Association of Fragmented QRS Complex with Short Term Outcome in Patients with Acute ST-Elevation Myocardial Infarction

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Abstract:

Background: Acute ST-elevated myocardial infarction is a life-threatening condition. Presence of fragmented QRS (fQRS) after acute STEMI is associated with alteration of myocardial activation due to myocardial scar and myocardial fibrosis. Previous studies have suggested that fQRS in acute STEMI is associated with increased mortality, morbidity, sudden cardiac death and recurrent adverse cardiovascular events. The study was designed to assess the association of fQRS complex with short-term outcome (in hospital and 30 days follow up) in patients with acute ST elevation myocardial infarction.

Methods: This prospective cohort study was conducted in the Department of Cardiology, Dhaka Medical College Hospital among the STEMI patients who were thrombolysed. All patients underwent serial ECG at admission, within first 12 hours, at 24 hours and at 48 hours for detecting the presence of fQRS complex. Patients showing fQRS involving infarct territory within 48 h of admission were included in the "fQRS group" and those who did not develop fQRS within 48 h of admission were included in the "without fQRS" group. 114 patients had fQRS complex and 104 patients were without fQRS in their ECG. In-hospital outcomes such as: death, heart failure, significant arrhythmias (VT, VF AF, SVT, 2° AV block, CHB), cardiogenic shock were recorded. Among the study patients, sixteen patients were lost to follow up in 30 days of index hospitalization. Finally, 202 patients were tracked for follow up regarding death or re hospitalization information by personal contact or over telephone. Statistical analysis was performed using the statistical package for social science (SPSS) 21.0 software for windows.

Results: Appearance of fQRS complex occurred at admission, within first 12 hours, 24 hours and 48 hours in 53.5%, 23.7%, 14.9% and 7.9% cases respectively. During index hospitalization, development of cardiogenic shock (27.19% vs 11.54%), heart failure (23.68% vs 9.62%) and significant arrhythmias were significantly higher in fQRS group (42.10% vs 11.53%, p<0.05). Although mean duration of hospitalization was similar in both groups (p>0.05), but in-hospital mortality was higher in fQRS group (11.40% vs 3.85%, p<0.05). Rate of re-hospitalization was significantly higher in patients with fQRS complex (21.69% vs 7.29% p<0.05). Overall mortality within 30 days of index hospitalization follow-up also differs significantly in presence of fQRS complex (19.81% vs 5.2%; p =0.006).

Conclusion: Presence of fQRS complex is associated with adverse short-term outcome in patients with acute ST elevation myocardial infarction. Hence, these patients need more aggressive and early invasive treatment to reduce morbidity and mortality.

Keywords: *Fragmented QRS, short term outcome, STEMI*

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Introduction:

Coronary artery disease is major cause of mortality globally and this health problem is reaching pandemic in developed as well as in developing countries.[1] According to an estimate by World Health Organization (WHO) in 2012, about one third of all deaths globally were attributed to CVD, and 7.4 million of those results from ischaemic heart disease.[2] Despite decreasing mortality trends of coronary artery disease (CAD) in many developed countries, increasing number is noticed in developing countries.[3] The ST-segment elevation myocardial infarction (STEMI) is a critical and acute disease that is life threatening to patients. The STEMI patients always have a higher incidence rate of in-hospital mortality and in-hospital adverse cardiovascular events.[4] Despites major advances in cardiac imaging techniques, the standard 12-lead electrocardiogram (ECG) continues to be the most used tool for the diagnosis, early risk stratification, triage and determination of appropriate therapies in patients with acute STEMI. Recent studies have shown that some of the newer ECG parameters can also be used to determine if patients are at higher risk. The most important of these new ECG parameters are fragmented QRS (fQRS) and QRS distortion.[5] Das, et al., (2006) defined fQRS as the QRS complex with the presence of an additional R wave (R') or notching in the nadir of the R wave or the S wave, or the presence of >1 R' (fragmentation) in 2 contagious leads, corresponding to a major coronary artery territory.[6] Data suggest that fQRS occurs in different populations such as coronary artery disease, cardiomyopathies, arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome, congenital heart disease, and long QT syndrome.[7] fQRS occurrence varies from 34% to 60% in patients with acute coronary syndrome (ACS) and usually appears within 48 hours.[8] It is not related to the type of myocardial infarction (MI) [ST-elevation MI (STEMI) or non-ST elevation MI (NSTEMI)].[9] Moreover, several reported that QRS fragmentations on surface ECG have been associated with larger infarcted area as well as with increased mortality, morbidity, sudden cardiac death and recurrent adverse cardiovascular events.[8,10,11] According to a study, cardiac fibrosis was the main causative mechanism for fQRS. Additionally, fQRS may represent altered ventricular depolarization, which can be derived from mechanisms such as non-homogeneous activation of ischemic ventricles in the setting of STEMI.[12]

