

A Preliminary Study of the Utility of Combined Cardiac Markers in the Evaluation of Patients Presenting Early with Suspected Acute Coronary Syndrome

J Lim,*^{MBChB, MRCP}, R C Hawkins,**^{MBChB, FRCPA}, K Ng,*^{MBBS, MRCP}, S P Chan,***^{MSc},
A Cheng,****^{FAMS, MD, FRCP}, K S Ng,^{†FAMS, MBBS, FRCP}

Abstract

Objective: The aim of the study was to investigate and compare the usefulness and accuracy of various cardiac markers [troponin I, creatine kinase MB (CKMB) mass, creatine kinase (CK), CKMB activity] to aid early diagnosis of myocardial infarction. We also examined the ability of the various cardiac markers to prognosticate future adverse cardiac events. **Materials and Methods:** Patients admitted within 8 hours of maximal chest pain suggestive of acute coronary syndrome with non-diagnostic electrocardiograms were recruited. Blood samples were obtained on admission to the wards and repeated 4 hours later. These results were later correlated to the final hospital discharge diagnosis. **Results:** The 37 patients in the study were a high-risk population with over 50% presenting with a Thrombolysis in Myocardial Infarction (TIMI) risk score of greater or equal to 3. Myoglobin was the most sensitive marker (100% sensitivity) in early prediction of patients who were subsequently diagnosed to have a myocardial infarction. Patients with an elevated troponin I level but normal CK and myoglobin levels had a significantly higher risk of developing a major adverse clinical event (MACE) within 3 months of the initial presentation. **Conclusion:** Myoglobin is the most sensitive marker when compared to CK, CKMB and troponin I for diagnosing patients presenting early with chest pain and a non-diagnostic electrocardiogram and who subsequently develop either a ST-elevation myocardial infarction or non-ST elevation myocardial infarction. Patients with an elevated troponin I level but normal CK and myoglobin levels are at higher risk of an adverse clinical event.

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Key words: Creatine kinase, Creatine kinase MB mass, Major adverse clinical event, Myoglobin, Troponin I

Introduction

The management of patients presenting with chest pain of recent onset can prove to be a diagnostic challenge. These patients vary from having atypical musculoskeletal pain, unstable angina pectoris (UAP), non-ST elevation myocardial infarction (NSTEMI), to early ST-elevation myocardial infarction (STEMI). For patients presenting with non-diagnostic electrocardiograms, the ability to differentiate quickly among these conditions becomes critical in order to make time-sensitive management decisions. Such identification has improved with the introduction of cardiac troponin T and I measurement.^{1,2} Despite their high diagnostic sensitivity and specificity, the value of the troponins is limited by their low sensitivity in the early detection of myocardial damage.³ Other markers,

such as myoglobin, creatine kinase MB (CKMB) mass and CKMB isoforms,^{4,6} may thus still have a role in ruling out acute myocardial infarction early, in the setting of an emergency department.

The primary objective of the study was to assess the diagnostic utility of a combination of cardiac markers to correctly identify patients with acute coronary syndrome presenting early with chest pain suggestive of myocardial ischaemia and non-diagnostic electrocardiograms. This approach has previously been shown to perform well in a western context^{7,8} but it has yet to be validated in a Singaporean environment, with its differences in patient demographics, symptoms and presentation patterns to hospital. In addition to the value of the markers for immediate patient diagnosis, we also examined their value in predicting

* Registrar

**** Consultant

† Senior Consultant

Department of Cardiology

** Consultant

Department of Pathology and Laboratory Medicine

*** Senior Medical Statistician

Department of Clinical Epidemiology

Tan Tock Seng Hospital

Address for Reprints: Dr Jimmy Lim, Department of Cardiology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

future cardiac events.

Material and Methods

Subjects

The study protocol was approved by the hospital's ethics committee. From December 1999 to March 2000, admissions to our hospital for evaluation of chest pain were considered for entry into the study. Inclusion criteria were typical anginal chest pain and entry into the study not greater than 8 hours from the onset of maximal chest pain. Exclusion criteria were recent myocardial infarction (less than 21 days from admission), renal impairment (serum creatinine >210 $\mu\text{mol/L}$), concurrent trauma and ST segment elevation (>1 mm in two consecutive leads) at the time of presentation.

