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RESEARCH ARTICLE

Does ischemia-modified albumin add prognostic value to the Thrombolysis In Myocardial Infarction risk score in patients with ST-segment elevation myocardial infarction treated with primary angioplasty?

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Abstract

Background: The aim of the present study was to evaluate whether or not an elevated ischaemia-modified albumin (IMA) level provides any additional prognostic information to the validated Thrombolysis In Myocardial Infarction (TIMI) risk score in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI). *Methods:* One hundred seven consecutive STEMI patients treated with primary PCI were included. The incidence of 30-day death was the prespecified primary end point. Serum IMA was measured immediately at hospital arrival. *Results:* The incidence of the primary end point was 6.5%. A significant predictive value of IMA in relation to the primary end point was indicated by an area under the ROC curve of 0.71 ($p = 0.01$). In the multivariate analysis, increased IMA remained a significant predictor of the primary end point after adjustment for TIMI risk predictors ($p = 0.019$). The area under the ROC curve for the TIMI risk score was 0.68 ($p = 0.03$). The addition of IMA to the TIMI risk score did not improve its prognostic value (area under the ROC curve 0.60, $p = 0.25$). *Conclusion:* IMA levels obtained at admission are a powerful indicator of short-term mortality in STEMI patients treated with primary PCI, but do not seem to be a marker that adds prognostic information to the validated STEMI TIMI risk score.

Keywords: *Ischaemia-modified albumin; TIMI-risk score; ST-segment elevation myocardial infarction; primary percutaneous coronary intervention*

Introduction

The Thrombolysis In Myocardial Infarction (TIMI) risk score for ST elevation myocardial infarction (STEMI) and other risk scores are popular and powerful prognostic tools for risk stratification in the acute phase of myocardial infarction (Killip & Kimball 1967, Morrow et al. 2000). In most cases they have been developed from selected populations of patients, very often treated with fibrinolytic therapy. Therefore they may not be relevant in most patients seen in today's practice and treated according to current guidelines. On the other hand, new biochemical markers, such as ischaemia-modified albumin (IMA), which has been demonstrated to be predictive in acute coronary syndromes (ACS), are not included in popular risk scores. Previous studies demonstrated that IMA levels obtained in the first hours after symptom onset have the capacity to predict short- and long-term outcomes in patients with ACS (Aparci et al. 2007, Consuegra-Sanchez et al. 2008). We also found that serum IMA levels obtained on admission, independently from

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other clinical variables, predict congestive heart failure in STEMI patients treated with primary percutaneous coronary intervention (PCI) (Dominguez-Rodriguez et al. 2008). Based on these findings, our study evaluated the hypothesis that admission IMA levels add prognostic information to the TIMI risk score in STEMI patients treated with primary PCI.

Materials and methods

Patients

We prospectively studied 125 STEMI patients treated in our hospital with primary PCI <6 h after the onset of chest pain. Pregnant women and patients with acute renal failure, suspected acute mesenteric ischaemia, peripheral vascular disease or brain ischaemia were not enrolled in the study. We excluded 18 patients because of inaccuracy of timing for sample acquisition. Thus, the study population comprised 107 patients. For consistency of the present study with the original STEMI TIMI-risk score analyses (Morrow et al. 2000), the same primary end point was used, namely, 30-day mortality. The STEMI TIMI risk score was assessed on admission for each patient. This risk score is readily applied at the patient's bedside. Each score is calculated as the simple arithmetic sum of the points assigned for the variables present at patient presentation (range 0–14 for STEMI TIMI risk scores) (Morrow et al. 2000). Each of eight independent clinical variables was assigned 1 to 3 points for STEMI TIMI-risk score estimation: (1) age ≥75 and 65–74 years (3 and 2 points, respectively); (2) systolic blood pressure <100 mmHg (3 points); (3) heart rate >100 beats min^{-1} (2 points); (4) Killip classes II–IV (2 points); (5) anterior STEMI or left-bundle branch block (1 point); (6) a history of diabetes, hypertension or angina (1 point); (7) body weight <67 kg (1 point); and (8) time to start of intravenous thrombolysis of >4 h (1 point). All patients were transferred immediately from the admission department to a catheterization laboratory where angiography, followed by PCI, was performed (mean door-to-balloon time was 20 min). Cardiac catheterization was performed by the femoral approach. The culprit coronary artery was catheterized first, followed by the non-culprit ones. All patients received standard routine medical care before and after primary PCI, and decisions regarding the number of balloon inflations and the use of stents were at the discretion of the interventional cardiologist. The study followed the principles of the Declaration of Helsinki and of the World Medical Assembly. The protocol was approved by the institutional ethics board, and documented informed consent was obtained from each patient.

