

The efficiency of cardiac biomarkers in the identification of patients with acute coronary syndrome

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Abstract

Background and objective: This study aimed to differentiate acute myocardial infarction from unstable angina upon the onset of chest pain, by evaluating the usefulness of combined biomarkers troponin I, ischemia modified albumin, and heart-type fatty acid binding protein as early as possible.

Methods: A cross-sectional study was conducted at the Department of Clinical Analysis, College of Pharmacy, Hawler Medical University. This study included 73 patients with suspected acute coronary syndrome, who attended to the Emergency and /or Cardiac Care Unit departments of Hawler Teaching Hospital and Rojhalat Emergency Hospital, Erbil, Iraq, and who were diagnosed with either acute myocardial infarction (n=45) or unstable angina (n=28) between 12 May 2013 and 25 January 2014. Serum troponin I, heart-type fatty acid binding protein, and ischemia modified albumin were determined twice, at between 30 minutes and 4 hours, and between 6 and 12 hours after the onset of chest pain.

Results: For diagnosing and differentiating between acute myocardial infarction and unstable angina, the sensitivity and specificity of serum troponin I cut-off value at (≤ 4) hours of chest pain was 53.3% and 100%, respectively. The sensitivity and specificity were 97.8% and 96.4 at 6-12 hours after onset of chest pain. The sensitivity and specificity of heart-type fatty acid binding protein cut-off values at (≤ 4) hours was 48.9% and 100%, respectively, increasing to 84.4% and 100% at 6-12 hours. The combined use of serum troponin I and heart-type fatty acid binding protein enhanced sensitivity to 73.3% at the first interval, and 100% at the second.

Conclusion: A combination of troponin I and heart-type fatty acid binding protein tests improves sensitivity in diagnosing and differentiating acute myocardial infarction and unstable angina within the first 4 hours of chest pain.

Keywords: Heart-type fatty acid binding protein; Ischemia modified albumin; Myocardial infarction; Troponin I; Unstable angina.

Introduction

In the United States each year, approximately 1.5 million out of 5 million people who attend emergency departments for chest pain and related symptoms, are hospitalized for acute coronary syndrome.¹ Frequently, ECG yields inconclusive results, and the clinical symptoms are unreliable for diagnosis of myocardial infarction. Therefore, there is a clear need for employing serum biochemical markers to confirm a diagnosis of myocardial injury.²

A simple, rapid diagnostic test for cardiac ischemia – which is a critically important indication of the risk of future cardiac events – would be a valuable diagnostic tool in such a situation. Tests for heart-type fatty acid binding protein (H-FABP) and ischemia modified albumin (IMA) appear particularly promising for this use.³ IMA is considered a 'gold standard' screening method candidate marker for the detection of myocardial ischemia as part of patient evaluation.⁴ H-FABP is released early

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into the plasma in cases of ischemia and/or myocardial injury, and a single measurement of this biomarker is regarded as highly sensitive and specific, allowing for prompt detection of emergency patients who are unsuitable for early discharge.⁵ ECG indicates diagnostic change in approximately 45% of patients who are diagnosed as having MI. Furthermore, typical clinical signs of ischemia are absent in one third of myocardial infarction cases.^{6,7} It appears, therefore, that the best approach would be to integrate ECG assessment with results on biochemical cardiac markers to improve the triage process and to avoid the premature discharge of patients whose presentation is unclear. This study aimed to ascertain the efficiency of these cardiac markers in the early diagnosis of, and differentiation between, patients with myocardial infarction and those with unstable angina, attending Emergency Departments and Cardiac Care Units.

Methods

This cross-sectional study was conducted at the Department of Clinical Analysis, College of Pharmacy, Hawler Medical University, Erbil, Iraq. Seventy three patients were selected with acute coronary syndrome attending the Emergency and/or Cardiac Care Unit (CCU) departments of Hawler Teaching Hospital and the CCU of Rojhalat Emergency Hospital, from 12 May 2013 to 25 January 2014.

