



Original Article

Prognostic value of frontal QRS-T angle in predicting survival after primary percutaneous coronary revascularization/coronary artery bypass grafting for ST-elevation myocardial infarction



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ARTICLE INFO

Article history:

Received 10 April 2019

Accepted 3 September 2019

Available online 9 September 2019

Keywords:

ST-elevation myocardial infarction

Risk score

Predictors of mortality

Frontal QRS-T angle

Percutaneous coronary revascularization

Central valley risk score

ABSTRACT

Background: Frontal QRS-T angle (FQRST) has previously been correlated with mortality in patients with stable coronary artery disease, but its role as survival predictor after ST-elevation myocardial infarction (STEMI) remains unknown.

Methods: We evaluated 267 consecutive patients with STEMI undergoing reperfusion or coronary artery bypass grafting. Data assessed included demographics, clinical presentation, electrocardiograms, medical therapy, and one-year mortality.

Results: Of 267 patients, 187 (70%) were males and most (49.4%) patients were Caucasian. All-cause mortality was significantly higher among patients with the highest (101–180°) FQRST [28% vs. 15%, $p = 0.02$]. Patients with FQRST 1–50° had higher survival (85.6%) compared with FQRST = 51–100° (72.3%) and FQRST = 101–180° (67.9%), [log rank, $p = 0.01$]. Adjusting for significant variables identified during univariate analysis, FQRST (OR = 2.04 [95% CI: 1.31–13.50]) remained an independent predictor of one-year mortality. FQRST-based risk score (1–50° = 0 points, 51–100° = 2 points, 101–180° = 5 points) had excellent discriminatory ability for one-year mortality when combined with Mayo Clinic Risk Score (C statistic = 0.875 [95%CI: 0.813–0.937]). A high (>4 points) FQRST risk score was associated with greater mortality (32% vs. 19%, $p = 0.02$) and longer length of stay (6 vs. 2 days, $p < 0.001$).

Conclusion: FQRST represents a novel independent predictor of one-year mortality in patients with STEMI undergoing reperfusion. A high FQRST-based risk score was associated with greater mortality and longer length of stay and, after combining with Mayo Clinic Risk Score, improved discriminatory ability for one-year mortality.

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Abbreviations: STEMI, ST-Elevation Myocardial Infarction; MACE, Major Adverse Cardiac Events; ECG, Electrocardiogram; FQRST, Frontal QRS-T angle; LOS, Length of stay; ER, Emergency Room; ACS, Acute Coronary Syndrome; PCI, Percutaneous Coronary Syndrome; CABG, Coronary Artery Bypass Grafting; MCRS, Mayo Clinic Risk Score; CHF, Congestive Heart Failure; TIMI, Thrombolysis in Myocardial Infarction; SCD, Sudden Cardiac Death.

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1. Introduction

In patients presenting with an ST-elevation myocardial infarction (STEMI), predicting risk of major adverse cardiovascular events (MACE) and risk of mortality helps to determine both immediate and short-term treatment strategies. Various electrocardiographic (ECG) criteria have been used as prognostic indicators for mortality in patients presenting with STEMI. Population-based studies have shown that certain ECG variables can be used for clinical risk

stratification for MACE/mortality. For example, the QRS duration has emerged as a predictor of mortality in patients with left ventricular dysfunction.^{1,2} Other studies have shown that T-wave loop dispersion and R-to-T total cosine (repolarization measurement) can also be used for risk stratification after myocardial infarction.³

Recent studies have identified the frontal QRS-T angle (FQRST) as a useful ECG measure of the dispersion between depolarization and repolarization.⁴ In addition, an increased spatial QRS-T angle has been shown to be associated with higher mortality in the general population.⁴ Although spatial QRS-T angle is not routinely measured on 12-lead ECGs, specialized software can easily be incorporated into ECG machines to calculate it. Alternatively, FQRST can easily be calculated from a routine 12-lead ECG and does not require specialized software. Studies have shown that frontal and spatial QRS-T angles are comparable and have a strong correlation.⁵ The prognostic role of FQRST in the prediction of MACE after acute STEMI has hitherto not been studied.

This study sought to determine in patients presenting with an STEMI: (1) if FQRST could be used as an independent predictor of all-cause mortality, (2) if FQRST can be incorporated as a variable in a point-of-care risk assessment score for predicting one-year all-cause mortality, (3) if FQRST can be used for assessment of hospital length of stay (LOS) and identify patients suitable for potential early discharge after an STEMI.

