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# DIRECT COMPARISON OF HIGH-SENSITIVITY CARDIAC TROPONIN I VERSUS CONVENTIONAL TROPONIN I FOR THE EARLY DIAGNOSIS OF NON-ST ELEVATION MYOCARDIAL INFARCTION

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**Contribution**

SS conceived the idea and designed study. ME and SK did data collection and manuscript writing. J did review. All authors contributed equally to the submitted manuscript.

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## ABSTRACT

**Objective:** To determine and compare the diagnostic value of high-sensitivity cardiac troponin I with conventional troponin I for the detection of non ST elevation acute myocardial Infarction (NSTEMI) in patients with chest pain.

**Methodology:** This is a cross sectional study done in two tertiary care hospitals Peshawar KPK from August 2016 to February 2017. Patients were enrolled according to the inclusion criteria of the study. In this study direct comparison of the two assays was done in making the diagnosis of NSTEMI in patients with acute chest pain and to assess the diagnostic utility of the assays used. The method used is Electro Chemiluminescene immunoassay "ECLIA" which is carried out on Elecsys and Cobase immunoassay analyzers (ROCHE Diagnostics) for conventional cardiac troponin I (cTnI) and The Architect STAT High troponin I (Abbott Diagnostic) for hs-cTnI.

**Results:** Sample size was calculated according to the kit used for detection of high-sensitivity troponin I and conventional troponin I sufficient for 100 samples. Therefore 86 patients sample size was selected and the rest of tests (14) were used for calibration and control. The study consisted of 86 patients with chest pain typical of acute coronary syndrome and ST-depression on electrocardiogram. The mean age of the patients was 59.21 +10.63 years. Of these 44 (51.1%) were females. There were 43 (50%) patients with positive history and 43 (50%) were with no history of ischemic heart disease. In this study 47(54.6%) patients were non-hypertensive, 43 (50%) were overweight, 5 (5.8%) were class 1 obese and only 1 (1.2%) was class 2 obese. About 48 were diagnosed as NSTEMI and 38 were diagnosed as unstable angina. The sensitivity of the cTnI for diagnosing NSTEMI was 60%, specificity was 89.1% with PPV of 82.7% and NPV of 72% and sensitivity of hs-cTnI for making diagnosis of NSTEMI was 94%, specificity was 92% with a PPV of 93.7% and NPV of 92.1%.

**Conclusion:** This study concludes that high- sensitivity cardiac troponin I assay has more diagnostic utility when compared with conventional troponin I assay.

**Key Words:** Myocardial infarction, Unstable angina, High-sensitivity troponin I assay, Conventional troponin I assay.

## INTRODUCTION

Myocardial infarction (MI) is the major cause of mortality and morbidity worldwide.[1] Myocardial infarction (MI) is defined as myocardial cell necrosis caused by prolonged myocardial ischemia.[2] According to the joint ESA/ACCF/ACCF Task Force in 2012,myocardial infarction is defined as symptoms of myocardial necrosis or ischemia accompanied by the detection of rise/ or fall of cardiac troponin with at least one value above the 99th percentile of the upper reference limit (URL) measured with a 10% co-efficient of variation.[3-5]

Acute coronary syndrome (ACS) is divided into two types,with ECG changes called ST-segment elevation myocardial infarction (STEMI) and with no electrocardiogram changes called non- ST-elevation myocardial infarction (NSTEMI) and unstable angina pectoris (UA)). To differentiate NSTEMI from unstable angina, cardiac markers like troponin I and troponin T are used.[6]

Cardiac markers like myoglobin,CK-MB and creatine kinase are non- specific and are also found in other muscular tissues. Cardiac troponin I and cardiac troponin T are cardiac specific and are only found in cardiac muscles.[7-9] According to the guidelines of American Heart Association, serial sampling and measurements of conventional cardiac troponin are recommended at the time of presentation and 3 to 6 hours after the onset of symptoms.[8,10-12] As a result of this, majority of the patients require prolonged hospital stay and evaluation before discharging from hospital. This leads to costly and unavoidable hospital admissions.[11-14]

In contrast to conventional troponin assays, high-sensitivity cardiac troponin assays determine a very low concentration of troponin I at presentation to the ED along with non- ischemic changes on ECG show the best prognostic ability in patients with suspected acute coronary syndrome (ACS) sensitivity troponin (hs-cTn) assays detect the concentration of the same protein which is detected by conventional assays but in a much lower concentration.[9,15-17]

