



## Original Article

## Fragmented QRS complex is an independent predictor of plaque burden in patients at intermediate risk of coronary artery disease



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## ABSTRACT

**Objective:** We aimed to evaluate the relationship between fragmented QRS complex and plaque burden in patients presented with typical chest pain and deemed to have intermediate pretest probability of CAD using coronary computed tomography angiography (CCTA).

**Methods:** We studied electrocardiograms (ECGs) obtained from 172 subjects ( $47.5 \pm 9.5$  years, 125 were men) presented with chest pain and had intermediate pretest probability for CAD. The presence was found and evaluation of CAD was performed with CCTA.

**Results:** Seventy four (43%) of the study cohort had CCTA-documented CAD. Meanwhile the frequency of fQRS in our cohort was (57%). 70 (71.4%) patients with fQRS had CAD compared with only 4 (5.4%) patients without fQRS ( $p < 0.001$ ). The number of leads with fQRS was correlated with the calcium score ( $p < 0.005$ ), segment stenosis score, segment involvement score, total plaque score (TPS), and E/e ratio ( $p < 0.001$ , for all). Multivariate analysis demonstrated that fQRS was a strong independent predictor for CAD (or = 2.15,  $p < 0.001$ ). ROC analysis showed that the number of leads  $\geq 3$  was the optimal number for predicting CAD (AUC = 0.89, sensitivity 88%, and specificity 83%,  $p < 0.001$ ).

**Conclusion:** Fragmented QRS was seen more often in patients with high plaque burden. We suggest that fQRS might provide a useful noninvasive prognosticator for subjects with intermediate pretest probability of CAD for further investigation.

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## 1. Introduction

Usually, it is accepted to recommend noninvasive testing in evaluation of subjects, who are complaining of chest and have intermediate pretest probability of coronary artery disease (CAD).<sup>1</sup> Yet, a considerable percentage of those patients had a normal or equivocal results. Furthermore, more than 95% of them have a favorable outcome along 2 years of follow-up, in spite of them having intermediate pretest probability of CAD.<sup>2–5</sup>

Das et al.<sup>6</sup> reported that the presence of fQRS complex in subjects with CAD was attributed to myocardial scarring, which resulted in delayed ventricular conduction, and they reported that fQRS has emerged as an independent predictor for major adverse cardiovascular events in individuals with CAD.

Coronary computed tomography angiography (CCTA) is a noninvasive test, which has a good image quality with high

specificity and negative predictive significance in detecting coronary artery stenosis.<sup>7,8</sup>

However, the significance of fQRS in patients with chest pain, who have intermediate pretest probability of CAD, is not clearly evaluated. We hypothesize that the presence of fQRS could be associated with coronary plaque burden in patients with chest pain and have intermediate pretest probability for CAD. Herein, we aimed to investigate the presence of fQRS and its relation to plaque burden in patients presented with chest pain and had intermediate pretest probability of CAD using CCTA.

## 2. Subjects and methods

About 172 subjects who presented with chest pain and had intermediate pretest probability for CAD were included in a prospective study.

## 2.1. Evaluation of the pretest probability of CAD

We categorized chest pain based on the following: Substernal or not; relation to exertion; duration of chest pain (relief within

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10 min with rest or with nitroglycerin). Then, chest pain was classified into: a) typical angina = the three described criteria, b) atypical angina = any two criteria of the three, and c) nonanginal pain = chest pain with one or none of the three criteria. The pretest probability of CAD was categorized with respect to age, sex, and character of chest pain into three categories: *low pretest probability* (10–20%) included asymptomatic men and women of all ages or women <50 years with atypical angina. *Intermediate pretest probability*, (between 20% and 80%) included men of all ages with atypical angina, women  $\geq$ 50 years with atypical angina or women 30–50 years with typical angina. *High pretest probability* (80–90%) included men  $\geq$ 40 years with typical angina or women  $\geq$ 50 years with typical angina.<sup>9,10</sup>

Exclusion criteria included previous myocardial infarction, coronary artery bypass grafting, resting or exercise electrocardiographic CAD, previous coronary stenting, extensive coronary artery calcification, significant arrhythmias, chronic liver disease, congenital/valvular heart disease. Patients with ejection fraction <50%, wall motion abnormalities, asthma allergy to contrast material, and those with serum creatinine  $\geq$ 2.0 mg/dl were also excluded.

