The Diagnostic Value of Cardiac Troponin T in the Detection of Acute Myocardial Infarction in Hospital USM Patients

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ABSTRACT: Acute myocardial infarction (AMI) was defined based on clinical findings, ECG abnormalities and cardiac enzymes. However with sensitive marker such as troponin the definition has been refined. In this study two cut-off values of troponin T (0.03ng/mL and 0.1ng/mL) were compared with the final diagnosis of AMI made by the physician. This was a retrospective study to determine the efficiency of cardiac troponin T in the diagnosis of AMI. Receiver operating curve (ROC) was obtained and calculated to determine the best cut-off point for troponin T. A total of 246 patients with acute coronary syndrome were recruited. Out of these, 48.8% of patients had AMI with 36.2% of them diagnosed as non-ST elevation MI and 12.6% as ST-elevation MI. The remaining 51.2% were diagnosed as unstable angina. Troponin T at the cut-off value of 0.03ng/mL had high sensitivity with low specificity (94.2% and 87.3%, respectively) whereas cut-off value of 0.1ng/mL had low sensitivity with high specificity (76.7% and 96.8%, respectively). The optimal cut-off value of troponin T in our patients was 0.037ng/mL with sensitivity and specificity of 90.0% and 90.5 %. Therefore, the best cut-off value of troponin T for the diagnosis of AMI was 0.037ng/mL with area under curve of 0.9652. However for the diagnosis, it should be matched with clinical findings.

Keywords: Acute myocardial infarction (AMI), troponin T, receiver operating curve (ROC)

Introduction

Acute myocardial infarction (AMI) is a major health problem worldwide with serious consequences in morbidity and mortality (Boersma *et al.*, 2003). More than 3 million people each year are estimated to have acute ST Elevation Myocardial Infarction (STEMI) with more than 4 million having non-ST Elevation Myocardial Infarction (NSTEMI) (White and Chew, 2008). For the diagnosis of AMI serum cardiac markers are used to support the diagnosis and among the many available biomarkers for the detection of AMI, cardiac troponin is the preferred biomarker. However, the presence of troponin in the circulation indicates myocardial necrosis rather than its mechanism which does not necessarily equate to Acute Coronary Syndrome (ACS) or AMI. Therefore, an elevated value of troponin in the absence of clinical evidence of ischaemia should prompt a search for other aetiologies of myocardial necrosis such as pulmonary embolism, myocarditis, congestive heart failure, aortic dissection and renal failure (Jaffe *et al.*, 2006).

Troponins are regulatory proteins found in cardiac and skeletal muscle. The myofibril is the primary site for troponin (94%-97%) with smaller cytoplasmic fraction (3%-6%). Troponin T (the tropomyosin-binding component), troponin I (the inhibitory component) and troponin C (the calcium-binding component) form a complex along with tropomysin which are located on the actin filament. They are essential for the calcium mediated regulation of skeletal and cardiac muscle contraction.

Cardiac troponin I and T subunits have different amino acid sequences encoded by different genes. They are different from troponins found in other muscle such as the skeletal muscle. Troponin C has isoform that is shared by both cardiac and slow-twitching skeletal muscle therefore it is not specific for the heart (Babuin and Jaffe, 2005). The human cardiac troponin I (cTnI) specificity is contributed by a post-translational addition of 31amino acid residues at the amino terminal end compared to skeletal muscle troponin I. Whereas the human cardiac troponin T (cTnT) unique specificity is given by the 11amino acid residues at the amino terminal. It is encoded by a different gene than that encodes for the skeletal muscle isoforms.

In acute myocardial infarction, 4-6 hours after onset of symptoms, troponin level begins to increase and reaching a peak at 12-24 hours. A significant increase in cardiac troponin value is defined as its plasma concentration exceeds the 99th percentile of that of a normal reference population (Thygesen and White, 2007). The troponin concentration may remain increase up to 5-10 days (cTnI) or 5-14 days (cTnT). The long lasting increase is probably due to continuous release of troponin from the degenerating myocytes. Typical increase and decrease of troponins concentration is essential for the diagnosis of AMI, especially in the presence of coexisting extracardiac conditions such as primary pulmonary hypertension, pulmonary embolism, renal failure, subarachnoid haemorrhage, sepsis and septic shock and stroke (Montorsi *et al.,* 2009).

A study conducted by the manufacturer of cardiac troponin T (Roche Diagnostic) on healthy volunteers suggested that the value of 0.03ng/mL is the lowest concentration at which 10% imprecision is achieved and based on the receiver operating curve (ROC) AMI optimized, value of ≥ 0.1ng/mL is the cut-off value for the diagnosis of AMI (Muller-Bardorff *et al.,* 1997). The value between the 0.03ng/mL and 0.1ng/mL is at the zone of cardiac injury and it is valuable inthe clinical interpretation.

