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The synergistic role of CKMB mass and high sensitivity Troponin T in the diagnosis of Acute Coronary Syndrome

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Abstract

Aim: To determine the synergistic role of CKMB mass (CKMBM) and high sensitivity Troponin T (hs-cTnT) in the diagnosis of Acute Coronary Syndrome (ACS).

Study Design: This was a cross-sectional study comprising of 140 individuals out of which 90 were cases and 50 healthy controls. The study was carried out in a tertiary care hospital between July 2014 to June 2015.

Materials and Method: On the basis of clinical history and 12 lead electrocardiogram initial diagnosis of acute coronary syndrome was made in the cases. High sensitivity troponin T and CKMB mass was measured in all the individuals.

Results: The sensitivity, specificity, positive and negative predictive value is 80.3%, 86.2%, 92.4% and 67.5% in case of CKMBM, while it is 98.3%, 65.5%, 85.7% and 95% in case of hs-cTnT, while the area under curve in case of CKMBM is 0.832 and in case of hs-cTnT is 0.819.

Conclusions: Thus, we have concluded that hs-cTnT and CKMBM correlate well in the diagnosis of ACS. But hs-cTnT can detect false positive cases which can be avoided by using CKMBM along with hs-cTnT in the diagnosis of ACS.

Keywords: Acute coronary syndrome, High sensitivity troponin T, CKMB mass, Sensitivity, Specificity

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Introduction

Myocardial ischemia ranges from ST-segment elevation myocardial infarction (STEMI) to non–ST-segment elevation myocardial infarction (NSTEMI) or unstable angina. Diagnosing myocardial infarction is a great challenge, the advent of testing for cardiac biomarkers, such as creatine kinase (CK-MB), and the troponin has facilitated this process. Characteristically an ideal cardiac biomarker should be sensitive and must have high specificity to the cardiac tissue. Cardiac troponin is the preferred marker for diagnosing myocardial damage but conventional cardiac troponin assays have low sensitivity during the initial few hours after the onset of chest pain; hence, the diagnosis of AMI is challenging.[1] Recently newer high sensitivity assays like Troponin T hs (hs-cTnT) are being used, which has improved the identification of patients with AMI presenting in the first 3 hours following the onset of symptoms. The hs-cTnT assays by definition measure cardiac troponin with adequate precision in majority of normal healthy subjects and its improved sensitivity may facilitate early diagnosis of AMI.[2] A variety of clinical conditions other than myocardial infarction may be associated with elevated cardiac hs-cTnT levels; these include acute pulmonary embolism, renal failure, acute or severe heart failure, sepsis/ critically ill patients, acute pericarditis, hypovolemia, cerebrovascular accidents, tachyarrythmias, myocardial contusion.[3,4] National Academy of Clinical Biochemistry (NACB) Laboratory Medicine practice has stated that CK-MB mass is an acceptable substitute when troponin is not available and CK-MB mass is far superior to CK-MB enzyme activity in its analytical and diagnostic performance.[5-8] As compared to CKMB activity, CKMB mass is measured in terms of its protein concentration. A recent study stated that high values of CK-MB activity were due to presence of atypical CK and thus could give falsely high results. Hence, CK-MB mass is a better biochemical parameter in case of acute coronary syndrome.[9] Thus, this study was undertaken to evaluate the performance of hs-cTnT and CKMB mass in patients of cardiac and non cardiac diseases and to check the significance in case and control group.

Materials and Method

This study consisted of 140 individuals between the age group of 30 to 80 years out of which 50 were healthy controls while 90 were cases, admitted to the emergency department and the cardiac intensive care unit of a tertiary care hospital within 6 hours of signs and symptoms of acute coronary syndrome. After taking a detailed clinical history, all the patients underwent a 12-lead electrocardiogram (ECG) recording on admission and a second 12-lead ECG after 6 hours. 61 out of the 90 patients who had acute chest pain and evidence of myocardial ischemia [their high sensitive Trop T was <100ng/L but more than 14ng/L in initial 6 hrs of presentation and rose by 100% after 6-12 hours of first estimation) were included in group 1 (cardiac diseases)], while 29 out of the 90 patients who had acute chest pain, but no subsequent evidence of

cardiac involvement (their hs-cTnT was <100ng/L but more than 14ng/L and did not have significant rise after 6-12 hours of first estimation) were included in group 2 (Non cardiac diseases). As a control (group 3) 50 normal individuals coming for routine checkup were taken. CK-MB mass level of more than 10ng/mL is indicative of myocardial infarction.[10]

