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ORIGINAL ARTICLE

Evaluation of Troponin I in Patients with Acute Myocardial Infarction in the Emergency Department

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ABSTRACT

Objectives: To evaluate and validate the cut-off values for troponin I (Trop I) in diagnosing acute myocardial infarction (AMI) in the emergency department (ED) and to establish the local healthy reference value.
Methods: 86 patients with chest pain and/or shortness of breath were admitted to the ED. Blood samples were collected at 0-3 hours, 6-9 hours and 12-24 hours post-admission and were assayed for (Trop I) and creatine kinase MB (CK-MB). The sensitivity, specificity and the area under the curve (AUC) were determined. Blood samples were also collected from 140 healthy volunteers.
Results: The AUC values for (Trop I) were found to be 0.830, 0.863 and 0.912 for the cut-off values of 0.33, 1.0, and 1.5 ng/ml, respectively. The AUC for CK-MB at admission time was found to be 0.736. The reference value based on the 99th percentile was found to be 0.12 ng/ml.
Conclusion: Trop I levels were identified in 81-88% of the patients with AMI, with higher sensitivity and specificity than the CK-MB levels.

Key Words: Troponin, Acute Myocardial Infarction, Emergency

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Indroduction

Coronary artery disease (CAD) remains to be the leading cause of morbidity and mortality throughout the world. A triage of patients with chest pain is one of the most difficult challenges faced by physicians in any ED. However, the diagnosis of acute myocardial infarction (AMI) is not always made in the emergency department (ED). Sometimes, patients admitted for other reasons develop symptoms of AMI while in the hospital. In addition, the admission of patients with low probabilities for acute coronary artery disease often leads to excessive hospital costs. These issues have put a lot of pressure on the ED physicians in deciding whether to diagnose AMI or to rule it out. One of the earliest known ways to diagnose AMI, in patients with chest pain, was frequent electrocardiography (ECG) testing and blood collection to measure biochemical cardiac markers [1]. Patients with negative results for these tests did not mostly have AMI. However, they were found to have unstable angina or other forms of acute cardiovascular disease.

The patient's history is an important component of the diagnosis, but yet, nonspecific symptoms could be present in up to one-third of the patients, especially in the diabetics and the elderly. Although 70% to 80% of the patients diagnosed with AMI present with ischaemic-type chest pain, less than 25% of the patients who are admitted with complaints of chest pain, are later diagnosed with AMI [2].

ECG is also a very valuable diagnostic tool that should be performed in patients presenting with chest pain. However, ECG can be nondiagnostic in up to 50% of patients and physician errors in ECG interpretation can occur for up to 12% of patients with chest pain [2],[3],[4].

Recently, many scientific committees have advised that the cardiac protein, troponin is a highly sensitive and specific marker of myocardial cell injury and have advised its measurement for the detection of acute myocardial infarction [5],[6].

Setting cut-off values is also an issue for troponin assays which are performed in a central laboratory. Laboratory staff must work with ED physicians to determine the type of assay and the cut-off to be used. A range of cut-off values is still being used, depending on the specific assay and the platform. Another key issue affecting these assays is the lack of g standardization of the immunoassay among the manufacturers.

By the current consensus, AMI is defined by the presence of troponin above the reference range. A peak troponin level that falls below the cut-off value rules out AMI, although the patient might still need to be evaluated for acute coronary syndrome. However, new research indicates that even a negative troponin result might be problematic and that it raises questions about the diagnostic cut-off value. However, the clinical laboratory community has long been split on its views about the best cut-off values for the troponin assay; some believe that it should be set at the 99th percentile of the reference population, while others believe that it should be set at the level at which the particular assay's coefficient of variation (CV) is less than 10%. The National Academy of Clinical Biochemistry endorses the 99th percentile cut-off, believing that this range identifies a greater number of at-risk patients [5].

Since it is widely accepted that the serum biochemical cardiac marker, creatine kinase, specifically its MB isoenzyme (CK-MB), lacks sufficient sensitivity and specificity, there is a need for a more sensitive and cardiac-specific marker for myocardial necrosis. Troponin I, one of the subunits of the troponin regulatory complex, binds to actin and inhibits interactions between actin and myosin. It is encoded by three different genes that are expressed at different levels in different types of muscles. Cardiac troponin I is not expressed in the human skeletal muscles during foetal development, after trauma to the skeletal muscles, or during the regeneration of the skeletal muscles. Unlike CK-MB, cardiac troponin I is highly specific for the myocardial tissue, is not detectable in the blood of healthy persons, shows a greater proportional increase above the upper limit of the reference interval in patients with myocardial infarction and may remain elevated for 7 to 10 days after an episode of myocardial necrosis.

