

Comparison between Cardiac Troponin I and CK-MB Mass in Acute Coronary Syndrome without ST Elevation

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Abstract

Background: There is uncertainty as to the comparative prognostic value between cardiac troponin I (cTnI) and CK-MB in acute coronary syndrome (ACS).

Objective: To compare the prognostic value between cTnI and CK-MB mass in patients with ACS without ST-segment elevation.

Methods: 1,027 patients were analyzed in a prospective way in a tertiary cardiology center. Combinations of biomarkers were examined: normal cTnI, normal CK-MB mass (65.5%), normal cTnI, elevated CK-MB mass (3.9%), elevated cTnI, normal CK-MB mass (8.8%), elevated cTnI, elevated CK-MB mass (20.7%). A multivariate analysis of clinical, electrocardiographic and laboratory variables determined the independent prognostic value of biomarkers for the event of death or (re)infarction within 30 days.

Results: Patients with at least one elevated biomarker were older ($p = 0.02$) and males ($p < 0.001$). The previous use of aspirin ($p = 0.001$), beta-blockers ($p = 0.003$) or statin ($p = 0.013$) was most frequent among those without elevated cTnI. Patients with both biomarkers elevated had more ST-segment depression ($p < 0.001$) or elevated creatinine ($p < 0.001$). In a multivariate analysis with the inclusion of cTnI, the CK-MB mass was not an independent variable for the event of death or (re) infarction within 30 days (odds ratio [OR] 1.16, $p = 0.71$). When cTnI was not included, we had the following values: age (OR 1.07; $p < 0.001$); male (OR 1.09; $p = 0.77$); diabetes mellitus (OR 1.95; $p = 0.02$); previous stroke (OR 3.21; $p = 0.008$); creatinine level (OR 1.63; $p = 0.002$); CK-MB mass (OR 1.96; $p = 0.03$). C-statistic 0.77 ($p < 0.001$).

Conclusion: With a dose of cTnI, CK-MB mass may be dispensable for prognostic evaluation. If cTnI is unavailable, CK-MB mass is acceptable for making a decision on treatment options. (Arq Bras Cardiol 2011;96(3):179-187)

Keywords: Acute coronary syndrome; troponin I; creatine kinase; myocardial infarction; prognostic.

Introduction

The cardiac troponins are considered the most specific markers of myocardial injury, demonstrating superiority in the diagnosis of acute myocardial infarction (AMI)¹. Their prognostic value has been convincingly demonstrated since 1992², and they have proven to be of great value to predict adverse cardiovascular events, such as death or myocardial infarction. They are essential for stratifying the risk of patients with acute coronary syndrome (ACS) without ST segment elevation (NSTEMI)³. However, they should not be analyzed separately for this purpose, because patients without elevation of cardiac troponin may be at a substantial risk of adverse events³.

The creatine phosphokinase MB fraction (CK-MB) has long been considered a marker for the diagnosis of AMI, but, it is less sensitive and specific, compared with the cardiac troponins³. Around 30% of patients with chest discomfort at

rest and who did not have elevated CK-MB will be diagnosed with AMI, when they are evaluated by the dosage of cardiac troponins³. Moreover, low levels of CK-MB can be found in the blood of healthy people, as well as elevated levels occur with skeletal muscle injury⁴.

Therefore, there is uncertainty as to the comparative prognostic value between cardiac troponins and CK-MB, particularly among non-selected populations of patients with ACS.

The objective of this research was to compare the prognostic value of cardiac troponin I (cTnI) and CK-MB mass in a consecutive population of patients clinically diagnosed with NSTEMI ACS (unstable angina or AMI).

Methods

Target population

The study included a prospective analysis of consecutive patients clinically diagnosed with NSTEMI ACS, who were admitted between July 1st 2004 and October 31st, 2006, to the emergency unit of a tertiary cardiology center. In order to be eligible, the patients had to be 18 years of age or older and their symptoms had to be consistent with acute coronary

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ischemia within the past 48 hours (retrosternal chest pain described as discomfort, tightness or burning that lasted more than 10 minutes; dyspnea or syncope of acute ischemic origin). We excluded those individuals who had unstable secondary angina⁵; confounding changes in the electrocardiogram (ECG) on admission (pacemaker rhythm, atrial fibrillation, bundle branch block); or those with suspected evolving myocardial infarction with ST elevation.

The local Research Ethics Committee approved the study protocol and all patients signed the consent form.

Electrocardiogram

As part of the routine of the emergency unit, all patients underwent a 12-lead ECG on admission, on a daily basis, if they showed recurrence of ischemic symptoms and after coronary artery bypass grafting or percutaneous coronary intervention (PCI).

