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ORIGINAL ARTICLE

Association of Cardiac Troponin I Levels with the Severity of Coronary Artery Disease in Non-ST Elevation Myocardial Infarction

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Abstract :

Background : Among the acute coronary syndromes (ACS), Non-ST-elevation myocardial infarction (NSTEMI) is the most common presentation and a leading cause of hospital admissions. Prognosis of patients with ACS are related to the magnitude of cardiac biomarker release. Hence it is essential to see the relationship of increase in troponin levels in the setting of NSTEMI with the severity of CAD.

Objective: This study was conducted to determine the association of cardiac troponin I (cTnI) with the severity of coronary artery disease in NSTEMI.

Method : A cross-sectional analytical study was conducted on 120 NSTEMI patients admitted in National Institute of Cardiovascular Diseases, Dhaka between August 2016 to March 2017. cTnI was measured using IMMULITE 1000 (Siemens, USA) which is a three-step assay, based on the immunochemistry technology. All patients underwent coronary angiography in the index hospitalization. Stenosis > 70% in any of the three major epicardial vessels was considered significant CAD. Extent of CAD was defined as significant single, two or three vessel CAD. Chi-square test was applied to test the association between cTnI levels and CAD extent. Severity of coronary artery disease was also analysed by Vessel score and Gensini score. Spearmen's Rank correlation test & Pearson's correlation test were applied to test the association of cTnI with Vessel score and Gensini score respectively.

Results: In the study, out of 120 patients, in 58 patients with cTnI levels < 10 folds upper limit of normal(ULN) (Group-I), (14) 24.1 % of the patients had single vessel, (18)31% had two vessel and (15)25.9 % had three vessel significant CAD, while among patients with cTnI levels > 10 folds ULN (Group-II) ,(11) 17.7 % of the patients had single vessel, (16)25.8% had two vessel and (29) 48.6% had three vessel significant CAD.There was an insignificant association between the cTnI levels and single vessel, two vessel CAD extent (p= 0.38, p= 0.52 respectively), however there was a statistically significant association between the cTnI levels and three vessel CAD (p=0.03) and also cTnI levels and multivessel disease (combined double vessel and triple vessel disease) (p=0.04). Mean vessel score was higher in group II than group I (2.101.02 vs. 1.641.07) with statistical significant difference (p=0.02). Mean Gensini Score was significantly higher in group II compared to group I (61.5±37.6 vs. 39.6±27.4, p<.001).There is a positive correlation between cTnI and coronary artery disease severity in terms of Gensini score (r=0.40, p=0.01).there is also a positive correlation between cTnI and coronary artery disease severity in terms of vessel score (r=0.28,p=0.01). Conclusion: Higher cTnI levels in NSTEMI are associated with severe CAD in the form of multi-vessel involvement with higher vessel score and Gensini score . Early coronary angiography should be considered especially in these patients & earlier revascularization would improve their clinical outcomes.

key words : NSTEMI, Vessel score, Gensini score, Severity of coronary artery disease.

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Introduction:

Cardiac troponins represent a major clinical shift in the diagnosis of NSTEMI. Because of the increased sensitivity and specificity of cardiac troponins relative to CK-MB, it is estimated that up to 30% of patients who present with rest pain and normal CK-MB levels and who were

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previously diagnosed with unstable angina should be reclassified as having NSTEMI when assessed with troponins (Bertrand,et al., 2000).

Qadir, et al., (2010) conducted a study providing insight into the association between the two cut off levels of cardiac troponin I (<10 folds ULN and >10 folds ULN) in NSTEMI and the number of major epicardial coronary vessels that have significant luminal narrowing (>70 % stenosis). The study demonstrated that among patients with cTnI levels < 10 folds ULN 22.5 % of the patients had single vessel, 36 % had two vessel and 30.6 % had three vessel significant CAD while among patients with cTnI levels > 10 folds ULN, 19.3 % of the patients had single vessel, 31.1 % had two vessel and 46.2 % had three vessel significant CAD. They found a statistically significant relationship only between cTnI level >10 folds ULN and severely affected three vessel CAD.

