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QRS Duration and AVR-St Elevation: Suggestive Predictor for LM/TVD among Non St Segment Elevation Acute Coronary Syndrome

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Abstract

Background: In patients with NSTEACS early non invasive prediction of LM/TVD helps to plan treatment strategy and predicts prognosis. Association of ST depression, aVR ST elevation with prognosis and coronary angiography outcome has been shown previously. Exercise induced QRS duration has sought attention previously but has been neglected in last decade. This study assesses association of various parameters and risk factors with LM/TVD along with sensitivity and specificity of various ECG variables in predicting LM/TVD.

Methods: We conducted observational study from single centre. All patients of NSTEACS underwent coronary angiography. Amongst them, patient having LM/TVD were enrolled in first group. All subsequent patients of NSTEACS who were SVD/DVD without LM involvement were enrolled in second group ie, Non LM/TVD group. Total 213 patients were enrolled in LM/TVD group and 209 in Non LM/TVD group. Thorough ECG evaluation of ST depression, ST elevation in aVR and QRS duration was done for all enrolled patients. Rest of investigations including coronary angiography was performed as per the AHA protocol. Correlation of various parameters with angiographic outcome was performed.

Results: Patients of higher age, higher weight and BMI, diabetic, dyslipidemic, maximum ST depression, aVR ST elevation, ST depression and high normal QRS were significantly prone for LM/TVD by univariate analysis.

However, by multivariate analysis diabetes and maximum ST depression lost their significance as an independent variable. Senstivity of ST depression > 0.5mm, aVR ST elevation >0.5mm and QRS duration with values > 91ms were 79.81%, 35.68% and 84.04% respectively. While specificity of ST depression > 0.5mm, aVR ST elevation >0.5mm and QRS duration with values > 91ms were 22.49%, 98.09% and 61.24% respectively.

Conclusion: Along with risk factor assessment ECG changes serve great importance in predicting LM/TVD. QRS duration is the most sensitive marker with acceptable specificity, while aVR ST elevation is most specific but least sensitive marker.

Keywords: NSTEACS, LM/TVD, QRS duration, aVR ST elevation

Introduction

NSTEACS is a state of myocardial ischemia due to instantaneous coronary blood flow reduction leading to ECG changes apart from ST elevation. NSTEACS contribute 70% of ACS [1]. Among all NSTEACS patients 60% share is of male patients. NSTEACS has fluctuating prognosis. Prognosis assessment is essential method to decide admission and treatment option. Various risk scores based on clinical and early noninvasive markers to stratify patients according to prognosis have been developed. The routinely used clinical scores are TIMI[2] (Thrombolysis In Myocardial Infarction) risk score and GRACE [3] (Global Registry of Acute Coronary Events) risk score. Scores like PURSUIT [4], Sanchis score [5], NCDR-ACTION etc, are now relegated for historic importance.

TIMI risk score for NSTEACS predicts percentage of all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization through 14 days after randomization. TIMI risk score depends on 7 variables at admission; 1 point is given for each variable ie; ≥65 years of age, ≥3 risk factors for CAD, prior coronary stenosis ≥50%, ST deviation on ECG, ≥2 anginal events in prior 24 hrs, use of aspirin in prior 7 days and elevated cardiac biomarkers [2]. In contrast to TIMI risk score GRACE risk score predicts in-hospital and postdischarge mortality or MI and it depends on age, heart rate, SBP, Killip class, creatinine level , cardiac arrest at the time of admission, ST deviation and cardiac enzymes [3]. Besides these scores factors like renal insufficiency [2]., tachycardia, hypotension, heart failure and new MR are also individually associated with poor prognosis [6,7].

TIMI and GRACE risk scores signify role of ECG in predicting prognosis [2,8]. ST segment deviation is only ECG finding described in these scores. NSTEACS has varying ECG presentation from normal to gross ST depression. 2 or more contiguous leads having ST depression of >0.05 mm suggest poor prognosis [9]. Prognosis is unaffected by T inversion with or without ST-T changes in NSTEACS [10]. In contrast ST elevation in STEMI which can predict culprit vessel, ST deviation in NSTEACS can predict prognosis but cannot predict culprit vessel. Another marker of ECG ie, QRS duration has been shown as sensitive marker of extensive myocardial ischemia over ST-T changes [11-13]. Besides, exercise induced QRS prolongation suggest immense and serious form of CAD [14,15]. ST elevation in lead aVR and positive Trop T is useful predictor of LM/TVD as shown in various studies [16-18].

