including aortic dissection, pulmonary embolism, and, most commonly, acute myocardial infarction (AMI). Although ECG can rule in ST elevation myocardial infarction (STEMI), it is not currently possible to diagnose or rule out non-ST elevation myocardial infarction (NSTEMI) without transport to the hospital for cardiac troponin (cTn) testing.

In the emergency department (ED), laboratory-based high-sensitivity cTn (hs-cTn) testing, can "rule out" AMI with serial troponin testing over as little as 1 hour, or following a single blood test with the use of validated risk assessment tools such as the HEART score or the Troponin-only Acute Coronary Syndromes (T-MACS) decision aid (Figure 1).[2-4] Although these were originally designed to be used with laboratory-based cTn assays, both T-MACS and HEART decision aids have also been validated using point-of-care assays.[5,6] More recently, the HEAR score and the History and ECG-only Manchester Acute Coronary Syndromes (HE-MACS) decision aid have

Editor's Capsule Summary

What is already known on this topic

Risk assessment tools for suspected acute myocardial infarction (AMI) and point-of-care troponin measurement can support clinical decisionmaking in the emergency department.

What question this study addressed

How accurate are the T-MACS, HE-MACS, HEART, and HEAR risk assessment tools and point-of-care troponin measurement for out-of-hospital diagnosis of AMI?

What this study adds to our knowledge

In this study of 812 out-of-hospital chest pain patients T-MACS had 98.3% sensitivity and 25.5% specificity for type 1 AMI. The other risk assessment tools and point-of-care troponin measurement alone had insufficient sensitivity to rule out AMI or insufficient specificity to be clinically useful.

How this is relevant to clinical practice

T-MACS may aid out-of-hospital decisionmaking aimed at ruling out aAMI, but other serious causes of chest pain still need to be considered.

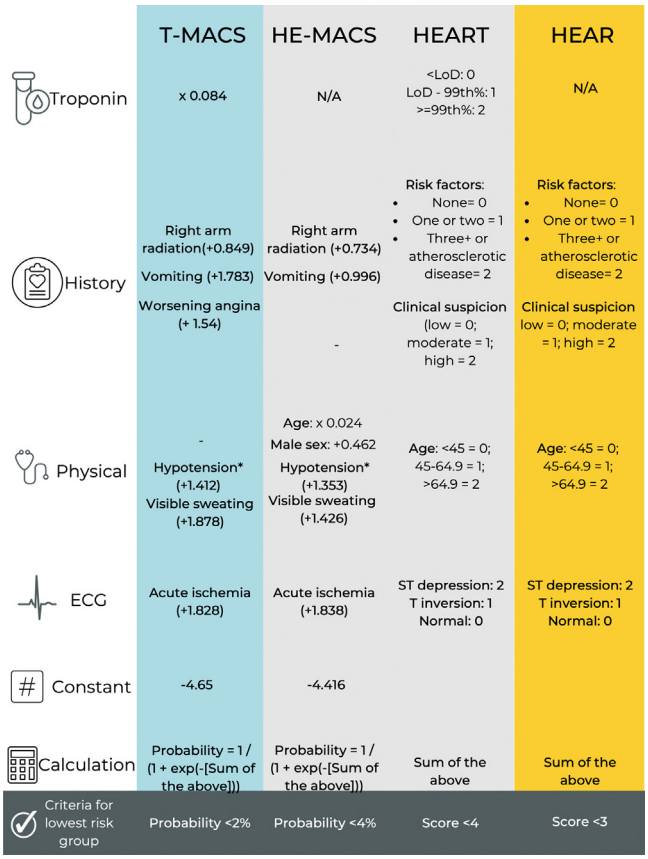

Figure 1. Details of the T-MACS, HE-MACS, HEART, and HEAR decision aids. For T-MACS and HE-MACS decision aids, the probability of ACS was calculated from the sum of the values depicted (x), as follows: $p-1/(1+e^{-x})$. *Hypotension = systolic blood pressure <100 mmHg on arrival. *ACS*, acute coronary syndrome; *LoD*, limit of detection; *HE-MACS*, History and ECG-only Manchester Acute Coronary Syndromes; *HEAR*, History, ECG, Age, Risk Factors; *HEART*, History, ECG, Age, Risk Factors, Troponin; *T-MACS*, Troponin-only Manchester Acute Coronary Syndromes; *99th %*, 99th percentile upper reference limit.

been developed to rule out NSTEMI without any troponin testing in the ED.[7,8]

The transfer of established ED risk stratification methods, with and without the requirement for cTn testing, to the out-of-hospital setting may support paramedics when deciding which high-risk patients require direct transfer to specialist centers, and which low-risk patients may be appropriately directed away from increasingly stretched ED services. In the short term, this may involve redirection to community-based ambulatory care facilities or urgent care centers. With further work, adoption of these decision aids may help guide paramedic clinical judgment such that it may be possible to identify patients with sufficiently low probability of AMI and other serious conditions, who could be safely left at scene and managed without any urgent ambulance transfer to the hospital.

