SEVERITY OF CORONARY ARTERY DISEASE IN NON-ST ELEVATION MYOCARDIAL INFARCTION (NSTEMI) PATIENTS WITH HIGH TROPONIN-I LEVEL

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Contribution

SAS conceived the idea, planned the study. GAS & MK did the data collection and drafted the manuscript. All the author contributed significantly in manuscript submission.

All authors declare no conflict of interest.

ABSTRACT

Objective: To determine the frequency of severity of obstructive coronary artery disease or left main coronary artery stenosis in NSTEMI patients with elevated Troponin-I level.

Methodology: This cross-sectional study was conducted at National Institute of Cardiovascular Diseases (NICVD), Karachi from 25 January to 24 July 2015. We included patients diagnosed with NSTEMI, between 40-72 years of age. Patients were classified as low risk (Group A) and high risk (Group B) based on criteria of elevated troponin I level more than tenfold the maximum threshold of the normal range. Chi square test or Fisher's Exact test, Kruskal-Wallis Test, and independent sample t-test were applied as appropriate and two sided $p \leqslant 0.05$ was used as a criterion for statistical significance.

Results: Total 123 Patients were included. There were 95 (77.24%) male patients. Mean age was 54.72 ± 8.27 years. Of total 25(20.33%) of the patients were in high risk group. Normal angiogram was observed in a significantly high number of lower risk group (Group A) as compared to higher risk group (Group B), 13(13.27%) vs. 0(0%). SVD was observed in 35(35.71%) vs. 1(4%) of patients of lower risk group and higher risk group. (p = 0.001), 2VD was observed in 26(26.53%) vs. 12(48%) (p= 0.036) and 3VD was observed in 24(24.49%) vs. 12(48%) (p = 0.022).

Conclusion: Elevated troponin I levels, more than tenfold of the maximum threshold of the normal range, in non-ST elevated myocardial infarction (NSTEMI) patients are strongly associated with more complex and severe coronary artery disease.

Key Words: Myocardial Infarction, NSTEMI, Angiography, Acute Coronary Syndrome, Troponin.

INTRODUCTION

Coronary artery disease (CAD) accounts for highest share in morbidity and mortality around the globe. According to The World Health Organization (WHO) estimates, cardiovascular diseases leads to the 31% of all deaths globally and low and middle income countries contributes 82% of this burden.[1] South Asian countries contribute significantly to the global burden.[2] The population of Indo-Pak subcontinent are among the populations with highest risks of CAD in the world and which is why coronary artery disease is the dominating cause of mortality among this population.[3]

As per the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, evaluation of troponin I level is a class I indication for the early diagnosis and risk stratification in patients presented with the clinical presenting symptoms of acute coronary syndromes.[4] Cardiac troponins are regulatory proteins that control the calcium-mediated interaction of actin and myosin, which results in contraction and relaxation of striated muscle.[5] Troponin I level is well established prognosis factor for the management of patients with non-ST elevated myocardial infarction (NSTEMI). Patients presented with elevated troponin I level of more than tenfold the maximum threshold of the normal range should be classified as high risk.[4,6]

It is generally required for the management of patients with coronary artery disease to perform coronary angiography and intervention. Normal coronary angiography is not uncommon in patients presented with the clinical presenting symptoms of ACS. Proportion of normal angiogram considerably varies in literature based on the definitions of normal; Levitt K et al. reported the proportion of normal angiogram from 18.4% to 76.9% and another study by Chandrasekaran B reported 1% to 12%.[7,8]

Past studies found significant association of elevated troponin I level with sever CAD involvement, severe clinical presentation and increased appearance of complex and culprit lesion on coronary angiography.[9-11]

The present study was designed to provide insight into the association between the levels of cardiac troponin I in NSTEMI and the number of major epicardial coronary vessels that have significant luminal narrowing (>70% stenosis). Despite the presence of studies which have evaluated the association of troponins to angiographic findings in the setting of ACS, studies evaluating angiographic correlations in terms of the number of significantly narrowed coronary arteries and the exact incidence of multivessel CAD with different cardiac troponin levels have been extremely limited in both international and local literature.

