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ORIGINAL ARTICLE

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# Presence of fragmented QRS is associated with left ventricular systolic dysfunction after surgery in patients with severe aortic regurgitation

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## Abstract

**Background and Aim of the study:** Chronic severe aortic regurgitation (AR) is associated with progressive accumulation of interstitial fibrosis and disruption of myocardial structure. After aortic valve replacement (AVR), the negative remodeling process reverses, and left ventricular ejection fraction (LVEF) improves but not in all patients. In this study, we aimed to investigate the association of fragmented QRS (F-QRS), which is a possible marker of myocardial fibrosis, with postoperative left ventricular (LV) systolic dysfunction.

**Methods:** A total of 147 consecutive patients with AVR were included in this study. F-QRS was identified by the presence of various RSR' patterns (QRS duration <120 ms) such as additional R wave (R prime)or notching of the R or S wave in at least two consecutive leads. Patients were compared in two groups based on the presence or absence of F-QRS. A logistic regression model was used to determine independent predictors of postoperative LV systolic dysfunction (LVEF <50%).

**Results:** Patients with F-QRS were associated with poor recovery of LV systolic function after AVR compared to the patients without F-QRS, regardless of preoperative LVEF ($p = .008$). F-QRS was found to be an independent predictor of postoperative LV systolic dysfunction (LVEF <50%). Lower preoperative LVEF and increased LV end diastolic diameter index were also found as independent risk factors for postoperative LV systolic dysfunction.

**Conclusions:** As a possible marker of myocardial fibrosis, F-QRS was associated with postoperative LV systolic dysfunction. Therefore, as a simple and convenient clinical parameter, F-QRS may be used to predict poor recovery of LVEF after AVR.

KEYWORDS

aortic regurtation, fragmented QRS, left ventricular ejection fraction

  

## 1 | INTRODUCTION

Chronic aortic regurgitation (AR) is a common valvular heart disease with an incidence that increases with age and reaches approximately 16% above 70 years of age.[1] The most common causes of AR are atherosclerotic degeneration of the valvular structures and congenital bicuspid aortic valve (BAV).[2] Chronic severe AR is associated with progressive accumulation of interstitial myocardial fibrosis which results in disruption of myocardial structure. Eventually, this negative remodeling process causes left ventricular (LV) systolic dysfunction.[3] Generally, after AVR, negative remodeling process reverses and LV systolic function improves.[4] On the other hand, in some patients, LVEF does not improve after surgery.[5] Postoperative LVEF is an important determinant of long-term prognosis in patients with severe chronic AR.[6] Therefore, it is valuable to identify the parameters predicting improvement or worsening of the LVEF after surgery. In previous studies, myocardial fibrosis was associated with poor postoperative LV systolic function in severe AR.[7,8] Cardiac magnetic resonance imaging (CMR) is known to be the gold standard determinant of myocardial fibrosis, however it is not a cost effective imaging method. Presence of fragmented QRS (F-QRS) complex on 12-lead electrocardiogram (ECG), probably represents inhomogeneous conduction throughout the scarred myocardium and found to be associated with myocardial fibrosis in a variety of cardiomyopathies.[9,10] Therefore, F-QRS complex can be used as a possible marker of myocardial fibrosis. In this study we aimed to investigate the relationship between the presence of F-QRS complex on ECG and postoperative LV systolic dysfunction.

## 2 | MATERIALS AND METHODS

### 2.1 | Patient selection

Patients with chronic severe AR who underwent primary isolated AVR at the Kosuyolu training and research hospital between October 2009 and March 2019 were retrospectively studied. The predominant valve pathology was AR in all cases. Indications for AVR were symptomatic severe AR in 37% of the patients, asymptomatic severe AR with LV systolic dysfunction (EF ≤50%) in 46% or LV dilatation (EF >50% with left ventricular end diastolic diameter [LVEDD] >70 mm or left ventricular end systolic diameter [LVESD] >50 mm or LVESD index [LVESDI] >25 mm/m$^2$) in 16% of the patients.[11] Of 287 patients operated for primary severe chronic AR, 147 were included in the study. Patient selection and exclusion criteria are presented in Figure 1. These remaining 147 patients were divided into two groups according to the presence or absence of F-QRS. Patients' clinical and demographic characteristics, etiology and duration of AR, past medical history, medications used before and after AVR including angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), calcium channel blockers, diuretics were reviewed from the medical records. Aortic cross-clamp duration (ACCD) and perioperative complications were retrospectively investigated from surgical data. Operations were performed by cardiac surgeons specialized in aortic valve disease. Follow-up data was collected from our outpatient clinical and echocardiographic records. The study was approved by the local ethics committee and the study protocol complied with the Declaration of Helsinki.

