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Identification of high-risk non-ST elevation myocardial infarction at presentation to emergency department. A prospective observational cohort study in North West England

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ABSTRACT

Objectives Early access to invasive coronary angiography and revascularisation for high-risk non-ST elevation myocardial infarction (NSTEMI) improves outcomes and is supported by current guidelines. We sought to determine the most effective criteria at presentation to emergency department (ED) to identify high-risk NSTEMI.

Setting Secondary care centre northwest England with national follow-up.

Participants 1642 consecutive patients (median age 59, 52% male) presenting to ED with a primary symptom of chest pain in whom there is suspicion of NSTEMI.

Primary and secondary measures Multivariate logistic regression analysis for the prediction of all-cause death (primary) and major adverse cardiac event (MACE defined as all-cause death, unplanned coronary revascularisation and adjudicated NSTEMI (third universal definition)) (secondary measure) at 1 year.

Results The incidence of adjudicated NSTEMI was 10.7%, and 1-year mortality was 6.3%. Independent predictors for all-cause death at 1 year were Global Registry of Acute Coronary Events (GRACE) >140, age (per decade increase) and high-sensitive cardiac troponin T (hs-cTnT) >50 ng/L. hs-cTnT >50 ng/L was associated with adjudicated index presentation NSTEMI in the greatest proportion of patients (61.7%). When using MACE at 12 months, as opposed to all-cause death, as an end point History, ECG, Age, Risk factors and Troponin (HEART) score ≥7 was included in the multivariate model and had better prediction of index NSTEMI than GRACE>140. Combining hs-cTnT >50 ng/L and a second independent predictor identified both a high proportion of index NSTEMI and elevated risk of all-cause death at 1 year.

Conclusions hs-cTnT >50 ng/L or HEART score ≥7 appear effective strategies to identify high-risk NSTEMI at presentation to emergency room with chest pain. Multicentre prospective studies enriched with early presenters, and with competitor high-sensitive and point-of-care troponins, are required to validate and extend these findings.

Trial registration number NCT02581540.

Strengths and limitations of this study

- This was a large prospective consecutive series of patients with suspected acute coronary syndrome.
- The diagnosis of myocardial infarction was adjudicated with one hundred percent national follow-up for clinically relevant events to 1 year.
- The index presentations were to a single centre thus limiting external validity.
- Presentations were late thus limiting extrapolation of findings to very early presenters with chest pain.
- Extrapolation to paramedic triage with point-of-care troponin is premature due to the differences in analytic sensitivity between point-of-care and laboratory-based sampling of troponin.

INTRODUCTION

For patients with acute coronary syndrome (ACS) without ST elevation, European Society of Cardiology guidelines recommend a target of performing coronary angiography between 2 and 72 hours after presentation depending on high-risk criteria.[1] The evidence is derived from a number of studies and meta-analyses,[2–9] but primarily driven by subgroup analysis of the largest study to date examining timing of invasive management (TIMing of intervention in patients with Acute Coronary Syndrome TIMACS study).[10] It is important to note that all the studies examining early versus late angiography for non-ST elevation myocardial infarction (NSTEMI) took place before the high-sensitivity troponin era. Biomarker positivity was not mandatory for any of the trials, a situation that would now be inconsistent with the third universal definition of myocardial infarction (MI)[11] or indeed the recently adopted fourth universal definition.[11] The timing of early invasive (and delayed) cardiac catheterisation varied

between studies. Furthermore, some studies[10] did not supply time from admission to diagnosis of MI.

The challenge for clinical pathways for ACS without ST elevation is mainly twofold. First, to diagnose NSTEMI early in an 'undifferentiated' chest pain population and to simultaneously determine risk based on simple criteria. Second, mobilisation of resources to organise invasive management of appropriately defined high-risk NSTEMI in a timely manner is a logistical challenge, particularly if coronary intervention is remote from presentation site for suspected NSTEMI. Such targets are difficult to achieve unless diagnosis and risk stratification are achieved at first medical contact (FMC) with direct transfer to the coronary interventional centre.

Risk scores are often used for the purpose of identifying high-risk MI and to expedite treatment and in particular coronary revascularisation. Of the risk scores, the History, ECG, Age, Risk factors and Troponin (HEART), thrombolysis in myocardial infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) are the most widely used from an international perspective and have the greatest evidence base.[12–14] All of these risk scores have troponins embedded as part of the risk equation. It is also established that high-sensitive troponin values alone are predictive of risk in suspected NSTEMI.[15] However, it is not clear to what extent high-sensitive troponins or ECGs or a range of simple parameters can predict both the diagnosis of NSTEMI and the benefit of revascularisation at presentation to accident and emergency department with chest pain.

We analysed simple predictors of high-risk NSTEMI. We also assessed the ability of TIMI, GRACE and History, ECG, Age, Risk factors and Troponin (HEART) score to identify high-risk NSTEMI from 1642 consecutive (individual patient) presentations to emergency room (ER) with suspected ACS in a major urban centre.

Methodology

This report details and analyses the high-risk cohort from Mersey Acute Coronary syndrome Rule Out Study (MACROS)[16] to investigate prognostic factors for death (from any cause) up to 1 year from presentation to ER with suspected ACS. This was a prespecified analysis. MACROS is a prospective observational cohort study of consecutive, unselected suspected NSTEMI presentations. The definition of suspected non-ST segment elevation was a primary presentation with chest pain and physician decision to sample troponin and undertake an ECG at presentation.

