ORIGINAL ARTICLE

DIFFUSE ST DEPRESSION WITH ST ELEVATION AVR IN ACUTE CORONARY SYNDROME AND ITS ASSOCIATION WITH SIGNIFICANT LEFT MAIN OR THREE VESSEL CORONARY ARTERY DISEASE AND ITS CONFOUNDERS

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Background: Global ST depression in 8 or more leads along with ST elevation in aVR has been considered as hallmark of widespread sub-endocardial ischemia. It has been associated with left main (LM) stem or three vessel disease (3VD). But different studies have shown different results. We collected data from patients to see association of these ECG changes with significant LM stem disease and/or significant (3VD). **Methods:** It was a prospective observational study performed at tertiary care cardiac center. All patients with acute coronary syndrome (ACS) having global ST depression and ST Elevation in aVR (that is ST depression of at least 0.5 mv in ≥8 leads along with ST elevation in aVR of at least 0.5 mv) and have undergone coronary angiogram were included. **Results**: Our study included 404 patients with above mentioned ECG findings. We observed significant LM stem or significant 3VD in 67% (n=274), 3VD in 55% (n=222) and significant LM stem in only 29% (n=118). Risk factors like diabetes, hypertension and smoking increase probability of these ECG changes up to 40.4%, 32.1% and 33.3% for significant LM stem disease and 62.7%, 57.1% and 57.5% for significant 3VD. Magnitude of ST elevation in aVR leads ≥1 mm increase sensitivity for LM stem disease 35% and for 3VD up to 60.4% and TIMI score ≥4 up to 36.7% for significant LM stem disease and 62.5% for significant 3VD. **Conclusion:** Global ST depression along with ST elevation in aVR in patients with ACS has low probability for significant LM stem intermediate probability for significant 3VD. Factors like presence of diabetes, hypertension, smoking, magnitude of ST elevation in aVR, and TIMI score improves its diagnostic yield.

Keywords: Global ST depression; Significant left main stem disease; Significant triple vessel disease; TIMI score

Citation: Ahmed S, Khatti S, Shah GA, Khan N, Rai L, Khan MZ, *et al*. Diffuse ST depression with ST elevation aVR in acute coronary syndrome and its association with significant left main or three vessel coronary artery disease and its confounders. J Ayub Med Coll Abbottabad 2023;35(1):43–9.

DOI: 10.55519/JAMC-01-10590

INTRODUCTION

Coronary artery disease is the common cardiovascular disorder worldwide with a prevalence of 156 million people around the world.[1] Prediction of significant left main (LM) coronary artery disease and significant three vessel coronary artery disease (3VD) is important because both are associated with poor survival and high mortality.[2–5] Acute coronary syndrome (ACS) consists of three patterns of unstable coronary artery disease that are associated with sudden rupture of plaque inside the coronary artery: Unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). Twelve lead ECG is important diagnostic tool for acute coronary syndrome it is usually initial investigation a patient with suspected acute coronary syndrome gets in emergency. Augmented vector right (aVR) lead in 12 lead ECG is commonly "ignored" and designated as the "neglected lead"[6]; Lead aVR is electrically opposite to the left-sided leads which are I, II, aVL and V4-6; therefore, ST depression in these leads will produce reciprocal ST elevation in aVR. Lead aVR also directly records electrical activity from the right upper portion of the heart, including the right ventricular outflow tract and the basal portion of the interventricular septum.[7] Diffuse ST depressions with the ST elevation in lead aVR are consistent with severe sub-endocardial ischemia, raising concern about multi-vessel disease and possibly LM obstruction.[8] ST segment elevation in aVR has also been associated with increased mortality due to its association with LM disease and 3VD.[9–11]

Diffuse ST-segment depression and ST-segment elevation in aVR has long been considered as marker of wide spread sub-endocardial ischemia. It has shown to be associated with 75% positive

predictive value of the LM stem disease or 3VD.[12] In acute LM coronary artery (LMCA) occlusion, ST-segment elevation in lead aVR can also occur as a mirror image of ST-segment depression in the lateral limb and precordial leads. Global sub-endocardial ischemia caused by acute LMCA occlusion can produce widespread ST-segment depression, especially in the lateral precordial leads, resulting in ST-segment elevation in lead aVR. As recommended by the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society (AHA/ACCF/HRS) for "resting ECGs that reveal ST-segment depression greater than 0.1 mV in 8 or more body surface leads coupled with ST-segment elevation in aVR and/or V1 but are otherwise unremarkable," is that the automated interpretation should suggest "ischemia due to multi-vessel or LMCA obstruction".[12] This recommendation was also in included in European society of cardiology guideline and advised for prompt management of these patients.[13,14]

On the other hand, different studies have shown different results regarding its accuracy; a study reported incidence of LMCA disease among these patients in only 23% of patients.[15] Even studies have shown diffuse ST depression with ST elevation in aVR was not found to be even the most common ECG pattern seen in patients presenting with LMCA obstruction.[16–18] Objectives of this study were to determine the association of global ST depression and ST elevation in aVR on ECG with significant LM stem disease or 3VD and associated confounder which can improve its sensitivity.