Therefore this study was conducted to determine the diagnostic efficiency of cardiac troponin T in the diagnosis of AMI at Hospital Universiti Sains Malaysia (Hospital USM), Kelantan, Malaysia. Although the manufacturer and studies elsewhere had established their respective cut-off points, it is essential to evaluate these cut-off values in the diagnosis of AMI among local patients. On the other hand, it is important to determine the cut-off point that gives the best sensitivity and specificity of the test.

Material and methods

A retrospective study was done beginning of January 2009 to March 2011 whereby a total of 246 patients were selected based on the request for troponin T in the Laboratory Information System (LIS) in Chemical Pathology Laboratory, Universiti Sains Malaysia. The inclusion and exclusion criteria were satisfied. The patients' clinical folders were traced from the record office. Details extracted from the patients' folders include the demographic data, onset of symptoms of chest

pain or discomfort, cardiovascular risk factors, clinical examination, ECG, troponin T results, initial provisional and final diagnosis of the patients.

The value of troponin T assay was compared with the final diagnosis made by the physicians. Two cut-off values of troponin T were evaluated in this study; the cardiac troponin T cut-off value ≥ 0.03ng/mL (Roche Elecsys) and ROC AMI cut-off value ≥0.1ng/ml. Elecsys troponin T value of ≥ 0.03 ng/ml was taken as positive for myocardial infarction and a value < 0.03 ng/mL as negative for myocardial infarction. However for ROC AMI, troponin T value of ≥ 0.1 ng/mL was taken as positive and specific for myocardial infarction.

Receiver operating curve was obtained and calculated to determine the best cut-off point for troponin T in our patients. The area under the curve (AUC) represents the most commonly used measurement of the diagnostic accuracy of a test.

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS) version 18.0.1 Further analyses were done using STATA 11.0SE.

This study was approved by the Ethical Committee (Human) of Universiti Sains Malaysia Kubang Kerian, Kelantan (USMKK/PPP/JEPeM [238.4(1.11)]).

Results

A total of 246 patients with Acute Coronary Syndrome were recruited during the study period from January 2009 to March 2011 in Hospital Universiti Sains Malaysia (Hospital USM), Kelantan, Malaysia. Out of 246 patients, 120 patients (48.8%) had acute myocardial infarction (AMI) with 89 patients (36.2%) diagnosed as non-ST elevation MI (NSTEMI) and 31 patients (12.6%) diagnosed as ST-elevation MI (STEMI). The remaining patients (51.2%) were diagnosed as unstable angina (UA).

The age of the patients ranged from 28 to 87 years old with a mean (SD) of 62.2(11.68) years. The age range of the patients was similar to the overall samples with a mean (SD) of

61.75(12.07) years. For female population, the age distribution was between 35 to 86 years old with a mean (SD) of 62.86(10.97).

The mean (SD) ages for patients with unstable angina and the patients with myocardial infarction were 60.94(11.87) and 63.43(11.38) years, respectively. Male preponderance was noted in both categories in this study. The demographic details and association between gender and risk factors with the final diagnosis of MI and UA are as in **Table 1**. Four cardiovascular risk factors were evaluated in this study namely, hypertension, type 2 diabetes mellitus, dyslipidaemia and smoking.

Table 1: Demographic and association of gender and risk factors with final diagnosis of MI and UA (N = 246).

Variables	**UA**	**MI**	**χ^2 statistics (df)**	**p-value**
	n(%)	**n(%)**		
Race				
Malay	120 (95.2)	110 (91.7)	1.31(2)	0.519
Chinese	5 (4.0)	8 (6.7)		
Indian	1 (0.8)	2 (1.7)		
Gender				
Female	50 (39.7)	38 (31.7)	1.719 (1)	0.190
Male	76 (60.3)	82 (68.3)		
Hypertension				
No	52 (41.3)	46 (38.3)	0.221 (1)	0.638
Yes	74 (58.7)	74 (61.7)		
Diabetes				
No	72 (57.1)	67 (55.8)	0.043 (1)	0.836
Yes	54 (42.9)	53 (44.2)		
Hyperlipidemia				
No	100 (79.4)	90 (75.0)	0.666 (1)	0.414
Yes	26 (20.6)	30 (25.0)		
Current smoker				
Non smoker	63 (50.0)	35 (29.2)	13.764 (2)	0.001
Ex smoker	33 (26.2)	33 (27.5)		
Smoker	30 (23.8)	52 (43.3)		

The diagnostic values of troponin T, which were from the final diagnosis made by physicians treating the patients, were evaluated by comparing them to the two different cut-off values (**Table 2**).