The MACROS cohort consists of 1785 consecutive unselected presentations (1642 patients) with chest pain to a single major urban hospital (Aintree University Hospitals NHS Foundation Trust), between June and November 2011 (inclusive). For multiple presentations during the recruitment period, the first presentation was taken as the index entry with subsequent representations, during study recruitment, assessed for outcomes. The methodology has been extensively detailed.[16] Chest pain onset, time of presentation and troponin sampling were noted during index presentation, to subsequently determine interaction of outcomes with time of troponin sampling relative to chest pain onset.

The National Health Service (NHS) number was recorded for each patient, and outcomes were determined from Health and Social Care Information Centre records of admissions to hospitals in England in the 12 months following initial presentation. Any patient with troponin elevation beyond the 99th percentile (>14 ng/L) underwent non-blinded adjudication, by two physicians for index presentation MI (using the third universal definition). For all subsequent admissions with any ischaemic heart disease or chest pain, International Classification Disease (ICD) codes (online supplementary tables)[16] were linked by NHS number to any hospital in England. These hospitals were contacted for retrieval of clinical records, laboratory results, ECGs and cardiac investigations. In the event of elevated troponin (biomarker), blinded and independent two physician adjudication (with resolution by a third in case of disagreement) of MI was undertaken. Urgent or emergency revascularisation was adjudicated by a single interventional cardiologist. Death was recorded from the morbidity and mortality division uploaded from the national database of morbidity and mortality. As a case ascertainment exercise, to identify cases missed by nationally collected ICD-10 codes, all patients were additionally screened for any coronary revascularisation, not identified by ICD-10 coding, in the regional cardiothoracic service (serving a population of 2.3 million). While all readmissions with elevated troponin were independently adjudicated for type 1 MI, index presentations were assessed separately but in a non-blinded fashion by two physicians.

The dataset has 100% follow-up for up to 1 year with full capture of all-cause death, urgent or emergency coronary revascularisation and any chest pain or any ischaemic heart disease coded representation (captured for adjudication). Table 1 describes the patient population. Eighteen variables were selected for univariate analysis (table 2). The primary end point used was all-cause death at 1 year but MACE (all-cause death, type 1 MI or urgent/emergency coronary revascularisation) as a secondary end point was also evaluated.

TIMI and GRACE scores were determined retrospectively from online calculators by research staff with the use of the chest pain proforma, patient record and ambulance proforma alone. To score positively for ST segment depression in GRACE and TIMI, planar depression of at least 0.5 mm after the J-point was required consistent with the Minnesota criteria.[17] Calculation of HEART score has been detailed in the principal MACROS paper.[16] The character of chest pain was scored exclusively on the narrative in the patient record and/or chest pain proforma. A score of 2 was ascribed when chest pain had documented features suggestive of cardiac chest pain and an absence of non-specific features. A score of 1 was given if there was combination of suspicious and non-specific symptoms and a score of 0 was given if there were only non-specific

Table 1 Patient population

	All	Death (6 weeks)	Death (1 year)	P values (death at 1 year vs all)
Totals	1642	25	104	
Age (median (IQR))	58.8 (47.0–72.3)	74.3 (67.2–87.3)	80.0 (70.2–86.7)	<0.001
Sex (male)	858 (52.3%)	13 (52.0%)	55 (52.9%)	0.826
Risk scores				
TIMI (mean (SD))	1.50 (1.58)	2.00 (1.42)	3.00 (1.60)	<0.001
HEART (mean (SD))	3.50 (2.30)	6.00 (1.85)	6.00 (2.25)	<0.001
GRACE (mean (SD))	101.5 (39.6)	158.0 (40.0)	150.5 (35.5)	<0.001
Hypertension	695 (42.3%)	16 (64.0%)	63 (60.6%)	<0.001
Smoking				
Current	457 (30.3%)	5 (20.0%)	21 (20.2%)	0.750
Previous	463 (30.7%)	10 (40.0%)	44 (42.3%)	0.750
Never	589 (39.0%)	9 (36.0%)	32 (30.8%)	0.750
Diabetes mellitus	237 (14.4%)	9 (36.0%)	29 (27.9%)	<0.001
Dyslipidaemia	432 (26.3%)	6 (24.0%)	31 (29.8%)	0.408
Family history of premature CAD*	337 (20.6%)	1 (4.0%)	6 (5.8%)	0.693
Previous MI	322 (19.6%)	7 (28.0%)	39 (37.5%)	0.000
Previous PCI	170 (10.4%)	2 (8.0%)	13 (12.5%)	0.471
Previous CABG	91 (5.5%)	1 (4.0%)	12 (11.5%)	0.014
Previous stroke	118 (7.2%)	5 (20.0%)	21 (20.2%)	<0.001
Hb (median (IQR)) g/dL	137 (124–148)	121 (103–127)	119 (103–131)	<0.001
Creatinine (median (IQR)) mmol/L	91.0 (79.0–105.0)	107.0 (76.0–129.0)	101.5 (76.5–139.0)	<0.001
Systolic BP (median (IQR))	131.0 (118.0–146.0)	119.0 (102.0–129.0)	129.0 (109.0–148.0)	0.114
Heart rate (median (IQR))	78.0 (67.0–90.0)	108.0 (76.0–121.0)	82.0 (70.5–106.0)	<0.001
CP onset/peak to presentation (median (IQR)) hours	9.7 (2.4–48.0)	16.2 (3.3–48.0)	6.0 (1.6–36.7)	0.473
Time of chest pain to presentation				
<6 hours	682 (42%)	11 (44.0%)	51 (49.0%)	0.066
≥6 hours	946 (58.7%)	13 (52.0%)	51 (49.0%)	0.066
ECG ischaemic†	466 (28%))	13 (52.0%)	55 (52.9%)	<0.001
ST depression ≥0.5 mm	90 (5.5%)	2 (8.0%)	16 (15.4%)	<0.001
T-wave abnormalities				
Nil	1262 (77.0%)	17 (68.0%)	72 (69.2%)	0.066
Flat	73 (4.5%)	2 (8.0%)	6 (5.8%)	0.066
Biphasic	31 (1.9%)	1 (4.0%)	2 (1.9%)	0.066
Inverted	274 (16.7%)	5 (20.0%)	24 (23.1%)	0.066
Current aspirin use	491 (30.0%)	11 (44.0%)	46 (44.2%)	0.001