QRS fragmentation has been identified as a marker of myocardial depolarization abnormalities and has been linked to poor long-term outcome in patients with ischemic as well as non-ischemic heart disease.[10] Kothi, et al., (2015) in their study found that, patients with fQRS had higher CK-MB levels on admission, low left ventricular ejection fraction compared to fQRS negative group.[11] In one study, patients with fQRS complexes on lead V4 -V6 in first acute anterior STEMI was associated with left ventricular apical thrombus formation.[13] fQRS predicts short-term and long- term mortality and major cardiac events and thus is helpful in risk stratification in patients with STEMI.[9] Therefore, the aim of present study was to assess the short-term outcome of fQRS complex in patients with acute STEMI.

Methods:

This prospective cohort study was conducted at the Department of Cardiology, Dhaka Medical College Hospital (DMCH), Dhaka between October, 2018 to September, 2019. The study protocol was approved by Ethical Review Committee (ERC) of Dhaka Medical College and Hospital. All the newly diagnosed acute STEMI patients admitted in the Department of Cardiology, DMCH within the study period who were thrombolysed and fulfilling the inclusion and exclusion criteria were included in this study by convenient purposive sampling Study subjects who came with late presentation after symptom of onset (>12 h), had contraindication for thrombolysis, who were not thrombolysed, had history of prior MI /PCI /CABG, significant primary valvular or congenital heart disease, having fQRS in previous ECG, bundle branch block on ECG (LBBB or RBBB), dependent on permanent pacemaker pacing, having other comorbidities such as chronic kidney disease, chronic liver disease, malignancy and unwilling to participate in the study were excluded. The study subjects were assessed first by attending doctor and then was evaluated by the principal investigator. Detailed history, physical examination and 12 lead standard surface ECG were done. Written consent was taken from the patient or accompanying attendant. All the subjects were evaluated for demographic profile (age, sex); and risk factors for coronary artery disease like diabetes, hypertension, dyslipidemia, smoking and family history of premature coronary artery disease. After thrombolysis, all patients were closely monitored in the coronary care unit. All patients underwent serial ECG at admission, within first 12 hours, at 24 hours and at 48 hours for detecting the presence of fQRS complex. Patients who showed fQRS involving infarct territory within 48 hours of admission were included in the "fQRS" group. Patients who did not develop fQRS within 48 hours of admission were included in the "without QRS" group. In-hospital

outcomes such as death, significant arrhythmias (VT, VF, AF, SVT, 2° AV block, CHB), heart failure, cardiogenic shock and outcome within 30 days of index hospitalization like death and re-hospitalization were recorded. All the information were recorded properly in the preformed data collection sheet and kept confidential. After compiling data from all patients, statistical analysis was done.

Results:

In this study, 114 patients had fQRS complex and 104 patients had no fQRS in their ECG. 16 patients were lost to follow up in 30 days of index hospitalization. So, finally at 30 days of index hospitalization, 202 patients were tracked & included in the study. Among them, 106 patients belonged to 'fQRS' group and 96 patients belonged to 'without fQRS' group.

Fig.1 shows that majority (43.1 %) of patients belonged to 50 - 59 years age group. The least number (3.2 %) of patients belonged to < 40-year age group.

In our study, patients with fQRS complex were significantly older (≥50 years) than patients without fQRS group (59.04±9.74 vs 55.76±8.99 years, p=0.01). Males were more prone to have fQRS after acute STEMI than females (85.96 vs 14.04, p= 0.005). The findings are depicted in Table I.

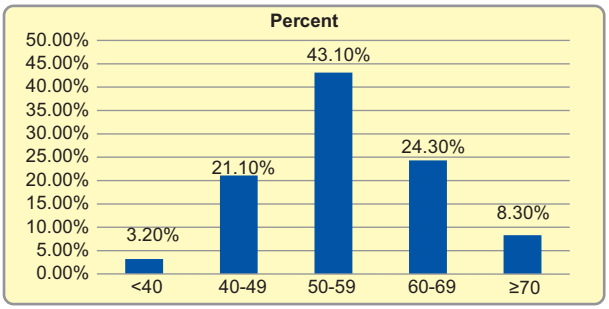

Figure 1: *Age distribution of study patients. (n=218)*

Figure 2 shows that, according to territory of STEMI, majority of acute STEMI was anterior (49.08%) followed by inferior (47.71%) and lateral (3.21%). Majority patients with fragmented QRS had inferior MI (54.39%) whereas majority of patients without fragmented QRS had anterior MI (55.77%).