Patients

Patients with ischemic chest pain, ST elevation, and unstable angina pectoris were diagnosed according to changes in ECG and cardiac enzymes (troponin I, CK-MB). The patients were classified into two groups. The first group included individuals with unstable angina who had chest pain at rest lasting for more than 10 minutes, with ECG changes including ST segment depression > 0.5mm and /or Dynamic T wave inversion. The second group included those with myocardial infarction who had severe chest pain with

or without radiation, and ST-elevation in at least two adjacent pericardial leads, >1mm in standard leads. The diagnosis was made by the cardiologist using all available clinical data, including patient histories and signs and symptoms, 12-lead ECGs, and cardiac markers (troponin, CK-MB).

Study protocol

The protocol specified early diagnosis patients with the acute coronary syndrome, assigned to early conservative treatment strategies, from both groups – the first within 30 minutes to 4 hours of the onset of chest pain; and the second within 6 to 12 hours of chest pain onset – to examine changes in serum IMA, H-FABP, and troponin I.

Inclusion criteria

Patients of both genders receiving care at the Emergency department, CCU, of the hospitals, with typical chest pain, and ECG changes suggestive of acute coronary syndromes within 30 minutes to 4 hours of onset.

Exclusion criteria

Exclusion criteria were: renal failure, liver failure, active malignancy, skeletal muscle injury, stroke, septic shock, congestive heart failure, heart disease unrelated to the acute coronary syndrome.

The study was approved by the Ethics Committee of Hawler Medical University, College of Pharmacy. All patients agreed to participate and gave their informed consent.

Statistical analysis

The statistical package for the social sciences (version 22) was used for data analysis. Statistical significance of mean difference (changes attributed to time interval) of a normally distributed quantitative outcome variable was assessed using the paired t-test, while ANOVA test was used for comparing more than two groups. The Chi-square (χ^2) test was used to test the statistical significance of the association between two categorical variables (presented on nominal or ordinal scales). A statistical significance level of

$P < 0.05$ was assumed. All analyzed tests were bilateral.

Receiver Operating Characteristic Curve (ROC) definition

ROC analysis provides a tool for the selection of optimal models and for discarding suboptimal ones, independently from (and prior to specifying) the cost context or the class distribution. ROC analysis is related in a direct and natural way to cost/benefit analysis in diagnostic decision making. This method allows for the selection of a typical cut-off value, which results in a highly valid test (highly specific, and with reasonably high sensitivity) through the ROC curve. The area beneath the curve suggests the usefulness of the test and facilitates comparison with other tests, with the proximity of the area indicating validity. The larger the area under the curve is (i.e., the closer to 1), the more valid the test since there is a considerable gain in sensitivity for minimal losses in specificity.

Test performance characteristics

The criteria for performance – or ‘validity’ – of a test include the issues of sensitivity, specificity, positive predictive value, and negative predictive value. ‘Sensitivity’ relates to the conditional probability that a diseased person will have a positive result. Its value can be changed by changing the cut-off point for positive test results. ‘Specificity’ is the conditional probability that a disease-free person will yield a negative test result. The proportion of false negatives is the conditional

probability that a diseased person will have a negative result (it equals $1 - \text{sensitivity}$); and the proportion of false positives is the conditional probability that a disease-free person will have a positive test result. Positive Predictive Value (PPV) describes the conditional probability that a person with a positive test result is actually diseased. Its value depends on the cut-off point for a positive test result and the prevalence of the disease in the screened population. Negative Predictive Value (NPV) describes the conditional probability that a person with a negative test result is actually free of the disease. ‘Accuracy’ (percent agreement) is the proportion of ‘true’ results occurring, taking all test results (positive and negative) into account.⁸

Results

The results presented in this study were based on analysis of two study groups with a history of ischemic heart disease: (n=28) individuals with unstable angina, with a mean age (mean \pm SD) of (59.25 \pm 2.3) years; and those with myocardial infarction (n=45), with a mean age (mean \pm SD) of (60.97 \pm 2.2) years. As shown in Table 1, no statistical difference was observed in mean ages. However, there was a statistically significant difference in gender distribution between the two study groups, with a higher percentage (60%) of females in the unstable angina group; and significantly more males (68%) in the acute myocardial infarction group, $P < 0.05$.

Table 1: Comparing the relative frequency of age and gender between unstable angina and acute myocardial infarction groups.

