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Research Article

Evaluation of the Efficacy of the Serodiagnostic Markers, CK-MB and Troponin, in the Acute Diagnosis of Myocardial Infarction

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Abstract

Objective: Patients who present to emergency services with chest pain must be evaluated for myocardial infarction (MI) using rapid and accurate diagnostic procedures. It is the objective of this study to evaluate the diagnostic efficacy of MI of the two serodiagnostic markers for myocardial damage, i.e. the MB fraction of creatine kinase (CK-MB) and the inhibitory subunit of troponin, cTnI, based only on their initial determinations on admission for chest pain patients to the emergency service.

Methods: This is a retrospective study on 380 patients (over four successive months in 2015 - 2016) who presented with chest pain to the Emergency Service of University Hospital at SUNY Downstate Medical Center in Brooklyn, NY and who were evaluated acutely for MI using EKG and who were also tested for serum levels of both CK-MB and cTnI (using the Abbott Architect immunoanalyzer for both analytes: cutoffs for CK-MB and cTnI of 5 ng/mL and 0.05 ng/mL, respectively). Many of these patients were further tested by at least one other diagnostic procedure that included echocardiography and coronary angiography.

Results: Of the 380 patients, 47 were found to have MI (prevalence of 12.3%). The sensitivity and specificity for CK-MB were 66 and 71%, respectively, and 89.4 and 73.3% for cTnI. Importantly, both tests were negative for 5 of the 47 patients with AMI (approximately 11%) suggesting that negative values for both markers does not rule out MI even though the negative predictive values for each test were high at 94 and 98%, respectively. We found that congestive heart failure (CHF) and end stage renal disease (ESRD) in 85 patients was a major cause of false positive values for both markers. By omitting these patients, the specificities of both tests for the remaining 295 patients increased by 14 and 9% for CK-MB and cTnI, respectively. We found that the positive predictive value using both tests increased from values below 40% to63%, showing that both tests should be performed on patients with acute chest pain.

Conclusion: Both markers can help in the diagnosis of acute MI but cannot be relied on as stand-alone tests due to their limited sensitivities and specificities (the latter especially for CK-MB) and, despite high negative predictive values, cannot rule out MI in patients negative for both markers. Since each marker identifies patients with MI that is not identified by the other marker, both should be used in patients with acute chest pain. Higher specificities (lower false positive values) for CK-MB can be achieved by establishing independent cutoffs for patients with CHF or ESRD.

Keywords: *Myocardial Infarct; CK-MB; Troponin; Sensitivity; Specificity; Confounding Factors*

Abbreviations

AMI: Acute Myocardial Infarction; CHF: Congestive Heart Failure; ESRD: End Stage Renal Disease; cTnI: Cardiac Troponin, Inhibitory Subunit; CK-MB: MB Isozyme of Creatine Phosphokinase

Introduction

Myocardial infarction refers to necrosis of cardiac myofibers which usually follows diminished blood flow in the coronary circulation [1]. In United States 16.5 million individuals have a degree of coronary heart disease with increased propensity of acute coronary syndrome and myocardial infarction in this population [2]. Observational studies have shown that myocardial infarction has an incidence of 141 to 230 per 100,000 population in different geographical areas of United States [3,4]. Myocardial infarction is a major contributor to overall mortality in the United States and around the world with a short term mortality rate of between 2.5 - 10 percent reported [5]. While revascularization, among other treatment modalities, have contributed to marked decrease in short term mortality following myocardial infarction [6], successful management of myocardial infarction is highly dependent on prompt and accurate diagnosis of myocardial infarction [7]. Fortunately, 70 - 80 percent of patients with AMI can be diagnosed in short time periods as having this condition by EKG changes, such as ST wave elevations and/or new or deepened q waves [8]. However, this technique is non-diagnostic in about 20-30 percent of AMI cases requiring use of other diagnostic techniques [8] that include echocardiography, imaging studies, coronary angiography [8,9] and testing for cardiac biomarkers, which has become an important part of the diagnosis and subsequent management plan of these patients.

The most common cardiac biomarkers used in current clinical practice include cardiac troponins (usually troponin I also called cTnI) and the MB isozyme of creatinine kinase (CK-MB) and values > 99th percentile of the normal population is suggestive of myocardial infarction [10,11]. These tests have the advantage that, like electrocardiography, they can be performed rapidly.