All participants underwent echocardiographic evaluation to obtain ejection fraction, mitral flow velocity, E/A ratio, mitral annular velocities ( $e'$  &  $a'$ ), and the E/ $e'$  ratio as a marker of left ventricular filling pressure. Blood urea, serum creatinine, fasting and postprandial blood sugar, lipid profile, and high-sensitivity C-reactive protein (hs-CRP) were obtained using standard laboratory techniques. Body mass index (BMI) was calculated as weight (kg)/height ( $m^2$ ). Each participant gave an informed written consent.

## 2.2. Fragmented QRS complex assessment

Resting 12-lead ECG with 12 derivation recordings (filter range: 0.15–150 Hz; AC filter: 60 Hz; 25 mm/s; 10 mm/mV) were obtained and analyzed. We defined fQRS as the presence of different RSR' patterns with or without Q waves in two contiguous derivations (QRS duration <120 ms): existence of an additional R wave ( $R'$ ), notching of R or S wave, or >1  $R'$  fragmentation without typical bundle branch block.<sup>11</sup> Two independent cardiologists, who were blinded to the patients' characteristics, analyzed ECG of each participant, with an excellent interobserver variability ( $k = 0.95$ ,  $p < 0.001$ ).

## 2.3. Coronary CCTA evaluation

Participants underwent CCTA with a 64-slice MDCT scanner (LightSpeed VCT; GE Medical Systems, Milwaukee, WI). Beta blocker (5 mg Bisoprolol) was given for all subjects to optimize heart rate less than 60 bpm. To obtain coronary artery calcium score, a noncontrast scan was performed and image acquisition as follows (64  $\times$  3 mm, tube rotation up to 200 mA at 120 Kv). Then a nonionic contrast enhanced electrocardiogram (ECG)-modulated scan (average 10 s, 64  $\times$  0.6 mm, with tube current up to 550 mA at 120 kV) was performed. The CCTA assessment was performed within a single breath-hold in inspiration for about 10–20 s.<sup>12,13</sup>

The calcium score of each lesion was obtained by multiplying the area by the density factor taken from the maximal HU in the lesion area. The total score was calculated with the sum of individual scores of all lesions.<sup>14</sup>

## 2.4. Measurement of plaque burden

Morphological assessment was performed for coronary artery segments with a diameter more than 2 mm. We defined coronary plaque as structure more than 1  $mm^2$  within and/or adjacent to the

vessel lumen, which was clearly distinguished from the lumen and adjacent pericardial fat tissue.

We acknowledged the following subsets of coronary artery stenosis for each segment: 1) no obstruction, 2) mild CAD (<25% stenosis), 3) moderate (25%–<50% luminal stenosis), 4) moderately severe stenosis (50–70%), and 5) severe stenosis (luminal obstruction >70%). For each segment, plaque was described as calcified plaque (>130 HU), noncalcified plaque (<130 HU), or mixed plaque.

The clinical coronary artery plaque scores were obtained. The SSS was calculated as a measure of overall coronary artery plaque extent. Each individual coronary segment was graded as having no to severe plaque (i.e., scores from 0 to 3) based on the extent of obstruction of coronary luminal diameter. The total plaque score was obtained by summation of the extent scores of all 16 individual segments (a total score ranging from 0 to 48). To assess the overall coronary artery plaque distribution, a segment involvement score (SIS) was considered. The SIS was calculated with the sum of the number of segments with coronary artery disease, ranging from 0 to 16. For severity classification, as regards the diameter stenosis: normal or no stenosis was assigned a score of 0, 1%–25% stenosis was assigned a score of 1, 26%–50% stenosis was assigned a score of 2, 51%–70% stenosis was assigned a score 3, 71%–99% stenosis was assigned a score of 4 and a score 5 for total occlusion.<sup>15–17</sup>

## 2.5. Statistical analysis

Study variables were continuous variables (mean  $\pm$  standard deviation) and categorical variables (percentages). The analysis of covariance was used to compare groups adjusted for sex, age, and hypertension, with log-transformed variables for nonnormally distributed variables. The correlation analysis was performed with Spearman's correlation methods. Multivariable logistic regression analysis was performed to assess independent variables that predict obstructive CAD. Receiver operating characteristic (ROC) curve analysis was used to investigate the optimal number of leads with fQRS to predict obstructive CAD in subjects with intermediate pretest probability for CAD. The SPSS 18.0 (Chicago, IL, USA) was utilized for statistical analysis.