Study Design: A cross sectional study was designed to select serum samples from these patients on admission (within 6 hours). Blood was collected from all the enrolled patients within 1 hr of admission, after collection blood was centrifuged and serum was separated and hs-cTnT and CKMB mass were measured from the serum, quantitatively using ECLIA (electro chemiluminescence immunoassay) based on electro chemiluminescence technology, sandwich principle. (Cobas e411, Roche, Mannheim, Germany)

Statistical analysis: Statistical analysis was done using demographic data presentation of subjects and distribution of CKMB mass levels in different study groups. Unpaired t test was employed to show significance of CKMB mass levels between different groups. The Sensitivity, specificity and Receiver operating characteristic curve (ROC curve) for CKMB mass and hs-cTnT were obtained and compared using Medcalc version 12.5.0. P values of less than 0.05 were considered to indicate statistical significance.

Results

The common age group of 140 patients are being enrolled is between 30 – 80 years of which 61 patients were from cardiac diseases having ischemic chest pain (34 patients with ST segment elevation, 27 patients without ST segment elevation which included patients with ST depression) with a mean age of 58.61±13.17. Among 61 patients from cardiac diseases had a mean age of 58.13±14.08 and 51 individuals were males. Whereas 29 patients from the non cardiac disease group had a mean age of 60.52±11.11 and 15 were males. The control group consisting 50 individuals had a mean age group of 55.50±10.92 and 31 individuals were males. The unpaired t test showed t = -1.551, degree of freedom = 138 and two tailed probability (P) = 0.1231. This showed that there was no significant difference between these age groups. Among all individuals, 97 were males and 43 were females. [Table 1] [Fig. 1]

Table 1: **Proportions of patients of cardiac diseases, non-cardiac diseases and controls**

Age in Years	Cardiac Cases (%)	Non Cardiac Cases (%)	Controls (%)	Total (%)
31-40	7 (5)	1(0.7)	2(1.4)	10(7.1)
41-50	6(4.3)	5(3.6)	17 (12.1)	28(20)
51-60	18(12.9)	7(5)	15(10.7)	40(28.6)
61-70	15(10.7)	11(7.9)	10 (7.1)	36(25.7)
71-80	15(10.7)	5(3.6)	6 (4.3)	26(18.6)
Total (%)	61(43.6)	29(20.7)	50(35.7)	140(100)

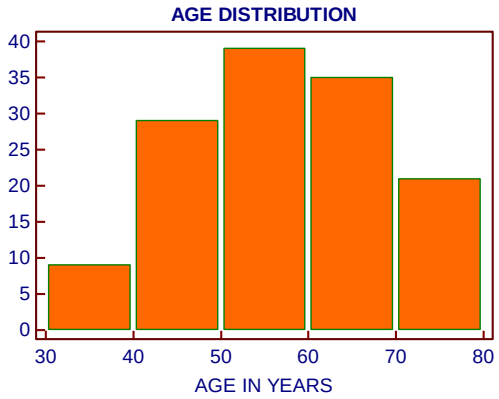

Fig. 1: Age distribution of study group

To find out whether there was any correlation of serum CKMB mass levels in between diseased patients and control group, unpaired 't' test was performed which showed that CK-MB mass levels were much higher in cases as compared to controls with Two tailed probability (P) of 0.0245. This showed that there was significant difference in values of CKMB mass between these two groups. [Table 2]

Table 2: Comparison of serum CKMB mass levels between cases and controls

Variables	Cases	Controls
Sample size	90	50
Mean value(ng/mL)	17.73	4.16
Standard error of mean	2.40	0.13
95% Confidence interval	12.96 to 22.50	3.90 to 4.41
t value	-4.205	
Degree of Freedom	138.0	
P value	P = <0.0001	

Table 3: Comparison of serum CKMB mass levels between cardiac and non-cardiac cases

Variables	Cardiac cases	Non cardiac cases
Sample size	61	29
Mean value(ng/mL)	22.47	7.76
Standard error of mean	3.37	0.54
95% Confidence interval	15.72 to 29.21	6.65 to 8.86
t value	-2.989	
Degree of Freedom	88.0	
P value	P = 0.0036	

When unpaired t test was performed between cardiac and non cardiac cases, the value P = 0.0036 suggested that levels of CKMB mass in patients of cardiac diseases were statistically significantly higher compared to patients of non cardiac diseases. [Table 3]

