The Role of Fragmented QRS (fQRS) As A Predictor of Major Adverse Cardiac Event within 30 days in Acute Coronary Syndrome Patients: A Retrospective Cohort Study

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ABSTRAK

Latar belakang: *beberapa penelitian menunjukkan komplek QRS terfragmentasi (fQRS) sebagai penanda bekas luka miokard, substrat aritmia ventrikel, remodeling ventrikel, dan aliran kolateral koroner yang lebih buruk, yang dapat meningkatkan insidensi kejadian kardiak yang merugikan (MACE) setelah infark. Penelitian ini bertujuan untuk mengidentifikasi peran fQRS sebagai salah satu faktor risiko untuk MACE (kematian jantung dan reinfarction) pada pasien sindrom koroner akut dalam 30 hari pengamatan.* ***Metode:*** *penelitian retrospektif kohort dilakukan dengan menggunakan data sekunder pasien sindrom koroner akut di Unit Perawatan Jantung Intensif Rumah Sakit Cipto Mangunkusumo dari Juli 2015 hingga Oktober 2017. Analisis multivariat menggunakan regresi logistik dengan mengambil skor GRACE (risiko sedang dan tinggi), eGFR rendah (<60 ml/ mnt), LVEF rendah (<40%), diabetes mellitus, usia lebih dari 45 tahun dan hipertensi sebagai faktor perancu,.* ***Hasil:*** *353 subjek berhasil dikumpulkan pada penelitian ini. QRS terfragmentasi ditemukan pada 60,9% subjek; lebih sering terjadi pada sadapan inferior (48,8%) dengan awitan rata-rata 34 jam. Kejadian kardiovaskular mayor (KKM) lebih tinggi pada kelompok fQRS vs non-fQRS (15,8% vs 5,8%). Analisis bivariat menunjukkan probabilitas 30 hari KKM yang lebih tinggi dalam kelompok fQRS (RR 2,72; 95% CI 1,3 -5,71p = 0,08). Analisis multivariat menunjukkan RR 2,79 (CI 95%: 1,29 - 4,43, p <0,05). EGFR yang rendah adalah perancu potensial dalam penelitian ini.* ***Kesimpulan:*** *fQRS persisten yang terjadi pada ACS selama rawat inap adalah prediktor independen untuk kematian 30 hari pasca kejadian kardiovaskular mayor.*

Kata kunci: *sindrom koroner akut, QRS terfragmentasi (fQRS), kejadian kardiovaskular mayor (KKM).*

ABSTRACT

Background: *some studies show fragmanted QRS (fQRS) as a marker of myocardial scar, ventricular arrhythmia, ventricular remodelling and worse coronary collaterals flow, which can increase the incidence of major adverse cardiac event (MACE) after infarction. This study aimed to identify the role of fQRS as one of the risk factors for MACE (cardiac death and reinfarction) in acute coronary syndrome patients within 30 days*

observation. ***Methods:*** *a cohort retrospective study was conducted using secondary data of acute coronary syndrome patients at Intensive Cardiac Care Unit Cipto Mangunkusumo Hospital from July 2015 to October 2017. Multivariate analysis were done by using logistic regression with GRACE score (moderate and high risk), low eGFR (< 60 ml/min), low LVEF (< 40%), diabetes mellitus, age more than 45 years and hypertension as confounding factors.* ***Results:*** *three hundred and fifty three (353) subjects were included. Fragmented QRS was found in 60,9 % subjects. It was more frequent in inferior leads (48.8%) with mean onset of 34 hours. Major adverse cardiac events were higher in fQRS vs. non-fQRS group (15.8% vs. 5.8 %). Bivariate analysis showed higher probability of 30 days MACE in fQRS group (RR 2.72; 95%CI 1.3 -5.71p=0.08). Multivariate analysis revealed adjusted RR of 2.79 (95% CI: 1.29 – 4.43, p<0.05). Low eGFR was a potential confounder in this study.* ***Conclusion:*** *persistent fQRS developed in ACS during hospitalization is an independent predictor of 30 days MACE cardiac death and re-infarction.*

Keywords: *acute coronary syndrome, fragmanted QRS (fQRS), major adverse cardiac event (MACE).*

INTRODUCTION

Acute coronary Syndrome (ACS) is the highest cause of death in the world from 2000 to 2015, with total death count of 5-11% during treatment. The rate doubles in a year.[1-5] Das et al[6] studied the presence of fragmented QRS (fQRS) waves on an electrocardiogram, which depicted ventricular conduction changes around the scarring myocardium in ACS patients.