In our study, 52.3% patients had fragmented QRS complex and 47.7% were without fragmented QRS complex.

Table-I

Demographic characteristics of acute STEMI patients with and without fQRS (n=218)

Parameter		With fQRS (n=114) No. (%)	Without fQRS (n=104) No. (%)	Total (n=218) No. (%)	p value
Age (in years)(Mean±SD)		59.04±9.74	55.76±8.99	57.43±9.40	[a]0.01[s]
Age group					
≥50 years		97(85.09%)	68(65.38%)	165(75.69%)	
<50 years		17(14.91%)	36(34.62%)	53(25.31%)	[b]0.001[s]
Sex	Male	98(85.96%)	73(70.19%)	171(78.44%)	[b]0.005[s]
	Female	16(14.04%)	31(29.81%)	47(21.56%)	

[a]p-value is determined by independent sample t-test. [b]p-value is determined by Chi-square test.
s= Significant

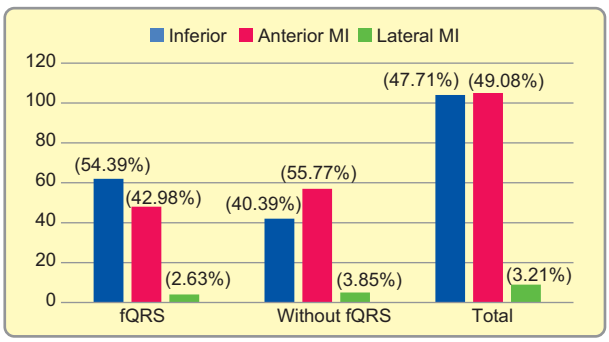

Figure 2: *Territory of STEMI among study patients (n=218)*

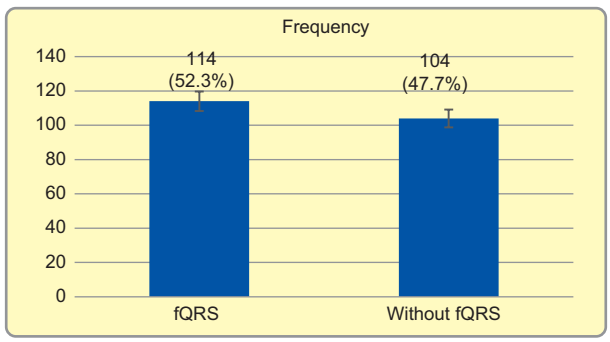

Figure 3: *Distribution of fQRS complex among the study patients. (n=218)*

Majority (53.5%) of patients developed fragmented QRS complex at admission, 23.7% within 12 hours of admission, 14.9% at 24 hours and 7.9% at 48 hours of admission.

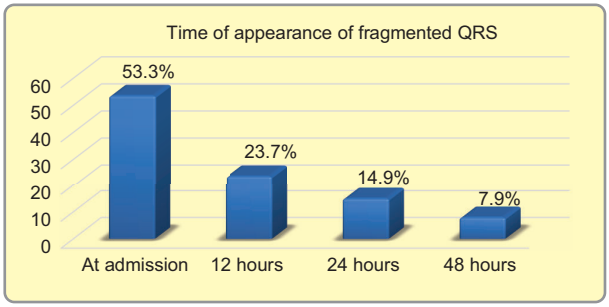

Figure 4: *Time of appearance of fragmented QRS among study patients (n=218)*

Among 218 patients, majority had a history of HTN (62.84%) followed by dyslipidemia (61.93%) and DM (37.61%); all of the risk factors had no statistically significant difference in distribution between the two groups (p value >0.05).

On admission, mean systolic BP and diastolic BP were significantly higher in patients with fQRS group (128.33±32.35 vs 117.12±22.94; p=0.004) and (84.12±17.23 vs 73.46±12.68; p<0.001) compared to without fQRS group. Similarly irregular pulse was significantly higher in fQRS group (9.65% vs 1.92%; p=0.016).

Table IV shows that, 27.19 % patients developed cardiogenic shock in fQRS group, 23.68% of fQRS patients developed heart failure which was statistically significant. Total 27.52% patients developed different types of arrhythmias which were more in fQRS group. Among the arrhythmias, VT (16.67% vs 4.81%) and AF (9.65% vs 1.92%) were statistically significant in fQRS group.