The following ECG abnormalities on admission were analyzed: ST segment depression equal to or greater than 0.5 millimeters (mm) in at least one lead, except for aVR, which was measured at 80 milliseconds from the J point, followed by horizontal or descending ST segment; T-wave inversion equal to or greater than 1 mm in two contiguous leads measured by nadir; pathological Q waves of at least 0.04 seconds or more, with a range greater than one third of the subsequent R wave in two contiguous leads.

Laboratory tests

All laboratory tests were analyzed at the local laboratory, using its reference limits. Two blood collections were carried out within the first 24 hours after the patients were admitted. The first collection was carried out to analyze the blood count, blood glucose, creatinine, cTnI, CK-MB mass and ultrasensitive C-reactive protein (CRP). The second collection was carried out 12 hours after the first one for the dosage of cTnI, CK-MB mass and ultrasensitive CRP. For the analysis of biomarkers, blood samples were collected in dry tubes without anticoagulant. Then, they were immediately centrifuged and kept in a freezer at minus 80° C. They were dosed by the automated chemiluminescence method with the IMULITE DPC Medlab system. The baseline value for cTnI was lower than 0.5 ng/ml with analytical sensitivity of 0.5 ng/ml. The baseline values for CK-MB mass were of up to 4.5 ng/ml. The intra-assay coefficient of variation was within the diagnostic range of 2.5%. We selected the higher value of cTnI, CK-MB mass and ultrasensitive CRP between the two samples for analysis in the study.

Analyzed endpoints

During hospitalization, patients were monitored by means of medical visits to the emergency unit, coronary care unit or to the ward and subsequently, after discharge, by telephone to check for the presence or absence of clinical endpoints. The primary endpoint of the study was the combined event of death from all causes or infarction (reinfarction) occurred within the period of 30 days. Within the first 24 hours after being admitted, the patient was considered had reached an endpoint of infarction (reinfarction) if there were ischemic

symptoms with ST-segment elevation. During this period, the elevation of CK-MB or cTnI, without ST segment elevation, was considered to be related to the event of admission. After 24 hours, the infarction was diagnosed by the presence of new Q waves or new elevations of CK-MB, above normal limits, with or without electrocardiographic changes. For patients undergoing PCI or coronary artery bypass grafting, the elevation above three or five times the normal limit of CK-MB, after the procedure, respectively, was necessary for the diagnosis of infarction related to the procedure^{6,7}.

Statistical analysis

The continuous variables are described as means \pm standard deviation and the categorical variables as simple or relative frequencies. CK-MB mass and cTnI were analyzed as dichotomous variables. The elevation of cTnI was considered when a value equal to or greater than 0.5 ng/ml was found, and the elevation of CK-MB mass was considered when a value greater than 4.5 ng/ml was found.

The population was divided into four groups with combinations of cTnI and CK-MB mass (normal cTnI and normal CK-MB mass, normal cTnI and elevated CK-MB mass; elevated cTnI and normal CK-MB mass, elevated cTnI and elevated CK-MB mass), and we analyzed the relationship between the number and type of biomarker that was elevated and baseline characteristics, treatment in the hospital and results. A univariate analysis was conducted with the groups that combined the elevation of biomarkers to examine the prognostic value of each one of them, separately, for the combined event of death or infarction (reinfarction) within 30 days.

For the descriptive analysis, a simple logistic regression model was used for variables previously selected as predictors of the combined event. The average odds ratios were calculated with their respective confidence intervals and descriptive levels. Next, a multiple logistic regression analysis was conducted to determine the independent prognostic value of cTnI and CK-MB mass, fitted for variables with significance level below 10% in the simple logistic regression analysis, as well as sex, even with significance level equal to or greater than 10%. The stepwise backward and forward methods were used in this analysis and the resulting models were compared for the preparation of a final model, which in turn included the sex variable. In the final model, variables with a p value below 0.05 were retained and considered significant. The predictive accuracy of the model was evaluated by C-statistic⁸ and the calibration was measured using the Hosmer-Lemeshow goodness-of-fit test.

All analyses were conducted using the SPSS program for Windows, version 13.0 (SPSS Institute, Chicago, Illinois).

Results

The study population comprised a total of 1027 patients. There were 589 men (57.4%) and the average age was 61.55 years (\pm 0.35). On admission, 724 patients (70.5%) reported experiencing two or more episodes of chest pain in the past 24 hours, and seven (0.7%) reported experiencing the symptoms more than 24 hours before, but less than 48 hours before. Upon admission, chest pain was reported by 782 patients

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(76.1%) and the ischemic equivalent occurred in nine, dyspnea in six (0.6%) and syncope in three (0.3%). 258 patients (25.1%) were diagnosed with AMI without ST elevation, 744 (72.4%) were diagnosed with IIB unstable angina and 25 (2.4%) with IIIC unstable angina. Hospital mortality was 2% (21 patients) and 2.2% (23 patients) had infarction (reinfarction) in the hospital. In 30 days, the proportion of patients with the combined event of death or infarction (reinfarction) was 5.3% (54 patients). The distribution of the types of infarction (reinfarction) in a 30-day period was of 12 patients (1.2%) with ST elevation and 27 patients (2.6%) without ST segment elevation. In one patient, the type of infarction (reinfarction) was not determined in the 30 day follow-up, because the patient experienced the event and subsequently died at another institution.