Methods:

This cross-sectional analytical study was conducted at National Institute of Cardiovascular Diseases, Department of cardiology, Dhaka from August 2016 to March 2017. By purposive sampling technique 120 cases were taken. Patients admitted with NSTEMI were selected for CAG during the index hospitalization in NICVD throughout the study period. They were enrolled consecutively following the inclusion and exclusion criteria. Cine angiographic films were analyzed independently by experienced operators. Significant CAD was defined as > 70% stenosis in any of the three major epicardial coronary arteries or a left main coronary artery stenosis > 50%. Branch vessel CAD was defined as > 70% stenosis in a major side branch of an epicardial artery (if > 2 mm in diameter). Angiograms revealing coronary artery stenosis < 70% in major epicardial coronary arteries were termed as non-obstructive CAD. Extent of CAD was defined as significant single, two or three vessel CAD involvement. Severity of coronary artery disease was also analysed by Vessel score and Gensiniscore.Vessel score was calculated and ranged from 0 to 3, depending on the number of vessels involved. The severity of CAD was defined as significant single, two or three vessel disease and significant left main coronary stenosis was scored as single vessel disease.The Gensini score was calculated from 14 coronary artery segments. The collected data were entered and analyzed by the Statistical Package for Social Sciences version 16.0 Software (SPSS Inc., Chicago, Illinois USA).Continuous variables such as age and troponin I levels were expressed as mean ± SD.Categorical variables including diabetes, hypertension, dyslipidemia, cigarette smoking, positive family history of CAD, ECG ischaemic abnormality, extent of CAD, significant left main artery stenosis and number of occluded vessels were presented as frequencies and percentages.Variables were analyzed by Chi-square test, t-test, Fishers' Exact test. Correlation was done by Pearson's Correlation & Spearman's Rank Correlation test where applicable. Logistic regression was used to demonstrate the independent predictors for having significant CAD.The Receiver Operating Characteristics (ROC) curve was used to test the accuracy of the findings found in logistic regression analysis.

Results :

All the patients were evaluated by echocardiography to see the LV ejection fraction. The mean ejection fraction of study patients was 56.7±8.1 %. It was 56.9±7.1% for the patients of group I and 55.9±8.9% for the patients of group II and the mean difference was not statistically significant (p=0.47).The mean lipid profile was found higher in group II compared to group I but did not reach the level of significance (p>0.05).

Table-I

Distribution of the study patients by ECG changes.

Characteristics	Total NSTEMI patients (n=120)		Group I (n= 58)		Group II (n = 62)		p value
	Number	%	Number	%	Number	%	
ST depression	29	24.2	9	15.5	20	32.3	0.03^{s}
T inversion	27	22.5	15	25.9	12	19.4	0.39^{ns}
Normal ECG	64	53.3	34	58.6	30	48.4	0.26^{ns}

Group I = Patients having cTnI ≤10 folds ULN, Group II = Patients having cTnI>10 folds ULN

s= Significant (p<0.05), ns= Not significant (p>0.05); p value reached from Chi-Square test

Table-II

Comparison of Left ventricular ejection fraction (LVEF) between the two groups.

