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The prognostic implications of a fragmented QRS pattern in patients diagnosed with heart failure

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ABSTRACT

Objectives: The purpose of this study was to investigate the potential association between the presence of a fragmented QRS (fQRS) pattern on electrocardiogram (ECG) and prognostic outcomes in patients with heart failure (HF).

Methods: In the study, 238 patients with a left ventricular ejection fraction of less than 35% were included. The presence of fQRS pattern on ECG was analyzed in all patients. Patients were divided into two groups based on the presence or absence of fQRS on ECG. The primary clinical end points were all-cause mortality and rehospitalization.

Results: Baseline demographic characteristics were comparable between the groups. Patients with fQRS had a higher frequency of coronary artery disease and atrial fibrillation (72 (76%) vs 90 (62%), $p = 0.023$; 27 (29%) vs 25 (17%), $p = 0.038$, respectively). Additionally, patients with fQRS had a higher rate of mortality and rehospitalization during the 5-year follow-up period compared to patients without fQRS. (30 (32%) / 28 (19%), $p = 0.028$; 56 (60%) / 50 (35%), $p < 0.001$, respectively). Multivariable logistic regression analysis revealed that the presence of fQRS was independently associated with mortality and rehospitalization ($p = 0.02$ and $p < 0.001$, respectively).

Conclusions: The results of this study suggest that the presence of fQRS on ECG in patients with HF is independently related to a higher risk of mortality and hospitalization. Therefore, the presence of fQRS may be a useful indicator of poor prognosis in these patients.

Keywords: Fragmented QRS, heart failure, hospitalization, mortality

Heart failure (HF) is a prevalent medical condition that can result in considerable morbidity, including recurrent hospitalizations and the risk of mortality. The global prevalence of HF has risen to approximately 23 million individuals, with HF with reduced ejection fraction (HFrEF) accounting for roughly 50% of all cases [1]. Identifying the predictors that accurately determine the prognostic outcome in patients with HF has the potential to improve risk stratification and monitoring, leading to better clinical outcomes for the patients.

The 12-lead electrocardiogram (ECG) is a valu-

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able diagnostic and prognostic tool in patients with HF. In patients with organic heart disease, the presence of bundle branch blocks on the ECG often results in wide QRS complexes, which can indicate a poor prognosis. Additionally, even in the absence of a widened QRS complex, fragmentation in the QRS complex may indicate myocardial scarring, which can lead to heterogeneous ventricular activation and dyssynchronous contraction [2]. Of note, patients with HF, regardless of the origin (e.g., ischemic), display more myocardial fibrosis than healthy individuals, and this fibrosis serves as a substrate for negative remodeling and arrhythmias [3]. Therefore, the presence of fragmented QRS (fQRS), irrespective of duration, can be a valuable indicator of myocardial scarring and a potential predictor of adverse outcomes in these patients.

Some studies have recently demonstrated that fQRS is linked to myocardial fibrosis and poor prognosis in HF patients [4, 5]. The prognostic value of fQRS is not limited to HF and is also observed in other conditions, including coronary artery disease and cardiac sarcoidosis [6, 7]. However, some previous research has reported contradictory results regarding the association between fQRS and adverse cardiovascular outcomes in HF patients [8, 9]. Therefore, the objective of this study is to explore the potential connection between the presence of fQRS and the incidence of mortality and hospital readmissions among HF patients.

METHODS

Study Population and Design

This study enrolled 238 HF patients with reduced left ventricle ejection fraction (LVEF) (≤ %35) between January 2015 and October 2017. Patients were under treatment in accordance with the recommendations of current HF treatment guidelines [10]. All patients were older than 18 years and provided written informed consent. Patients were considered to be ischemic in origin if they had significant coronary artery disease, which was confirmed by coronary angiography and defined as greater than 50% stenosis in the left main stem or greater than 70% stenosis in a major coronary vessel. The New York Heart Association (NYHA) functional classification was used to describe patients' symptoms and exercise capacity. The clinical information and laboratory findings were collected from patient files retrospectively.

