Evaluation of combined biochemical markers in the diagnosis of acute coronary syndrome in Nineveh governorate

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Received	Accepted
12.6.2011	30.10.2011

ABSTRACT

Objective: To evaluate the importance of combination of biochemical markers in patients with Acute Coronary Syndrome (ACS) and to determine the optimal biochemical strategy for highly sensitive, early diagnosis of myocardial injury.

Patients and methods: This study was carried out in coronary care unit in Ibn- Sena Teaching Hospital in Mosul city from January to November, 2008. Two hundred and forty nine patients with (ACS) presented with chest pain and one hundred and eleven apparently healthy subjects. Four cardiac markers Creatine Kinase (CK) and Creatine Kinase-MB (CK-MB) activities (markers of necrosis), myoglobin (marker of muscle injury), and troponin I (marker of necrosis) were estimated in addition to CK-MB index. The collected data were analyzed by chi square, unpaired t-test and analysis of variance (ANOVA). Receiver Operating Characteristics (ROC) analysis was used to assess the role of selected parameters in the diagnosis of ACS and to determine optimal cut-off values for all biochemical markers.

Results: The optimal cut-off value of each of 5 parameters with reasonable validity were used to define single test criteria. The serum troponin I was with highest validity among other parameters. The serum troponin I was used in combination with each of the remaining 4 criteria and the test performance was assessed. All combinations were associated with higher specificity than that of serum troponin I alone. However, the accuracy of serum troponin I alone 94.0% was higher than the accuracy of all other combinations.

Conclusion: The study has suggested that combining troponin I, myoglobin and CK-MB index yields satisfactory diagnostic sensitivity and thus provide valuable information for clinicians in managing Acute Coronary Syndrome (ACS).

Key words: Troponin I, myoglobin, Creatine Kinase (CK), Creatine Kinase-MB (CK-MB), CK-MB index, acute coronary syndrome, biochemical markers.

الخلاصة

الأهداف: تقييم أهمية ربط الواسمات الكيمياوية الحيوية مع بعضها في تشخيص مرضى تناذر الشرايين التاجية الحاد الذين ادخلوا وحدة العناية المركزة.

طريقة العمل : شملت الدراسة على 249 مريضا يعانون من الم الصدر بعد أن تم إدخالهم وحدة العناية المركزة في مستشفى ابن سينا التعليمي وذلك لوجود أعراض احتمالية احتشاء العضلة القلبية الحاد. أظهر التشخيص ألسريري أن هنالك 193 مريضا مصابا باحتشاء العضلة القلبية الحاد و 56 مريضا مصابا بذبحة صدرية غير مستقرة.

تم احتساب عدد من الواسمات الكيمياوية الحيوية لأمراض الشرايين التاجية وشملت على Troponin I (دالة موت الأنسجة) و Myoglobin (دالة أذى العضلة) و CK-MB & CK (دالة موت الأنسجة) تمت المقارنة مع مجموعة سيطرة (111) من الأشخاص الأصحاء العاديين. تم تحليل النتائج بواسطة اختبار مربع كاى و جدول تحليل التباين و اختبار تى .واستخدمت طريقة أل ROC لبيان حساسية و خصوصية المتغيرات ولإثبات دورها في تشخيص المرض والتفريق بين احتشاء العضلة القلبية والذبحة القلبية غير المستقرة.

ألنتائج : قيم الحد القاطع المناسب للواسمات بالصلاحية المعقولة استعملت لتعريف معايير الاختبار للواسمة الواحدة . أن المتغير المثالي للتفريق بين احتشاء العضلة القلبية الحاد و الذبحة القلبية غير المستقرة هو مستوى Troponin I في المصل. تم جمع Troponin I مع بقية الواسمات الكيمياوية واجري اختبار قياس قيم.

إضافة إلى كون Troponin I لوحده يحمل أعلى حساسية 94.8%. تشير النتائج إلى أن عند الجمع بين الواسمات الكيمياوية الحيوية كل على حدة مع أل Troponin I تكون هناك خصوصية أعلى مما عليه في أل Troponin I لوحده ومع ذلك فان الدقة في Troponin I لوحده هي الأعلى (94.0%)

الاستنتاج: إن جمع الواسمات الكيمياوية الحيوية (Myoglobin + Troponin I+ CK-MB index) حين دخول المرضى في العناية المركزة يساعد كثيرا في تشخيص احتشاء العضلة القلبية الحاد.