2. Methods

2.1. Study population

We retrospectively analyzed 267 consecutive patients who presented to the emergency room of a tertiary-care hospital from January 2014 to January 2015 with a presumed diagnosis of acute coronary syndrome (ACS) and met ECG criteria for STEMI. We calculated that a sample size of 230 patients would be required to show a significant difference with an α value of 0.05 and beta of 0.2 to achieve a power of 80%. Patients who were found to have either pre-existing left bundle branch block, paced rhythm on ECG, or left ventricular hypertrophy by ECG criteria were excluded. In addition, those subjects in whom 12-lead ECG data could not be obtained or interpreted were excluded from the study. Diagnosis of STEMI was based on ST segment elevations measuring 0.2 mV in leads V1 to V3 or 0.1 mV in all other leads with these changes being present in at least two contiguous leads. Myocardial infarction was diagnosed by symptoms of ischemia and elevation in cardiac biomarkers, as listed by the Joint European Society of Cardiology and the American College of Cardiology.^{6,7}

2.2. Frontal QRS-T angle measurement

A 12-lead ECG was obtained with the patient in the supine resting position using a Philips Page Writer Touch Interpretive ECG Machine (Philips Medical Systems, Andover, MA, USA). The ECGs were obtained at a paper speed of 25 mm, a gain of 10 mV, and a paper format of 3 × 4. For every patient, the first ECG recording was used to collect variables including heart rate, PR interval, QRS duration, QT interval, corrected QT interval, QRS axis, and T-wave axis. FQRST was measured as the absolute difference between the frontal QRS and frontal T-wave axis calculated as T-wave axis – QRS axis; and if greater than 180°, the difference was subtracted from 360° to obtain a continuous variable ranging from 0° to 180°.⁸ Based on the relative risk associated with increasing values of FQRST, they were classified into three groups of 1–50°, 51–100°, and 100–180°.

2.3. Clinical characteristics

A 12-lead ECG as well as basic laboratory and radiographic investigations were obtained at the time of presentation to the emergency room. All subjects underwent emergent coronary angiography and based on the findings underwent either Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG). Concurrent treatment with unfractionated Heparin/low molecular weight heparin and periprocedural intravenous glycoprotein IIb/IIIa inhibitors or bivalirudin was utilized as per the discretion of the operator. After stent placement, patients received adjunctive dual antiplatelet therapy with Aspirin and a thienopyridine antagonist, mostly clopidogrel.

2.4. Outcomes

Mortality data during current admission were obtained from hospital records. Subsequently, one-year mortality data were obtained either from the hospital, California Department of Public Health, or Social Security Death Index records. The standardized risk score [Mayo Clinic Risk Score (MCRS)] was calculated for all patients on presentation.⁹ The MCRS was developed to predict MACE using the following multivariates: cardiogenic shock (5 points), left main coronary artery disease (5 points), serum creatinine level >265 $\mu\text{mol/L}$ (3 points), urgent or emergent procedure (2 points), New York Heart Association \geq III (2 points), presence of thrombus (2 points), multivessel disease (2 points), and age/number of decades after 30 years (1 point). MCRS has been externally validated in 3264 PCI patients from the National Heart, Lung, and Blood Institute Dynamic registries between 1997 and 1999 (C statistic 0.76; Hosmer–Lemeshow statistic $p = 0.28$).¹⁰ The study was approved by the local IRB of our institution.

3. Statistical analysis

The data collected from medical charts and laboratory reports were tabulated using Microsoft Excel spreadsheets, whereas, statistical analysis was performed using SPSS Software (PASW for Windows, Rel. 18.0.0.2009; SPSS Inc., Chicago, IL, USA). Continuous variables were summarized as either mean \pm SD or median (interquartile range) and compared across groups using a *t* test, Mann–Whitney *U* test, or Kruskal–Wallis test as appropriate. Categorical variables were summarized as percentages of the group total and comparisons between groups were analyzed using either Fisher exact test or chi-square test, where deemed appropriate. Assessment of the bivariate relationship between mortality and each risk factor was carried out using data from the 267 patients included in our study. Variables that were identified as significant (*p*-value less than 0.1) during univariate analysis were then fitted in a logistic regression model by a backward elimination method to adjust for confounders and to determine if variables of interest were associated with an increased risk of mortality. The cumulative occurrence of all-cause mortality as a function over time was obtained by the Kaplan–Meier method after ensuring that all the assumptions of Kaplan–Meier analysis were met. The event curves were created to compare survival based on FQRST (1) Group 1: 1–50°, (2) Group 2: 51–100°, and (3) Group 3: 100–180°. Comparisons between curves were made using a log-rank test. Taking the risk probabilities as test variable and the actual outcome as state variable, receiver operating characteristic (ROC) analysis was performed to get the C statistic which is the area under the ROC curve. Statistical significance was determined by a *p*-value less than 0.05.