All routine investigations and management were carried out according to standard clinical practice. In addition, serum blood samples for the measurement of cardiac troponin I, creatine kinase (CK), CKMB mass and myoglobin were taken at entry into the study (Time 1) and 4 hours later (Time 2). These samples were spun and stored at -20°C for batch analysis at the end of the study. The physicians treating the patients were blinded to the results of troponin I and myoglobin levels.

The final clinical diagnosis was decided based on history, serial electrocardiographic data, routine CK, CK percentage activity, CKMB mass and subsequent investigations such as exercise stress testing or diagnostic coronary angiography. All patients were categorised into one of the following:

1. ST-segment elevation MI (STEMI)
2. Non-ST segment elevation MI (NSTEMI)
3. Unstable angina pectoris
4. A non-acute coronary syndrome cardiovascular condition (e.g. acute pericarditis)
5. A non-cardiac condition with another specific disease or a non-cardiac condition that is undefined (the latter two defined as atypical chest pain).

Information regarding further adverse cardiac events within a 3-month period following discharge was based on notes from outpatient follow-up or hospital re-admissions. Patients without follow-up notes were contacted by telephone to determine their clinical status.

Definitions

STEMI and NSTEMI are defined as based on clinical definitions recommended by the American College of Cardiology/American Heart Association⁹ and an elevated CK level.

Major adverse clinical events (MACE) included a composite of death, stroke, re-admissions for cardiac complications, repeat myocardial infarction and ischaemia-

driven revascularisation.

The TIMI risk score was calculated based on seven clinical variables that included age >65 years, >3 traditional risk factors for coronary artery disease, prior known coronary stenosis of >50%, ST-segment deviation on electrocardiogram at presentation, at least 2 anginal events in the prior 24 hours while at rest, use of aspirin in the last 7 days, and elevated serum cardiac markers including troponins.

Analytical Techniques

CK and CKMB activity was measured on the Hitachi 917 clinical chemistry analyser (Roche Diagnostics) using manufacturer-supplied reagents. Troponin I and myoglobin were measured on the Abbott AxSYM while CKMB mass was measured on the Vitros ECI.

The manufacturers' recommended cut-off values for the various biomarkers for the diagnosis of acute myocardial infarction are as follows: troponin I, 2.0 ng/mL; myoglobin, 116 ng/mL; CKMB mass, 2.0 ng/mL; CK, 210 u/L.

All reference intervals used were based on the ranges recommended by the manufacturers except for troponin I values. Results above the cut-off values were defined as positive.

At present the manufacturer's cut-off value for troponin I (AxSYM) is 2.0 ng/mL (based on the 95th percentile of the reference population). New guidelines set by the European Society of Cardiology and the American College of Cardiology¹⁰ have now recommended that the cut-off value of the troponins for diagnosis of myocardial necrosis should be set at a level above the 99th percentile of a reference population if the assay imprecision (co-efficient of variation) is <10%. This analytical goal is unfortunately unattainable for the present generation of troponin assays. We have therefore used the lowest Abbott troponin I concentration with assay imprecision <10% of 0.8 ng/mL as the cut-off in our study.

Statistical Method

Logistic regression was applied to test whether cardiac markers were significant in predicting MACE and occurrence of myocardial infarction. The data were entered into Stata 6.0 (Stata Corporation, 702 University Drive East, College Station, TX 77840, USA) and all statistical tests were carried out at 5% level of significance. Receiver operator characteristics (ROC) analysis was carried out with Analyse-It add on for Microsoft Excel (Analyse-It Software Ltd, UK).

Results

A total of 37 patients were enrolled in this study. All eligible patients consented to entry into the study. The

small number of patients recruited was due to the majority of patients presenting later than 8 hours from onset of chest pain.

Using the clinically based TIMI risk score for NSTEMI,¹¹ 54% of the patients had a TIMI 3 score or worse. The patients' characteristics are shown in Table I.

The first blood sample was taken at a median interval of 235 (range 30 to 420) minutes from onset of maximal chest pain. The second blood sample was taken at a median interval of 240 (range 220 to 260) minutes after the first sample. Of the 9 patients who were diagnosed to have sustained a myocardial infarction on discharge, the median interval to first blood sample was 225 minutes (range 30 to 285).