LM/TVD on coronary angiography is poor prognostic marker in NSTEACS patients. Non-invasive early identification of LM/TVD is helpful to decide prognosis and treatment strategy. Previously described scores predict poor prognosis but not necessarily correlated with LM/TVD. Early diagnosis of LM/TVD may be helpful to

direct the patient for urgent CABG if required. In present study we assessed various risk factors associated with severe form of CAD (LM/TVD). This study throws light on ECG association with angiographic outcomes. This study assess in association of QRS duration, ST depression and aVR ST elevation with LM/TVD in patient with NSTEACS. We also calculated sensitivity, specificity of ST depression, aVR ST elevation and QRS duration to predict LM/TVD.

Methods

Study group: Patients who presented to emergency with constricting retrosternal chest pain and which occurs at rest or minimal exertion and persisted for ≥10 minutes were evaluated. This pain could be associated with or without radiation to arms, nausea, vomiting, dyspnea, abdominal pain or diaphoresis and were diagnosed NSTEACS in emergency. These were admitted in cardiology department as per the AHA recommendation in our tertiary care centre of Indian subcontinent. Patients underwent investigation as per the AHA protocol and underwent coronary angiography with intention to treat. Patients having LM/TVD on coronary angiography were enrolled in first group and subsequently next patient of NSTEACS with non LM/TVD in coronary angiography were enrolled in other group. Patient with ECG abnormalities affecting QRS duration and ST-T changes such as LBBB, RBBB, ventricular pacing, ventricular pre excitation, LVH, anti arrhythmic drugs, Q wave MI, occurrence of PCI within 6 month, previous CABG, patient with non ischemic or atypical pain were excluded. These patients were enrolled from March 2017 to November 2018.

Study design

This is a single centre observational study from a developing country. All patients underwent detailed history regarding symptomatic assessment and treatment history. Patients who were on OMT and non-responding were also included. These subjects underwent risk factor assessment by history and lab examination.

Investigation

Lipid profile and diabetic status assessment were done by various lab test for all patients. Liver and kidney function test were also done to avoid undue confounding factors. Subsequently all patients underwent ECG with (BPL CARDIART 9108), every 24 hours of hospital stay and also during emergency like clinical detoriation as and when required. ECGs were evaluated at standardization of 20mm Volt and at rate of 50 mm/second for ST-T assessment and QRS duration respectively. These measurement were done by manual calliper.

All subject's quantitative TropT were analysed at the time of admission to classify type of ACS (unstable angina or Non ST elevation MI). All enrolled patient during period of hospitalisation underwent 2D echocardiography by available echo machine (Philips EPIQ7 and Philips iE33) to look for any regional wall motion abnormalities, ejection fraction etc.

In patients who underwent coronary angiography with intention to treat, lesions were assessed by 2 different observers by visual eyeballing. Patients were grouped as LM/TVD group or Non LM/TVD group. LM/TVD group included either left main disease with SVD/DVD/TVD or TVD without left main. Non LM/TVD group included only SVD or DVD without any left main disease.

Statistical Analysis

Continuous data was summarised in the form of mean and S.D. Count Data was expressed in form of proportions and percentage. Shapiro wilk test and levene test were performed to test normalcy of distribution and homogeneity of variance respectively. The difference in

mean in 2 groups was analysed using student t test. Difference in proportion would be analysed using chi-square test. Diagnostic validity analysis was done by 2×2 table. Logistic regression was used for prediction of LM/TVD on the bais of independent factors; the level of confidence would be kept 95% for all statistical analysis.