Previous out-of-hospital work demonstrated that HEART and HEAR scores[9-11] can discriminate risk, but their optimal use has yet to be defined. Neither T-MACS nor HE-MACS decision aid has previously been evaluated in the out-of-hospital environment. We, therefore, aimed to evaluate the diagnostic accuracy of 4 cardiac risk assessment tools (T-MACS, HE-MACS, HEART, and HEAR) and a point-of-care cTn test alone, for the diagnosis of AMI in the out-of-hospital environment.

MATERIALS AND METHODS

Design and Setting

The Pre-hospital Evaluation of Sensitive Troponin study was a prospective diagnostic test accuracy study involving 4 ambulance services and 12 EDs in the United Kingdom. The protocol has been published.[12] This study was approved by the National Ethics Service (Ref 18/ES/0101),

registered at ClinicalTrials.gov (identifier NCT03561051), and has been reported in accordance with the Standard for Reporting of Diagnostic Accuracy Studies guidelines.[13]

All participating paramedics were provided with the following training, either online or face to face: (1) fundamentals of good clinical practice; (2) study protocol training, which included data collection requirements for the 4 decision aids studied; (3) venepuncture training (paramedics were trained to draw blood from an intravenous cannula); and (4) ECG interpretation. Participating paramedics routinely interpreted ECGs for signs of STEMI and undertook intravenous cannulation. However, they were not routinely required to interpret ECGs for ischemia or to draw blood, hence the requirement for additional training.

Participant Selection

Adult patients (aged ≥18 years) receiving an emergency ambulance response were eligible for inclusion if they had chest pain and suspected NSTEMI. Exclusion criteria were as follows: STEMI, presence of another condition that required immediate transfer to the hospital, inability to give informed verbal consent, and the absence of chest pain in the 24 hours prior to paramedic attendance. If paramedics did not suspect that a patient's symptoms could potentially represent AMI, they did not enroll them in the study.

All participants providing initial verbal consent in the ambulance to participate in the study proceeded to have a 4.5-mL venous blood sample drawn into a lithium heparin Vacutainer (Becton-Dickinson) from an intravenous cannula placed as part of normal care.

Data Collection

Out-of-hospital environment. Attending paramedics contemporaneously recorded all clinical data required to calculate the T-MACS, HE-MACS, HEART, and HEAR scores out-of-hospital using a structured case report form and used only their own clinical interpretation of the history and ECG. Clinical care otherwise progressed as normal, and the patient was conveyed to the hospital. The out-of-hospital data collected were later assimilated into risk assessment tool results but were not used to guide clinical care in any way, and the ambulance dispatch process was unaffected. We also collected data on patient demographics, risk factors for coronary artery disease, and the time of symptom onset.

Hospital environment. On arrival to the hospital, the patient's out-of-hospital blood sample was secured by members of the study research team. Samples were tested within 4 hours of sample collection using the Roche Cobas h232 point-of-care cardiac troponin T (cTnT) assay. This assay does not have a defined 99th percentile upper reference limit (URL) but has a limit of detection of 0.04 ng/mL, which is the threshold used for diagnosis. This describes the assay for the index test, not the reference standard, which is described below.

As soon as possible after ED attendance, the study team at the relevant hospital approached patients for written informed consent. If this was not possible, participants were contacted by telephone to obtain either written informed consent (by email) or witnessed verbal consent (by telephone). If written informed consent was not provided, participants were withdrawn from the analysis.

Outcome Measures

The primary outcome/target condition was a diagnosis of type 1 AMI,[14] established at the time of initial hospital admission. Secondary outcomes at 30 days were the following: (1) the development of a major adverse cardiac event, which included all-cause death, all-coronary revascularization procedures, and all AMIs, and (2) the diagnosis of type 1 or type 2 AMI.[14] Discharge diagnoses were retrieved from case notes of all participants.

The reference standard for the determination of myocardial injury in each patient was a concentration of cTn of above the 99th percentile URL as determined by the laboratory cTn assay in use at the study site to which the patient presented. Prior to study commencement, site protocols for the diagnosis of myocardial injury were evaluated and confirmed to be in accordance with national (National Institute for Health and Care Excellence)[15,16] and/or international (European Society of Cardiology)[3] guidance.

Outcomes were adjudicated independently by 2 investigators (EC and JC) who had access to routine-care cTn test results, clinical information, cardiac investigation results, and clinical outcomes up to 30 days but were blinded to the results of out-of-hospital point-of-care cTn tests and any calculated risk assessment tool outcomes. Adjudication was performed according to the Fourth Universal Definition of Myocardial Infarction,[14] and any discrepancies were resolved by a third investigator (RB).