Ejection fraction (percent)	Study patients						p value
	Total NSTEMI patients (n=120)		Group I (n= 58)		Group II (n = 62)		
	Number	%	Number	%	Number	%	
≤35 (Severe)	1	0.8	0	0.0	1	1.6	
36-44 (Moderate)	7	5.8	2	3.4	5	8.1	
45-54 (Mild)	31	25.8	14	24.1	17	27.4	
≥55 (Normal)	81	67.5	42	72.4	39	62.9	
Mean ± SD(Range)	56.7±8.1(35-75)		56.9±7.1(40-75)		55.9±8.9(35-74)		0.47^{ns}

Group I = Patients having cTnI ≤10 folds ULN, Group II = Patients having cTnI>10 folds ULN
s= Significant (p<0.05); p value reached from unpaired t test

Table-III

Biochemical status of the study patients (n=120)

Biochemical parameters	Group I (n= 58) Mean±SD	Group II (n = 62) Mean±SD	p value
Total Cholesterol(mg/dl)	193.3±37.2	205.5±40.5	0.19^{ns}
Triglyceride (mg/dl)	151.0±32.4	155.7±33.9	0.24^{ns}
LDL cholesterol (mg/dl)	115.5±23.8	117.1±28.7	0.56^{ns}
HDL cholesterol (mg/dl)	38.8±5.8	34.9±4.6	0.48^{ns}
S. creatinine (mg/dl)	1.12±0.20	1.21±0.27	0.29^{ns}
RBS (mg/dl)	8.3±3.2	9.2±3.4	0.11^{ns}
Cardiac troponin I (ng/dl)	3.6±1.9	27.2±17.6	$<0.001^{S}$

Group I = Patients having cTnId”10 folds ULN, Group II = Patients having cTnI>10 folds ULN
s = Significant (p<0.05), ns = Not significant (p>0.05); p value reached from unpaired t-test.

Regarding the extent of CAD, triple vessel diseases were frequently more in group II compared to group I with significant association (p=0.03). Multi-vessel disease was significantly higher in group II compared to group I (p=0.04). The remaining vessels were almost identical in group I and group II with insignificant association (p>0.05). Left main stem disease (LM) was significantly higher in group II compared to group I (12.9% vs. 8.3%, p=0.04). LAD, LCX, RCA and Ramus Intermedius arteries were more frequently in group II compared to group I but failed to get statistical level of significance (p>0.05).Single occluded vessel was significantly higher in group II than group I (48.4% vs. 19%, p=0.001). Double occluded vessel were more in group II than group I (9.7% vs. 3.4%, p=0.19) but failed to reach the level of significance.

Vessel score-3 were significantly higher in group II (p=0.02) patients than that in group I. Score -1 & 2 were more in group II patients than group I with insignificant association. Mean vessel score was higher in group II than group I (2.101.02 vs. 1.641.07) with statistical significant difference (p=0.02). Mean Gensini Score was significantly higher in group II compared to group I (61.5±37.6 vs. 39.6±27.4, p<.001). Moderate to Severe CAD was found 74.2% and 53.4% in group II and group I respectively. None or mild CAD was found 46.6% and 25.5% in group I and group II respectively. Severe CAD patients were significantly more in group II than group I (p=0.01). None or mild CAD patients were significantly more in group I than group II (p=0.01).

Scatter plot diagram shows that there is a positive correlation between cTnI ng/dl and coronary artery disease severity in terms of vessel score (r=0.28). It indicates that whenever cTnI is increasing the vessel score is also increasing in the same sequence. This correlation was statistically significant (p=0.01) by Spearmen’s Rank correlation test. The diagram also shows that there is a positive correlation between cTnI ng/dl and coronary artery disease severity in terms of Gensini score (r=0.40).

It was observed that correlation was statistically significant (p=0.01) by Pearson's correlation test

Univariate and multivariate binary logistic regression analysis revealed that out of the expected 7 variables diabetes mellitus and cTnI>10 ng/dl were found to be the independently significant predictors for having significant coronary artery disease with ORs being 3.22 vs. 2.95 and 2.50 vs. 2.67 respectively.The area under the Receiver operating characteristic (ROC) curves for cTnI (>10 ng/dl) was 0.83 (95% CI: 0.762 – 0.902, p<0.001) in the prediction of the severity of coronary artery disease among the study patients. Hence the prediction by logistic regression analysis was significantly best with accuracy 83%.