The study was in accordance with the Declaration of Helsinki and was approved by the institutional review board. The main exclusion criteria were: acute coronary syndrome experienced within last 3-months, acute myocarditis, clinically significant heart valvular disease, hemodynamic instability, heart electrical activity disorders (e.g., Brugada syndrome), wide QRS (> 120 ms, due to bundle branch block, pacemaker rhythm, etc.), and limited life expectancy. Patient enrollment process is depicted in Fig 1.

Echocardiography Acquisition and Analysis

Transthoracic echocardiography (TTE) was performed using a Philips iE33 echocardiography machine and X5 transducer in the left lateral decubitus position. The evaluation included M-mode, 2-dimensional, and Doppler studies, following the recommendations of the current echocardiography guidelines [11]. The left ventricular ejection fraction was quantified using modified Simpson's method [12] from apical 4-chamber views by manually tracing the end-diastolic and end-systolic endocardial borders.

Electrocardiogram Analysis

All patients underwent a 12-lead electrocardiogram (ECG) during clinical visits using a filter range of 0.5 Hz-150 Hz, an AC filter of 60 Hz, and a speed of 25 mm/s and amplitude of 10 mm/mV. Two independent, experienced cardiologists who were unaware of the study design and patients' clinical data analyzed the ECGs. The presence of fQRS was determined based on the criteria of RSR' patterns with or without Q waves in two continuous derivations (QRS time < 120 ms), the presence of an additional R wave (R' wave) or notching within the S wave, and the presence of more than 1 R waves without typical bundle branch block.

Statistical Analysis

The normality of the data was analyzed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation for normally distributed data and median and interquartile range for non-normally distributed data. Comparisons between

