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Diagnostic approach in prediction and diagnosis of Myocardial infarction: High Sensitive TroponinI vs Conventional troponin I assay

Dr.Jyothi Allamsette[1], Suneetha Padala[2]
1Consultant Biochemist, 2Senior Biochemist
Department of Laboratory Medicine, Care Hospitals, Hyderabad
Corresponding Author: Dr.Jyothi

Abstract:
Recently high sensitive cardiac troponin I assays permit use of lower thresholds for the early diagnosis of myocardial infarction. The objective of this study was to compare diagnostic performance of a new high sensitive troponin I to that of conventional troponin I in subjects with chest pain admitted to emergency department of care hospitals. Both assays were analyzed on Beckman Coulter DxC 860i fully automated analyzer. The precision, accuracy , ROC analysis, Correlation and inter-rater reliability of the assay were evaluated. The diagnostic performance of high sensitive cardiac troponin assay was excellent and these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of a chest pain.

Keywords: *High sensitive troponin I, Myocardial Infarction, Inter-Rater reliability*

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I. Introduction

Acute Myocardial Infarction (AMI) is one of the leading cause of death and disability worldwide. Approximately 10% of all the patients seeking medical attention at the emergency department (ED) report chest discomfort, a complaint that reflects many potential causes ,including AMI[1] .Rapid identification of patients with AMI is of profound clinical importance for fast initiation of medical treatment and management [2].In addition ,rapid rule out of patients without AMI can overcome prolonged patient anxiety, unnecessary resource use and overcrowding in the emergency department [3,4].

Measurement of cardiac troponins (Ctn) in patient plasma is central for diagnosis of patients with acute coronary syndrome, complementing with clinical evaluation and the interpretation of ECG. With advances in technology, a new era in troponin assays is approaching. Previous generation Troponin assays have been used as diagnostic and pro diagnostic markers in acute coronary syndrome patients and for risk stratification to guide triage decisions and helps in treatment selection [5.]High Senstive Immunoassays have been developed that can very precisely detect slightly elevated and rising plasma concentrations of Cardiac Tn very early after onset of clinical symptoms.

An increased cardiac troponin concentration is defined as a value exceeding the 99 th percentile (with optimal precision defined by total CV <10%) of a normal population. This discriminatory 99th percentile is designated as the decision level for the diagnosis of myocardial infarction(MI) and must be determined by for each specific assay with appropriate quality control in each laboratory.

High sensitive assays for cardiac troponin must fulfill the criteria required by the International Federation For Clinical Chemistry (IFCC) of 10% total imprecision at the 99 th percentile of a reference normal population and detection of Cardiac Tn in at least 50% individuals belonging to that of population [6].

The new assay is precise ,having small CV levels even at the 99 % in reference population[7,8] .The objective of current study is to evaluate the diagnostic performance of hs TnI for the early diagnosis of acute myocardial infarcts.

II. Materials & Methods

This is a prospective, observational study, including 50 patients with chest pain admitted to the emergency department of a tertiary hospital, between July and October 2019.

All patients with chest pain undergoing ECG or Coronary angiogram were included. Biochemical analysis of high sensitive Troponin I and conventional Troponin I were done in study population on Beckman Coulter DXC 860i fully automated analyzer using conventional Tn I and hsTn I Beckman Kits. The

measurement range of this one step Chemi-luminescence immunoassay extends from 2.3 to 27,027 pg/ml for hsTnI and 0.01 to 100 ng/ml for TnI respectively as per manufacturer claim.

The performance characteristics of hsTnI were evaluated by performing inter and intra assay precision checks, internal and external quality control and correlation by linear regression analysis. The accuracy of hsTnI was assessed by Receiver Operating Characteristics (ROC) curve. Clinical agreement analysis was carried out by using Cohen's Kappa calculation.