Some studies showed fQRS as a marker of myocardial scar, ventricular arrhythmia substrate, ventricular remodelling and worse coronary collaterals flow, so that it can increase the incidence of major adverse cardiac event (MACE) after infarction.[6-12] In contrast, a study by Wang et al.[13] failed to show that fQRS was superior than Q wave as a predictor of myocardial scar (1.7% vs. 31.7% sensitivity). Lorgis et al.[14] in 2013 showed that fQRS was not a predictor for MACE (reinfarction, heart failure and death) in 2 years observation.

Acute coronary syndrome patients in developing countries have different characteristics compared to those in developed countries. In developing countries, patients tend to have late presentation of infarct symptoms, delayed treatment and limited access to cardiac health center.[15] This study is the first in Indonesia, as a developing country, to predict the role of fQRS as one of the risk factors for MACE (cardiac death and reinfarction) in ACS patients within 30 days observation.

METHODS

This was a retrospective cohort study, which included all ACS patients at the Intensive Cardiology Care Unit (ICCU) Ciptomangunkusumo Hospital, within the period of July 2015 to October 2017. Electrocardiograms were recorded using Bionet/ Cardiotouch 3000 machine, low-pass filter setting, AC 60 Hz and a cut off of 150 Hz was defined. Das et al (2006) defined that fragmented QRS was present as an additional wave on R (R‘) or notch on R or S waves nadir, or the existence of more than one R’ on 2 successive leads, which related to the territory of the main coronary artery on a 12-lead ECG, with a duration of less than 120 ms.6 (**Figure 1**). Electrocardiograms were recorded in serial during hospitalization at emergency department and ICCU.

Fragmented QRS criteria were fQRS pattern, with a QRS width of less than 120 msec and persistent during hospitalization. Acute coronary syndrome and reinfaction criteria were set according to the Third Universal Definition of Myocardial Infarction by the American Heart Association (AHA) in 2012.[16] Cardiac deaths were all deaths caused by myocardial infarction, sudden cardiac death/ lethal arrythmia, and acute lung oedema, which was assessed by a cardiology consultant.

Inclusion criteria of this study were all ICCU patients with new or recurrent ACS (STEMI, NTEMI and unstable angina pectoris) of more than 30 days of last incident. Acute coronary

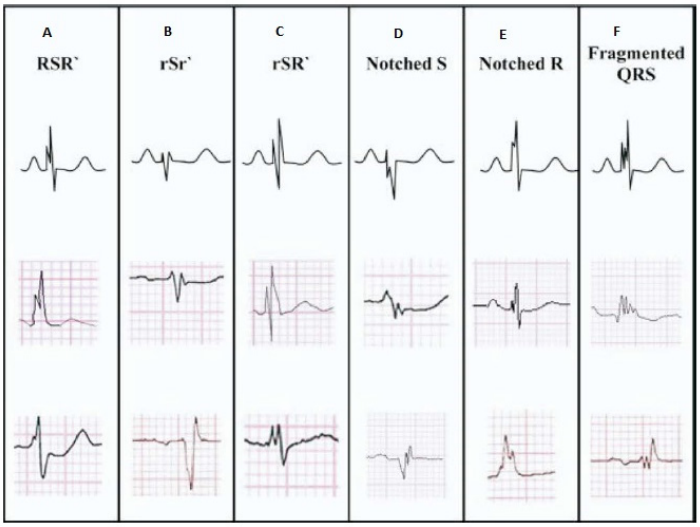

Figure 1. Six Type of Fragmented QRS (fQRS) Pattern[6]

syndrome patients with wide QRS (QRS duration >120 ms), which was present as a prior history of arrhythmia, congenital heart disease , severe valvular heart disease and patients using pacemaker and those with incomplete data of medical record and ECG data (also known as complete missing data) were excluded from this study.