Unlike many other serodiagnostic tests that are performed to aid in the diagnosis of human disease, there is a further demand on biomarkers for MI in that they must meet severe time constraints. When patients present to emergency services with chest pain, if the cause is AMI, these biomarkers must be positive for this condition at the time of admission to the emergency service, usually within six or so hours after the onset of chest pain, i.e. the sensitivity of these tests must be high at these times, usually considered to be minimally at the 90 percent level.

However, cardiac biomarkers have been found to have diagnostic limitations in that their sensitivities may be significantly less than 100 percent [9,12-14]. For example, not all patients with myocardial infarction will have increased serum troponin levels, and not every patient with increased troponin levels has an obstructed coronary artery [13,14]. Even at relatively high levels of sensitivity, these markers also have significantly lower specificities, that can result in unnecessary hospital admissions and treatment with the attendant expenses required.

Furthermore, values for sensitivity, specificity, and positive and negative predictive values vary among testing centers due to such factors as use of differing cutoffs for positive results and, especially in troponin testing, lack of standardization, use of different monoclonal antibodies, modified forms of troponin T and troponin I and antibody cross-reactivity as summarized in a recent Medscape publication [15]. In addition, studies on the diagnostic efficacy of these biomarkers vary with respect to timing: Some studies focus on initial values obtained while others follow serial values.

Single or initial determinations for both cardiac markers yield lower sensitivities than serial levels [16]. However, following serial values requires several additional hours which during which time treatment cannot be withheld. Therefore, serial values constitute con-

firmation of diagnosis but cannot be relied upon to provide acute diagnosis and therefore may not be suitable for rapid diagnosis in an emergency medicine setting.

Earlier studies suggested that combined use of both markers in acute MI result in high sensitivities and specificities [17]. In a number of later studies, troponin was found to have higher sensitivity and specificity than CK-MB [14] although other studies suggest comparable values [16,18]. Some studies that have found higher sensitivities and specificities of troponin in diagnosing MI, have advocated that routine CK-MB testing be discontinued for diagnosis of myocardial infarction [19-21]. However, in addition to the results of studies that found similar values for sensitivity and specificity of both cardiac markers, it has been found that numbers of AMI cases occur in which there is discordance between troponin and CK-MB findings. In a number of these cases (approximately ten percent), CK-MB was found to be elevated while troponin was not allowing for the correct diagnosis in these cases to be made [22]. These patients were found to have lower risk for in-hospital mortality than in patients with elevated troponin either alone or in concert with CK-MB. CK-MB also has a significantly shorter half-life than that of troponin allowing for its use in identification of re-infarction [15]. These and other studies suggest that CK-MB testing is important as at least an adjunct to troponin testing.

In this study, we evaluate the efficacy of performing concurrent serum CK-MB and troponin levels performed at or close to admission time for patients, in a predominantly African American catchment area, who presented with acute chest pain to the emergency service of a major inner city hospital in Brooklyn, NY.

Methods

Sample analysis: All serum assays for CK-MB and the cardiac inhibitory subunit of troponin (cTnI) were performed by immunoassay on the Architect Plus Analyzer (Abbott Laboratories, North Chicago, IL).

Case selection: This study (approved by our Institutional Review Board, IRB No. 923989) was aimed at evaluating the diagnostic efficacy of both markers for detecting MI in patients with complaints of chest pain acutely, i.e. single determinations at or close to the time of their presentation to the Emergency Department at the University Hospital of SUNY Downstate Medical Center, over the period, December, 2015 - March, 2016. Only patients who were tested for both markers simultaneously were included in our study.

Diagnosis of MI: Patients were diagnosed as having myocardial infarction if one or more of the following criteria, based on the third universal definition of myocardial infarction set by ESC/ACCF/AHA/WHF in 2012 [8], applied: EKG evidence of myocardial infarction (e.g. ST segment elevation), angiographic or autopsy evidence of coronary artery obstruction; and imaging (e.g. echocardiography) evidence of new loss of viable myocardium or a new regional wall motion abnormality.

Data extraction and entry: The data were extracted from the electronic medical health record of the patients and entered into an anonymized Microsoft Excel file. The troponin and CK-MB results were entered both as quantitative measures as well as binary measures based on the cut-off threshold used for the Architect Plus analyzer in our laboratory (0.05 ng/mL for troponin and 5 μg/mL for CK-MB).

