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QRS COMPLEX FRAGMENTATION AS A PREDICTOR OF MORTALITY AND REHOSPITALISATION IN THE FIRST 6 MONTHS IN ACUTE CORONARY SYNDROME IN HAJI ADAM MALIK GENERAL HOSPITAL, MEDAN

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Abstract

Background: QRS fragmentation (fQRS) on the ECG is associated with partial damage to the cardiac conduction system. fQRS increases the risk of major cardiovascular events.

Objective: Assessing fQRS as a predictor of mortality and rehospitalization on the first 6 months in ACS patients.

Methods: This is observational analytic study with ambispective cohort. Sampling was done consecutively from ACS patients who came to HAM Hospital starting January 2020 and followed for the next 6 months. fQRS was assessed from ECG at first admission. The prognostic performance was assessed with chi-square test and the strength of the prognostic model was assessed using AUC.

Results: From 96 patients, 52 were STEMI and 44 were NSTEMI, which 36 patients (37.5%) showed fQRS. Patients with fQRS were 5,2 times to have rehospitalization (p < 0,001; 95% CI: 2,63-10,28) and 7,8 times to have mortality (p < 0.001; 95% CI: 2.39-25.22) in the first 6 months. The performance of the fQRS in predicting the incidence of rehospitalisation and 6-month mortality were 0,781 and 0,669.

Conclusion: fQRS is useful as predictor of rehospitalization and mortality rate in the first 6 months for ACS patients.

Introduction

QRS fragmentation (fQRS) on the ECG is associated with myocardial scarring, ischemia, and fibrosis stemming from defects in signal transduction and ventricular depolarisation processes.[1,2] The fragmentation originates from abnormally small areas of the myocardium where ventricular activation is delayed and is asynchronous. Partial damage to the conduction system in the ventricles causes notching of the QRS segment on the ECG.[3]

The presence of a fQRS in susceptible patients increases the risk of major cardiovascular events, including MI, need for vascularisation, cardiac death, and all causes for mortality in patients with known ischemic heart disease. It has also been reported that a fQRS in patients with a history of Q wave MI signifies a higher risk of recurrent cardiac events, such as fatal or non-fatal MI.[4]

A study by Lorgis et al. with 307 AMI patients, found that persistent fQRS on a 12-lead ECG was a marker of decreased survival after AMI, while transient fQRS was associated with recurrent AMI.[5]

Tarek et al. yielded that the presence of fQRS on ECG during ACS event indicated myocardial scarring or fibrosis and described the severity of the coronary lesion.[6]

In Indonesia itself, a study by Zulkarnain et al., at Haji Adam Malik Hospital Medan in patients with STEMI, found that the presence of fQRS increased the risk of major cardiovascular events during treatment.[7] A study by Tobing et al., at the same hospital, found that fQRS could detect myocardial scar tissue as evidenced by myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT). It was also found that fQRS could be a marker of a worsening left ventricular function, such as ejection fraction and end systolic volume.[8] A study by Pinem et al. at the same hospital, found that fQRS could be used as a predictor of the incidence of multivessel disease in STEMI patients, with a sensitivity of 66.7% and a specificity of 88.2%.[9]

Considering the simplicity and cost-effectiveness of differentiating a f QRS on the ECG and its potential prognostic value, more studies in different populations are needed to develop more robust knowledge.[4]

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In this study, the authors aimed to assess the ability of fQRS which is a simple and objective measurement as a predictor of mortality and rehospitalisation in the first 6 months in acute coronary syndrome patients at H. Adam Malik General Hospital Medan.

Methods

Research population

Sampling was carried out consecutively on ACS patients who came to Haji Adam Malik General Hospital from January 2020 and were followed for the next 6 months. This study involved 96 ACS patients with QRS complex duration ≤ 120 ms. Patients with incomplete medical record and were unable to be contacted for follow-up were excluded from the research subject. This research was an observational analytic study conducted in an ambispective cohort.