Until recently, creatine kinase and CK-MB fractions were used most often to evaluate patients with acute chest pain and suspected acute myocardial infarction (AMI) [7]. Recently, a joint committee of the European Society of Cardiology, the American College of Cardiology (ESC/ACC) and the International Federation of Clinical Chemistry (IFCC) issued new criteria which acknowledge that elevations in biochemical cardiac markers are essential for the diagnosis of AMI, as symptoms may be atypical or nonspecific and electrocardiogram changes may be absent or nonspecific [8],[9],[10],[11]. By this time, cardiac troponin had replaced CK-MB as the biomarker of choice for the detection of cardiac injury [12].

However, the interpretation of the troponin test results can be problematic. The test characteristics vary considerably depending on the cut-off value which has been used to define as abnormal, the troponin fraction which has been used (T or I) and the time from the onset of myocardial ischaemia. For example, an increase in the cutoff value will decrease sensitivity but will improve specificity [13]. Because the troponin tests rely on the damage to the myocardial cells and the release of troponin into the circulation, the sensitivity initially increases with the number of hours from the onset of chest pain and then decreases as the enzyme is cleared from the circulation. However, many reports on which the current estimates of sensitivity and specificity are based, do not report the time from the onset of symptoms, or only provide the lowest value obtained during the first 24 hours. Decision making in the ED is often based on previously obtained values and it is therefore important to carefully describe the accuracy of the test at different times [10].

Given these features of cardiac troponin I as a biochemical marker of myocardial necrosis, we designed the present study to evaluate the potential variation between different cut-off values to achieve better sensitivity and specificity for the diagnosis of myocardial infarctions at our institute.

Patients and Methods:

Data from a total of 86 patients were collected from the ED at King Fahad National Guard Hospital in Riyadh (Kingdom of Saudi Arabia), in a retrospective study covering a two-month period in 2006. Of the 86 patients, 61 (71%) were males and 25 (29%) were females, with a mean age of 56 years. All patients were local citizens of Saudi Arabia. Chest pain and/or shortness of breath were the main complaints of those patients. Clinical history, physical examination, ECG, CK-MB and troponin I measurements were performed for all the patients. Blood serum samples were collected to analyze CK-MB and troponin I values by the ADVIA Centaur System (Siemens, USA), by using two-site sandwich direct chemiluminometric immunoassay technology. This method uses constant amounts of polyclonal and monoclonal antibodies.

Blood samples were collected in serum separator tubes (Greiner Bio-one, Germany) and they were labeled and allowed to clot for 15 minutes. The samples were then centrifuged for 10 minutes at 3000 rpm by using a Multifuge 35R. Three levels of quality control materials were used (Bio-Rad, USA) for each assay. The results were transmitted and stored in the Laboratory Information System (LIS) (Cerner, USA), which interfaced with the Advia Centaur analyzer. The data were then retrieved retrospectively from the LIS. No clinically significant interference from haemoglobin, triglycerides, or bilirubin was observed in this assay. The linearity range of the assay was reported and verified as 0.15-50.00 ng/mL and any value above 50ng/mL needed to be diluted [14]. The within-run and between-run CVs by using 2.38 ng/mL of troponin I were 2.3% and 5.0% respectively. The sample volume required for the assay was 100 uL per reading for each sample.

Blood serum samples were also collected from 140 healthy male donors ranging in age from 18 to 58 years and the evaluation of serum troponin I levels was performed on the same analyzer, ADVIA Centaur System (Siemens, USA), according to the manufacturer's instructions. The 99^{th} percentiles of the distribution of these samples were calculated.

The diagnostic cut-off value used in our lab was 1.5ng/mL (that is, a value higher than this cut-off was considered to be indicative of a myocardial infarction). No clinically significant interference from haemoglobin, triglycerides, or bilirubin was observed in this assay. The sensitivity and specificity at different cut-off values were measured and the receiver operating characteristic (ROC) curve and the area under the curve (AUC) were calculated and wherever possible, were compared.

