

# High prevalence of fragmented QRS on electrocardiography in Japanese subjects with diabetes irrespective of metabolic syndrome

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## Original investigation

**Keywords:** diabetes mellitus, metabolic syndrome, fragmented QRS, fQRS, electrocardiography, myocardial fibrosis, myocardial scar formation, diabetic cardiomyopathy

**Posted Date:** December 10th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-123784/v1>

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# Abstract

## Background

Fragmented QRS (fQRS) on electrocardiography is a marker of myocardial fibrosis and myocardial scar formation. fQRS has been reported as a reliable predictor of adverse cardiac events in several populations. We investigated the relationship of fQRS with diabetes mellitus (DM) and metabolic syndrome (MetS) in Japanese patients.

## Material and methods

Our study enrolled a total of 702 subjects (435 without DM and 267 with type 2 DM) who had a routine health checkup at the Hokuriku Health Service Association (Toyama, Japan) in October 2014. Based on MetS and DM status, participants were categorized into one of the following four groups: DM+ MetS + (157 subjects); DM+ MetS - (110 subjects); DM- MetS + (82 subjects); and DM- MetS- (353 subjects). fQRS was assessed using the results of electrocardiography.

## Results

The prevalence of fQRS was statistically higher in patients with DM+MetS+ (36%) and DM+MetS- (36%), than those with DM-MetS+ (18%) or DM-MetS- (9%) ( $p < 0.001$ ). Significant differences were observed between the fQRS(+) and fQRS(-) groups for age, gender, waist circumference (WC), heart rate, hypertension, HbA1c, TC, MetS, and DM. The area under the receiver-operating curve for traditional risk factors and DM was 0.72 ( $p=0.0021$ , 95% confidence interval [CI]: 0.68-0.77), and for traditional risk factors and MetS it was 0.69 ( $p=0.1478$ , 95% CI: 0.64-0.73). Patients with DM had more than three-fold higher likelihood of showing fQRS (odds ratio, 3.41; 95% CI, 2.25-5.22;  $p<0.0001$ ) compared to the reference group without DM, after adjusting for age, gender, dyslipidemia, hypertension, and WC.

## Conclusion

fQRS was observed more frequently in DM than in MetS and control subjects. DM was the most significant determinant for fQRS among MetS and other traditional metabolic risk factors in the general Japanese population.

## Background

A fragmented QRS (fQRS) on a resting 12-lead electrocardiogram (ECG) includes various QRS complex morphologies [1]. QRS complex morphologies include Q wave, various RSR' patterns, additional R wave (R') or notching in the nadir of the S wave, the presence of  $>1$  R' (fragmentation) in 2 contiguous leads, corresponding to a major coronary artery territory. Several reports have demonstrated that fQRS correlates with the presence of a myocardial scar and fibrous tissues [2, 3]. Furthermore, a fQRS reflects myocardial conduction abnormalities, likely due to myocardial fibrosis, which is considered a prognostic marker for lethal cardiac arrhythmias [4].

Cardiac fibrosis is often observed in the early stage of diabetes mellitus (DM), and myocardial hypertrophy, interstitial fibrosis, capillary endothelial changes, and capillary basal laminar thickening are the common histopathological abnormalities in DM [5-7]. Myocardial fibrosis in DM manifests as diastolic dysfunction which results in heart failure with a preserved ejection fraction (HFpEF) [8]. The amount of myocardial fibrosis is a predictor of long-term survival for patients with HFpEF [9]. Furthermore, myocardial fibrosis has a negative impact on regional and global myocardial function and does not regress, even with an intensive glycemic management [10, 11]. Due to the negative consequences of a diagnosis of myocardial fibrosis on patients with DM, the detection of these high-risk patients will have a clinically significant impact.

Our study sought to improve the outcome of patients with DM and myocardial fibrosis by investigating the presence and frequency of fQRS in patients with DM and metabolic syndrome (MetS). Using a retrospective analysis of the general Japanese patient population, we report a significant correlation between fQRS and DM, however, no significant correlation was observed in patients with MetS. The link between fQRS and DM provides an important diagnostic tool to assess cardiac dysfunction in patients with this devastating endocrinological condition.