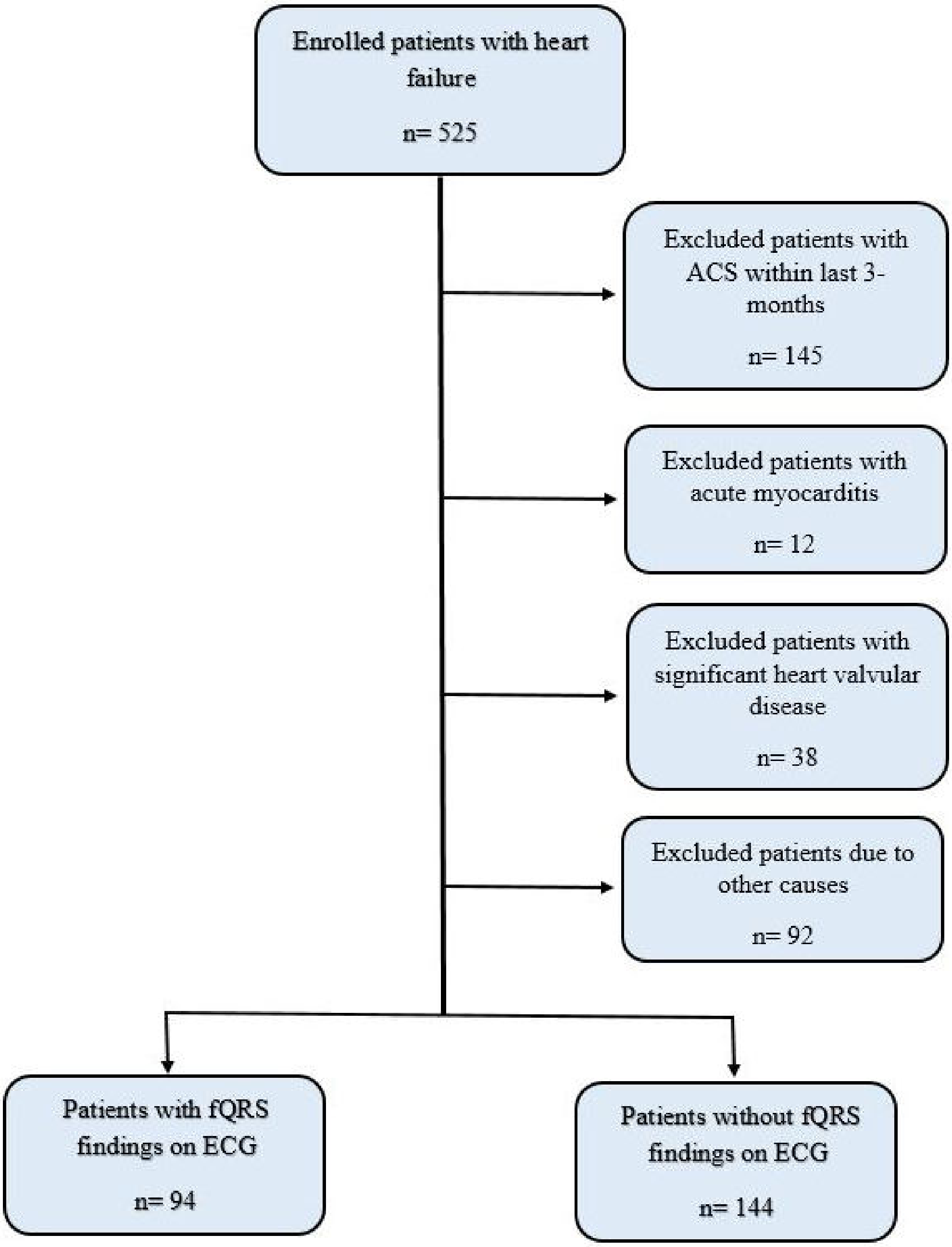

Fig. 1. **Enrollment flow diagram. FQRS = fragmented QRS, ACS = acute coronary syndrome, ECG = electrocardiogram.**

two groups were made with the independent samples T-test for normally distributed data and with Mann-Whitney U test for non-normally distributed data. Categorical variables were expressed as frequency and percentage. Logistic regression models were used to assess associations with all-cause mortality and rehospitalization. Multivariable regression analyses using stepwise elimination were employed. Only clinically meaningful candidate predictors were considered in the multivariable analysis. The results of multivariable regression analyses were presented as odds ratio (OR) with 95% confidence interval (CI). The two-sided significance level was set at 5%. Statistical analyses were performed using SPSS Statistics, version 25.0 (IBM Corp, Armonk, New York).

RESULTS

Study Population

Out of the 238 compensated HF patients who participated in the study, 94 patients were found to have the fQRS pattern. Table 1 summarizes the baseline demographic and clinical characteristics according to fQRS presence. Patients with and without fQRS had a similar proportion of male patients (28 (30%) vs 41 (28%), $p = 0.827$). The mean age was 64.9 ± 9.8 years in patients with fQRS and 64.4 ± 11.2 years in patients without fQRS.

No statistically significant differences were observed between the two groups in terms of smoking

Table 1. Baseline characteristics of the study population according to fQRS presence

