

New Cutoff for High Sensitivity Troponin to Better Risk Stratify Patients with Non-ST Elevated Myocardial Infarction

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Abstract

Background: The diagnosis of Non-ST Elevated Myocardial Infarction (NSTEMI) is dependent on elevation of high sensitivity troponin (Hs-troponin). The current cutoff point for Hs-troponin is highly sensitive but not specific for obstructive coronary artery disease (CAD). This study aims to determine the best cutoff point for diagnosing CAD in patients presented with NSTEMI. **Methods:** Our study included all patients admitted as NSTEMI that underwent coronary angiography (CAG). They were grouped into two groups: A and B. Group A has obstructive CAD of 70% or more stenosis and group B with non-obstructive CAD. Patients were assessed for their demographics, clinical history, laboratory and imaging results. Using SPSS version 22, the pooled cohort of patients were analyzed at significant level < 0.05 and the data were tested for significant correlations between two predetermined groups. **Results:** Group A comprised 87.6% of the patients and both groups had a median age of 53 years. In Group A, 91% were males, 54% diabetics, 54% hypertensives, and median Hs-troponin was 145 ng/L. While in group B, 88% were males, 39% diabetics, 60% hypertensives, and median Hs-troponin was 54 ng/L. There was significant correlation between the two groups in the percentage of diabetes and median troponin level ($p < 0.05$). A ROC curve has identified a level of 127 ng/dL as the best cutoff of Hs-troponin in detecting obstructive CAD ($p = 0.03$). Interestingly, 60% of patients in group B had alternative diagnoses. **Conclusion:** Hs-troponin is sensitive but less specific for obstructive CAD. However, increasing its cutoff value will improve its specificity.

Keywords

Non-Obstructive Myocardial Infarction, Cardiac Biomarkers, Coronary

1. Background

Acute coronary syndrome with normal or near normal coronary arteries, commonly known as Myocardial Infarction/Injury with Non-obstructive Coronary Arteries (MINOCA), can be caused by many etiologies like coronary disorders, myocardial disorders, or non-cardiac disorders [1] [2] [3]. These etiologies include: coronary spasm, microvascular dysfunction, myocarditis, hypertensive heart disease, stroke, sepsis, and pulmonary embolism [1] [4]. All these conditions result in rise of cardiac enzymes; thus, the challenge arises in making a decision whether the patient is suffering myocardial injury, ischemic infarction requiring further cardiac intervention [1]. These challenging situations have increased currently with the introduction of high sensitivity cardiac troponin assay in view of its low specificity [1]. In a review article by Pasupathy *et al.*, the prevalence of MINOCA was reported as 6%, ranging from 1% - 15%. Moreover, 14% of patients with acute myocardial infarction have been found to have non-obstructive coronary artery disease defined as coronary stenosis of less than 50%. Research has shown that two third of patients with MINOCA present as NSTEMI [1] [3].

Risk stratification in patients with NSTEMI is of extreme importance as VIRGO study found the prevalence of MINOCA is five times more in women than men and higher in patients with lower traditional cardiac risk factors. Another study showed that the prevalence of MINOCA is higher in younger patients as well [5] [6] [7] [8]. This has resulted in multiple risk scores being developed such as: Thrombolysis in Myocardial Infarction score, HEART score and Global Registry of Acute Coronary Events. These scores incorporate Hs-troponin as inherent factor included in the assessment of cardiovascular risks in addition to other clinical risk factors of coronary artery disease [4]. All these risk scores use the current cutoff value of Hs-troponin of 14 ng/dL which is sensitive, but lack specificity for myocardial infarction. The American College of Cardiology recently published an article suggesting that an absolute value of Hs-Troponin of 52 ng/dL is an indication to rule in acute myocardial injury [9]. Furthermore, the European Society of Cardiology recent 2020 guidelines have incorporated four confounders that result in rise of Hs-troponin: renal dysfunction, time to chest pain, age and gender [10].

The aim of this research is to better stratify patients by determining statically if a new cutoff value of Hs-troponin is of more significance than the current value of 14 ng/dL in identifying obstructive coronary artery disease in patients with NSTEMI.

2. Methods

This is a cohort of patients admitted between 1st of April 2018 through 31st of

March 2019 in Rashid hospital. The inclusion criteria were all patients who were above 18 years old, having documented diagnosis of NSTEMI, and underwent coronary angiography regardless of the result and management strategy. The sample size was calculated at 80% power with marginal error of 5%. According to the literature there is a 15% possibility of normal CAG in patients undergoing coronary angiography this will equate to a sample size of 15 patients per arm for paired T test comparing the two group means [1] [2] [3]. Data was collected using a structured questionnaire present in an excel spreadsheet that included: demographics (age, gender and ethnicity), previous risk factors for cardiac disease, laboratory findings (Low Density Lipoprotein value, Hemoglobin-A1C, and highest Hs-troponin value), and CAG finding. Patients were divided into two groups according to the CAG findings. Group A with obstructive CAD defined as coronary artery stenosis of 70% or more underwent coronary intervention, or advised for surgical or medical management. And Group B with non-obstructive CAD defined as normal or non-obstructive coronary artery disease of less than 50%.