In this study, patients with fragmented QRS had significantly higher (11.40%) mortality rate compared to those without fragmented QRS (3.85%), (p= 0.016). However, duration of hospital stay was similar in both groups.

Table VI shows that, total 30 days mortality in fragmented QRS group was significantly higher compared to those without fragmented QRS (19.81% vs 5.2%, p=0.006). Re-hospitalization within 30 days of index hospitalization was also higher (21.69%) among patients with fragmented QRS compared to without fragmented QRS group (7.29%). (p=0.013).

Multivariate logistic regression analysis was done to see the overall combined effects of determinants of short-term adverse outcome among acute STEMI patients. Age e”50 years and fQRS were found to retain the significance as an independent risk factor with the OR of 3.64 and 4.18 respectively.

Table-II

Distribution of risk factors among acute STEMI patients with and without fQRS. (n=218)

Parameter	With fQRS (n=114) No. (%)	Without fQRS (n=104) No. (%)	Total (n=218) No. (%)	p value
Smoking				0.100^{ns}
Current	44(38.59%)	26(25%)	70(32.11%)	
Past	32(28.07%)	36(34.62%)	68(31.19%)	
Never	38(33.33%)	42(40.38%)	80(36.7%)	
HTN	75(65.79%)	62(59.62%)	137(62.84%)	0.346^{ns}
DM	41(35.96%)	41(39.42%)	82(37.61%)	0.599^{ns}
Dyslipidaemia	75(65.79%)	60(57.69%)	135(61.93%)	0.219^{ns}
Family history of premature CAD	25(21.93%)	16(15.38%)	41(18.81%)	0.217^{ns}

(p-value is determined by Chi-square test)
ns= Not significant

Table-III

Clinical characteristics of acute STEMI patients with and without fQRS on admission (n=218)

Parameter	With fQRS (n=114) No. (%)	Without fQRS (n=104) No. (%)	Total (n=218) No. (%)	p value
Systolic BP (mmHg) (Mean±SD)	128.33±32.35	117.12±22.94	122.98±28.73	[a]0.004[s]
Diastolic BP (mmHg) (Mean±SD)	84.12±17.23	73.46±12.68	79.04±16.11	[a]<0.001[s]
Pulse				[b]0. 016[s]
Regular	103(90.35%)	102(98.07%)	205(94.04%)	
Irregular	11(9.65%)	2(1.92%)	13(5.96%)	

[a]p-value is determined by independent sample t-test.
[b] p-value is determined by Chi-square test.
S=Significant

Table-IV

In-hospital short term outcome in acute STEMI patients with and without fQRS (n=218)

Parameter	With fQRS (n=114) No. (%)	Without fQRS (n=104) No. (%)	Total (n=218) No. (%)	p value
Cardiogenic shock	31(27.19%)	12(11.54%)	43(19.72%)	0.004[s]
Heart failure	27(23.68%)	10(9.62%)	37(16.97%)	0.006[s]
Complete heart block	12(10.53%)	5(4.81%)	17(7.80%)	0.116[ns]
Significant arrhythmias	48 (42.10%)	12 (11.53%)	60 (27.52%)	<0.001[s]
VT	19(16.67%)	5(4.81%)	23(10.55%)	0.001[s]
VF	6(5.26%)	2(1.92%)	8(3.67%)	0.342[ns]
SVT	12(10.53%)	4(3.85%)	16(7.34%)	0.1[ns]
AV block	10(8.77%)	3(2.89%)	16(7.34%)	0.122[ns]
AF	11(9.65%)	2(1.92%)	14(6.42%)	0.034[s]

p-value is determined by Chi-square test
s=Significant
ns=Not significant

Table-V

Duration of hospital stay and in hospital mortality of acute STEMI patients with and without fQRS (n=218)

Parameter	With fQRS (n=114) No. (%)	Without fQRS (n=104) No. (%)	Total (n=218) No. (%)	p value
Hospital duration (Mean±SD) in days	5.44±1.62	5.37±1.26	5.4±1.46	[a]0.709[ns]
In-hospital mortality	13(11.40%)	3(3.85%)	16(7.34%)	[b]0.016[s]

[a]p-value is determined by independent sample t-test.
[b]p-value is determined by Chi-square test.
s=Significant, ns=Not significant

Table-VI

Outcome within 30 days of index hospitalization among acute STEMI patients with and without fQRS (n=202)