Symptoms and signs suggestive of acute myocardial infarction (AMI) and unstable angina which constitute acute coronary syndrome (ACS) are non specific and have low sensitivity for diagnosis of this condition[1]. The World Health Organization (WHO) definition and diagnosis of AMI, is currently two out of three: characteristic chest pain, diagnostic electrocardiogram changes and elevation of the biochemical markers in the blood samples[2].

The electrocardiogram (ECG) may never show the classical features of ST elevation and new Q waves. Hence, in the early stage, there is no enough evidence in these patients for clear diagnosis and risk stratification[3].

Biochemical marker identification which is sensitive and specific for myocardial ischemia and can easily and rapidly measured in serum would be clinically valuable[3]. Elevated levels of cardiac markers: Creatine kinase (CK-MB) activities (marker of necrosis), in addition to troponin I (marker of necrosis), and myoglobin (marker of muscle injury), could be useful in early diagnosis of acute coronary syndrome when patients admitted to coronary care unit (CCU)[3].

Use of the combination of a marker that appears early (myoglobin) and either Creatine Kinase CK-MB isoenzyme (CK-MB) or cardiac troponin I (TnI) may facilitate rapid exclusion of AMI and enable discharge of patients who do not require prolonged observation[4]. Myoglobin is advantageous because it appears 1 to 2 hours after symptom onset, and studies have demonstrated its high sensitivity for detection of AMI within the first few hours after presentation[(4)]. However, use of myoglobin alone has significant limitations. Myoglobin has low specificity for cardiac necrosis in patients with renal failure or skeletal muscle trauma[5]. Also, given that serum myoglobin rises and falls quickly in AMI, a single measurement at presentation may be normal for patients who present early and who present 24 hours after symptom onset[6]. On the other hand, CK-MB and cTnI appear 3 to 6 hours after symptom onset and remain elevated for

24 to 36 hours and 7 to 10 days, respectively[7]. However, these markers must be ordered as a panel in the ED because no single marker meets all criteria for an ideal marker of AMI diagnosis for all patients who arrive at the ED at various times after the onset of the symptoms[8].

The aim of this study was to evaluate the importance of combination of biochemical markers in patients with Acute Coronary Syndrome (ACS) and to determine the optimal biochemical strategy for highly sensitive, early diagnosis of myocardial injury.

Subjects and methods

This study was carried out in Ibn- Sena Teaching Hospital in Mosul from January 2008 to November 2008. It was carried out on 249 patients with Acute Coronary Syndrome (ACS) who were presented with chest pain where 193 (77.5%) patients with a diagnosis of possible Acute Myocardial Infarction (AMI) and 56 (22.5%) patients with Unstable Angina (UA) . A control group that includes 111 apparently healthy subjects who attended the Out-Patient department was chosen for comparison. None of the control subjects had any chronic diseases and they were not taking regular medicine. All patients who admitted to the CCU were with provisional diagnosis of ACS. The patients were looked for risk factors, "Smokers" were defined as patients currently smoking at the time of admission; Hypertension was defined by self-report of a diagnosis and use of an anti-hypertensive medication, or if systolic blood pressure > 140 mmHg or if diastolic blood pressure> 90 mmHg[9]; "Diabetes" as patients on insulin or taking oral hypoglycemic agent[10]; " Hypercholesterolemia " as total cholesterol of >5.0 mmol/L on admission[11]. A family history for CHD is considered positive if relatives have experienced an MI prior to the age of 50 in men, and 55 in women[1].

History of ischemic heart diseases is defined as any group of acute or chronic cardiac disabilities resulting from insufficient supply of oxygenated blood to the heart, or is a group of diseases characterized by reduced blood supply to the heart muscle usually due to coronary artery disease (atherosclerosis of coronary arteries)[11]. Male gender and obesity were also considered as risk factors[1].

All patients had cardiac markers tested within 12 hours post chest pain[12]. Their ECG was assessed and any ischemic or progressive changes were documented[12]. Anthropometric Measurements were also taken. The socioeconomic state was grouped into low, medium and good. The study was carried out with the cooperation of senior cardiologist in Coronary Care Unit (CCU). On admission, patients satisfying two out of the three criteria of WHO were considered as having myocardial infarction[2]. The definitive diagnosis of myocardial infarction required all three criteria to be satisfied. Patients with chest pain and non-Q ECG pathology but with no changes in cardiac enzymes were diagnosed as having unstable angina[13]. The case notes were analyzed and

information regarding the duration of chest pain, risk factors, socio-economic status, Body mass index and ECG changes were obtained on a purpose designed data collection sheet.