Follow-up. Patients were followed up for secondary outcomes after 30 days by reviewing the hospital chart and contacting the participant and/or their general practitioner. Electronic patient records were interrogated by clinical research nurses who had received study protocol training. They were not strictly blinded to point-of-care cTn results, but the outcomes of the 4 decision aids under evaluation were not available. Data pertaining to 30-day major adverse cardiac events, such as death and coronary revascularization

procedures, were collected and any patient with a reference troponin concentration of above the 99th percentile URL was independently adjudicated for AMI as described above. Remote monitoring of a sample of records at each site was undertaken (by EC) to verify the accuracy of data collection.

Sample Size

Based on previous work, we anticipated that the specificity of T-MACS would be approximately 45% for AMI[5] and that approximately 10% of participants would have AMI. Using the method described by Flahault et al[17] and assuming we could identify an algorithm with 100% sensitivity and negative predictive values (NPVs), the lower bound of the 95% confidence interval (CI) would be >90% for sensitivity and >98% for NPVs with a sample size of 605 participants. Accounting for the potential loss to follow-up and missing data (approximately 5% to 10% based on the experience in previous similar studies), we planned to include a total of 700 participants with complete data for analysis.

Statistical analysis. Full details of the statistical analysis were set out in a master statistical analysis plan prior to commencing the study (available on request). Analyses were undertaken by the trial statistician (MH). Data were presented as frequencies and percentages or as means and SDs or medians with interquartile ranges, depending on normality of distribution. Performance of scores at predefined cut points was assessed using 2 by 2 tables to calculate the sensitivity, specificity, positive predictive value, and NPV with 95% CIs by dichotomizing the outputs as "rule out" versus "other" and "rule in," using the exact Clopper-Pearson method.

The T-MACS, HE-MACS, HEART, and HEAR risk assessment tools were calculated using previously reported methods.[4,5,7,18] Patients were categorized into "rule out" groups if they were assigned to the T-MACS "very low–risk" group (<2% probability of AMI), the HEART score "low-risk" group (≤3 points), the HE-MACS "very low–risk" group (<4% probability of AMI), or the HEAR score "low-risk" group (≤1 point). We considered that AMI would be "ruled in" for patients in the "high-risk" groups with each risk score, as had been reported previously (≥95% probability of AMI for T-MACS; ≥50% for HE-MACS; ≥7 points for HEART). The HEAR score does not have a high-risk group.

Out-of-hospital point-of-care cTn results were used for the calculation of T-MACS and HEART risk assessment tools. The limit of detection of the point-of-care cTn assay was 0.04 ng/mL. However, T-MACS will only classify those patients with a cTn concentration of <0.01 ng/mL as at a "very low–risk." Therefore, for T-MACS calculation, we considered that all patients with undetectable point-of-care cTn concentrations had a point-of -care cTn concentration of 0.009 ng/mL. The HEART score was similarly modified; patients scored 0 point for a cTn concentration of <0.04 ng/mL and 2 points otherwise. After stakeholder consultation in the design phase, paramedics were asked to classify ECGs as "normal" or "abnormal." Any abnormalities were considered "positive" when applying the T-MACS and HE-MACS decision aids.

RESULTS

Recruitment occurred between February 26, 2019, and March 23, 2020. The flow of participants is illustrated in Figure 2. We recruited more participants than originally stated to account for greater than anticipated attrition regarding point-of-care cTn testing. The baseline characteristics are summarized in Table 1 and a comparison of baseline characteristics between patients with and without point-of-care cTn results available is shown in Table E1 (available at http://www.annemergmed.com). Other than a slightly higher prevalence of prior myocardial infarction in the group with missing point-of-care cTn results (26.5% versus 34.0%), there did not appear to be any clinically important differences between the groups.

Of the 812 participants included in the study, 104 (12.8%) had an adjudicated diagnosis of type 1 AMI relating to their initial hospital admission. A further 16 (2.0%) patients were diagnosed with type 2 AMI within 30 days, all except one of whom was diagnosed on the index admission. A total of 12 patients were lost to follow-up at 30 days, including 2 who had an initial diagnosis of type 1 AMI, 9 who had no AMI, and 1 patient who had missing data for the adjudication of AMI.

The T-MACS and HE-MACS decision aids yielded the lowest probability of AMI for patients in the lowest risk groups (0.9% [n=1] and 0.0% [n=0], respectively). The probability of a "false-negative" diagnosis of AMI was higher for both a HEART score of ≤3 (4.1% [n=8] for type 1 AMI) and a HEAR score of ≤1 (5.6% [n=5] for type 1 AMI). A total of 38.8% of all patients had a HEART score of ≤3, whereas 22.5% of patients were assigned to the very low–risk group with T-MACS. Although there were no "false-negative" diagnoses with the HE-MACS decision aid, the proportion ruled out was small (2.6%) (Table 2).