Table-IV

Distribution of the study patients by extent of CAD.(n=120)

No.of diseased vessels	Total NSTEMI patients (n=120)		Group I (n= 58)		Group II (n = 62)		p value
	Number	%	Number	%	Number	%	
SVD	25	20.8	14	24.1	11	17.7	0.38^{ns}
Multi vessel disease	78	65.0	33	56.9	45	72.6	0.04^{S}
DVD	34	28.3	18	31.0	16	25.8	0.52^{ns}
TVD	44	36.7	15	25.9	29	48.6	0.03^{S}
Branch vessel diseae	4	3.3	2	3.4	2	3.2	1.00^{ns}
Non obstructive	7	5.8	5	8.6	2	3.2	0.38^{ns}
Normal CAG	6	5.0	4	6.9	2	3.2	0.35^{ns}

Group I = Patients having cTnI ≤10 folds ULN, Group II = Patients having cTnI>10 folds ULN
SVD= Single vessel disease, DVD= Double vessel disease, TVD= Triple vessel disease.
s = Significant (p<0.05), ns= Not significant (p>0.05);
p value reached from Chi square test Fisher's Exact test (for cell frequency <5)

Table-V

Comparison of the study patients by site of lesion (n=120)

Vessels	Total NSTEMI patients (n=120)		Group I (n= 58)		Group II (n = 62)		p value
	Number	%	Number	%	Number	%	
LM	10	8.3	2	3.5	8	12.9	0.04^{s}
LAD	81	67.5	35	60.3	46	74.2	0.10^{ns}
Proximal	37	45.7	19	54.3	18	39.1	
Middle	34	42.0	13	37.1	21	45.7	
Distal	5	6.2	1	2.9	4	8.7	
Diagonal	5	6.2	2	5.7	3	6.5	
LCX	78	65.0	35	60.3	43	69.4	0.30^{ns}
Proximal	23	29.5	8	22.9	15	34.9	
Middle	28	35.9	9	25.7	19	44.2	
Distal	16	20.5	11	31.4	5	11.6	
OM	11	0.0	7	0.0	4	0.0	
RCA	72	60.0	32	55.2	40	64.5	0.29^{ns}
Proximal	24	33.3	14	43.8	10	25.0	
Middle	29	40.3	11	34.4	18	45.0	
Distal	14	19.4	5	15.6	9	22.5	
RPLV	1	1.4	0	0.0	1	2.5	
RPDA	3	4.2	1	3.1	2	5.0	
RV branch	1	1.4	1	3.1	0	0.0	
RI	2	0.0	1	0.0	1	0.0	1.00^{ns}

** The frequencies did not add up to 100% as more than one vessel were involved.
Group I = Patients having cTnId"10 folds ULN, Group II = Patients having cTnI>10 folds ULN
s = Significant (p<0.05), ns= Not significant (p>0.05);
p value reached from Chi square test and Fisher's Exact test (for cell frequency <5)
LM=Left main stem disease, LAD=Left anterior descending artery, LCX= Left circumflex artery, OM= Obtuse marginal arteries, RI= Ramus intermedius artery, RCA=Right coronary artery, RPLB= Right postero-lateral branches, RPDA= Right posterior descending artery, RV branch= Branch to right ventricle.

Table-VI

Comparison of the study patients by number of occluded vessels (n=120)

Vessels	Total NSTEMI patients (n=120)		Group I (n= 58)		Group II (n = 62)		p value
	Number	%	Number	%	Number	%	
No occlusion	71	59.2	45	77.6	26	41.9	<0.001[s]
Single vessel	41	34.2	11	19.0	30	48.4	0.001[s]
Double vessel	8	6.7	2	3.4	6	9.7	0.19[ns]
Triple vessel	0	0.0	0	0.0	0	0.0	

Group I = Patients having cTnI ≤10 folds ULN, Group II = Patients having cTnI>10 folds ULN
s = Significant (p<0.05), ns= Not significant (p>0.05)
p value reached from Chi square test and Fisher's Exact test (for cell frequency <5

