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The prognostic value of fragmented QRS in patients undergoing transcatheter aortic valve implantation

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ABSTRACT

Background: Although transcatheter aortic valve implantation (TAVI) can successfully correct aortic narrowing, pre-existing pathophysiological alterations in the left ventricle are still a concern in terms of long-term mortality. This study aimed to examine the predictive role of fQRS morphology on long-term prognosis in patients undergoing TAVI due to severe aortic stenosis.

Methods: A total of 117 patients undergoing TAVI due to severe aortic stenosis were included in this retrospective cohort study. Patients were assigned into two groups based on the presence (n = 36) or absence (n = 81) of fQRS. Predictors of long-term survival were estimated.

Results: In-hospital mortality was higher in fQRS group (5.5% vs. 1.2%, p = 0.0224). In the long-term, fQRS (OR: 3.06, 95% CI 1.29–7.27, p: 0.01), LVEF <50% (OR: 2.54, 95% CI 1.07–6.02, p: 0.03) and presence of atrial fibrillation (OR: 2.42, 95% CI 1.05–5.60, p: 0.03) emerged as significant independent predictors of short survival.

Conclusion: Presence of fQRS on ECG, an indirect indicator of myocardial fibrosis, seems to have the potential to be used as a prognostic marker after TAVI procedure. Large prospective studies are warranted.

Introduction

Transcatheter aortic valve implantation (TAVI) represents a viable therapeutic option in high-risk patients unsuitable for surgery [1]. As compared to standard medical treatment TAVI is associated with lower rates of all-cause mortality, cardiac mortality, and repeated hospitalizations as well as with better symptomatic improvement [1]. In recent years we have witnessed an increase in success rates as well as a decrease in complications in patients undergoing TAVI procedures, mostly attributable to increased clinical expertise, completion of the learning curve process, and availability of smaller vascular access sheath systems [2]. Although the procedure can successfully correct the pathology associated with the aortic narrowing, pre-existing pathophysiological alterations in the left ventricle remain a major concern in terms of long-term mortality. Presence of fragmentation of QRS complex (fQRS) (without typical bundle-branch block, QRS morphology involving a variety of RSR′ patterns) in 12-lead electrocardiogram shows the presence of depolarization abnormality associated with myocardial fibrosis [3]. fQRS is believed to represent a dynamic process associated with myocardial fibrosis and scar formation [4]. Patients with aortic stenosis generally have compensatory hypertrophy and interstitial fibrosis of the left ventricle. Fragmented QRS pattern may be identified in ECG recordings of patients with aortic stenosis as a result of myocardial fibrosis.

Despite lack of robust clinical evidence, depolarization abnormalities have been suggested to be predictive of ventricular arrhythmias and sudden cardiac death [5,6]. Several studies have investigated the predictors of long term mortality after TAVI procedure [7–11], although, to the best of our knowledge, none have examined the potential predictive role of fQRS.

This study aimed to examine the effect of fQRS morphology on long-term prognosis in patients undergoing TAVI due to severe aortic stenosis.

Materials and methods

Study population

A total of 117 consecutive patients undergoing TAVI in the cardiology unit due to severe aortic stenosis between December 2012 and

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November 2016 were included. Patients were excluded if they had other conditions that could be associated with fragmented QRS in ECG (e.g. history of myocardial infarction or coronary bypass surgery), as were those with severe coronary lesions (left main coronary artery > 50% or other coronary arteries > 70% stenosis) and those with an ejection fraction ≤ 30%. The study was a retrospective cohort study. Patients were assigned into two groups based on the presence (n = 36) or absence (n = 81) of fQRS.

Pre-operative and post-operative data were retrieved from the hospital database and preoperative demographic and clinical characteristics, and ECG and echocardiography results were assessed. In addition, postoperative clinical findings were evaluated. Those who did not attend a follow-up visit within the past 6-month period were contacted with phone and invited to our facility for outpatient assessments. Time of death was recorded for those subjects who died during the study period.

Electrocardiographic analyses

12-Lead ECG (25 mm/s paper speed, 10 mm/mV, filter range 0.05–150 Hz with notch filter at 50/60 Hz) recordings were obtained from all patients before and after TAVI. ECG readings were performed by two-independent clinicians with naked eye without the use magnifying glasses. In case of conflict, the final decision was made by consensus. Fragmented QRS was defined as the presence of various RSR′ patterns (QRS duration < 120 ms) with or without Q wave, which include an additional R wave (R′ prime) or notching of the R wave or S wave, or the presence of more than one R′ (fragmentation) without typical bundle branch block [5]. An example for fQRS on ECG is shown in Fig. 1.