The test characteristics (measures of diagnostic accuracy) for each pathway studied are shown in Table 3. The data demonstrate that point-of-care cTn alone (cutoff, 0.04 ng/mL) had high specificity for the diagnosis of AMI (95.6%, 95% CI 93.3% to 97.3%) but low sensitivity (51.7%, 95% CI 38.4% to 64.8%). Sensitivity improved to 85.0% if only

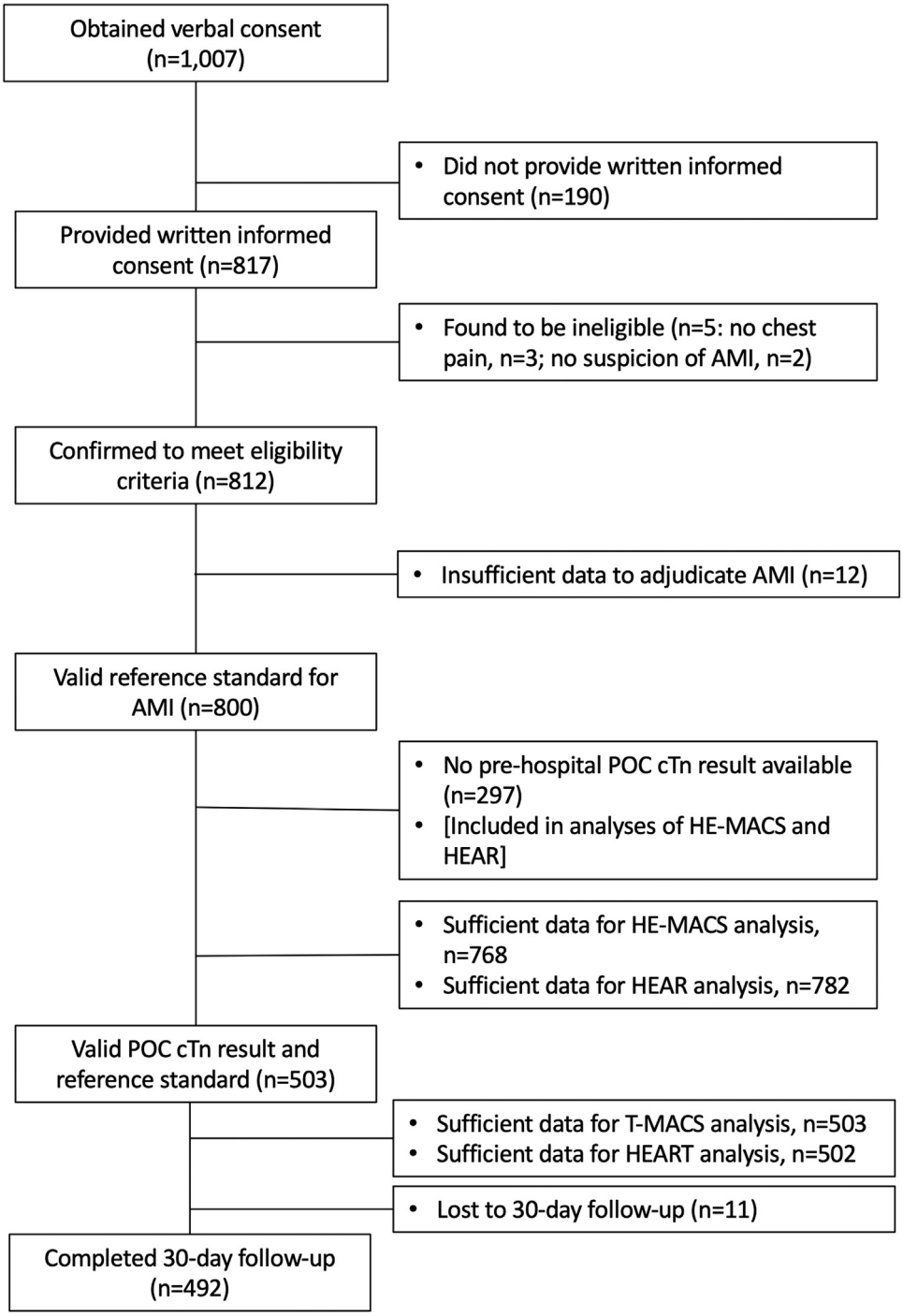

Figure 2. Participant flow diagram. *AMI*, acute myocardial infarction; *cTn*, cardiac troponin; *POC*, point-of-care.

patients with a normal ECG and undetectable cTnI concentrations were considered to have AMI "ruled out." The decision aids achieved higher sensitivity, as reported in Table 3.

A summary of all clinical events that occurred in patients who would have had AMI "ruled out" by each decision aid is shown in Table E2, whereas the discharge diagnoses in those patients are described in Table E3. In summary, no patients in the lowest risk groups for any decision aid died or had a cardiac arrest within 30 days. One (0.9%) patient in the T-MACS "very low–risk" group had an infrarenal aortic dissection noted on computed tomography scan, although this required no intervention. The patient was admitted to a general hospital ward and was discharged

Table 1. Baseline characteristics of included patients.