Table-V1I

Distribution of the study patients according to vessel score (n=120)

Vessel Score	Group I (n= 58)		Group II (n = 62)		p value
	Number	%	Number	%	
Score – 0	11	19.0	6	9.7	0.14[ns]
Score – 1	14	24.1	11	17.7	0.38[ns]
Score – 2	18	31.0	16	25.8	0.52[ns]
Score – 3	15	25.9	29	46.8	0.02[s]
Mean SD	1.641.07		2.101.02		0.02[S]

Group I = Patients having cTnI ≤10 folds ULN, Group II = Patients having cTnI>10 folds ULN
s=Significant (p<0.05), ns= Not significant (p>0.05); p value reached from Fisher's Exact test and Chi Square test.

Table-VIII

Distribution of the study patients according to CAD severity (by GensiniScore) (n=120)

CAD severity (by Gensini Score)	Group I (n= 58)		Group II (n = 62)		p value
	Number	%	Number	%	
Moderate to Severe CAD (≥36 points)	31	53.4	46	74.2	0.01[s]
None or mild CAD (<36 points)	27	46.6	16	25.8	0.01[s]
Mean ± SD(Range)	39.6±27.4(0-112)		61.5±37.6(0-196)		<0.001[s]

Group I = Patients having cTnI ≤10 folds ULN, Group II = Patients having cTnI>10 folds ULN
s = Significant; p value reached from Chi Square test and unpaired t- test.

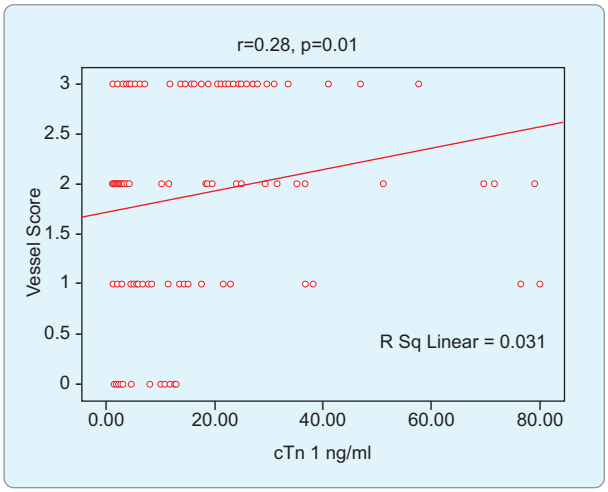

Figure 1 : *Scatter plot diagram showing correlation between cTnI and vessel score.*

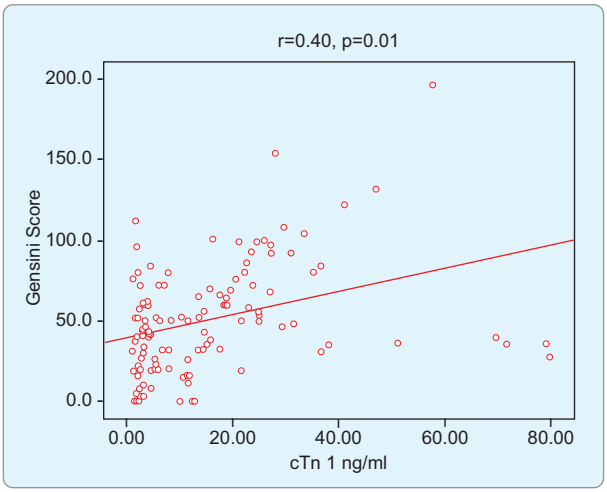

Figure 2 : *Scatter plot diagram showing correlation between cTnI and Gensini score*

Table IX

Univariate and multivariate binary logistic regression analysis of having significant coronary artery disease (CAD).