MATERIAL AND METHODS

Study was prospective observational study performed in NICVD and its satellite center after approval from ethical committee. We collected data of 404 of patients with ACS from July 2020 to July 2021; all patients were having global ST depression and ST Elevation in aVR (that is ST depression of at least 0.5 mv in ≥8 leads along with ST elevation in aVR of at least 0.5 mv). Patients with paced rhythm, left or right bundle branch block, ECG criteria of left ventricular hypertrophy, history of prior coronary artery bypass surgery, and patients with concomitant known valvular heart disease and patient on digoxin therapy were excluded from the study. All patients were admitted after giving loading dose of aspirin and clopidogrel after that dual antiplatelet therapy, anticoagulation and anti-ischemic therapy was continued during hospital course or until cardiac catheterization. After taking informed consent these patients were taken as early invasive strategy of ACS. Significant LM disease was defined as having angiographically ≥50% stenosis and significant stenosis of other vessel (left anterior disease, left circumflex, and right coronary artery) were defined as having angiographically ≥70% stenosis of either main vessel or their major side branch >2 mm size (i.e., diagonal, OM).

After informed consent, baseline characteristics, duration of chest pain, co-morbidities, TIMI score, ejection fraction if prior echo was done, whether coronary angiogram was performed if so, then left main stem significant disease and number of vessels having significant disease were noted.

RESULTS

Out of 412 patients 8 patients did not undergo cardiac catheterization due to excessive co morbidities and/or patient's lack of consent for coronary angiogram so were excluded from the study; a total of 404 patients were included in the study. Baseline, clinical and angiographic characteristics of patients along with duration of chest pain are given in table-1. Out of 404 patients with diffuse ST depression and ST Elevation in aVR only 29.2% (n=118) had significant left main stem disease, 55% (n=222) had triple vessel disease and 67.82% (n=274) has either LM stem or 3VD.

On the other hands 24.5% (n=98) had two vessel disease and 15.3% (n=62) had single vessel disease and 3.46% (n=14) have no significant coronary artery disease at all. Among patient with LM stem disease 8 (1.9%) patients have isolated LM stem disease, 16.3% (n=66) patients have significant LM stem along with significant 3VD (Table-2).

Patient with LM stem majority were male and had hypertension as major risk factor followed by diabetes and smoking table-2. Significant LM stem disease was 37.7% in male patients while it was only 8.4% in female patients. Amongst age group of patients ≤50 years LM stem disease was 30.3% vs. 28.7% in patients with age >50 years. Patients with diabetes, hypertension and smoking have almost equal proportion of significant LM stem disease with these ECG findings. Presence of diabetes, hypertension and smoking increase the probability of LM stem disease (40.4%, 32.1% and 33.3%) respectively (Figure-1). We found that patient with STE in aVR ≥1 mm was more associated with LM stem than patient with STE in aVR <1 mm (35% vs. 18.7%) and TIMI score of more than ≥4 have more association with significant LM stem disease than TIMI <4 (36.7% vs. 16.2%). Patients with left ventricular (LV) dysfunction and these ECG changes were more associated with significant LM stem disease than patients with normal LV function (36.7% vs. 21.4%).

Amongst patients with triple vessel disease and similar ECG findings again majority of patients were male and their baseline characteristics are

shown in table-3. Significant 3VD was 60.9% in male patients while it was 52.5% in female patients. However as opposed to the finding in LM stem disease patients with age more than 50 years with these ECG findings were more likely associated 3VD than patients with age ≤50 years (59.58% vs. 42.85%). Presence of diabetes, hypertension and smoking increase the probability of LM stem disease (62.7%, 57.1% and 57.5%) respectively (Figure-1).

Patients with STE in aVR ≥1 mm was more associated with 3VD than patient with STE in aVR <1 mm (60.4% vs. 16.2%) and LV dysfunction was not associated with higher incidence of 3VD in these patients than patients with normal LV function (54.76% with normal LV function than 53.33% with some form of LV dysfunction), However patients with moderate to severe LV dysfunction with ejection fraction of ≤35% were more associated with significant 3VD than patient with normal ejection fraction (58.62% vs. 54.76%). Same as for LM stem patients with these ECG changes and TIMI ≥4 was more associated with 3VD than patients with TIMI <4 (62.5% vs. 41.8%).