Device and procedure

TAVI procedure was performed under general anesthesia using a trans-femoral approach. The Amplatz Extra Stiff Guide Wire was advanced to the apex of the left ventricle using a 16-F sheath through the femoral artery. A balloon valvuloplasty was applied on the aortic valve with ventricular pacing at a rate of 80–200 beats/min, and the device was implanted. Under fluoroscopic guidance, an aortic valve prosthesis was inserted into the native aortic annulus. After achievement of optimal opening, aortic root, aortic valve and pericardium were visualized. Dual antiplatelet chemotherapy (100 mg of acetylsalicylic acid plus 75 mg of clopidogrel) was administered to all patients for 6 months following surgery.

Statistical analysis

SPSS statistical software pack (SPSS 17.0 for Windows, Inc., Chicago, IL, USA) was used for data analysis. In addition to descriptive statistics (mean, standard deviation), for the comparison of quantitative data Student's *t*-test was used for parameters with normal distribution and Mann-Whitney *U* test was used for parameters without normal distribution. Fisher's exact test and chi-square test were used for the comparison of qualitative data. Overall survival estimates were done using Kaplan-Meier test and univariate comparisons were performed using log-rank test. Overall survival was defined as the time elapsed between the date of TAVI procedure and death from any cause; and patients alive at the last follow up were censored. Univariate predictors of overall survival were entered into Cox proportional hazards model to identify independent predictors of mortality. Significance was assessed at a p level of <0.05.

Results

Patient characteristics

Table 1 shows demographical, clinical and echocardiographic characteristics of the two groups. Mean age was higher in fQRS group (p = 0.04). In addition, patients with fQRS were significantly more likely to have atrial fibrillation and a past history of cerebrovascular