Demographic Characteristic	All Patients (n=812)	Patients With Any AMI (n=120)	No AMI (n=680)	Missing Data for AMI Adjudication (n=12)
Age (y) (mean [SD]; range)	63.9 (15.1) 19-96	69.4 (13.5) 26-95	63.0 (15.1) 19-96	60.0 (18.0) 33-87
Recorded sex is female	347 (42.7%)	38 (31.7%)	302 (44.4%)	7
Recorded sex is male	465 (57.3%)	82 (68.3%)	378 (55.6%)	5
Previous hyperlipidaemia	187/808 (23.1%)	31/119 (26.1%)	154/677 (22.7%)	2/12
Previous hypertension	428/809 (52.9%)	78/119 (65.5%)	345/678 (50.9%)	5/12
Previous diabetes	159/809 (19.7%)	31/119 (26.1%)	126/678 (18.6%)	2/12
Previous cerebrovascular accident or transient ischemic attack	79/808 (9.8%)	19/119 (16.0%)	60/677 (8.9%)	0/12
Previous peripheral vascular disease	33/808 (4.1%)	7/119 (5.9%)	26/677 (3.8%)	0/12
Prior myocardial infarction	238/811 (29.3%)	52/119 (43.7%)	183/680 (26.9%)	3/12
Prior percutaneous coronary intervention or coronary artery bypass graft	196/810 (24.2%)	40/119 (33.6%)	153/679 (22.5%)	3/12
Family history of heart disease	403/786 (51.3%)	60/119 (50.4%)	338/656 (51.5%)	5/11
Current smoking	193/795 (24.3%)	35/118 (29.7%)	155/666 (23.3%)	3/11
Time from symptom onset	786 with eligible data	116 with eligible data	658 with eligible data	
<3 h	451 (57.4%)	74 (63.2%)	372 (56.4%)	5
3-6 h	116 (14.8%)	16 (13.7%)	99 (15.0%)	1
6-12 h	103 (13.1%)	13 (11.1%)	86 (13.3%)	4
12-24 h	68 (8.7%)	9 (8.5%)	58 (8.6%)	1
24 h to 1 wk	48 (6.1%)	4 (3.4%)	43 (6.7%)	1

after 2 days, with no further events noted at follow-up. No patient in the "very low–risk" groups for T-MACS or HE-MACS decision aid was assigned a discharge diagnosis of AMI or pulmonary embolism. Nine (4.6%) and 5 (5.6%) patients in the "low-risk" groups with a HEART score of $\leq$3 or a HEAR score of $\leq$1, respectively, were given a discharge diagnosis of AMI, although there were no pulmonary embolism or aortic dissections.

For "ruling in" AMI, the T-MACS "high-risk" group had the highest positive predictive value, at 65.0% for type 1 AMI and 80.0% for either type 1 or type 2 AMI. The prevalence of type 1 AMI was 41.5% in those with a "high-risk" HEART score ($\geq$7), whereas the prevalence of type 1 or 2 AMI was 47.7% in the same group. The prevalence of AMI was lower (23.6% for type 1 AMI and 26.8% for type 1 or type 2 AMI) in the "high-risk" group for HE-MACS. Point-of-care cTn testing alone had a positive predictive value of 60.8% (95% CI 46.1% to 74.2%) for type 1 AMI.

LIMITATIONS

A limitation of our study was the amount of missing data. Of the 817 patients who provided written informed consent, only 503 (62%) had a point-of-care cTn assay, full data for T-MACS, and adequate reference standard investigation to permit adjudication of AMI. The predominant reason for exclusion from the final analysis was the lack of point-of-care cTn testing. There were many explanations for this. At times, the supply chain of point-of-care cTn cartridges was compromised, whereas at other times, paramedics would recruit participants (particularly outside routine working hours) when research nurses at relevant EDs were unable to attend within 4 hours to run the point-of-care cTn test. However, this reflects the logistic challenge of undertaking a multicenter study of this nature. Noting the similarity of baseline characteristics between patients with complete data and those with missing point-of-care cTn results, it is unlikely that these factors have substantially affected our findings.

Further, we included patients with pain or discomfort as a potential symptom of AMI. We did not include patients with syncope, palpitations, or dyspnea. Therefore, our findings cannot be extrapolated to those groups. We could not assess interobserver reliability in this study as only one paramedic typically attended patients. Finally, we classified patients with a point-of-care cTn result of <0.04 ng/mL as being at a "very low risk" using the T-MACS decision aid, whereas the original T-MACS model required cTn concentrations to be below 0.01 ng/mL for patients to be at a "very low risk." This could lead to underestimation of the potential sensitivity and NPV when a more sensitive assay

Table 2. T-MACS, HE-MACS, and HEART scores.