*CAD= coronary artery disease. defined as first degree relative with myocardial infarction, or coronary revascularisation under the age of 65
†Definition of ischaemic ECG: atrial fibrillation or atrial flutter with ventricular rate ≥110, other arrhythmia, LBBB, paced rhythm, ST segment elevation, ST segment depression, T-wave inversion or T-wave flattening or biphasic T waves in two contiguous leads.
BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CP, chest pain; GRACE, Global Registry of Acute Coronary Events; Hb, haemoglobin; HEART, History, ECG, Age, Risk factors and Troponin; LBBB, left bundle branch block; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

features. Researchers were prompted to grant high suspicion (a score of 2), if there was central chest pain with at least one additional feature such as radiation to the arm/neck/jaw or sweating or relief with glyceryl trinitrate or provocation of chest pain with exertion or emotion/stress. Largely due to education and widespread dissemination of a chest pain proforma prior to study commencement, it was possible to score the history component for HEART

Table 2 Results of single variable logistic regression,

Prognostic variable	N (% of total population, n=1642)	OR (95% CI) (for death at 1 year)	P value	NSTEMI N (%)	MI at 1 year n (%)*	Revascularisation† at 6 weeks n (%)	Revascularisation† at 1 year n (%)	Death at 6 weeks n (%)	Death at 1 year n (%)
hs-cTnT (ng/L)‡									
Median (IQR)	6.2 (3.2–15.2)	1.02 (1.01 to 1.03)	<0.001	0.816	55.2 (24.2–140.2)	23.2 (11.2–43.2)	88.7 (35.2–170.2)	63.2 (21.2–155.2)	37.2 (27.2–74.2)
hs-cTnT >50 ng/L	149 (9.1%)	5.70 (3.62 to 8.97)	<0.001	92 (61.7)	5 (3.4)	38 (25.5)	40 (26.8)	11 (7.4)	33 (22.1)
hs-cTnT >100 ng/L	83 (5.1%)	3.64 (2.00 to 6.63)	<0.001	61 (73.5)	1 (1.2)	28 (33.7)	29 (34.9)	5 (6.0)	15 (18.1)
ST segment depression ≥0.5 mm	90 (5.5%)	3.59 (2.01 to 6.43)	<0.001	33 (36.7)	2 (2.2)	15 (16.7)	17 (18.9)	2 (2.2)	16 (17.8)
ST segment depression ≥1.0 mm	68 (4.1%)	3.85 (2.03 to 7.30)	<0.001	24 (35.3)	2 (2.9)	13 (19.1)	15 (22.1)	2 (2.9)	13 (19.1)
Sex									
Female	781 (47.7%)	0.96 (0.64 to 1.43)	0.826	71 (9.1)	9 (1.2)	16 (2.0)	22 (2.8)	12 (1.5)	48 (6.1)
NSTEMI/Unstable angina	342 (21.2%)	3.03 (2.01 to 4.56)	<0.001	180 (52.6)	15 (4.4)	55 (16.1)	58 (17.0)	5 (1.5)	44 (12.9)
NSTEMI	180 (11%)	3.17 (1.99 to 5.07)	<0.001	180 (100)	12 (6.7)	50 (27.8)	53 (29.4)	2 (1.1)	27 (15)
Age§									
Median (IQR)	58.8 (47.0–72.3)	2.46 (2.06 to 2.93)	<0.001	74.3 (63.3–82.5)	74.3 (62.9–82.2)	62.6 (54.6–74.3)	62.2 (54.6–74.1)	74.3 (67.2–87.3)	80.0 (70.2–86.7)
GRACE									
Median (IQR)	96(70–128)	1.03 (1.03 to 1.04)	<0.001	0.852	140 (115–162)	135 (120–150)	115 (96–143)	111 (96–142)	158 (141–173)
GRACE >140	292 (17.8%)	14.17 (9.09 to 22.09)	<0.001	86 (29.5)	10 (3.4)	17 (5.8)	18 (6.2)	19 (6.5)	73 (25.0)
HEART									
Median (IQR)	3 (2–5)	1.51 (1.39 to 1.66)	<0.001	0.765	7 (6–8)	7 (4–8)	7 (5–8)	7 (5–8)	6 (4–7)
HEART ≥7	199 (12.1%)	5.96 (3.90 to 9.11)	<0.001	113 (56.8)	13 (6.5)	34 (17.1)	37 (18.6)	7 (3.5)	42 (21.1)
TIMI									
Median (IQR)	1 (0–3)	1.77 (1.57 to 1.99)	<0.001	0.776	3 (3–4)	4 (2–5)	3 (2–4)	3 (2–4)	2 (2–4)
TIMI ≥5	87 (5.3%)	5.23 (3.03 to 9.02)	<0.001	42 (48.3)	8 (9.2)	7 (8.0)	9 (10.3)	4 (4.6)	20 (23.0)
≥3 risk factors	573 (34.9%)	1.40 (0.93 to 2.09)	0.106	91 (15.9)	14 (2.4)	26 (4.5)	35 (6.1)	13 (2.3)	44 (7.7)
Atherosclerotic disease	503 (30.6%)	3.10 (2.07 to 4.63)	<0.001	97 (19.3)	19 (3.8)	17 (3.4)	24 (4.8)	12 (2.4)	58 (11.5)
Previous MI	322 (19.6%)	2.66 (1.75 to 4.04)	<0.001	65 (20.2)	16 (5)	9 (2.8)	13 (4.0)	7 (2.2)	39 (12.1)
>1 episodes of CP/angina	311 (19.1%)	1.49 (0.94 to 2.37)	0.101	83 (26.7)	8 (2.6)	37 (11.9)	40 (12.9)	7 (2.3)	26 (8.4)
Pulmonary oedema	27 (1.7%)	4.24 (1.67 to 10.74)	0.008	12 (44.4)	2 (7.4)	1 (3.7)	1 (3.7)	1 (3.7)	6 (22.2)
History of heart failure	93 (5.7%)	5.14 (3.02 to 8.78)	<0.001	19 (20.4)	6 (6.5)	1 (1.1)	2 (2.2)	4 (4.3)	21 (22.6)
Diabetes mellitus	237 (14.4%)	2.47 (1.57 to 3.89)	<0.001	44 (18.6)	8 (3.4)	8 (3.4)	11 (4.6)	9 (3.8)	29 (12.2)