Reporting: In order to report the results, we followed the guidelines set forward by the American Heart Association on evaluation of cardiac markers [23].

Results

A total of 380 patients met the selection criteria of the study. Of these 47 were found to have MI (prevalence = 12.4 percent) using, as "gold standards", electrocardiography (ST segment elevation, Q waves), echocardiography and coronary angiography. All of the remaining 333 patients (87.6 percent) were found not to have myocardial infarction. This prevalence value for myocardial infarction is in accord with

prevalence values in other studies on patients who presented to emergency services with complaints related to acute coronary events [24].

The overall average troponin level was 1.676 ng/mL (SD: 10.309). The average troponin level in patients with myocardial infarction (MI) was 12.881 ng/mL (SD: 26.990) versus 0.094 (SD: 0.322) in patients without MI. The overall average CK-MB level was 7.518 (SD: 20.241). The average CK-MB level in patients with MI was 27.509 ng/mL (SD: 50.942) versus 4.725 ng/mL (SD: 6.787) in patients without MI. The difference in CK-MB and troponin levels between patients with and without MI is statistically significant, i.e. asymptotic p-values based on the Mann-Whitney U test were < 0.0001 for both using an alpha value cutoff of 0.05.

Results using both markers were in agreement as to the absence or presence of AMI in 272 of the 380 patients, 71.6 percent.

Sensitivity: Our laboratory employs a cutoff value of 5 ng/mL for CK-MB and 0.05 ng/mL for troponin. As shown in table 1, based on these cutoffs, CK-MB had a sensitivity of 66% and a specificity of 70.7% for MI while troponin had a sensitivity of 89.4% and a specificity of 73.3%. Although cTnI was found to have a high sensitivity of 89.4 percent, as can be seen in table 2, five patients or 10.6 percent of patients with AMI were found to be falsely negative using this marker. Thus, negative troponin results cannot eliminate AMI as a possible cause of chest pain. The sensitivity of CK-MB was lower than that for cTnI at 66 percent. Using the above respective cutoffs for both markers, cTnI and CK-MB, concurred in 31 of the 47 AMI cases; cTnI identified an additional 11 cases for which CK-MB was negative (Table 2).

Marker	SENS	SPEC	PPV	NPV
Troponin	89.4 (85.3)[2]	73.3 (82.4)	32.1(38.7)	98.0 (97.7)
CK-MB	66.0 (64.7)	70.6 (84.3)	24.0 (34.9)	93.7 (94.8)

Table 1: *Percent sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) for troponin and CK-MB in diagnosing MI[1].*

[1]Cutoffs for CK-MB and troponin (cTnI) were 5 ng/mL and 0.05 ng/mL, respectively.

[2]Percentages in parentheses are for the sensitivity, specificity and positive and negative predictive values for patients without the complications of CHF and ESRD.

Entry	Troponin	CK-MB	Fraction Positive	Percent Positive
1	+	+	31/47	66.0
2	+	-	11/47	23.4
3	-	+	0/47	0.0
4	-	-	5/47	10.6

Table 2: *Details for sensitivity: Total positive patients = 47[1].*

[1]Cutoffs for CK-MB and troponin (cTnI) were 5 ng/mL and 0.05 ng/mL, respectively.

Specificity: Both cTnI and CK-MB were found to have relatively low specificities of 73.3 and 70.6 percent, respectively due to significant numbers of false positives as can be seen in table 3. As shown in table 1, this resulted in low positive predictive values for both markers, i.e. 32.1 and 25.8 percent for cTnI and CK-MB, respectively. On the other hand, the negative predictive values for cTnI and CK-MB were high at 98 and 94 percent, respectively. However, these values do not reflect the significant number of the five false negatives (Table 2). This finding and the low specificities and positive predictive values for each marker suggest that neither marker on its own would be sufficient for acute diagnosis of AMI.

Entry	Troponin	CK-MB	Number	Percent
1	+	+	45/333	13.5
2	+	-	44/333	13.2
3	-	+	53/333	15.9
4	-	-	191/333	57.4

Table 3: *Details for specificity: Total negatives = 333[1].*

[1]Cutoffs for CK-MB and troponin (cTnI) were 5 ng/mL and 0.05 ng/mL, respectively.

Confounding factors: We have investigated these results further by examining possible factors that might cause the high level of false positive test results. From prior studies and review of the charts of the patients in this study, we found that 85 patients had either congestive heart failure (CHF) or end stage renal disease (ESRD) that can cause false elevations of the two markers.