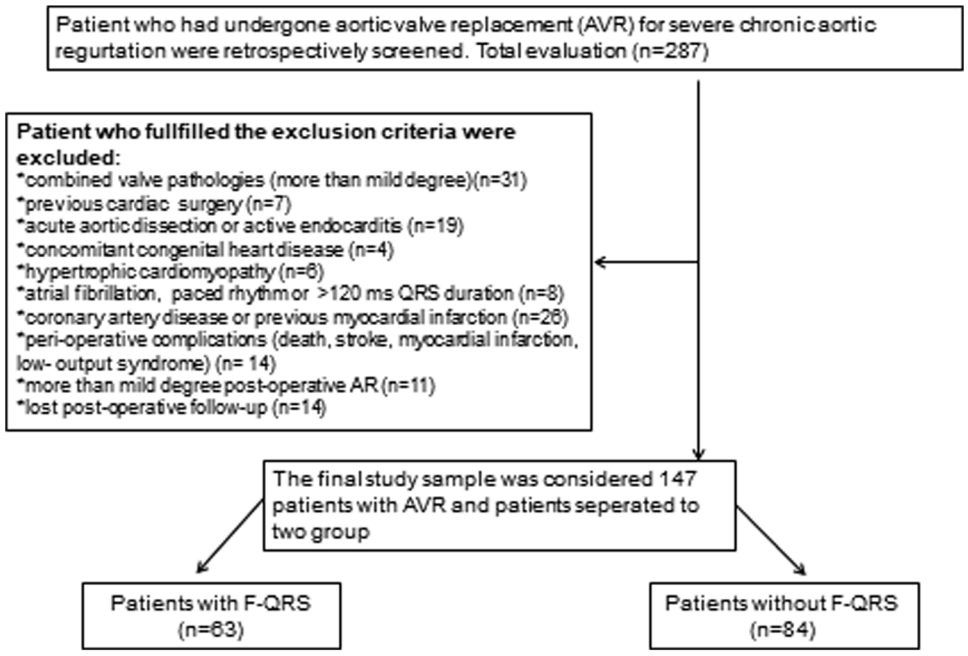


**FIGURE 1** Patient inclusion and exclusion criteria In the Figure 1, we summarized the inclusion and exclusion criteria for the study

## 2.2 | Echocardiographic analysis

Two-dimensional transthoracic echocardiography (TTE) (GE Vivid-7 between 2009 and 2014 years and Philips Epiq-7 between 2014 and 2019 years) was performed in all patients within 1–3 weeks before AVR and 1 year after the surgery. Echocardiographic measurements were performed according to the recommendations of the American Society of Echocardiography.[12] Comprehensive echocardiographic analyses were performed to evaluate the AR severity before AVR such as; the vena contracta width (the narrowest area of the regurgitant jet), the ratio of the regurgitant jet width to the LV outflow diameter, holo-diastolic reverse flow in the proximal descending aorta, effective regurgitant orifice area and regurgitant volume.[13] LVEF was calculated with the modified biplane Simpson method using the apical four-chamber and two-chamber views.[12] LVEDD and LVESD were indexed by dividing LVEDD and LVESD (in mm) by body surface area (BSA) (in $m^2$). LV mass (LVM), LVM index (LVMI), and relative wall thickness were calculated as previously described by Devereux et al.[14] All measurements were made at the end of expiration and in at least three consecutive cycles. The averages of three measurements were used for the analysis. The same procedure was applied 1 year after AVR for echocardiographic examination. All echocardiographic measurements and analyzes were performed by three cardiologists specialized in echocardiography. Any disagreement between the echocardiographers was resolved with consensus.