## **Materials And Methods**

### **Study Population**

This was a retrospective cross-sectional observational study. We examined the clinical records of patients who had a routine health checkup at Hokuriku Health Service Association (Toyama, Japan) the first week of October 2014. The study protocol was approved by the Ethics Committee of the University of Toyama (IRB# R2019028) and the Hokuriku Health Service Association. Written informed consent was obtained from all participants. The Hokuriku Health Service Association performs approximately 150 000 annual health examinations on workers and their families and has recently reported a large-scale study on new-onset atrial fibrillation [12]. One investigator in the Hokuriku Health Service Association was blinded to the clinical information, except for the existence of DM and MetS in the population. This blinded investigator randomly selected 702 patients from the cohort to have similar numbers of DM+MetS+, DM+MetS-, and DM-MetS+ patients to increase the efficiency of group comparisons.

### **Annual health examination**

The annual health examination includes a 12-lead ECG, chest X-ray, blood pressure (BP) measurement, heart rate (HR), body mass index (BMI), blood glucose, hemoglobin A1c (HbA1c), total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG), uric acid, liver enzyme (aspartate aminotransferase, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase), renal function (blood urea nitrogen, creatinine), urinalysis and testing for blood cell count and blood chemistry. The examination also contains a self-reported health questionnaire which includes information on previous history of stroke, DM, hypertension, dyslipidemia, myocardial infarction, angina pectoris and arrhythmia. Prior cardiovascular disease reported in the questionnaire are listed in Table 1.

## Assessment of Cardiovascular Risk Factors

Hypertension was diagnosed if peripheral blood pressure was  $\geq 140/90$  mm Hg, or if the health questionnaire indicated current antihypertensive medications [13]. DM was diagnosed using HbA1c  $\geq 6.5\%$  (National Glycohemoglobin Standardization Program), a fasting blood glucose concentration of  $\geq 126$  (7.0 mol/L) mg/dL, or a random blood glucose concentration of  $\geq 200$  mg/dL (11.1 mol/L) [14], or if the health questionnaire indicated current medications for DM. MetS was defined using the criteria of the Japanese Society of Internal Medicine (JIM) [15], which includes a waist circumference (WC) more than 85 cm in men or 90 cm in women, and two or more of the following: (1) TG 150 mg/dL (1.7 mmol/L) and/or HDL cholesterol  $< 40$  mg/dL ( $< 1.03$  mmol/L) for both of men and women, or the health questionnaire indicated current lipid-lowering medications, (2) a systolic BP of 130 mmHg, diastolic BP 85 mmHg, or the health questionnaire indicated current antihypertensive medications; or (3) a fasting blood glucose of 110 mg/dL (6.1 mol/L), or the health questionnaire indicated current medications for DM. Obesity was defined as BMI  $\geq 25$  kg/m<sup>2</sup> following the Japan Society for the Study of Obesity criteria [16].

## ECG Acquisition and Analysis

A 12-lead surface ECG was obtained from all patients in the supine position with electrocardiogram FCP-7431 (Fukuda Denshi Co., Ltd., Tokyo, JAPAN; filter range 0.16 Hz–100 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV). fQRS was defined following the criteria by Das et al. [1]. QRS complex morphologies included various RSR' patterns, including an additional R wave (R'), notching of the R wave or the S wave, or the presence of  $>1$  R' (fragmentation) in two continuous leads corresponding to a major lead set for major coronary artery territory. An fQRS was present if found in  $\geq 2$  contiguous anterior leads, lateral leads, or inferior leads. In cases with bundle branch block (BBB), we followed the fragmented BBB evaluation [17]. Right BBB (RBBB) and left BBB (LBBB) were defined by the standard ECG criteria (QRS duration  $\geq 120$  ms), and f-BBB was defined as various RSR' patterns with or without a Q wave, with  $>2$  R waves (R') or  $>2$  notches in the R wave, or  $>2$  notches in the downstroke or upstroke of the S wave, in 2 contiguous leads corresponding to a major coronary artery territory. Other ECG findings were evaluated with Minnesota-code statements by the ECG records and manual checks. All ECGs were assessed with a single cardiologist blinded to the patients' clinical and laboratory characteristics. The concordance rate in detecting the fQRS was 97% to the other cardiologists who already published papers on fQRS. [18, 19].

## Statistical Analysis

Continuous variables were expressed as means  $\pm$  standard deviation (SD) and categorical variables were expressed as percentages. A comparison of the categorical variables between the groups was performed using a  $\chi^2$  test. Continuous variables were compared using an unpaired t test and a Mann Whitney U test. Multivariable regression analysis was used to assess independent contributors. For stepwise analysis, parameters having an association to fQRS with  $p < 0.10$  were entered into the analysis. Odds ratios (ORs) for the existence of fQRS were calculated using logistic regression. The results of multivariate regression

analyses were presented as OR with a 95% confidence interval (CI). The predictive ability of DM and other risk factors for the presence of fQRS was evaluated using receiver-operating curve (ROC) analysis calculating the area under the curve (AUC) and standard error (SE).  $p < 0.05$  was considered statistically significant. Statistical analysis was done using JMP Pro 15.3 on Mac (SAS Institute Inc., Cary, NC, USA).