To evaluate the possible effects of these conditions on levels of the two markers, we determined the mean values for both markers in the 333 non-AMI patients for patients without either condition and compared them with the mean values for patients with either condition. We found that the mean cTnI value for the group with neither condition was 0.074 (SD 0.33) ng/mL while the value for patients with ESRD rose to 0.17 (SD 0.28) ng/mL and to 0.18 (SD 0.29) in patients with CHF ($p < 0.0001$ using the Mann-Whitney test for both comparisons) and that the mean CK-MB value for the group with neither condition was 3.75 (SD 4.78) ng/mL which rose to 10.26 (SD 11.98) for patients with ESRD and 9.14 (SD 11.39) for patients with CHF ($p < 0.0001$ using the Mann-Whitney test for both comparisons). These results suggest that each condition is associated with significant increases in the values of each marker and that higher reference ranges for each marker should be determined for patients with either of these conditions resulting in higher cutoff values that would decrease the number of false positives. We are currently exploring baseline ranges for both markers in the patients with either of these conditions but who were found not to have AMI in an expanded survey of such patients.

Based on these findings, we removed the 85 patients with these conditions from the 380 patients and re-computed the test parameters for this group of 295 patients. The results are shown in table 4-6.

Marker	SENS	SPEC	PPV	NPV
Troponin	85.3	82.4	38.7	97.7
CK-MB	64.7	84.3	34.9	94.8

Table 4: *Percent sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) for troponin and CK-MB in diagnosing MI[1]for 295 patients without CHF or ESRD.*

[1]Cutoffs for CK-MB and troponin (cTnI) were 5 ng/mL and 0.05 ng/mL, respectively.

Entry	Troponin	CK-MB	Fraction Positive	Percent Positive
1	+	+	22	64.7
2	+	-	7	20.6
3	-	+	0	0.0
4	-	-	5	14.7

Table 5: *Details for sensitivity for MI for the 295 patients without CHF or ESRD: Total positive patients = 34[1].*

[1]Cutoffs for CK-MB and troponin (cTnI) were 5 ng/mL and 0.05 ng/mL, respectively.

Entry	Troponin	CK-MB	Number	Percent
1	+	+	13	5.0
2	+	-	33	12.6
3	-	+	28	10.7
4	-	-	187	71.6

Table 6: *Details for specificity for the 295 patients without CHF or ESRD: Total negatives =261[1].*

[1]Cutoffs for CK-MB and troponin (cTnI) were 5 ng/mL and 0.05 ng/mL, respectively.

Results on patients without complicating factors: These tables, as summarized in table 1, where all of the parameters that were calculated for the results without CHF or ESRD are shown in parentheses allowing direct comparison, show that removing the cases with CHF and ESRD caused significant increases in the specificities and positive predictive values for both markers without significantly decreasing the sensitivities or negative predictive values. Thus, with a small (4 percent) decrease in sensitivity for troponin and a 1 percent decrease in sensitivity for CK-MB, there was a marked increase in specificities of 9 and 14 percent for troponin and CK-MB, respectively, and a corresponding increase in positive predictive values for troponin and CK-MB of 7 and 11 percent, respectively. The high negative predictive values for both markers were virtually unchanged.

Use of combined markers to identify patients likely to have AMI: However, despite the increases is positive predictive values for each marker, the values still remain low, below 40 percent. Since the positive predictive value gives the probability that a patient with a positive value for these markers has AMI, these values cannot identify patients who are likely to have this condition. We have therefore explored the possibility of using both markers together to identify patients who are at significant risk for AMI and for whom treatment might be initiated. In these investigations, we have used the criterion that both markers should be positive to identify patients at risk. Using this criterion, we have determined the numbers of patients who were found to be positive for both markers who were diagnosed as having AMI and who were positive for both markers and were found to be negative for AMI. The positive predictive value for these patients can thus be directly calculated. From tables 5 and 3 for the 380 patients, there were 31 true positives and 45 false positives, giving a positive predictive value of 40.8 percent. From tables 5 and 6 for the 295 patients without complicating conditions, there were 22 patients who were found to be truly positive and 13 who were falsely positive, giving a positive predictive value of 63 percent. Using this criterion, it is therefore possible to raise the positive predictive value by 23 percent, a significant increase that allows for identifying patients who are likely (with an approximately 2 out of 3 chance) to have AMI. These results are summarized in figure 1 which shows the sensitivity, specificity and positive predictive value for AMI for troponin alone on all 380 patients, on the 295 patients who did not carry a diagnosis of either CHF or ESRD and for troponin and CK-MB for the same 295 patients.

