Improving early risk stratification in patients presenting to emergency department with suspected acute coronary syndrome

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KEY MESSAGES

1. In patients presenting to the emergency department with chest pain of possible acute coronary syndrome, the use of both the modified thrombolysis in myocardial infarction (mTIMI) score and the modified history, electrocardiography, age, risk factors and troponin (mHEART) score, together with the high-sensitivity cardiac troponin T (hs-cTnT) test and electrocardiography, enables safe and early discharge in 20% of cases.
2. A scoring system that combines the results of mTIMI, mHEART, hs-cTnT, electrocardiography, and heart-type fatty acid-binding protein may accurately risk-stratify patients for deposition decision.

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Introduction

Chest pain is one of the most common complaints in patients presenting to the emergency department. Acute coronary syndrome (ACS) cannot be immediately excluded in most patients presenting with chest pain, and is confirmed in about 15%-25% of cases. Its evaluation is a lengthy process that involves serial electrocardiography (ECG) and troponin tests taken 3-6 hours apart. Crowding in the emergency department and the need for acceptable risk stratification have prompted the search for safe and cheap but effective accelerated chest pain pathways to rule out short-term major adverse cardiac events (MACE) in patients suspected to have ACS to enable early discharge and to risk-stratify patients for appropriate deposition and utilisation of hospital resources.[1-4] The high-sensitivity cardiac troponin T (hs-cTnT), the heart-type fatty acid-binding protein (H-FABP), the thrombolysis in myocardial infarction (TIMI) score, and the history, ECG, age, risk factors and troponin (HEART) score have been used in the diagnosis of acute myocardial syndrome, and to rule out short-term MACE in chest pain patients. The coronary artery calcium score (CACS) has been shown to correlate positively with the 5-year cardiac event rate.

This study aimed to (1) investigate any correlation between the MACE rate within 1 and 6 months and CACS, H-FABP, hs-cTnT, TIMI score, and HEART score, and (2) evaluate the predictive values of CACS, H-FABP, hs-cTnT, TIMI score, and HEART score and various combinations.

Methods

This study was conducted from November 2012 to December 2014. It was a 2-year prospective observational cohort study of adult patients who presented to the emergency department of the Prince of Wales Hospital with chest pain suspicious of ACS origin. Ethical approval was obtained from the local ethics review board. Patients were excluded if their initial ECG were suggestive of ACS, acute myocardial infarction, or other abnormality that would require admission to hospital, or if they had a history of coronary artery bypass grafting or coronary stent implantation, contraindication to β-blockade if prescription of β-blockade was required due to a resting heart rate over 80 beats per minute, or if they were unable to be contacted after discharge or unable to give consent, or if they were female patients with known or suspected pregnancy.

Patients were recruited consecutively on weekdays between 09:00 and 17:00. Apart from the routine chest pain protocol that included clinical assessment, ECG, and hs-cTnT test, three additional steps were performed: (1) H-FABP point-of-care test on presentation and 3 hours later, (2) modified TIMI (mTIMI) score on presentation, and (3) CACS within 2 months of presentation. All physicians and cardiologists responsible for patient management were blinded to test results. The modified HEART (mHEART) score was completed retrospectively. The outcomes with regard to the MACE within 1 and 6 months were obtained through phone contact with the patients and access to the medical records.

For both mTIMI and mHEART scores, a hs-cTnT of ≤14 ng/L was considered negative. Only the presence of ST-deviation of >0.05 mV was considered in the initial ECG result and scored one point in mHEART.

The primary outcome was the number of patients with MACE within 1 and 6 months after presentation. The prognostic performance of CACS, H-FABP, hs-cTnT, mTIMI, and various combinations in predicting MACE was assessed. MACE was defined as relating to safety outcome (consisting of all-cause mortality, cardiac arrest, readmission with myocardial infarction and cardiogenic shock) or effectiveness outcome (consisting of revascularisation, ventricular arrhythmia, or high-degree atrioventricular block needing intervention).