Study variables	Unstable angina (n = 28)	Acute MI (n = 45)	P value
Age group (years)			
Mean \pm SD	59.25 \pm 2.26	60.9. \pm 2.23	0.430
Gender			0.013
Female	17(60.7%)	14(31.1%)	
Male	11(39.3%)	31(68.9%)	
Total	28 (100.0%)	45 (100.0%)	

All study biomarkers were estimated at two different intervals (30 mins – 4 hrs and 6-12 hrs of chest pain onset). As shown in Table 2, there was no statistically significant difference in mean measurements of troponin I between the two study intervals in the unstable angina group (0.4 ng/ml versus 0.2 ng/ml), at $P > 0.05$. In contrast, the difference in the mean concentration of troponin I did reach high statistical significance between the study intervals in acute myocardial infarction (1.7ng/ml versus 13.4 ng/ml respectively), at $P < 0.001$. The mean of troponin I concentration was significantly higher in the acute myocardial infarction group, compared to the unstable angina

group in both study intervals, at 1.7 ng/ml versus 0.4 ng/ml respectively in the first study interval, and 13.4 ng/ml versus 0.2 ng/ml respectively in the second, with a significance of $P < 0.001$. The results for ischemia modified albumin (IMA), as shown in Table 3, showed no statistically significant difference in mean concentrations between the study intervals, for the unstable angina group (19.8 ng/ml versus 18.4ng/ml respectively), at $P > 0.05$. The difference in mean concentrations of IMA was highly significant between study intervals in the acute myocardial infarction group, however, at 18.4ng/ml versus 16.6ng/ml, respectively ($P < 0.05$).

Table 2: The changes in serum troponin-I after 6-12 hours compared to baseline values (≤ 4 hours) within and between study groups.

Study groups	Troponin-I(ng/ml)		<i>P</i> (Wilcoxon) (sign rank test) <i>P</i> value (paired t-test)
	first 4 hours	(6 to12 hours)	
Unstable angina			
Range	(0 to 1.2)	(0 to 1.4)	
Mean± SD (Troponin I)	0.4± 0.23	0.2± 0.17	0.140
N	28	28	
Acute MI			
Range	(0.1 to 175)	(0.7 to 167)	
Mean± SD (Troponin I)	1.7± 0.9	13.4± 2.5	<0.001
N	45	45	
<i>P</i> (t-test) for difference in Mean between 2 groups	<0.001	<0.001	

Table 3: The changes in serum Ischemia modified albumin (IMA) after 6-12 hours compared to its baseline values (≤ 4 hours) within and between study groups.

Ischemia modified albumin(ng/ml)			
Column title? Col	Study groups	first 4 hours	(6 to 12 hours) <i>P</i> value (paired t-test)
Unstable angina			
Mean± SD		19.8 ± 3.35	18.4± 4.26
N		28	28
Acute MI			
Mean± SD		18.4±3.88	16.6± 3.24
N		45	45
<i>P</i> (t-test) for difference in mean between 2 groups		0.12 NS	0.044

The mean concentration of IMA was higher to a statistically significant degree in the second study interval (6-12 hrs) in the unstable angina group compared to the acute myocardial infarction group (18.4 ng/ml versus 16.6 ng/ml respectively), at $P < 0.05$. As shown in Table 4, statistically significant higher mean concentrations of H-FABP were found in the AMI compared to the unstable angina group, in both study intervals, at 10.5 ng/ml versus 5.6 ng/ml respectively in the first time interval, and 16.4 ng/ml versus 5.2 ng/ml respectively in the second, at $P < 0.001$ significance. No statistically significant difference in H-FABP levels was found in the unstable angina group between the two intervals ($P > 0.05$).

Use of the ROC curve in assessing the biomarkers in both study intervals, for differentiating acute myocardial infarction from unstable angina

All study biomarkers were tested for their

validity in diagnosing and differentiating acute myocardial infarction from unstable angina, by examining the area under the receiver operating characteristic (ROC) curve and its statistical significance ('significance' being higher than the 0.5 ROC area of an equivocal test). As shown in table 5, there was a highly statistically significant larger area under the ROC curve for troponin I, in both study intervals: 0.82 for the first and 0.994 for the second ($P < 0.001$). The area for heart type fatty acid binding protein (H-FABP) was associated with ROC area of (0.768) in the first study interval and (0.942) in the second, and also showed a statistically significant difference from the 0.5 area of the equivocal test ($P < 0.001$).