(Table/Fig 1) Sensitivity, Specificity and area under curve values of troponin I and CK-MB in emergency department (ED) patients.

Elapsed time	0-3 hrs		6-9 hrs		12-24 hrs		
Cutoff(ng/ml)	Sens%	Spec%	Sens%	Spec%	Sens%	Spec%	AUC
0.33 (Trop I)	88	77	87	84	81	88	0.830
1.0 (Trop I)	62	90	76	90	59	97	0.863
1.5 (Trop I)	57	95	73	97	60	98	0.912
5.0 (CK-MB)	81	64	80	67	62	75	0.736

Results:

In the present study, the total number of patients who were suspected of having AMI was 86. They were admitted to the emergency department under the suspicion of having AMI. Of these, 54 (63%) patients were confirmed to have AMI and 32 (37%) were excluded as having other cardiac or pulmonary disorders. Three cut-off values, 0.33ng/mL, 1.0ng/mL and 1.5 ng/mL were selected to evaluate the troponin I assay sensitivity and specificity. Each one of these cut-off values was also evaluated at different times (0-3, 6-9 and 12-24 hours after admission time). Only one cut-off value (5.0ng/mL) was evaluated for CK-MB.

Table 1 shows the sensitivity, specificity and the AUC values for troponin I and CK-MB at

different cut-off values and at different times which elapsed since admission. During the first three hours of admission, at the cut-off values of 0.33, 1.0, and 1.5 ng/ml for troponin I, the sensitivity values were found to be 81%, 62%, and 57%, while the specificity values were found to be 77%,
90%, and 95%, respectively. As time elapsed (6 to 9 hours after admission), the sensitivity values were found to be 87%, 76%, and 73%, while the specificity values were found to be 84%, 90%, and 97%, respectively, for the same set of cut-off values. After 12 to 24 hours, the sensitivity values were found to be 81%, 59% and 60%, with specificity values of 88%, 97% and 98%, respectively. The AUC values for trop I were calculated from the ROC curves and were found to be 0.830, 0.863, and 0.912 for the cut-off values of 0.33, 1.0, and 1.5 ng/ml respectively. At a 5.0 ng/ml cut-off value, CK-MB provided sensitivity and specificity values of 81% and 64% at the time of admission, 80% and 67% at 6 to 9 hours and 62% and 75% at 12 to 24 hours after admission. The AUC value for CK-MB at the time of admission was found to be 0.736. The healthy population reference value based on the 99th percentile was found to be 0.12ng/ml.

Discussion:

In the present study, 63% of our patients were confirmed to have AMI. We noticed that early after admission, the sensitivity of troponin I was almost similar to the specificity at lower cut-off values. However, at higher cut-off values, the sensitivity decreased and the specificity increased. When 6 to 9 hours had elapsed after admission, the sensitivity improved, but the specificity remained almost unchanged at all cut-off points. When the time from admission increased further (12 to 24 hours from admission), the sensitivity and specificity values remained almost the same. The AUC values indicated that the best cut-off value for diagnosing AMI in our population was 1.5ng/mL and the best time point to test for AMI was between 6 and 9 hours after admission. In contrast, CK-MB measurement had a higher sensitivity than its specificity between 6 and 9 hours after admission, which was still lower than that of troponin I.

Hamm et al. found that 63% of their patients were suffering from cardiac problems and had been admitted to the CCU [9]. This percentage was consistent with our findings, in which we reported the same percentage of patients to have AMI in the ED.

Our study shows that the sensitivity and specificity of our troponin I measurement assay were superior to those of the CK-MB isoenzyme assay in evaluating patients with AMI. Many studies have demonstrated similar conclusions, noting that an elevated level of cardiac troponin I in an ischaemic setting was associated with subsequent myocardial infarction and death, even when CK-MB levels were not elevated [2],[3].

