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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)



Article DOI: 10.21474/IJAR01/8950 **DOI URL:** http://dx.doi.org/10.21474/IJAR01/8950

RESEARCH ARTICLE

"CORRELATION OF CORRECTED QT INTERVAL WITH QUANTITATIVE CARDIAC TROPONIN-I LEVELS AND ITS PROGNOSTIC ROLE IN NON ST ELEVATION MYOCARDIAL INFARCTION.

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Manuscript Info

Manuscript History

Received: 22 February 2019 Final Accepted: 24 March 2019 Published: April 2019

Abstract

Background: There is a large body of evidence of specific myocardial injury markers such as cardiac troponin I (cTnI) and cardiac troponin T (cTnT) for short and long-term prognostic values of NSTE-ACS mortality and new infarction. Objective: The present study was conducted to assess the correlation between corrected QT interval with cardiac troponin-I levels in NSTE-MI patients and to assess if prolonged corrected QT interval independently predicts higher 30-day Major Adverse Cardiac Events (MACE) in NSTE-MI patients. Material and Method: we enrolled 301 patients with the diagnosis of NSTEMI. Demographic variables at admission were age, gender, arterial pressure, history of CAD, hypertension, diabetes mellitus, smoking, dyslipidemia, previous coronary revascularization, and medication before entering the study. All patients were classified at admission according to the TIMI score for NSTE-ACS.Cardiac troponin I was measured in all cases with the sample collected 24 hr after the beginning of last angina episode. Concentrations ≥ 0.01 ng/ml were considered to be positive. A second measurement was done after 12 h in patients in whom the first determination is negative. Corrected QT interval(longest) measurement was done according to American Heart association guidelines. Patients were treated as per protocol. Major adverse cardiovascular events (includes, death due to cardiovascular cause, Non-fatal Myocardial Infarction and Recurrent Unstable Angina and ensuing urgent revascularization.) that were observed up to 30 days post discharge. Results: Troponin-I values and QTc interval was significantly higher in patients with diabetes and dyslipidemia, who presented with higher TIMI scores, severe LV systolic dysfunction ,higher killip class and hypotension and with multivessel disease, did not differ significantly according to culprit vessel. There was significant correlation with coefficient of 0.637 between QTc-max and Troponin I.Patients with MACE had significantly higher mean Troponin - I and mean OTc interval. **Conclusion:** Corrected OT interval has a strongly positive significant correlation with quantitative troponin I level in NSTEMI patients and Prolonged corrected OT interval is independently predictive of higher

rate of major adverse cardiovascular events after NSTEMI within 30 days post discharge.

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Introduction:-

The latest American College of Cardiology and the American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines recognize the importance of early risk stratification in the management of NSTE-ACS and recommend an integrated approach to risk assessment. The information required for this assessment is derived from the patient's history and physical examination, electrocardiogram (ECG) and cardiac biomarkers. ^{1,2}

It has been shown that the corrected QT interval prolongation is an independent risk marker in NSTE-ACS . However, there is scarce information about its relationship with other variables of known prognostic value, such as cardiac troponins.

There is a large body of evidence of specific myocardial injury markers such as cardiac troponin I (cTnI) and cardiac troponin T (cTnT) for short and long-term prognostic values of NSTE-ACS mortality and new infarction.³⁻⁶

Several studies have been published showing the prolonged corrected QT interval (QTc) in 12 lead ECG as an independent risk marker in NSTE-ACS with or without acute ischemic changes, both at 30-day post-discharge or long-term followup.⁷⁻⁹

Aims and objectives:-

1)To assess the correlation between corrected QT interval and cardiac troponin-I levels in NSTE-MI patients. 2) To assess if prolonged corrected QT interval independently predicts higher 30-day Major Adverse Cardiac Events (MACE) in NSTE-MI patients.

Methods:-

Patients with NSTEMI (defined as abnormal cardiac Troponin $I \ge 0.01$ ng/ml)was included in the study . A standard ECG recorded, at admission then at 6hr, 12hr, 24hr and 48hr post-admission. Blood samples were obtained at admission for complete blood count, serum urea, creatinine, electrolytes, A Fasting lipid profile was also done within 24 hrs of admission. Upon admission to the hospital all patients received conventional treatment according to existing departmental protocol.

