

## Fragmented QRS in inferior leads is associated with non-alcoholic fatty liver disease, body-mass index, and interventricular septum thickness in young men

### ORIGINAL INVESTIGATION

#### ABSTRACT

**Objective:** Fragmented QRS (fQRS) has been shown to be related to coronary heart disease, heart failure, hypertension, cardiac arrhythmia, and metabolic syndrome. Although fQRS in lateral leads is shown to be associated with a poor outcome in patients with a known cardiac disease, the knowledge about the significance and prevalence of fQRS in inferior leads is scarce. This study aimed to investigate the prevalence and predictors of fQRS in inferior leads in healthy young men.

**Methods:** A total of 1,155 men underwent electrocardiography (ECG), hepatic ultrasonography, and routine biochemical tests. A total of 210 eligible men with fQRS in inferior leads (group 1) and 770 eligible men without fQRS in inferior leads (group 2) were compared with each other in terms of clinical, demographic, and laboratory parameters.

**Results:** The prevalence of fQRS in inferior leads was found to 21.4%. Body mass index (BMI), systolic blood pressure (BP), creatinine, and alanine aminotransferase levels; non-alcoholic fatty liver disease (NAFLD) percentage; and interventricular septum thickness (IVST) were significantly greater in group 1 than those in group 2. BMI, IVST, NAFLD, creatinine, ALT, and systolic BP were entered in a model of multiple regression analyses to predict fQRS, a dependent variable. NAFLD was the best independent predictor of fQRS ( $\beta=6.115$ ,  $p=0.001$ ). BMI ( $\beta=1.448$ ,  $p=0.014$ ) and IVST ( $\beta=1.058$ ,  $p=0.029$ ) were the other independent predictors of fQRS in inferior leads.

**Conclusion:** This study demonstrated the association of fQRS in inferior leads with NAFLD, BMI, and IVST in young men.

**Keywords:** body mass index, electrocardiography, non-alcoholic fatty liver disease, echocardiography

#### INTRODUCTION

Fragmented QRS (fQRS) is defined as the presence of R' wave or notching of R or S patterns with or without Q waves on a 12-lead resting electrocardiography (ECG) (1). It indicates heterogeneous depolarization of the ventricular myocardium that can occur owing to ischemia, fibrosis, or scar. Recent studies have shown the relationship of fQRS with various cardiovascular diseases such as coronary heart disease (CHD), dilated cardiomyopathy, heart failure, hypertension, cardiac arrhythmias, and metabolic syndrome (2-9).

Although fQRS in lateral leads is shown to be associated with a poor outcome in patients with a known cardiac disease, the knowledge about the significance and prevalence of fQRS especially in inferior leads is scarce (3). A limited number of studies have reported that the prevalence of fQRS in healthy individuals ranges from 7.2% to 19.7%, with the conclusion that fQRS in inferior leads is not associated with poor clinical outcomes, especially in healthy individuals (10, 11).

This study aimed to investigate the prevalence and predictors of fQRS in inferior leads in healthy young men.

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## METHODS

### Study population

Recruitment to the study was conducted according to the principles outlined in the Helsinki Declaration for investigations in human subjects. The Ethics Committee approved the protocol. The participants gave written informed consent. The study population consisted of outpatient men who were referred to our army check-up center for general young health screening from January 2020 to December 2020. A total of 1,155 men underwent ECG, transthoracic echocardiography (TTE), blood pressure (BP) measurement, hepatic ultrasonography (USG), and routine biochemical tests during the specified period. Participants with a history of CHD or valvular heart disease, hypertension, systolic heart failure, diabetes mellitus, chronic kidney disease, chronic liver disease other than steatosis, excessive alcohol drinking, and hypothyroidism or hyperthyroidism were excluded from the study population. The age, height, and weight of the participants were recorded. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of the height in meters ( $\text{kg}/\text{m}^2$ ). The systolic BP and diastolic BP of all the participants were measured with a sphygmomanometer after at least 15 minutes of resting. Participants' cigarette exposure was questioned and cigarette exposure was defined as active smokers and former smokers who had quit smoking for less than 2 years. Current or past excessive alcohol drinking was defined by an average daily consumption of alcohol  $\geq 30$  g per day.