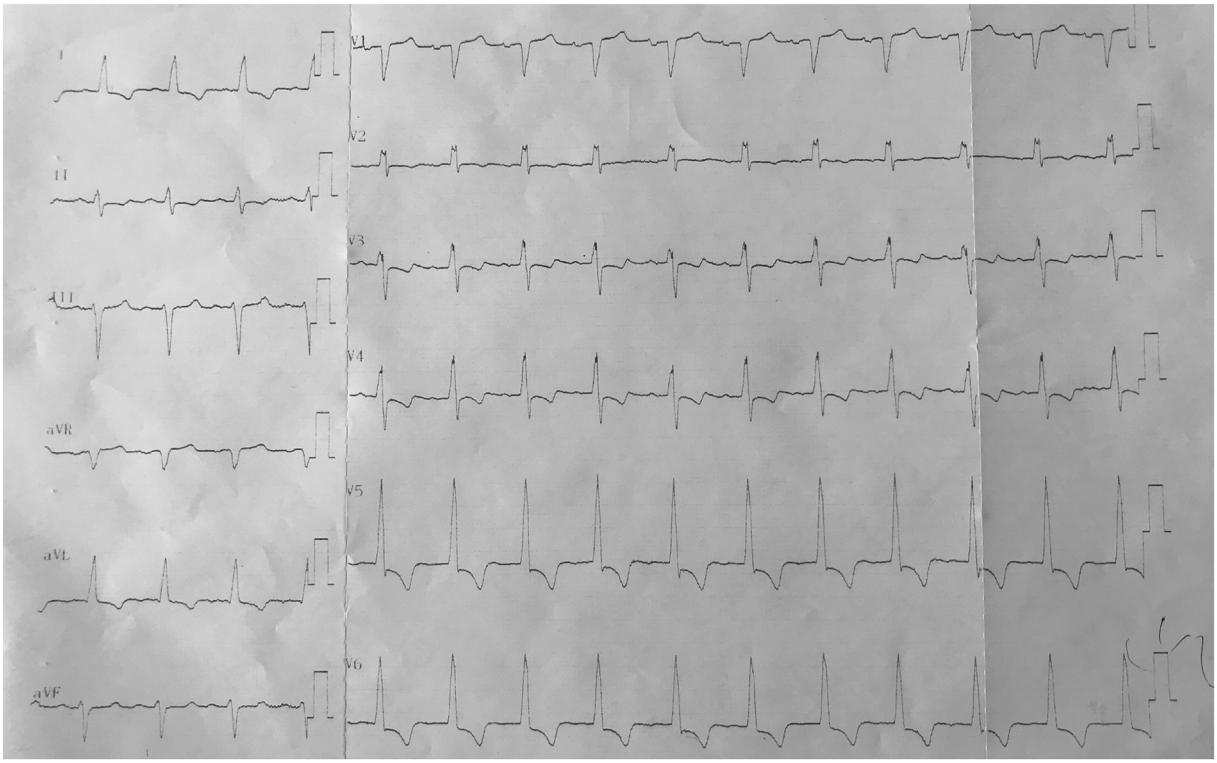

Fig. 1. An example of typical fQRS pattern on electrocardiography on leads V2, V3 and V4.

Table 1
Baseline characteristics of the two groups.

	fQRS (n = 36)	Non-fQRS (n = 81)	p
Age (years)	80.2 ± 4.9	78.4 ± 3.5	**0.04**
Female gender	23 (63.8%)	44 (54.3%)	0.33
Diabetes	15 (41.6%)	26 (32%)	0.31
Hypertension	23 (63.8%)	47 (57.3%)	0.55
Dyslipidemia	7 (19.4%)	19 (23.4%)	0.53
COPD	11 (30.5%)	29 (35.8%)	0.55
Peripheral vascular disease	6 (16.6%)	11 (13.5%)	0.66
Non-critical coronary artery stenosis	13 (36.1%)	35 (43.2%)	0.27
Previous cerebrovascular accidents	5 (13.8%)	3 (3.7%)	**0.04**
Serum creatinine > 1.5 mg/dl	4 (11.1%)	12 (14.8%)	0.59
Atrial fibrillation	13 (36.1%)	15 (18.5%)	**0.04**
Aortic mean gradient (mm Hg)	44.6 ± 5.0	45.1 ± 5.4	0.61
Aortic valve area (cm^2)	0.75 ± 0.15	0.72 ± 0.14	0.41
LVEF (mean %)	49.7 ± 10	50.5 ± 8.8	0.70
PAB (>60 mm Hg)	7 (19.4%)	18 (22.2%)	0.73
Logistic EuroSCORE (mean ± SD) %	21.8 ± 3.3	20.6 ± 3.5	0.21
STS score (mean ± SD) %	10.1 ± 3.8	9.8 ± 4.5	0.70

fQRS, fragmented QRS; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; PAB, pulmonary arterial pressure.

event (p = 0.04, for both comparisons). Other demographic, clinical, and echocardiographic data were similar between the groups (p > 0.05).

Edwards Sapien XT transcatheter heart valves (Edwards Lifesciences, Irvine, CA, USA) and CoreValve prostheses (Medtronic, Minneapolis, MN, USA) were used in 30 and 6 patients, respectively, in the fQRS group. In the non-fQRS patients, Edwards Sapien XT transcatheter heart valves (Edwards Lifesciences), CoreValve prosthesis (Medtronic), and Direct Flow Medical valve (Direct Flow Medical Inc.) were used in 56, 20, and 5 subjects, respectively.

Clinical and echocardiographic outcomes

Table 2 shows clinical outcomes after TAVI procedure. TAVI was successful in 100% of the procedures, while the rate of vascular complications was higher in fQRS patients than in non-fQRS patients (16.6% vs. 4.9%, p = 0.03). Study groups were comparable with regard to other clinical results (p > 0.05 for all).

Follow-up survival

The duration of follow-up was significantly longer in non-fQRS patients as compared to fQRS patients (23.0 ± 9.1 vs. 15.1 ± 8.2 months, respectively p < 0.001). In-hospital mortality was 5.5% in fQRS group (n = 2, one due to major stroke and one patient referred to surgery after development of acute mitral failure), and 1.2% in non-fQRS group (n = 1, due to major stroke) (p = 0.0224). The long-term mortality in fQRS patients during a mean follow-up of 15.1 ± 8.2 months (range: 1–36 months) was 27.7% (n = 10) and the corresponding figure was 16.0% (n = 13) in non-fQRS subjects during a mean follow-up of 23.0 ± 9.1 months. The two groups were not significantly different in terms of mortality (p = 0.140). However, a Kaplan-Meier survival analysis revealed significantly decreased survival for the fQRS group compared to the non-fQRS group (log rank p < 0.05) (Fig. 2).