Variables of interest	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Advance age>50	0.95 (0.446 – 2.010)	0.88^{ns}	0. 76 (0.321 – 1.788)	0.55^{ns}
Smoking	1.64 (0.758 – 3.542)	0.21^{ns}	1.37 (0.586 – 3.224)	0.47^{ns}
Hypertension	1.17 (0.545 – 2.460)	0.70^{ns}	0.96 (0.419 – 2.181	0.92^{ns}
Dyslipidemia	1.13 (0.238 – 1.879)	0.57^{ns}	0.94 (0.147 – 2.2018)	0.49^{ns}
Diabetes mellitus	3.22 (1.393 – 7.424)	0.006^{s}	2.95 (1.218 – 7.170)	0.02^{s}
ST depression	2. 98 (0.936-9.455)	0.07^{ns}	3.21 (0.920-11.212)	0.06^{ns}
cTnI>10 ng/dl	2.50 (1.162 – 5.397)	0.02^{s}	2.67 (1.112 – 6.398)	0.03^{s}

s = Significant (p<0.05), ns = Not significant (p>0.05)

Area Under the Curve

Test Result Variable(s): Predicted probability

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.832	.036	.000	.762	.902

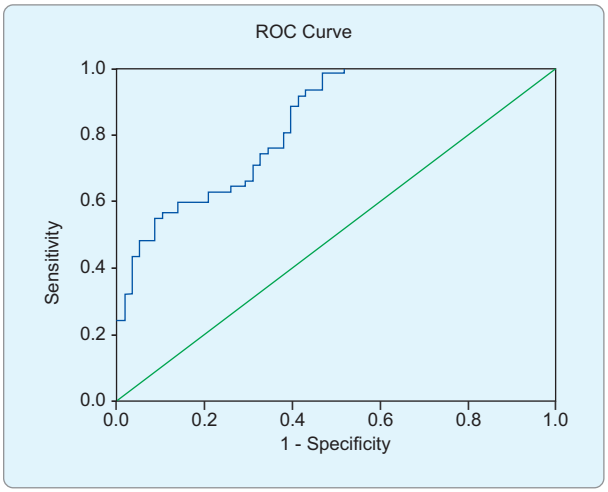

Figure 3: *Receiver operating characteristic (ROC) curves for cTnI>10 ng/dlin predicting the severity of CAD (Gensini score).*

Discussion:

In our study, single vessel coronary artery disease was significantly higher in Group-I compared to Group- II. Double vessel coronary artery disease was higher in Group-II compared to Group-I but not statistically significant. Triple vessel coronary artery disease was significantly higher in Group-II compared to Group-I. Similar result was also shown in the work of Qadir. Multivessel (combined DVD & TVD) disease was significantly higher in Group –II compared to Group –I. Qadir did not show that statistically significant but multivessel disease was higher in patients having cTnI> 10 folds ULN.

Mean Vessel score was significantly higher in Group-II compared to Group-I. Mean Gensini score was significantly higher in group-II compared to group-I. Mean Vessels score and Gensini score were significantly higher in patients having severe triple vessel disease that was shown in the study (Salim, et al.,2015).

In this study, there is significantly positive linear correlation between cTnI level and Vessel score, cTnI level and Gensini score. Similar result was also shown in the work of Salim, et al, involving relationship between HbA1c and severity of CAD in NSTEMI. Univariate and multivariate analysis clearly showed that cTnI>10 folds ULN was found to be an independently significant predictors for having significant coronary artery disease. Similar result was also shown in other studies (Qadir,et al., 2010) .

Absence of CAD is an uncommon finding in patients undergoing coronary angiography for ACS (Rigatelli,et al., 2004). Our study revealed that 4 (6.9 %) patients with cTnI< 10 folds ULN and only 2 (3.2%) patients in the cTnI> 10 folds ULN group had a perfectly normal coronary angiogram. There were more females with normal coronary angiograms in the lower troponin I level group.