Table 2: Distribution of patients based on two different cut-off values

Classification	Physician's final diagnosis n (%)	Elecsys cut-off ≥0.03ng/mL n (%)	AMI ROC cut-off ≥0.1ng/mL n (%)
MI	120 (48.7%)	129(52.4)	96(39%)
UA	126 (51.3%)	117(47.6)	150(61.0)

Note: Cutoff ≥ 0.03ng/ml (Roche Elecsys 3rd generation Troponin T assay) & cutoff ≥ 0.1ng/ml [ROC AMI] (Muller-Bardoff *et al*., 1997)

Matrix of diagnosis using two different cut-off values was provided in **Table 3** and the diagnostic value of troponin T assay at different cut-off values was given in **Table 4**.

Table 3: Matrix of diagnosis using two different cut-off values

Classification	AMI ROC cut-off			
	≥0.03ng/mL		≥0.1ng/mL	
	UA n(%)	MI n(%)	UA n(%)	MI n(%)
MI	7(6.0)	113(87.6)	28(18.7)	92(95.8)
UA	110(94.0)	16(12.4)	122(81.3)	4(4.2)

Table 4: The diagnostic value of troponin T assay at different cut-off values

Troponin T cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Elecsys (≥0.03ng/mL)	94.17	87.30	87.60	94.02
AMI ROC (≥0.1ng/mL)	76.67	96.83	95.83	81.33

PPV: Positive predictive value NPV: Negative predictive value

Discussion

Myocardial infarction (MI) is the leading killer disease worldwide with increasing yearly mortality rate. It is previously predominant in developed countries, but the current scenario shows that it is now more common in developing countries (White and Chew, 2008). The annual incidence of NSTEMI is higher than STEMI and its diagnosis is more difficult to establish (Bassand *et.al.,* 2007).Similar findings were noted in our study (N=246) with 74.2% NSTEMI and 25.8% STEMI. In view of the increasing trend of mortality, early diagnosis and stratification of MI is very important in order to instill timely and specific treatment.

For early diagnosis of AMI cardiac troponin is the preferred biomarker. Recommendations from European Society of Cardiology (ESC), American College of Cardiology (ACCF) and World Heart Federation (WHF) task forces mandated that cardiac troponins are the biochemical gold standard for the diagnosis of myocardial necrosis. Based on the "universal MI" definition, AMI should be diagnosed in the presence of an increasing and /or decreasing pattern of cardiac troponin if there are symptoms of myocardial ischemia or ECG changes indicative of ischemia. However an increase cardiac troponin value is not synonymous with MI and it could occur in many other conditions associated with myocardial damage (Katus *et al.*, 2012).

In this study, the diagnostic value of troponin T assay at two levels of 0.03ng/mL and 0.1ng/mL was evaluated and compared with the final diagnosis of AMI made by physicians who used troponin T as the gold standard. Analysis on the ROC curve showed that the optimal cut-off values used for the diagnosis of acute myocardial infarction by physicians were at 0.037ng/mL with area AUC of 0.9652. At this point, the sensitivity was 90.0% and specificity was 90.5%. The positive predictive value (PPV) and negative predictive value (NPV) were 87.60% and 94.02%, respectively. When comparison was made with the sensitivity and specificity quoted by the manufacturer, the specificity was almost similar (87% vs 87.3%) and sensitivity found in this study was lower (97% vs 94.17%). The differences in the sensitivity and specificity could be related to the time blood sample was taken. Reichlin *et al.* (2009) reported that the time of patient's presentation to the hospital and the time blood sample was taken could be the cause for

the discrepancy. Low sensitivity at the time of the patient's presentation could be due to the delayed increase in circulating levels of troponins.

Study done by Apple and Murakami (2005) reported that the cut-off value of ≥0.03 ng/mL for third generation troponin T assay with an imprecision of ≤10% is meant for the diagnosis of myocardial injury irrespective of its mechanism and is not exclusively for the diagnosis of myocardial infarction. Other studies concluded that value ≥0.03 ng/mL is the cut-off used for the diagnosis of AMI (Aakre *et al.*, 2010; Januzzi Jr *et al.*, 2010). In this study, the optimal cut-off value of 0.037ng/mL was found to be the value for diagnosing AMI. However there was a trade off in sensitivity when higher cut-off value was used and a trade off in specificity when a lower cut-off value was used.

This study showed that at the cut-off value of troponin T ≥ 0.1ng/mL, the sensitivity was only 76.67% but the specificity was 96.83% with NPV of 81.33% and PPV of 95.83%. This cut-off value is more specific for the diagnosis of MI. Many other studies have also reported that cardiac troponin T cut-off value of ≥ 0.1ng/ml is the optimized value for the diagnosis of acute myocardial infarction by ROC analysis (Muller-Bardorff *et al.*, 1997; Klein *et al.*, 1998; Apple *et al.*, 2002).