## 2.3 | Electrocardiography analysis

12-Lead ECGs were recorded in all patients before AVR. All standard ECGs were obtained at rest using an ECG recorder (GE Marquette Medical Systems) at a speed of 25 mm/s, 60 Hz (range: 0.5–150 Hz) standardized at 1 mV/cm. Archived ECGs were analyzed for the presence or absence of F-QRS. ECG analysis was performed with a digitizing tablet using MUSE (R) Cardiology Information System (version 7.1.1.) connected to a personal computer. 12-Lead ECG analysis was carried out by two independent electrophysiologists blinded to the study. In case of any discrepancy between the two electrophysiologists, it was resolved with consensus. F-QRS complex was defined as present or absent for each lead in the 12-lead ECG before AVR. Presence of F-QRS complex was defined in various RSR' patterns including additional R wave (R prime), notching of the R or S wave or more than two R primes in at least two consecutive leads matching to a large coronary artery area without the characteristic of bundle branch block (V1–V5 corresponding to anterior region, D2-D3-AVF corresponding to inferior region, D1-AVL-V6 corresponding to lateral region) in patients with a QRS duration less than 120 ms. Any QRS morphology with QRS duration ≥120 ms, such as bundle branch block or intraventricular conduction delays, were excluded from the study.

## 2.4 | Statistical analysis

All statistical analyses were performed using "rms," "glm," "Hmisc," and "ggplot2" packages with R-studio version 4.01 (R statistical software, Institute for Statistics and Mathematics). Continuous variables were presented as median and interquartile range (IQR 25th–75th), whereas categorical variables were presented as counts and percentages. For continuous data paired data comparison Wilcoxon rank test used, while for the comparison of the categorical data $\chi^2$ test was used if cell lower than 5, otherwise Fisher-exact test was used. We used Cohen Kappa coefficient for demonstrating interrater reliability for F-QRS.

### 2.4.1 | Primary outcome

The primary outcome was LVEF less than 50% in the first year after surgery.

### 2.4.2 | Candidate predictors

It is important that the candidate predictors to be included in the statistical models were supposed to be clinically and physiologically plausible and that their association with LVEF had been demonstrated in previous studies. The candidate predictors were chosen according to these principles. We evaluated two primary models. The first model included 10 predictor variables (full model). The candidate predictors were preoperative LVEF, F-QRS, gender, age, diabetes mellitus (DM), hypertension (HT), LVEDD index (LVEDDI), LVESD index (LVESDI), LVMI, ACCD. To decrease the complexity of full model and to yield reduced form models that would be more practical for bedside use, we performed stepdown backward variable selection with an alpha criterion 0.25. Variables with more than 25% missingness were not included in the models. For collinarity detection we checked variance inflation factor (VIF), and there were no variables with VIF values over 5 in the models.

### 2.4.3 | Statistical modeling

We used a logistic regression method to examine the relationship between primary outcome (dichotomous postoperative first year LVEF <50%) and candidate predictors. Effects of individual predictors on our logistic model were reported using odds-ratio and 95% confidence interval (CI). The postoperative first year LV systolic dysfunction (LVEF <50%) was used for the model response variable. We performed stepwise backward variable selection with an alpha criterion .25, after this reduced model included F-QRS, preoperative LVEF, LVEDDI and age. The relative importance of each predictor in the full model was estimated with partial $\chi^2$ value for each predictor.