III. Results and Discussion

Statistical Analysis:

Continuous variables are presented as mean ±SD and categorical variables are expressed as numbers and percentages. The diagnostic performance of hs Troponin I and Troponin I were evaluated by using concentrations obtained in the study population. Correlation study was carried out between two continuous variables by using Pearson's correlation coefficient. Receiver operating characteristic curves (ROC) were constructed to assess the sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV) and all data presented with their 95% confidence intervals (95% CIS) throughout the concentrations of hsTnI and TnI to compare the accuracy of these markers in the diagnosis of cardiac disease. Clinical agreement analysis was done by using Cohen's Kappa statistics and percent agreement. Cohen's Kappa statistics measures inter-rater reliability. Statistical analysis was done by using Med Cal software version.

Results and discussion:

During this study period , a total of 50 subjects have been submitted to the emergency department with chest pain. Out of 50 subjects 56% of individuals were identified were with clinical suspicion of AMI.

Imprecision study results:

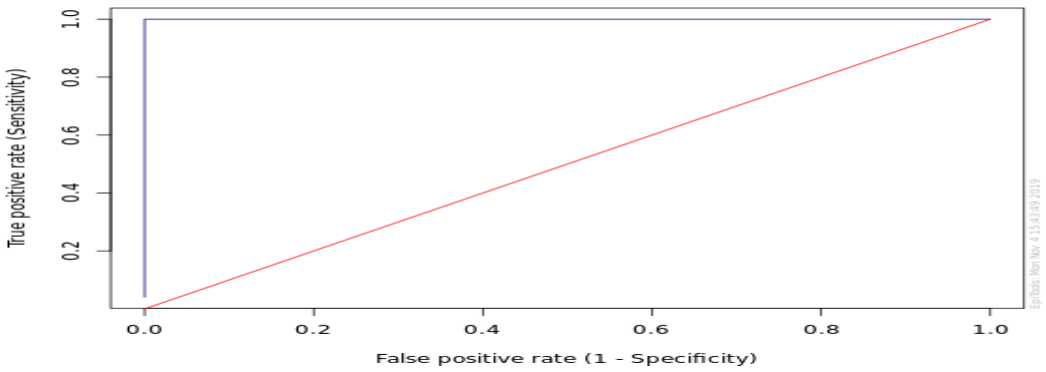
The total imprecision of hs Tn I was reported in table 1. The high sensitive Troponin I assay yielded a total CV <8% at all three Internal Quality Control levels.

Table 1:

	Mean (pg/mL)	**Total Imprecision SD (Pg/mL)**	**Total Imprecision (CV%)**
Within-Run (n=9)	1111.03	45.36	4.1
Between-Run (n= 9)	1119.47	44.71	4.0
Within Laboratory (Internal Quality Control) (n=9)	166.3	11.91	7.2

ROC Analysis (Accuracy Check):

Figure 1: ROC Analysis: Receiver Operating Curve for hs troponin I.



The ROC analysis for high sensitive troponin I for the study population are shown in figure 1. The area under the curve (AUC) for high sensitive troponin I was calculated and it shows 1. The area under the ROC curve was plotted as recommended by Delong et al[9].

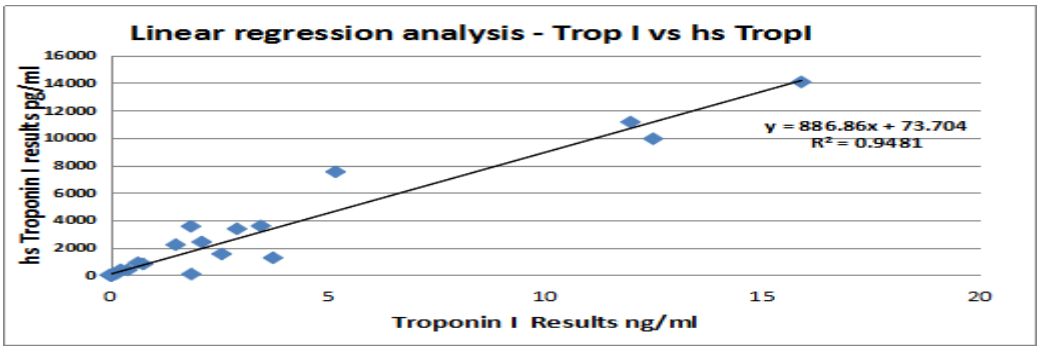
Table2 : Sensitivity and specificity analysis for Troponin-I and hs Troponin-I