	Patients with fQRS (n = 94)	Patients without fQRS (n = 144)	*p* value
Demographics on admission			
Age (years)	64.9 ± 9.8	64.4 ± 11.2	0.715
Male, n (%)	28 (30)	41 (28)	0.827
BMI (kg/m^2)	28.2 ± 5.3	27.5 ± 6.1	0.320
Initial physical examination			
Systolic BP (mmHg)	122.0 ± 22.6	117.8 ± 21.1	0.149
NYHA classification	3.0 ± 0.7	3.1 ± 0.7	0.490
Medical history, n (%)			
Hypertension	61 (65)	87 (60)	0.486
Diabetes mellitus	37 (39)	63 (43)	0.503
Chronic obstructive pulmonary disease	8 (8)	21 (14)	0.161
Smoking	44 (46)	76 (52)	0.368
Ischemic heart disease	72 (76)	90 (62)	0.023
Atrial fibrillation	27 (29)	25 (17)	0.038
Laboratory characteristics			
Haemoglobin (g/dL)	12.1 ± 2.0	11.6 ± 2.0	0.082
Creatinine (mg/dL)	1.20 (1.00 - 1.50)	1.29 (0.91 - 1.58)	0.785
Sodium (mEq/L)	135.6 ± 6.4	136.2 ± 5.8	0.407
Potassium (mEq/L)	4.4 ± 0.8	4.4 ± 0.7	0.819
Glucose (mg/dL)	142.5 ± 69.5	135.4± 67.9	0.435
CRP (mg/dL)	12 (5 - 55)	13 (4 - 25)	0.191
Albumine (g/dL)	3.5 ± 0.6	3.6 ± 0.6	0.116
Medication, n (%)			
Beta-blocker	69 (73)	111 (77)	0.518
ACE-I / ARB	81 (86)	106 (73)	0.021
Spironolactone	28 (29)	62 (43)	0.039
Digoxin	21 (22)	43 (30)	0.201
Furosemid	28(30)	28(19)	0.066

Data are shown as mean ± standard deviation or n (%) or mean (range). FQRS = fragmented QRS, BMI = body mass index, NYHA = New York Heart Association, CRP = C-reactive protein, ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker

Table 2. Echocardiography characteristics of the study population according to fQRS presence

	Patients with fQRS (n = 94)	Patients without fQRS (n = 144)	*p* value
Ejection fraction (%)	25.5 ± 7.7	27.6 ± 6.9	0.029
Left atrial diameter (mm)	46.2 ± 6.4	47.7 ± 8.4	0.162
Mitral regurgitation level	2.0 ± 0.9	2.2 ± 0.9	0.077
LV mass index (g/m2)	151.3 ± 45.7	147.0 ± 34.7	0.410
PASP (mmHg)	49.3 ± 14.6	49.8 ± 15.4	0.819

Data are shown as mean ± standard deviation. LVEF = left ventricular, PASP = pulmonary artery systolic pressure

status, hypertension, diabetes mellitus, and chronic obstructive pulmonary disease frequency. However, patients with fQRS exhibited a higher frequency of ischemic heart disease and atrial fibrillation compared to those without fQRS (72 (76%) vs 90 (62%), p = 0.023; 27 (29%) vs 25 (17%), p = 0.038, respectively). The laboratory levels, including creatinine, hemoglobin, sodium, potassium, glucose, CRP, and albumin, did not differ significantly between the two groups. In terms of treatment for HF, no significant differences were found in the frequency of Beta-blocker, Digoxin, and Furosemide use between the two groups. However, there was a statistically significant difference in the frequency of angiotensin-converting enzyme inhibitor and angiotensin-receptor blocker (ACE-I/ARB) and Spironolactone use between the groups (81 (86%) vs 106 (73%), p = 0.021; 28 (29%) vs 62 (43%); p = 0.039, respectively).

Echocardiography Findings

Table 2 provides a detailed assessment of the echocardiography characteristics according to the groups. The group of patients with fQRS had significantly lower LVEF levels compared to the group without fQRS (25.5 ± 7.7 vs 27.6 ± 6.9, p = 0.029). There were no significant differences observed between the two groups in relation to other echocardiographic parameters, such as left atrial diameter, mitral regurgitation level, LV mass index, and PASP levels.