Demographic variables at admission registered were age, gender, arterial pressure, history of CAD, hypertension, diabetes mellitus, smoking, dyslipidemia, previous coronary revascularization, and medication before entering the study. After basal characterization and TIMI scoring ¹⁰, all patients were followed-up for 30 days after discharge.

QT interval measurement was done according to American Heart association guidelines. , maximum interval taken in the ECG within 48h post admission. AHA linear regression formula was used to calculate QTc according to $HR.^{11,12}$ Corrected QT(QTc)= Observed QT +1.75(observed HR-60)

Cardiac troponin I was measured with the sample collected 24 hr after the beginning of last angina episode. A second measurement was done after 12 h in patients in whom the first determination is negative

Major adverse cardiovascular events (MACE) that were observed up to 30 days post discharge were death due to cardiovascular cause, Non-fatal Myocardial Infarction (defined by increased cardiac biomarkers, characteristic dynamic and evolving electrocardiographic changes. and prolonged chest discomfort), and Recurrent Unstable Angina and ensuing urgent revascularization. Patients were divided into two groups according to the presence (group A) or absence (group B) of MACE.

Inclusion criteria:

Male and female patients, more than 18 years of age, admitted with diagnosis of Non-ST elevation myocardial infarction, with or without acute ischemic ECG changes.

Exclusion criteria:

1.ST-segment-elevation-AMI,Unstable Angina-ACS. 2.Flat T wave (< 1 mm),Wide QRS, Ventricular hypertrophy 3.Serum potassium \leq 3.5.meq/I or > 5.5 meq/L,Serum calcium <8.5 mg/dl or > 10.5 mg 4.Severe valvular disease or

cardiomyopathy 5.Patients receiving antiarrhythmic or QT interval modifying drugs 6. Wolff-Parkinson-White abnormality, atrial fibrillation, atrial flutter or frequent extrasystoles (> 10/min)

Statistical analysis:

Continuous variables with normal distribution were expressed as mean \pm standard deviation (SD) and continuous variables with non-normal distribution were expressed as median (interquartile range). Unpaired Student's t test was used to compare continuous variables, and Chi square test was used to compare continuous variables, as appropriate. Spearman's correlation test was employed to establish the correlation between troponin-I level and QTc max values. Multivariate logistic regression analysis was performed to identify independent predictors of MACE.

Ethic Statement:

Study procedure was approved by Institutional Ethics Committee of S.C.B. Medical college and Hospital, Cuttack, Odisha (Regd. No ECR/84/Inst/OR/2013) while grant for the study was approved by the institutional Review Board vide Ref. No. 766/15.1.2019. Written consent was sorted prior to participation from respondents by means of informed consent.

Results:-

Mean age of the patients was 54.2 ± 12.3 years. 212 (70.4%) were males and 89 (29.6%) were females. Mean age of male and femals patients was 52.2 ± 12.4 years and 58.8 ± 10.7 years, respectively. Maximum no of patients 172 (57.1%) patients were in 46-70 years age group.

AGE GROUP	NO. OF PATIENTS	PERCENTAGE
<45 YEARS	90	29.9
46-70YEARS	172	57.1
>70 YEARS	39	13.0
TOTAL	301	100.0

Maximum no patients 158 (52.5%) were either active smokers or had stopped smoking in past six months, 113(37 .5%) patients were diabetics and 102 (34%) had a history of hypertension. 63(20.9%) patients had history of CAD and dyslipidemia was present in 108 (36%) patients

RISK FACTOR	TOTAL	PERCENTAGE
DIABETES	113	37.5
HYPERTENSION	102	34
CAD	63	20.9
SMOKERS	158	52.5
DYSLIPIDEMIA	108	36

Mean value of maximum troponin I levels in total sample population was 3.53 ± 2.88 ng/ml. Mean value was not significantly different between male(3.73 ± 2.96 ng/ml,) and female sex(3.06 ± 2.65 ng/ml,). (p = 0.06)and was not significantly different according to age groups. (p>0.1).

Mean Troponin I value was significantly higher in patients with diabetes 4.12 ± 3.14 ng/ml, vs patients without diabetes 3.17 ± 2.66 ng/ml (P=0.006)and in patients with dyslipidemia 3.84 ± 3.05 ng/ml, vs patients without dyslipidemia, 3.09 ± 2.58 ng/ml (p = 0.02).