### Electrocardiography

Standard 12-lead surface resting ECGs (filter range, 0.5–150 Hz, 25 mm/s, 10 mm/mV) were recorded for all the patients. These ECGs were evaluated by cardiologists blinded to the patient data. Heart rate (HR) and QRS duration were noted. Subjects with fQRS in other leads except inferior leads, QRS duration longer than 120 ms, and incomplete or complete right and left bundle branch block were excluded. fQRS was defined by the presence of various RSR' patterns (QRS duration  $< 120$  ms) with or without Q wave, which includes an additional R wave (R') or notching of the R wave or S wave, or the presence of  $> 1$  R' fragmentation without typical bundle branch block in 2 contiguous inferior leads (Fig. 1) (5). The standard 12-lead ECG was analyzed without using any magnification.

## HIGHLIGHTS

- Fragmented QRS in lateral leads is shown to be associated with a poor outcome in patients with a known cardiac disease.
- The knowledge about the significance and prevalence of fragmented QRS in inferior leads is scarce.
- The prevalence of fragmented QRS in inferior leads was found to be 21.4% in this study.
- In this study, we demonstrated the association of fragmented QRS in inferior leads with non-alcoholic fatty liver disease, body mass index, and interventricular septum thickness in young men.

### Hepatic ultrasonography

Hepatic USG was performed by a high-resolution B mode topographic ultrasound system equipped with a convex 3.5 MHz probe (Siemens ACUSON X300 Ultrasound System; Siemens Medical Solutions Inc, Munich, Germany) by a single experienced radiologist blinded to participants' details. Hepatic steatosis was noted. Non-alcoholic fatty liver disease (NAFLD) was diagnosed on the basis of characteristic sonographic features, that is, evidence of diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualization of intrahepatic vessel borders and diaphragm (12).

### Transthoracic echocardiography

Complete 2-dimensional TTE was obtained in all patients. Standard parasternal and apical views were obtained in the left lateral decubitus position using a Vivid 3 Pro ultrasound machine (GE Vingmed Ultrasound, Milwaukee, WI, USA). Images were digitally stored and reviewed by a single cardiologist blinded to the patients' information. The left ventricular ejection fraction (EF), interventricular septum thickness (IVST), and posterior wall thickness (PWT) were measured on M-mode traces recorded in the parasternal long axis view. Mitral inflow was assessed from the apical 4-chamber view with pulsed wave Doppler by placing a 1–2 mm sample volume between the tips of the mitral leaflets during diastole. E- and A-wave velocities were measured from the mitral inflow profile. Measurements were done according to established standards (13).

### Laboratory

Blood for biochemical analysis was taken after fasting for 12 hours. Routine biochemical investigations and cholesterol parameters of the patients were calculated using the Abbott ARCHITECT c16000 (Abbott Laboratories, Chicago, IL, USA) auto-analyzer. The hematologic tests were performed using the Abbott Cell Dyn Ruby analyzer (Abbott Diagnostics, Chicago, Illinois, USA). Thyroid-stimulating hormone (TSH) test was performed using the chemiluminescent microparticle immunoassay method of the Abbott Architect I 2000 immunoanalyzer (Abbott Diagnostics, USA).

### Statistical analysis

Continuous variables were presented as mean  $\pm$  standard deviation or median (minimum–maximum), and categorical variables were expressed as number and percentage (%). The Shapiro–Wilk test was used to identify the normally distributed variables. The continuous variables were compared across the groups using the student's *t*-test or the Mann–Whitney U test. The categorical variables were compared using the chi-square test. To determine the independent predictors of fQRS, multiple logistic regression analysis with enter method was performed. Variables that were found to be statistically significant in the univariate analysis were entered in the regression model. The results of the regression analysis were presented as odds ratio and 95% confidence interval. All data were analyzed with SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The value  $p < 0.05$  was considered statistically significant.