## Results

The clinical and laboratory characteristics of patients enrolled in our study are summarized in Table 1. Overall, the prevalence of fQRS was 21% in our study population. Subjects with fQRS, as compared to those without the condition, were different in age, gender, WC, HR, HbA1c, TC, and prevalence of hypertension, MetS, and DM.

The prevalence of fQRS was statistically higher in DM subjects (36%) than DM-MetS+ subjects (18%) and control subjects (9%) ( $p < 0.001$ ) (Figure 1). The prevalence of fQRS among DM subjects was similar, irrespective of MetS.

Using receiver-operating curve (ROC) analyses for fQRS, the area under the curve (AUC) was 0.72 for patients with DM and traditional risk factors (age, gender, WC meeting JIM MetS criteria, hypertension, and dyslipidemia (red)), 0.68 for patients with MetS and traditional risk factors (green) and 0.67 for patients with traditional risk factors only (blue) (Figure 2a). The AUC for the ROC was 0.72 (95% CI: 0.68-0.77) for DM and traditional risk factors, which is significantly different than those with traditional risk factors alone ( $p = 0.0021$ ). Conversely, the AUC for the ROC was 0.69 (95% CI: 0.64-0.73) for MetS and the traditional risk factors, which was significantly different from that of traditional risk factors alone ( $p = 0.1478$ ).

We next used multivariable analysis to compare the contributions of DM on fQRS. Compared to the reference group without DM, subjects with DM had more than three-fold higher likelihood of showing fQRS (OR, 3.41; 95% CI, 2.25-5.22;  $p < 0.0001$ ), after adjusting for traditional risk factors (Table 2: Model 1).

Our stepwise analysis showed that age and DM were significant contributors to the presence of fQRS. Subjects with DM had more than three-fold higher incidence of fQRS than those without DM (OR, 3.81; 95% CI, 2.55-5.76;  $p < 0.0001$ ) after adjusting for age (Table 2: model 2). The AUC for the ROC analyses of fQRS was 0.71 for DM and age (red), 0.65 for MetS and age (green), and 0.63 for only age (blue) (Figure 2b). The AUC for the ROC with DM and age was only significantly different from age ( $p < 0.0001$ ). Together taken, our data demonstrate a significant correlation between fQRS and DM, which may hold clinical significance potential in the future.

## Discussion

The objective of our study was to determine whether diabetes mellitus (DM) or metabolic syndrome (MetS) were significant risk factors for a fragmented QRS (fQRS) using electrocardiography. A higher frequency of patients with fQRS was observed in DM, compared to those without DM. DM was

characterized by cryptic progressive accumulation of interstitial myocardial fibrosis and impairment of diastolic function in patients with long-standing DM. The degree of myocardial fibrosis appeared to have a significant effect on clinical progression, resulting in HFpEF. Myocardial fibrosis could not be detected by standard echocardiographic examination until it had progressed. It has been shown that the amount of myocardial fibrosis detected on contrast-enhanced magnetic resonance imaging (MRI) is closely correlated to quantitative histopathology [20]. Even though it has high sensitivity and specificity, the applicability of MRI to all DM patients is limited due to technical and financial issues.

fQRS on a standard 12-lead ECG is a sensitive and highly specific diagnostic marker of myocardial fibrosis in patients with known or suspected coronary artery disease and congenital heart disease [17, 21, 22]. In previous studies, significant elevation in the frequency of fQRS has been observed in DM, MetS, and other diseases without obvious cardiovascular symptoms. Bayramoglu et al. reported a prevalence of fQRS of 28% [23], Eren et al. reported 37.5% [24] among DM in a Turkish population and using coronary angiography, Mahfouz reported 62% in Egyptian DM [25]. In previous studies on MetS, 20% of patients showed fQRS in one study [26], and 26.1% of MetS patients compared to 14.6% of control subjects in another [27]. Among patients with systemic lupus erythematosus at diagnosis, 59.1% had fQRS [28]. fQRS was detected in 32.4% of ankylosing spondylitis patients compared to 7.14% in the control group [29]. 37.5% of patients with rheumatoid arthritis compared to 5% of control subjects had fQRS [30]. In thalassemia major, 86% of patients with cardiac involvement had fQRS, and 22% of patients with non-involvement [31]. Our results are consistent with these previous studies, highlighting the clinical usefulness of determining fQRS for patients with subclinical myocardial fibrosis, in DM and MetS.