Mann-Whitney *U* test, Chi-square test, Fisher exact test, and univariate and multivariate logistic regressions were used to compare characteristics

TABLE 1. (a) Univariate and (b) multivariate logistic regression for major adverse cardiac events (MACE) within 1 and 6 months

(a)

Variables	MACE within 1 month					MACE within 6 months				
	OR (95% CI)	P value	No. (%) of MACE	Area under the curve (95%CI)	P value	OR (95% CI)	P value	No. (%) of MACE	Area under the curve (95%CI)	P value
Electrocardio-graphy			42					63		
ST deviation	3.80 (1.99-7.24)	<0.001	19 (45)	0.64 (0.54-0.73)	0.003	3.07 (1.77-5.33)	<0.001	25 (40)	0.61 (0.53-0.69)	0.004
High-sensitivity cardiac troponin T										
0-14	1		5 (11)			1		10 (16)		
>14-28	6.80 (2.18-21.26)	0.001	8 (19)			6.74 (2.93-15.51)	<0.001	15 (24)		
>28-42	14.69 (3.69-58.57)	<0.001	4 (10)			9.78 (3.05-31.30)	<0.001	5 (8)		
>42	51.80 (18.77-142.90)	<0.001	25 (60)	0.86 (0.79-0.92)	<0.001	44.49 (19.96-99.20)	<0.001	33 (52)	0.84 (0.78-0.90)	<0.001
Heart-type fatty acid-binding protein										
0-7	1		24 (59)			1		38 (61)		
>7-14	1.93 (0.55-6.74)	0.304	3 (7)			2.64 (1.03-6.75)	0.0427	6 (10)		
>14-21	9.64 (3.10-29.95)	<0.001	5 (12)			8.51 (2.88-25.17)	<0.001	6 (10)		
>21	31.81 (10.47-96.64)	<0.001	9 (22)	0.67 (0.57-0.78)	<0.001	51.05 (13.81-188.74)	<0.001	12 (19)	0.66 (0.58-0.75)	<0.001
History, electro-cardiography, age, risk factors and troponin score										
0-3	1		1 (2)			1		4 (6)		
4-6	21.64 (2.93-159.88)	0.003	30 (72)			7.63 (2.69-21.61)	<0.001	42 (67)		
7-10	69.14 (8.66-552.32)	<0.001	11 (26)	0.73 (0.67-0.80)	<0.001	31.88 (10.01-101.51)	<0.001	17 (27)	0.72 (0.66-0.79)	<0.001
Thrombolysis in myocardial infarction score										
0-1	1		5 (12)			1		6 (10)		
2-3	3.69 (1.38-9.88)	0.009	23 (55)			4.80 (2.00-11.63)	0.0005	35 (56)		
4-7	7.07 (2.47-20.23)	<0.001	14 (33)	0.67 (0.59-0.75)	<0.001	9.97 (3.89-25.55)	<0.001	22 (35)	0.69 (0.62-0.75)	<0.001
Coronary artery calcium score										
0	1		4 (16)			1		6 (14)		
1-150	0.57 (0.10-3.12)	0.512	2 (8)			0.74 (0.21-2.68)	0.651	4 (9)		
>150-300	4.37 (1.05-18.12)	0.042	4 (16)			2.84 (0.77-10.50)	0.117	4 (9)		
>300-450	5.80 (1.23-27.36)	0.026	3 (12)			6.67 (1.89-23.51)	0.003	5 (11)		
>450	7.73 (2.42-24.70)	0.001	12 (48)	0.74 (0.63-0.85)	<0.001	12.31 (4.84-31.33)	<0.001	25 (57)	0.78 (0.70-0.86)	<0.001

(b)