METHODOLOGY

This cross-sectional study was conducted after approval of ethical review committee of the institution. Sample size was calculated based on 19.3% as expected prevalence of single vessel disease among the patients with high troponin-I level, 95% confidence level and 7% absolute precision.[9] Consecutive sample of patients diagnosed with NSTEMI admitted in adult cardiology department of National Institute of Cardiovascular Diseases Karachi, from 25th January to 24th July 2015, were enrolled in the study. After explaining the procedure a written informed consent was taken from the patient. Patient's demographics and clinical history was taken by the principal investigator. ECG was done by trained ECG technician. The blood sample for troponin-I level was taken by peripheral venipuncture done by expert nurses in the presence of principal investigator after aseptic measures. For all the selected subjects coronary angiography was performed by expert interventional cardiologists, with an experience of at least ten years, who were blinded to the patients clinical information and cardiac troponin-I status. Coronary artery disease was defined as severe if ⩾70% stenosis seen in coronary arteries.

For all the included patients' demographic profile, risk factors (DM, HTN, Smoking, Dyslipidemia, Family history of CAD), troponin-I level, and coronary angiography findings were recorded using a predefined structural questionnaire. Selected subjects were divided into two groups as per their troponin I level, Group A, low risk group, with less than tenfold the maximum threshold of the normal range and Group B, high risk, with more than tenfold the maximum threshold of the normal range. Statistical Package for Social Sciences (SPSS) version 21 was used for compilation and analysis of data. Descriptive statistics such as mean ± SD, median (IQR), maximum and minimum were calculated for continuous variables and frequency and percentages were calculated for categorical variables such as age and troponin I level. Chi square or Fisher's Exact test, Kruskal-Wallis test, and independent sample t-test were applied as appropriate and two sided $p \leqslant 0.05$ was used as a criterion for statistical significance.

RESULTS

Of total 123 patients, there were 95 (77.24%) male and 28 (22.76%) female patients. Mean age was 54.72 ± 8.27 years ranged over 35 to 70 years. Most of the patients 70 (56.91%) were hypertensive followed by 50 (40.65%) diabetic, and 44 (35.77%) smokers. The overall, mean ± SD, torponin I level was 5.15 ± 4.42 ng/ml ranged from 3.0 to 25.0 ng/ml. Baseline characteristics of the patients are summarized in Table 1.

Sever coronary artery disease observed in 110 [89.43%] patient on coronary angiography and number of involved

vessels were 36 (29.27%), 39 (31.71%) and 37 (30.08%) for single, two, and three respectively. Left main trunk disease found in only 8 (6.5%) patients in which two vessels involvement were found in 1 (0.81%) and rest of the 7 (5.69%) were with three vessels involvement. Coronary angiographic findings are summarized in table 2.

Sever coronary artery disease was observed in significantly higher number of patients with elevated torponin I level, with p-value of 0.044. Similarly, occurrence of single vessel, two vessels, and three vessel involvement were significantly higher among patients with elevated torponin I level, with p-value of 0.001, 0.036, and 0.022 respectively. Left main trunk disease was observed in only 8 (6.5%) patients, and is not significantly different in torponin I elevated and non-elevated groups. Three vessels involvement was observed in seven out of eight patients with left main trunk disease.

Statistically significant association of torponin I level was observed with number of vessels involved with Independent-Samples Kruskal-Wallis Test p < 0.001. Box plot of torponin I level by number of vessel involved is presented in figure 1.