The TACTICS-TIMI-18 sub study involving 895 patients revealed that in patients who present with symptoms of

ACS and have no critical epicardial CAD angiographically, the presence of an elevated troponin was still associated with an adverse prognosis (Dokainish,et al., 2005).

Aijaz and Hanif, (2016) have shown that around 39% of the NSTEMI patients who underwent angiography had coronary occlusion. In our study 49 patients (40.9%) had occluded vessels. Single occluded vessel was significantly higher in Group 11 than Group 1(P=0.001). Both single and double occluded vessel prevalance are more in patients having cTnI> 10 folds ULN. Several other studies have shown variable findings and, depending upon the difference in patient selection, the percentage of occluded coronaries was found to be around 29%(Jurlander,et al.,2000) to 63% (Okamatsu,et al., 2004).

The reason for having higher OCA prevalence in our study might be late presentation of patients to a medical facility, prior undetected MI, or missed STEMI due to lack of early identification of ischaemic heart disease in a developing world setup.

In our study, ST depression in ECG presented greater in group II patients compared to that in group I (32.3% vs. 15.5%) with statistically significant association (p = 0.03). Ciric-Zdravkovic (2007) proved that serum cardiac troponin level is related to ST deperession size changes. Troponin I levels are much more elevated with ST depression depth increase (Æiriæ-Zdravkoviæ,et al., 2007). The study was supported by Miah and his collegues. In 2011 they conducted one cross sectional study in NICVD, Bangladesh, which found that magnitude of ST-segment depression positively correlate with the severity of coronary artey disease (Miah,et al., 2017).

According to the site of significant (>70%) coronary stenosis left anterior descending artery (LAD) was the vessel commonly involved with significant stenosis in both the groups. In patients with cTnI levels < 10 folds ULN, LAD was in 35 (60.3%), followed by left circumflex artery (LCX) in 35 (60.3%) and then right coronary artery (RCA) in 32 (55.2%) patients. While in patients with cTnI levels >10 folds ULN, LAD was the commonest vessel, 46 (74.2%), followed by LCX 43 (69.4%) and then RCA 40 (64.5%). In the study by Qadir, the left anterior descending artery (LAD) was the vessel most commonly involved with significant stenosis in both the groups. In patients with cTnI levels < 10 folds ULN, LAD was the commonest vessel 97 (87.3%), followed by right coronary artery (RCA) 79 (71.1%) and then left circumflex artery (LCX) 46 (41.4%). In patients with cTnI levels >10 folds ULN, LAD was the commonest vessel, 104 (87.3%), followed by RCA 82 (68.9%) and then LCX artery 74 (62.1%). Moreover in our study more involvement of left main stem (>50% stenosis) was observed in group II patients compared to group I which is statistically significant.

Randomized studies have confirmed that early coronary intervention also attenuates the adverse prognostic impact of troponin elevations (Bavry, et al., 2004). Overall, the results of our study suggest that elevated troponin I levels are associated with a greater severity and extent of myocardial ischaemic territory during the index event of NSTEMI.

The important part of our study is we have seen the association of cTn I levels with the severity of CAD in NSTEMI both qualitatively by the number of vessels involved and quantitatively by counting the Vessel score and Gensini score. Such a study is not available in international literature.

Lastly, Logistic regression analysis was used to identify independent predictors for CAD. Using this model, diabetes mellitus [odds ratio(OR) 2.95, 95% confidence interval (CI) 1.218 – 7.170] and cTn-I level >10 ULN [odds ratio (OR) 2.67, 95% confidence interval (CI) 1.112 – 6.398] were found to be independent predictor of CAD. Therefore, statistically significant correlation of higher troponin values (>10 folds ULN) with the severity of coronary artery disease in NSTEMI is established.

Conclusion:

It may be concluded that the patients having higher troponin levels in NSTEMI tend to have severe CAD in the form of multi-vessel involvement with higher Vessel score and Gensini score and they need early coronary angiography and prompt revascularization.

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