Univariate analysis was performed to determine the potential predictors of mortality including sex, hypertension, diabetes mellitus, COPD, left ventricular ejection fraction <50%, pulmonary hypertension, non-critical coronary artery stenosis, peripheral vascular disease, atrial fibrillation, fQRS, pacemaker implantation, and cerebrovascular accident. Those variables with a potential survival effect in Kaplan-Meier analyses (fQRS, EF < 50, COPD, and atrial fibrillation) were assessed using a Cox-regression model. Multivariate analysis identified fQRS (OR: 3.06, 95% CI 1.29–7.27, p: 0.01), LVEF <50% [odds ratio (OR): 2.54, 95% CI 1.07–6.02, p: 0.03] and presence of atrial fibrillation (OR: 2.42, 95% CI 1.05–5.60, p: 0.03) as significant independent predictors of mortality (Table 3).

Table 2
Comparison of clinical outcomes.

	fQRS (n: 36)	Non-fQRS (n: 81)	p
Total mortality	10 (27.7%)	13 (16.0%)	0.14
Stroke	2 (5.5%)	2 (2.4%)	0.39
Need for pacemaker	3 (8.3%)	3 (3.7%)	0.29
Vascular complications	6 (16.6%)	4 (4.9%)	**0.03**
Pericardial tamponade	1 (2.7%)	0	0.13
Erythrocyte transfusion (U)	1.16 ± 1.2	0.86 ± 1.2	0.21
Postoperative days in hospital	5.3 ± 2.5	4.9 ± 1.9	0.39
Postoperative mean aortic gradient	4.1 ± 1.7	4.5 ± 1.5	0.22
Postoperative mild aortic insufficiency	4 (11.1%)	6 (7.4%)	0.51

TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; NYHA, New York Heart Association.

Discussion

Our results suggest that presence of atrial fibrillation, fragmented QRS, and a left ventricular ejection fraction < 50% may be associated with a negative long-term effect on survival in patients undergoing TAVI. Until now, although various studies have examined the predictive role of clinical and laboratory parameters on survival after TAVI, we believe that our study represents the first of its kind in assessing the association between survival in these patients and fQRS, which is a marker of myocardial scar formation that can be readily assessed using routine ECG recordings.

In a review of long-term survival rates in TAVI, 83%, 75%, 65%, 48%, and 28% of the patients were still alive at 1, 2, 3, 5, and 7 years after the procedure, respectively (thirty-one studies were included, with a total of 13,857 patients) [12]. In the current study, the survival rates were 72.3% during 15.1 ± 8.2 months of follow up (1–36) in fQRS group vs. 84% in non-fQRS group during a follow-up of 23.0 ± 9.1 months (1–36). Several studies involving large case-series have also examined the predictors of mortality during follow up ranging between 3 and 5 years. For instance, Zahn et al., in their German Transcatheter Aortic Valve Implantation Registry Study (1444 patients), identified the following predictors for 5-year mortality using Cox

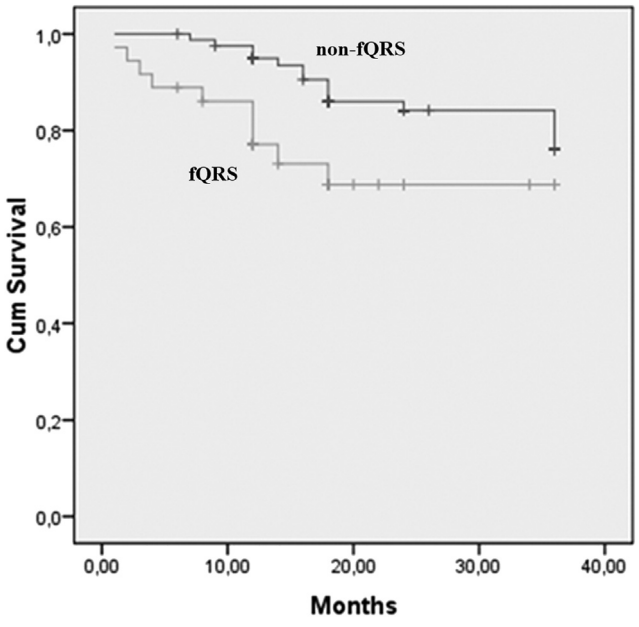

Fig. 2. Kaplan-Meier survival curves for fQRS and non-fQRS groups (log-rank p < 0.05). Upper curve, non-fQRS group; lower curve, fQRS group.