FQRS assessment and the incidence of mortality and rehospitalisation

After recording the data from medical records to establish the diagnosis of ACS, then the fQRS assessment was carried out based on the ECG recording when the patient was first admitted. Then it was determined whether or not there was an incidence of mortality and rehospitalisation in the first 6 months. The data collected were then analysed statistically.

Statistical analysis

The data were analysed with the SPSS program. Data normality was tested with Kolmogorov-Smirnov test if the number of samples was above 50 and with Shapiro-Wilk test if the number of samples was below 50. Bivariate analysis was tested with Chi square test if X^2 condition is met, or with Fisher Exact test if the condition is not met. For numeric variables, T Independent test was used if the data were normally distributed, and with Mann-Whitney test if the data were not normally distributed. Then multivariate analysis will be carried out using logistic regression test. The p-value of ≤ 0.05 was statistically significant. The strength of the prognostic model will then be assessed using the area under the receiver- operator curve (AUC)

Results and Discussion

A total of 96 research subjects were obtained, of which 52 were with STEMI, 44 samples were with NSTEMI. From all ACS samples, 36 of them showed a QRS fragmentation on their ECG. Samples with mortality outcomes for the first six months were obtained as many as 17 samples and 33 samples underwent rehospitalisation in the first 6 months. The basic characteristics of the research subjects are presented in table 1.

From the previous literatures it has been known that the presence of abnormalities in the QRS complex represents conduction disturbances and the presence of scar tissue in the myocardium. fQRS is associated with ventricular dysfunction and congestive heart failure. In patients with coronary heart disease, fQRS is an independent predictor of cardiovascular events and future ischemic events.[10]

fQRS is considered important because there are no specific residual markers in patients with myocardial infarction. In these patients, the fQRS was the only evidence of a previous myocardial infarction. The mechanism of the occurrence of fQRS is based on an imbalance of electrical activity in the ventricles due to scarring and/or ischemia recorded on the ECG.[11]

Table 4.1. Basic characteristics of research subjects

Characteristics	n = 96
Demography dan Risk Factors	
Mean Age, years old (SB)	55,97 (9,88)
Gender, n (%)	
Male	83 (86,5 %)
Female	13 (13,5 %)
History of hypertension, n (%)	49 (51 %)
History of DM, n (%)	49 (51 %)
History of dyslipidemia, n (%)	66 (68,8 %)
Smoking, n (%)	78 (81,3 %)
Clinical Characteristics	

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Diagnosis	
STEMI	52 (54,2 %)
NSTEMI	44 (45,8 %)
Killip class, n (%)	
Killip I	72 (75 %)
Killip II	24 (25 %)
Revascularisation, n (%)	
PCI	79 (82,3 %)
CABG	17 (17,7 %)
Median GRACE score, (min-max)	103 (56-181)
Multivessel disease, n (%)	45 (46,9 %)
First 6 months mortality, n (%)	17 (17,7 %)
First 6 months rehospitalisation, n (%)	33 (34,3 %)
Laboratory results	
Median hemoglobin, g/dL (min-max)	13,60 (11,2 – 17,7)
Median creatinine, mg/dL (min-max)	0,95 (0,38 – 2,27)
Median CKMB, u/L (min-max)	86,5 (20 – 512)
Median troponin I, ng/dL (min-max)	3,63 (0,1 – 32,0)
Median KGDP, mg/dL (min-max)	123 (73 – 243)
Median KGD2JPP, mg/dL (min-max)	159 (78 – 343)
Median HbA1C, % (min-max)	6,4 (4,6 – 13,6)
Median total cholesterol, mg/dL (min-max)	202 (14 – 344)
Median triglyceride, mg/dL (min-max)	167 (57 – 318)
Mean HDL, mg/dL (SB)	38,39 (13,25)
Mean LDL, mg/dL (SB)	154 (33 – 287)
Diagnostic Findings	
Cardiomegaly, n (%)	71 (74 %)
Median FEVK, % (min-max)	43 (25 – 67)
QRS fragmentation, n (%)	36 (37,5 %)
Median QRS duration, s (min-max)	0,08 (0,01 – 0,12)
Median QT correction, s (min-max)	0,42 (0,36 – 0,63)