Data was analyzed using SPSS software version 22. Statistical tests were carried out at 95% confidence interval and results considered significant at a p-value of 0.05 or less. For variables where their numerical data is non-skewed the mean is reported (Hemoglobin and LDL) while for variables with skewed data the median is reported (all other variables with numerical data). On the other hand, for categorical variables the percentage is reported. Correlation was investigated using T-test for non-skewed numerical data, Mann-Whitney test for skewed numerical data and chi-square test for categorical data.

An ethics approval was obtained from Dubai Scientific Research Ethics Committee, DHA holding the reference number of DSREC/RRP/2019/13.

3. Results

Two hundred and two patients fulfilled the inclusion criteria out of all 263 patients admitted as NSTEMI (**Table 1**) in the study period. Group A included 177 patients (87.6%) of which 91% were males, meanwhile Group B had 25 patients (12.4%) of which 88% were males. The median age in both groups was 53 years old. There is significant difference between group A and B in percentage of diabetics ($P = 0.014$) and Median Hs-troponin ($P = 0.03$), but no significant differences reported in relation to hypertension, smoking, HbA1C, or LDL (**Table 2**). The confounding variables were presented in **Table 3** that showed no statistical significance between both groups.

Troponin as a diagnostic biomarker for myocardial infarction

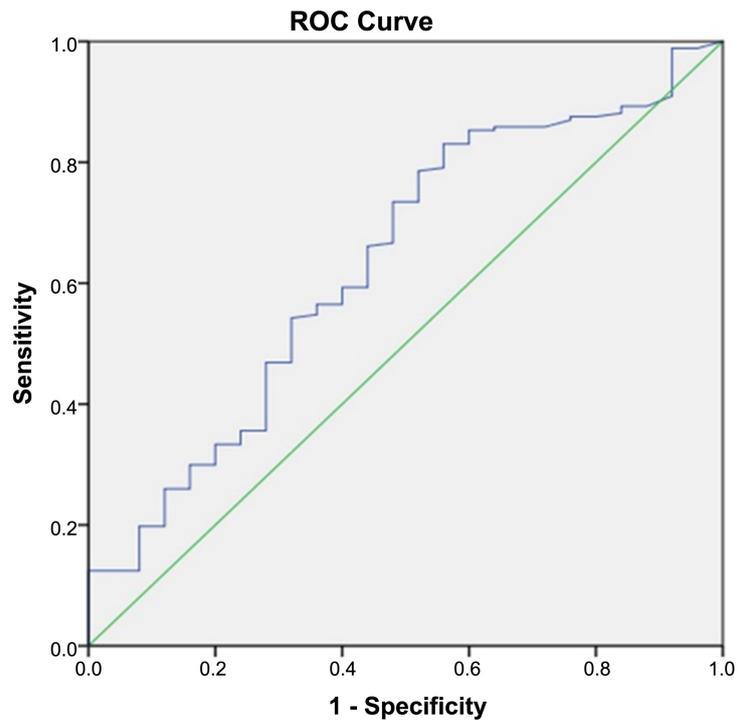
A receiver operating characteristic curve (ROC) was obtained to statistically measure a diagnostic cutoff value for troponin as a cardiac biomarker for NSTEMI (**Figure 1**) considering CAG as the gold standard test. The ROC analysis showed an Area Under the Curve (AUC) of 0.634 (0.51 - 0.751) with a p value of 0.03 at confidence interval of 95%. Studying the sensitivities and specificities

Table 1. NSTEMI characteristics of our 202 patients.

Variables		Group A	Group B
ECG findings	ST depression and unspecific changes	70%	48%
	Other ECG changes	6%	12%
	No changes	24%	40%
Presenting Symptoms	Typical cardiac chest pain	87%	68%
	Others	6%	20%
	Unknown	7%	12%
Cardiac Enzymes	Hs-Troponin (>14 ng/L)	100%	100%
	CK-MB (>24 ng/L)	55%	68%

Table 2. Comparison of different variables between CAG groups, total of 202 patients and chi square test used for statistical analysis.

Variables	Group		P-Value
	obstructive CAD	Non-obstructive CAD	
Smoker (%)	37	40	0.799
Diabetic (%)	54	39	0.014
Hypertensive (%)	54	60	0.588
Median hs-Troponin (ng/L)	145	54	0.030
Median HBA1C (%)	6.100	5.750	0.135
Mean LDL (mg/dL)	126.48	121.22	0.567



Diagonal segments are produced by ties.

Figure 1. ROC Curve of our data for 202 patients admitted as NSTEMI plotting the sensitivity and specificity at each value.

Table 3. Comparing confounding variables between patients with obstructive CAD (Group A) and non-obstructive CAD (Group B), total of 202 patients.