### Table 1: Demographic variables of Study Population (n=123)

		Total (n=123)	Group A (n=98)	Group B (n=25)	**p-value
Gender	Male	95 [77.24%]	76 [61.79%]	19 [15.45%]	0.529
	Female	28 [22.76%]	22 [17.89%]	6 [4.88%]	
Age (years)	Mean ± SD	54.72 ± 8.27	54.22 ± 8.42	56.64 ± 7.51	0.194
	Median (IQR)	55 (10)	54.5 (10)	56 (9.5)	NA
	Min-Max	35 - 70	35 - 70	40 - 70	NA
	40 to 50 years	41 [33.33%]	36 [29.27%]	5 [4.07%]	0.285
	51 to 60 years	53 [43.09%]	40 [32.52%]	13 [10.57%]	
	61 to 70 years	29 [23.58%]	22 [17.89%]	7 [5.69%]	
Comorbids	Hypertension	70 [56.91%]	52 [42.28%]	18 [14.63%]	0.068
	Diabetic	50 [40.65%]	34 [27.64%]	16 [13.01%]	0.008*
	Smoking	44 [35.77%]	32 [26.02%]	12 [9.76%]	0.117
	Family History of IHD	19 [15.45%]	13 [10.57%]	6 [4.88%]	0.155
	Dyslipidemics	13 [10.57%]	8 [6.5%]	5 [4.07%]	0.093
Troponin I Level (ng/ml)	Mean ± SD	5.15 ± 4.42	3.6 ± 0.52	11.23 ± 7.08	<0.001*
	Median (IQR)	3.6 (1.4)	3.4 (0.72)	8.67 (8.26)	NA
	Min-Max	3 - 25	3 - 4.9	5.06 - 25	NA

*Statistically significant at 5% level of significance
**P-values are based on t-test for mean and Chi-Square or Fisher's Exact Test for categorical variables

Table 2: Coronary Angiography Finding in Study Population (n=123)

		Total (n=123)	Group A(n=98)	Group B(n=25)	**p-value
Sever Coronary Artery Disease	Yes	110 [89.43%]	85 [86.73%]	25 [100%]	0.044*
	No	13 [10.57%]	13 [13.27%]	0 [0%]	
Number of Vessels Involved	Single	36 [29.27%]	35 [35.71%]	1 [4%]	0.001*
	Two	38 [30.89%]	26 [26.53%]	12 [48%]	0.036*
	Three	36 [29.27%]	24 [24.49%]	12 [48%]	0.022*
Left Main Trunk Disease	Yes	8 [6.5%]	5 [5.1%]	3 [12%]	0.205
	No	115 [93.5%]	93 [94.9%]	22 [88%]	
Vessels Involvement with Left Main Trunk Disease	Two	1 [0.81%]	1 [1.02%]	0 [0%]	0.797
	Three	7 [5.69%]	4 [4.08%]	3 [12%]	0.148

*Statistically significant at 5% level of significance
**P-values are based on Fisher's Exact Test

Figure 1: Troponin-1 Level by Number of Vessels

Kruskal-Wallis Test p-value <0.001
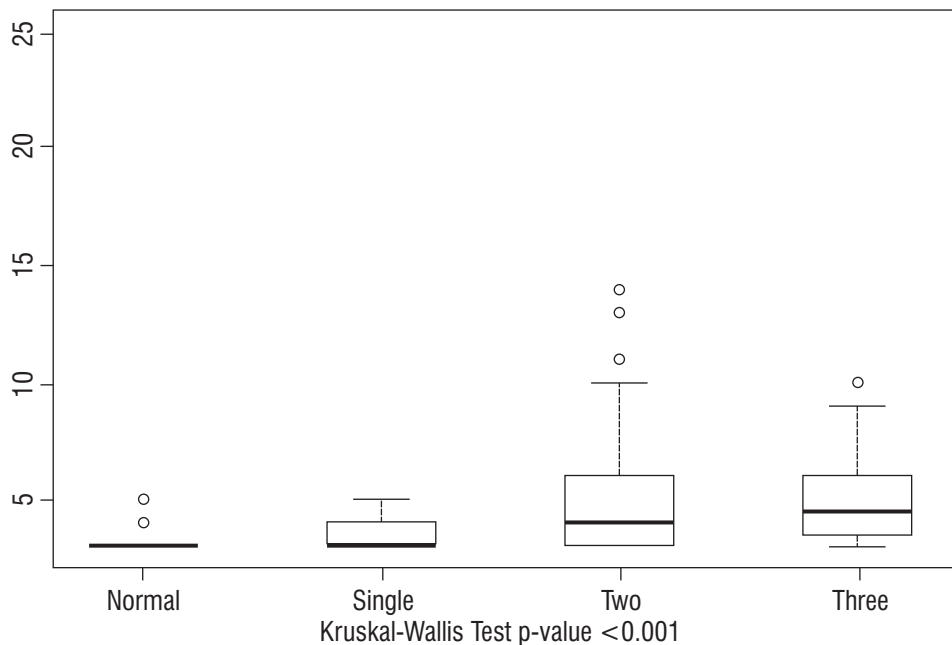
DISCUSSION