Measurements of IMA

A blood sample to measure IMA levels was drawn immediately at hospital arrival. IMA measurement was performed using an indirect method based on the albumin cobalt binding (ACB) colorimetric assay. Serum IMA was measured by the addition of a known amount of Co^{2+} ($CoCl_2.6H_2O$, 1 g l^{-1}; SIGMA, Madrid, Spain) to serum specimen and further measurement of the unbound Co^{2+} by colorimetric assay using dithiothreitol (DTT, 1.5 g l^{-1}; Sigma), as previously described by Bar-Or D et al. (2000). All the reagents were prepared in fresh before assay. An inverse relationship exists between the amount of albumin-bound cobalt and the intensity of the colour. The absorbance of the mixture was read at 470 nm with a microplate spectrophotometer reader (Benchmark Plus, Bio-Rad, Hercules, CA, USA). The blank of each sample was prepared similarly with the exclusion of DTT. IMA is expressed in absorbance units (A.U.). All samples were analyzed in duplicate at the same time, in the same plate and in the same session. The intra-assay coefficient of variation for 14 replicate samples was 3.98%. The interassay coefficient of variation for 18 replicate samples was 5.16%.

Statistics

Continuous variables are expressed as the mean ± SD and categorical variables as percentages. Comparisons of the continuous variables between groups were made using the *t*-test or Mann–Whitney *U* statistical test. Associations between two categorical variables were tested by the χ^2 or Fisher's exact test. The predictive value of IMA and the TIMI risk score was tested by the area under the receiver operator characteristic (ROC) curve. Based on this analysis, the best cut-off points were identified and used for calculation of sensitivity, specificity and predictive values of the primary end point. Multivariable analysis by logistic regression was performed in order to evaluate whether or not IMA is an independent predictor of the primary end point, after correction for the TIMI risk variables or potential confounder variables. A new score (TIMI risk–IMA score) was obtained by adding 1 point if IMA was higher than its cut-off point. The area under the ROC curve was used to evaluate the accuracy of the new score. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed with StatXact 5.0.3 (Cytel Co., MA, USA) and MedCalc 9.6.0 (Frank Schoonjans, Belgium).

Results

The study population consisted of 107 STEMI patients aged 62.5 ± 12.6 years (range 32–82) and treated with

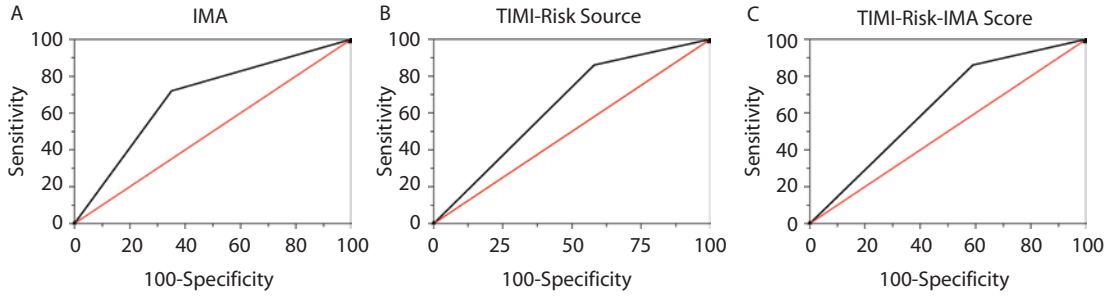

Figure 1. Receiver operator characteristics curves of ischemia modified albumin (IMA) (Panel A), TIMI-Risk Score (Panel B) and TIMI-Risk-IMA Score (Panel C).

Table 1. Baseline characteristics.