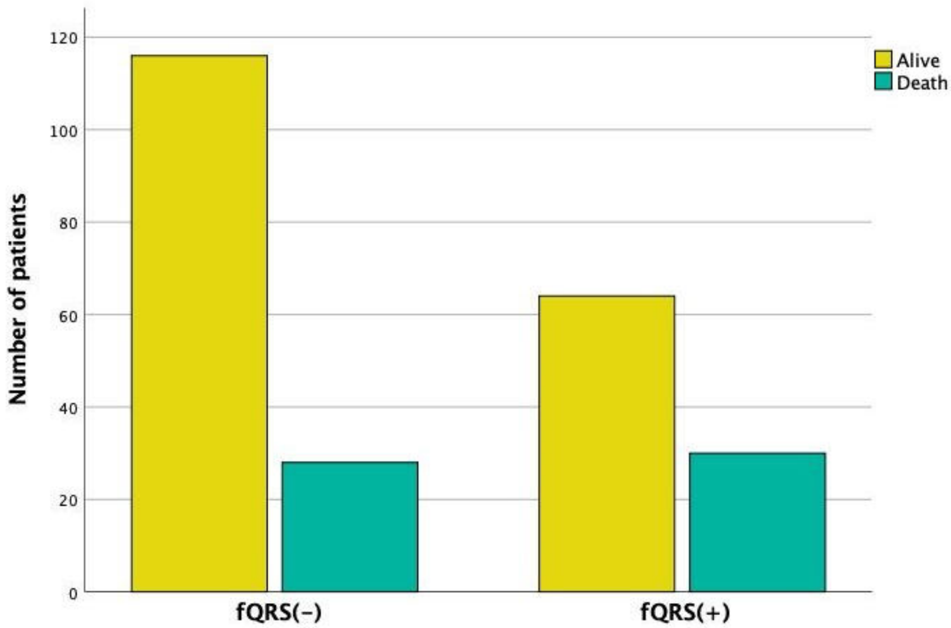

Fig. 2. Demonstration of alive/death rates for patients with and without fQRS pattern. fQRS = fragmented QRS.

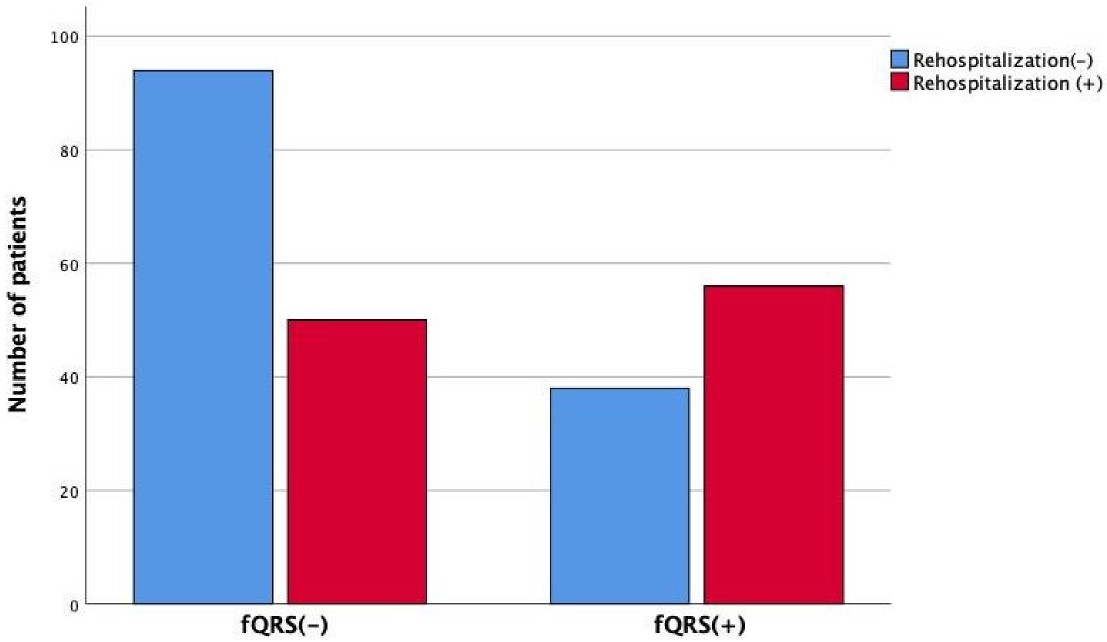

Fig. 3. **Demonstration of rehospitalization rates for patients with and without fQRS pattern. fQRS = fragmented QRS.**