**TABLE 1** Clinical and echocardiographic characteristics of the overall cohort before and after surgery

| Variables | All (*n* = 147) | F-QRS negative (*n* = 84) | F-QRS positive (*n* = 63) | *p* Value |
|---|---|---|---|---|
| BSA ($m^2$) | 1.88 (1.77–2.01) | 1.86 (1.78–2.02) | 1.89 (1.77–2.01) | .34 |
| Male (*n*, %) | 107 (72.8) | 58 (69) | 49 (77.8) | .24 |
| Diabetes (*n*, %) | 24 (16.3) | 17 (20.2) | 7 (11.1) | .14 |
| Hypertension (*n*, %) | 37 (25.2) | 22 (26.2) | 15 (23.8) | .74 |
| Age (years) | 50.5 (38–61.5) | 46.5 (34–56) | 56 (47–64.5) | <.001* |
| Pre-op LVEF (%) | 45.4 (38.5–47.8) | 45.3 (39.3–48.3) | 45.4 (38.4–47.6) | .12 |
| Post-op LVEF (%) | 48.0 (40.5–54.8) | 52.0 (47.2–56.5) | 43.4 (36.6–47.3) | <.001* |
| Pre-op LVEDDI ($mm/m^2$) | 35.5 (32.5–38.5) | 35.3 (32.2–38) | 35.8 (32.5–39.0) | .66 |
| Post-op LVEDDI ($mm/m^2$) | 29.5 (26.6–32.4) | 29.3 (26.2–31.4) | 29.5 (27.1–33.0) | .08 |
| Pre-op LVESDI ($mm/m^2$) | 25.0 (22.6–27.4) | 24.5 (21.9–26.9) | 25.9 (23.9–29.3) | .01 |
| Post-op LVESDI ($mm/m^2$) | 21.2 (18.4–23.7) | 20.9 (18.2–23.3) | 21.6 (18.9–24.9) | .06 |
| Pre-op IVS (mm) | 12.0 (12.0–13.0) | 12.0 (12.0–13.0) | 13.0 (12.0–13.5) | .52 |
| Post-op IVS (mm) | 11.0 (10.0–12.0) | 11.0 (10.0–12.0) | 11.0 (10.0–12.0) | .16 |
| Pre-op PW (mm) | 12.0 (11.0–13.0) | 12.0 (11.0–13.0) | 12.0 (11.0–13.0) | .45 |
| Post-op PW (mm) | 10.0 (10.0–12.0) | 10.0 (10.0–11.0) | 11.0 (10.0–12.0) | .39 |
| Pre-op LVMI ($g/m^2$) | 201 (179–232) | 199 (180–224) | 206 (177–237) | .71 |
| Post-op LVMI ($g/m^2$) | 126 (105–149) | 124 (102–139) | 137 (113–157) | .01* |
| Pre-op RWT | 0.36 (0.33–0.39) | 0.36 (0.32–0.39) | 0.36 (0.34–0.40) | .77 |
| Post-op RWT | 0.38 (0.35–0.42) | 0.39 (0.36–0.42) | 0.38 (0.34–0.41) | .16 |
| ACCD | 54 (48.3–63.8) | 55 (49–66) | 54 (48–58) | .37 |
| Etiology (*n*, %) | | | | |
| Bicuspid aortic valve | 54 (36.7) | 32 (38.1) | 22 (34.9) | .07 |
| Senile degenerative | 33 (22.4) | 12 (14.3) | 21 (33.3) | |
| Rheumatic | 27 (18.4) | 18 (21.4) | 9 (14.3) | |
| Annulo-aorticectasia | 18 (12.2) | 11 (13.1) | 7 (11.1) | |
| Others | 15 (10.2) | 11 (13.1) | 4 (6.3) | |
| Valve types (mechanic) (*n*, %) | 134 (91.2) | 75 (89.3) | 59 (93.7) | .35 |
| Medical therapy | | | | |
| Diuretic | 62 (42.8) | 34 (40.4) | 28 (44.4) | .07 |
| ACEI-ARB | 102 (70.0) | 53 (63.0) | 49 (77.7) | |
| Ca channel blocker | 24 (16.3) | 13 (15.4) | 11 (17.4) | |

*Note*: Data are presented as median with interquartile range, or as numbers (%).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BSA, body surfacearea; F-QRS, fragmented QRS; IVS, interventricular septum; LVEDDI, left ventricular end diastolic diameter index; LVEF, left ventricular ejection fraction; LVESDI, left ventricular end systolic diameter index; LVMI, left ventricular mass indesx; PW, posterior wall; RWT, relative wall thickness.

*$p \leq .05$.