With the population divided into four groups combining cTnI and CK-MB mass, Table 1 shows the clinical characteristics and outcomes according to the elevation of biomarkers. Patients with at least one elevated biomarker were older ($p = 0.02$) and males ($p < 0.001$). A prior PCI was performed more in patients without elevation of biomarkers ($p = 0.05$). The previous use of aspirin ($p = 0.001$), beta-blockers ($p = 0.003$) and statins ($p = 0.013$) was more frequent in patients without elevation of cTnI. Patients with elevation of both biomarkers had more ST depression on the admission ECG ($p < 0.001$) and higher creatinine level ($p < 0.001$). Higher baseline heart rate also occurred more often in those with elevated cTnI ($p < 0.0001$). During hospitalization, there was no significant difference regarding the administration of aspirin ($p = 0.84$), beta-blockers ($p = 0.34$), clopidogrel ($p = 0.09$) and statins ($p = 0.16$). However, patients with elevated cTnI were more intensively treated with inhibitors of angiotensin converting enzyme ($p = 0.05$).

Coronary angiography was performed in 734 (71.5%) patients, being more recommended for those with at least one biomarker elevated ($p < 0.001$). Patients with only one coronary artery compromised had less elevation of biomarkers, while the ones with three-vessel coronary artery disease appeared more frequently in groups with elevated biomarker, especially cTnI ($p < 0.001$). The left ventricular ejection fraction was measured in 662 patients (90.2%), and it was significantly lower in patients with elevated cTnI ($p < 0.001$). Percutaneous coronary intervention or coronary artery bypass grafting surgery were more frequent among those with at least one elevated biomarker (cTnI or CK-MB mass) ($p < 0.001$).

The combined event of death or infarction (reinfarction) within 30 days, according to the groups combining cTnI and CK-MB mass, is shown in Figure 1.

Figure 1 shows the univariate analysis with the groups combining the elevation of biomarkers to examine the prognostic value of each one of them, separately, for the combined event. Among patients without elevated cTnI, the proportion of the combined event was 3.2% for patients without elevation of CK-MB mass *versus* 7.5% for patients with elevated CK-MB mass ($p = 0.155$). Among patients without elevated CK-MB mass the proportion of the combined event was 3.2% for patients without elevation of cTnI *versus* 9.9% for patients with elevated cTnI ($p = 0.006$). Among patients with elevated cTnI, the rate of the combined event was 9.9% for

patients with normal CK-MB mass *versus* 9.4% for patients with elevated CK-MB mass ($p = 0.892$). Among those with elevated CK-MB mass, the combined event rate was 7.5% when cTnI was normal *versus* 9.4% with elevated cTnI ($p > 0.999$).

The data in Table 2 refer to the simple logistic regression analysis of variables with a p value below 10% and which were selected for the multiple logistic regression analysis.

In a multiple logistic regression analysis, including cTnI and CK-MB mass, after fit for variables with a significance level $< 10\%$ in the simple logistic regression analysis (Table 2), CK-MB mass was not a significant independent predictor for the combined event of death or infarction (reinfarction) in 30 days (odds ratio [OR] 1.16; confidence interval [CI] 95% 0.52 to 2.58; $p = 0.71$). Likewise, there was no interaction effect between the two biomarkers (OR 0.40; CI 95% 0.08 - 1.90, $p = 0.25$). The following variables did not have statistical significance either: male, smoker, prior stable angina, peripheral arterial disease, previous coronary artery disease $\geq 50\%$, heart rate, ST segment depression, hematocrit, hemoglobin, leukocyte count, ultrasensitive CRP.

Then, two independent models of multiple logistic regression were run, and one of them did not include CK-MB mass: increase in age, in years (OR 1.06, CI 95% 1.03 to 1.09, $p < 0.001$); male sex (OR 1.09; CI 95% 0.59 to 2.01, $p = 0.79$); previous history of diabetes mellitus (OR 1.90, CI 95% 1.06 to 3.42, $p = 0.03$); previous stroke (OR 3.34, CI 95% 1.40 to 8.00, $p = 0.007$); creatinine elevation (OR 1.61, CI 95% 1.18 to 2.21; $p = 0.003$); elevation of cTnI (OR 2.34; CI 95% 1.30 to 4.21; $p = 0.004$). The C-statistic of this model was 0.771; CI 95% 0.706 - 0.836; $p < 0.001$. In another model, the cTnI was not included: increase in age, in years (OR 1.07; CI 95% 1.03 to 1.09, $p < 0.001$); male sex (OR 1.09; CI 95% 0.59 to 2.02; $p = 0.77$); previous history of diabetes mellitus (OR 1.95; CI 95% 1.08 to 3.50; $p = 0.02$); previous stroke (OR 3.21; CI 95% 1.35 to 7.61; $p = 0.008$); creatinine elevation (OR 1.63; CI 95% 1.19 to 2.23, $p = 0.002$); elevation of CK-MB mass (OR 1.96; CI 95% 1.07 to 3.58, $p = 0.03$). The C-statistic of this model was 0.772; CI 95% 0.705 to 0.839; $p < 0.001$. Therefore, it is possible to notice that when cTnI is not included in the analysis, CK-MB mass emerges as an independent prognostic variable for the combined endpoint of death or infarction (reinfarction) within 30 days.