TABLE I: PATIENT DEMOGRAPHICS BY TIMI RISK SCORE

Characteristics	TIMI <3	TIMI ≥ 3
Number of patients	17	20
Age (years)		
Mean	52	64
Range	38 to 75	41 to 88
Male (%)	82	65
Diabetes mellitus type 2 (%)	29	40
Hypertension (%)	59	70
Hyperlipidaemia (%) (LDL >2.6 mmol/L)	88	95
Previous myocardial infarction (%)	24	30
Previous coronary artery bypass surgery (%)	6	10
Previous percutaneous coronary intervention (%)	0	6
ST segment depression (%) (>1 mm horizontal ST depression)	6	75

The sensitivity and specificity of each cardiac marker for the diagnosis of acute myocardial infarction at Time 1 and 2 is summarised in Table II.

Based on the hospital discharge diagnosis, there were 5 patients diagnosed with ST-elevation MI, 4 with non-ST elevation MI, 13 patients with unstable angina pectoris, and 2 with stable angina pectoris. The remaining 13 patients were diagnosed with atypical chest pain.

Of all the markers, myoglobin had the highest sensitivity and specificity at Time 1 with a sensitivity of 100% and a specificity of 100% for diagnosing acute myocardial infarction (odds ratio of 196; $P < 0.01$). The ROC curve of myoglobin compared with troponin I and CK at Time 1 is shown in Figure 1.

Various combinations of results from Time 1 and Time 2 did not improve further the diagnostic accuracy of myoglobin taken at Time 1 for prediction of acute myocardial infarction (based on hospital discharge diagnosis). All of the cardiac enzymes studied were predictive of a likelihood of a MACE (Table III).

The TIMI risk score when applied to patients in this study group was also predictive of the occurrence of both myocardial infarction and a MACE within 3 months with an odds ratio of 2.18. However, this failed to reach statistical significance (range 0.49 to 9.58)

Discussion

Patients presenting early to the emergency department with chest pain and non-diagnostic electrocardiograms are common dilemmas because of the critical need to make time-sensitive management decisions. While high-risk patients would benefit from various therapeutic options, such as the use of glycoprotein IIb/IIIa inhibitors¹² and the

TABLE II: CARDIAC MARKER SENSITIVITY AND SPECIFICITY

Diagnosis at discharge	Time 1				Time 2 (4 hours later)			
	AMI		No AMI		AMI		No AMI	
	Number	Sensitivity	Number	Specificity	Number	Sensitivity	Number	Specificity
Myoglobin	9		28		9		28	
Test positive	9	100%	0	100%	9	100%	2	93%
Test negative	0		28		0		26	
Creatine kinase	9		28		9		28	
Test positive	4	44%	1	96%	8	89%	2	93%
Test negative	5		27		1		26	
CKMB mass	9		27		8		26	
Test positive	6	67%	1	96%	8	100%	3	88%
Test negative	3		26		0		23	
Troponin I (Axsym)	9		28		9		28	
Test positive	5	56%	2	93%	9	100%	6	78%
Test negative	4		26		0		22	

Sensitivity and specificity as compared to clinical diagnosis on discharge.

AMI: acute myocardial infarction; CKMB mass: creatine kinase MB mass

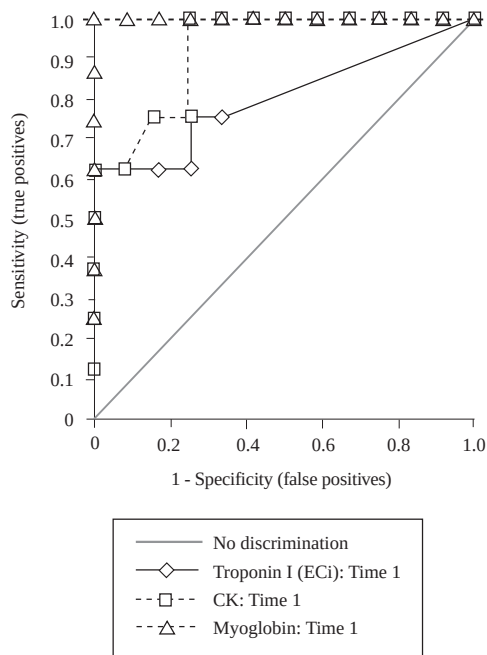


Fig. 1. ROC analysis for myoglobin, creatine kinase and troponin I at Time 1. Area under the curve for myoglobin 1.00, creatine kinase 0.922 and troponin I 0.802.