Association with Mortality and Rehospitalization

During the 5-year follow-up period, patients with fQRS had a higher rate of mortality and rehospitalization compared to patients without fQRS (56 (60%) / 50 (35%), $p < 0.001$; 30 (32%) / 28 (19%), $p = 0.028$, respectively) (Figs. 2 and 3).

The study utilized logistic regression analysis models to evaluate the relationship between various parameters and the prognostic outcome. Table 3 presents the findings of the regression analysis models for

Table 3. **Multivariable logistic regression analysis for association with mortality and rehospitalization**

	Mortality			Rehospitalization		
Variables	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Age (years)	1.022	0.987-1.058	0.214	1.033	1.000-1.068	0.051
Male	0.818	0.383-1.748	0.604	1.777	0.824-3.821	0.142
NYHA	3.357	2.058-5.557	**< 0.001**	5.532	3.198-9.569	**< 0.001**
LVEF	0.252	0.107-4.411	0.600	0.420	0.302-0.756	**0.048**
IHD	1.703	0.816-3.552	0.156	1.301	0.602-2.812	0.504
Hypertension	1.609	0.813-3.183	0.172	1.418	0.699-2.875	0.333
Diabetes mellitus	0.713	0.349-1.457	0.354	0.879	0.425-1.820	0.729
Sodium level	0.912	0.866-0.959	**< 0.001**	0.926	0.877-0.979	**0.006**
fQRS presence	2.192	1.130-4.248	0.020	4.128	2.028-8.388	**< 0.001**
Creatinine level	0.955	0.679-1.343	0.791	1.118	0.772-1.619	0.554
ACEİ/ARB use	1.790	0.771-4.156	0.175	1.428	0.614-3.323	0.408
Beta-blocker use	0.522	0.218-1.247	0.143	1.673	0.712-3.932	0.237

NYHA = New York Heart Association, LVEF = left ventricular ejection fraction, IHD = Ischemic heart disease, fQRS = fragmented QRS, ACE-I = angiotensin-converting enzyme inhibitor, ARB, angiotensin-receptor blocker the association with mortality and rehospitalization. The multivariable models included the parameters of age, gender, NYHA classification, LVEF, ischemic heart disease, hypertension, diabetes mellitus, fQRS presence, sodium level, creatinine level, ACEI/ARB, and beta-blocker use. For mortality, NYHA classification, sodium level, and fQRS presence were identified as statistically significant independent predictors (NHYA classification: OR: 3.357, $p < 0.001$; sodium level: OR: 0.912, p < 0.001; fQRS presence: OR:2.192, $p = 0.020$). For rehospitalization, NYHA classification, LVEF, sodium level, and fQRS presence were found to be statistically significant independent predictors (NHYA classification: OR: 5.532, $p < 0.001$; LVEF: OR: 0.420, $p = 0.048$; sodium level: OR: 0.926, $p = 0.006$; fQRS presence: OR: 4.128, $p < 0.001$).

DISCUSSION

The objective of our study was to investigate how the presence of fragmented QRS (fQRS) relates to the prognosis of heart failure (HF) patients. Our study identified three key findings: firstly, patients with fQRS had a higher prevalence of ischemic heart disease and atrial fibrillation compared to those without fQRS. Secondly, over a 5-year follow-up period, patients with fQRS had a greater risk of mortality and rehospitalization. Lastly, our logistic regression analysis revealed that the presence of fQRS is independently linked to both mortality and rehospitalization in HF patients.