From our study, we were able to draw several important conclusions. First, fQRS has a stronger correlation with hyperglycemia than with insulin resistance. JIM criteria refers to MetS as an insulin-resistant state, since abdominal adiposity is an indispensable component of this criterion [32]. No previous reports have compared the contribution of DM and MetS on fQRS. In this study, using a routine health checkup in a Japanese patient cohort separated according to the presence of DM and MetS, we found a higher frequency of fQRS in subjects with DM, compared to those with MetS. Hypertension is the most prevalent MetS component in the general Japanese population. A previous report showed a high prevalence of fQRS in subjects with hypertension [33]. In the current study, the contribution of hypertension on fQRS was not significant. Since cardiac fibrosis in hypertension parallels left ventricular hypertrophy [34], we consider that participants with hypertension in this study could be well-managed with blood pressure medication.

In relation to diabetic cardiomyopathy (DCM) [35, 36], it is conceivable to postulate that myocardial scar formation relates to the initial appearance of myocardial damage in DCM [8, 37, 38]. Furthermore, in patients with DM, the amount of myocardial fibrosis significantly affects clinical status, as well as long-term mortality and morbidity. Also, several studies have indicated that a quantitative assessment of myocardial fibrosis can provide additional prognostic information in patients with DM [39-41]. The clinical significance of fQRS is related to its association with myocardial fibrosis and heterogeneity in myocardial conduction [42]. It has been shown that patients with fQRS have significant heterogeneity of

myocardial conduction and an increased risk of ventricular tachycardia [43]. Accordingly, the evaluation of fQRS in DM subjects appears to be particularly important when we speculate on the possibility of DCM [23, 44].

Though our study was comprehensive in nature, retrospective analyses always carry a degree of limitation. Specifically, our study lacked a clinical follow-up, therefore, we could not conclude whether or not the presence of fQRS was clinically significant in patients with DM. Furthermore, we did not perform cardiac MRI, which is considered to be a gold standard in myocardial fibrosis and a meaningful tool to evaluate DCM, irrespective of myocardial damage [45]. Participants with prior-cardiovascular disease in this study were low (1.7%) and did not correlate with fQRS. Further studies are required to improve the predictive efficacy of fQRS in DM patients and provide the experimental impetus to further inform on the pathophysiology of DCM.

The primary objective of our study was to find a useful diagnostic tool to detect CHF candidates in the very early stage. A high prevalence of fQRS in DM patients suggests the need for an additional biomarker to clarify them as candidates of heart failure. Our study provides the groundwork to further investigate these important correlations between myocardial fibrosis and DM.

## Conclusion

We compared the prevalence of fQRS in patients with DM and MetS to examine the contribution of persistent hyperglycemia and insulin-resistant state. We found that patients with diabetes showed a higher prevalence of fQRS compared to those with MetS. We postulate that the persistent hyperglycemic state contributed to the existence of fQRS suggesting myocardial fibrosis. Our findings suggest that fQRS could be a biomarker for diabetic cardiomyopathy with increased myocardial fibrosis.

## Abbreviations

DM, diabetes mellitus

MetS, metabolic syndrome

JIM, Japanese Society of Internal Medicine

BMI, body mass index

HDL, high density lipoprotein

LDL, low density lipoprotein

fQRS, fragmented QRS

OR, odds ratio



CI, confidence interval

SE, standard error

WC, waist circumference

ROC, receiver-operating curve

AUC, area under the curve

DCM, diabetic mellitus cardiomyopathy

BP, blood pressure

CHF, congestive heart failure

MRI, magnetic resonance imaging

ECG, echocardiogram

HR, heart rate

HbA1c, hemoglobin A1c

TC, total cholesterol

SD, standard deviation

CI, confidence interval

BBB, bundle branch block

TG, triglyceride

ALT, aspartate aminotransferase, alanine aminotransferase

HFpEF, heart failure with a preserved ejection fraction

## **Declarations**

### **Ethics approval and consent to participate**

All procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent, or a substitute for it, was obtained from all patients included in the study. The study protocol was approved by the Ethics Committee of the University of Toyama (IRB# R2019028) and

the Hokuriku Health Service Association. Written informed consent was obtained from all the participants when they enrolled in the health checkup.