Troponin concentrations above the 99th percentile of the upper reference limit (URL) measured with a 10% co-efficient of variation (CV) are the most sensitive and specific cardiac markers for myocardial infarction.[2,6,18] Conventional troponin (cTn) assays cannot detect 50% disease free individuals while high-sensitivity assays can detect 90% cases.[17]

According to the International Federation of Clinical Chemistry (IFFC),high- sensitivity cardiac troponin assays should measure cTn concentrations above the limit of detection in > 50% of healthy subjects with a co-efficient of variation of < 10% at the 99th percentile Whereas conventional troponin assays measure cTn above the limit of detection in >35% of healthy subjects with a co- efficient of variation between 10% and 20%.[19] High –sensitivity assays are more precise at the 99th percentile upper reference limit (URL), and measure with very high precision concentrations above the limit of detection of the assay.[19,20] With high-sensitivity assays the extra admission burden on ED have overcome because the troponin become detectable within 90 to 180 minutes of the myocardial injury.[21]

## METHODOLOGY

This cross-sectional study included patients with chest pain suggestive of ischemia from August 2016 to February 2017 presented to two tertiary care hospitals of Peshawar, KPK. Non-probability consecutive sampling was used.Inclusion criteria was patients with chest pain suggestive of ischemia, patients with ECG evidence of ST-depression, either sex, any age and willing to participate. Exclusion criteria was patients with ST-elevation on ECG, unable to provide informed consent and unwilling to participate.

Blood serum samples were simultaneously measured with both high-sensitivity cardiac troponin I assay and conventional troponin I assay. The hs-cTnI was measured through The Architect STAT High Troponin I (Abbott Diagnostics) with a cutoff value for males was 34 ng/ l and for females was 16 ng/l with a CV of 10%. The cTnI was measured with ROSHE Diagnostics, the cutoff value of which was 0.003 ng/ml with a CV ( co-efficient variation) of 10%.

All the data was recorded in a pre designed proforma and analyzed in SPSS version 20. Mean + S.D was calculated for continuous variables. Frequency and percentages were calculated for categorical variables. Test variables were categorical and compared by using chi square test $p < 0.05$ was taken as significant. The sensitivity, specificity, Positive Predictive value (PPV) and Negative Predictive Value (NVP) were determined by their specific formulas.

## RESULTS

Results are based on the findings obtained from 86 patients with chest pain typical of acute coronary syndrome (ACS) and ST-depression on electrocardiogram (ECG), using SPSS version 20. The mean age of the patients was 59.21 +10.63 years (range 40—90 years), and 44 (51.1%) were women and 42 (48.8%) were men. There was no difference in the past history of ischemic heart disease (IHD). There were 43 (50%) patients with positive history of IHD and 43 (50%) were with no history of IHD. In this study 47(54.6%) patients were non- hypertensive and 39(45.3%) were hypertensive. Among these 86 patients, 37(43%) had normal BMI, 43(50%) were overweight,5 (5.8%) were class 1 obese and only 1 (1.2%) was class 2 obese. The general characteristics of the patients are shown in table 1.

**Table 1: Baseline Variables of the Study Population (n=86)**

| Variables | | Frequency (percentage) |
|---|---|---|
| Age | All Subjects | 40----90 |
| Gender | Female | 44 (51.2%) |
| | Male | 42 (48.8%) |
| Blood Pressure | Non Hypertensive | 47 (54.5%) |
| | Hypertensive | 39 (45.3%) |
| Body Mass Index BMI(kg/m2) | Normal | 37 (43%) |
| | Overweight | 43 (50%) |
| History of Ischemic Heart Disease | Obesity Class I | 5 (5.8%) |
| | Obesity Class II | 1 (1.2%) |
| | Present | 43(50%) |
| | Absent | 43(50%) |

**Table 2: Single Table Analysis of hs-cTnI (n=86)**

| | Positive | Negative | Total |
|---|---|---|---|
| Positive | 45 | 3 | 48 |
| Negative | 3 | 35 | 38 |
| | 48 | 38 | 86 |

**Table 3: Statistical Analysis of hs-cTnI (n=86)**

| Parameters | Percentage |
|---|---|
| Sensitivity | 93.75% |
| Specificity | 92.11% |
| Positive Predictive Value | 93.75% |
| Negative Predictive Value | 92.11% |
| Diagnostic Accuracy | 93.20% |
| Positive Likelihood Ratio | 11.80% |
| Negative Likelihood Ratio | 6.79% |
| Chi-quare Test | 0.000 |