In a series of 123 patients with NSTEMI, normal angiogram was observed in 13 [10.57%] of the patients while Levitt K et al. reported the proportion of normal angiogram in 18.4% to 76.9% at different centers[7] and another study by Chandrasekaran B reported 1% to 12%.[8] In our study normal angiogram was observed significantly higher in lower risk group (group A) as compare to higher risk group (group B), 13 (13.27%) vs. 0 (0%). Frequency of normal angiogram was significantly higher in non-diabetic patients, 12 (16.4%) vs. 1 (2%), with p-value of 0.008.

Extensive clinical utility of troponin I level for the diagnosis of myocardial infarction (MI) is as a result of its high sensitivity and specificity but several etiologies, may be non-cardiac, can be the primary cause of elevated troponin.[12-14] Thus, additional diagnostic evidence can be obtained using other diagnostic methods such as ECG.

In our study, elevated troponin I level (more than tenfold the maximum threshold of the normal range) was observed in 25 [20.33%] of the patients and frequency was significantly higher in diabetic patients, 16 (32.0%) vs. 9 (12.3%), with p-value of 0.008. The reported frequency of elevated troponin levels in the literature vary widely, depending on the manufacturer unit of measurement and cut-off value selected. Study conducted by Qadir F et al. matching the unit and criteria with our study reported 52% frequency of elevated troponin in study of 230 consecutively selected patients with NSTEMI.[9] Another study by López-Fernández S et al. 19% in 219 NSTEMI patients.[10] Mahajan N et al. outlines the other potential causes that can lead to elevated cardiac

troponin in patients with normal angiograms, which include tachycardia (themodynamic compromise), myocarditis, congestive heart failure, gastrointestinal bleeding, severe aortic stenosis, pericarditis, diabetic ketoacidosis, collagen vascular disease, chronic obstructive pulmonary disease exacerbation, and coronary spasm.[13]

In our study statistically significant association of troponin I level and severity of coronary artery disease, in terms of number of occluded vessel, was observed with p-values of 0.001, 0.036, and 0.022 for single vessel, two vessels, and three vessels respectively. López-Fernández S et al. reported significant association in NSTEMI patients and reported mean number of vessels of 1.95 ± 1 vs. 1.56 ± 1 in higher risk group and lower risk group with p-value of 0.038 and frequency of three vessels reported in 39.0% vs. 36.0% in higher risk and lower risk group with p-value of 0.001.[10] In another study by Qadir F et al. reported the same association with frequency of single vessel in 22.5% vs. 19.3% in lower risk group and higher risk group, frequency of two vessels in 36.0% vs. 31.0%, and frequency of three vessels in 30.6% vs. 46.2%.[9] In our study, number of occluded vessel was found to be strongly associated with age and diabetes with chi-square test p-value of 0.026 and 0.043 respectively.

Left main trunk disease was observed in only 8 out of 123, frequency of left main trunk disease was observed in 12.0% vs. 5.1% in higher risk and lower risk group with p-value of 0.205. López-Fernández S et al. reported 7% vs. 4% and Qadir F et al. reported 10.0% vs. 5.4% in higher risk and lower risk group[9,10].

Thus, the results of our study extend previous observations; tenfold elevated then maximum threshold of the normal

range troponin I level in non-ST elevated myocardial infarction (NSTEMI) patients is strongly associated with more complex and server coronary artery disease.

LIMITATIONS

The finding of this study may be pertinent to the specific segment due to less diversified socioeconomic, geographic, and ethnic distribution of patients flow to our center. Lastly this study only evaluated the severity of coronary artery disease (CAD) in the form of occluded number of vessel and other angiographic findings such as lesions complexity, intracoronary thrombus, and TIMI flow were not assessed. From future prospective extended multi center studies are needed to further validate the association.

CONCLUSION

Elevated troponin I levels, more than tenfold of the maximum threshold of the normal range in non-ST elevated myocardial infarction (NSTEMI) patients are strongly associated with more complex and severe coronary artery disease.

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