### **Consent for publication**

All authors have approved the final article for submission.

### **Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

### **Funding**

This work was supported by JSPS KAKENHI [Grant Number JP18K08505]. The study sponsor was not involved in the design of the study or the collection, analysis, interpretation of data, writing the report, or the decision to submit the report for publication.

### **Authors' contributions**

All the authors contributed to the care of the participants, data collection, and discussion. MK, MYN, MS, AE, ATN, HH, SF, and KT contributed to clinical discussions from an endocrinological viewpoint. KY, YN, and TY contributed to clinical reviews from a cardiovascular viewpoint. KY wrote the manuscript.

### **Acknowledgments**

The authors would like to express their gratitude to Dr. Tetsuo Konno, previously in the Department of Cardiology, Kanazawa University, for inspiring interest in fQRS. We express our sincere appreciation to the collaborative staff in the Hokuriku Health Service Association for their contributions.

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## Tables

Table 1. A comparison of clinical characteristics between patients with and without fQRS

Parameter	Total	fQRS(+)	fQRS(-)	p value
Number of the subjects	702	144 (21%)	558 (79%)	
Demographic				
Age, y.o.	51 ± 8	54 ± 8	50 ± 8	<0.0001
Gender, male%	532 (76%)	121 (84%)	411 (74%)	0.0096
BMI, Kg/m <sup>2</sup>	25 ± 4	25 ± 4	25 ± 4	0.3265
WC, cm	88 ± 11	90 ± 11	88 ± 11	0.026
Systolic blood pressure, mmHg	127 ± 16	129 ± 16	127 ± 16	0.1278
Diastolic blood pressure, mmHg	79 ± 12	79 ± 12	79 ± 12	0.6478
Heart rate, bpm	71 ± 12	69 ± 10	72 ± 12	0.0025
Smoking, n (%)	263 (37%)	56 (39%)	207 (37%)	0.5538
Diseases				
DM, %	267 (38%)	96 (67%)	171 (31%)	<0.0001
MetS, %	239 (34)	73 (51%)	168 (30%)	<0.0001
DM&MetS, %	161 (23%)	59 (41%)	102 (18%)	<0.0001
Hypertension, %	276 (39%)	75 (52%)	201 (36%)	0.0004
Dyslipidemia, %	409 (58%)	79 (55%)	330 (59%)	0.3533
Prior cardiovascular disease, %	10 (1.7%)	3 (2.3%)	7 (1.5%)	0.4883
Test values				
HbA1c, %	6.4 ± 1.4	6.8 ± 1.5	6.3 ± 1.3	<0.0001
Total cholesterol, mg/dL	207 ± 35	198 ± 34	209 ± 35	0.0008
Triglyceride, mg/dL	152 ± 123	144 ± 97	154 ± 129	0.3587
HDL-cholesterol, mg/dL	58 ± 15	56 ± 14	59 ± 16	0.0542
LDL-cholesterol, mg/dL	126 ± 33	121 ± 32	127 ± 33	0.0604
Creatinine, mg/dL	0.8 ± 0.2	0.8 ± 0.2	0.8 ± 0.2	0.4089
Alanine aminotransferase, U/L	29 ± 19	28 ± 18	29 ± 20	0.5632

fQRS, fragmented QRS; DM, diabetes; MetS, metabolic syndrome; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; WC, waist circumference.

Data are means  $\pm$  standard deviations or n (%) unless otherwise specified.

Table 2. Binary logistic regression analysis of independent predictors for the presence of fQRS

Independent variables	Model 1	P value	Model 2	P value
	OR (95% CI)		OR (95% CI)	
DM	3.41 (2.25-5.22)	<0.0001	3.81 (2.55-5.76)	<0.0001
Age, every 10 years-old	0.72 (0.55-0.93)	0.0127	0.69 (0.53-0.88)	0.0035
WC meeting JIM MetS criteria	1.38 (0.88-2.17)	0.1597	-	-
Dyslipidemia	1.28 (0.85-1.94)	0.2402	-	-
Gender, male/female	1.34 (0.80-2.29)	0.2777	-	-
Hypertension	1.21 (0.80-1.82)	0.3732	-	-