Table 4: The changes in serum Heart-type fatty-acid binding protein (H-FABP)-after 6-12 hours compared to its baseline values (<4 hours) within and between study groups.

Heart type fatty acid binding protein (H-FABP) (ng/ml)			
Study groups	first 4 hours	(6 to 12 hours)	P value (paired t-test)
Unstable angina			0.52
Mean± SD	5.6± 2.92	5.2± 2.46	
N	28	28	
Acute MI			<0.001
Mean ± SD	10.5 ±6.08	16.4 ±9.92	
N	45	45	
P (t-test) for difference in mean between 2 groups	<0.001	<0.001	

Table 5: ROC area for selected biochemical measurements when used as test to predict acute MI differentiating it from unstable angina.

Study biomarkers	AUC	P value
troponin I-(6 to 12 hours)	0.994	<0.001
Heart-type fatty-acid binding protein (H-FABP)-(6 to 12 hours)	0.942	<0.001
troponin I-first 4 hours	0.820	<0.001
Heart-type fatty-acid binding protein (H-FABP)-first 4 hours	0.768	<0.001
Ischemia modified albumin (IMA)-first 4 hours	0.624	0.08
Ischemia modified albumin (IMA)-(6 to 12 hours)	0.602	0.14

This larger area indicates greater validity in predicting and differentiating AMI from unstable angina (Table 6) for serum troponin I in the first 4 hours post-onset of chest pain. The optimum cut-off value, associated with the highest Matthew's correlation coefficient (MCC) (0.552), is ≥ 1.25 ng/ml – this means the subject is anticipated to have AMI if their serum troponin I concentration is 1.25 ng/ml or higher. A positive test at ≥ 1.25 ng/ml value is associated with a sensitivity of 53.3% and specificity of 100%. In a clinical setting, where the chances of a diagnosis of AMI are anticipated to be equal (50:50), given a positive test, one can expect AMI with a confidence of 100%. Testing negative less than cut-off value (1.25 ng/ml) in the pretest probability condition (10%) can exclude the probability of MI with a confidence level of 95.1%. Thus, measuring serum troponin I in the first 4 hours post-onset, within the optimum cut-off value (1.25 ng/ml), can distinguish only 53.3% of patients with AMI – meaning 46.7% with AMI will give false negatives in the first interval. As shown in Table 5, H-FABP was associated with a ROC area of (0.768) and was statistically significantly different from the 0.5 area of the equivocal test ($P < 0.001$). Table 6 shows the optimum cut-off value of this test, which is associated with (0.518) MCC; the subject is expected to have AMI (as opposed to unstable angina) if they have a H-FABP

test of 10.05 ng/ml or higher. A positive test within this cut-off value is associated with 48.9% sensitivity and 100% specificity. In clinical situations where the probability of AMI in the first study interval is 50%, given a positive test, AMI (as opposed to unstable angina) can be expected, with a confidence level of 100%. Testing negative with a pretest probability of 10% can exclude the probability of having AMI with a confidence level of 94.6%. The test for troponin I at 6-12 hours, at the highest MCC (0.942), the optimum cut-off value, was (≥ 1.15 ng/ml); this is 97.8% sensitive and 96.4% specific, as shown in Table 6. Testing positive at this cut-off value would establish the diagnosis of acute MI with 96.5% confidence, in clinical situations, when the expectation is 50% of AMI rather than unstable angina. When the diagnosis of AMI is highly probable (90% pretest probability) based on clinical symptoms, the confidence level of a positive result is further increased to 99.6%. Testing negative with a pretest probability of 10% excludes the diagnosis of AMI with a confidence level of 99.7%. Table 6 also shows the optimum cut-off value for H-FABP associated with the highest MCC (0.822) in the second study interval, which is (≥ 9.15 ng/ml), where the subject is expected to have AMI rather than UA. A positive test at this cut-off value establishes the diagnosis of AMI (as opposed to UA) with 84.4% sensitivity and

Table 6: Validity parameters for troponin I and H-FABP in both study time interval when used as test to predict acute MI differentiating it from unstable angina.