HF is a complex syndrome that causes shortness of breath and exercise intolerance due to impaired blood filling or ejection from the heart. It results in high rates of mortality and hospitalization, with a 1-year mortality rate of 7.2% and a 1-year hospitalization rate of 31.9% in patients with chronic HF [13]. While there are pharmacological and device-based treatments available that have demonstrated benefits for patients with reduced ejection fraction, the effectiveness of these therapies is not guaranteed and can be costly. In fact, studies have shown that only a minority of patients who receive device treatment actually receive appropriate therapy at 5 years [14]. As a result, it's critical to identify patients who are at higher risk for poor outcomes in order to improve their chances of survival and minimize the need for hospitalization. Using ECG parameters for risk stratification of HF patients may be a practical and cost-effective approach, as ECG is widely available in most healthcare settings.

The results of our study showed that HF patients who presented with fQRS had a higher prevalence of comorbidities, including coronary artery disease and atrial fibrillation. Furthermore, these patients experienced poorer clinical outcomes in terms of mortality and rehospitalization when compared to those who did not exhibit without fQRS, over a 5-year follow-up period. The presence of myocardial fibrosis is a crucial factor in the development of ventricular arrhythmias among patients with left ventricular dysfunction. Studies using cardiac magnetic resonance imaging have demonstrated that myocardial fibrosis acts as an arrhythmogenic substrate, particularly among patients with ischemic heart disease caused by a previous infarction [15]. Studies have also demonstrated that the presence of a fQRS on a 12-lead ECG is a result of myocardial conduction abnormalities due to scar tissue in patients with CAD [16]. Moreover, fQRS was found to be comparable to the epsilon wave observed in arrhythmogenic right ventricular cardiomyopathy [17]. The incidence of fQRS was found to be notably greater in patients with Brugada syndrome who experienced ventricular fibrillation (VF) compared to those who had syncope or were asymptomatic [18]. We speculate that the presence of fQRS indicates the existence of scars in the myocardium, which in turn create an environment that is contribute to the occurrence of reentry and potentially life-threatening ventricular arrhythmias, leading to poor outcomes in HF patients. Moreover, the higher incidence of atrial fibrillation in patients with fQRS may be explained by the fact that fibrosis can affect the function of the ventricles, resulting in increased left ventricular end-diastolic pressure that may also affect the left atrium, thereby increasing the risk of arrhythmia.

Recently, fQRS has been shown to predict cardiac events in various populations [19, 20], but there have also been reports of contradictory findings from some researchers [8, 9]. These discrepancies may be attributed to differences in study design, such as the inclusion of patients only in sinus rhythm or the enrollment of predominantly male participants. In our study, we included patients with atrial fibrillation and maintained a balance between male and female participants. Further research is required to investigate the effectiveness of fQRS in risk stratification for HF.

Identifying fQRS on an ECG is a simple task for clinicians, but it can have significant implications for risk stratification and management of HF patients. The detection of fQRS can lead to more focused monitoring and follow-up care. Moreover, a greater burden of fQRS may indicate a higher risk of arrhythmias, which can be used to identify patients who may benefit from device therapy for HF. Future research could examine the potential of fQRS in other patient populations to prevent arrhythmic events.

Limitations

This study has some limitations that need to be discussed. First, the results were derived through a post-hoc analysis. Second, the sample size of the study (n = 238) is relatively small. Third, the study was conducted at a single center, which may limit the generalizability of the results to other populations. Last, the number of leads with fQRS on ECG was not examined.

CONCLUSION

In patients with heart failure, the presence of fragmented QRS on ECG was associated with a higher risk for all-cause mortality and rehospitalization.

Authors' Contribution

Study Conception: AD, AA; Study Design: AD; Supervision: AD, HAB; Funding: N/A; Materials: N/A; Data Collection and/or Processing: HAB, AA; Statistical Analysis and/or Data Interpretation: AD, AA; Literature Review: MY, ÖŞ; Manuscript Preparation: AD, AA and Critical Review: AD, AA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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