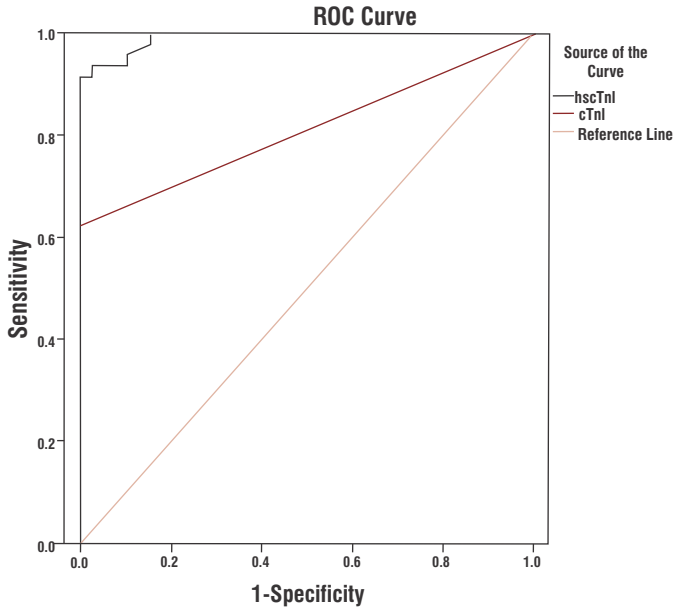
**Table 4: Statistical Analysis of cTnI (n=86)**

| Parameter | Percentage |
|---|---|
| Sensitivity | 60% |
| Specificity | 89.13% |
| Positive Predictive Value | 82.76% |
| Negative Predictive Value | 71.93% |
| Diagnostic Accuracy | 75.58% |
| Positive Likelihood Ratio | 5.52% |
| Negative Likelihood Ratio | 44.88% |

The cutoff value of The ROSHE Diagnostic System for cTnI was 0.003 ng/ml with a CV( co-efficient variation) of 10%. The sensitivity of the cTnI for diagnosing NSTEMI was 60%, specificity was 89.1% with PPV of 82.7% and NPV of 72%.The total false positive tests were 5 and 16 were false negative tests detected on cTnI. The true positive tests were 24 in number and true negative tests were 41 that are detected on cTnI as shown in the table 2.

The hs-cTnI was measured through The Architect STAT High Troponin I (Abbott Diagnostics) with a cutoff value for males was 34 ng/ l and for females was 16 ng/l with a CV of 10%. Statistical analysis show the sensitivity of hs-cTnI for making diagnosis of NSTEMI was 94%, specificity was 92% with a PPV of 93.7% and NPV of 92.1%. The total false positive tests were 3 and 3 false negative were detected on hs-cTnI. The total true positive tests were 45 in number and true negative tests were 35 in number as depicted in table 2.

**Figure1: Analysis of High-Sensitivity and Conventional Troponin I for the Detection of Non-ST Elevation Myocardial Infarction.**




Diagonal segments are produced by ties

## DISCUSSION

Troponin tests are advised to diagnose myocardial infarction (MI) and to rule out other similar conditions having similar signs and symptoms. Troponin I or troponin T, both tests can be performed but troponin I is more specific. Cardiac troponin I and troponin T are proteins found in cardiac muscle and are released into the blood after cardiac necrosis.[19]

Before 2009, there was no exact definition of a high-sensitivity assay but in 2012 the definition of high-sensitivity assays by experts is, "it should have a coefficient of variation (CV) of <10% at the 99th percentile value in the healthy population. To be classified as high-sensitivity assays, concentrations below the 99th percentile should be detectable above the assay's limit of detection for >50% of healthy individuals in the population of interest.".[22]

In the present study direct comparison of the two assays has been done in making the diagnosis of NSTEMI in patients with acute chest pain and to see the diagnostic utility of the assays used. The assays used are Electro Chemiluminescene immunoassay " ECLIA" which is used on Elecsys and Cobase immunoassay analyzers (ROSHE Diagnostics) for conventional cardiac troponin I (cTnI) and The Architect STAT High troponin I (Abbott Diagnostic) for hs-cTnI.

The cutoff value of The ROCHE Diagnostic System for cTnI was 0.003 ng/ml with a CV (co-efficient variation) of 10%. The sensitivity of the cTnI for diagnosing NSTEMI was 60% while the specificity was 89.1% with PPV of 82.7% and NPV of 72%. The total false positive tests were 5 and 16 were false negative tests detected on cTnI. The true positive tests were 24 in number and true negative tests were 41 that are detected on cTnI as shown in the table 2.