Decision Aid	Very Low Risk	Low Risk	Moderate Risk	High Risk
T-MACS	113/503 (22.5%) AMI (T1): 1 (0.9%) AMI (T1/2): 2 (1.8%) MACE: 2 (1.8%)	42/503 (8.3%) AMI (T1): 4 (9.5%) AMI (T1/2): 4 (9.5%) MACE: 3 (7.1%)	308/503 (61.2%) AMI (T1): 29 (9.4) AMI (T1/2): 33 (10.7%) MACE: 26 (8.4%)	40/503 (8.0%) AMI (T1): 26 (65.0%) AMI (T1/2): 32 (80.0%) MACE: 18 (45.0%)
	Very Low Risk	**Low Risk**	**Moderate Risk**	**High Risk**
HE-MACS	20/768 (2.6%) AMI (T1): 0 (0.0%) AMI (T1/2): 0 (0.0%) MACE: 0 (0.0%)	83/768 (10.8%) AMI (T1): 1 (1.2%) AMI (T1/2): 2 (2.4%) MACE: 0 (0.0%)	508/768 (66.2%) AMI (T1): 64 (12.6%) AMI (T1/2): 72 (14.2%) MACE: 26 (5.1%)	157/768 (20.4%) AMI (T1): 37 (23.6%) AMI (T1/2): 42 (26.8%) MACE: 23 (14.6%)
	Low Risk (≤3)	**Moderate Risk (4-6)**		**High Risk (≥7)**
HEART	195/502 (38.8%) AMI (T1): 8 (4.1%) AMI (T1/2): 9 (4.6%) MACE: 8 (4.1%)	242/502 (48.2%) AMI (T1): 24 (9.9%) AMI (T1/2): 29 (12.0%) MACE: 21 (8.7%)		65/502 (13.0%) AMI (T1): 27 (41.5%) AMI (T1/2): 31 (47.7%) MACE: 19 (29.2%)
		Low Risk (≤1)		**"Other" Risk (>1)**
HEAR		90/782 (11.5%) AMI (T1): 5 (5.6%) AMI (T1/2): 5 (5.6%) MACE: 4 (4.4%)		692/782 (88.5%) AMI (T1): 97 (14.0%) AMI (T1/2): 110 (15.9%) MACE: 79 (11.4%)

MACE, major adverse cardiac event.

is used. Future research should therefore focus on the evaluation of diagnostic accuracy when a more sensitive point-of-care cTn assay is used.

DISCUSSION

Our findings show that the T-MACS decision aid has a high NPV and sensitivity for AMI in the out-of-hospital environment. The other decision aids studied either had an NPV and sensitivity that are likely to be considered too low for clinical implementation,[19] or (in the case of HE-MACS) could only "rule out" AMI in a very small proportion of patients (about 1 in 40). If implemented, T-MACS could identify about 1 in 5 patients as at a "very low risk" for AMI.

In the short term, this may enable more effective out-of-hospital triage with the lowest risk patients diverted away

Table 3. Diagnostic accuracy of the 4 decision aids studied and the point-of-care cTn assay (using out-of-hospital blood samples), both alone and in combination with ECG.

Gold Standard	Test	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Type 1 AMI only	Troponin	51.7% (38.4%, 64.8%)	95.6% (93.3%, 97.3%)	60.8% (46.1%, 74.2%)	93.8% (91.2%, 95.8%)
	Troponin + ECG	85.0% (73.4%, 92.9%)	55.6% (50.9%, 60.3%)	20.2% (15.5%, 25.7%)	96.6% (93.6%, 98.4%)
	T-MACS	98.3% (91.1%, 100%)	25.5% (21.4%, 29.8%)	15.4% (11.9%, 19.4%)	99.1% (95.1%, 100%)
	HE-MACS	100% (96.4%, 100%)	3.05% (1.87%, 4.68%)	13.8% (11.4%, 16.5%)	100% (83.2%, 100%)
	HEART score	86.4% (75.0%, 94.0%)	42.2% (37.5%, 47.0%)	16.8% (12.8%, 21.5%)	95.8% (92.0%, 98.2%)
	HEAR	95.1% (88.9%, 98.4%)	12.1% (9.75%, 14.8%)	14.2% (11.7%, 17.0%)	94.2% (87.0%, 98.1%)
Type 1 or 2 AMI	Troponin	53.5% (41.3%, 65.5%)	97.1% (95.1%, 98.4%)	74.5% (60.4%, 85.7%)	92.9% (90.2%, 95.1%)
	Troponin + ECG	84.5% (74.0%, 92.0%)	56.6% (51.8%, 61.2%)	23.8% (18.7%, 29.6%)	95.8% (92.6%, 97.9%)
	T-MACS	97.2% (90.2%, 99.7%)	25.9% (21.8%, 30.3%)	18.0% (14.3%, 22.2%)	98.2% (93.7%, 99.8%)
	HE-MACS	100% (96.9%, 100%)	3.12% (1.92%, 4.78%)	15.7% (13.2%, 18.6%)	100% (83.2%, 100%)
	HEART	87.0% (76.7%, 93.9%)	43.0% (38.2%, 47.8%)	19.8% (15.5%, 24.7%)	95.3% (91.3%, 97.8%)
	HEAR	95.7% (90.1%, 98.6%)	12.4% (9.94%, 15.1%)	16.1% (13.4%, 19.1%)	94.2% (87.0%, 98.1%)

CI, confidence interval; *cTn*, cardiac troponin; *NPV*, negative predictive value; *PPV*, positive predictive value.

from crowded EDs to urgent care centers or community facilities for further confirmatory investigation, where available. In both the United Kingdom and United States, urgent care centers are typically walk-in facilities focusing on the delivery of care for patients with minor illness or injuries. Facilities vary, with some having access to extensive laboratory and radiology facilities, whereas others rely on point-of-care testing platforms. They enable patients in some communities to receive care locally, although they are not usually equipped to provide definitive specialist care.[20,21] Meanwhile, the highest risk patients could be transported directly to heart attack centers, reducing the need for unnecessary secondary transfers and easing the burden on emergency medical services.