Due to the clinical importance of these two biomarkers, both of which have proven to be more efficient than the other at different moments, in this study we also chose to analyze the combination of both biomarkers in an independent logistic regression model. In order to do that, the absence of change in both was considered to be the baseline, and the odds ratio was adjusted for each one of the remaining three categories in relation to the baseline. In the data of Table 3, it is possible to observe that when there is elevation of CK-MB mass, but without elevation of cTnI, there is no significant increase in risk of occurrence of death or infarction (reinfarction) within 30 days with respect to the absence of change in both. The odds ratio is significantly higher only when there is elevation of cTnI (C-statistic of 0.776; CI 95% 0.712 to 0.840; $p < 0.001$; Hosmer-Lemeshow test with $p = 0.901$).

Figure 2 shows the area under the ROC (receiver operating characteristic) curve⁹ of the models in which each one of the

Table 1 - Characteristics according to the combination of elevation of cardiac troponin I and CK-MB mass

Clinical feature	Normal cTnI and normal CK-MB mass (n=683)	Normal cTnI and elevated CK-MB mass (n=40)	Elevated cTnI and normal CK-MB mass (n=91)	Elevated cTnI and elevated CK-MB mass (n=213)	p
Age in years*	61.01 (±0.42)	63.08 (±1.62)	64.58 (±1.15)	61.66 (±0.77)	0.02
Male, n (%)	359 (52.6)	27 (67.5)	50 (54.9)	153 (71.8)	< 0.001
Diabetes mellitus, n (%)	211 (30.9)	13 (32.5)	35 (38.5)	70 (32.9)	0.531
Smoking, n (%)	136 (19.9)	6 (15.0)	21 (23.1)	50 (23.5)	0.502
Previous infarction, n (%)	303 (44.4)	22 (55.0)	40 (44.0)	86 (40.4)	0.37
Previous percutaneous coronary intervention, n (%)	210 (30.7)	19 (47.5)	22 (24.2)	60 (28.2)	0.05
Previous coronary artery bypass grafting surgery, n (%)	149 (21.8)	12 (30.0)	12 (13.2)	58 (27.2)	0.03
Heart rate (bpm)*	73.44 (±0.48)	71.83 (±1.91)	75.63 (±1.12)	77.57 (±1.04)	< 0.001
Systolic blood pressure (mmHg)*	139.57 (±0.99)	148.23 (±4.79)	143.20 (±3.00)	143.29 (±1.94)	0.071
Diastolic blood pressure (mmHg)*	84.12 (±0.54)	87.77 (±2.18)	85.86 (±1.68)	87.90 (±1.14)	0.008
Previous medications					
Aspirin, n (%)	499 (73.1)	36 (90.0)	61 (67.0)	133 (62.4)	0.001
Beta-blocker, n (%)	409 (59.9)	30 (75.0)	47 (51.6)	105 (49.3)	0.003
Inhibitor of angiotensin converting enzyme, n (%)	398 (58.3)	24 (60.0)	49 (53.8)	106 (49.8)	0.157
Statin, n (%)	319 (46.7)	26 (65.0)	38 (41.8)	83 (39.0)	0.01
ST segment depression ≥ 0.5 mm, n (%)	83 (12.2)	6 (15.0)	27 (29.7)	73 (34.3)	< 0.001
Elevated creatinine (mg/dl)*	1.07 (±0.015)	1.21 (±0.097)	1.15 (±0.058)	1.31 (±0.067)	< 0.001
Medications during hospitalization					
Beta-blocker, n (%)	635 (92.9)	39 (97.5)	81 (89.0)	200 (93.9)	0.34
Aspirin, n (%)	665 (97.4)	39 (97.5)	88 (96.7)	209 (98.1)	0.84
Intravenous nitroglycerin, n (%)	643 (94.1)	37 (92.5)	84 (92.3)	204 (95.8)	0.54
Inhibitor of angiotensin converting enzyme, n (%)	564 (82.6)	31 (77.5)	83 (91.2)	186 (87.3)	0.05
Statin, n (%)	640 (93.7)	40 (100.0)	84 (92.3)	205 (96.2)	0.16
Clopidogrel, n (%)	604 (88.4)	37 (92.5)	73 (80.2)	182 (85.4)	0.09
Enoxaparin, n (%)	491 (71.9)	28 (70.0)	61 (67.0)	153 (71.8)	0.80
Coronary angiography during hospitalization, n (%)	454 (66.4)	31 (77.5)	66 (72.53)	183 (85.9)	< 0.001
Single-vessel disease, n (%)	105 (23.1)	6 (19.4)	12 (18.2)	23 (12.6)	
Two-vessel disease, n (%)	108 (23.8)	6 (19.4)	15 (22.7)	49 (26.8)	< 0.001
Three-vessel disease, n (%)	129 (28.4)	15 (48.4)	36 (54.5)	95 (51.9)	
Left ventricular ejection fraction (%) * †	58.32 (±13.03)	58.00 (±12.40)	55.53 (±14.64)	51.30 (±15.10)	< 0.001
Percutaneous coronary intervention or coronary artery bypass grafting surgery, n (%)	236 (34.5)	15 (37.5)	54 (59.3)	112 (52.6)	< 0.001