Parameter	With fQRS (n=114) No. (%)	Without fQRS (n=104) No. (%)	Total (n=218) No. (%)	p value
30 days mortality	21(19.81%)	5(5.2%)	26(12.62%)	0.006[s]
Re-hospitalization	23(21.69%)	7(7.29%)	30(14.85%)	0.013[s]

p-value is determined by Chi-square test
s=Significant

Table-VII

Multivariate logistic regression analysis to detect independent predictors of short-term adverse outcome among acute STEMI patients (n=218)

Variable of interest	OR	95% CI		p value
		Lower bound	Upper bound	
Age ≥50 years	3.64	1.23	9.39	0.03[s]
Male	2.03	0.25	7.05	0.28[ns]
fQRS	4.18	1.15	12.17	0.03[s]

s=Significant
ns=Not significant

Discussions:

This prospective cohort study was performed in the Department of Cardiology, Dhaka Medical College Hospital, Dhaka during the period from October 2018 to September 2019. The general objective of the study was to find out the association of fragmented QRS (fQRS) complex with short term outcome in patients with acute STEMI. Two hundred and eighteen hospitalized patients having first acute STEMI and who were thrombolysed were included in this study after fulfilling the inclusion and exclusion criteria. Then they were divided into two groups, patients with fQRS group and patients without fQRS group based on the appearance of fQRS within 48 hours of admission in surface ECG. Among them sixteen patients were lost to follow up within 30 days of index hospitalization. Finally, 202 patients were tracked within 30 days of index hospitalization and included in the study

In this study, among the 218 patients, the mean age of total patients was 57.43±9.40 (ranges 35-81) years. The mean age of patients with fQRS group was 59.04±9.74 and patients without fQRS was 55.76±8.99 years. Tanriverdi, et al., (2015) also found that mean age of the patients was 63.2 ± 11.9 years.[5] Attachaipanich and Krittayaphong, (2019) in their study found that the mean age of the patients was 58.31±10.53 years.[14]

In our study, males were predominant 171 (78.44%). Male and female ratio was 3.64:1. Sex distribution between 'fragmented QRS' group and 'without fragmented QRS' group was statistically significant (p-value 0.005). Attachaipanich and Krittayaphong, (2019) found 76.1% males out of 452 patients in their study on fragmented QRS as a predictor of in-hospital life-threatening arrhythmic complications in STEMI patients.[14]

In this study, 114 (52.3%) patients had fQRS and 104 (47.7%) patients had no fQRS in surface ECG. Majority of the patients developed fQRS at admission (53.5%). Umapathy, et al., (2018) found around 61.5% of study subjects had fQRS in surface ECG, of which 42.2% developed at admission.[9] But Attachaipanich and Krittayaphong (2019) found only 21.2% STEMI patients had fragmented QRS complex in their study.[14] In many studies, fQRS rates have been reported to be between 28 and 54%.[8,11,15,16] The reasons of fQRS rates distribution over such a wide range may be due to the differences between studies regarding treatment methods used, periods of time in which fQRS were evaluated, and variability in the ranges of ûlters adopted in ECG imaging.

In this study, 49.08% had anterior wall, 47.71% had inferior wall and 3.21% had lateral wall involvement.

Majority of patients with fragmented QRS had inferior MI (54.39%) whereas, majority patients without fragmented QRS had anterior MI (55.77%). Difference in distribution of site of infarction between these two groups was statistically not significant (p value 0.117). In the study of Attachaipanich and Krittayaphong, (2019), distribution of inferior wall MI, anterior wall MI, and lateral wall MI among study subjects was 51%, 49% and 14.6% respectively.[14] Xia and Feng, (2018); Lorgis, et al., (2013) reported that fQRS was most often detected by inferior ECG leads (57%) with no significant differences between fQRS group and without fQRS group.[4,17]

In this study, mean systolic BP and diastolic BP of all patients with acute STEMI was 122.98±28.73 and 79.04±16.11 mm Hg respectively with 94.04% regular pulse: all of which was statistically significant between patients with and without fragmented QRS complex (p<0.05). Xia and Feng, (2018) found significantly higher hemodynamic instability rates in the f-QRS group (41%) compared to the patients without fragmented QRS group (25%).[4]