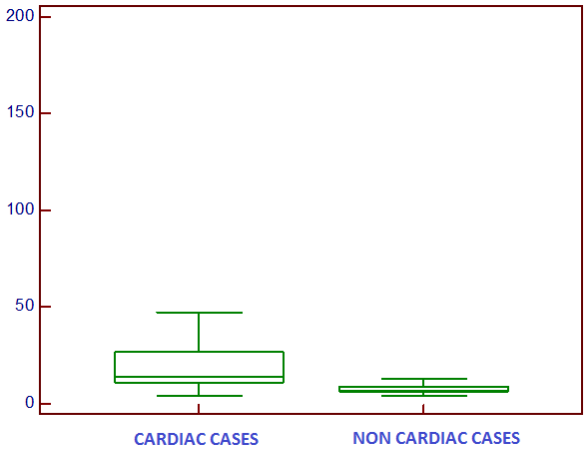

Fig. 2: Box and whisker plot showing comparison of CKMB mass levels between cardiac and non cardiac cases

In order to check the performance of hs-cTnT and CKMB mass for rule-in and rule-out of cardiac and non cardiac patients, we obtained ROC curves, from which we calculated sensitivities, specificities, positive and negative predictive values and likelihood ratios. Finally, we compared the area under curve (AUC) of the ROC curves. In case of CKMB mass in initial 6 hours, the AUC was 0.832(P<0.001) while in case of hs-cTnT in initial 6 hours the same was 0.819 (95% CI: 0.709 to 0.930; P<0.001). The cut off for CKMB mass was considered as >10 ng/mL which was obtained from ROC curve (AUC 0.832; 95% CI: 0.751 to 0.914; P<0.001).

Table 4: Sensitivity, Specificity, Positive Predictive Valve (PPV), Negative Predictive Value (NPV), Positive likelihood ratio(PLR), Negative likelihood ratio (NLR) and Area Under the Curve (AUC) of CKMB mass and hs-cTnT during initial 6 hours of presentation at the Optimum Cut-off Value Obtained From the ROC taking significant rise in hs-cTnT as standard marker

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	PLR (%)	NLR (%)	Area Under Curve
CKMB(ng/mL)	80.3	86.2	92.4	67.5	5.82	2.85	0.832
hs-cTnT (ng/L)	98.3	65.5	85.7	95	0.23	0.0025	0.819

The statistical data for CKMB mass and hs-cTnT are posted in Table 4. Sensitivity (98.3%) and negative predictive value (95%) was higher for hs-cTnT. CKMB mass, however, had higher specificity (86.2%), positive Likelihood Ratio (5.82), and positive predictive value (92.4%). The ROC curves were comparable as depicted in Fig. 3.

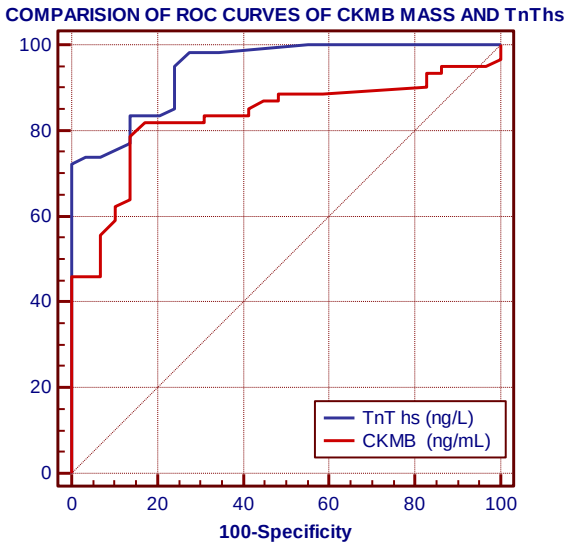

Fig. 3: Comparison of ROC curves of CKMB mass and hs-cTnT

Discussion

In this study, we compared the diagnostic utility of hs-cTnT with CKMB mass assay, in the evaluation of patients with cardiac and non cardiac diseases. The advantage of introducing hs-cTnT assay is that it causes an increase in the number of diagnosis of acute myocardial infarction (AMI) but the drawback is that sometimes it may be positive in non AMI cases. Adoption of the European Society of Cardiology /American College of Cardiology redefinition of MI with the use of the 99th percentile value as cutoff ultimately has increased the frequency of AMI diagnosis.[11] With a decrease in the diagnostic cutoff by implementing more sensitive and precise assays, sensitivity can be increased but specificity decreases owing to detection of more acute, subacute, and chronic cardiac diseases not related to ACS.[12] We evaluated the diagnostic performance of the CKMB mass assay at the cut-off of 10 ng/ml with the diagnostic performance of more sensitive and precise hs-cTnT assay at the 99th percentile cutoff (14 ng/L) in cases of cardiac and non cardiac diseases.