All subjects were followed for 30 days for the incidence of cardiac death and or re-infarction that need hospitalization. Confounding factors were age of more than 45 years, hypertension, diabetes mellitus, history of coronary heart disease, left ventricle ejection fraction less than 40%, eGFR less than 60 ml/min and moderate to high risk for GRACE score. Electrocardiogram interpretation was confirmed among two observers, the main researcher and one independent cardiologist by determining Kappa value (a kappa value between 2 observers of 0.72 was considered good). If there were disagreement between 2 observers, a third independent cardiologist observer would confirm the result. This study has been approved by the Ethics Committee of Faculty of Medicine, Universitas Indonesia.

Sample size was calculated using the two-independent proportions test formula for cohort study and we obtained a minimum sample size of 336 subjects. Bivariate analysis was performed using the 2 x 2 table to determine relative risk (RR) probability on the occurrence of MACE within 30 days between fragmented QRS vs. non-fragmented groups. QRS groups and Chi square test were used to determine p value by using SPSS statistics version 23.0. Multivariate analysis with logistic regression were done, including GRACE score (moderate and high risk), low eGFR (<60 ml/min), low LVEF (<40%), diabetes mellitus, age more than 45 years and hypertension as confounding factors.

RESULTS

Out of 392 registered subjects with ACS, 33 subjects were excluded because 11 subjects had complete bundle branch block, 14 subjects had rhythm abnormalities (11 with atrial fibrillation and 4 with total AV block), 5 subjects had no ECG data and 3 subjects had unreadable ECG. Total sampling was performed using consecutive technique, w hich had been done by taking all data of 359 subjects. Of 359 subjects, 6 subjects were excluded because of loss to follow up. At the end of the study, 353 subjects were eligible for final analysis.

There was no significant different proportion between fQRS and non-fQRS groups based on baseline characteristics (**Table 1**). Fragmented QRS were found in 60.9% (215 subjects) with major locations of fQRS area at inferior (48.8%) and anterior (20.0%) and the mean onset of 34 hours (SD 39.8 hours). The proportion of cardiac death and reinfarction were 11.9% with

Table 1. Baseline characteristics of patients by the presence of fQRS waves

Variables	Total (n,%) (n = 353)	fQRS group (n,%) (n = 215 (60.9%))	Non-fQRS Group (n,%) (n = 138 (39.1%))
Sex			
- Male	240 (68)	145 (67.4)	95 (68.8)
- Female	113 (32)	70 (32.6)	43 (31.2)
Age (year), mean (SD)		56.96 (11.21)	56.5(10.57)
Age			
- < 45 y.o	45 (12.7)	28 (13)	17 (12.3)
- 45-60 y.o	183 (51.8)	106 (49.3)	77 (55.8)
- >60 y.o	125(35.5)	81 (37.7)	44 (31.9)
Risk Factors			
- Diabetes mellitus	148 (41.9)	90 (41.9)	58 (42)
- Hypertension	232 (65.7)	147 (68.4)	85 (61.6)
- Dyslipidemia	237 (67.1)	147 (68.4)	90 (65.2)
- Smoking	150 (42.5)	90(41.9)	60 (43.5)
- History of prior coronary artery disease	139 (39.4)	79 (36.7)	60 (43.5)
ACS Onset (hour), Median (range)		8 (0.3 - 336)	8 (0.5 - 504)
Type of ACS			
- UAP	88 (25)	56 (26)	32 (23.2)
- NSTEMI	129 (36.5)	72(33.5)	57 (41.3)
- STEMI	136(38.5)	87 (40.5)	49 (35.5)
Infarct location			
- Anterior	134 (38)	87 (40.5)	47 (34.1)
- Inferior	89 (25.2)	50 (23.3)	39 (28.3)
- Lateral	64 (18.1)	37 (17.2)	27 (19.6)
- Others	66 (18.7)	41 (19)	25 (18)
Infarct Area			
- Large infarction	125 (35.4)	87(40.5)	47 (34.1)
- Small infarction	228 (64.6)	128 (59.5)	91 (65.9)
GRACE Score Category			
- Mild	230 (65.2)	136 (63.3)	94 (68.1)
- Moderate	78 (22.1)	50 (23.3)	28 (20.3)
- High	45 (12.7)	29 (13.4)	16 (11.6)
EF (%), Median (range)b		49 (16 -81)	49 (15 - 76)
LVEF categoryb			
- LVEF < 40%	92 (27.1)	55 (26.8)	37 (27.6)
- LVEF ≥ 40%	247 (72.9)	150 (73.2)	97 (72.4)
eGFR, Median (Range, ml/minute/m^2)		80 (4.1 -131)	70.3 (2.9 - 124)
eGFR category			
- eGFR < 60	115 (32.6)	62 (28.8)	53 (38.4)
- eGFR ≥ 60	238 (67.4)	153 (71.2)	85 (61.6)
Heart rate, median (range)		75 (45-130)	75 (42. 120)
PQ time, median (range), msec		200 (120-280)	200 (120-240)
QRS interval, median (range), msec		60 (40-100)	60 (40-100)
QTc, median (range), msec		400 (260-520)	360 (280-550)