In the longer term, it may be possible to safely leave patients at the scene. Such an approach would need to be underpinned by an emphasis on shared decisionmaking, access to specialist support, and robust "safety-netting" and will require additional training for paramedics and research to study the safety and feasibility of deploying such a clinical pathway. It is also important to note that training and decision aids may be required to assist paramedics in considering possible alternative for serious diagnoses such as pulmonary embolism or aortic dissection. Software or online applications may help future implementation, avoiding the need for paper checklists and permitting computerized calculation of outputs (especially for T-MACS and HE-MACS).

In this study, it appears that there were few serious alternative diagnoses in the "rule out" groups. There were no deaths or cardiac arrests within 30 days. However, there were some clinically important diagnoses. For example, one patient in the T-MACS "very low–risk" group was assigned a diagnosis of infrarenal aortic dissection, although this required no intervention and the patient was discharged uneventfully on day 2. Within the T-MACS "very low–risk" group was one patient with an adjudicated diagnosis of AMI. That patient had a laboratory cTn concentration of 78 ng/L (99th percentile, 14 ng/L) in the ED, rising to over 1,000 ng/L. The out-of-hospital ECG showed inferior STEMI, which had not been recognized. The patient was at a "moderate risk" with HE-MACS owing to their age. Another patient was assigned a discharge diagnosis of congestive cardiac failure following inpatient echocardiography, and two with lower respiratory tract infections. It may therefore be inappropriate to leave all "very low–risk" patients at the scene with no further follow-up arranged. Defining an appropriate care pathway including relevant clinical follow-up will be an important goal for future work.

In recent years, there has been growing interest in the use of out-of-hospital point-of-care cTn assays to "rule out" AMI. The FAMOUS-TRIAGE study recruited 1,127 patients in the out-of-hospital environment, recorded the data required for the calculation of the HEART score, and measured hs-cTn concentrations using stored samples in a central laboratory.[22] In that study, 36% of patients had a "low-risk" HEART score ($\leq$3) and none developed a major cardiac event within the following 30 days. Subsequently, the same investigators evaluated the safety of out-of-hospital clinical decisionmaking directed by a HEART score of $\leq$3 in a before-and-after implementation study in a cohort of 536 patients.[23] The incidence of a major adverse cardiac event was 2.9% among 172 patients prior to implementation and 1.3% among the 149 (28%) patients who were not transported to the hospital after implementation of the HEART score.

The strength of our study is that we examined the diagnostic accuracy for NSTEMI with reference standard laboratory-based hs-cTn testing in EDs. Our findings suggest that a very low–risk T-MACS decision aid outcome is likely to achieve higher sensitivity for NSTEMI than a HEART score of $\leq$3 and is therefore more likely to ensure patient safety after implementation.

Because they do not require point-of-care cTn testing with its costs and training requirements, HE-MACS and HEAR decision aids could be ideal for use in the out-of-hospital setting. However, we found that a HEAR score of $\leq$1 had relatively low sensitivity for implementation. If patients were to receive a full clinical evaluation at an ambulatory or urgent care center, then this may be deemed acceptable. The HE-MACS decision aid had 100% sensitivity for type 1 AMI, but it would only avoid transport for 2.6% of patients, which would have limited the effect on resource utilization. The use of T-MACS decision aid with a point-of-care cTn assay may therefore be the optimal strategy. These findings will be tested in a formal health economic analysis.

Future work should focus on the following aspects: (1) prospective validation of our findings in a larger sample; and (2) the feasibility of implementing point-of-care cTn testing in the out-of-hospital environment, with evaluation of effectiveness, safety, and cost-effectiveness of clinical implementation. This will require careful attention to paramedic training requirements, including device training, ECG training, the use of decision aids, and importantly, how to screen for other possible serious diagnoses such as aortic dissection and pulmonary embolism. Furthermore, the development of point-of-care cTn assays with higher analytical sensitivity and precision than contemporary point-of-care tests[24] is likely to yield further improvement

in diagnostic sensitivity and NPV. Future work should evaluate potential improvement in diagnostic accuracy and efficiency using such assays in the out-of-hospital environment (both when used alone and in combination with T-MACS and HEART decision aids). Finally, it will be important to ensure the external validity of our findings in other health care systems, which may have different patient demographics and risk tolerance.