Mean Troponin I value varied significantly according to TIMI score,SBP, Killip classes,LVEF. Mean value was lowest $(2.9 \pm 2.6 \text{ ng/ml})$ in TIMI 0-2 group (p = 0.01), and highest $(5.9 \pm 2.7 \text{ ng/ml})$ in TIMI 5 -7 group (p < 0.01). Mean value was highest at 6.07 ± 2.56 ng/ml in SBP <90 mm Hg group lowest at 3.10 ± 2.69 ng/ml in SBP 90-140 mmHg group (p < 0.01). Mean value was 3.01 ± 2.59 ng/ml in Killip class I group (p < 0.01) and 6.11 ± 2.88 ng/ml in Killip class higher than I group (p < 0.001).Mean value was highest at 6.37 ± 2.41 ng/ml in LVEF <35 % group (p < 0.01), and lowest at 1.49 ± 0.75 ng/ml in LVEF >50% group (p < 0.01), respectively.

Patient Profile & Trop-I Level

PATIENT PROFIL	LE	MEAN TROP I LEVEL (ng/ml)
	18-45yrs	3.38 ± 3.03
	46-70yrs	3.49 ± 2.78

AGE (in years)	>70yrs	4.06 ± 2.98
	PRESENT	4.12 ±3.14
DIABETES	ABSENT	3.17 ± 2.66
	PRESENT	3.56 ± 2.95
HYPERTENSION	ABSENT	3.5 ± 2.81
	PRESENT	3.84 ± 3.05
DYSLIPIDEMIA	ABSENT	3.09 ± 2.58
	PRESENT	3.72 ± 3.08
SMOKING	ABSENT	3.15 ± 2.42
	PRESENT	3.33 ± 2.84
CAD	ABSENT	3.58 ± 2.90
	0-2	2.90 ± 2.60
	3-4	3.70 ± 2.90
TIMI SCORE	5-7	5.90 ± 2.70
	<90	6.07 ± 2.56
SYSTOLIC BLOOD PRESSURE	90-140	3.10 ± 2.69
(mmHg)	>140	3.85 ± 3.04
	1	3.01 ± 2.59
KILLIP CLASS	>1	6.11 ± 2.88
	<35	6.37 ± 2.41
LVEF(%)	35-50	2.49 ± 2.28
	>50	1.49 ± 0.75

Mean value of maximum QTc interval in total population was 472.31 ± 28.65 ms. and did not differ significantly between male patients (471.9 ± 28.6 ms), and female patients (473.3 ± 28.7 ms) p=0.7. Mean valueQTc, in age group of less than 70 years was 470.81 ± 28.78 ms which was significantly lower than mean value in more than 70 year age group, 482.41 ± 25.94 ms, (p = 0.018).

Mean corrected QT interval was significantly higher in patients with diabetes 478.74 ± 30.29 ms, compared to patients without diabetes 468.45 ± 26.97 ms(p = 0.002) and with dyslipidemia 475.24 ± 29.96 ms, compared to patients without dyslipidemia 466.52 ± 26.07 ms (p=0.014), did not differ significantly among patients with or without hypertension, history of smoking, and history of CAD.

Mean value was lowest at 463.58 ± 26.16 ms, in TIMI 0 -2 group (p <0.001), and highest at 504.31 ± 21.78 ms, in TIMI 5 -7 group (p <0.001), respectively. Mean value was lower at 470.65 ± 28.05 ms, in SBP ≥ 90 mmHg group, and higher at 498.41 ± 25.88 runs in SBP <90 mmHg group (p <0.001), respectively. Mean value was lower at 468.22 ± 27.43 ms, in Killip class 1, and higher at 492.38 ± 26.19 ms in Killip class > 1 group (p < 0.001). Mean value was lower at 469.09 ± 28.15 ms, in LVEF $\geq 35\%$ group, and higher at 490.15 ± 24.81 ms in LVEF < 35% group (p <0.001), respectively.