Variables	MACE within 1 month (n=24/552)				MACE within 6 months (n=43/540)			
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Electrocardiography								
ST deviation	1.36 (0.38-4.84)	0.639			1.35 (0.48-3.78)	0.569		
High-sensitivity cardiac troponin T								
0-14	1		1		1		1	
>14-28	6.98 (0.79-61.42)	0.080	6.795 (1.115-41.431)	0.001	6.61 (1.71-25.55)	0.006	4.453 (1.464-13.549)	0.009
>28-42	39.27 (3.65-422.40)	0.002	30.032 (4.494-200.673)	<0.001	13.44 (2.29-78.81)	0.004	8.973 (1.873-42.996)	0.006
>42	143.95 (17.04-1216.21)	<0.001	106.787 (21.475-531.023)	<0.001	71.67 (15.57-329.84)	<.001	41.634 (12.747-135.978)	<0.001
Heart-type fatty acid-binding protein								
0-7	1		1		1		1	
>7-14	0.27 (0.05-1.50)	0.133	0.256 (0.050-1.322)	0.104	0.40 (0.11-1.49)	0.171	0.382 (0.104-1.400)	0.146
>14-21	1.71 (0.30-9.93)	0.548	0.945 (0.198-4.516)	0.511	1.47 (0.26-8.33)	0.663	1.243 (0.236-6.557)	0.797
>21	3.51 (0.54-22.73)	0.188	3.236 (0.614-17.040)	0.047	11.08 (1.36-90.22)	0.025	8.343 (1.113-62.536)	0.039
History, electrocardiography, age, risk factors and troponin score								
0-3	1				1			
4-6	2.42 (0.17-33.71)	0.511			0.53 (0.10-2.80)	0.454		
7-10	1.07 (0.05-25.55)	0.967			0.35 (0.04-3.12)	0.344		
Thrombolysis in myocardial infarction score								
0-1	1				1			
2-3	0.19 (0.03-1.40)	0.103			0.75 (0.15-3.83)	0.729		
4-7	0.21 (0.021-2.09)	0.182			0.60 (0.09-4.06)	0.600		
Coronary artery calcium score								
0	1				1		1	
1-150	0.29 (0.04-2.02)	0.212			0.47 (0.11-2.05)	0.316	0.408 (0.096-1.731)	0.224
>150-300	1.91 (0.34-10.92)	0.466			1.05 (0.21-5.13)	0.957	0.885 (0.186-4.205)	0.878
>300-450	2.62 (0.38-18.21)	0.330			3.40 (0.70-16.39)	0.128	2.610 (0.607-11.224)	0.197
>450	2.77 (0.56-13.60)	0.210			6.81 (1.94-23.90)	0.003	4.851 (1.617-14.559)	0.005

with MACE. Statistical significance was set at P<0.05. Results of the diagnostic tests were categorised to calculate the prediction accuracy of combined tests. The calibration of a model for the prediction of the risk of MACE combining the use of five tests was estimated using the Hosmer-Lemeshow goodness-of-fit test.[5] Sensitivity, specificity, positive and negative predictive values, and area under the receiver operating characteristic curve (AUROC) were used to assess the performance of tests and model.

Results

A total of 604 patients were enrolled, of whom 552 had test results for all six predictors (ECG, hs-cTnT, H-FABP, mHEART, mTIMI, and CACS) and 1-month follow-up. 12 patients were lost to follow-up at 6 months. MACE occurred in 42 (7.0%) patients within 1 month and in 63 (10.5%) patients within 6 months.

Comparison of the baseline characteristics (age, gender, ethnicity, smoking status, comorbidities, and

medication history) of patients with and without MACE within 1 month showed that only gender differed significantly. Occurrence of MACE within 6 months was strongly associated with a history of diabetes and congestive heart failure.

Emergency revascularisation contributed the largest proportion (26/58) of MACE within 1 month, followed by non-ST elevation myocardial infarction (STEMI) and STEMI. From 1 to 6 months, there was a minimal increase in the number of non-STEMI and STEMI cases and the increase in MACE was mainly attributed to emergency revascularisation and all-cause mortality.

In univariate logistic regression, all six predictors (ie ST-deviation of >0.05 mV in initial ECG, initial hs-cTnT concentration of >14 ng/L, initial H-FABP concentration of >14 mg/L, mHEART score of ≥4, mTIMI score of ≥2, and CACS of >150) were individually associated with MACE within 1 month (Table 1). Results were similar for MACE within 6 months except that the threshold for association in H-FABP decreased to >7 mg/L, and in CACS increased to >300. Hs-cTnT had the highest prediction accuracy for MACE within 1 and 6 months, as shown by its highest AUROC.

In multivariable logistic regression, only variables with a P value of <0.2 were included. hs-cTnT of >14 ng/L and H-FABP of >21 mg/L remained in the model with a P value of <0.05. hs-cTnT of >14 ng/L, H-FABP of >21 mg/L, and CACS of >450 were associated with a higher risk of MACE within 6 months.

Both mTIMI of >0 and mHEART of >2 had 100% sensitivity and negative predictive value, and 11.6% and 17.1% specificity, respectively, for MACE (Table 2). Combined use of mTIMI and mHEART when either one was negative ruled out MACE within 1 month, with increased specificity to 22.0% and no loss in sensitivity.