cTnI - cardiac troponin I; CK-MB - creatine kinase MB fraction; n - number of patients. * Continuous variables are presented as mean ± standard error. † The left ventricular ejection fraction can be quantified in 662 patients (90.2%).

biomarkers was included, separately and in combination, for the combined event of death or myocardial infarction (reinfarction) within 30 days.

Discussion

The AMI diagnosis, based on the criteria of the World Health Organization¹⁰, was partly made on the basis of the

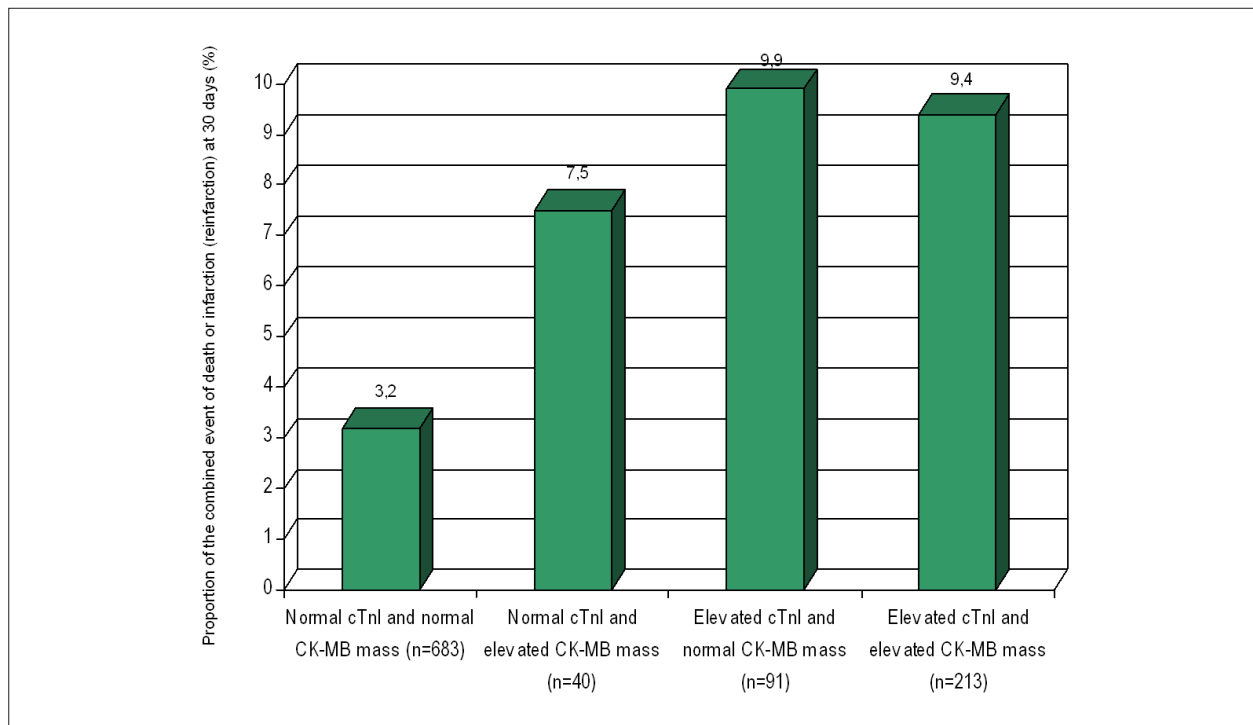


Figure 1 - Proportion of the combined event of death or infarction (reinfarction) at 30 days according to the combination of elevation of biomarkers. cTnI - cardiac troponin I, CK-MB - creatine kinase MB fraction, n - number of patients.