The primary end point used was all-cause death at 1 year as outcome.
*Adjudicated MI at 1 year (excluding index infarction).
†Emergency or urgent coronary revascularisation.
‡Note that hs-cTnT was divided by 10 and included as a continuous variable in the single variable models. Therefore, an OR of 1.02 should be interpreted as the odds of death at 1 year increasing by a factor of 1.02 for every increase in hs-cTnT of 10 ng/L.
§Note that age was divided by 10 and included as a continuous variable in the single and multiple variable models. Therefore, an OR of 2.46 should be interpreted as the odds of death at 1 year increasing by a factor of 2.46 for every increase in age of 10 years.
CP, chest pain; GRACE, Global Registry of Acute Coronary Events; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitive cardiac troponin T; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

score for all our patients. Definitions of high-risk scores (GRACE >140, TIMI ≥5, HEART ≥7), in terms of numerical values, were accepted definitions of these scores from the seminal papers of these respective scores.[12 14 18]

High-sensitivity cardiac troponin T assay

The assay used was the high-sensitivity troponin T (Roche Elecsys). This has been previously evaluated extensively and found to fulfil the definition of high sensitivity with 10% coefficient variation at the 99th percentile.[19]

Performance of this assay across a number of centres has previously been evaluated.[19] Analysis was undertaken in-house with COBAS e601 analysers using a standard 18 min assay. Quality control of assay (in-house) at Liverpool Clinical laboratories revealed a coefficient of variation of 11% at low value troponins (<10 ng/L). External quality assurance provided by the independent United Kingdom National External quality assurance scheme (NEQA) revealed interhospital coefficient of variation of 10% (SD 0.5) low-level troponin values. Assay performance (NEQA) was undertaken monthly throughout the duration of the study.

During recruitment of the study, there was a downward shift in the Roche Elecsys hs-cTnT that was a result of calibration of specific LOTS.[20] We recomputed hs-cTnT values by adjusting for the shift by reference to local laboratory calibration and that determined by a number of groups including the manufacturer.[20 21] The adjusted or recomputed values were used in the analysis.

Patient and public involvement

The study was formally presented to the SURE group at Liverpool Heart and Chest Hospital. This is a patient representative body. The patient group endorsed the research. They were enthused by the size of the study and the comprehensiveness of follow-up. Dissemination of the study was suggested to the regional network (Cheshire and Mersey Cardiac Network) and patient representative bodies, such as SURE, and to media outlets.

The research question was informed partly as a consequence of patient concern of missed MIs and delayed definitive treatment to high-risk NSTEMI cases. This was particularly relevant as the cardiothoracic centre is remote from the receiving centre (emergency department (ED) for patients with MI, as is the case in many regions in the UK and Europe).

Patients were not involved in the conduct of the study.

Statistics

All analyses were performed using Stata V.15.

Cross-tabulations of death at 1 year with elevated troponin and ST segment depression were produced, and Pearson's χ^2 test performed for categorical variables and a two-sample t-test for continuous variables.

Single variable logistic regression models were fitted with death at 1 year as outcome. ORs and p values (from likelihood ratio (LR) χ^2 test compared with the null model) are provided. Continuous variables were considered in single-variable logistic regression models, and an LR χ^2 test was performed to see if they were significant.