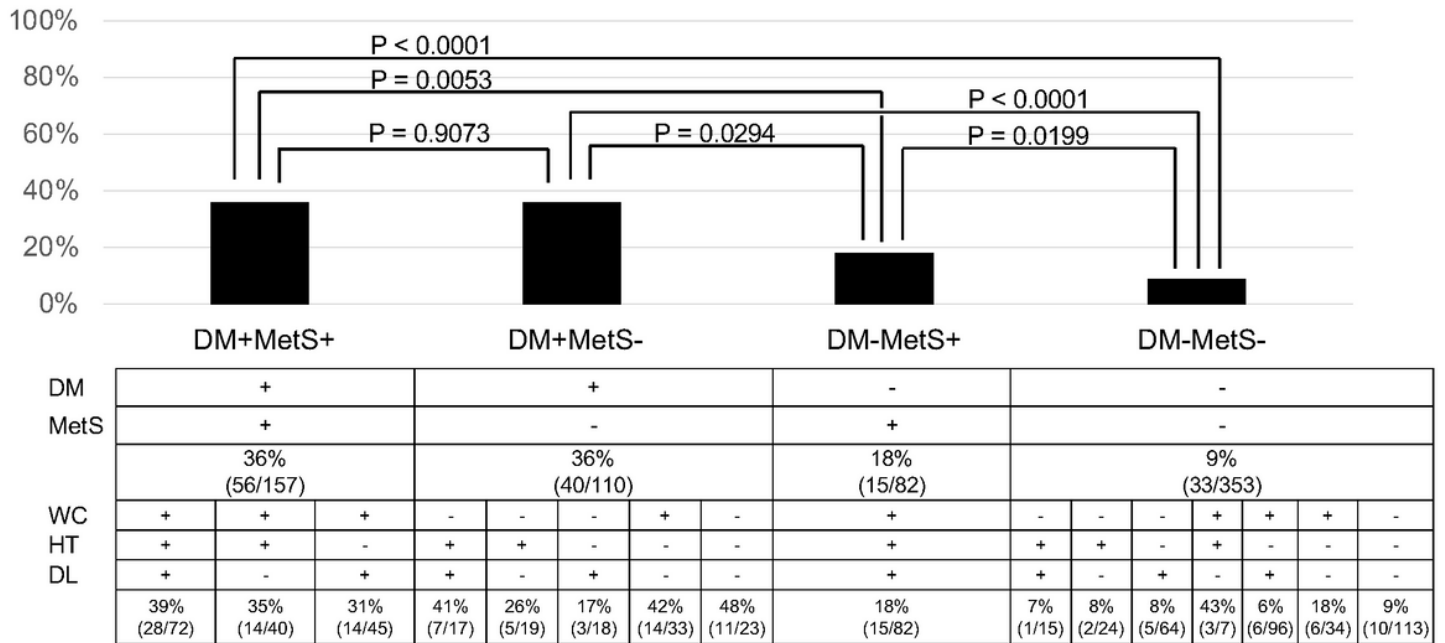
Model 1. ORs for fQRS were calculated using logistic regression with adjustment for age, gender, hypertension, dyslipidemia, DM, and waist circumference meeting JIM MetS criteria.

Model 2. OR for fQRS were calculated using logistic regression with adjustment for age and DM after pre-elimination of the variables with backward:LR method.

OR, odds ratio; CI, confidence interval; fQRS, fragmented QRS; DM, diabetes; MetS, metabolic syndrome; WC, waist circumference; JIM, Japanese Society of Internal Medicine