CK-MB measurements. Subsequent studies showed that cardiac troponins are prognostic indicators that are more sensitive and specific in patients with ACS¹¹. In 2000, the European Society of Cardiology and the American College of Cardiology published a new definition of infarction based on the elevation of troponin or CK-MB, as one of such criteria^{12,13}. Nowadays, since the cardiac troponins are considered important predictors of adverse outcomes in ACS patients, recent guidelines^{3,14} have prioritized the use of these biomarkers in the early assessment of this population. There is strong evidence that patients with ACS and elevated troponin are at increased risk of myocardial infarction or death within 30 days¹⁵. For the definition of AMI, it has been recommended that the elevation of cardiac troponins be defined as a value that exceeded the 99th percentile of a reference sample^{7,16}, with a coefficient of variation that is $\leq 10\%$ to reduce false negative or positive outcomes.

The risk stratification in patients with NSTEMI ACS is performed and immediately started upon admission, so as to facilitate therapy-related decisions in the first contact with the patient, being considered a key point for the initial evaluation, because patients will be treated differently, according to their risk of death or recurrent ischemic events¹⁷. Current guidelines suggest implementing this strategy as early as possible, with the recommendation of antithrombotic and maximum anti-ischemic therapy for those at high risk and, secondly, early discharge, after a brief period of observation, for the ones at the lowest risk^{3,14,18,19}. Patients with chest discomfort shall undergo an early risk stratification, with a focus on anginal symptoms, findings of the physical examination,

electrocardiographic changes and dosage of biomarkers of cardiac injury (Class I; Level of Evidence C)³. With the emergence of cardiac troponins, a question arises regarding the comparative prognostic value between them and CK-MB.

Yee KC et al evaluated the independent prognostic value of CK-MB mass in 542 consecutive patients with ACS and negative troponin¹¹. The data from this study demonstrated higher morbidity and mortality in those with negative troponin and CK-MB elevation, compared with those without CK-MB elevation. The researchers concluded that, in patients with negative troponin, the dosage of CK-MB significantly identified patients at higher risk of death and major cardiac events at six months follow-up. However, the prognostic value of CK-MB mass in patients with elevated troponin was not evaluated.

In a prospective observational study of 3,138 patients with ACS and with or without ST elevation, the researchers analyzed the measurements of CK or CK-MB and cardiac troponin in the first 24 hours of hospitalization²⁰. The biomarkers were interpreted in a dichotomous way (normal versus elevated). In patients with normal CK or CK-MB, the mortality rate at one year was 6.5% for patients with normal troponin versus 12.5% for those with elevated troponin (unadjusted OR of 2.06; CI 95% 1.37 to 3.11, $p = 0.001$). Similarly, among patients with elevated CK or CK-MB, elevated troponin was associated with higher proportion of deaths in one year (6.8% versus 11.7%, unadjusted OR = 1.83, CI 95% 1.14 to 2.93; $p = 0.01$). For patients with normal troponin levels, the mortality rate at one year was similar, regardless of the status of CK or CK-MB (6.5% versus 6.8%, $p = 0.86$). Among patients with high troponin levels, the mortality rate

Table 2 - Exploratory analysis of potential determinants of the combined endpoint of death or infarction (reinfarction) at 30 days

Variable	All the patients (n = 1,027)	With combined endpoint (n = 54)	Without combined endpoint (n = 973)	Odds ratio [CI 95%]	p
Clinical and demographic					
Age in years*	61.55 (± 0.35)	68.56 (±1.47)	61.16 (±0.35)	1.06 [1.04-1.09]	< 0.001
Male, n (%)	589 (57.4)	34 (62.9)	555 (57.0)	1.28 [0.73-2.26]	0.39
Smoking, n (%)	213 (20.7)	5 (9.2)	208 (21.3)	0.38 [0.15-0.95]	0.03
Diabetes mellitus, n (%)	329 (32.0)	26 (48.1)	303 (31.1)	2.05 [1.18-3.56]	0.01
Previous stable angina, n (%)	312 (30.4)	22 (40.7)	290 (29.8)	1.62 [0.93-2.83]	0.09
Peripheral arterial disease, n (%)	52 (5.1)	6 (11.1)	46 (4.7)	2.52 [1.03-6.19]	0.05
Stroke, n (%)	56 (5.5)	8 (14.8)	48 (4.9)	3.35 [1.50-7.50]	0.007
Previous coronary artery disease ≥ 50%, n (%)	584 (56.9)	37 (68.5)	547 (56.2)	1.70 [0.94-3.05]	0.07
Baseline heart rate (bpm) *	74.43 (±0.41)	77.46 (±2.06)	74.26 (±0.41)	1.02 [1.00-1.04]	0.08
Electrocardiogram					
ST segment depression ≥ 0.5 mm in at least one lead, except for aVR, n (%)	268 (26.0)	24 (44.4)	244 (25.0)	2.39 [1.37-4.17]	0.002
Laboratory					
Hematocrit (%)*	40.68 (±0.14)	39.57 (±0.70)	40.74 (±0.15)	0.95 [0.89-1.00]	0.06
Hemoglobin (g/dl)*	13.89 (±0.05)	13.47 (±0.25)	13.91 (±0.05)	0.84 [0.71-1.00]	0.04
Leukocytes (x10 ⁹ /mm ³)*	7.98 (±0.08)	8.61 (±0.44)	7.94 (±0.08)	1.09 [0.99-1.19]	0.07
Creatinine (mg/dl)*	1.13 (±0.02)	1.66 (±0.21)	1.11 (±0.02)	2.04 [1.50-2.77]	< 0.001
Elevation of cTnI, n (%)	304 (29.6)	29 (53.7)	275 (28.2)	2.94 [1.69-5.12]	< 0.001
Elevation of CK-MB mass, n (%)	253 (24.6)	23 (42.6)	230 (23.6)	2.40 [1.37-4.19]	0.002
Ultrasensitive CRP > 0.8 mg/dl, n (%)	480 (46.7)	34 (63.0)	446 (45.8)	2.00 [1.14-3.53]	0.01