Result

422 patients were enrolled in total. 213 were included in LM/TVD group. 209 were enrolled in Non LM/TVD group (**Table 1**). In LM/TVD group 65.7% were males, 46.5% were smokers, 51.6% were hypertensive, 15 % had family history of CAD. Similarly non LM/TVD group comprised of 62.7% males, 47.4% smokers, 49.8% hypertensives and 9.6% with family history of CAD. There was no significant difference in proportion of both the groups having raised biomarker of MI in the form of TropT. It was raised in 44.1% and 42.1% in LM/TVD and non LM/TVD group respectively. There was no significant difference in terms of frequency of ST depression > 0.5 mm; it was 79.8% and 77.5% in LM/TVD and non LM/TVD group respectively.

In LM/TVD group 32.9% had LM disease in the form of LM-SVD, LM-DVD, LM-TVD in decreasing order of percentage. 67.1 % had TVD without LM involvement. Non LM/TVD group had predominantly single vessel disease with 64.6%.

Demographic difference

There was significant difference in mean age and BMI in both the groups **(Table 1)**. Mean age of LM/TVD group was significantly higher with values 59.19±13.28 years, while in non LM/TVD group it was 55.52±12.92 years (P=0.001). There was significant difference in BMI in both the groups. Mean BMI in LM/TVD group was in overweight range with 27.01±4.26 while in non LM/TVD it was nearer to upper limit of normal range with value 24.84±7.91. This difference in BMI was attributed by significant difference in weight with P= 0.0001.

Risk Factor of CAD

Both the groups differ in frequency of diabetes and dyslipidemia **(Table 1)**. In LM/TVD group diabetics were 50.7% while in non LM/TVD these were 40.2% (P=0.030). Dyslipidemia as assessed by lipid profile was predominant in LM/TVD group and was 32.4% in comparison to 20.6% in latter (P=0.006). Higher BMI, diabetes and dyslipidemia suggested metabolic syndrome was prevalent in LM/TVD group.

ECG and Biomarkers

Though ST depression was seen in 79.8% in LM/TVD group and 77.5% in non LM/TVD group and its proportion was not significantly different with P=0.564, but mean of maximum ST depression was significantly higher (P<0.05) with former having 1.17±1.60 mm and 0.93±1.23 mm in latter **(Table 1)**. Mean QRS duration in LM/TVD group was significantly higher with value 98.53±16.45 ms vs 89.20±18.72 ms in non LM/TVD group (P=0.0001). aVR ST elevation > 0.5mm was seen significantly in higher proportion of LM/TVD group with 53.5% (P=0.001). Also, mean of aVR ST elevation was higher in this group with value 0.65±1.65 mm (P=0.0001). There was no significant difference in mean of Trop T value.

Logistic regression

The presence of LM/TVD disease is associated with many factors (vide supra), therefore multivariate logistic regression analysis was performed to assess independent variable effect. Multivaraiate logistic regression showed age, BMI, dyslipidemia, QRS interval, aVR ST elevation were independent variables which significantly predicted angiographic LM/TVD **(Table 2)**. In contrast diabetes, ST

depression failed to show independent effect to predict LM/TVD.

Sensitivity and Specificity

Assessment of sensitivity and specificity of various ECG variables and their cutoff showed, ST depression > 0.5mm has fair sensitivity with poor specificity with values 79.81% and 22.49% respectively **(Table 3)**. aVR ST elevation >0.5mm is highly specific but poorly sensitive with values of 98.09% and 35.68% respectively. QRS duration with values > 91ms has good senstivity with acceptable specificity of values 84.04% and 61.24% respectively. Also, ROC curve and their corresponding area **(Figure1-3)** suggest that QRS duration has better predictive ability for determining NSTEACS with LM/TVD disease over aVR ST elevation and maximum ST depression.