The results of the bivariate test showed that FEVK, DM, GRACE score, and fQRS were significantly related to the incidence of rehospitalisation in the first 6 months. Among the patients who underwent rehospitalisation in the first 6 months, 25 of them had an ECG with fQRS morphology on admission ($p<0.01$). Among the patients undergoing rehospitalisation, 24 of them had a history of diabetes mellitus ($p=0.002$). Rehospitalised patients also had lower left FEVK and higher GRACE scores than non-rehospitalised patients ($p < 0.01$)

Table 4.2 Bivariate analysis of factors affecting rehospitalisation in 6 months

Characteristics	Rehospitalisation in the first 6 months		P value
	Yes (n = 33)	No (n=63)	
Mean Age, years old (SB)	55,46 (9,61)	56,26 (10,1)	0,699[a]
Gender			
Male	30	53	0,356[c]
Female	3	10	
History of hypertension			
Yes	17	32	0,946[c]
No	26	31	
History of DM			
Yes	24	25	**0,002[c]**
No	9	38	
History of dyslipidemia			
Yes	24	42	0,543[c]
No	9	21	
History of smoking			
Yes	29	49	0,228[c]

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No	4	14	
Diagnosis			
STEMI	16	36	0,521[c]
NSTEMI	17	27	
Killip class, n (%)			
Killip I	27	45	0,264[c]
Killip II	6	18	
Revascularisation, n (%)			
PCI	29	50	0,198[c]
CABG	9	8	
GRACE score			
GRACE > 118	18	1	**< 0,01[c]**
GRACE ≤ 118	15	62	
Multivessel disease			
Yes	15	30	0,84[c]
No	18	33	
Diagnostic Findings			
Mean hemoglobin, g/dL	13,76 (1,26)	13,87 (1,73)	0,758[a]
Mean creatinine, mg/dL (SB)	1.0 (0,32)	1,01 (0,35)	0,801[a]
Median CKMB, u/L	86 (20-474)	87 (23-512)	0,303[b]
Median troponin I, ng/dL	2,56 (0,16-32)	4,5 (0,1-32)	0,259[b]
FEVK category			
EF < 40%	18	6	**<0,01[c]**
EF ≥ 40%	15	57	
QRS fragmentatino			
Yes	25	11	**< 0,01[c]**
No	8	52	
Median QRS duration, s	0,08 (0,06-0,11)	0,08 (0,01-0,12)	0,315[b]
Median QT correction, s	0,42 (0,38-0,63)	0,42 (0,36-0,59)	0,821[b]

a: Uji T test; b: Mann whitney; c: Chi square

The results of the bivariate test showed that FEVK, DM, GRACE score, and fQRS were significantly related to the incidence of mortality in the first 6 months. Among the patients who experienced mortality in the first 6 months, 10 of them showed ECG features with fQRS morphology on admission ($p < 0.01$). Among the patients with mortality, 14 had a history of diabetes mellitus ($p = 0.004$). Patients undergoing rehospitalisation also had lower left FEVK and higher GRACE score than those who did not undergo rehospitalisation ($p < 0.01$).