cTnI - cardiac troponin I; CK-MB - creatine kinase MB fraction; Ultrasensitive CRP - Ultrasensitive C-reactive protein; CI - confidence interval. *Continuous variables are presented as mean ± standard error.

Table 3 - Multiple logistic regression model for endpoint of death or infarction (reinfarction) at 30 days, including combinations of elevation of cardiac troponin I and CK-MB mass

Variable	β-coefficient	Odds ratio [CI 95%]	p
Increase in age in years	0.06	1.06 [1.03-1.09]	< 0.001
Male	0.07	1.07 [0.58-1.98]	0.83
History of diabetes mellitus	0.64	1.91 [1.06-3.44]	0.03
Previous stroke	1.23	3.41 [1.42-8.19]	0.006
Elevated creatinine	0.48	1.61 [1.18-2.20]	0.003
Combination of cTnI and CK-MB mass			
cTnI normal and normal CK-MB mass		-	0.02
Normal cTnI and elevated CK-MB mass	0.80	2.22 [0.62-8.80]	0.22
Elevated cTnI and normal CK-MB mass	1.00	2.72 [1.17-6.33]	0.02
Elevated cTnI and elevated CK-MB mass	0.89	2.43 [1.24-4.77]	0.01
Constant	-8.28	0.00	< 0.001

cTnI - cardiac troponin I, CK-MB - creatine kinase MB fraction; CI - confidence interval.

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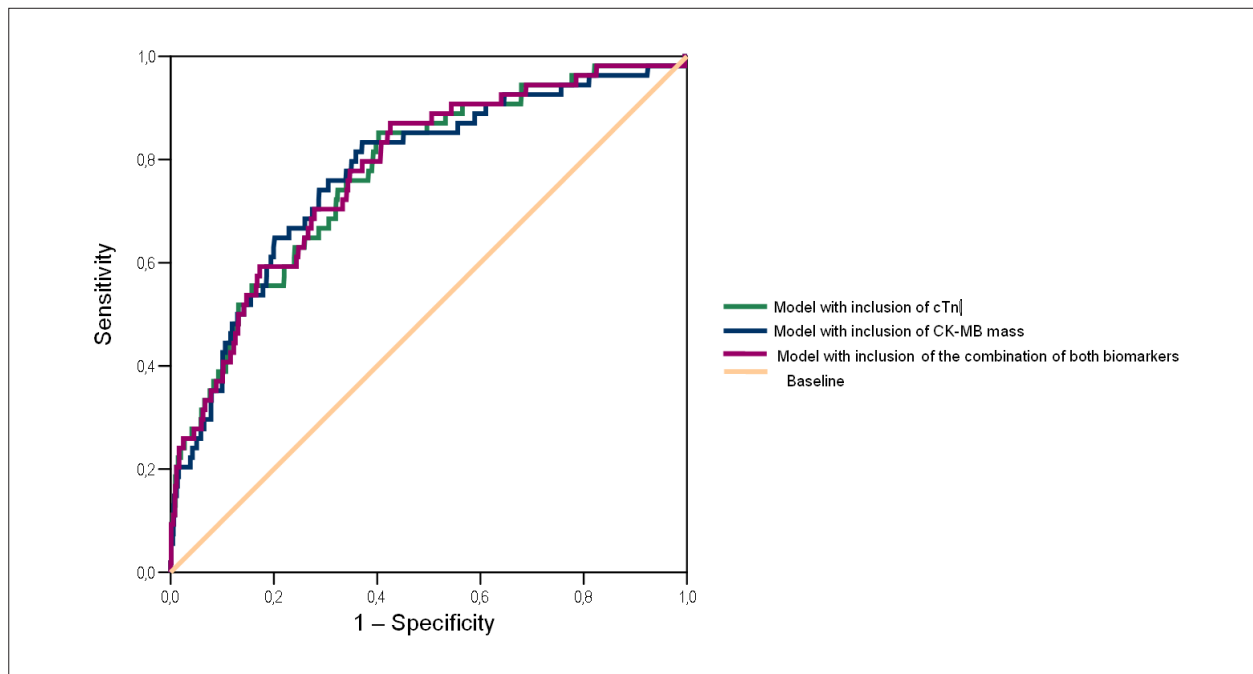