Despite the excellent sensitivity and specificity of the assay for diagnosing acute myocardial infarction in this group of patients, the major limitation of this third generation assay was the relatively low sensitivity in detecting cardiac injury in patients who presented early to the hospital following the symptoms of MI. This resulted in delayed diagnosis of AMI among these patients leading to increase in complications (Reichlin, *et al.*, 2009). A new rapid assay which is highly sensitive is urgently needed. Currently with the introduction of high sensitive cardiac troponin T (hs-Trop T) assay, the diagnosis of AMI can be made within 2-3 hours after the onset of chest pain. This is of paramount important in the management of patients with AMI. Early markers of MI such as myoglobin and creatine kinase MB would be of no use in the diagnostic laboratories that is capable of utilizing troponin T.

Conclusion

Early diagnosis of AMI is critical in order to avoid serious consequences in morbidity and mortality. In Hospital USM the best cut-off point of troponin T in the diagnosis of AMI was ≥ 0.03 ng/ml. However the calculated cut-off value of troponin T for our patients was 0.037ng/ml with an area under curve of 0.9652. At this point the sensitivity and specificity were 90.0% and 90.5%, respectively. Even with this, the interpretation of the troponin T value should always be matched with the clinical findings for the final diagnosis of AMI.

References

Apple, F.S., Murakami, M.M. (2005*).* The diagnostic utility of cardiac biomarkers in detecting myocardial infarction*. Clinical Cornerstone,* 7; S25-S30.

Apple, F.S., Wu, A.H.B., Jaffe, A.S. (2002). European Society of Cardiology and American College of Cardiology guidelines for redefinition of myocardial infarction: how to use existing assays clinically and for clinical trials. *American Heart Journal,* 144; 981-986.

Aakre, K., Landaas, S., Hagve, T. (2010). Use of troponin analysis in Norwegian hospitals. *Tidsskr Nor Laegeforen,* 130; 278-281.

Babuin, L., Jaffe, A.S. (2005). Troponin: the biomarker of choice for the detection of cardiac injury. *CMAJ,* 173; 1191-1202.

Bassand, J-P., Hamm, C.W., Ardissino, D., Boersma, E., Budaj, A., Fernandez-Aviles, F., Fox, K., Hasdai, D., Ohman, E.M., Wallentin, L., Wijns, W. (2007). Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *European Heart Journal,* 28; 1598-1660.

Boersma, E., Mercado, N., Poldermans, D., Gardien, M., Vos, J., Simoons, M.L. (2003). Acute myocardial infarction. *The Lancet,* 361; 847-858.

Jaffe, A.S., Babuin, L., Apple, F.S. (2006). Biomarkers in acute cardiac disease: The present and the future. *Journal of the American College of Cardiology,* 48; 1-11.

Januzzi Jr, J.L., Bamberg, F., Lee, H., Truong, Q.A., Nichols, J.H., Karakas, M., Mohammed, A.A., Schlett, C.L., Nagurney, J.T., Hoffmann, U. (2010). High-sensitivity troponin T

concentrations in acute chest pain patients evaluated with cardiac computed tomography. *Circulation,* 121; 1227-1234.

Katus, H.A., Giannitsi, E., Jaffe, A.S. (2012). Interpreting changes in troponin - clinical judgment is essential. *Clinical Chemistry,* 58; 39-43.

Klein, G., Kampmann, M., Baum, H., Rauscher, T., Vukovic, T., Hallermayer, K., Rehner, H., Müller-Bardorff, M., Katus, H.A. (1998). *Clinical performance of the new cardiac markers troponin T and CK-MB on the Elecsys 2010. A multicentre evaluation. Wiener Klinische Wochenschrift,* 110; 40.

Muller-Bardorff, M., Hallermayer, K., Schroder, A., Ebert, C., Borgya, A., Gerhardt, W., Remppis, A., Zehelein, J., Katus, H.A. (1997). Improved troponin T ELISA specific for cardiac troponin T isoform: assay development and analytical and clinical validation. *Clinical Chemistry,* 43(3); 458-466.

Montorsi, P., Villa, M. Dessanai, M.A. (2009). Temporal profile of protein release in myocardial infarction. *Heart and Metabolism,* 43; 31-35.

Reichlin, T., Hochholzer, W., Bassetti, S., Steuer, S., Stelzig, C., Hartwiger, S., Biedert, S., Schaub, N., Buerge, C., Potocki, M. (2009). Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. The *New England Journal of Medicine,* 361; 858-867.

Thygesen, A.J., White, H.D. (2007). Joint ESC/ACCF/AHA/WHF task force for redefinition of myocardial infarction. Universal definition of myocardial infarction. *European Heart Journal,* 28; 2525-2538.

White, H.D., Chew, D.P. (2008). Acute myocardial infarction. *The Lancet,* 372; 570-584.