In the bivariate analysis of the groups with rehospitalisation and without rehospitalisation within 6 months, there were significant differences in the GRACE score, DM, FEVK and fQRS variables. The same was found in the group with and without mortality in the first 6 months. The GRACE score is the most commonly used predictor tool for ACS patients, including STEMI, NSTEMI, and UAP. The remarkable ability of the GRACE score in predicting the risk of death from AMI has been demonstrated for the risk of death over a six-month or even longer period of up to six years.[12] The GRACE score was designed to be representative of a population in assessing the outcome of ACS patients.[13]

ACS patients with DM are known to have three times higher mortality than patients without DM. Another study showed ACS patients with DM had a significantly higher mortality rate at 30 days and one year than patients without DM. DM patients presenting with UAP and NSTEMI had almost the same one-year mortality rate as STEMI patients without DM (7.2% (DM) vs. 8.1% (non-DM) mortality in the first year).[14]

Table 4.3 Bivariate analysis of factors affecting mortality at 6 months

Characteristic	Mortality in the first 6 months		P
	Ya (n = 17)	Tidak (n = 79)	
Mean Age, years old (SB)	58,12 (10,28)	55,51 (9,80)	0,326[a]
Gender			
Male	16	67	0,309[c]

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Female	1	12	
History of hypertension			
Yes	8	41	0,717[c]
No	9	38	
History of DM			
Yes	14	35	**0,004[c]**
No	3	44	
History of dyslipidemia			
Yes	12	54	0,857[c]
No	5	25	
History of smoking			
Yes	16	62	0,134[c]
No	1	17	
Diagnosis			
STEMI	9	43	0,968[c]
NSTEMI	8	26	
Killip class, n (%)			
Killip I	13	59	0,877[c]
Killip II	4	20	
Revascularisation, n (%)			
PCI	15	64	0,687[c]
CABG	2	15	
GRACE score			
GRACE > 118	14	5	**<0,001**
GRACE ≤ 118	3	74	
Multivessel disease			
Yes	9	36	0,581[c]
No	8	43	
Diagnostic Findings			
Median hemoglobin, g/dL	13,4 (11,2-14,4)	13,8 (11,2-17,7)	0,168[b]
Median creatinine, mg/dL	0,99 (0,44-1,83)	0,92 (0,38-2,27)	0,264[b]
Median CKMB, u/L	109 (23-314)	86 (20-512)	0,300[b]
Median troponin I, ng/dL	2,56 (0,16-18,43)	4,34 (0,1-32,0)	0,364[b]
FEVK category			
EF < 40%	10	14	**<0,01[c]**
EF ≥ 40%	7	65	
QRS fragmentation			
Yes	10	26	**< 0,01[c]**
No	7	53	
Median QRS duration, s	0,08 (0,06-0,11)	0,08 (0,01-0,12)	0,416[b]
Median QT correction, s	0,42 (0,38-0,48)	0,42 (0,36-0,63)	0,760[b]

a: Uji T test; b: Mann whitney; c: Chi square

Based on the chi-square test, the relationship of fQRS to the mortality and rehospitalisation rate showed statistically significant relationship. It can be concluded that patients with fQRS ECG features are 5.2 times more likely to undergo rehospitalisation in the first 6 months and 7.8 times more likely to have a mortality events in the first 6 months. ($p < 0,001$).

The study by Akbarzedah et al. also found a higher six-month mortality rate in the group with fQRS ($p = 0,032$). They also found that there was no significant difference in mortality during treatment in the group with fQRS or without fQRS.[4] Generally, early mortality in the group with fQRS was due to malignant arrhythmias, while long-term mortality was due to heart failure due to the remodelling process and the formation of scar tissue in the myocardium. An analytical study with a mean follow-up of 14–53 months also showed that patients with fQRS had a higher mortality rate than the non-fQRS group (RR 1,71; 95% KI 1,02 – 2,85).[14]

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Table 4.4. Relationship of fQRS to rehospitalisation and mortality rate

Variable	Relative risk	P value	95% CI	
			min	max
Rehospitalisation	5,2	< 0,001	2,63	10,28
Mortality	7,8	< 0,001	2,39	25,22