Positive if \geq cut-off value	Sensitivity	Specificity	Accuracy	Matthews correlatin coefficient	PPV at pretest probability =		NPV at pretest probability = 10%
					50%	90%	
First 4 hours							
Tropl ≥ 1.25	53.3	100.0	71.2	0.552	100.0	100.0	95.1
H-FABP ≥ 10.05	48.9	100.0	68.5	0.518	100.0	100.0	94.6
6 to 12 hours							
Tropl ≥ 1.15	97.8	96.4	97.3	0.942	96.5	99.6	99.7
H-FABP ≥ 9.15	84.4	100.0	90.4	0.822	100.0	100.0	98.3

100% specificity. In clinical situations, where the expectation is of AMI, as opposed to UA, is at a pretest probability of 50%,90%; given a positive test one can expect AMI with a confidence level of 100% for a 50:50 chance; and at 100% for a pretest probability of 90%. Testing negative in with a pretest probability of 10% excludes a diagnosis of AMI with a confidence level of 98.3%.

Predicting acute myocardial infarction and differentiating it from unstable angina by assessing a combination of study biomarkers, at both study intervals:

It is apparent that a combination of cTnl and H-FABP can be considered to generate a positive test when one or both are positive. In both study intervals, the improvement is mainly in sensitivity, which was 73.3% at 30 mins-4 hrs. where the sensitivity was 53.3% for troponin I, and 48.9% for H-FABP when each one was used without other(see Table 6), and 100% at 6-12 hrs post-onset of chest pain, since the specificity of the component tests was already high (100% for the first interval; and 96.4% for the second – see Table 7). A combination of using troponin I and H-FABP is most valid and can be regarded as reliable, for both study intervals, in diagnosing and differentiating acute myocardial infarction from unstable angina.

The ischemia modified albumin test shows no statistically significant area by ROC analysis, and thus can be considered of lesser importance in this context.

Discussion

It is suggested that the measurement of cardiac biomarkers for myocardial injury plays an important role in the diagnosis and treatment of acute coronary syndrome. Each of the three key biomarkers will now be discussed briefly in this regard.

Troponin I

Cardiac troponin is considered the 'gold standard' for the diagnosis of the acute coronary syndrome. In the present study, serum troponin I (0.4 ng/ml; 0.2 ng/ml) for both time intervals in the UA group (Table 2), was less than that found in the MI group (1.7 ng/ml; 13.4 ng/ml) for both intervals, and exceeded the recommended cut-off AMI value established by Tmimi *et al.*⁹ Thus, it could be regarded a superior marker for differentiation between UA and AMI. It has been shown in prior work¹⁰ that a slight elevation of cTnl (above the lowest detection limit of ≤ 0.19 ng/ml) as established by Anwaruddin *et al.*⁴) is a valid predictor of adverse events in patients with ACS. Thus, the measurement of cTnl in patients with a clinical history consistent with ACS derives benefits regarding early invasive management

Table 7: Validity parameters for two types of tests combinations at the optimum cut-off value when used to predict acute MI differentiating it from unstable angina.

Positive if \geq cut-off value	Sensitivity	Specificity	Accuracy	Matthew's correlation coefficient	PPV at pretest probability =		NPV at pretest probability = 10%
					50%	90%	
Combination of troponin-I and H-FABP at optimum cut-off value-first 4 hours	73.3	100.0	83.6	0.716	100.0	100.0	97.1
Combination of troponin-I and H-FABP at optimum cut-off value-(6-12 hours)	100.0	96.4	98.6	0.971	96.6	99.6	100.0

strategies. The ROC curve analysis showed that cTnI has a ROC curve area of 0.820 (Table 5). This was significantly larger than that of the equivocal area (0.5) in the first interval, which indicates that troponin I is consistent as an indicator of AMI versus unstable angina. The higher the cut-off value, the more the sensitivity decreases, and the specificity increases. In the first interval (≤ 4 hrs), the optimum cut-off for cTnI was 1.25 ng/ml, with a sensitivity of 53.3% and a specificity of 100% (Table 6). A slight insensitivity (a sensitivity of 53.3%) gave early false negative results for cTnI, highlighting the need for multiple timed samples. The present study confirms the published data⁹, in that it was found this test was slightly poor in terms of sensitivity (i.e., some cases of AMI are missed) within the first interval following chest pain onset. In the first study interval, if the probability of having AMI versus unstable angina in patients with chest pain was 50%, cTnI revealed AMI with a confidence level of 100%, with equal or higher cut-off value (1.25 ng/ml).