4. Results

4.1. Study population

Of 267 patients, 187 (70%) were males and most (49.4%) patients were Caucasian. Patients with the highest FQRST (100–180°) were more likely to have a history of diabetes, hypertension, congestive heart failure (CHF), and myocardial infarction as shown in Table 1. Admission and peak troponin levels did not differ significantly between the three groups of the FQRST. Heart rate, QRS duration, and incidence of atrial fibrillation were greater among patients with highest FQRST, whereas ST segment resolution did not differ between the three groups. Likewise, Thrombolysis in Myocardial Infarction (TIMI) Grade 3 flow after reperfusion and time to reperfusion did not differ between the three groups. Medical therapy did not differ significantly between the three groups; however, patients with higher FQRST were less likely to have received glycoprotein IIb/IIIa inhibitors during the procedure, as shown in Table 1.

4.2. Mortality

At one year, 62 (23.3%) patients died due to all causes. 36 (13.5%) patients died due to cardiac-related causes, whereas 43 (16.1%) died during index admission and 11 (4.1%) died within six months of hospitalization. Stratification of endpoints by FQRST is shown in Table 2. All-cause mortality was significantly higher among patients with the highest (101–180°) FQRST [28% vs. 15%, $p = 0.02$]. When stratified by gender, survival was significantly worse among females for all groups of FQRST (Fig. 1). Variables that were strongly

associated with one-year mortality as per univariate analysis are outlined in Table 3. After adjusting for significant variables identified during univariate analysis (age, female gender, brain natriuretic peptide levels, cardiac arrest), a stepwise backward model showed that FQRST remained a significant predictor of mortality (OR = 2.04 [95% CI: 1.31–13.50], $p = 0.04$).

4.3. Risk stratification

A risk score was also developed to predict mortality at one year, giving 0 points for FQRST of 1–50°, 2 points for FQRST between 51 and 100°, and 5 points for FQRST between 101 and 180°. The points were assigned based on estimated regression coefficients using the method described by Sullivan et al.¹¹ Patients with a low risk score (0–3 points) had significantly lower mortality than those with a high (≥ 4 points) risk score (19% vs. 32%, $p = 0.02$). Fig. 2A represents the ROC curve for MCRS, where C statistic for the predicted risk is 0.67 (standard error = 0.04) with a 95% confidence interval (0.59, 0.76). Subsequently, we combined the FQRST risk score with the standardized MCRS, which improved the discriminatory power of the MCRS risk score with a C statistic of 0.71 (standard error = 0.04), 95% confidence interval (0.63, 0.79) [$p < 0.001$], as shown in Fig. 2B.

4.4. Length of stay

The median LOS among all patients was three days (interquartile range [IQR]: 2, 8 days). As shown in Fig. 3A, the median LOS was significantly higher among patients with FQRST $\geq 100^\circ$ than those with FQRST 0–50° and 50–100°, respectively ($p < 0.001$). In

Table 1
Clinical characteristics.