Apple et al. evaluated the diagnostic accuracy of the troponin I assay in detecting AMI by using the Advia Centaur assay [16]. They measured troponin I levels at admission and 6 to 24 hours after admission in plasma samples from 371 patients who arrived in the ED with chest pain. They chose the 99th percentile level of 0.04 ng/mL as a cut-off value. They confirmed that 41 (13%) patients had AMI with clinical sensitivity and specificity values of 74% and 84% respectively at admission and 94% and 81% at 6 to 24 hours after admission. They also showed that the ROC curve had a significantly higher accuracy for diagnosing AMI after 6 to 24 hours, as compared to its use at admission (P=0.001) [16]. These data are in agreement with our data. In the study performed by Apple et al. the diagnostic cut-off value for troponin I was lowered from 0.6ng/mL to 0.3, with a value of 0.4 or greater being considered as indicative of an AMI, as well as a risk stratification cut-off point. Based on the assay that they employed, the data in the literature suggested that patients with troponin I values greater than 0.1 µg/L were at risk; however, the CV in their assay was not completely acceptable at the 0.1 µg/L level [16].

In another meta-analysis study, the sensitivity and specificity of the troponin I analysis for the detection of myocardial infarction, 8 hours after the onset of symptoms, were 84% and 81%, respectively [17],[18]. The sensitivity and specificity in our study at this time point were 87% and 84%, respectively, with a cut-off of 0.33 ng/mL.

The results described by Ebell, showed that troponin I sensitivity increased from 10% to 45%

(depending on the cut-off value) within 1 hour of the onset of pain to more than 90% after 8 or more hours [19]. That study also showed that the specificity increased from 80% at 1 hour after the onset of chest pain to 95% after 12 hours. The peak abnormal value in the first 24 hours after admission to the ED had an area under the receiver operating characteristic curve of 0.99 and was very useful for ruling out AMI when the value of Trop I was not detectable or when it was below the cut-off value.

In another study by Acharya and Man, 378 Asian patients were clinically confirmed to have acute coronary syndrome on the basis of clinical manifestations and ECG changes over a period of eight months [20]. Out of 378 patients, 102 (26.9%) were confirmed to have AMI and 276 (73.0%) were found to have unstable angina and other cardiac dysfunctions. In their study, the sensitivity values of CK-MB and troponin I for the detection of AMI in their study were 84.3% and 96%, respectively. These values were higher than the values which were detected in our study, but they did not indicate at what interval the blood samples were collected. The different ethnicity of the patients could be another factor which affected the sensitivity. In addition, the methods which were used in that study to measure CK-MB and troponin I were from Dimension AR (Siemens, USA) and General Biologics Corporation (Taiwan), which could have contributed to the variations which were noted between these studies.

In the study by Ross et al. [21], cardiac markers and the ECG of 153 patients who presented to the ED with chest pain, were retrospectively evaluated. The sensitivity of using CK-MB or ECG independently to diagnose AMI was found to be 88% or 69%, respectively. When a troponin I level greater than 0.6ng/mL was used as a positive cut-off value, the sensitivity and specificity were found to be 94% and 81% at 0 or 6 hours, respectively. We reported a lower sensitivity (76%) and higher specificity (90%); this may be due the use of a higher cutoff value (1.0 ng/mL) and differences in the immunoassay method used in each study. When a troponin I cutoff value of 2.0 ng/mL was used, the sensitivity and specificity in the study carried out by Ross et al. were 85% and 91%, respectively, as compared to the CK-MB and ECG reports which were similar to our findings at a troponin cut-off value of 1.5 ng/mL.

The 99th percentile value of the troponin I level was found to be 0.12 ng/mL in our population. The technical information provided by the manufacturer for the Advia Centaur cardiac troponin I assay has indicated that the 99th percentile was found to be 0.10 ng/ml [22]. In the WEQAS study [23], Williams et al have reported 0.19 ng/ml for the 99th percentile.

We conclude that the diagnostic value of using troponin I in our population is similar to that reported in other populations. We also conclude that troponin I is superior to CK-MB for the diagnosis of AMI in the ED. This test is particularly useful in ruling out AMI when the value is below the cut-off level of 6 or more hours after the onset of chest pain.

Our most important conclusion is that the sensitivity of the troponin test, like that of any other cardiac enzyme, is highly dependent on the number of hours which have elapsed since the onset of chest pain. The test is slightly insensitive (i.e., it misses out some cases of AMI) within the first 6 hours after the onset of chest pain, when patients often present to the ED. However, by 12 or more hours after the onset of pain, the test is quite sensitive and a value of the troponin below the cut-off is strong evidence against the presence of AMI.

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The authors of this manuscript have certified that they have complied with the Principles of Ethical Publishing in the International Journal of Cardiology' [24].

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