Table-1: Baseline clinical and angiographic characteristics

Characteristics	Total
Total (N)	**404**
Gender	
Male	70.8% (286)
Female	29.2% (118)
Age (years)	57.37 (±10.27)
30 to 50 years	27.7% (112)
51 to 65 years	51.5% (208)
> 65 years	20.8% (84)
Duration of symptom (hours)	59.19 (±61.86)
Co-morbid conditions	
Diabetes mellitus	42.6% (172)
Hypertensive	69.3% (280)
Smoking	32.7% (132)
Hyperlipidaemia	5.9% (24)
Family history of CAD	2% (8)
Chronic kidney disease	5% (20)
Ejection fraction (%)	47.13 (±8.91)
Ejection fraction not assessed	39.6% (80)
≤35%	14.4% (58)
35 to 50%	45% (182)
> 50%	20.8% (84)
ST elevation (STE) in aVR	
STE in aVR ≥ 1mm	66.3% (268)
STE in aVR < 1mm	33.7% (136)
ST depression	
II,III,Avf	6.9% (28)
V4-V6	93.1% (376)
Thrombolysis in myocardial infarction (TIMI) score	
TIMI < 4	36.6% (148)
TIMI ≥ 4	63.4% (256)
Significant left main (LM) disease	29.2% (118)
LM stenosis (%)	70.51 (±14.31)
LM isolated	6.8% (8)
LM + SVD	10.2% (12)
LM + 2VD	27.1% (32)
LM + 3VD	55.9% (66)
Number of vessels involved	
None	10.9% (22)
SVD	15.3% (62)
2VD	24.3% (98)
3VD	55% (222)
Left anterior descending artery (LAD)	81.7% (330)
LAD Diffuse disease	34.7% (140)
Left circumflex (LCx)	81.7% (330)
LCx Diffuse disease	24.8% (100)
Right coronary artery (RCA)	65.3% (132)
RCA Diffuse disease	22.8% (92)

CAD=coronary artery disease, SVD= single vessel disease, 2VD two vessel disease, 3VD three vessel disease.
Diffuse disease is defined as stenosis of ≥70% and of ≥ 20 mm lengths angiographically.

Table-2: Association of significant Left Main diseases with baseline clinical and angiographic characteristics

Characteristics	Significant LM Disease		*p*-value
	Yes	No	
Total (N)	**118**	**286**	**-**
Gender			
Male	91.5% (108)	62.2% (178)	<0.001*
Female	8.5% (10)	37.8% (108)	
Age (years)	56.85 (±9.57)	57.59 (±10.57)	0.511
30 to 50 years	28.8% (34)	27.3% (78)	0.753
51 to 65 years	54.2% (64)	50.3% (144)	0.477
> 65 years	16.9% (20)	22.4% (64)	0.221
Duration of symptom (hours)	60.9 (±58.14)	58.49 (±63.51)	0.723
Co-morbid conditions			
Diabetes mellitus	57.6% (68)	36.4% (104)	<0.001*
Hypertensive	76.3% (90)	66.4% (190)	0.051
Smoking	37.3% (44)	30.8% (88)	0.204
Hyperlipidemia	8.5% (10)	4.9% (14)	0.166
Family history of CAD	1.7% (2)	2.1% (6)	0.791
Chronic kidney disease	5.1% (6)	4.9% (14)	0.936
Ejection fraction (%)	46.25 (±9.18)	47.55 (±8.8)	0.185
Ejection fraction not assessed	11.9% (14)	23.1% (66)	0.01*
≤35%	16.9% (20)	13.3% (38)	0.340
35 to 50%	55.9% (66)	40.6% (116)	0.005*
> 50%	15.3% (18)	23.1% (66)	0.078
ST elevation (STE) in aVR			
STE in aVR ≥ 1mm	79.7% (94)	60.8% (174)	<0.001*
STE in aVR < 1mm	20.3% (24)	39.2% (112)	
ST depression			
II,III,Avf	5.1% (6)	7.7% (22)	0.348
V4-V6	94.9% (112)	92.3% (264)	
Thrombolysis in myocardial infarction (TIMI) score			
TIMI < 4	20.3% (24)	43.4% (124)	<0.001*
TIMI ≥ 4	79.7% (94)	56.6% (162)	