Variable	FQRST 1–50° (n = 118)	FQRST 51–100° (n = 65)	FQRST 100–180° (n = 84)	p-value
Demographics				
Age (years)	59 ± 14	61 ± 14	68 ± 14	<0.001
Male Gender	85 (31.8%)	44 (16.5%)	58 (21.7%)	0.81
Body Mass Index (kg/m ²)	28.67 ± 6.50	29.35 ± 5.84	26.94 ± 6.03	0.05
Clinical characteristics				
Diabetes type 2	25 (9.4%)	17 (6.4%)	32 (12.1%)	0.03
Smoking	55 (20.6%)	30 (11.2%)	34 (44.6%)	0.66
Hypertension	75 (28.1%)	48 (18%)	70 (26.2)	0.01
Hyperlipidemia	65 (24.3%)	35 (13.1%)	54 (20.2%)	0.09
Congestive heart failure	17 (6.4%)	17 (6.4%)	43 (16.1%)	<0.001
Previous myocardial infarction	27 (10.1%)	23 (8.6%)	43 (16.1)	<0.001
Laboratory data				
Admission troponin (ng/ml)	26.95 ± 113	22.23 ± 73.93	35.04 ± 152.37	0.82
Peak troponin (ng/ml)	54.15 ± 94.39	111.6 ± 380.11	43.28 ± 75.88	0.15
Hematocrit (%)	41.60 ± 6.44	40.11 ± 70	40.21 ± 5.85	0.35
Electrocardiographic data				
Heart rate (beats/min)	77.92 ± 23.82	81.65 ± 26.25	93.46 ± 27.21	<0.001
PR Interval (ms)	160.78 ± 66.79	148.41 ± 52.42	148.11 ± 59.20	0.27
QRS duration (ms)	90.46 ± 15.95	91.43 ± 19.03	114.60 ± 33.90	<0.001
Corrected QT interval (ms)	412.92 ± 34.07	425.15 ± 34.63	451.74 ± 45.21	<0.001
Atrial fibrillation	15 (5.6%)	8 (3%)	27 (10.1%)	0.002
ST-elevation resolution	87 (73.7%)	45 (69.2%)	48 (57.8%)	0.06
Angiographic data				
Multivessel (≥ 2 vessels) disease	42 (43.8%)	30 (55.6%)	36 (69.2%)	0.011
TIMI ^a Grade 3 flow achieved	87 (73.8%)	48 (73.8%)	54 (64.3%)	0.14
Time to reperfusion (minutes)	29.63 ± 79.10	36.44 ± 93.87	33.60 ± 68.55	0.86
Medical therapy				
Aspirin use	37 (39.8%)	23 (24.7%)	33 (35.5%)	0.43
Beta-blocker use	31 (37.3%)	25 (30.1%)	27 (32.5%)	0.19
Statin use	37 (41.6%)	23 (25.8%)	29 (32.6%)	0.77
ACEI use	37 (37%)	19 (19%)	44 (44%)	0.002
Heparin use	26 (41.9%)	21 (33.9%)	15 (24.2%)	0.10
Enoxaparin use	17 (37%)	10 (21.7%)	19 (41.3%)	0.27
Glycoprotein IIb/IIIa use	64 (24.2%)	34 (12.8%)	29 (10.9%)	0.02

^a Thrombolysis in Myocardial Infarction.

Table 2
Outcomes based by frontal QRS-T angle measured on admission ECG in ST-elevation myocardial infarction patients.

Outcomes	FQRST 1–50° (n = 118)	FQRST 51–100° (n = 65)	FQRST 100–180° (n = 84)	p- value
Cardiac death	9 (19.1%)	11 (23.4%)	16 (34%)	0.15
Index admission mortality	14 (32.6%)	14 (32.6%)	15 (34.9%)	0.20
1-year mortality	17 (27.4%)	18 (29%)	27 (32.1%)	0.01
Length of stay (days)	5.47 ± 7.92	5.63 ± 8.43	9.64 ± 14.00	0.01

addition, patients with high-risk score (≥ 4 points) had significantly longer LOS (6 [IQR:2, 12] days vs. 2 [IQR:2, 7] days, $p < 0.001$) than those who had a low (0–3 points) risk score [Fig. 3B]. Thus, the risk score was not only useful for mortality risk stratification but, also to potentially identify patients suitable for early discharge.

5. Discussion

Our study evaluated the utility of FQRST obtained from a point-of-care 12-lead ECG for risk assessment in patients presenting with STEMI and undergoing revascularization. The study has the following key findings: (1) Higher FQRST was associated with a greater risk of one-year mortality, both during unadjusted and adjusted analysis after adjusting for risk factors; (2) FQRST-based risk score can be used for risk stratification with a higher score associated with a greater one-year mortality; (3) FQRST-based risk score when incorporated with an established standardized risk score (MCRS) helps to improve the discriminatory power of MCRS; (4) FQRST-based risk score can be used for identifying patients suitable for early discharge from the hospital.