The hs-cTnI was measured through The Architect STAT High Troponin I (Abbott Diagnostics) with a cutoff value for males was 34 ng/ l and for females was 16 ng/l with a CV of 10%. Statistical analysis show the sensitivity of hs-cTnI for making diagnosis of NSTEMI was 94%, specificity was 92% with a PPV of 93.7% and NPV of 92.1%. The total false positive tests were 3 and 3 false negative were detected on hs-cTnI. The total true positive tests were 45 in number and true negative tests were 35 in number as depicted in table 2.

In the present study,significant difference is reported between hs-cTnI and cTnI (ROC AUC,0.991 versus 0.809) in the diagnosis of NSTEMI. Our study results are comparable to some extent to the study results of 23 and also to.[24]

Till Keller, Tanja Zeller enrolled 1818 patients consecutively with chest pain suggestive of acute myocardial infarction. By using the 99th percentile cut off, the sensitivity of hs-cTn I on admission was 82.3% and NPV was 94.7% while after 3 hours of admission, the sensitivity became 98.2% with 99.4% NPV. By using the LoD as a diagnostic threshold, the sensitivity and NPV were 100% with 35.3% specificity and this is because 74% of patients had hs-cTnI values above the LoD at the time of admission. There was no further improvement in the NPV even with different relative changes, so there was a safe rule out of MI.[25]

When compared with high sensitivity troponin I, the conventional troponin I (cTnI) assay also using the 99th percentile as a cut off value, had 79.4% sensitivity and 94.0% NPV on the time of admission. The sensitivity became 98.2% with 99.4% NPV. Using the LoD as a diagnostic threshold, the sensitivity was 87.4% with 96.0% NPV on admission and this is less than the NPV of hs-cTnI assay with using the LoD as a cut off value.[25]

In the present study, the sensitivity of hs-cTnI was 94% with 92% NPV at the time of admission and the sensitivity of cTnI was 60%

with 72 &% NPV at the time of admission. I did direct comparison of the both assays and took just one sample at the time of admission.

In another study, Yader Sandoval, Stephen Smith enrolled 1631 consecutive patients with chest pain suggestive of AMI, presented to the ED. Of the 1631 patients, 210 (12.9%) patients were diagnosed with MI by the use of cTnI, in these 210 patients, 71 (4.4%) were having T1MI and 139 (8.5%) were having T2MI and 279 (17.1%) patients were having myocardial injury. By using hs-cTnI, 170 (10.4%) patients were diagnosed with MI out of these patients, 68 (4.2%) had T1MI and 102 (6.3%) patients had T2MI and 245(15.0%) patients had myocardial injury.

Serial cTnI measurements at 0 and 3 h, the sensitivity was 93.5% with 98.7% NPV for AMI and at 6 h sensitivity was 98.3% with 99.6% NPV.

Serial hs-cTnI measurements at 0 and 3 h, the sensitivity were 95.4% with 99.4% NPV for MI whereas at 6 h sensitivity was 98.7% with 98.8% NPV.

They concluded that both the conventional troponin I assay as well as high- sensitivity troponin I assay were excellent in diagnosing AMI with the use of 99th percentile and serial measurements.[26]

While in this study, total 86 patients were enrolled with acute chest pain. Out of these 86 patients, 48 (56.0%) patients were diagnosed as NSTEMI with hs-cTnI and 29 (33.7%) patients were diagnosed as NSTEMI by using cTnI .Sensitivity of hs-cTnI at the time of admission was 94.0% with 92.0% NPV while sensitivity of cTnI at the time of admission was 60.0% with 72.0% NPV. So, in my study there was a gross difference between high sensitivity troponin assay and conventional assay. We conclude that high sensitivity troponin I assay is excellent in diagnosing AMI as compared to conventional troponin I assay.

Marie West Wood and Thea Van Asselt did a systemic review and cost- effectiveness analysis of the high-sensitivity troponin assay for the early diagnosis of AMI in patients presenting with acute chest pain. They concluded in their study that undetectable or immeasurable levels of cardiac troponins (below the LoD/LoB of the assay) on presentation to the emergency department, can only be measured by using the high-sensitivity troponin T and troponin I assays and it is sufficient to diagnose or rule out NSTEMI in patients presenting with acute chest pain and it decreases the unnecessary admission in the emergency department. Sensitivity of high-sensitive troponin I assay at the time of presentation and at the 99th percentile threshold was 80% and specificity was 93%.[27]

## LIMITATIONS

The limitations of the current study are that the sample size is too small. It should be large for more accurate and better results. The study should be multicentre. Limited duration of the study.

# CONCLUSION

This study concludes that high- sensitivity cardiac troponin I assay has more diagnostic utility when compared with conventional troponin I assay. High- sensitivity troponin I can detect the protein in a much lower concentration which conventional troponin I cannot detect at that concentration.

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