Patient Profile And Corrected Qt Interval

PATIENT PROFILE		MEAN QTc MAX (ms)
AGE(in years)	<70	470.81 ± 28.78
	>70	482.42 ± 25.94
DIABETES	PRESENT	478.74 ± 30.29
	ABSENT	468.45 ± 26.97
HYPERTENSION	PRESENT	473.33 ± 28.77
	ABSENT	471.11 ± 28.57
DYSLIPIDEMIA	PRESENT	475.24 ± 29.96
	ABSENT	466.52 ± 26.07
SMOKING	PRESENT	472.89 ± 28.76
	ABSENT	471.17 ± 28.55
CAD	PRESENT	472.53 ± 29.27
	ABSENT	472.25 ± 28.55

TIMI SCORE	0-2	463.58 ± 26.16
	3-4	475.17 ± 28.03
	5-7	504.31 ± 21.78
SYSTOLIC BLOOD PRESSURE	<90	498.41 ± 25.88
(mmHg)	≥90	470.65 ± 28.05
KILLIP CLASS	I	468.22 ± 27.43
	>I	492.38 ± 26.19
LVEF (%)	<35	490.15 ± 24.81
	≥35	469.09 ± 28.15

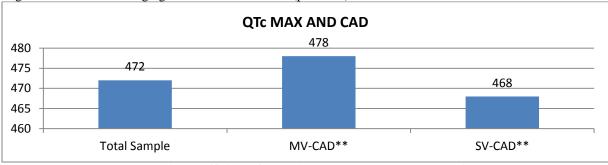
Maximum patients have single vessel disease i.e 181(60.1%) out of which 114 (62.9%) patients had Left anterior descending artery (LAD) ,24 (13.2%) patients had Left circumflex artery (LCX) and Forty three (23.7%) patients had Right coronary artery (RCA) as culprit vessel. Multivessel disease with significant lesion in vessel other than culprit artery was found in 101 (33.5%) patients. Out of which 51(50.5%) patients had LAD ,Seventeen (16.8%) patients had LCX and 26(25.7%) patients had RCA as the culprit vessel. Nineteen (6.3%) patients had either non significant CAD or normal angiogram and 14 patients (13.9%) had significant Left Main disease . Culprit vessel could not be identified in 7 patients (6.9%) as more than 1 vessel was critically diseased

VESSEL INVOLVED IN CAG	NO. OF PATIENTS	PERCENTAGE
SINGLE VESSEL DISEASE	181	60.1
MULTI VESSEL DISEASE	101	33.5
NORMAL CORONARIES	19	6.3

Mean Troponin-I value was significantly higher in patients with multivessel disease 4.14 ± 3.20 ng/ml vs single vessel disease on angiogram 3.17 ± 2.62 ng/ml(p<0.005)



Mean corrected QT interval was significantly higher in patients with multivessel disease (478.16 \pm 30.50 ms), vs single vessel disease on angiogram 468.89 \pm 26.02 ms (p =0.009).



The Spearman correlation coefficient of 0.637 between QTc-max and Troponin- I, (p <0.001).

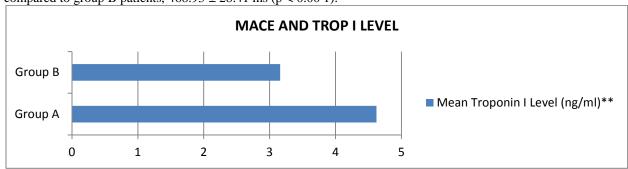
Mace

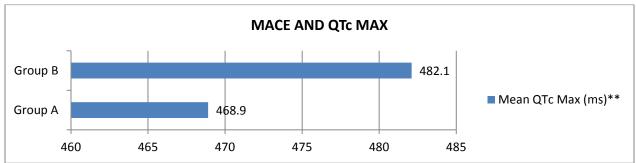
MACE has occurred in 77 out of 301 patients (25.6%) within 30 days follow-up after hospital discharge. These patients were classified into Group A. Out of these patients, 14/301 (4.6%) patients expired, including 3 cases of sudden cardiac death, 22/301 (7.3%) patients had suffered recurrent MI. Forty one out of 301 (13.6%) patients suffered Unstable Angina requiring revascularization within 30 days. The 224 out of 301 (74.4%) patients who did not suffer MACE within 30 days post discharge, were classified into Group B.