As CACS was not associated with MACE within 1 month in the multivariate analysis and was not readily available in the emergency department setting, we focused on ECG, initial hs-cTnT, H-FABP, mHEART, and mTIMI to derive a model for early

TABLE 2. Prognostic performance of individual and add-on tests for major adverse cardiac event (MACE) within 1 month (n=552)

Variable*	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Area under the curve (95% CI)
Electrocardiography (ECG)	45.2 (31.2-60.1)	82.1 (78.8-85.1)	16.0 (11.5-21.7)	95.2 (93.8-96.4)	2.53 (1.74-3.69)	0.67 (0.51-0.88)	0.64 (0.60-0.68)
Thrombolysis in myocardial infarction (TIMI) score	100 (91.6-100)	11.6 (9.2-14.5)	7.8 (5.8-10.4)	100 (94.4-100)	1.13 (1.12-1.17)	0 (0-0.73)	0.56 (0.52-0.60)
History, electrocardiography, age, risk factors and troponin (HEART) score 2	100 (91.6-100)	17.1 (14.2-20.5)	8.3 (6.2-11.0)	100 (96.2-100)	1.21 (1.19-1.26)	0 (0-0.49)	0.59 (0.55-0.63)
HEART score 3	97.6 (87.7-99.6)	39.3 (35.3-43.4)	10.8 (9.9-11.6)	99.5 (97.8-99.9)	1.61 (1.48-1.74)	0.06 (0.01-0.42)	0.69 (0.65-0.72)
Heart-type fatty acid-binding protein (H-FABP)	41.5 (27.8-56.6)	91.1 (88.4-93.2)	25.4 (17.9-34.7)	95.5 (94.2-96.5)	4.64 (2.96-7.27)	0.64 (0.50-0.83)	0.66 (0.62-0.70)
Coronary artery calcium score (CACS)	84.0 (65.4-93.6)	38.0 (34.0-42.2)	6.0 (5.0-7.2)	98.0 (95.5-99.2)	1.35 (1.13-1.63)	0.42 (0.17-1.04)	0.61 (0.57-0.65)
High-sensitivity cardiac troponin T (hs-cTnT)	88.1 (75.0-94.8)	72.1 (68.3-75.7)	19.2 (16.6-22.1)	98.8 (97.3-99.4)	3.16 (2.66-3.76)	0.17 (0.07-0.38)	0.80 (0.77-0.83)
Either +ve for ECG or hs-cTnT	92.9 (81.0-97.5)	62.0 (57.9-65.9)	15.5 (13.8-17.4)	99.1 (97.7-99.7)	2.44 (2.13-2.79)	0.12 (0.04-0.34)	0.77 (0.74-0.81)
Either +ve for H-FABP or hs-cTnT	87.8 (74.5-94.7)	70.8 (66.9-74.5)	18.1 (15.6-20.8)	98.8 (97.3-99.4)	3.01 (2.53-3.58)	0.17 (0.08-0.39)	0.79 (0.76-0.83)
Both +ve for TIMI & hs-cTnT	88.1 (75.0-94.8)	72.1 (68.3-75.7)	19.2 (16.6-22.1)	98.8 (97.3-99.4)	3.16 (2.66-3.76)	0.17 (0.07-0.38)	0.80 (0.77-0.83)
Both +ve for HEART2 and hs-cTnT	88.1 (75.0-94.8)	72.3 (68.5-75.9)	19.3 (16.7-22.2)	99.8 (97.4-99.4)	3.18 (2.67-3.79)	0.16 (0.07-0.38)	0.80 (0.77-0.83)
Both +ve for HEART3 and hs-cTnT	85.7 (72.2-93.3)	72.7 (68.8-76.2)	19.0 (16.4-22.1)	98.5 (97.1-99.3)	3.14 (2.61-3.77)	0.20 (0.09-0.41)	0.79 (0.76-0.82)
Both +ve for CACS and hs-cTnT	80.0 (60.9-91.1)	77.9 (74.2-81.2)	14.6 (11.7-18.1)	98.8 (97.5-99.4)	3.62 (2.81-4.66)	0.26 (0.12-0.56)	0.79 (0.75-0.82)
Both +ve for TIMI and HEART2	100 (91.6-100)	22.0 (18.7-25.6)	8.8 (6.6-11.6)	100 (97.0-100)	1.28 (1.26-1.34)	0 (0-0.38)	0.61 (0.57-0.65)

* Positive is defined as ECG with ST deviation, TIMI of >0, HEART2 of >2, HEART3 of >3, H-FABP of >7, and CACS of >0

risk stratification. Using the Hosmer-Lemeshow goodness-of-fit test to estimate the probability of MACE within 1 month, the risk score model had adequate calibration (P=0.44) and outstanding discrimination (AUROC=0.91, 95% confidence interval=0.87-0.95) [Table 3].