5.1. FQRST and mortality

Several studies have shown that ECG measures of depolarization and repolarization can be used to determine short- and long-term prognosis after ACS.^{12,13} FQRST calculates the vector dispersion between myocardial depolarization and repolarization. In other words, a wide QRS-T angle reflects structural aberrancies affecting the regional pathophysiological changes in ionic channels which affect the sequence of repolarization, in turn, increasing arrhythmogenicity and susceptibility for sudden cardiac death (SCD) due to malignant ventricular arrhythmias.¹⁴ This correlation between FQRST and SCD is noted across a wide range of cardiac dysfunction, including, CHF, ACS, stable coronary artery disease, hypertrophic

cardiomyopathy, as well as in seemingly normal cardiac structure and function.¹⁵ Lingman et al demonstrated that QRS-T angle improved prediction of SCD after ACS in addition to traditional cardiac risk factors.¹⁶ Hence, FQRST serves as a useful surrogate for damaged/jeopardized myocardium at risk, thereby, predicting STEMI mortality, as confirmed in our study.

5.2. FQRST and gender

Gender differences in QRS-T angle have been demonstrated in several studies.^{17,18} The variability in heart size, physiology, and hormonal influences may likely contribute to differences in ventricular depolarization between men and women. Females have been shown to have greater divergence of the L-type calcium current among different layers of the myocardium and a lower density of the repolarizing Kr and Ks currents.¹⁹ National Health and Nutritional Examination Survey (NHANES III) data showed that the distribution of QRS-T angle differs between males and females with abnormal spatial QRS-T angle being associated with increased all-cause mortality among both genders.²⁰ The Woman's Health Initiative showed that a wide QRS-T angle was associated with a four-fold increase in the incidence of CHF.²¹ In our study, survival was significantly lower among females than males, across differing distributions of QRS-T angles. Among females, smaller body mass, coronary artery anatomy, and hormonal influences may render the myocardium more susceptible to damage and less durable with respect to recovery. However, these findings will need further validation in larger cohorts.

5.3. FQRST risk score

FQRST widening can be used to create a simple risk score based on FQRST subdivided into three groups: (1) Group 1: 1–50°, (2) Group 2: 51–100°, and (3) Group 3: 100–180°. The

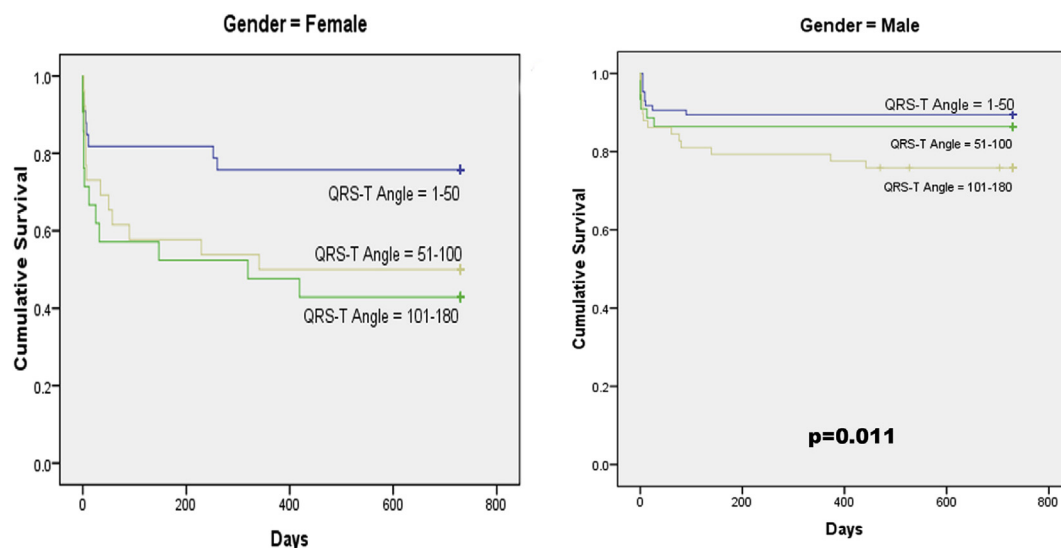


Fig. 1. Kaplan–Meier survival curves among patients presenting with ST-elevation myocardial infarction based on frontal QRS-T angle measured during admission, and stratified by gender. Survival among females was significantly worse for all three groups of frontal QRS-T angles.

Table 3
Univariate analysis of variables used to predict survival at one year.