Multivariate analysis in this study is useful to determine which independent variables are the most dominant and have an effect on mortality and rehospitalisation in 6 months. From the 6-step multivariate analysis using logistic regression involving several clinical parameters, this study showed that there were 3 independent factors that could predict the incidence of rehospitalisation in ACS patients, namely GRACE score, FEVK, and fQRS. The results of the multivariate test of factors related to the incidence of rehospitalisation below obtained an R squared of 0.84, which shows that the modelling of the variables below can explain 84% of the incidence of rehospitalisation, while the other 16% is explained by other factors. From the results of the multivariate test analysis showed that ACS patients with fQRS showed 5.5 times more likely to undergo rehospitalisation in the first 6 months.

The multivariate analysis of DM was not able to describe its ability as an independent predictor of mortality and rehospitalisation in 6 months. This is in line with a previous study, which found that DM had no significant effect on mortality at 30 days and six months. However, in this study, DM was known to be an independent predictor of mortality in the first year (OR 2,7; 95% KI 1,2 – 6,3; p = 0,02).[15]

FEVK is one of the strongest predictors for predicting sudden cardiac death in patients with coronary heart disease, and the risk of sudden cardiac death increases as FEVK decreases. In a study conducted by Bezirnov, it was shown that FEVK <30% had a risk of 4,49 greater one-year mortality events (p <0,001). Meanwhile, for the 30%≤ FEVK < 49% group, the mortality rate was 1,83 times greater for the first year (p < 0,001).[16]

Table 4.5. Multivariate analysis of factors associated with rehospitalisation in the first 6 months

Variable	OR	P value	95% CI	
			min	max
GRACE > 118	7,8	0,003	2,00	31,5
EF <40%	3,88	0,03	1,63	15,1
fQRS	5,51	0,006	1,63	18,5

The results of the multivariate test of the factors related to the morality score below obtained an R squared of 0,64, which indicates that the modelling of the variables below can explain 64% of rehospitalisation events, while the other 36% are explained by other factors. From the results of multivariate test analysis showed that ACS patients with fQRS showed 2,9 times more likely to experience mortality in the first 6 months.

Table 4.6. Multivariate analysis of factors associated with mortality in the first 6 months

Variable	OR	P value	95% CI	
			min	max
GRACE > 118	15,2	0,001	3,14	73,6
EF < 40%	3,51	0,02	2,12	6,78
fQRS	2,9	0,01	5,42	15,2

Table 4.7. f QRS diagnostic test for rehospitalisation

Variable		Rehospitalisation		P Value	Sens (%)	Spec (%)	NPV (%)	PPV (%)
		Yes	No					
fQRS	Yes	25	11	< 0,001	75,7	82,5	86,7	69,4
	No	8	52					

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Tabel 4.8. fQRS diagnostic test for mortality

Variable		Mortality Yes	Mortality No	P Value	Sens (%)	Spec (%)	NPV (%)	PPV (%)
fQRS	Yes	14	22	< 0,001	82,3	72,1	95	38,8
	No	3	57					

Based on the results of the diagnostic test, fQRS can predict the incidence of rehospitalisation with a sensitivity of 75.7% and a specificity of 82.5%. Meanwhile, fQRS can predict the incidence of mortality with a sensitivity of 82.3% and a specificity of 72.1%.

Myocardial ischemia or the presence of scar tissue in the myocardium is one of the markers for a poorer prognosis because it tends to be at risk for ventricular arrhythmias and heart failure. fQRS indicates the presence of inhomogeneous electrical activity in ischemic ventricular areas or scar tissue due to coronary heart disease. Mapping of the epicardium and endocardium in patients with coronary heart disease and in patients with dilated cardiomyopathy with ventricular arrhythmias reveals a fragmented ECG reading around the myocardial scar. fQRS is associated with higher mortality and decreased survival in patients with coronary heart disease. fQRS is also a diagnostic marker for arrhythmogenic right ventricular dysplasia (ARVD) or cardiomyopathy, which is associated with the presence of scar tissue in the right ventricle.[17] Mortality is mainly due to ventricular arrhythmias and heart failure. Therefore, fQRS is associated with the presence of scar tissue in the myocardium, which creates a re-entry mechanism and perpetuates the occurrence of malignant ventricular arrhythmias.[18]