Table 1: Comparison of various variables in LM/TVD group vs Non LM/TVD group

Variable	LM/TVD (N=213)	Non LM/TVD (N=209)	Significance (P value)
Age (years)	59.19±6.64	55.52±6.46	<0.001
Male Sex	140 (65.7%)	131 (62.7%)	0.514
Weight (Kg)	72.64±9.46	67.35±11.01	<0.001
Height (m)	1.65±0.08	1.65±0.08	0.724
BMI (kg/m^2)	27.01±4.26	24.84±3.96	<0.001
Smoker	99 (46.5%)	99 (47.4%)	0.855
Hypertension	110 (51.6%)	104 (49.8%)	0.699
DM	108 (50.7%)	84 (40.2%)	0.030
Dyslipidemia	69 (32.4%)	43 (20.6%)	0.006
Family History of CAD	32 (15%)	20 (9.6%)	0.088
NSTEMI	94 (44.1%)	88 (42.1%)	0.674
Trop T	0.25±0.48	0.25±0.51	0.456
ST depression ≥ 0.5mm	170 (79.8%)	162 (77.5%)	0.564
aVR ST elevation	114 (53.5%)	47 (22.5%)	<0.001
QRS Interval (ms)	98.53±8.23	89.20±9.36	<0.001
ST-segment depression (mm)	1.17±0.80	0.93±0.62	0.001
aVR ST elevation (mm)	0.65±0.82	0.13±0.26	<0.001
EF (%)	52.22±5.72	53.8±3.50	0.001
Angiographic Outcome	LM+SVD -30 (14.1%) LM+DVD -25 (11.7%) LM+TVD -15 (7.05%) TVD -143 (67.14%)	SVD - 135 (64.6%) DVD - 75 (35.9%)	

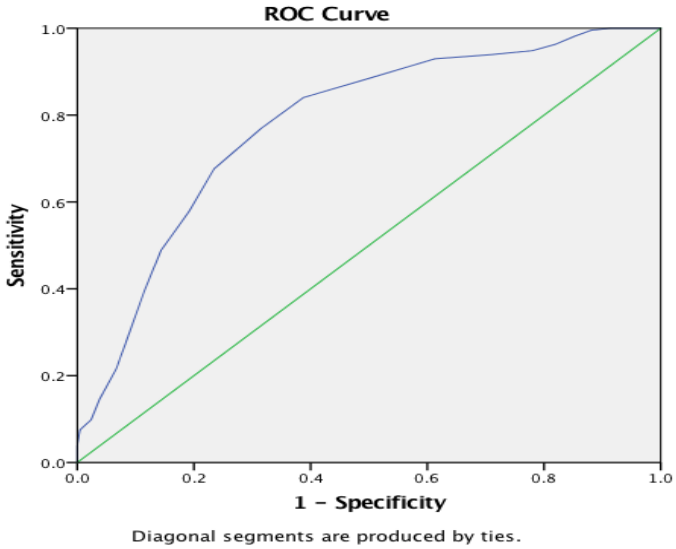
Table 2: Multivariate logistic regression analysis for assessment of relation between various variables and angiographic outcome of NSTEACS in the form of LM/TVD

Variable	Significance	Odds with 95% C.I
Age	<0.001	0.92(0.89-0.96)
Sex	0.325	0.77 (0.46-1.29)
BMI	0.005	0.91 (0.85-0.97)
DM	0.829	0.94 (0.55-1.61)
Dyslipidemia	0.029	0.52 (0.29-0.93)
Family History of CAD	0.223	0.61 (0.28-1.34)
QRS Interval	<0.001	0.91 (0.88-0.94)
Maximal ST-segment depression (mm)	0.060	1.44 (0.98-2.12)
aVR ST elevation (mm)	<0.001	0.19 (0.09-0.38)

Table 3: Senstivity and Specificity of various ECG variables

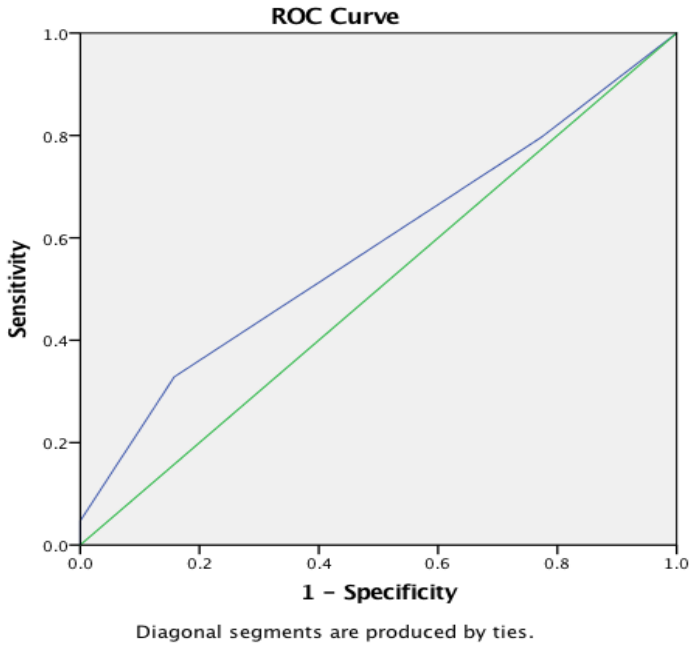
ECG Variables	Senstivity	Specificity
QRS Duration >91 ms	84.04%	61.24%
ST depression >0.5mm	79.81%	22.49%
ST depression >1.5mm	32.86%	84.21%
aVR ST elevation >0.5mm	35.68%	98.09%