### 2.4.4 | Nomogram

Nomogram provides graphical depiction of all the variables in the model (we used it for full-model) in addition to enabling the user obtain predicted values manually.

## 3 | RESULTS

The AR etiology of patients was as follows: BAV in 54 (36.7%) patients, a degenerative valve in 33 (22.4%), a rheumatic valve in 27 (18.4%), annuloaortic ectasia in 18 (12.2%) and others in 15 (10.2%).

**TABLE 2** Changes in LV size and ejection fraction after AVR with Wilcoxon test

| Variables | Pre-op median value | Post-op median value | *p* Value |
|---|---|---|---|
| LVEF (%) | 45.4 | 48.0 | <.001* |
| LVEDD (mm) | 66.0 | 55.0 | <.001* |
| LVEDDI (mm/m$^2$) | 35.48 | 29.47 | <.001* |
| LVESD (mm) | 46.0 | 40.0 | <.001* |
| LVESDI (mm/m$^2$) | 25.01 | 21.18 | <.001* |
| IVS (mm) | 12 | 11 | <.001* |
| PW (mm) | 12 | 10 | <.001* |
| LVMI (mm/m$^2$) | 200.6 | 125.8 | <.001* |

Abbreviations: AVR, aortic valve replacement; CI, confidence interval; IVS, interventricular septum; LVEDD, left ventricular end diastolic diameter; LVEDDI, left ventricular end diastolic diameter index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESDI, left ventricular end systolic diameter index; LVMI, left ventricular mass index; mm, millimeter; PW, posterior wall.
*$p \leq .05$.

Other causes included leaflet prolapse and rudimentary left coronary cuspid. AVR was performed with a mechanical prosthesis valve in 134 (91.2%) patients, and a bioprosthesis valve in 13 (8.8%) patients. Ascending aortic repair was performed in 18 patients together with AVR. The median ACCD was 54 (48.3–63.8) minutes. There were 63 patients (42.8%) in the group with F-QRS, and 84 patients (57.2%) in the group without F-QRS (Table 1). There was a %97 concordance between two electrophysiologists in determining the presence or absence of F-QRS. Cohen's Kappa coefficient (k) was used to measure inter-rater reliability for F-QRS and the result was 0.97.

Of the 147 patients included in this study, there were 107 men and 40 women with a median age of 50.5 years. The median age was 56 in patients with F-QRS, and 46.5 in those without F-QRS ($p < .001$). Parameters including gender, BSA, DM, HT, AR etiology, type of AVR, ACDD were not significantly different between the two groups. Of the patients, 70.0% were using ACEI or ARB, 42.8% were using diuretic therapy and 16.3% were using calcium channel blockers (Table 1).

Table 2 shows the echocardiographic parameters before and after the surgery. Before AVR, the median preoperative LVEF was 45.4%, the median LVEDDI was 35.48 mm/m$^2$ and the median LVESDI was 25.01 mm/m$^2$. In the first year after AVR, the median LVEF increased and LV dimensions decreased significantly. The median LVEF increased from 45.4% to 48.0% ($p < .001$). Both LVEDDI and LVESDI decreased (35.48 vs. 29.47 mm/m$^2$, 25.01 vs. 21.18 mm/m$^2$, respectively) ($p < .001$) (Table 2).

The median preoperative LVEF was similar between the two groups (45.4% vs. 45.3%). However, after the surgery, the median LVEF decreased from 45.4% to 43.4% in patients with F-QRS, and increased from 45.3% to 52.0% in patients without F-QRS. The median postoperative LVEF was much better in the group without F-QRS compared to the patients with F-QRS ($p < .001$) (Table 1).

The median LVEDDI and LVESDI were also similar between the two groups and there was no statistical difference (Table 1).

Before AVR, the median IVS was 12.0 mm, PW was 12.0 mm and LVMI was 201 g/m$^2$. After the surgery, LVMI decreased from 201 to 126 g/m$^2$ ($p < .001$). Both IVS and PW also decreased significantly (12.3 vs. 11.0 mm, 12.0 vs. 10.0 mm, respectively) ($p < .001$) (Table 2). The median LVMI was similar between the two groups before AVR. However, postoperative LVMI was higher in patients with F-QRS compared to the patients without F-QRS ($p = .001$) (Table 1).