Characteristics	
Number of patients, *n*	107
Age (years)	62.3 ± 12.8
Male	61 (57%)
Hypertension	38 (35%)
Diabetes mellitus	37 (34%)
Hypercholesterolemia (>5 mmol l^{-1})	53 (49%)
Smokers	55 (51%)
Previous myocardial infarction	12 (11%)
Previous angina pectoris	18 (17%)
Previous coronary angioplasty	7 (6%)
Total cholesterol (mmol l^{-1})	5.5 ± 1.1
Triglycerides (mmol l^{-1})	2.1 ± 0.7
Troponin I peak level (ng ml^{-1})	89 ± 35
Creatinine clearance (ml min^{-1})	85 ± 28
Serum albumin (g dl^{-1})	4.1 ± 1.2
Ischaemia-modified albumin (A.U.)	0.347 ± 0.057
TIMI grade flow 0 before PCI	107 (100%)
TIMI grade flow 3 after PCI	107 (100%)
Left anterior descending	52 (48%)
Left circumflex	20 (19%)
Right coronary	35 (33%)
Use of stent	107 (100%)
No. of inflations	
<3	68 (63%)
≥3	39 (37%)
Duration of inflations (s)	153.4 ± 58
Mean pressure of inflations (atm)	15.9 ± 3.2
Left ventricular ejection fraction (%)	51 ± 12
Systolic blood pressure (mmHg)	130 ± 30
Heart rate (beats min^{-1})	107 ± 22
Killip class II, III or IV	25 (23%)
Aspirin	107 (100%)
Clopidogrel	107 (100%)
Glycoprotein IIb/IIIa inhibitor	107 (100%)
Enoxaparin	89 (83%)
Beta-blockers	97 (91%)
Nitrates	40 (37%)
Statins	107 (100%)
Angiotensin-converting enzyme inhibitors	72 (67%)

Data are expressed as mean ± SD, or number (percentage). TIMI, Thrombolysis In Myocardial Infarction; PCI, percutaneous coronary intervention.

Table 2. Prevalence of Thrombolysis In Myocardial Infarction (TIMI) risk score factors.

STEMI (n = 107)	%
Age 65–74/≥75 years	35.5/1.4
Systolic blood pressure <100 mmHg	7
Heart rate >100 beats min^{-1}	12.8
Killip class II/IV	23.3
Anterior STEMI	48.5
History of diabetes, hypertension or angina	86.9
Weight <65 kg	6.5
Time to intravenous thrombolysis starting >4 h	0

STEMI, ST elevation myocardial infarction.

primary PCI. No patient was lost during follow-up. During the follow-up period, seven (6.5%) patients met the primary end point. All the patients died due to cardiovascular reasons. Baseline characteristics of the studied population are presented in Table 1. Because of the anticipated low incidence of death in patients with a low STEMI TIMI risk score and the relatively small number of patients with a high STEMI TIMI risk score, patients were classified into three subgroups (45%, 38% and 17% of patients with a STEMI TIMI risk score <4, ≥4 and < 8, and ≥ 8, respectively). The TIMI-risk score data of study cohorts are presented in Table 2.

Time from onset of symptoms to blood sample collection of IMA, troponin I and albumin concentration had a mean of 4.2 ± 1.6 h. IMA levels at admission were higher among patients who met with the primary end point (0.379 ± 0.050 vs 0.316 ± 0.065 A.U., p = 0.01). A significant predictive value of IMA in relation to the primary end point was indicated by an area under the ROC curve of 0.71 (95% confidence interval (CI) 0.61–0.79, p = 0.01) (Figure 1A). The cut-off point of best performance by this analysis was 0.35 A.U. This cut-off had a sensitivity of 71% for the prediction of the primary end point, which provided a negative predictive value of 97%. The specificity was 64%, implying a positive predictive value of 12%. The comparison between the two groups defined by the IMA cut-off (0.35 A.U) showed similar clinical characteristics and hospital treatment, with the exception of the heart rate at admission,

Table 3. Baseline characteristics and treatment of the two groups defined by ischaemia-modified albumin (IMA) cut-off point.

	IMA ≤0.35 (A.U.) (n=66)	IMA >0.35 (A.U.) (n=41)	p-Value
Age (years)	62 ± 13.4	63 ± 11.8	0.69
Male	40 (61%)	21 (51%)	0.63
Hypertension	24 (36%)	14 (34%)	0.49
Diabetes mellitus	21 (32%)	16 (39%)	0.30
Hypercholesterolemia (>5 mmol l^{-1})	32 (48%)	21 (51%)	0.47
Smokers	37 (56%)	18 (44%)	0.15
Previous angina pectoris	12 (18%)	6 (15%)	0.85
Troponin I peak level (ng ml^{-1})	83 ± 31	95 ± 40	0.08
Creatinine clearance (ml min^{-1})	89 ± 31	81 ± 25	0.14
Serum albumin (g dl^{-1})	3.8 ± 1.5	4.1 ± 1.8	0.37
Anterior wall infarction	30 (45%)	22 (54%)	0.63
No. of inflations			
<3	40 (61%)	28 (68%)	0.90
≥3	22 (33%)	17 (41%)	0.74
LVEF (%)	47 ± 7.4	48 ± 6.4	0.47
Systolic blood pressure (mmHg)	125 ± 20	120 ± 15	0.14
Heart rate (beats min^{-1})	95 ± 28	110 ± 33	0.01
Killip class II, III or IV	15 (23%)	10 (24%)	0.98
Aspirin	66 (100%)	41 (100%)	1
Clopidogrel	66 (100%)	41 (100%)	1
Glycoprotein IIb/IIIa inhibitor	66 (100%)	41 (100%)	1
Enoxaparin	55 (83%)	34 (82%)	0.98
Beta-blockers	62 (94%)	35 (85%)	0.87
Nitrates	25 (38%)	15 (37%)	0.97
Statins	66 (100%)	41 (100%)	1
ACEI	42 (64%)	30 (73%)	0.71
Subgroups of TIMI risk score			
<4	48 (73%)	0 (0%)	< 0.001
≥4 and <8	33 (50%)	8 (19%)	
≥8	0 (0%)	18 (44%)	