About 10 ml of venous blood were collected from patients on admission to the CCU. The blood samples were collected in vials. Blood allowed to clot fully by leaving for 15 minutes in water bath at 37 °C, then serum was separated by centrifugation at 3000 rpm for 10 minutes. The serum sample was divided into two aliquots and stored at -20 °C. The first aliquot was for analysis of (CK) and CK-MB activities using BIOLABO CK-NAC UV method and BIOLABO CK- MB UV method respectively (in the department of biochemistry)[14]. The second aliquot was for analyses of troponin I and myoglobin using ELISA monoclonal antibody (Biochek, Foster City, USA) for both parameters[15,16]. The upper reference limits for the quantitative cardiac markers used in this study were: CK activity 174U/L for men and 140 U/L for women; CK-MB activity ≥ 25 IU ; Troponin ≥ 0.4 ng/mL and myoglobin ≥ 54.5 ng/mL. CK ratio value or index (CK-MB /CK) × 100 ≥ 6% is considered suggestive for AMI.

Statistical analyses: The collected data were analyzed statistically by chi square, unpaired t-test and analysis of variance (ANOVA) test. The cut-off values for all biochemical markers were determined by Receiver Operating Characteristics (ROC) curve analysis. A ROC is a graphical representation of the tradeoff between the true positive and false positive rates for every possible cut off of the test result. In essence, the ROC curve is the tradeoff between sensitivity and specificity[17]. A large area under curve (AUC), as shown in the table, means the test being assessed to a better diagnostic test. If the area is 1.0, the test has both 100% sensitivity and 100% specificity and represents an ideal test. If the area is 0.5, the test has 50% sensitivity and 50% specificity – the same as getting heads on the flip of a coin. Therefore, the closer the AUC is to 1.0, the better the test is for diagnosis[17]. The values for: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPP) were also calculated[18]. All results were considered significant at $p < 0.05$.

The study received the agreement of the Ethical committee of Nineveh Governorate Health Department and approval of Mosul College of Medicine- Postgraduate Studies Committee. Subjects were informed about the purpose of the study and oral consent was obtained from the patients and the controls after the study had been explained to them.

Results

Description of Study Sample

As shown in Table 1, the age of study subjects ranged between 26 and 90 years. The mean age in MI, UA patients and controls were 55.4±10 , 56.6±12.2 and 57.3±11.9 years respectively. There was male preponderance among MI cases (male to female ratio 1.76/1) while the ratio in UA cases was (0.65/1) which means that UA is more frequent in females

than males. BMI 25-30 kg/m^2 was present in 52.3% and 53.6% of MI and UA respectively, while 24.4 and 10.7% of MI and UA respectively were obese. The mean duration of UA was shorter than that of MI.

Frequency distribution of the risk factors among the studied patients

There were no significant differences between MI and UA cases in the prevalence rate of diabetes mellitus, hypercholesterolemia, cigarette smoking and family history of myocardial ischemia. Obesity and history of previous attack of myocardial ischemia were more frequent among MI cases (24.4% and 30.6%) compared to unstable angina cases (10.7% and 14.3% respectively). More than 30% of patients had more than four risk factors (Table 2).

Using Test Combinations

At time of admission to coronary care unit, the combination of serum troponin I, myoglobin, CK activity, CK-MB activity and CK-MB index was performed. The optimal cut-off values determined by selecting the point on each curve at maximum curvature in ROC curve for each of 5 parameters with reasonable validity (Figure 1).

As shown in Table 3. serum troponin I was the most valid test when used alone in differentiating MI from unstable angina cases. The optimal cut-off value of each of 4 tests with reasonable validity were used to define single test criteria. After that, combination test criteria were used to improve the specificity of diagnosis by considering a subject as positive if the test positive on both criteria, otherwise the subject will be considered negative.

The serum troponin I was used in combination with each of the remaining 4 criteria and the test performance was assessed. All combinations were associated with higher specificity than that of serum troponin I alone. However, the accuracy of serum troponin I alone 94.0% was higher than the accuracy of all other combinations (Table 4). In this study, a large proportion of unstable angina (33 patients from 89 unstable angina patients), which is 13.2% of total (249 ACS patients), would be reclassified as having acute myocardial infarction due to utilizing cardiac markers. All combinations were associated with higher or equal specificity than that of serum troponin I alone (91.1%), while the accuracy of serum troponin I alone (94.0%) was higher than the accuracy of all other combinations.

Cardiac Biochemical Markers Combination

Triple combination of TnI, myoglobin with CK-MB/CK Ratio offered a high improvement over the combination of TnI and myoglobin testing recording (triple panel sensitivity, 91.2%; specificity, 96.45% and highest accuracy 92.4%) for diagnosis of myocardial infarction which means the best combination among others (Table 4).