We used the logistic regression method to identify the predictors associated with postoperative LV systolic dysfunction (LVEF <50%). Patients with F-QRS were associated with poor recovery of LV systolic function after AVR compared to the patients without F-QRS, regardless of preoperative LVEF value (odds ratio: 7.94; CI: 2.08–30.28; $p = .008$) (Figure 2). Preoperative lower LVEF and increased LVEDDI were also associated with postoperative LV systolic dysfunction (Table 3). Preoperative low LVEF was found as the most contributing predictor for postoperative LV systolic dysfunction. Second most important variable was F-QRS (Figure 3).

In the reduced model, preoperative lower LVEF, the presence of F-QRS, and increased LVEDDI were associated with postoperative LV systolic dysfunction (Table 4). We also developed a nomogram to estimate the probability of postoperative first year LV systolic dysfunction (LVEF <50%) according to these predictors (Figure 4). Consequently, preoperative lower LVEF, F-QRS and increased LVEDDI had the best performance for the prediction of postoperative LV systolic dysfunction (LVEF <50%).

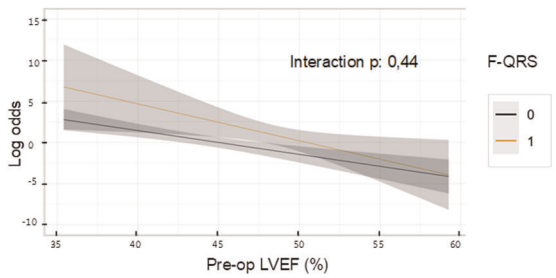


**FIGURE 2** The probability of postoperative LV systolic dysfunction (LVEF <50%). In the Figure 2, the probability of LV systolic dysfunction (LVEF <50%) in the first year after surgery were plotted according to all regression variables (F-QRS, preoperarive LVEF, hypertension, diabetes, age, gender, preoperative LVEDDI, preoperative LVESDI, preoperative LVMI, ACCD). Patients with F-QRS and impaired preoperative LV systolic function were significantly associated with postoperative LV systolic dysfunction (LVEF <50%). P-interaction between F-QRS and preoperative LVEF was: 0.44. ACCD, aortic cross-clamp duration; F-QRS, fragmented QRS; LVEDD, left ventricular end diastolic diameter; LVEDDI, LVEDD index; LVEF, left ventricular ejection fraction

| Variables | Univariate, odds ratio, CI | *p* Value | Multivariable, odds ratio, CI | *p* Value |
|---|---|---|---|---|
| Pre-op LVEF | 0.77 (0.70–0.85) | <.001 | 0.73 (0.64–0.83) | <.001* |
| F-QRS | 4.32 (1.82–10.26) | <.001 | 7.94 (2.08–30.28) | .008* |
| Gender (male) | 1.22 (0.61–2.41) | .57 | 0.55 (0.19–1.59) | .55 |
| Age | 1.02 (0.99–1.05) | .07 | 1.03 (0.98–1.06) | .17 |
| Diabetes | 0.44 (0.18–1.10) | .08 | 0.53 (0.15–1.90) | .42 |
| Hypertension | 0.66 (0.31–1.4) | .28 | 0.93 (0.29–3.03) | .88 |
| LVEDDI | 1.19 (1.10–1.29) | <.001 | 1.28 (1.08–1.51) | .004* |
| LVESDI | 1.17 (1.06–1.28) | <.001 | 0.91 (0.75–1.08) | .28 |
| LVMI | 1.01 (0.99–1.02) | .11 | 0.99 (0.98–1.01) | .92 |
| ACCD | 1.02 (0.99–1.04) | .07 | 1.01 (0.99–1.03) | .36 |

Abbreviations: ACCD, aortic cross clamp duration; CI, confidence interval; F-QRS, fragmented QRS; LVEDDI, left ventricular end diastolic diameter index; LVEF, left ventricular ejection fraction; LVESDI, left ventricular end systolic diameter index; LVMI, left ventricular mass index.