Variables that had p<0.1 in the single-variable logistic models were considered for inclusion in the multiple variable model. Inclusion of variables in the model was determined by backwards selection based on the minimum Akaike Information Criterion (AIC), using the swaic command in Stata (table 2 details the variables included in the multivariate model).

The same procedures for determining multiple variable logistic regression models were used for the subgroup analysis, which were performed on patients with troponin >99th percentile (hs-cTnT >14 ng/L), those with adjudication of MI or unstable angina at presentation, patients not undergoing revascularisation to 1 year and early presenters with chest pain.

The composite risk scores included independent variables such as age and ST depression, which were also analysed as independent variables. Therefore, we analysed variables in the multivariate models to understand if apparently independent variables had a correlation coefficient >0.8. The correlation matrices for variables considered for multivariable models indicated that the largest coefficients were <0.6 suggesting appropriateness and independence of all factors in the multivariate model.

When making comparisons between hs-cTnT and the GRACE score, the result for hs-cTnT was included in the composite GRACE score.

Kaplan-Meier survival curves were plotted by GRACE score (≤140 and >140) and hs-cTnT (<50 and ≥50 ng/L, and single-variable Cox proportional hazards models fitted to obtain HRs.

RESULTS

The total population was 1642 individual patients who presented consecutively with suspected NSTEMI over a period of 6 months. Seven hundred five (43%) and 638 (39%) presented via ambulance (either directly or via general practitioner) or self-presented to ER, respectively. The median age was 59 (IQR 47–72); 52% were male, 14% diabetic, 20% had a history of previous MI; 10% and 6% had a history of percutaneous coronary intervention and coronary artery bypass surgery, respectively. The median time from chest pain to presentation was 9.7 hours (IQR 2.4-48 hours). Forty-two per cent presented <6 hours from onset of chest pain. Four hundred forty-four patients (27%) were discharged directly from ED at a median of 363 min (IQR 271–468 min). Table 1 details the patient population, with categorisation by survival status at 6 weeks and 12 months (see online supplementary table S1 incorporating MACE at 6 weeks and 12 months). Unsurprisingly, patients dead by 1 year were older with higher risk scores (HEART, TIMI and GRACE scores). Interestingly, there were strong associations of mortality with a previous history of MI, CABG and stroke. In terms of presentation, ECG, ST depression but not T-wave changes were associated with death at 1 year.

One hundred eighty (11%) were adjudicated as suffering from type 1 MI (NSTEMI) and 342 (20.8%) with type 1 MI (NSTEMI) or unstable angina (defined as patients with normal cardiac troponin levels and typical angina at rest, a deterioration of a previously stable angina and in cases of positive cardiac exercise testing or cardiac catheterisation with coronary arteries found to have a stenosis of 70% or greater).

Primary outcome: all-cause death at 1 year

Out of 1642, 104 (6.3%) patients had died at 365 days. Table 2 illustrates 18 variables tested for logistic single variable regression with death at 1 year as the outcome. Descriptions are noted for associations with adjudicated type 1 MI at presentation and urgent or emergency coronary revascularisation up to 6 weeks following presentation. The rationale, of the analysis and the data presentation, was to identify a single factor or composite risk score in a chest pain population that predicted both a high percentage of adjudicated MI and was associated with adverse outcome (higher than average 1-year mortality >6.3%).

GRACE score >140 and hs-cTnT >50 ng/L had the highest OR for all-cause death at 6 weeks and 1 year. When emergency/urgent revascularisation and MI was added as an end point to all-cause death (MACE), hs-cTnT >100 ng/L and HEART ≥7 had stronger associations (online supplementary table S2). GRACE >140 was associated with adjudicated NSTEMI in only 29.5% of cases. By contrast, an hs-cTnT >50 ng/L was associated with an adjudicated index diagnosis of type 1 MI (NSTEMI) in 61.7% of cases.

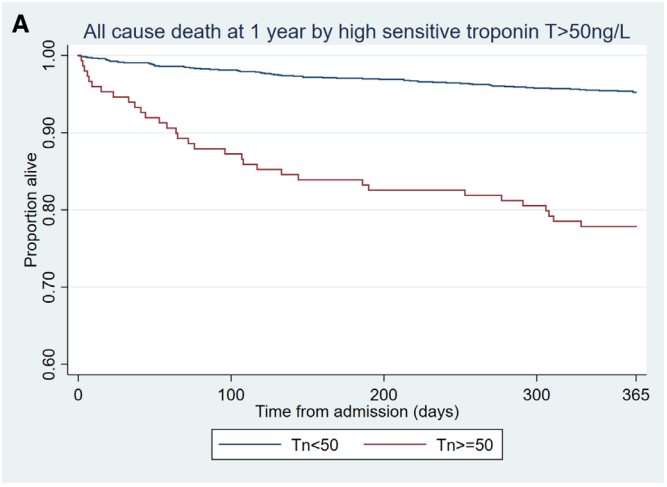
Independent predictors of all-cause death

Table 3 illustrates multivariate analysis of predictors for death at 1 year. Apart from GRACE >140, no other high-risk composite score (HEART ≥7 or TIMI ≥5) independently predicted death at 1 year in this population. Other factors that were independent predictors at 1 year for all-cause death were age (per decade increase), hs-cTnT >50 ng/L, a history of heart failure and diabetes mellitus. ST depression (≥0.5 or ≥1.0 mm) was not significantly associated with all-cause death at 1 year in multivariate analysis but there are insufficient numbers to determine if ≥2 or 3 mm ST segment depression would strongly correlate with death at 1 year on multivariate analysis. The analysis was repeated without composite risk scores (which include elevated troponin, age and ECG changes in their composite score). The results were consistent with the same independent variables featuring in the multivariable model.