Heart-type fatty acid binding protein (H-FABP)

In acute myocardial infarction, the sensitive indicator of ischemia, heart type fatty acid binding protein, may be considered a potential marker for early diagnosis ACS; this cardiac biomarker level increases well before markers for cardiac necrosis.¹¹ It starts increasing within an hour following myocardial cell damage, and peaks between 6 and 8 hours post pain onset, returning to normal between 24 and 30 hours post pain onset.¹² H-FABP levels >7 ng/ml in patients presenting with chest pain is considered positive for AMI¹³, while in a study by Aktuğlu *et al.*,¹⁴ normal levels of H-FABP were stated to range between 0.24 and 2.55 ng/ml. In this study, the mean concentration of H-FABP was 5.6 ± 2.92 ng/ml and 5.2 ± 2.46 ng/ml respectively for the two time intervals in unstable angina; this was significantly less than AMI means in both time intervals (10.5

ng/ml and 16.4 ng/ml respectively – see Table 4). The above information reveals the means in both study intervals in the unstable angina group were higher than normal range and less than the AMI cut-off values. This potentially confirms our hypothesis regarding the usefulness of H-FABP in diagnosing and differentiating unstable angina from AMI in the early stages. The application of optimum cut-off values for both study biomarkers in the first time interval indicates the same efficacy for the ruling-in of MI (PPV, 100%). However, H-FABP also provided an important ruling-out of MI (NPV 94.6%) (Table 6). Similar results have been observed by Reiter *et al.*¹⁵ However, H-FABP levels measured at presentation were significantly higher in patients with AMI than those who were non-ST elevation myocardial infarction (NSTEMI). In contrast, the data of Alansari and Croal¹⁶ showed that H-FABP and myoglobin offer little clinical value, compared to cTnI, when measured at presentation in patients presenting with chest pain (3-12 hours).

Ischemia modified albumin (IMA)

In the present study, mean concentrations of IMA in both study time intervals in the UA group were higher than those in the AMI group, with a significant difference found in the second interval between the two groups (at 18.4 ng/ml, 16.6 ng/ml respectively – Table 3). As has previously been reported by Wudkowska *et al.*¹⁷ IMA concentrations do not differentiate ACS and NSTEMI patients from those with unstable angina.

The predictive power of troponin I and H-FABP in combination, in diagnosing MI and differentiating it from unstable angina, at both time intervals

Application of a combined approach provides reasonable diagnostic discrimination for both the ruling-out (NPV) and the ruling-in (PPV) of MI, including in patients presenting within the early hours of chest pain onset (30 min-4 hrs). The use of both biomarkers together, to their optimum cut-off value, provide

a substantial improvement in sensitivity, 73.3% with 100% specificity, for the diagnosis of MI and its differentiation from unstable angina, on admission, where the sensitivity was 53.3% for troponin I, and 48.9% for H-FABP when each one was used without other. Thus, it is recommended that this approach be applied for the first time interval, for early definitive diagnosis, with possible subsequent diagnostic or therapeutic interventions.

Conclusion

Troponin is an early discriminator between AMI and UA, and H-FABP showed reasonable validity for the same purpose, particularly when the suspected ACS patient is at the critical query period (first study interval). The validity of Troponin I and H-FABP as diagnostic biomarker increases with time and becomes more useful in confirming the diagnosis and differentiation of myocardial infarction from unstable angina by 6-12 hours after the onset of chest pain. Ischemia modified albumin (IMA) concentrations do not differentiate patients with acute myocardial infarction from patients with unstable angina. The approach of combining testing of troponin I with testing of H-FABP in the first 4 hours following the onset of chest pain seems promising for discriminating between patients with acute myocardial infarction and those with unstable angina. This approach may prove to be of clinical significance in the early diagnosis (ruling-in of MI) and stratification of risk in patients with the acute coronary syndrome.

Competing interests

The authors declare no competing interests.

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