A study conducted by Reddy et al. in 2004, stated that conventional troponin T is more specific than CKMB mass in the diagnosis of AMI, but in our study since we have used hs-cTnT instead of conventional Troponin T its specificity is lower as compared to the latter. This probably is because the fundamental feature of diagnostic tests is a linkage between sensitivity and specificity which produces a relatively large decrease in specificity for a small gain in sensitivity.[13] Hence by using hs-cTnT we have increased the sensitivity and negative predictive value as compared to conventional troponin T and the drawback of decrease in specificity and positive predictive value was improved by using CKMB mass and could lead to an overall increase in the accuracy of diagnosis.

Reichlin T et al.[14] conducted a study of different cardiac troponins, CKMB and myoglobin in patients with recent onset of chest pain and other symptoms suggestive of acute coronary syndrome. The area under curve (AUC) for Roche hs-cTnT was 0.92 (95% CI: 0.87 to 0.97); specificity was 80% and positive predictive value was 50%. The AUC for CK-MB was 0.80 (95% CI: 0.72 to 0.88) and the AUC for myoglobin was 0.79 (95% CI, 0.69 to 0.89). The AUC for Roche hs-cTnT in case of unstable angina was 0.76 (95% CI: 0.71 to 0.81). While in our study the AUC for Roche hs-cTnT was 0.819 (95% CI: 0.709 to 0.930), specificity was 65.5% and positive predictive value was 85.7%. In case of CKMB mass the AUC was 0.832(95% CI: 0.751 to 0.914); specificity was 86.2% and positive predictive value was 92.4%. Therefore although in our study the specificity of hs-cTnT was low this limitation was overcome by using CKMB mass as an adjuvant whose specificity was higher. Furthermore the positive predictive value of hs-cTnT was higher in our study as compared to the study conducted by Reichlin et.al.

In a study conducted by Giannitsis et al[15] the baseline hs-cTnT using 99th percentile cut off 14 ng/L, the sensitivity was 61.54%, specificity was 77.42%, PPV was 69.57% and NPV was 70.59%. While in follow up samples within 3 hours, the sensitivity, specificity, PPV and NPV was 84.62%, 57.14%, 78.57% and 66.67% respectively and in follow up samples within 6 hours the corresponding values were 100%, 70.97%, 73.53% and 100% respectively. Whereas in case of our study, the corresponding values for 0-6 hours hs-cTnT were 98.3%, 65.5%, 85.7% and 95% respectively, as also in our study, the higher analytical sensitivity of hs-cTnT resulted in a larger rate of MI diagnosis among those cases classified as non MI compared with the CKMB mass assay, thereby—and not unexpectedly— lowering the diagnostic specificity. However, when hs-cTnT is combined with another specific cardiac biomarker like CKMB mass, the overall outcome can be improved.

In a similar study Aldous et al.[16] compared hs-cTnT and contemporary troponin assays in 332 patients having chest pain suggestive of AMI. For baseline hs-cTnT using 99th percentile cut off of 14 ng/L, the sensitivity was 83.6%, specificity was 83.8%, PPV was 71.9% and NPV was 91.2%. Whereas in case of our study, the corresponding values for baseline hs-cTnT were 98.3%, 65.5%, 85.7% and 95%. It is obvious that sensitivity, PPV and NPV are high in our study although specificity was lower. They compared hs-cTnT with conventional cTnT, for which using 99th percentile cut off of 0.01 μg/L, the sensitivity was 62.7%, specificity was 95.5%, PPV was 87.3% and NPV was 83.8%. While in case of our study using CKMB mass, the sensitivity was 80.3%, specificity was 86.2%, PPV was 92.4% and NPV was 67.5%. Specificity and sensitivity of cTnT were the highest and lowest, respectively, but CKMB mass had the highest PPV and PLR.

There are concerns regarding reduced specificity in assays with higher analytical sensitivity and the inherent risk put to patients who undergo invasive investigations and potent treatments who are then discovered to have 'falsely' elevated biomarkers. Thus with increase in analytical sensitivity the specificity of a biomarker is compromised. However, the gain in sensitivity may be particularly important in patients with a short duration from symptom onset to admission. A negative hs-cTnT test has a high negative predictive value, and may thus serve as an exclusionary test early in the diagnostic process. Thus the overall performance or accuracy for the diagnosis of AMI can be improved by using CKMB mass as an adjuvant along with hs-cTnT which has higher specificity and positive predictive value.