TABLE III: PREDICTION OF MACE WITHIN 3 MONTHS

Cardiac marker	Odds ratio	95% confidence interval
Creatine kinase	9.5	1.6 – 55
Myoglobin	12.5	2.1 – 71
CKMB mass	16.2	2.6 – 100.5
Troponin I	41.2	6 – 281

consideration of an early invasive strategy, low-risk patients end up occupying high dependency or coronary care unit beds unnecessarily.

Despite numerous studies demonstrating the superiority of cardiac troponins over CK for the diagnosis of myocardial necrosis, we have used the measurement of CK levels in our study for the diagnosis of myocardial infarction. This was to allow us to compare the utility of various cardiac markers to our then standard practice of using CK. In addition, the result of these newer cardiac markers were not made available to the clinician and the final discharge diagnosis was made based on history, electrocardiograms, CK, CKMB levels and various other invasive and non-invasive imaging studies.

Our results indicate that the use of myoglobin could effectively diagnose acute myocardial infarction within 5 hours of a history of maximal chest pain. All patients with a discharge diagnosis of myocardial infarction had a significantly elevated level of myoglobin on the first sample taken.

At present, myoglobin is not routinely measured in our hospitals. This has been due to the lack of specificity of myoglobin, with elevations also seen in skeletal muscle injury (such as following trauma, rhabdomyolysis, after intra-muscular injections and vigorous exercise) as well as cardiac muscle injury. In our study, however, we have shown that when patients with a significant history of muscle injury or trauma are excluded, this lack of specificity should not be a problem.

Studies have shown a superiority of cardiac troponins to prognosticate patients presenting with chest pain when compared to the use of CK levels.¹³ In addition, there is a sub-group of patients who have elevated troponin levels but normal CK levels. These patients are also at a higher risk of a MACE.¹⁴

In our study, 6 patients had an elevated troponin I level with normal CK and myoglobin levels. They belonged to this high-risk sub-group, with 5 of these patients (83%) experiencing a MACE at 3 months after initial presentation (odds ratio 30; range 2.5 to 354; $P < 0.007$). Conversely, only 3 out of 22 patients (14%) who had a normal troponin I level experienced a MACE at 3 months.

This finding would suggest that patients with a rise in troponin I level but who have normal CK or myoglobin levels are at a higher risk of future adverse events and may need more aggressive investigations and intervention. In addition, there may be a need for us to establish our own cut-off values for troponins for use in our local population, rather than rely on those recommended by the manufacturers', which are based mainly on western populations.

Investigators involved in the FRISC II substudy¹⁵ described a U-shaped curve with troponin T measurements in predicting future re-infarction rates. Patients in that study with intermediate levels of troponin T had higher rates of re-infarction than patients with undetectable or severely elevated levels. We were unable to demonstrate this in our study. This may be due to the small number of patients involved.

The TIMI risk score for NSTEMI, which is an easy to apply clinical score, is also predictive of future cardiac events when applied to our local population (odds ratio 2.18; range 0.49 to 9.58). Due to the small number of patients in this study, this did not reach statistical significance.

Conclusion

The main finding of this study was that myoglobin is the most sensitive and specific early marker for diagnosing patients presenting early with chest pain and a non-diagnostic electrocardiogram who subsequently developed

either ST-elevation myocardial infarction or non-ST elevation myocardial infarction.

Patients with an elevated troponin I level and normal CK or myoglobin levels are at higher risk of a future MACE and should be investigated more vigorously. On the other hand, patients with normal troponin I levels are at lower risk and could be managed more conservatively.

The results of this study suggest that a combination of myoglobin and troponin I should be measured in patients presenting with suspected acute coronary syndrome and non-diagnostic electrocardiograms provided that patients with a possible elevated myoglobin from a non-cardiac source are excluded. Routine use of this combination of enzymes at the appropriate time intervals could result in better risk stratification of patients on presentation, reduce unnecessary admissions to the coronary care unit and allow better identification of high risk patients who would be at an increased risk of future MACE after discharge. Further studies with larger number of subjects recruited will be necessary to confirm the findings of this preliminary study.

With the recommendation that the cut-off value of troponins be based on 99th percentile of a normal population, hospitals that are now adopting troponin level measurements may need to determine their own cut-off values. Levels based on western populations may not be appropriate when applied to our own population. Further studies to obtain these cut-off values are also required.

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