Table 3 Results of multivariable logistic regression with death at 1 year as outcome

Explanatory variable	OR (95% CI)	P value
GRACE >140	3.50 (1.98 to 6.49)	<0.001
Age*	1.71 (1.37 to 2.11)	<0.001
hs-cTnT >50 ng/L	1.80 (1.07 to 3.05)	0.028
History of heart failure	1.77 (0.97 to 3.22)	0.062
Diabetes mellitus	1.58 (0.96 to 2.62)	0.075
C-statistic: 0.853		

*OR per decade increase in age.
GRACE, Global Registry of Acute Coronary Events; hs-cTnT, high-sensitive cardiac troponin T.



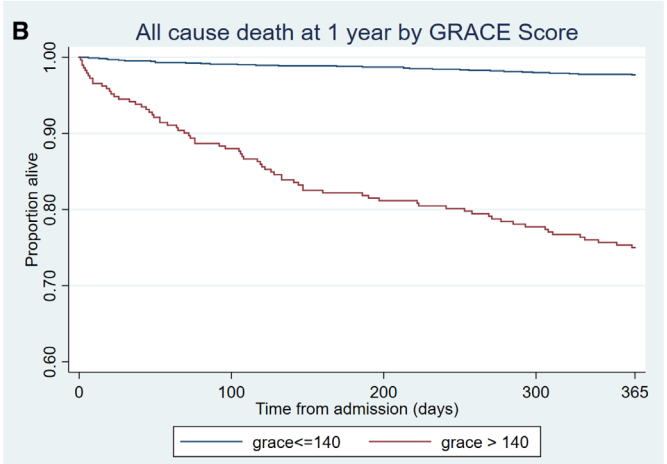


Figure 1 A. All-cause death at 1 year by high-sensitive cardiac troponin T (hs-cTnT). Kaplan-Meier (KM) survival curve by hs-cTnT >50 ng/L HR 5.21 (95% CI 3.45 to 7.88), p<0.001. (B) All-cause death at 1 year by Global Registry of Acute Coronary Events (GRACE) score. KM survival curve by GRACE score, HR 12.43 (95% CI 8.17 to 18.94), p<0.001.

Figure 1A,B illustrates Kaplan-Meier curves for GRACE score >140 and hs-cTnT >50 ng/L with death to 1 year as outcome, with associated HRs.

Sensitivity analyses

We conducted further analyses in subgroups including troponin >99th percentile (hs-cTnT >14 ng/L) (n=460 patients with 78 deaths at 1 year), those with adjudication of MI or unstable angina at presentation (n=342), patients not undergoing revascularisation to 1 year (n=1538 with 104 deaths) and early presenters with chest pain. Online supplementary table S3 details the

findings on multivariate analysis for patients with hs-cTnT >14 ng/L. Hs-cTnT >50 ng/L was included as an independent predictor using AIC model selection. A history of heart failure and diabetes as a comorbid condition were independent predictors in this subpopulation. Online supplementary table S4 details independent predictors for those with adjudicated NSTEMI or unstable angina. hs-cTnT was no longer an independent factor. Both the subpopulations (hs-cTnT >14 ng/L and adjudicated NSTEMI or unstable angina) are likely to dilute the influence of hs-cTnT on all-cause mortality as both ischaemic and non-ischaemic causes of chest pain with elevated troponin are strongly linked to adverse outcome. Online supplementary table S5 describes the population who did not undergo revascularisation (as revascularisation could influence prognosis); hs-cTnT >50 ng/L was an independent predictor in this cohort. There were insufficient events to repeat the analysis with early presenters using death alone as an outcome. We determined the interaction of time of chest pain relative to hs-cTnT check and the predictors of death in the main multivariate analysis. There was no interaction of timing of chest pain to hs-cTnT check and the fitness of the model for the total population or any of the subgroups.

Secondary outcome: major adverse outcome events

We also determined the influence of switching the end point to 12 months MACE as compared with all-cause death. Online supplementary table S6 illustrates the results. HEART ≥7 was now included in the model. A dissection of the data revealed higher index and subsequent MI prediction with HEART ≥7 as compared with GRACE >140; 63.3% of patients with HEART ≥7 had MI at 1 year compared with 32.9% for those with GRACE >140 (table 2, composite of columns 5 and 6). Twenty-five per cent of patients with GRACE score >140 died compared with 21.1% of patients with HEART ≥7 (table 2). Interestingly, female gender was protective against MACE suggesting lower index MI and coronary revascularisation rates.

We analysed the combinations of hs-cTnT >50 ng/L at presentation with another independent factor (age ≥60 and GRACE >140) on multivariate analysis for all-cause death (table 4), as well as a range of other factors correlating with all-cause death at 1 year. This illustrates unsurprisingly the summative effects of this model as a predictor of high-risk NSTEMI. Either GRACE >140, supra-median age (age ≥60) or HEART ≥7 in combination with hs-cTnT >50 ng/L identified >55% index MI with high short-term (6 weeks) and medium-term mortality. One year HEART ≥7+hs-cTnT >50 ng/L was associated with revascularisation in nearly 30% of patients (almost double compared with GRACE >140). The combination of hs-cTnT >50 ng/L and ST depression had the strongest association with coronary revascularisation, although this constituted only 1.9% of the population.