## 3. Results

One hundred seventy two subjects (125 males and 47 females, mean age of  $47.5 \pm 9.5$  years) were enrolled. CCTA evidence of any obstructive CAD was present in 74 (43%). The calcified or mixed coronary plaque was observed in 49 (66%), while the noncalcified plaques were found in 25 (34%). Among the vessels with coronary artery stenosis >50%, 42 (56.7%) had single vessel disease, 25 (33.8%) had two vessel disease, and 7 (9.5%) had three vessel disease. The total plaque score (TPS) was  $8.2 \pm 4.1$ , SSS was  $7.9 \pm 4.4$ , and the SIS was  $5.6 \pm 2.5$ , while, the CACS was  $292 + 261$  (Table 1). Data analysis showed that out of the 172 subjects enrolled for the study, fQRS were detected in 98 (57%) patients. Table 2 shows a comparison between patients with fQRS and those without fQRS. All the demographic data were comparable among subjects with and without fQRS except smoking habit ( $p < 0.01$ ), LDL-cholesterol ( $p < 0.05$ ), and hs-CRP ( $p < 0.01$ ), which were higher in those with fQRS. In addition, left ventricular filling pressure (E/ $e'$ ) was significantly increased in patients with positive fQRS ( $p < 0.001$ ). Importantly, patients with fQRS had a higher prevalence of CAD than those without CAD (71.4% vs 5.4%,  $p < 0.001$ ), Fig. 1.

We found that the number of leads with fQRS was positively correlated with SSS ( $r = 0.581$ ,  $p < 0.001$ ) Fig. 2, SIS ( $r = 0.460$ ,  $p < 0.001$ ), and total plaque score (TPS) ( $r = 0.293$ ,  $p < 0.01$ ), Table 3. Furthermore, fQRS was significantly correlated with E/ $e'$  ratio

**Table 1**  
Demographic characteristics and CCTA data of all studied cohort.

Variable	n = 172
Age	47.5 ± 9.5
Male n (%)	125 (73%)
Body mass index (kg/m <sup>2</sup> )	24.5 ± 2.9
Smoking n (%)	86 (50%)
Family history of premature CAD n (%)	35 (20%)
Hypertension n (%)	101 (59%)
Diabetes mellitus n (%)	73 (42%)
Fragmented QRS complex n (%)	98 (57%)
Total cholesterol mg/dL	195 ± 43
LDL-C (mg/dL)	123 ± 39
HDL-C (mg/dL)	41 ± 6
TG (mg/dL)	189 ± 85
Hs-CRP (mg/L)	3.1 ± 1.2
CCTA	
• Coronary calcium score, mm <sup>3</sup>	292 ± 261
• Negative coronary artery disease	98 (57%)
• Positive coronary artery disease (>50% stenosis)	74 (43%)
Calcified plaque or mixed plaque	49 (66%)
Noncalcified plaque	25 (34%)
Segment stenosis score	7.9 ± 4.4
Segment involvement score	5.6 ± 2.5
The total plaque score	8.2 ± 4.1
Number of stenosed vessels	
- One-vessel disease	42 (56.7%)
- Two vessel disease	25 (33.8%)
- Multivessel disease	7 (9.5%)

CCTA: Coronary computed tomography angiography HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TG: Total glycosides; hs-CRP: High-sensitivity C-reactive protein.

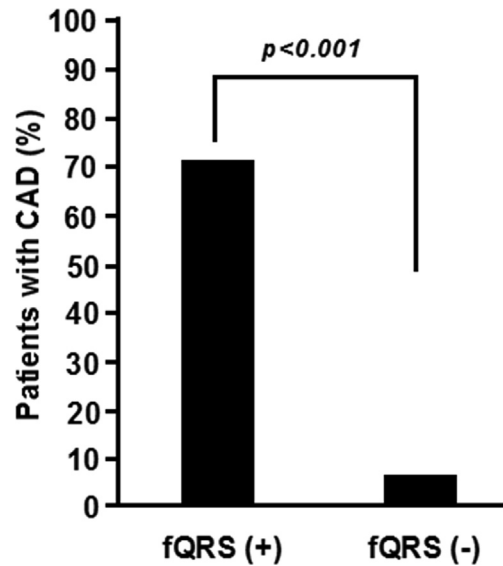
( $p < 0.001$ ) as a marker of diastolic filling pressure and diastolic function of the left ventricle (Fig. 3).