Table 1. Frequency distribution of the study sample by socio-demographic variables

	Control (n=111)		MI (n=193)		UA (n=56)	
	No.	%	No.	%	No.	%
1. Age (years)						
<50	24	21.6	32	16.6	11	19.6
50-59	26	23.4	75	38.9	23	41.1
60-69	43	38.7	58	30.1	13	23.2
≥70	18	16.2	28	14.5	9	16.1
Mean ± SD	57.3 ± 11.9		55.4 ± 10.0		56.6 ± 12.2	
Range	30-79		26-80		26-90	
2. Gender						
Male	58	52.3	123	63.7	22	39.3
Female	53	47.7	70	36.3	34	60.7
Male to Female ratio	1.09:1		1.76:1		0.65:1	
3. BMI (kg/m^2)						
Normal (18.5-25)	52	46.8	45	23.3	20	35.7
Overweight (25-30)	57	51.4	101	52.3	30	53.6
Obese (>30)	2	1.8	47	24.4	6	10.7
4.Socio-economic status						
Low	44	39.7	84	43.5	32	57.1
Medium	46	41.4	56	29.0	16	28.6
High	21	18.9	53	27.5	8	14.3
5. Duration of pain Mean±SD (hour)			7.63±2.61		5.34±1.52 *	

*Significant differences from MI data at $P < 0.05$

Table 2. Frequency distribution of the risk factors among the studied patients

Risk factors	MI (n=193)		UA (n=56)		*p*-value
	No.	**%**	**No.**	**%**	
Hypertension	107	55.4	24	42.9	NS
Diabetes mellitus	67	34.7	21	37.5	NS
Hypercholesterolemia	61	31.6	11	19.6	NS
Family history of Ischemic heart disease	35	18.1	10	17.9	NS
Previous attack of Ischemic heart disease	59	30.6	8	14.3	0.008
Cigarette smoking	64	33.2	19	33.9	NS
Obesity	47	24.4	6	10.7	0.014
Gender (male)	123	63.7	22	39.3	0.001

NS = Not significant according to Chi-square test

Table 3. ROC area for the measured parameters for the differentiation of MI from UA in cases with ischemic heart disease.

Parameters	Area	*p*-value	95% C.I.
Serum CK (U/L) 147.0 Optimal cut-off value	0.886	<0.001	0.840-0.931
Serum CK-MB (U/L) 9.0 Optimal cut-off value	0.865	<0.001	0.815-0.915
Serum myoglobin (ng/mL) 52.5 Optimal cut-off value	0.896	<0.001	0.847-0.945
Serum troponin I (ng/mL) 1.55 Optimal cut-off value	0.924	<0.001	0.874-0.973
CK-MB/CK Ratio or Index 2.18 Optimal cut-off value	0.794	<0.001	0.736-0.852

Table 4. The validity parameters of the cut-off value for troponin alone and in combination with the other measured parameters when used to differentiate MI from UA in cases with ischemic heart disease

Serum	Sensitivity	Specificity	Accuracy	PPV at pretest prob. = 50%	PPV at pretest prob. = 90%	NPV at pretest prob. = 10%
Troponin I (ng/mL)	94.8	91.1	94.0	91.4	99.0	99.4
Troponin I+ CK	88.1	94.6	89.6	94.2	99.3	98.6
Troponin I + Myoglobin	88.1	91.1	88.8	90.8	98.9	98.6
Troponin I + CK-MB	80.8	96.4	84.3	95.7	99.5	97.8
Troponin I +CK-MB/CK Ratio or Index	93.8	91.1	93.2	91.3	99.0	99.3

Table 5. The validity parameters of the cut-off value for the triple combination of the measured parameters when used to differentiate MI from UA in cases with ischemic heart disease

Combinations of parameters	Sensitivity	Specificity	Accuracy	PPV at pretest prob. = 50%	PPV at pretest prob. = 90%	NPV at pretest prob. = 10%
CK + CK-MB + Myoglobin	77.2	94.6	81.1	93.5	99.2	97.4
CK + CK-MB + Troponin I	78.9	96.4	82.7	95.6	99.5	97.6
CK + CK-MB + Ratio*	83.4	83.9	83.5	83.8	97.9	97.9
CK-MB + Myoglobin +Troponin	75.1	98.2	80.3	97.7	99.7	97.3
CK-MB + Myoglobin + Ratio*	79.3	94.6	82.7	93.6	99.3	97.6
Myoglobin + Troponin I+ Ratio*	91.2	96.4	92.4	96.2	99.6	99.0