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Data sharing statement: Please contact Richard Body for any queries regarding access to data. Reasonable requests for anonymous (de-identified) participant data that are in accordance with relevant regulatory approvals will be granted, from the date of publication for a period of 5 years after study completion. These data are currently stored securely and, to date, have not been published in a public repository.

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REFERENCES

1. United Kingdom Health Security Agency. National Ambulance Syndromic Surveillance System: Bulletin (England) [Internet]. 2022. Accessed April 8, 2022. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1044889/UKHSA_NASS_Bulletin_2021_52.pdf
2. Body R, Morris N, Reynard C, et al. Comparison of four decision aids for the early diagnosis of acute coronary syndromes in the emergency department. *Emerg Med J*. 2020;37:8-13.
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;42:1289-1367.
4. 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;168:2153-2158.
5. Body R, Almashali M, Morris N, et al. Diagnostic accuracy of the T-MACS decision aid with a contemporary point-of-care troponin assay. *Heart*. 2019;105:768-774.
6. McDowell G, Almashali M, Morris N, et al. 153 Best-heart score: a re-evaluation of the heart score in the era of point of care troponin testing. In: Acute Coronary Syndromes [Internet]. BMJ Publishing

Group Ltd and British Cardiovascular Society; 2019.p. A127–A127. Accessed April 8, 2022. https://heart.bmj.com/lookup/doi/10.1136/heartjnl-2019-BCS.150
7. Moumneh T, Penaloza A, Cismas A, et al. Evaluation of HEAR score to rule-out major adverse cardiac events without troponin test in patients presenting to the emergency department with chest pain. *Eur J Emerg Med*. 2021;28:292-298.
8. Todd F, Duff J, Carlton E. Identifying low-risk chest pain in the emergency department without troponin testing: a validation study of the HE-MACS and HEAR risk scores. *Emerg Med J*. 2022;39:515-518.
9. Cooper JG, Ferguson J, Donaldson LA, et al. The Ambulance Cardiac Chest Pain Evaluation in Scotland Study (ACCESS): a prospective cohort study. *Ann Emerg Med*. 2021;77:575-588.
10. van Dongen DN, Fokkert MJ, Tolsma RT, et al. Value of prehospital troponin assessment in suspected non-ST-elevation acute coronary syndrome. *Am J Cardiol*. 2018;122:1610-1616.
11. Stopyra JP, Harper WS, Higgins TJ, et al. Prehospital modified HEART score predictive of 30-day adverse cardiac events. *Prehosp Disaster Med*. 2018;33:58-62.
12. Alghamdi A, Cook E, Carlton E, et al. PRe-hospital Evaluation of Sensitive TrOponin (PRESTO) study: multicentre prospective diagnostic accuracy study protocol. *BMJ Open*. 2019;9:e032834.
13. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527.
14. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation [Internet]. 2018;138. Accessed July 3, 2019. https://www.ahajournals.org/doi/10.1161/CIR.0000000000000617
15. National Institute for Health and Care Excellence. High-sensitivity troponin tests for the early rule out of NSTEMI. Diagnostic guidance [DG40] [Internet]. 2020. Accessed January 1, 2021. https://www.nice.org.uk/guidance/dg40
16. National Institute for Health and Care Excellence. Recent-onset chest pain of suspected cardiac origin: assessment and diagnosis. Clinical guideline [CG95] [Internet]. 2016. Accessed January 2, 2022. https://www.nice.org.uk/guidance/cg95
17. Flahault A, Cadilhac M, Thomas G. Sample size calculation should be performed for design accuracy in diagnostic test studies. *J Clin Epidemiol*. 2005;58:859-862.
18. Alghamdi A, Howard L, Reynard C, et al. Enhanced triage for patients with suspected cardiac chest pain: the History and Electrocardiogram-only Manchester Acute Coronary Syndromes decision aid. *Eur J Emerg Med*. 2019;26:356-361.
19. 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;166:752-754.
20. NHS England. About urgent and emergency care [Internet]. NHS England. Accessed February 17, 2023. https://www.england.nhs.uk/urgent-emergency-care/about-uec/
21. American College of Emergency Physicians Board of Directors. Urgent care centers. *Ann Emerg Med*. 2017;70:115-116.
22. Ishak M, Ali D, Fokkert MJ, et al. Fast assessment and management of chest pain patients without ST-elevation in the pre-hospital gateway (FamouS Triage): ruling out a myocardial infarction at home with the modified HEART score. *Eur Heart J Acute Cardiovasc Care*. 2018;7:102-110.
23. Tolsma RT, Fokkert MJ, van Dongen DN, et al. Referral decisions based on a pre-hospital HEART score in suspected non-ST-elevation acute coronary syndrome: final results of the FamouS Triage study. *Eur Heart J Acute Cardiovasc Care*. 2022;11:160-169.
24. Apple FS, Smith SW, Greenslade JH, et al. Single high-sensitivity point-of-care whole-blood cardiac troponin I measurement to rule out acute myocardial infarction at low risk. *Circulation*. 2022;146:1918-1929.