Figure 1: ROC Curve of QRS duration



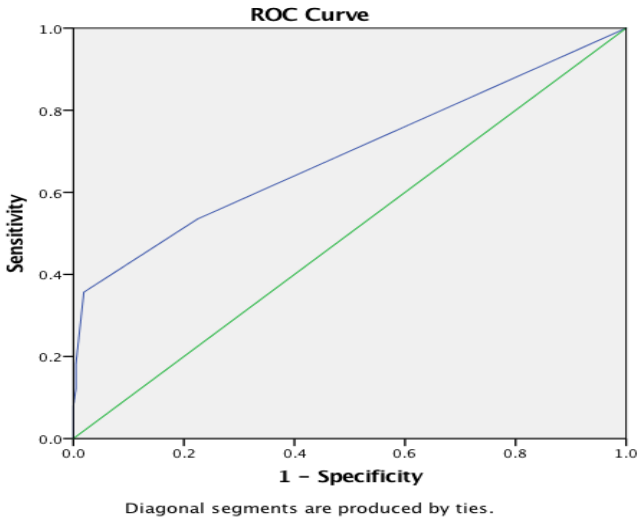
Area under Curve=0.78 (95% C.I : 0.73 to 0.82, P<0.001)

Figure 2: ROC Curve of ST depression in patients with NSTEACS



Area under Curve=0.58 (95% C.I : 0.52 to 0.63, P=0.005)

Figure 3: ROC Curve of aVR ST elevation in patients with NSTEACS



Area under Curve=0.69 (95% C.I : 0.64 to 0.74, P<0.001)

Discussion

Our study has shown that age, BMI, dyslipidemia and diabetes are significant risk factors for predicting left main and TVD in patients with NSTEACS. Mean age was approximately 4 years higher among LM/TVD group with value 59.19±13.28 years. Majority of the patients among LM/TVD group were obese with mean BMI 27.01±4.26 kg/m^2. Incidences of diabetes and dyslipidemia were approximately 10% higher among LM/TVD group with values 50.7% and 32.4 % respectively. Previous studies including OASIS registry suggest age, male sex, diabetes, hypercholestrolemia and metabolic syndrome as poor prognostic marker of CAD. Diabetes is strongly associated with other cardiovascular risk factors like

obesity, hypertension and dyslipidemia. In diabetics 80% are obese, 70 % hypertensive and 70% have raised LDL [19]. This clustering of risk factor leads to increased risk of CAD and poorer prognosis. Diabetes itself is a major risk factor for multivessel CAD. Most common cause of death among diabetics is CAD [20]. Most of the time diabetics are not eligible for PCI. Even if eligible, they may have poorer outcome, as diabetes affects course of healing of vessel in post PCI period, this mechanism leads to increased risk of stent thrombosis and stent restenosis [21,22]. Arca M et al concluded that dyslipidemia is independently a major atherogenic risk factor for CAD, MACE and atherogenic dyslipidemia and also has significant correlation with insulin resistant diabetes [23]. Previous study also proved dyslipidemia to be significantly associated with higher coronary artery calcium [24]. This increased CAC is a risk factor for multivessel CAD.

This hyperlipidemia, hypercholesterolemia, and metabolic Syndrome had significantly increased risk of multivessel CAD in patients with subclinical CAD. Pathogenesis of these risk factors are explained by chronic inflammation. Diabetes, hyperinsulinemia, hypercholesterolemia and metabolic syndrome are strongly correlated to inflammatory markers like IL6 and TNFα. This inflammatory mileu leads to increased risk of atherogenesis.