Univariate Cox proportional hazards regression analyses showed that male gender ( $p < 0.01$ ), smoking ( $p < 0.05$ ), LDL-C ( $p < 0.03$ ), hs-CRP ( $p < 0.01$ ), E/e' ratio ( $<0.03$ ), and number of leads with fQRS ( $p < 0.001$ ) were significantly associated with CAD on CCTA. While, with multivariate Cox proportional hazards regression analysis, the number of leads with fQRS was the strongest independent predictor for coronary plaque burden in subjects with chest pain, who had intermediate pretest probability of CAD (OR: 2.15, 95% CI: 1.27–3.99;  $p < 0.001$ ) Table 4. ROC analysis showed that the number of leads with fQRS  $\geq 3$  was the optimal number to predict CAD in subjects with intermediate pretest probability of CAD. This optimal number yielded a sensitivity of 88% and a specificity of 83% (AUC = 0.89) to discriminate subjects with intermediate pretest probability for CAD (Fig. 4).

**Table 2**  
A comparison between patients with those without fragmented QRS.

Variable	fQRS (+) n (98)	fQRS (-) n (74)	p value
Age (years)	47.9 ± 9.8	47.2 ± 8.3	0.38
Male n (%)	125 (73)	47 <sup>27</sup>	0.005
Body mass index (kg/m <sup>2</sup> )	24.9 ± 4.7	24.5 ± 3.8	0.25
Hypertension	59 (60%)	42 (57)	0.47
Diabetes mellitus	26 (27.7)	22 <sup>23</sup>	0.13
Family history of CAD	20 (21%)	17 (23%)	0.21
Smokers n (%)	59 (60)	27 <sup>36</sup>	<0.05
Total cholesterol (mg/dl)	199 ± 59	185 ± 36	0.35
LDL-cholesterol (mg/dl)	145 ± 28	99 ± 35	<0.05
HDL-cholesterol (mg/dl)	42 ± 9	47 ± 11	0.19
hs-CRP (mg/L)	4.3 ± 1.1	1.4 ± 1+0.07	<0.01
Triglycerides (mg/dl)	155 ± 65	143 ± 52	0.09
Ejection fraction%	69 ± 8	66 ± 8	>0.05
E/e'	9.8 ± 1.2	5.1 ± 0.6	<0.01
Myocardial ischemia on CTA: n (%)	70 (71.4)	4 (5.4)	<0.001

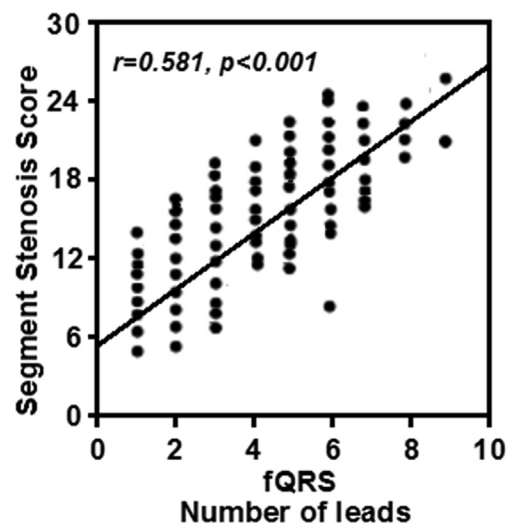
CCTA: Coronary computed tomography angiography.



**Fig. 1.** Distribution of coronary artery disease in patients with and without fragmented QRS complex (fQRS) in subjects with chest pain and intermediate risk for coronary artery disease.

#### 4. Discussion

We found a higher incidence of fQRS in subjects with any CCTA evidence of CAD, compared with those without CCTA evidence of CAD. We investigated the cut-off number of leads with fQRS for prediction of the presence of CAD in the setting of intermediate pretest probability for CAD. Interestingly, when the cut-off number of leads set at  $\geq 3$  leads, we might predict the presence of CAD. Furthermore, we observed that patients with fQRS had a higher values of hs-CRP and LDL-cholesterol, in spite of comparable others with cardiovascular risks factors among both groups. These findings suggest that systemic inflammatory changes, in association with high LDL-cholesterol, have a significant impact on the development of ischemic changes that initiate a process of fibrosis, scarring, and consequently ventricular electrical aberration-conduction abnormalities, which resulted in QRS fragmentation.<sup>18</sup>