[a] Dyslipidemia: Completely missing data 1.9% (n=7); [b] LVEF: Completely missing data 3.6 % (n=14)
eGFR: Estimated Glomerular Filtration Rate, GRACE: Global Registry of Acute Coronary Events, LVEF: Left Ventricle Ejection Fraction, msec: millisecond, NSTEMI: Non ST Elevation Myocardial Infarction, SD: standard deviation, ACS: acute coronary syndrome STEMI: ST elevation Myocardial Infarction, UAP: unstable angina pectoris, QTc: QT corrected, y.o: year old.

Table 2. Bivariate analysis of fQRS and MACE (cardiac death and reinfarction)

Variables	MACE		Total (n)	RR (95% CI)	p value
fQRS	Yes	No			
Yes	34 (15.8%)	181 (84.2%)	215 (100%)	2.72 (1.3 -5.71)	0.008
No	8 (5.8%)	130 (94.2%)	138 (100%)		
Total	42	311	353		

MACE: major adverse cardiac event; RR: Relative risk; p: probability

proportion of cardiac death of 7.9% (28 subjects) and reinfarction was 4.0% (14 subjects).

The proportion of MACE in fQRS group was 15.8%; while the proportion in the group without fQRS was 5.8%. In bivariate analysis, fQRS increased probability of MACE during 30 days in ACS patients with crude relative risk (RR) of 2.72 (95% CI: 1.3-5.71. p=0.008). (**Table 2**)

Multivariate analysis were done by using logistic regression with GRACE score (moderate and high risk), low eGFR (<60 ml/min), low LVEF (<40%), diabetes mellitus, age more than 45 years and hypertension as confounding factors (p<0.25. **Table 3**). Our study revealed that the adjusted RR was 2.79 (95% CI: 1.29 – 4.43, p<0.05). Low eGFR was a potential confounder in this study. (**Table 4**)

Table 3. Bivariate analysis between confounding factors and 30 day MACE

Variable	RR (95% CI)	p value
Age (≥ 45 yo)	2.92 (0.73-11.67)	0.159
Hypertension	1.66 (0.85-3.27)	0. 177
Diabetes Mellitus	1.67 (0.94-2.96)	0.103
Dyslipidemia	0.92 (0.505-1.67)	0.924
History of coronary disease	1.15 (0.65-2.04)	0.746
LVEF (< 40%)	2.07 (1.15-3.72)	0.033
eGFR (< 60)	2.38 (1.36-4.15)	0.003
Type of infarction (STEMI)	0.71 (0.38-1.32)	0.365
GRACE score category Moderate-High	5.27 (2.74-10.11)	0.001

DISCUSSION

The present study showed that the proportion of MACE in fQRS vs. no fQRS groups was 15.8% and 5.8%. Bivariate analysis showed an increased probability of MACE within 30 days in fQRS group with crude relative risk (RR) of 2.72 (95% CI 1.3-5.71. p=0.008). Of the 42 MACE occurred within 30 days, there were 28 (7.9%) with cardiac death and 14 (4.0%) with reinfraction. The causes of death were sudden cardiac death (53.6%), cardiogenic shock (17.9%) and lethal arrhythmia (14.3%). Yudhatama et al[10] showed an increased risk of