DISCUSSION

As far as we are aware, no previous work has analysed the prognostic impact of a range of simple variables and risk scores, at FMC, in a consecutive suspected ACS (ST elevation excluded) population in the era of high-sensitive troponin. The importance of this work is underlined by the need for early identification and potential transfer of high-risk NSTEMI to a centre capable of undertaking early coronary revascularisation.[1]

This analysis confirms that type 1 MI (NSTEMI) represents a fraction of patients presenting to ED with chest pain. We have demonstrated that a single hs-cTnT >50 ng/L is one effective means of detecting high-risk NSTEMI. Over 60% of cases are adjudicated as NSTEMIs and there is evidence of an adverse prognostic impact both in univariate and multivariate analysis. Independent predictors of all-cause mortality (age, GRACE >140 and hs-cTnT >50 ng/L) are consistent with findings of individual patient meta-analysis,[7] even though the meta-analyses were in a confirmed NSTEMI population. However, the recently published VERDICT study[22] only found a GRACE score >140 to benefit patients with NSTEMI who underwent an early invasive approach. It is not clear whether high-sensitive troponins were used in all hospitals in Very EaRly versus Deferred Invasive evaluation using Computerized Tomography (VERDICT) and second a binary analysis of elevated versus normal troponin was used rather than the degree of elevation beyond the 99th percentile, as in this analysis. It is important to note the difference between prognostic impact of a marker and the interaction of this marker with proposed intervention to lower risk which could also explain discrepancies between our analysis and that of VERDICT. In contrast to a confirmed NSTEMI population, ST segment depression on ECG was not independently associated with mortality at 1 year in our analysis.[10]

The analysis in table 4 is exploratory and driven by twin aims: identification at presentation to ED of a high-risk NSTEMI, and capacity of a network to cater for high-risk NSTEMI transfers. The combination of hs-cTnT >50 ng/L and either age >60 or GRACE score >140 or HEART score ≥7 identified a very high-risk population and could be leveraged depending on agreed definitions of high risk and capacity in a network.

The combination of ST depression and hs-cTnT >50 ng/L is an attractive proposition in terms of both identifying ACS (as opposed to other diagnoses) and predicting high-risk status and potential benefit of revascularisation. However, HEART score ≥7 which incorporates chest pain and ECG and troponin (uniquely for risk scores in a semi-quantitative fashion) did not independently predict death at 1 year in multivariate analysis. It did though independently predict MACE due to a higher association with index adjudicated MI (table 2). GRACE score >140 strongly influences mortality both on univariate and multivariate analysis. Less than 30% of patients with GRACE >140 had an adjudicated type 1 MI thus highlighting the need for combination with another

Table 4 Combination of prognostic variables in the prediction of death for patients with suspected acute coronary syndrome (univariate analysis)

Prognostic variable	N (%)	OR* (95% CI)	C-statistic	P value	NSTEMI index diagnosis N (%)	MI at 1 year† N (%)	Revascularisation‡ at 6 weeks n (%)	Revascularisation‡ at 1 year n (%)	Death at 6 weeks n (%)	Death at 1 year n (%)
hs-cTnT >50 ng/L+GRACE>140	86 (5.2)	12.21 (7.43 to 20.08)	0.64	<0.001	48 (55.8)	4 (4.7)	13 (15.1)	13 (15.1)	11 (12.8)	32 (37.2)
hs-cTnT >50 ng/L+age≥60	114 (6.9)	8.00 (4.99 to 12.84)	0.63	<0.001	70 (61.4)	4 (3.5)	23 (20.2)	24 (21.1)	11 (9.6)	32 (28.1)
hs-cTnT >50 ng/L+ST depression ≥0.5 mm	32 (1.9)	4.37 (1.84 to 10.35)	0.53	0.003	21 (65.6)	0 (0.0)	12 (37.5)	12 (37.5)	2 (6.3)	7 (21.9)
hs-cTnT >50 ng/L+ST depression ≥1.0 mm	27 (1.6)	4.42 (1.74 to 11.21)	0.52	0.006	17 (63.0)	0 (0.0)	10 (37.0)	10 (37.0)	2 (7.4)	6 (22.2)
hs-cTnT >50 ng/L+history of diabetes mellitus	31 (1.9)	12.06 (5.73 to 25.39)	0.56	<0.001	16 (51.6)	4 (12.9)	2 (6.5)	2 (6.5)	6 (19.4)	13 (41.9)
hs-cTnT >50 ng/L+history of heart failure	24 (1.5)	16.59 (7.25 to 37.94)	0.55	<0.001	12 (50.0)	1 (4.2)	1 (4.2)	1 (4.2)	3 (12.5)	12 (50.0)
hs-cTnT >50 ng/L+HEART score ≥7	106 (6.5)	5.69 (3.44 to 9.41)	0.59	<0.001	75 (70.8)	3 (2.8)	28 (26.4)	30 (28.3)	5 (4.7)	25 (23.6)

*OR for death at 1 year.
†Excluding index myocardial infarction.
‡Refers to emergency or urgent coronary revascularisation.
GRACE, Global Registry of Acute Coronary Events; HEART, History, ECG, Age, Risk factors and Troponin; hs-cTnT, high-sensitive cardiac troponin T; NSTEMI, non-ST elevation myocardial infarction.

variable such as multiples of hs-cTnT beyond 99th percentile (table 4). It is probable that in an 'unselected' population with suspected ACS a high GRACE score reflects haemodynamic strain caused by several pathologies such as pulmonary embolism, myocarditis, cardiomyopathy, pneumonia.