	Troponin-I	hs Troponin-I
Sensitivity	92.6	100
Specificity	100	100
Positive Predictve Value	100	100
Negative Predictive Value	91.67	100
Accuracy	96	100
Cut-off	0.04	21.0

Linear Regression analysis:

Figure 2: Regression analysis and Pearson's correlation coefficient calculation between Troponin I and high sensitive troponin I

Correlation between troponin I and high sensitive troponin I shows good correlation and r value was 0.95 (Pearson: Y=886.86x + 73.704, R2=0.9481)



Clinical Agreement Analysis:

The positive and negative agreement between the Troponin I assay and the high sensitive troponin assay were calculated using data collected from 50 subjects. The positive and negative agreements are presented in the table 3 below.

Table 3: Clinical Agreement analysis between troponin I assay and hs troponin I assay

	Troponin I (Positive)	Troponin I (Negative)	Row Marginals
hs Troponin I (Positive)	26	4	30
Hs Troponin I (Negative)	2	24	26
Column Marginals	28	28	56

Calculation of Cohen's kappa is performed by using the following formula where Po represents actual observed agreement, and Pe represents chance agreement.

$$\text{Cohen's kappa } (\kappa) = \frac{Po-Pe}{1-Pe}$$

There are a number of statistics that have been used to measure amount of agreement between raters (inter-rater reliability). Use of correlation coefficients such as Pearson's r may be a poor reflection of the amount of agreement between raters resulting in extreme over or underestimates of the true level of rater agreement 10. Cohen's kappa (κ) is a robust statistic useful for either inter-rater or intra-rater reliability testing. Similar to correlation coefficients, it can range from -1 to +1, where 0 represents the amount of agreement that can be expected from random chance, and 1 represents perfect agreement between the raters. While kappa values below 0 are possible, a negative kappa represents agreement worse than expected or disagreement.

Table 4: Interpretation of Cohen's kappa

Value of Kappa	Level of Agreement	% of Data that are Reliable
0-0.20	None	0-4%
0.21-0.39	Minimal	4-15%
0.40-0.59	Weak	15-35%
0.60-0.79	Moderate	35-63%
0.80-0.90	Strong	64-81%
Above 0.90	Almost perfect	82-100%

Percent agreement (Po) is 0.89 while the kappa is 0.80 which falls into strong level of clinical agreement between troponin I and hs troponin I assay.

Finally, among unselected patients undergoing hs troponin I measurements on clinical indication hs troponin I concentration <LoD at presentation may facilitate the rule out of AMI, regardless of the etiology or ECG findings with an excellent diagnostic sensitivity. Sandoval Y et al11 also observed a similar outcome in rule out of AMI by using single hs troponin I concentration.

IV. Conclusion

In Conclusion, hs troponin I showed excellent diagnostic performance in terms of precision, accuracy, correlation and clinical outcome when compared to conventional troponin I assay. The above study suggests the adoption of high sensitive troponin I in clinical practice to rule in or rule out AMI.

The sensitivity of the hs Troponin I may also lead to further applications in future. The use of this biomarker in the early identification of silent heart disease or highly risk population may ultimately lead to improvement in the primary prevention of cardiac disease.

Limitations:

However the study has its limitations. This is a retrospective (hindering the blinded analysis) single-center study, with a small sample of patients, especially patients with AMI. We cannot exclude the possibility that better results might have been found with a larger sample.

Our study has some other limitations first we performed only a single measurement of hs troponin I. A second value could have provided more data as described in Collinson PO et al12 study which reported that a doubling in high sensitive troponin I concentration in 3 hrs of chest pain was associated with true diagnosis of AMI. We did not assess the effect of the sensitive troponin assays on clinical management.

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