Variable	Mortality in 1 Year (n = 62/267)	
	(95% Confidence Intervals)	p - value
Gender (male)	3.83 (2.11–6.94)	<0.001
Race (Caucasian)	0.83 (0.40–1.69)	0.60
Age	1.06 (1.04–1.08)	<0.001
Basic metabolic index	0.91 (0.86–0.96)	<0.001
Systolic blood pressure	0.99 (0.98–1.00)	0.10
Diastolic blood pressure	0.98 (0.97–0.99)	0.03
Diabetes type 2	0.76 (0.41–1.41)	0.45
Smoker	2.90 (1.54–5.46)	0.001
Hypertension	1.36 (0.70–2.65)	0.37
Hyperlipidemia	1.47 (0.83–2.61)	0.19
Congestive heart failure	3.15 (1.74–5.71)	<0.001
Atrial fibrillation	1.40 (0.70–2.81)	0.35
Previous myocardial infarction	1.28 (0.71–2.31)	0.41
Cerebrovascular accident	3.83 (1.77–8.31)	0.001
Killip Class 2	5.11 (2.56–10.21)	<0.001
Killip Class 3	5.31 (1.34–21.26)	0.02
Killip Class 4	7.33 (2.81–19.11)	<0.001
Troponin at admit	1.00 (0.99–1.00)	0.64
WBC count	1.09 (1.04–1.14)	<0.001
Neutrophil/lymphocyte ratio	1.05 (1.01–1.09)	0.01
Hematocrit	0.90 (0.84–0.96)	0.001
Glomerular filtration rate	0.98 (0.97–0.99)	<0.001
Chronic kidney disease stage	12.27 (3.29–45.72)	<0.001
Admit troponin	1.00 (0.99–1.00)	0.64
Brain natriuretic peptide	1.000 (1.10–1.20)	0.003
Left ventricular hypertrophy	1.28 (0.67–2.56)	0.51
Heart rate	1.01 (1.00–1.02)	0.05
PR interval	1.000 (0.99–1.00)	0.85
QRS duration	1.00 (0.99–1.02)	0.17
Corrected QT interval	1.00 (0.99–1.01)	0.33
QRS-T admit (51–100)	2.28 (1.08–4.81)	0.03
QRS-T admit (101–180)	2.81 (1.41–5.60)	0.003
T-wave changes	2.81 (1.21–6.55)	0.02
ST segment elevation	1.58 (0.88–2.86)	0.13
Cardiac arrest on presentation	16.36 (8.10–33.07)	<0.001
TIMI flow preprocedure	1.008 (0.634–1.604)	0.97
TIMI flow postprocedure	1.068 (0.482–2.369)	0.87

strength of the FQRST-based risk score lies in its accuracy, simplicity, and use of routinely measured objective variables. In addition, the risk score eliminates the need for interpreting normograms and use of specialized computerized applications or diagnostic hand-held devices, further improving its user-friendliness. This study has, therefore, proven the first of its kind to exemplify the clinical utility and cost-effectiveness of the proposed risk score entailing FQRST to predict mortality after STEMI. Numerous studies have previously validated the MCRS which combines eight variables to predict cardiovascular complications after PCI.^{9,10} Our study is unprecedented in conceptualizing and then methodically demonstrating that combining FQRST risk score with the MCRS significantly augments the latter's discriminatory power.

5.4. FQRST and length of stay

De Luca et al demonstrated that patients with very low Zwolle risk scores could be discharged sooner from the hospital, thus, reducing LOS and increasing cost savings.²² Similarly, another cost-effective utility of FQRST-based risk score could be early discharge of low-risk patients leading to reduced LOS. In our study, patients with low FQRST-based risk score (0–3 points) had significantly shorter LOS than those with high (>4 points) score. Identification of this “low-risk” population early on during the hospitalization can further augment resource utilization by facilitating early discharge while still providing safe and efficient care after STEMI.