The results relate to presentation to ED and further work with point-of-care troponins will be required for field assessment. The results may not be translatable to other high-sensitivity troponins, but we tested the ranges (>×3 99th percentile and >×5 99th percentile) to evaluate which performs better. Thus, there maybe general rules for other populations and differing high-sensitive troponins as long as the 99th percentile has been determined and the analytical precision is consistent with high-sensitivity troponin.[23]

Limitations

In an observational study, we cannot impute improved prognosis on the basis of associations; either with index MI or with revascularisation.

We used all-cause death as an outcome rather than cardiac death as incorporated in some studies. This is not to imply that high-sensitivity troponin can predict non-cardiac death but to accept the uncertainty of cause of death, particularly for out-of-hospital deaths and the probability of misdiagnosis and therefore miscoding of cause of death. Using all-cause death grants a safer estimate of high-risk NSTEMI.

We repeated analysis using MACE. The results of the logistic regression analysis and the best-fit model for multivariate independent predictors revealed a strongly positive result for HEART ≥7, which supplanted GRACE >140. While HEART ≥7 predicted MI better than GRACE >140, it was less often associated with death. This illustrates an important limitation in interpretation of data. While HEART ≥7 most likely predicted cardiovascular death (subsequent to MI), GRACE >140 was most likely predictive of non-cardiovascular death. The dynamics and multivariable model could be different if cardiac death was the end point. However, in a real-world setting with a substantial proportion of out-of-hospital deaths and a low post-mortem rate it may not be possible to distinguish between cardiac and non-cardiac deaths with any reasonable certainty. From a pragmatic point of view, high HEART score maybe preferable to GRACE as a comparison of risk scores alone as it is more likely to be associated with possibilities of coronary revascularisation and thus an improvement in prognosis.

Presentations were late in this cohort and early presenters may diminish the 'performance' of point-of-care troponin. Furthermore, there was delay in testing hs-cTnT (median 166 min) potentially overestimating the positive predictive value of hs-cTnT >50 ng/L for a diagnosis of MI. However, we found no interaction in outcome (multivariable analysis) with time of chest pain relative to admission. Further analysis in a cohort enriched with early presenters and earlier sampling of hs-cTnT is warranted to confirm these results.

Although follow-up was nationwide (eight hospitals with representations with chest pain/ischaemic heart disease code extracted for adjudication), presentations were to a single centre thus limiting its external validity.

CONCLUSION

hs-cTnT >50 ng/L alone, or in combination with an additional independent predictor, in the context of suspected ACS, appears an effective strategy to identify high-risk NSTEMI. Analyses with early presenting cohorts are necessary to extend these results.

Interpretation

The findings of this analysis could help inform NSTEMI pathways and reduce mortality for high-risk NSTEMI by earlier redirection for revascularisation. However, such a strategy needs testing in a separate analysis to specifically determine if this change to cardiac pathways leads to improved prognosis. It is also important to point out that in the event of redirection to a centre with coronary revascularisation facilities, there is potential for dramatic reduction on length of stay.

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Contributors AK conceived the idea of the project, developed conversations with ED clinicians. PG, FF, LM, AK entered data and computed risk scores from definition tables and relevant charts/proforma. AK, MF, KA, BP were consultant adjudicators for type 1 and type 2 myocardial infarction. RG undertook analysis and derived FU data from national linked database for hospital admissions per defined ICD-10 codes. AK and MO wrote the manuscript. MO provided important intellectual input to the analysis. AK is the guarantor of the data. JD undertook most of the statistical analysis for the study.

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Competing interests AK has the following potential conflicts of interest: free of charge material from Roche for research. Submissions pending for research funds for Roche and Abbott. Funding for national conferences from Daiichi Sankyo, Bayer. Funding for research from Bayer Pharmaceuticals. Speaker and expert consultation fees from AstraZeneca, Menarini, Bayer, Daiichi Sankyo.

Patient consent for publication Not required.

Ethics approval This manuscript conforms to the International Committee of Medical Journal Editors recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals. This was an all-comers chest pain study with national (English) hospital involvement for any representation with possible MI. The project was registered with the hospital research department and the regional ethics board, which granted full consent to undertake this study. (North West England regional ethics board, Integrated Research Application System project ID 6661). To allow for complete follow-up, special permission was granted, in the absence of individual consent, via a confidential advisory group (UK government home office appointed). This approved the recruitment of the consecutive chest pain population and collection of data from any hospital nationwide to facilitate the retrieval of clinical records, investigations and blood results for patients with possible ACS (15/CAG/0171) (http://www.hra.nhs.uk/).

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Data availability statement Data are available on reasonable request. The data are de-identified. By entering a shared agreement anonymised data may be available. The database is 'owned' by the Aintree University Hospitals NHS Foundation Trust and would be available from the research department.

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