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Original Research Article

Cardiac Troponin I and CK-MB in Diagnosis of Acute Coronary Syndrome in Patents without ST Elevation

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Abstract: There is uncertainty as to the comparative prognostic value between cardiac troponin I (cTnI) and CK-MB in acute coronary syndrome (ACS). The objective is to compare the prognostic value between cTnI and CK-MB mass in patients with ACS without ST-segment elevation. Total 127 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. 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 ($p < 0.001$). 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.

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

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 1992 [2], 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 (NSTE) [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 events [3]. 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 troponins [3]. 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 troponins [3]. Moreover, low levels of CK-MB can be found in the blood of healthy people, as well as elevated levels occur with skeletal muscle injury [4]. 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 NSTE ACS (unstable angina or AMI) [6].

METHODS

Target population

The study included a prospective analysis of patients clinically diagnosed with Acute Coronary Syndrome, who reported to OPD or admitted in IPD of Guru Gobind SINGH Medical College, Faridkot In order to be eligible, the patients had to be 18 years of age or older and their symptoms had to were admitted be consistent with acute coronary 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 angina [5]; 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.

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 to analyze the blood count, blood glucose, creatinine, and 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°. 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 0.5ng/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.

Statistical Analysis

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.

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

RESULTS

The study population comprised a total of 127 patients. There were 78 men (57.4%) and the average age was 61.55 years (± 0.35). On admission, 114 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 78 patients (76.1%) and the ischemic equivalent occurred in nine, dyspnea in six (0.6%) and syncope in three (0.3%). 58 patients (25.1%) were diagnosed with AMI without ST elevation, 74 (72.4%) were diagnosed with IIIB 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) [7]. 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. 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 ($p < 0.0001$). Coronary angiography was performed in 74 (71.5%) patients, being more recommended for those with at least one biomarker elevated ($p < 0.001$) [8]. The left ventricular ejection fraction was measured in 112 patients (90.2%), and it was significantly lower in patients with elevated cTnI ($p < 0.001$) [9]. 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 [8]. 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 ($p > 099$). 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 included 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. biomarkers was included, separately and in combination, for the combined event of death or myocardial infarction (reinfarction) within 30 days.

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

Variable	All the patients (n = 127)	With combined endpoint (n = 54)	Without combined endpoin (n = 73)	t 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

DISCUSSION

Subsequent studies showed that cardiac troponins are prognostic indicators that are more sensitive and specific in patients with ACS [11]. Nowadays, since the cardiac troponins are considered important predictors of adverse outcomes in ACS patients, recent guidelines [3, 4] 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 days [10]. 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 ≤ 10% to reduce false negative or positive outcomes. The risk stratification in patients with NSTE 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 events [7]. 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, 4].

Table 3: Multiple logistic regression models 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			
cTnl normal and normal CK-MB		-	0.02

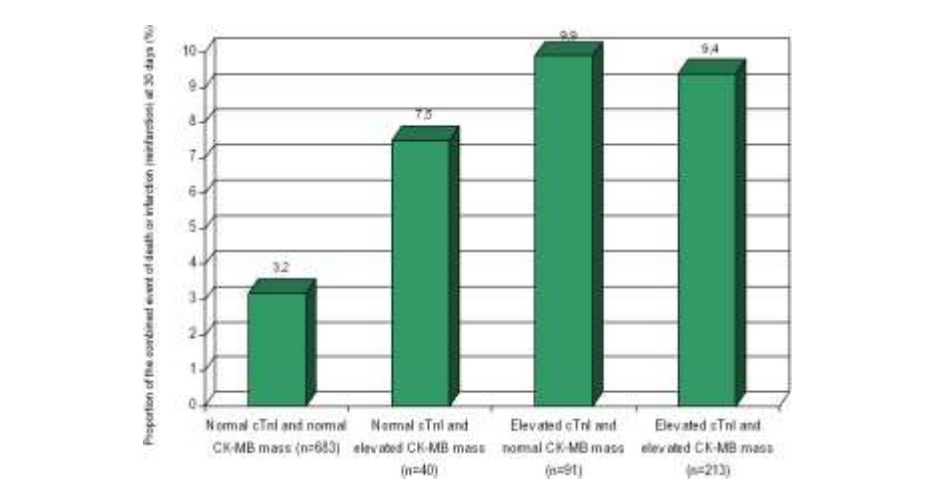

Fig-1: Proportion of the combined event of death or infarction (reinfarction) at 30 days according to the combination of elevation of biomarkers. cTnI - cardiac troponin I, CK-MB - creatine kinase MB fraction, n - number of patients

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 troponin [11]. 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 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 hospitalization [10]. 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 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 [4]. 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.

CONCLUSIONS

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 [7]. 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 [3, 4] 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 outcomes [2, 5]. Therefore, the prognostic significance of CK-MB mass would be underestimated when cTnI is included in the analysis.

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