Data are expressed as mean ± SD, or number (percentage). TIMI, Thrombolysis In Myocardial Infarction; LVEF, left ventricular ejection fraction; ACEI, angiotensin-converting enzyme inhibitors.

Table 4. Stepwise multivariate logistic-regression model incorporating ischaemia-modified albumin (IMA), albumin and Thrombolysis In Myocardial Infarction (TIMI) risk score for 30-day death.

Variable	OR (95% CI)	p-Value
Continuous variables		
IMA	1.5 (1.1–2.3)	0.01
Albumin	1.2 (0.80–1.8)	0.95
TIMI risk score	1.1 (0.93–1.3)	0.09
Dichotomous variables		
IMA >0.35 A.U	4.6 (1.2–10.8)	0.001
TIMI risk score >4	1.9 (0.88–7.2)	0.07

OR, odds ratio; CI, confidence interval.

which was higher among those with IMA >0.35 A.U. A significant difference was also observed between the subgroups of the TIMI risk score for STEMI in relation to the IMA cut-off (Table 3).

In the multivariate logistic-regression model incorporating IMA, TIMI risk variables and heart rate as predictive variables of the primary end point, IMA was the only independent predictor of the primary end point (odds ratio (OR) 4.4; 95% CI 1.82–24.08; p=0.019). The area under the TIMI-risk ROC curve in relation to the primary end point was 0.68 (95% CI 0.58–0.77; p=0.03), indicating that the score obtained at admission accurately predicted the primary end point (Figure 1B). According to this analysis, the cut-off point of best performance was 4, implying a sensitivity of 85% for prediction of the primary end point, and a negative predictive value of 98%. The specificity was 41%, with a positive predictive value of 9%. When the sample was divided into two groups defined by this point, the primary end point took place in individuals with a TIMI risk score >4, while those with a TIMI risk score ≤4 were free of adverse outcome (6.5 vs 0%, p=0.01). The modified TIMI risk score was calculated by adding 1 point if IMA >0.35 A.U. The addition of IMA to the TIMI risk score did not improve its accuracy, with an area under the curve ROC of 0.60 (95% CI 0.45–0.70, p=0.25) (Figure 1C). In addition, in the multivariate logistic-regression model incorporating IMA, albumin and TIMI risk score, IMA was the only independent variable for 30-day death (Table 4).

Discussion

The primary finding of the present prospective study was that IMA is an independent predictor of 30-day death in STEMI patients treated with primary PCI. Moreover, we showed for the first time that admission IMA levels do not add prognostic information to the validated STEMI TIMI risk score. IMA is a marker of ischaemia that seems to be related to the production of reactive oxygen species, which modify the NH_2-terminus of serum albumin (Roy at al. 2006). Recently, Bar-Or et al. (2008) clarified the mode of action of the cobalt–human serum albumin binding assay by direct observations of cobalt binding to human serum albumin. The main determinants of the cobalt–human serum albumin binding assay mechanism of action include, but are not limited to, the proportion of the intact N-terminus of human serum albumin, human serum albumin concentration, the plasma cysteine/cystine ratio, plasma pH and the state oxidation of cys34 of human serum albumin.