Variable	Group A	Group B
Median Creatinine (mg/dL)	0.9	0.8
Mean Hemoglobin (g/dL)	14.25	14.21
Median CPK (mg/L)	216	191

of the ROC curve; it was deduced that the best cutoff value for the Hs-troponin is 127 ng/L.

4. Discussion

Troponin has been acknowledged as a cardiac biomarker of choice for diagnosis and management of NSTEMI by the American Heart Association (AHA), American College of Cardiology (ACC) and the European Society of Cardiology [11] [12]. However, the ACC and AHA emphasize that elevation of troponin is not always due to atherosclerotic coronary artery disease [11]. Currently, 14 ng/L is considered as the cutoff value for a positive Hs-troponin result when evaluating patients with NSTEMI. This value is highly sensitive but lack specificity. When conducting a ROC curve on our data a Hs-troponin value of 14 ng/L had a sensitivity of 99.9% with an only 4% specificity. Further studying the ROC curve, a level of 127 ng/L was the best cutoff for Hs-troponin not compromising specificity, which showed a sensitivity of 58% and specificity of 68%. The test specificity will increase with increasing Hs-troponin level, while sensitivity decreases and vice versa. This curve has an AUC of 0.634 indicating a low diagnostic accuracy (<0.7) despite being statistically significant ($P = 0.03$) [13]. This directs that Hs-troponin is statistically significant as a biomarker for acute myocardial infarction but not without using additional clinical risk stratification.

The presence of higher percentage of diabetes, which is a known risk factor for atherosclerotic cardiovascular events, as well as a higher median Hs-Troponin value in group A patients representing a higher chance of acute coronary syndrome and the likelihood of an underlying obstructive coronary artery disease as the myocardial damage is greater. The absence of significant difference between the groups in the confounding variables such as smoking status, history of hypertension, LDL value, creatinine, hemoglobin and CPK; gives more weight to use Hs-troponin as a determinant factor for predicting obstructive coronary artery disease.

An alternative diagnosis was found in those with a non-obstructive CAD (group B). Cardiac diagnoses were found in 32% of them which included valvular diseases, arrhythmogenic cardiomyopathy, myopericarditis, myocarditis, chest trauma and arrhythmias; bigeminy, ventricular tachycardia, and supra-ventricular tachycardia. This indicates that the elevated troponin in these patients was due to a myocardial injury rather than a myocardial ischemic infarction. Furthermore, 20% of group B had non-cardiac diagnoses which included bladder cancer, sarcoidosis, H. Pylori infection, gastric ulcer, and anemia. Several published

articles support that these alternative cardiac and non-cardiac diagnoses are associated with elevated hs-troponin without any significant obstructive coronary artery disease [14] [15] [16] [17] [18].

Although our sample size is calculated to confer 80% power, our research is uni-centered and conducted in one-year time interval; a limitation that can be easily overcome by further research. This will confer more power and clarify the accuracy of Hs-troponin in detection of obstructive coronary artery disease in patients admitted with NSTEMI.

5. Conclusion

Our study concludes that at the current cutoff point of 14 ng/L is less specific in detecting obstructive coronary artery disease. A new level of 127 ng/L is proposed as it holds a good specificity for detecting obstructive coronary artery disease. Further study is recommended to evaluate this result in a large-scale population. The additional use of clinical cardiac risk stratification can improve the accuracy of Hs-troponin in predicting obstructive coronary artery disease.

Declarations

Ethical Approval and Consent to Participate

An ethics approval was obtained from Dubai Scientific Research Ethics Committee, DHA holding the reference number of DSREC/RRP/2019/13.

Availability of Data and Material

Data is available with the authors in an excel sheet.

Consent for Publication

Not applicable.

Funding

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Declaration of Helsinki

An ethics approval was obtained from Dubai Scientific Research Ethics Committee, DHA holding the reference number of DSREC/RRP/2019/13.

Consent Form

Not applicable.

Authors' Contributions

All Authors have read and approved the manuscript.

OA: Has done the data collection and statistic analysis.

AA Has formulated the methodology, did the data base of variable collection and written a part of the discussion.

AB: Formulated the aim of the research and assured integrate of the scientific content; in addition, edited the final manuscript.

HA: Has helped in the data collection and written a part of the discussion.

SB: Has provided the patients files that fulfill the inclusion criteria and edited the final manuscript.

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Conflicts of Interest

Authors have no relationships relevant to the contents of this paper to disclose.

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Abbreviations

NSTEMI: Non-ST Elevation Myocardial Infarction

ACS: Acute Coronary Syndrome

Hs-troponin: High sensitivity troponin

CK-MB: Creatine Kinase-Myocardial Band

CAG: Coronary angiography

CAD: Coronary artery disease

AUC: Area Under the Curve

ROC: receiver operating characteristic curve

AHA: American Heart Association

ACC: American College of Cardiology

MINOCA: Myocardial Infarction/Injury with Non-obstructive Coronary Arteries