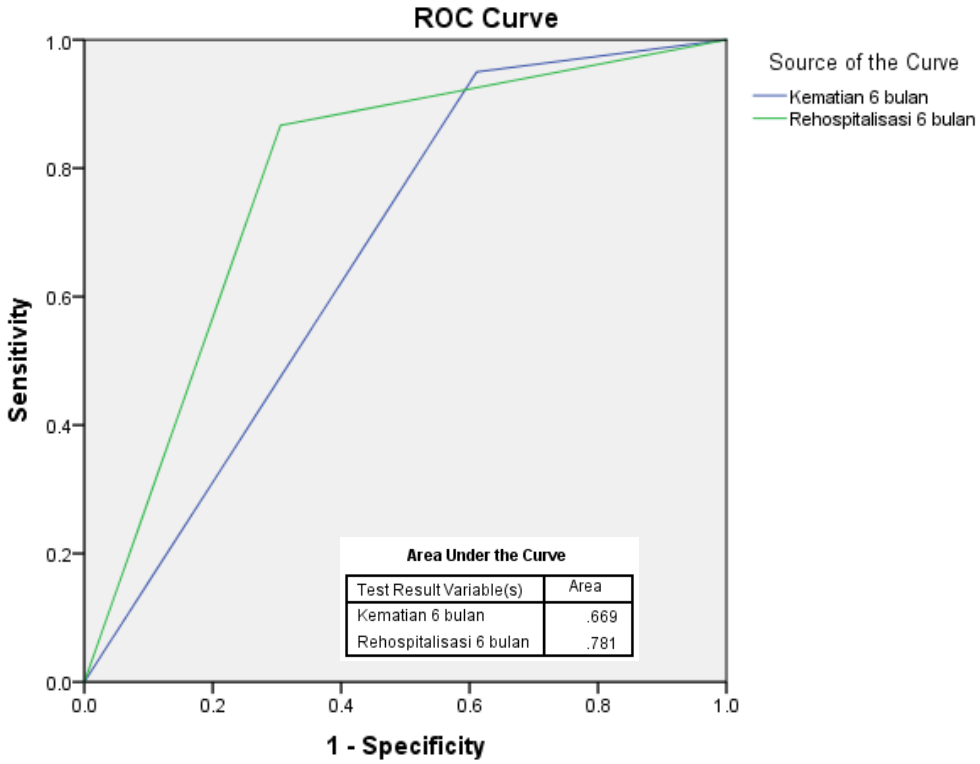

Figure 4.1. ROC curve of fQRS to the rehospitalisation and mortality rate

From the results of the ROC curve analysis, the area under the curve (AUC) for the incidence of rehospitalisation and mortality was 0,67 and 0,78, respectively. This shows that fQRS is good enough to be used as a modality to predict the incidence of rehospitalisation and mortality in the first 6 months. Other studies have also obtained the same results. A study with a follow-up of 34 ± 16 months, found that fQRS was an independent predictor of incident mortality (HR 1.68; 95% KI 1.89 – 2.38; p = 0.003).[18]

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Conclusion

Fragmentation of the QRS complex can be used as a predictor of incident rehospitalisation and mortality in the first 6 months in patients with acute coronary syndrome. GRACE score, FEVK, DM, and fQRS significantly influence rehospitalisation figures in the first 6 months. GRACE score, FEVK, DM, and fQRS also significantly affect mortality in the first 6 months. GRACE score, FEVK, and fQRS can be used as an independent predictor factor of rehospitalisation incident within 6 months and can also be used as an independent predictor of mortality within 6 months.

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