Figure 2 - Areas under the ROC (receiver operating characteristic) curve of the various models of multiple logistic regression for the combined event of death or infarction (reinfarction) at 30 days. cTnI - cardiac troponin I, CK-MB - creatine kinase MB fraction.

did not differ significantly by the status of CK or CK-MB (12.5% versus 11.7%, $p = 0.69$). In a multivariate logistic regression model, the researchers concluded that the high dosage of troponin was independently associated with higher mortality at one year follow up, while CK or CK-MB did not have any prognostic value ($p = 0.44$). The data from this study support only the use of cardiac troponin as a biomarker for diagnosis of myocardial infarction, as well as for risk stratification in an unselected population of patients with ACS. However, CK or CK-MB and troponin were not analyzed in independent logistic regression models, so as to investigate the effect of collinearity between such biomarkers.

In a prospective study evaluating 401 consecutive patients with chest pain of cardiac origin, the researchers examined the independent prognostic value of cTnT and CK-MB mass with adjustment for clinical and electrocardiographic variables²¹. A multiple logistic regression analysis revealed that, when only CK-MB mass (without the inclusion of cTnT) was included in the model, CK-MB mass emerges as an independent marker ($p = 0.002$) for major cardiovascular events at 6-months follow-up. However, when cTnT is included in the analysis, CK-MB mass loses this independent prognostic value ($p = 0.83$), where $cTnT > 0.1 \mu\text{g/l}$ ($p = 0.0004$), ST segment depression $> 1 \text{ mm}$ ($p = 0.003$) and the presence of heart failure ($p = 0.016$) emerge as prognostic variables. Therefore, CK-MB mass appears to follow the prognostic ability of cTnT, showing that it is not an independent variable when cTnT is analyzed together.

Kontos MC et al, in a study evaluating the 30-day mortality of 2,181 consecutive patients without ST elevation who had been admitted to the coronary care unit, noted that mortality was higher for patients with diagnostic criteria for myocardial

infarction based on elevation of CK-MB mass and cTnI, with the mortality being lower among those without elevation of both biomarkers and intermediate for patients who were diagnosed with infarction only by the criterion of elevated cTnI, but not of elevated CK-MB mass²².

This observational study of patients with NSTEMI ACS has important information. Inclusion criteria were related to the symptoms on admission that were consistent with the clinical diagnosis of ACS, with no selection of patients at highest risk by electrocardiographic changes or elevations of myocardial necrosis markers. Thus, the outcomes of the analysis can be generalized to the real world in a consistent way.

Data of the clinical history, physical examination, laboratory tests routinely carried out on admission, inflammatory biomarkers and of myocardial necrosis were included in the variables studied. The endpoints selected were those for which there is no doubt as to their definition as death or infarction (reinfarction). Therefore, endpoints without consistency in the definition, such as urgent coronary artery bypass grafting for recurrent ischemia, were not analyzed.

The study shows that when both biomarkers in the same model are analyzed together, in a way that is similar to the studies previously cited in this discussion, the inherent power of cTnI masks the prognostic significance of CK-MB mass. This fact is clearly and statistically demonstrated when the analysis does not include cTnI, only CK-MB mass as a biomarker of necrosis. CK-MB mass emerges as an independent prognostic variable for the event of death or infarction (reinfarction) within 30 days. The non-continuance of CK-MB mass as a prognostic variable, when cTnI is also included in the analysis, can be explained by the problem of collinearity^{23,24} between these two biomarkers. This should reflect the

greater specificity that is inherent in cardiac troponins, in the detection of myocardial injury that adversely implies adverse outcomes²⁵. Therefore, the prognostic significance of CK-MB mass would be underestimated when cTnI is included in the analysis.

Limitations of the study

CK-MB mass and cTnI were assessed as binary variables. The quantitative analysis of myocardial necrosis markers would imply the assessment of the myocardial extension degree for the risk of adverse events. Serial ECGs were not evaluated. The analysis of ischemic changes that occur in other ECG following the initial ECG, even in the absence of symptoms, is valuable information that shall be investigated and which would involve unfavorable outcomes. The study population was considered at a single center and, one may say that it would not be possible to generalize the model to the real world of other centers.

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Conclusion

It is possible to conclude that, with the availability of cTnI, the dosage of CK-MB mass may be dispensable for prognostic evaluation. However, in the absence of cTnI, the dosage of CK-MB mass is an acceptable alternative.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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