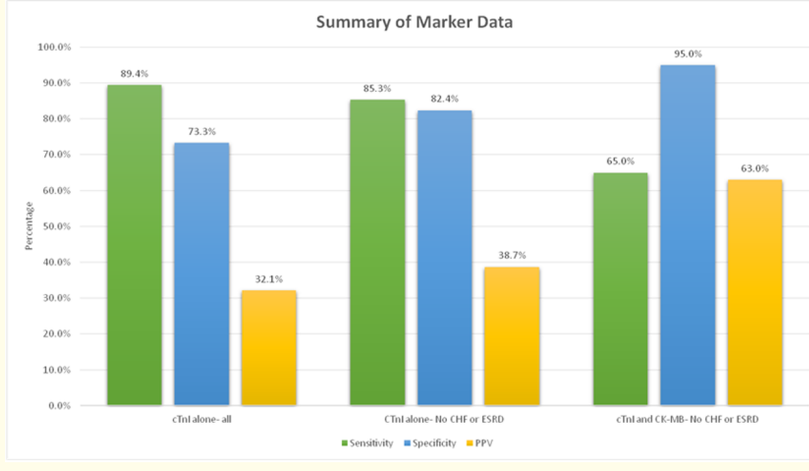

Figure 2: *Sensitivity (green bars), specificity (blue bars) and positive predictive value (yellow bars) for AMI for troponin alone on all 380 patients, on the 295 patients who did not carry a diagnosis of either CHF or ESRD and for troponin and CK-MB for the same 295 patients. Source: Laskar., et al.*

Discussion

The critical requirement for any test for AMI is that it have a high sensitivity when performed at the time of patient presentation so that most patients with AMI presenting with chest pain to an emergency service can be identified and treated rapidly. The problem is the occurrence of significant numbers of false positive test results that can result in patients' being treated unnecessarily, incurring the risk of treatment morbidity and significant treatment costs. At present, it seems that neither serodiagnostic marker, cTnI and CK-MB, has sufficiently high sensitivity to serve as a definitive test to diagnose AMI at the time of patient presentation. An important factor in causing low predictive values is the low prevalence of AMI in the patient population. The sensitivity of cTnI for the 380 patients in our study was 89.4 percent which would be considered high for most markers used in the diagnosis of chronic diseases but not for AMI where the requirement is for the rapid diagnosis of acute, life-threatening disease. Furthermore, the low specificity of this test (73.3%) due to a large number of false positive cases lowers the positive predictive value to low values (38.9%) making the likelihood of AMI low. Similar analysis applies to CK-MB whose sensitivity is unacceptably low at 66% and whose specificity is also low and is similar to that for cTnI.

Our strategy in this study was to improve the ability of both tests to capture patients who have AMI and to provide a high positive predictive value identifying patients at risk despite the low prevalence and to trigger implementation of treatment. We have found that by removing patients who have confounding conditions that significantly increase the number of false positive results and lower the positive predictive value and by requiring that both tests be positive to identify patients at risk, the positive predictive value for both tests increases to 63%. This approach is similar to a multi-test procedure that included three serodiagnostic markers (cTnI, CK-MB and myoglobin) that resulted in high positive predictive values [30]. One drawback with this approach is that requiring both tests to be positive reduces the sensitivity of the two test approach to 66%.

These findings suggest a two step approach that can result in improved outcomes using both markers. The first is to hold all patients with positive cTnI and divide them into two groups: the first group is the 66 percent who also have a positive CK-MB. This group might be considered to have sufficient risk that treatment can be initiated. The second group who have positive troponin but negative CK-MB should be tested further by another method such as angiogram (if feasible), echocardiogram or combined CT-echocardiogram. Our results also suggest that patients with negative cTnI should be further tested for AMI by one or more of these other tests since this test will result in a significant number of false negative results.

Conclusion

CTnI is a useful but limited diagnostic biomarker in diagnosing AMI in patients with acute chest pain, provided it is used in conjunction with CK-MB on patients who do not have concurrent complicating conditions, in particular CHF and ESRD.

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