Table 3
Univariate (log rank) and multivariate (cox regression) analysis of potential predictors for long-term mortality.

Variables	Univariate		Multivariate	
	Mean survival (months)	p	OR (95% CI)	p
LVEF				
<50%	29.0 ± 1.7	**0.05**	2.54 (1.07–6.02)	**0.03**
>50%	32.8 ± 1.1			
PHT				
Absent	31.5 ± 1.1	0.34		
Present	32.6 ± 1.8			
Hypertension				
Absent	31.2 ± 1.5	0.77		
Present	31.8 ± 1.3			
Diabetes mellitus				
Absent	31.6 ± 1.2	0.59		
Present	31.7 ± 1.5			
COPD				
Absent	32.6 ± 1.0	**0.08**	1.98 (0.87–4.51)	0.10
Present	28.5 ± 1.8			
Non-critical coronary artery stenosis				
Absent	30.4 ± 1.4	0.39		
Present	32.9 ± 1.4			
Peripheral vascular disease				
Absent	31.1 ± 1.3	0.17		
Present	29.6 ± 1.5			
fQRS				
Absent	32.7 ± 0.9	**0.02**	3.06 (1.29–7.27)	**0.01**
Present	27.6 ± 2.2			
Gender				
Male	32.4 ± 1.4	0.27		
Female	30.2 ± 1.3			
Pacemaker implantation				
Absent	31.9 ± 1.0	0.97		
Present	21.6 ± 2.1			
Cerebrovascular accident				
Absent	32.0 ± 1.0	0.55		
Present	26.0 ± 6.9			
Atrial fibrillation				
Absent	32.3 ± 1.0	**0.03**	2.42 (1.05–5.60)	**0.03**
Present	28.1 ± 2.3			

OR, odds ratio; CI, confidence interval; LVEF, left ventricular ejection fraction; PHT, pulmonary artery hypertension; COPD, chronic obstructive pulmonary disease; fQRS, fragmented QRS.

proportional hazard analysis: female gender, renal failure, prior mitral regurgitation ≥II°, residual aortic regurgitation ≥II°, atrial fibrillation, low gradient aortic stenosis, prior decompensation, frailty, surgical TAVI, age, prior myocardial infarction, urgent TAVI and diabetes mellitus [11]. In the UK Transcatheter Aortic Valve Implantation Registry (870 patients), Duncan et al. reported 3 and 5-year survival rates of 61.2% and 45.5%, respectively, and identified renal dysfunction, atrial fibrillation, logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) ≥18.5, respiratory dysfunction, and ventricular dysfunction (left ventricular ejection fraction < 30%) as independent predictors of mortality. Additional predictors for 5-year mortality included coronary artery disease and age [8]. In a single-center study from Italy (338 patients), D'Onofrio et al. found that para-valvular leak, acute renal failure, and previous myocardial infarction were independent predictors of death at a mean follow-up of 22.3 ± 17.8 months [7]. In the study by Toggweiler et al. from Vancouver (88 patients), the presence of COPD and more than moderate aortic regurgitation after implantation were the only two significant correlates of 5-year mortality [10]. A study from a high-volume center in the US by Escarcega et al. (511 patients) found that vascular complications, more than mild aortic insufficiency, atrial fibrillation and in-hospital stroke were independent predictors of mortality [9]. Consistent with previous publications, LVEF <50% (OR: 2.54, 95% CI 1.07–6.02, p = 0.03) and atrial fibrillation (OR: 2.42, 95% CI 1.05–5.60, p = 0.03) emerged as independent predictors of medium-term mortality in this study. On the other hand, presence of fQRS in ECG, which has not been investigated previously, also was also an independent predictor of mortality after TAVI.

Myocardial fibrosis has a negative impact on prognosis not only in aortic stenosis (AS) but also in other cardiac pathologies [13]. Varying degrees of interstitial fibrosis and impaired myocyte ultrastructure in the left ventricular myocardium are typical for AS. These degenerative changes initially starting in the subendocardial space spread to whole myocardium over time, leading to myocyte loss in conjunction with replacement- or scarring-fibrosis. Presence of fQRS in ECG recordings is indicative of myocardial fibrosis [13]. Fragmented QRS in 12-lead electrocardiography represents a dynamic process that has been described in ventricular scar formation occurring after myocardial infarction as well as in a number of other cardiac conditions such as ventricular aneurysm, idiopathic dilated cardiomyopathy, myocardial fibrosis, sarcoidosis, Brugada syndrome, arrhythmogenic right ventricular dysplasia, and myocarditis [14].