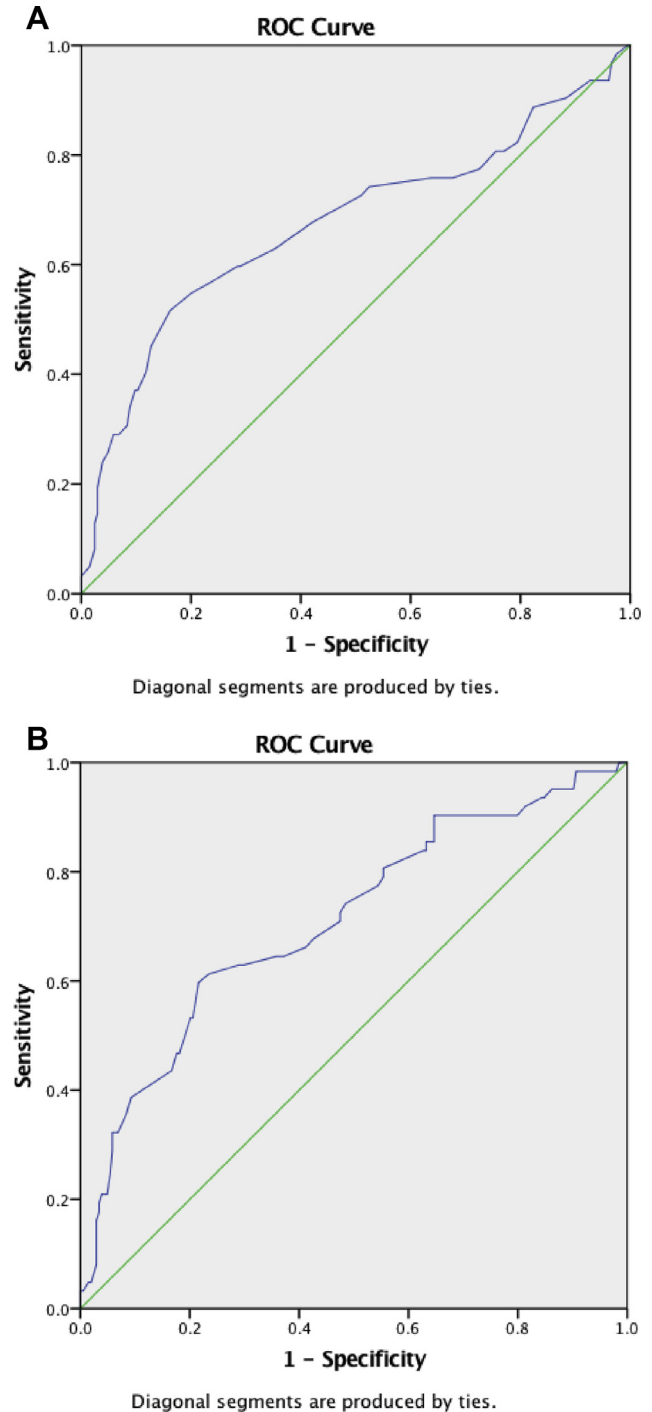


Fig. 2. Receiver operating characteristic (ROC) curve analysis comparing the risk score developed and actual outcome of one-year all-cause mortality among (A) Mayo Clinic Risk Score and (B) Mayo Clinic Risk Score combined with the FQRST score. Addition of frontal QRS-T angle–based risk score to the standardized Mayo Clinic Risk Score increased the C statistic of the area under curve (AUC) to 0.71 ($p < 0.001$).

6. Limitations

Our study outcomes are derived from a single tertiary health care center and may not be representative of other populations. However, our data set is unique due to its biodiversity illustrated by a high percentage of minority representation, including Hispanics and Asians. Owing to the retrospective nature of the study, there is always a potential for selection bias in spite of adjusting for