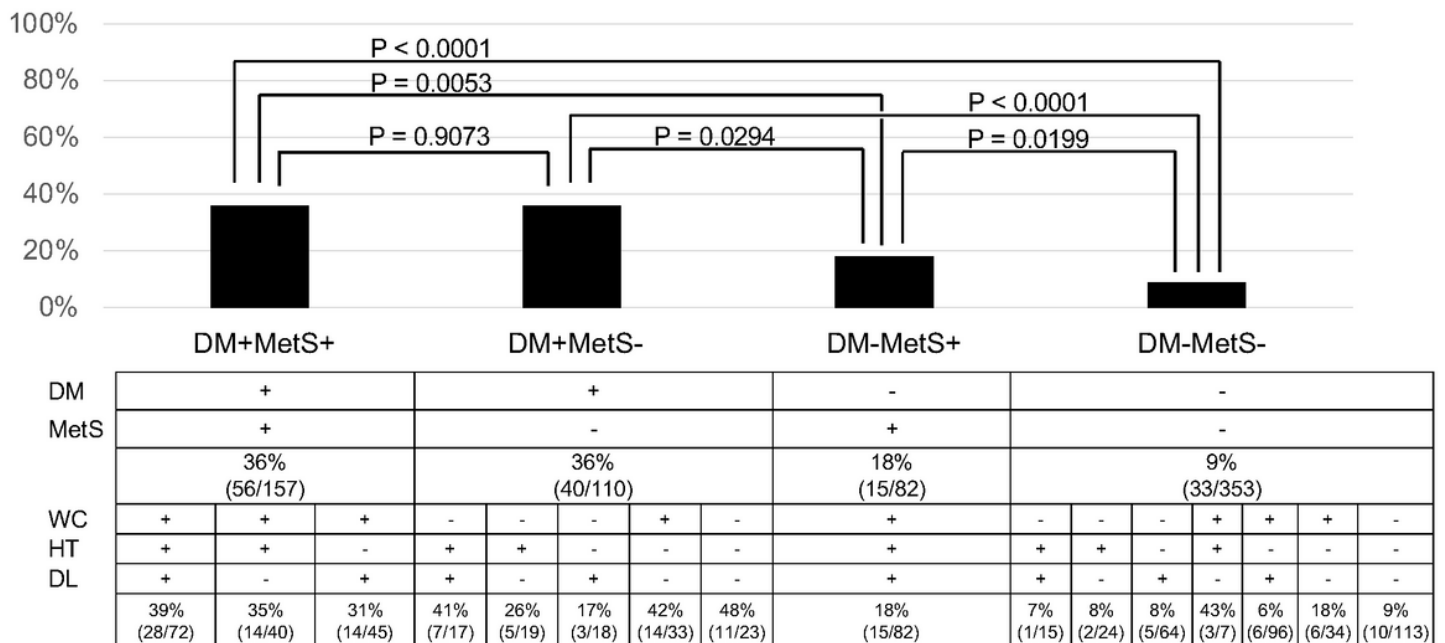
## Figures





**Figure 1**

Prevalence of fQRS among the following groups; DM+MetS+, DM+MetS-, DM-MetS+, and DM-MetS. A comparison of the categorical variables between the groups was performed using a  $\chi^2$  test. The table below the graph indicates the corresponding MetS component factors for each group. fQRS, fragmented QRS; DM, diabetes; MetS, metabolic syndrome; WC, waist circumference; HT, hypertension; DL, dyslipidemia.



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Figure 2a

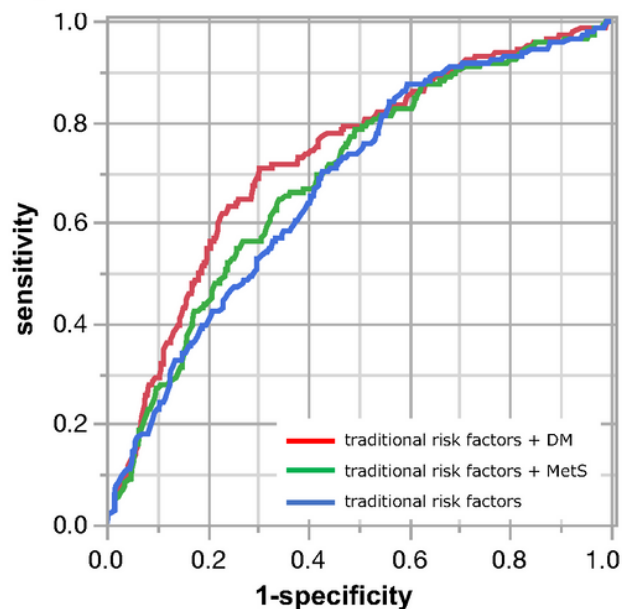
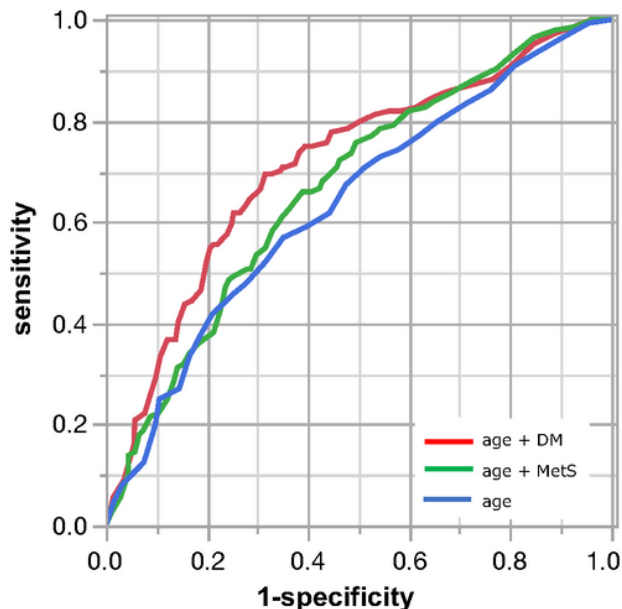