A significant correlation between AS severity and presence of fQRS has also been reported, with up to 46% of AS patients exhibiting fQRS complexes [15]. In a study examining fQRS in patients with aortic stenosis, Acikgoz et al. found that fQRS could have a significant role in predicting the severity of stenosis and prognosis [16]. In that study, presence of fQRS was an independent predictor of ventricular tachyarrhythmia (VTA) and/or mortality in patients with ischemic or non-ischemic cardiomyopathy, while it appeared to be a diagnostic marker for arrhythmogenic right ventricular dysplasia [17,18]. Furthermore, in patients with hypertrophic cardiomyopathy, which is pathologically similar to that seen in patients with aortic stenosis, presence of fQRS in ≥3 leads was associated with ventricular tachyarrhythmias or sudden cardiac death (VTA/SCD) [19].

Although findings consistent with myocardial fibrosis were found to have a negative effect on survival in patients undergoing aortic valve replacement (AVR) [20], it should be borne in mind that the duration of cross-clamping during cardiopulmonary bypass and inadequate myocardial protection may also lead to untoward effects on the left ventricle in AVR, with a potential negative influence on long-term survival. Transferomal TAVI undertaken in high-risk aortic stenosis patients unfeasible for surgery has not been reported to be associated with negative effects on the myocardium. In studies involving AVR patients, fibrosis was either directly identified in biopsies obtained during surgery or indirectly using techniques such as late gadolinium enhancement (LGE) or cardiac magnetic resonance (CMR) imaging [21]. fQRS represents a practical marker of ventricular fibrosis in our study and survival analyses showed a significantly lower long-term survival in patients undergoing TAVI in the presence of fQRS in their ECG recordings (p < 0.05).

Most of the studies on the effect of fQRS on mortality and morbidity involved patients with acute coronary syndrome. Liang et al. found an increased rate of fQRS in the first 48 h in patients with non-ST elevation myocardial infarction (NSTEMI) than in those with unstable angina (UA) (p = 0.047), with significantly higher mortality in those with fQRS after 5-years of follow-up (p < 0.001) [22]. In one study, study participants were examined with MRI 1 week after myocardial infarction, and those with fQRS had significantly higher microvascular obstruction, and a correlation between fQRS and increased infarct size, myocardial perfusion abnormalities, reduced left ventricular ejection fraction, and elevated left cardiac volume. The authors concluded that fQRS may be a reliable marker of infarction size and acute ventricular remodeling based on their findings [23]. Again, major adverse cardiac events (MACE) and recurrent angina were found to be significantly increased among NSTEMI patients with fQRS [24]. In another study involving patients with ST-segment elevation myocardial infarction (STEMI), presence of fQRS was predictive of new-onset atrial fibrillation (AF) [25].

Left ventricular function and patient-related risk factors are among determinants of mortality after TAVI. Similar to previous reports, atrial fibrillation and LVEF < 50% were independent predictors of long-term mortality in multivariate Cox regression in our study; however, presence of FQRS also emerged as a significant predictor based on our findings ($p < 0.05$). Therefore, fQRS may allow reliable prognostic estimations using a basic and inexpensive diagnostic technique (ECG) in the cardiac assessment of these patients. In aortic stenosis patients without left ventricular dysfunction, the myocardial status is generally overlooked, and the severity of stenosis and ejection fraction comprise the primary focus of attention. However, fibrosis in the LV plays a significant role in the progression of cardiac failure and is a predisposing factor for arrhythmia and sudden death. Patients with fQRS should be carefully monitored after TAVI owing to a possibly higher risk of arrhythmia and sudden death.

This study has several limitations. The sample size is relatively small due to the single-center nature of our study. Confirmatory studies with larger sample size may be conducted. In addition, the study had a retrospective design. A prospective study with pre-operative cardiac MR imaging and fQRS recordings may allow better assessment of the mortality risk in association with myocardial fibrosis.

Conclusions

Presence of fQRS on ECG, an indirect indicator of myocardial fibrosis, seems to be predictive of long-term survival of patients after TAVI procedure. Large prospective studies examining the prognostic role of this practical and simple finding are warranted.

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Declarations of interest

None.

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