**RESULTS**

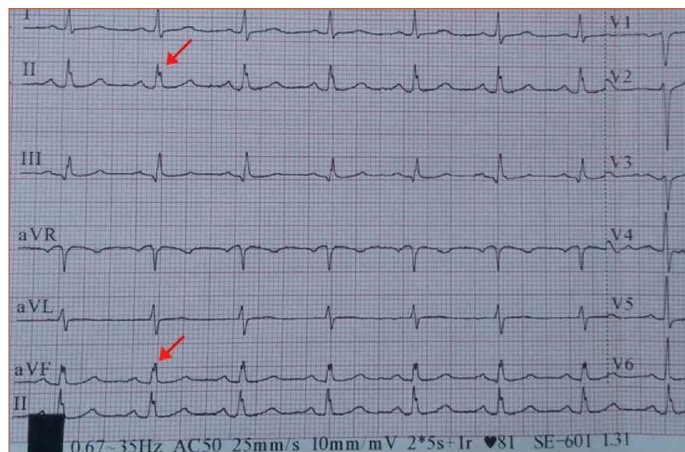
During the recruitment period, 1,155 consecutive subjects were assessed for enrollment eligibility. We excluded 175 subjects on the basis of predetermined criteria. The eligible 980 participants constituted the final study group. In total, 210 participants with fQRS in inferior leads were labeled as group 1, whereas the remaining 770 participants without fQRS in inferior leads were labeled as group 2. We found that the prevalence of fQRS in inferior leads was 21.4% in the whole study population.

Baseline demographic, biochemical, and clinical parameters are shown in Table 1. The mean age, diastolic BP, smoking, glucose, TSH, aspartate aminotransferase, hemoglobin, and sedimentation levels were not different in between the 2 groups. BMI, systolic BP, creatinine, and alanine aminotransferase (ALT) levels were significantly higher in group 1 than in group 2. BMI was 25.9±2.38 kg/m<sup>2</sup> in group 1 and 24.4±2.64 kg/m<sup>2</sup> in group 2 (p<0.001).

ECG, TTE, and hepatic USG parameters of study groups are shown in Table 2. HR, QRS duration, EF, PWT, E wave, and A wave were not different between the 2 groups. IVST (12±0.7 mm vs. 11±0.5 mm, p=0.015) was significantly greater in group 1 than in group 2.

Of the 980 participants included in the study, 255 (26%) met the clinical criteria for diagnosis of NAFLD. Group 1 had 98 (46.7%) participants with NAFLD. Group 2 had 157 participants with NAFLD (20%). There were significant differences between the 2 groups in terms of NAFLD percentage (p<0.001). The prevalence of NAFLD in this study was found to be 26% and is compatible with previous epidemiological studies (14, 15).

BMI, IVST, NAFLD, creatinine, ALT, and systolic BP were entered in a model of multiple regression analysis to predict fQRS, a dependent variable. NAFLD was the best independent predictor of fQRS (β=6.115, p=0.001). BMI (β=1.448, p=0.014) and IVST (β=1.058, p=0.029) were the other independent predictors of fQRS (Table 3).



**Figure 1. Red arrows represent fQRS in inferior leads. fQRS - fragmented QRS**

**Table 1. Clinical, biochemical, and parameters of study groups**

	Group 1 (n=210)	Group 2 (n=770)	P-value
Age, years <sup>a</sup>	26.8±6.3	26.5±6.2	0.703
BMI, kg/m <sup>2a</sup>	25.9±2.38	24.4 ± 2.64	<0.001
Systolic BP, mm Hg <sup>b</sup>	125 (20)	120 (15)	0.004
Diastolic BP, mm Hg <sup>b</sup>	80 (10)	75 (12)	0.062
Smoking, %	39.2	40.5	0.883
Glucose, mg/dL <sup>b</sup>	88 (10)	87 (10)	0.442
Creatinine, mg/dL <sup>a</sup>	0.88±0.18	0.81±0.14	0.018
ALT, U/L <sup>b</sup>	28 (20)	21 (12)	0.007
AST, U/L <sup>b</sup>	14 (7)	15 (7)	0.944
TSH, mU/ml <sup>b</sup>	1.58 (1.28)	1.73 (1.26)	0.365
Hemoglobin, g/dL <sup>a</sup>	13.4±0.8	13.7±0.9	0.556
Sedimentation, m/hr <sup>b</sup>	3 (4)	4 (3)	0.074

<sup>a</sup>Mean ± standard deviation.