In our study, not only aVR ST elevation was significantly prevalent among LM/TVD group also the absolute values were higher among the same. Thus higher aVR ST elevation is a poor prognostic marker. aVR ST elevation >0.5 mm is highly specific (98.09%) but poorly sensitive (35.68%) marker of LM/TVD. Trop T and aVR ST elevation firmly predicts LM/TVD as suggested by Kosuge M et al previously. Also, Lim KD et al and Westerhout et al already established Trop T as poor prognostic marker in [25-28]. Though in our study the number of NSTEMI patients in LM/TVD group didn't differ with patients in non LM/TVD group as was the case of absolute value of TropT. This can be probably explained by strict admissions of NSTEACS patients in our centre, ignorance and sensitivity of third world people towards CAD which prevents followup to health centre for same.

In our study ST depression among precordial ECG leads were prevalent in both groups of LM/TVD group or non LM/TVD group and there was no significant difference (79.8% in LM/TVD group Vs 77.5% in non LM/TVD group). However, mean of absolute value of maximum ST depression was significantly higher (P = 0.001) in LM/TVD group with value 1.17±1.60 mm. ST depression > 1.5mm has good specificity (84.21%) but poorly sensitive (34.26%). ST depression in patient of NSTEACS and its clinical significance and prognostic correlation has been already demonstrated in previous studies [29-32].

In our study Mean QRS duration was 98.53±16.45 ms which was significantly higher among LM/TVD group in comparison to non LM/TVD group with value 89.20±18.72 ms. Also QRS duration >91ms has good sensitivity of 84.04 % and fair specificity of 61.24%. Thus among all ECG markers ST depression, aVR ST elevation and QRS duration, QRS duration is the most sensitive marker. Hamlin RL et al and Holland RP et al has reported ischemia leads to leakage of K^+ which leads to slow conduction. This slow conduction velocity leads to QRS prolongation [33,34]. Cantor et al has demonstrated QRS prolongation is closely associated with proximal coronary artery occlusion than to distal/small coronary artery vessels [12,13]. Exercise induced QRS prolongation without bundle branch block was closely associated with

number of diseased vessel, extent of myocardium supplied by diseased vessel and segment of myocardium dysfunction.

Conclusion

Like previous demographic studies age, dyslipidemia, obesity came out to be significant risk factor for severe form of CAD on the basis of angiography. ECG findings like aVR ST elevation is most specific marker of LM/TVD while QRS duration >91ms is most sensitive marker of LM/TVD. Considering all ECG markers ie, aVR ST elevation, QRS duration and ST depression one can non-invasively predict LM/TVD with good amount of accuracy.

Strength and Limitation

Our study can be implemented on whole population because of large number of patients enrolled in severe CAD group ie LM/TVD group. Though sample in our study had uniform distribution but predominant form of severe CAD in our study was triple vessel disease not left main. This was a single centre study so population studied was from localized geographical area. It's a study from a third world country due to which it may not be implemented on western or developed country. Since ECG was studied by manual calipers so accuracy of values were up to 2 ms in QRS duration and 0.5mm of ST deviation. In coronary angiography lesions were estimated on visual basis not by quantitative coronary angiography which lacks accuracy. In our study borderline lesions were not confirmed by FFR this may overestimate significant CAD. Despite limitations our study acquired most practical method of lesion and ECG assessment. Thus practically it holds great importance.

Abbreviation

NSTEACS: Non ST elevation Acute Cornary Syndrome

SVD: Single Vessel Disease

DVD: Double Vessel Disease

TVD: Triple Vessel Disease

LM: Left Main disease

TIMI: Thrombolysis In Myocardial Infarction

GRACE: Global Registry of Acute Coronary Events

CAD: Coronary Artery Disease

AHA: American Heart Association

LBBB: Left Bundle Branch Block

RBBB: Right Bundle Branch Block

LVH: Left Ventricular Hypertrophy

MI: Myocardial Infarction

PCI: Percutaneous Coronary Intervention

CABG: Coronary Artery Bypass Graft

OMT: Opyimal Medical Therapy

MACE: Major Adverse Cardiac Event

FFR: Fractional Flow Reserve

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