In our study, 63.3% patients were smoker and about 18.81% had a family history of CAD; both of which had no statistical significance between two groups (p >0.05). The majority had a history of HTN (62.84%) followed by dyslipidemia (61.93%) and DM (37.61%); all of which had no statistically significant difference in distribution between with and without fragmented QRS (p>0.05). Kothi, et al., (2015) also found no statistical significance regarding smoking, hypertension, diabetes, family history of CAD.[11] Several other studies also noted similar findings (Cho, et al., 2019 and Umapathy, et al., 2018)[9,15]

In this study, 19.72% patients developed cardiogenic shock and 16.97% had heart failure (p <0.05). Around 7.80% had complete heart block which was statistically not significant. 27.52% patients had developed different types of arrhythmias, of which significant arrhythmias were predominant in patients with fQRS group. VT was present in 16.67% of study subjects followed by SVT (10.53%), AF (9.65%), AV block (8.77%) and VF (5.26%). Distribution of different types of arrhythmias was statistically significant between two groups (p-value < 0.001). Erdinler et al., (2014) found 8.3% patients had VT, 12% had VF, 8.3% had cardiogenic shock in fQRS patients compared to patients without fQRS group.[18] These findings are consistent with previously reported findings.[19,20,21,22,23] This relatively high incidence of in hospital life threatening arrhythmias in STEMI patients with fQRS was significantly associated with increased in hospital mortality highlighting the clinical importance of this condition.[14,25]

In this study, mean duration of hospital stays between patients with and without fQRS was 5.44±1.62 days vs 5.37±1.26 days which was statistically almost similar (p-value 0.709). The study of Attachaipanich and Krittayaphong, (2019) also found no significant difference in median length of hospital stay between the fQRS and without fQRS groups (5 days [IQR: 3–9] vs. 5 days [IQR: 3–8], respectively; p = 0.821).[14]

In our study, total in-hospital mortality was 16 (7.34%) whereas patients with fQRS had higher (11.40%) mortality rate compared to patients without-fQRS group (3.85%). The distribution of in-hospital mortality between these two groups was statistically significant p <0.05. Erdinler et al., (2014) also found significantly higher (6.5%) in-hospital mortality among patients with fQRS.[18]

Total 16 (7.34%) patients were lost to follow up within 30 days of index hospitalization period. Total death within 30 days of index hospitalization follow-up period was 26 (12.62%). Among these subjects, 21(19.81%) patients had mortality in fQRS group compared to 5(5.2%) patients in without fQRS group. Re-hospitalization within the above-mentioned period was also higher among patients with fQRS group compared to without fQRS group (21.69% vs 7.29%). Distribution of both death and re-hospitalization between two groups was statistically significant (p <0.05). Xia and Feng, (2018) found 14% mortality of patients with fQRS group compared to 6% in patients without fQRS group after acute STEMI which was statistically significant (p-value 0.010).[4] Almost all other studies found that acute STEMI patients with fragmented QRS always have a higher incidence of in-hospital mortality and in-hospital adverse cardiovascular events. [5,14,24,26]

The mechanism of the association between fQRS and mortality in STEMI has not been fully described in the literature. fQRS has been shown to be associated with multivessel involvement, the presence of a myocardial scar, and left ventricular dysfunction, all of which indicate poor prognosis in STEMI patients.[27] fQRS has also been shown to be associated with ventricular arrhythmias, which could be a potential factor that drives the association between f-QRS and mortality.[8,28] Our study suggests that there were significantly more adverse cardiac events in patients with fQRS group compared to patients without fQRS group. Multiple-factor logistic regression analysis to determine the independent predictors suggests that age ≥50 years and fQRS are independent predictors of adverse short-term outcome in patients with acute STEMI.

Conclusion:

The assessment of fQRS by surface ECG is a simple, widely available and non-invasive modality that maybe useful for identifying patients with higher cardiac risk. This study demonstrated that patients with fragmented QRS complex following acute ST segment elevated myocardial infraction were associated with higher in hospital adverse outcome as well as increased mortality and re hospitalization during 30 days follow-up. Hence, fQRS after STEMI can help us in risk stratification and planning intensive treatment of a sub group of patients to reduce morbidity and mortality.

Limitations of the study:

Although the result of this study supports the hypothesis, there are some facts to be considered which might have affected the result of the current study. It was a single center study. Study population was small. Purposive sampling was done instead of random sampling. Therefore, the results of the study may not reflect the exact picture of the country. Follow up of the patients for longer duration was beyond scope.

Recommendations:

Further prospective study with larger sample and longer follow up period is recommended. Patients with acute STEMI should be screened for fQRS. Early detection of fQRS in patients with acute STEMI should alert us to plan for aggressive treatment for these group of patients.

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