CAD=coronary artery disease, LM=left main. *Significant at 5%

Table-3: Association of three vessel diseases with baseline clinical and angiographic characteristics

Characteristics	Three Vessel Disease		*p*-value
	Yes	No	
Total (N)	**222**	**182**	**-**
Gender			
Male	72.1% (160)	69.2% (126)	0.532
Female	27.9% (62)	30.8% (56)	
Age (years)	58.34 (±9.27)	56.19 (±11.31)	0.036*
30 to 50 years	21.6% (48)	35.2% (64)	0.002*
51 to 65 years	58.6% (130)	42.9% (78)	0.002*
> 65 years	19.8% (44)	22% (40)	0.595
Duration of symptom (hours)	61.64 (±70.92)	56.21 (±48.8)	0.381
Co-morbid conditions			
Diabetes mellitus	48.6% (108)	35.2% (64)	0.006*
Hypertensive	72.1% (160)	65.9% (120)	0.183
Smoking	34.2% (76)	30.8% (56)	0.460
Hyperlipidemia	7.2% (16)	4.4% (8)	0.234
Family history of CAD	2.7% (6)	1.1% (2)	0.250
Chronic kidney disease	6.3% (14)	3.3% (6)	0.165
Ejection fraction (%)	47.13 (±9.04)	47.13 (±8.82)	0.994
Ejection fraction not assessed	21.6% (48)	17.6% (32)	0.311
≤35%	15.3% (34)	13.2% (24)	0.544
35 to 50%	42.3% (94)	48.4% (88)	0.227
> 50%	20.7% (46)	20.9% (38)	0.969
ST elevation (STE) in aVR			
STE in aVR ≥ 1mm	73% (162)	58.2% (106)	0.002*
STE in aVR < 1mm	27% (60)	41.8% (76)	
ST depression			
II,III,Avf	7.2% (16)	6.6% (12)	0.809
V4-V6	92.8% (206)	93.4% (170)	
Thrombolysis in myocardial infarction (TIMI) score			
TIMI < 4	27.9% (62)	47.3% (86)	<0.001*
TIMI ≥ 4	72.1% (160)	52.7% (96)	

CAD=coronary artery disease. *Significant at 5%

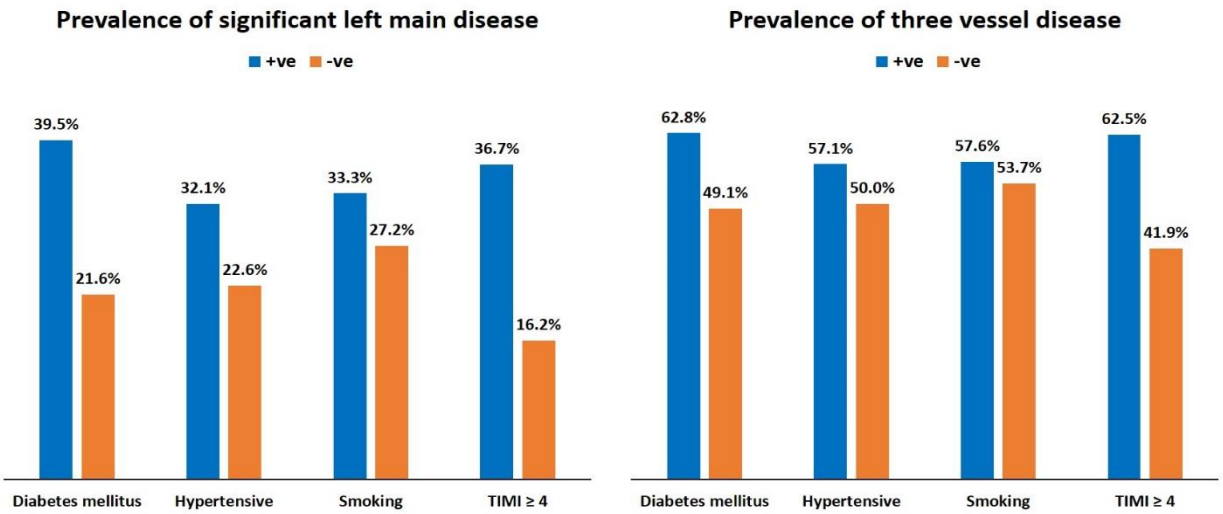

Figure-1: Prevalence of significant left main disease and three vessel diseases by co-morbid conditions and TIMI score