Figure 2b



	AUC	SE	95%CI	p-value to *
traditional risk factors + DM	0.72	0.024	0.68-0.77	0.0021
traditional risk factors + MetS	0.69	0.025	0.64-0.73	0.1478
* traditional risk factors only	0.67	0.024	0.62-0.72	-

	AUC	SE	95%CI	p-value to *
age + DM	0.71	0.025	0.66-0.76	<0.0001
age + MetS	0.67	0.025	0.62-0.71	0.0444
* age only	0.64	0.026	0.58-0.68	-

## Figure 2

The predictive ability of DM and other risk factors for the presence of fQRS was evaluated using ROC analysis calculating AUC and SE. ROC curve analyses showed the predictive values for established fQRS risk factors. Traditional risk factors included age, gender, smoking, hypertension, dyslipidemia and WC meeting JIM MetS criteria. a) Red line represents DM and traditional risk factors (AUC 0.72); the green line MetS and traditional risk factors (AUC 0.69); the blue line is traditional risk factors only (AUC 0.67). b) The red line represents DM and age (AUC 0.71); the green line MetS and age (AUC 0.67); the blue line representing age only (AUC 0.64). The red lines in a) and d) were consistent with Model 1 and Model 2 presented in Table 2, respectively. fQRS, fragmented QRS; DM, diabetes; MetS, metabolic syndrome; JIM, Japanese Society of Internal Medicine; WC, waist circumference; ROC, receiver-operating curve; AUC, area under the curve; SE, standard error.

Figure 2a

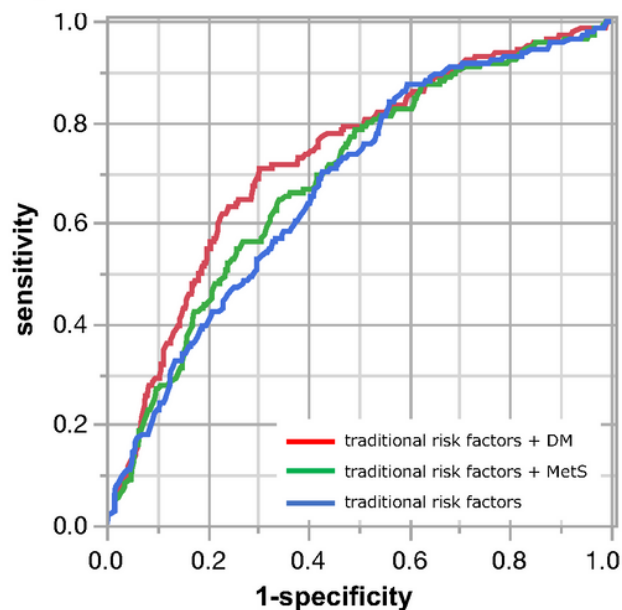
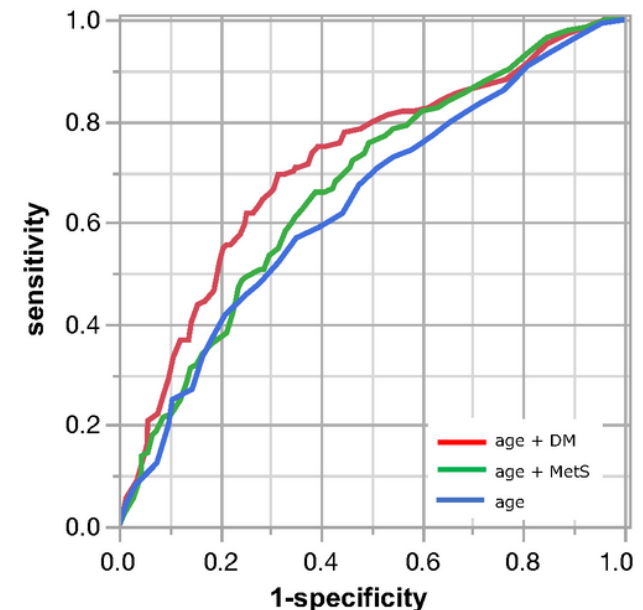


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