Discussion

CACS was more useful in longer term risk prediction but not useful in prediction of MACE within 1 month. CACS was not useful for diagnosis of ACS. mTIMI and mHEART individually, together with initial results of hs-cTnT and ECG, could identify patients with chest pain for safe discharge within 2 hours of arrival. If both mTIMI of 0 and mHEART of ≤2 are used, it would allow safe early discharge of 123 (20.4%) patients, of whom 35 were admitted under the current chest pain protocol, with no evidence of MACE within 1 month. This is a relative increase in discharge rate of 75% compared with using mTIMI alone, and a 46% increase compared with using mHEART alone. Nonetheless, the staff time saved by early discharge of these patients must be balanced to ensure all patients to have an accurate mTIMI and/or mHEART assessment. 1st hs-cTnT alone, 1st ECG alone, combined 1st hs-cTnT and ECG, and 1st H-FABP yielded high specificity, and may be useful to determine MACE within 1 month, but their sensitivity was <95%, which indicated that they were not suitable to identify patients for early discharge.

A more sophisticated scoring system that combines ECG, initial hs-cTnT, H-FABP, mTIMI, and mHEART can accurately risk-stratify patients who present to the emergency department with chest pain of possible ACS cause to predict MACE within 1 month. Compared with the current 6-hour chest pain protocol, the new combined system can discharge 52 (8.7%) more patients earlier with a decreased number of MACE in the discharged group (3 vs 2). More accurate identification of high-

TABLE 3. Chart with score from -14 to 69 for estimating the probability of major adverse cardiac event (MACE) within 1 month using five diagnostic tests

Test	Category			
Electrocardiography				
ST deviation	No	Yes		
Score	0	10		
High-sensitivity cardiac troponin T				
Value	0-14	14-28	28-48	>42
Score	0	17	28	37
Thrombolysis in myocardial infarction score				
Value	0-1	2-3	4-7	
Score	0	-14	-14	
History, electrocardiography, age, risk factors and troponin score				
Value	0-3	4-6	7-10	
Score	0	21	14	
Heart-type fatty acid-binding protein				
Value	0-7	7-14	14-21	>21
Score	0	-9	5	15

Variable	Very low risk (<2%), risk score of <14		Low risk (2-5%), risk score of 14-23		Moderate risk (5-70%), risk score of 24-61		High risk (≥70%), risk score of ≥62	
	MACE	No MACE	MACE	No MACE	MACE	No MACE	MACE	No MACE
Admitted patients	2	125	1	55	30	108	5	1
Median (interquartile range) length of stay (days)	3.5 (2.0-)	3.0 (2.0-5.0)	2.0	3.0 (2.0-5.0)	7.5 (4.0-12.25)	4.0 (3.0-8.0)	4.0 (2.5-12.0)	10.0
Discharged patients	0	198	1	40	2	32	0	0
MACE								
Safety	0	-	2	-	24	-	5	-
Effectiveness	2	-	1	-	19	-	3	-
Both	0	-	1	-	11	-	3	-

risk patients may facilitate patient deposition and decisions about more invasive diagnostic procedures.

The study has limitations. Abnormal renal function predicts death, and we did not adjust for its effect on troponin levels. Other tests would cover for this in cross check. Calculation in increased patients identified for early discharge assumed that patients were not admitted for reasons other than minimising the risk of MACE, although initiation of a chest pain protocol suggested that ACS was the primary concern of the emergency physician.

Conclusions

In patients presenting to the emergency department with chest pain of possible ACS, a combination of mTIMI and mHEART scores, ECG, hs-cTnT, and H-FABP results may efficiently risk-stratify those at risk of MACE within 1 month. CACS may be more useful in longer term risk prediction, but not useful for MACE within 1 month.

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