Table 4. Crude OR and adjusted OR and adjusted RR for fQRS and 30-day MACE with 6 confounding factors

fQRS variables	OR (95% CI)	P value	Effect of Confounding Factors with Adjusted OR
Crude RR	2.72 (1.3-5.71)	0.008	
Crude OR	2.8 (1.24-6.31)	0.013	
Adjusted OR			
+ GRACE score	2.727 (1.18-6.28)	0.019	2.8%
+ eGFR	3.115 (1.32-7.32)	0.009	12.4%
+ LVEF < 40%	3.25 (1.37- 7.69)	0.007	4.1%
+ DM	3.25 (1.36-7.71)	0.008	0
+ Age > 45 y.o	3.252 (1.37-7.72)	0.008	6.1%
+ Hypertension *	3.136 (1.31-7.46)	0.010	3.6%
Adjusted Relative Risk[a]	2.79 (1.29-4.43)	<0.05	

* Fully adjusted OR

[a] Adjusted Relative Risk with Zhang et al. 1998 conversion formula

ventricular arrhythmia (ventricular fibrillation. ventricular tachycardia and premature ventricle contraction) in fQRS group with adjusted HR of 2.8 (95% CI: 2.2 - 5.4, p<0.001). Survival rate during treatment was worse in fQRS group compared to non-fQRS group (126 hours vs. 170 hours, logrank p<0.001).

Das. et al.[6] and Kadi et al.[17] identified fQRS as a conduction disturbance marker, which was recorded in late potential on signal averaged electrocardiogram (SAECG) from the fibrotic myocardial zone of infarction. Late potential is generated from prolonged refractory period and repeated excitation from infarct area due to slow and inhomogenous conduction. This repeated excitation process is called re-entry mechanism, which increases the risk for having ventricular arrhythmias and sudden cardiac death in ACS patient.[18]

A study by Sheng et al.[7] in STEMI patients showed that there was an increased risk of arrhythmia maligna 4 times higher and left ventricle systolic dysfunction (LVSD) 7.5 times higher in fQRS group than non fQRS group. A retrospective cohort study by Kadi et al.[8] indicated fQRS as a predictor of poor formation of collateral coronary artery flow in patients with chronic total coronary without prior myocardial infarction (OR 8.4 .95% CI 1.97-35.7. p=0.004). This may cause the infarction area prone to occlusion and having recurrent myocardial ischemia.

Multivariate analysis with logistic regression were done, including GRACE score (moderate and high risk), low eGFR (<60 ml/min), low LVEF (<40%), diabetes mellitus, age more than 45 years and hypertension as confounding factors. Our study revealed an adjusted RR of 2.79 (95% CI: 1.29 – 4.43; p<0.05). Low eGFR was a potential confounder in this study. In subjects with eGFR lower than 60 ml/min, we found that atherosclerosis and cardiac remodelling were accelerated, which might be due to the activation of the renin-angiotensin-aldosteron system and sympathetic nerve system, increased inflammatory process and impaired balance between Nitric oxide (NO) and Reactive Oxygen Species (ROS).[5]

The clinical implication of fQRS as an important myocardial scar marker is correlated with re-entry substrate of arrhythmia, poor collateral coronary artery flow and myocardial remodeling, which can increase the risk of 30-day MACE. Administration of either antiremodelling or antiarrhytmic therapy for ACS patient with persistent fQRS should be considered.[19] Yet. further studies on the efficacy of these agents are necessary.

This study is the first in Indonesia that evaluates the role of fQRS as a predictor of 30-day MACE in ACS patients. This study has limitation as it is a single-centered study at a tertiary referral hospital.

CONCLUSION

Fragmented QRS increases the probability of MACE (cardiac death and reinfarction) in 30 days in ACS patients with an adjusted relative risk of 2.79 (95%CI: 1.294 - 4.43).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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