*$p \leq .05$.

**TABLE 3** The probability of postoperative LVEF less than 50% with univariate and multivariable logistic regression model (Full model)

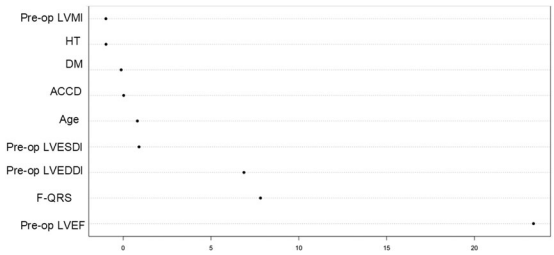


**FIGURE 3** Relative importance of each predictor for postoperative LV systolic dysfunction (LVEF <50%) In the Figure 3, we summarized the relative importance of each predictor in the full model. Preoperative lower LVEF was ranked as the most contributing predictor for postoperative LV systolic dysfunction. Additionally, second most important variable was F-QRS complex. F-QRS, fragmented QRS; LVEF, left ventricular ejection fraction

**TABLE 4** Reduced model for the probability of postoperative LVEF less than 50% with multivariable logistic regression model (stepdown backvard selection with $\alpha = .25$)

| Variables | Multivariable odds ratio, CI | *p* Value |
|---|---|---|
| Pre-op LVEF | 0.73 (0.65–0.82) | <.001* |
| F-QRS | 6.91 (2.10–22.75) | .001* |
| Age | 1.02 (0.99–1.05) | .16 |
| LVEDDI | 1.15 (1.04–1.28) | .006* |

Abbreviations: AVR, aortic valve replacement; CI, confidence interval; F-QRS, fragmented QRS; LVEDDI, left ventricular end diastolic diameter index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index.

*$p \leq .05$.

## 4 | DISCUSSION

In the present study, we showed that, the preoperative lower LVEF, the presence of F-QRS and increased preoperative LVEDDI were the main independent predictors for postoperative LV systolic dysfunction (LVEF <50%) within the first year after AVR. The presence of F-QRS, after preoperative LVEF, was the most important predictor of postoperative LV systolic dysfunction (LVEF <50%).

Chronic severe AR is associated with both volume and pressure overload. In the early period of chronic severe AR, eccentric LV hypertrophy and dilatation compensates for increased volume load, so the LV systolic function remains normal. However, the increased volume load surpasses the myocardial compensation mechanisms over time, eventually LV systolic function starts to fail. Although LV systolic dysfunction is reversible at first, eventually the increased wall stress stimulates cardiac fibroblasts for fibronectin and collagen synthesis, leading to collagen accumulation and subendocardial fibrosis. This negative remodeling process eventually causes irreversible LV systolic dysfunction.[3]

CMR with late gadolinium enhancement enables identification and quantification of myocardial fibrosis.[15] However, cardiac magnetic resonance imaging (MRI) is not a cost effective imaging technique in routine clinical practice. Myocardial fibrosis also causes inhomogeneous conduction throughout the scarred myocardium, which results in F-QRS formation.[9] In previous studies, F-QRS was found to be associated with ventricular scar formation in various cardiovascular diseases including idiopathic dilated cardiomyopathy, coronary artery disease, HT, and hypertrophic cardiomyopathy.[9,10,15] F-QRS was also