MACE EVENTS	NO. OF PATIENTS	PERCENTAGE
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DEATH	14	18.18
MYOCARDIAL INFARCTION	22	28.57
URGENT REVASCULARISATION	41	53.24

Group A patients were significantly older $(60.19 \pm 11.64 \text{ years})$ compared to group B(52.13 \pm 11.9 years) (p <0.001). Proportion of males was significantly more in Group B, 167 (74.6%) vs 45 (58.4%) in group A (p 0.007). Diabetes was significantly more frequent in Group A, 40 (51.9%) patients vs 73 (32.6%) in group B (p = 0.004). Dyslipidemia, Hypertension, Smoking, and history of CAD did not differ significantly among group A and B patients. Group A patients had significantly higher mean Troponin I level 4.62 ± 3.01 ng/ml, compared to group B patients, 3.16 ± 2.74 ng/ml (p < 0.001). and significantly higher mean corrected QT interval 482.16 ± 27.23 ms, compared to group B patients, 468.93 ± 28.41 ms (p < 0.001).





In multivariate analysis of a logistic regression model with variables with p < 0.05, TIMI score > 2 (OR 9.9, p < 0.001, 95% CI 3.90-25.52) was the strongest independent predictor for MACE followed by QTc > 468 ms (OR 2.6, p = 0.018, 95% CI 1.38-5.09) after adjusting for other variables. Troponin I, age, sex, diabetes, SBP < 90 mmHg, Killip class higher than 1, LVEF < 35%, and MV-CAD were not independent predictors of MACE.

Discussion:-

Troponin I levels correlated significantly with poor prognostic markers in ACS. Highest quartile of troponin I values was seen in patients who presented with higher TIMI scores, severe left ventricular systolic dysfunction ,higher killip class and hypotension. (similar to study by lindahl et al,) .In our study, Mean Troponin I value was also significantly higher in patients with multivessel disease on angiogram (P=0.005) with respect to single vessel disease group, and did not differ significantly according to culprit vessel.

In FRISC II study, Troponin T levels did not correlate with severity of underlying coronary artery disease on angiography ¹³ But in recent studies in stable CAD patients high sensitivity troponin increases with number of vessels with significant stenosis, as well as number of significant stenosis. ¹⁴

Mean QTc interval did not differ significantly between male and female \pm patients but varied significantly according to patient's age, with age (< 70 years, mean QTc was significantly lower, p = 0,01). with diabetes, p<0.001 or dyslipidemia (p<0.001).

Mean QTc varied significantly according to TIMI score, killip class, systolic BP and left ventricular ejection fraction at presentation, with highest value in TIMI 5-7 group(p<0.001), killip class >1,(p<0.001),SBP<90mm Hg and LVEF <35%(p<0.001)

Multivessel disease have higher Mean QTc value compared to single vessel disease (p=0.009). The QTc values did not differ according to culprit vessel. Our finding were comparable from the study published by Jimenez – Candil et al in NSTEACS patients ,

There was significant correlation between QTc Max and Troponin I level with a correlation coefficient of 0.637 between QTc-max and Troponin I, (p <0.001).

On multivariate analysis, Troponin I level was independently predicted by, Age group (p=0.04), LVEF (p <0.001), and TIMI score (p < 0.001), after adjusting for sex, diabetes, dyslipidemia , Killip class, SBP, ST deviation, and MV-CAD. Maximum QTc interval was independently predicted by LVEF (p < 0.001) and TIMI score (p<0.001), after adjusting for all other variables.

Patients with MACE had significantly higher mean Troponin - I level higher mean QTc interval (p<0.001).

Mueller et al ¹⁵,Lindahl et al ¹³ showed that the risk of in hospital and long term mortality increased with absolute level of troponin-T.According to Gadaleta et al, ⁹Susan et al (reported QTc>0.458) ¹⁶, Jimenez Candil et al ¹⁷ the QTc interval was found to be an independent predictor of MACE risk in NSTEACS population.

Limitation:

This was a relatively small study sample, with even smaller number of patients in various subgroups, therefore a larger cohort of patients is required to further validate these results.

High sensitivity troponin assays are not widely available. Use of high sensitivity assays instead of conventional assay might affect the result of predictive model in multivariate analysi and long term follow up assessment of MACE is advisable.

Conclusion:-

Corrected QT interval has a strongly positive significant correlation with quantitative troponin I level in NSTEMI patients. Prolonged corrected QT interval is independently predictive of higher rate of major adverse cardiovascular events after NSTEMI within 30 days post discharge.

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