**Fig. 2.** Correlation between number of fQRS and SSS in patients with coronary artery disease.

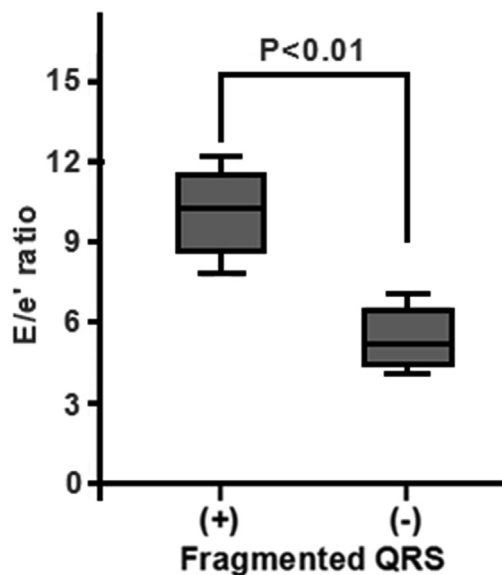
**Table 3**

Correlation analysis of fQRS complex and other variable in patients with CAD in the study cohort.

Fragmented QRS		
Variable	r	p value
Low-density lipoprotein-C	0.249	<0.03
High-sensitivity C-reactive protein	0.315	<0.005
E/e'	0.425	<0.001
Calcium score	0.328	p < 0.005
Segment stenosis score	0.374	<0.001
Segment involvement score	0.460	<0.001
The total plaque score	0.293	<0.01

We found an obvious higher prevalence (57%) of fQRS in our cohort. Oner, et al.<sup>19</sup> found that 26.1% of patients with metabolic syndrome had fQRS. Moreover, Terho, et al.<sup>20</sup> demonstrated that 21.9% of patients with acute myocardial infarction had fQRS complexes, while, the prevalence was 60% in patients with chronic renal failure as reported by Adar, et al.<sup>21</sup> The different percentages among different studies and ours might be attributed to ethnicity or due to small sample volume enrolled in our study.

Notably, the detection of any CAD in individuals without known CAD, who have an intermediate pretest probability of CAD, is of critical importance. Revealing and evaluation of high-risk atherosclerotic plaque by assessing coronary artery calcium score and coronary plaque burden with coronary computed tomographic angiography has a significant impact in clinical practice. This might



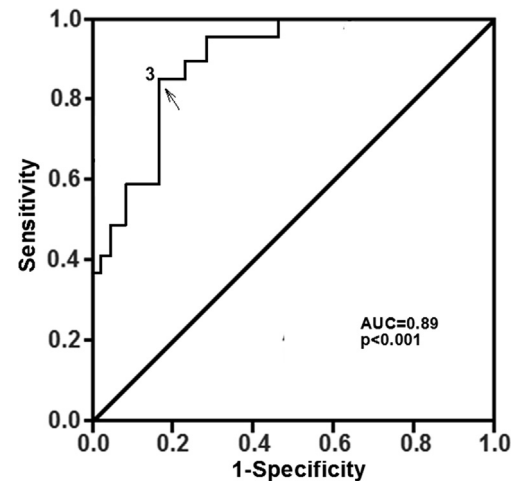
**Fig. 3.** Correlation between number of fQRS and left ventricular filling [E/e'] in patients with coronary artery disease.

**Table 4**

Univariate and multivariate logistic regression analysis to determine the independent predictor for plaque burden.

	Univariate regression			Multivariate regression		
	OR	95% CI	p	OR	95% CI	p
Male gender	0.71	0.33–1.25	<0.01	0.99	0.51–1.85	<0.05
Smoking	1.59	0.83–3.14	<0.05			
LDL-C	1.65	1.13–2.48	<0.03			
hs-CRP (mg/L)	1.41	1.09–1.85	<0.01			
E/e'	1.63	0.83–2.79	<0.03			
Number of leads with fQRS	7.92	2.15–18.13	<0.001	2.15	1.27–3.99	<0.001

LDL-C: Low-density lipoprotein cholesterol, hs-CRP: High-sensitivity C-reactive protein; E/e': ratio of early diastolic mitral flow velocity to the early mitral annulus velocity.



**Fig. 4.** Receiver operating characteristic (ROC) curve analysis to identify positive coronary artery disease with CCTA. The cut-off value of number of leads with fQRS was set at  $\geq 3$ .

increase the efficiency of diagnosis of significant coronary stenosis in the assessment of acute chest pain.<sup>22</sup> Nonetheless, it is a costly test and not available universally. This gives a value for easily applicable and less costly tests, like fQRS complex on surface ECG for risk stratification of subjects presented with chest pain and have intermediate pretest probability for CAD and to avoid the need for more costly and invasive procedures. Hence, in our study we tried to find any relation between the presence of fQRS complex and coronary CT angiography findings in subjects presented with chest pain and have an intermediate pretest probability of CAD.