<sup>b</sup>Median (interquartile range).

Group 1: Subjects with fQRS in inferior leads.

Group 2: Men without fQRS in inferior leads.

P<0.05 was considered statistically significant.

ALT - alanine aminotransferase; AST - aspartate aminotransferase; BMI - body mass index; BP - blood pressure; TSH - thyroid stimulating hormone.

**Table 2. ECG, TTE, and hepatic USG parameters of the study groups**

	Group 1	Group 2	P-value
HR, bpm <sup>a</sup>	80 (7)	78 (7)	0.618
QRS duration, ms <sup>b</sup>	92.5±14.6	90±15.4	0.842
EF, % <sup>a</sup>	62 (5)	63 (4)	0.855
IVST, mm <sup>b</sup>	12±0.7	11±0.5	0.015
PWT, mm <sup>b</sup>	10±0.5	9.5±0.5	0.055
E wave, m/s <sup>b</sup>	0.8±0.1	0.75±0.1	0.376
A wave, m/s <sup>b</sup>	0.6±0.1	0.62±0.1	0.679
NAFLD, n (%)	98 (46.7)	157 (20)	<0.001

<sup>a</sup>Median (interquartile range).

<sup>b</sup>Mean ± standard deviation.

Group 1: Subjects with fQRS in inferior leads. Group 2: Men without fQRS in inferior leads

P<0.05 was considered statistically significant.

ECG - electrocardiography; EF - ejection fraction; fQRS, fragmented QRS; HR - heart rate; IVST - interventricular septum thickness; NAFLD - non-alcoholic fatty liver disease; PWT - posterior wall thickness; TTE - transthoracic echocardiography; USG - ultrasonography

**Table 3. Multiple linear regression model identifying independent factors associated with fQRS**

Variable	Multiple analysis	
	OR (95% CI)	P-value
IVST	1.058 (1.006-1.112)	0.029
NAFLD	6.115 (2.582-14.668)	0.001
Creatinine	1.034 (0.778-1.375)	0.817
ALT	0.994 (0.962-1.026)	0.620
BMI	1.448 (1.115-1.816)	0.014
Systolic BP	1.025 (0.965-1.089)	0.416

P<0.05 was considered statistically significant.

ALT - alanine aminotransferase; BMI - body mass index; BP - blood pressure; CI - confidence interval; fQRS - fragmented QRS; IVST - interventricular septum thickness, NAFLD - non-alcoholic fatty liver disease; OR - odds ratio.

## DISCUSSION

In this study, we investigated the prevalence and predictors of fQRS in inferior leads in young men. First, we found that NAFLD was the best independent predictor of fQRS in inferior leads. Second, BMI and IVST were also independent predictors of fQRS in inferior leads. Finally, we found that the prevalence of fQRS in inferior leads in otherwise healthy young men was 21.4%. We believe that these findings could help in diagnosing NAFLD in young men using ECG.

Recent studies have focused on assessing the prognostic significance of fQRS mainly in patients with CAD, dilated cardiomyopathy, heart failure, hypertension, and cardiac arrhythmias (2-9). However, little is known about the prevalence and significance of fQRS in the general population. The most comprehensive study published to date was conducted by Terho et al. (10) in middle-aged and otherwise healthy population. The prevalence of fQRS was found to be 19.7% in that study. They concluded that fQRS is a common finding, especially in the inferior leads without any association with increased risk of mortality in subjects without a known cardiac disease. The findings of this study support those of the aforementioned study in this context. We found the prevalence of fQRS in inferior leads in otherwise healthy young men as 21.4%.

Our study also revealed another important and novel finding. NAFLD was shown to be the best independent predictor of fQRS in inferior leads. Previous studies have shown that NAFLD is associated with different ECG disorders such as atrial fibrillation, conduction defects, and QT prolongation (16). To the best of our knowledge, this was the first time that NAFLD was shown to be associated with fQRS.