DISCUSSION

ST elevation of 0.1 mv in AVR along with ST depression in 8 or more leads are traditionally considered as diagnostic of LM stem or LM stem equivalent disease.[7] Even some authors have recommended holding of P2Y12 inhibitors as they may undergo CABG due to its strong association with LM and 3VD.[19] It has shown to be associated with 75% positive predictive value for the LM stem disease or 3VD. American Heart Association has recommended this finding as suggestive of LM stem or multi-vessel disease and even European Society of Cardiology has recently has recommended these types of patients for immediate cardiac catheterization.[12,13]

Many studies have contradicted these findings, two studies published by Ashraf Hussien *et al*. and Knotts RJ *et al*. shows that ST-segment elevation in aVR with global ST-segment depression is associated with significant LM coronary artery disease in 44.7% and 23% respectively.[15,20] Another study showed that among patients with these ECG changes prevalence of significant LM/3VD was 19% and isolated LM stem disease was only 4%.[19] Our study showed predictive value of these ECG changes of 67.8% for either LM stem disease or 3VD, only 29.2% for significant LM stem disease and 55% for 3VD. In a review article Nikus *et al*. classify the electrocardiographic changes in case of subtotal occlusion of LMCA which includes widespread ST-segment depression with maximal changes in lead V4-6 with inverted T waves and ST-segment elevation in lead aVR.[21] Another study suggested that 10% of such patients have acute thrombotic occlusion.[22] In contrast in our study, we found only four patients (<1%) had total/subtotal occlusion of LM stem in patients with ACS and these ECG findings.

We have observed that these ECG findings were more associated with 3VD than isolated LM stem disease. Male gender has significantly increased association with significant LM stem disease or 3VD as compared to female gender. There was almost equal proportion of significant LM stem and 3VD with age ≤50 as compared to those with age >50 years. TIMI score is rapid prognostic tool to asses 14 days mortality in patients with non-ST elevation acute coronary syndrome. When taken along with these ECG findings TIMI Score of 4 or more increase probability of detection of significant LM stem disease and 3VD. Presence of risk factors like hypertension, diabetes or smoking also improves the sensitivity of these ECG findings for significant LM stem or 3VD. In observation given by Ashraf Hussien *et al*. in his study the magnitude of ST elevation in aVR ≥1 mm, diabetes and duration of QRS complex were only strong predictors of detecting significant LM stem or 3VD with these ECG changes [20]. Another study by Masami Kosuge *et al*. found only ST elevation in aVR ≥1 mm and positive troponins to be strong predictors of LM stem/ 3VD but did no found relation of risk factors like diabetes, also they did not include TIMI score and LV function in their data.[12] We found diabetes, hypertension, smoking, ST elevation in aVR ≥1 mm, TIMI score ≥4 and LV dysfunction on echocardiogram were more associated with significant LM stem or 3VD but no any association was noted with change in QRS complex. Analysis of the results of the Global Registry of Acute Coronary Events (GRACE) showed a prevalence of LM or 3VD increased by 10.1% with

minor (0.5–1 mm) and by 29.6% with major (>1 mm) ST elevation in lead aVR while we noted 56% with (<1 mm) and by 74% with major (≥1 mm) ST elevation in lead aVR.[23]

A regional study showed 52% had significant LM stem/3VD as compared to 68% in our study in the patients with ST Elevation in aVR, they only included patients with reciprocal ST depression of lead II,III AVF as compared to our inclusion criteria already described and did not mentioned any confounders.[24]

Based on the above findings of strong association of Global ST depression along with ST elevation in aVR with 3VD or significant LM stem disease with the frequency of 67.8%, we suggest that risk stratification scores should also be considered with these ECG findings to improve sensitivity for identification of high-risk patients with these ECG changes. Although troponin values were not included in our data, we suggest that it should also be included in score along with age, risk factor, TIMI score and LV dysfunction and magnitude of ST-segment elevation in aVR lead. The score will help filter out those high-risk patients that require emergent revascularization due to high-risk anatomy.

CONCLUSION

Global ST depression along with ST elevation in aVR has a strong association with significant 3VD but low association with isolated significant LM stem disease. Additional factors like risk factors (diabetes, hypertension, and smoking), magnitude of ST elevation in aVR and TIMI score may add in diagnostic yield of these ECG changes. We suggest that a score can be applied to these patients to improve diagnostic yield of these ECG changes.

AUTHORS' CONTRIBUTION

SA, SK: Conceived the idea, designed the study. SA, GAS, NUK: Data collection. LR, MZK, SAB, NR: Manuscript writing. SA, NUK: Review the manuscript, and SA supervised the entire project.

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Submitted: January 15, 2022	*Revised: September 24, 2022*	*Accepted: September 25, 2022*

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