Since the development of the ACB assay, investigators have assessed IMA levels in a variety of clinical settings. Roy and colleagues (2004) reported that in patients with

atrial fibrillation, IMA levels are significantly elevated at 1 and 6 h after direct-current cardioversion, especially in those with electrocardiographic evidence of post-direct-current cardioversion ischaemia. Sinha et al. (2004) evaluated ECG, troponin T and IMA levels individually and in combination in patients diagnosed with non-ischaemic chest pain, unstable angina and myocardial infarction with ST- or non-ST-segment elevation. In this population, they found IMA measurements to be the most sensitive of the three diagnostic tests and declared it to be highly sensitive for the diagnosis of myocardial ischaemia in patients presenting with symptoms of ACS (Sinha et al. 2004). Investigators have also reported IMA to be a sensitive measure of the magnitude and duration of ischaemia induced during PCI (Quiles et al. 2003, Sinha et al. 2003). A subsequent PCI study supported this finding and also demonstrated a greater increase in IMA levels from baseline in patients without collateral coronary artery circulation than in those with it (Garrido et al. 2004). Moreover, recent results from our group have demonstrated that serum IMA concentrations may be a useful biomarker for the identification of incomplete ST-segment resolution in STEMI patients presenting to hospital within 6 h of the onset of pain (Dominguez-Rodriguez et al. 2008).

To date, very few studies have assessed the prognostic value of IMA. Consuegra-Sanchez et al. (2008) evaluated 207 patients (9.7% with STEMI) who presented to the emergency department with acute chest pain suggestive of ACS within 3 h of the onset of symptoms. They documented that a total of 31 patients experienced the 30-day combined end point (cardiac death, myocardial infarction, recurrent angina) and 16 patients died during the 1-year follow-up. Therefore, the authors suggest that IMA is an independent predictor of short- and long-term adverse outcome in patients presenting to the emergency department with typical acute chest pain. In contrast, Worster et al. (2005) evaluated 189 patients with symptoms suggestive of ACS who presented to the emergency department within 6 h the onset of chest pain; 24 of them developed adverse events within 72 h after their arrival at the emergency department. They estimated the diagnostic efficacy demonstrating the association of IMA levels above or below the 80 U ml^{-1} threshold value for the three times (time 0, 3 and 6 h) and the maximum value at any time revealed a maximum sensitivity of 92.3%, found among patients with an IMA level above 80 U ml^{-1} when tested at 6 h. The maximum specificity by IMA measurement was 24.3%, found among patients with serum IMA concentrations of 80 U ml^{-1} or less when tested at time 0. In consequence the authors suggest that measuring IMA within 6 h after the onset of chest pain is a poor predictor of cardiac events in the very short term.

Risk stratification is designed to err on the safe side, avoiding underestimation of the chance of developing an undesired event. Thus, prediction focuses on sensitivity and often lacks specificity. Consequently, even those classified as high risk by the TIMI risk score have a greater chance of remaining free of a recurrent event (Antman et al. 2000). Whether or not it is recommended to include a new marker in the routine evaluation of ACS patients depends on how much improvement in specificity is obtained, because sensitivity is already high. Based on this rationale, we tested the score modified by IMA. The TIMI risk–IMA score did not demonstrate improvement in the ROC curve. Prognostic information is not added to the validated STEMI TIMI risk score because total occlusion of the culprit artery causes acute tissue necrosis that prevails over ischaemia, limiting the release of modified human serum albumin to the systemic circulation. In addition, with myocardial necrosis, less albumin will be exposed to circulating free radicals resulting in lesser IMA production (Sinha et al. 2004, Bar-Or et al. 2008). Because of the difficulty of pinpointing the exact time of onset of an ischaemic event, there is always the possibility that IMA was initially raised but had already decreased below the diagnostic cut-off at the time of the blood draw. Unfortunately, in our study we did not carry out serial sampling measurements that could have increased assay sensitivity for the STEMI patients. These intriguing findings do not detract from the fact that IMA is a sensitive marker of ischaemia, rather that necrosis.

The major limitation of our study is the sample size, as the power of the study to detect an impact of IMA levels on outcome was not enough for all TIMI-risk score levels. Therefore, STEMI patients were divided into three TIMI-risk score subgroups. In addition, in the multivariate analysis incorporating TIMI risk score, it did not reach statistical significance because of the low sample size. On the other hand, the cut-off level for IMA established in our study may not necessarily be predictive in other populations of patients with a shorter or longer delay from the onset of symptoms.

In conclusion, we have shown for the first time, that IMA levels obtained on admission are a powerful indicator of short-term mortality in STEMI patients treated with primary PCI, but do not seem to be a marker that adds prognostic information to the validated STEMI TIMI risk score. Further larger studies are needed to test the impact of IMA in the prognosis of STEMI patients.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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