NAFLD is the most common chronic liver disease in Western countries and affects approximately 25% of the adult population. Growing evidence indicates that patients with NAFLD are at substantial risk for the development of hypertension, CHD, cardiomyopathy, and cardiac arrhythmias (17). Since these diseases have been shown to be associated with fQRS in the literature, it is thought that NAFLD may also be associated with fQRS. Moreover, a recent study showing the relationship between metabolic syndrome and fQRS strengthens the possibility that NAFLD, considered as the hepatic component of the metabolic syndrome, may be associated with fQRS (18). At this point, the novelty of our findings becomes apparent. Our results showed that NAFLD was associated with fQRS in healthy young men for the first time in literature.

Although early recognition and treatment is crucial, the diagnosis of NAFLD is quite problematic. Value of screening for NAFLD in the community is limited owing to = cost, low predictive value of non-invasive tests, risks of liver biopsy, and lack of effective treatments. Therefore, the National Institute for Health and Care Excellence guideline has recommended screening NAFLD in higher-risk groups with diabetes, metabolic syndrome, and obesity (19). Moreover, measuring hepatic enzymes levels is not very effective in determining NAFLD because the levels can be within normal limits even in advanced disease (20). As a result, most young men with NAFLD will not be diagnosed because they do not fall into the high-risk group

if the current guidelines are followed. Therefore, our results are important because they showed that NAFLD was associated with fQRS in inferior leads in healthy young men. ECG, an easily available medical tool, may aid in the diagnosis of NAFLD in young men earlier in the disease course.

Owing to a combination of shared risk factors, the exact mechanism of increased CVD risk in subjects with NAFLD is difficult to discern (21). Although endothelial dysfunction, oxidative stress, altered lipid metabolism, and insulin resistance all have been extensively studied as an underlying mechanism, recent interest has focused on the other suspects. It has been suggested that myocardial fat accumulation and epicardial adipose tissue (EAT) play an important role in the relationship between NAFLD and CVD (22, 23).

EAT, a depot of visceral fat directly overlying the myocardium, is recognized as a metabolically active endocrine organ that secretes adipokines associated with detrimental myocardial and coronary vascular dysfunction (24, 25). Although the underlying mechanism is not entirely clear, the association of NAFLD and BMI with fQRS as shown in our study may be related to EAT. Both NAFLD and high BMI were shown to be related to thicker EAT (22, 23, 26). Interestingly, a recent magnetic resonance imaging (MRI) study has shown that increased EAT volume index is independently associated with increased myocardial fat accumulation and interstitial myocardial fibrosis (27). Cardiac fibrosis is a well-known underlying mechanism of occurrence of fQRS in various cardiac pathologies. Bekar et al. (28) showed fQRS as an independent predictor of EAT in hypertensive patients in their recent study. Yaman et al. (11) showed that the presence of fQRS was associated with increased EAT in a healthy population. Therefore, we speculate that increased epicardial fat content and its relation to myocardial fibrosis may explain the association of NAFLD and BMI with fQRS as shown in our study.

Another interesting finding of this study was that IVST was an independent predictor of fQRS in inferior leads. Accumulating evidence indicates that myocardial structure in left ventricular hypertrophy is affected by myocyte hypertrophy and a progressive accumulation of fibrous tissue within the cardiac interstitium (29, 30). The association between myocardial fibrosis and fQRS was shown in clinical studies (4, 31). The results of this study supports previous studies by showing a statistically significant association between fQRS and IVST.

### Study limitations

Our study had some limitations. First, we enrolled only male subjects because our center serves military personnel. Therefore, it is not possible to draw conclusions for both sexes. Second, we did not measure EAT. We can only speculate about EAT's possible impact on fQRS. To better understand the role of EAT in this process, echocardiography and MRI studies measuring epicardial and myocardial fat content are needed in subjects with NAFLD. Third, we did not include fQRS in the lateral or anterior leads because of the predetermined study protocol. Therefore, it is impossible for us to comment on lateral fQRS, which seems clinically more important. The strength of this study is that a substantial number of otherwise healthy young men can be referred to USG to confirm the diagnosis of NAFLD early in disease course by fQRS in ECG.

## CONCLUSION

In conclusion, our study showed the association of fQRS in inferior leads with NAFLD, BMI, and IVST in young men. ECG may help in diagnosing NAFLD in otherwise healthy young men.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

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