*Ratio= CK-MB/CK Ratio or Index

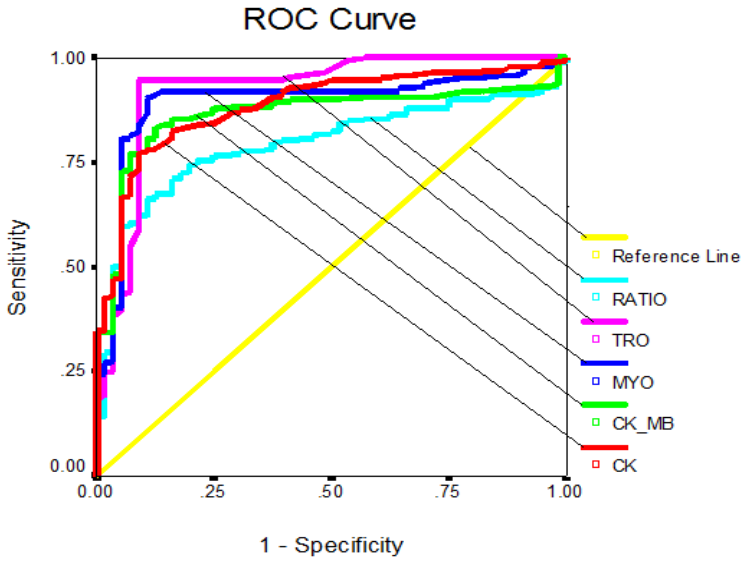

Figure 1. ROC curve for different cut-off values of selected parameters when used to diagnose MI from UA in subjects with ischemic heart disease

Discussion

The National Academy of Clinical Biochemistry (NACB) has recommended that the protocol for using cardiac markers in evaluation of patients with possible ACS should include an" early marker such as myoglobin or CK-MB, which is reliably increased in the blood within 6 h after symptoms onset, and a "definitive" marker (such as TnI or TnT), which is increased in the blood after 6-9 h with a high sensitivity and specificity for myocardial injury and remains with abnormal levels for several days thereafter[19]. The use of combination of marker that appears early [myoglobin] and either CK-MB or cardiac troponin I may facilitate rapid exclusion of MI and enable discharge of patients[20]. As for diagnostic purposes, an algorithm applying a panel of biochemical markers reflecting different aspects in ACS appears to be a promising option for improving risk stratification[21]. In contrast multimarker strategies incorporating CK-MB or myoglobin in combination with troponin I results have only been evaluated by few authors[20-24]. However, it makes intuitive sense that combinations of two or more cardiac biomarkers increase the early predictive value of these types of strategies[25].

In this study, four markers were used in addition to CM-MB index as criteria that favor the diagnosis and differentiation of MI from UA in cases of ACS, when equal to or higher than an optimal cut-off value. When the subject is positive in at least three of these

tests he is considered to have diagnosis of AMI. Troponin I sensitivity was the highest one among other parameters with (99.4%) negative predictive value. But however, at these cut-off values, the diagnostic predictive value for combination of two tests was less significant (Table 4).

In the present study, a combination of TnI and CK-MB index can achieve a diagnostic sensitivity of 93.8% for AMI with a 99.3% negative predictive value at time of admission to CCU, which is the highest diagnostic sensitivity among other combination. This is consistent with the study of Engel and Rockson where the sensitivity of combination of TnI and CK-MB index was 90.6% at time of presentation[24]. However, the combination of myoglobin and TnI can achieve a diagnostic sensitivity of 88.1% for AMI with a 98.6% negative predictive value, at presentation to CCU which similar to the results of others [23,27,28]. Thus, the combination of a highly sensitive marker such as myoglobin with a highly specific marker such as troponin might optimize diagnostic accuracy.

The triple combination of the measured parameters when used to diagnose patients with ACS showed combination of myoglobin,troponin I and CK-MB ratio recorded high sensitivity 91.2% with a specificity of 96.45% and highest accuracy 92.4% and high positive predictive value 99.6%. These results are in line with the study of Hsu *et al* where a triple marker panel of myoglobin, TnI and CK-MB had a sensitivity of 93% and specificity of 95% and the study of Rathore *et al* which showed a sensitivity of 85.7% and specificity of 96.5% and positive predictive value 92.3% for the same combination[20,29].

Most studies have compared only two or three markers at the same time and have not compared them with the initial electrocardiogram.

In conclusion, no single biochemical marker can be used to predict diagnosis in AMI patients, therefore, it is conceivable that combination of biochemical markers may help for this purpose. Combination of Troponin I, myoglobin and CK-MB index can achieve the best diagnostic yield.

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