A lot of studies had demonstrated that fQRS is an independent predictor of impaired myocardial perfusion, cardiac remodeling, and reduced left ventricular ejection fraction in patients with coronary heart disease and is strongly correlated with unfavorable events<sup>23–25</sup>

Another interesting aspect in the current study is that, patients with fQRS had impaired left ventricular diastolic function evidenced by increased E/e' ratio, in spite of normal ejection fraction and mitral E/A ratio on conventional echo-Doppler assessment.

The association between fQRS, atherosclerosis, and diastolic dysfunction may be explained by the presence of CAD in our cohort. A probable cause of the relationship between fQRS and diastolic dysfunction could be myocardial remodeling and fibrosis due to CAD causing both diastolic dysfunction and inhomogeneous myocardial activation.<sup>26,27</sup> Furthermore, previous investigators had found that<sup>19,28</sup> the existence of fQRS was significantly associated with subclinical LV dysfunction.

Few previous studies tried to introduce a set of findings that help in risk stratification of patients with chest pain and have an

intermediate pretest probability for CAD, who are probable to get slight or no advantage from noninvasive testing. This conception of not testing subjects with intermediate pretest probability for CAD goes in line with guideline recommendations to not test unless the pretest probability of obstructive CAD is greater than 10%.<sup>29,30</sup>

With multivariate logistic regression analysis, we found an independent association between the number of leads with fQRS and plaque burden in our cohort. The following two reasons may explain the relationship between them: first, studies showed that fQRS was related to increased hs-C reactive protein level, so the development of fQRS may be associated with systemic inflammation in patients with CAD.<sup>31,32</sup> Inflammatory response mediated by oxygen free radical usually results in microvascular dysfunction. Second, coronary lesion with more plaque burden and calcium score may increase the risk of plaque from falling down and embolizing microvasculature to some extent.

Myocardial ischemia has been found to cause heterogeneous fibrosis,<sup>33,34</sup> and it was thought that this could result in QRS fragmentation on surface ECG. Pietrasik, et al.<sup>35</sup> suggested that fQRS might be a useful marker to identify myocardial ischemia and higher risk for unfavorable outcomes.

Chest pain is a fuzzy complain that has several causes related to either cardiovascular or noncardiovascular source. Chest pain related to CAD is the commonest type of cardiovascular pain in subjects presented to emergency departments. Besides, it constitutes nearly one-fifth of all mortalities attributed to CAD. The socioeconomic import, unfavorable outcomes of CAD are critical considerations for risk stratification and make judicious, early precise diagnosis and cost-effectively managing CAD of the extreme value.<sup>36</sup>

ROC curve analysis revealed that the number of leads  $\geq 3$  was the optimal number to coronary plaques with a sensitivity of 88% and a specificity of 83%. These findings demonstrate the usefulness of fQRS to predict higher fibrotic burden in myocardium in subjects with intermediate pretest probability for CAD. Therefore, fQRS might be of prognostic importance and may be of value in the monitoring of patients with chest pain, who have intermediate pretest probability for CAD.

Yet, Terho et al. reported that, in spite of the prognostic significance of fQRS in different CV diseases, it may not be related with adverse outcomes in subjects without a known cardiac disease.<sup>20</sup>

The ability to identify a subset of subjects with intermediate pretest probability of CAD, who might safely defer noninvasive testing, is appealing of given concerns about the low yield of testing in current practice and the associated costs.

#### 4.1. Limitation

Several limitations were encountered. First, all the coronary artery lesions on CCTA were not confirmed by invasive coronary angiography. Second, we did not set a control group for the CAD screening. Third, myocardial fibrosis was not documented by imaging methods or biochemical or pathological markers. No follow-up study for our cohort was performed. Hence, we recommend that further studies are needed to clarify the significance of fQRS in predicting plaque burden.

## 5. Conclusion

We found that fragmented QRS was seen more often in patients with high plaque burden. fQRS might provide a useful noninvasive tool for selection of subjects with chest pain, who have intermediate pretest probability of CAD for further investigation.

## Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee.

## Consent

Informed consent was obtained from all individual participants included in the study.

## Conflict of interest

All authors declare that they have no conflict of interest.

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