Conclusion

From this study it was concluded that hs-cTnT is sensitive enough to diagnose acute coronary syndrome and CKMB mass levels correlate well with it. hs-cTnT can be used to detect early and minimal myocardial cell injury in case of acute myocardial infarction. However, by employing hs-cTnT the chances of detecting false positive cases increases, which can be improved using CKMB mass. So, an added value by a specific marker CKMB mass would help in the decision making power of myocardial ischemia and early intervention. This additive information of using both biomarkers may be significant and thus the combined use of these two biomarkers in clinical practice is suggested.

Limitations

We noted the following limitations of our study. We cannot exclude the possibility that patients admitted to a chest pain unit represent a more selected population than patients admitted to an emergency department. Therefore, our data may not be generalized for other settings. Nevertheless, we believe that serial sampling and concomitant use of CKMB mass or other specific markers will increase clinical specificity and thus the usefulness of hs-cTnT in less-selected emergency populations.

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References

1. McCann CJ, Glover BM, Menown IB, Moore MJ, McEneny J, Owens CG, et al. Novel biomarkers in early diagnosis of acute myocardial infarction compared with cardiac troponin T. Eur Heart J 2008;29:2843-50.
2. Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. Clin Chem 2009;55:1303–6.
3. Jeremias A, Gibson CM. Narrative review: Alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. Ann Int Med. 2005;142:786-792.
4. Roongsritong C, Warraich I, Bradley C. Common causes of troponin elevations in the absence of acute myocardial infarction: Incidence and clinical significance. Chest. 2004;125:1877-1884.
5. Apple FS,Jesse RL, Newby LK, Wu AH, Christensn RH. National Academy of Clinical Biochemistry and IFCC committee for Standardization of markers of cardiac damage Laboratory Medicine Guidelines: Analytical issues for biochemical markers of myocardial infarctions. Clinical Chemistry 2007;53(4):547-551.
6. Santos ES, Baltar VT, Pereira MP, Minuzzo L, Timerman A, Avezum A. Comparison between cardiac troponin I and CK-MB mass in myocardial infarction without st elevation. Arquivos Brasileiros de Cardiologia 2011;96(3):179-187.
7. Christenson RH, Vaidya H, Landt Y, Bauer RS, Green SF, Apple FA, Jacob A, Magneson GR, Naq S, Wu AH, Azzazy HM. Standardization of Creatine Kinase MB mass assays: The use of Recombinant CKMB as a reference material. Clinical Chemistry 1999;45(9):1414-1423.
8. Wu AH, Gornet TG, Harker CC, Chen HL. Role of Rapid immunoassays for urgent (Stat) Determinations of Creatine Kinase Isoenzyme MB. Clinical Chemistry 1989;35(8):1752-1756.
9. Fleming JJ, Janardhan HP, Jose A, Selvakumar R. Anomalous Activity Measurements of Creatine (Phospho) Kinase, CK-MB Isoenzyme in Indian Patients in the Diagnosis of Acute Coronary Syndrome. Indian Journal of Clinical Biochemistry 2011;26(1): 32-40.
10. J.Wallach. Interpretation of Diagnostic Tests. 8th edition Lippincott Williams and Wilkins; 2007:126-128.
11. Kavsak PA, MacRae AR, Lustig V, Bhargava R, Vandersluis R, Palomaki GE, et al. The impact of the ESC/ACC redefinition of myocardial infarction and new sensitive troponin assays on the frequency of acute myocardial infarction. Am Heart J 2006;152:118–25.
12. Schulz O, Paul-Walter C, Lehmann M, Abraham K, Berghöfer G, Schimke I, Jaffe AS. Usefulness of detectable levels of troponin, below the 99th percentile of the normal range, as a clue to the presence of underlying coronary artery disease. Am J Cardiol 2007;100:764 – 769.
13. Riegelman RK, Hirsch RP. Questions to ask in studying a study and testing a test: how to read the medical literature. 2nd ed. Boston, Little Brown; 1989. p. 75-77.
14. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–867.
15. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254–261.
16. Aldous SJ, Florkowski CM, Crozier IG, Elliott J, George P, Lainchbury JG. Comparison of high sensitivity and contemporary troponin assays for the early detection of acute myocardial infarction in the emergency department. Ann Clin Biochem. 2011 May;48(Pt 3):241-8.