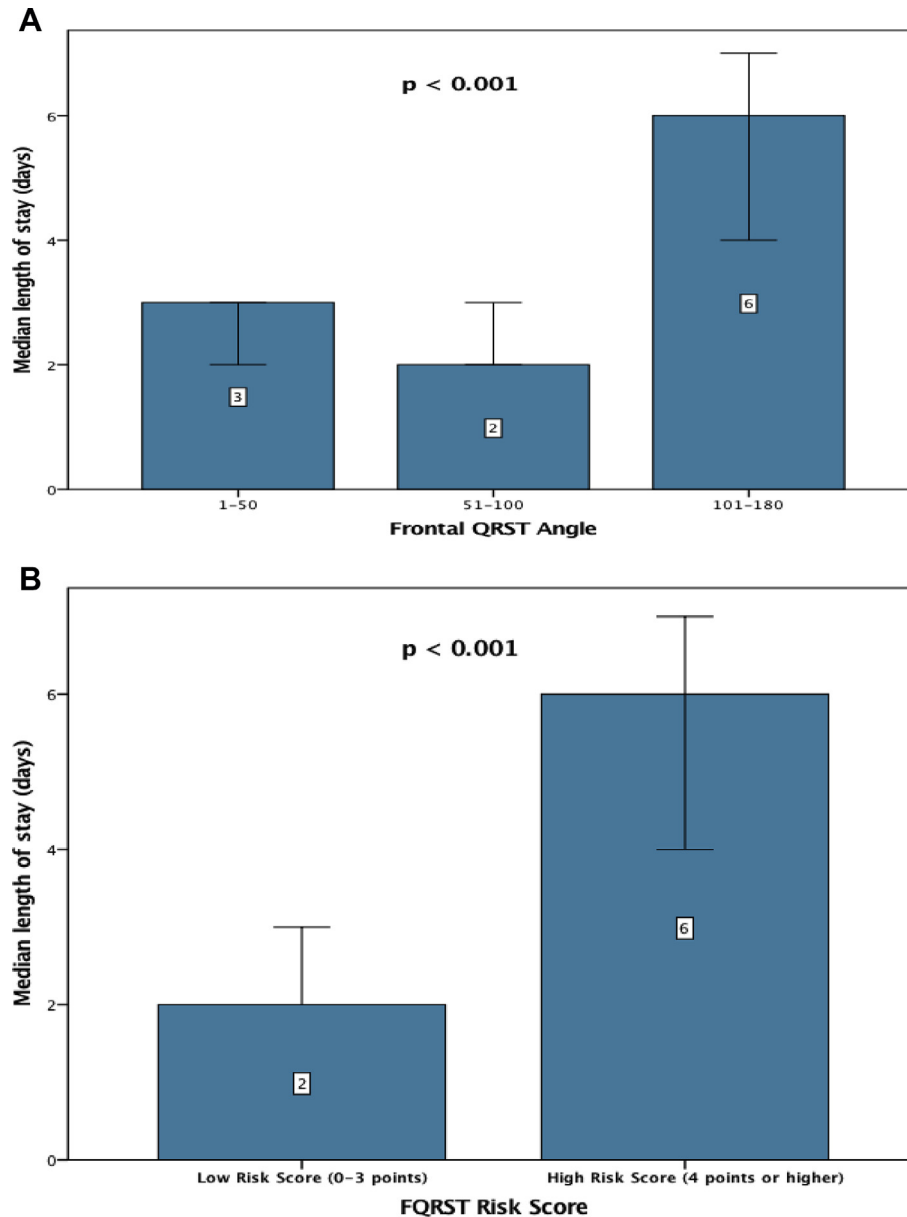


Fig. 3. Length of stay stratified by (A) frontal QRS-T angle 1–50, 51–100, and 101–180°; (B) Frontal QRST risk score. Length of stay was significantly higher among patients with (A) frontal QRS-T angle >100° compared with those ≤ 100° and those with a (B) frontal QRST risk score ≥ 4 points.

potential confounders. Normal ranges for FQRST are well known and may vary by age and gender; however, an abnormal QRS-T angle is found in up to 2% of the general population.^{23,24} We recognize that nonmyocardial factors unrelated directly to the genesis of ACS such as autonomic tone, electrolyte, and hormonal derangements could all alter FQRST. Owing to time constraints of meeting door-to-balloon time of 90 min, detailed chemistry including potassium levels are not obtained. Hence, we were unable to evaluate the role of electrolyte imbalances on FQRST values in our study. Additional causes of MACE could not be reliably obtained during follow-up and hence were not evaluated in the study.

7. Conclusion

The study has provided several important results in an ethnically and gender diverse contemporary PCI- or CABG-treated STEMI population. FQRST widening is an independent predictor of

mortality in patients presenting with STEMI and can be used for creating a simple but robust “point-of-care” prognostic risk score, which predicts all-cause mortality at one year. The risk score, when combined with a standardized risk score such as MCRS, improved the discriminatory power for risk assessment after STEMI. Finally, this score can potentially be used to identify low-risk patients suitable for early discharge yielding significant health care cost savings.

Conflict of interests

All authors have none to declare.

Acknowledgments

The authors gratefully acknowledge the help of Dr. Mark T. LownBEng, PhD, MBBS, and Dr. Chris P. Gale BSc, MBBS, PhD, Med,

from Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, for their guidance and insight in performing this study.

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