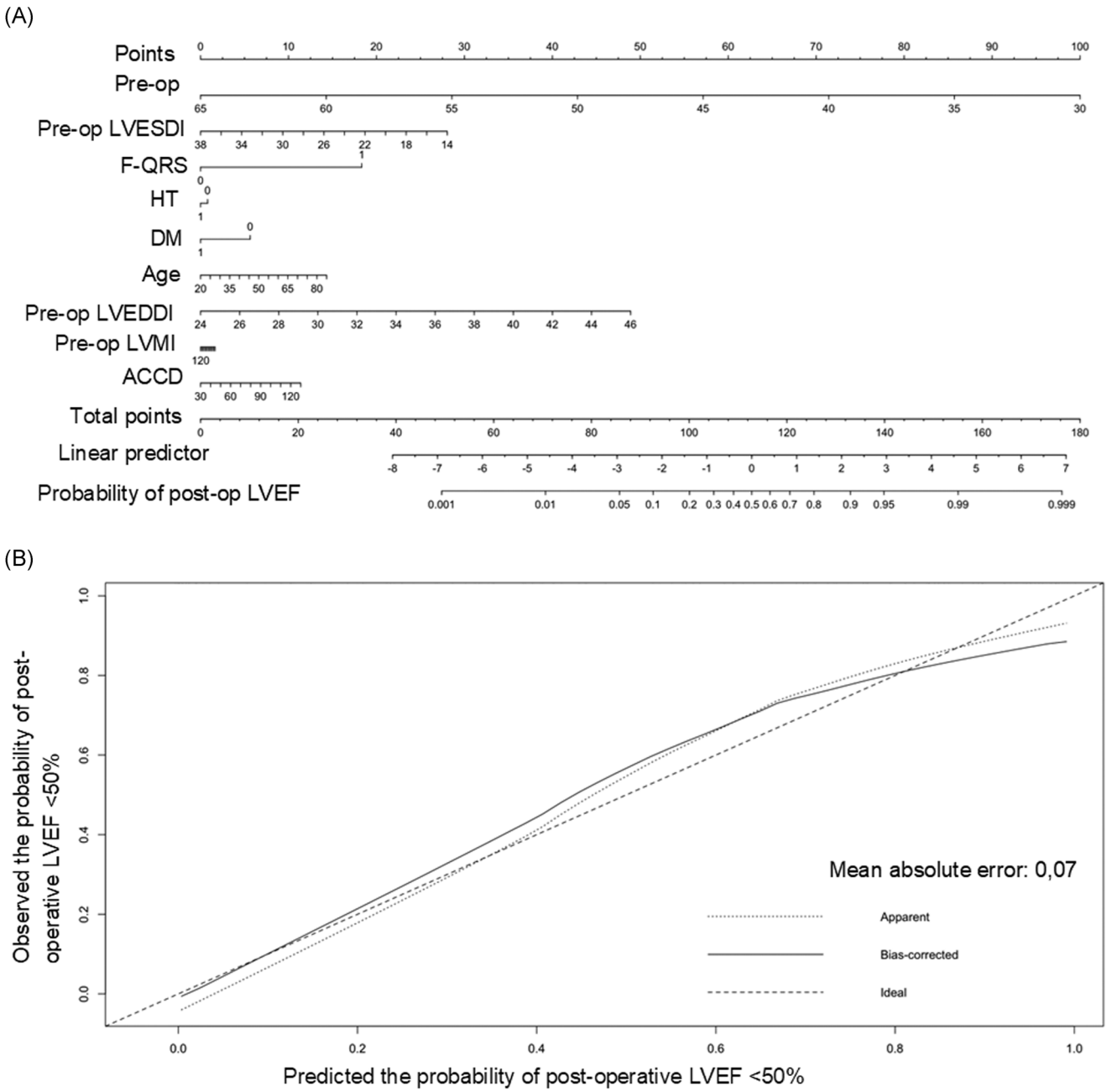


**FIGURE 4** A nomogram for the prediction of postoperative LV systolic dysfunction (LVEF <50%). (A) We developed a nomogram using variables in the full-model and variable coefficient in estimating the probability of postoperative LV systolic dysfuncton (LVEF <50%). As an example, preoperative LVEF 45% with F-QRS, LVEDDI 36 mm/m$^2$, LVESDI 28 mm/m$^2$, LVMI 120 g/m$^2$, ACCD 60 min, age 50 years, no hypertension, no diabetes. According to our nomogram, the probability of postoperative LVEF being less than 50% is equal to 80% for this patient. (B) The corrected calibration depicted fairly agreement with the apparent calibration, in our calibration plot mean absolute error was 0.07. F-QRS, fragmented QRS; LVEDD, left ventricular end diastolic diameter; LVEDDI, LVEDD index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index

found as a possible marker of myocardial fibrosis in severe aortic stenosis (AS).[16] Furthermore, significant correlation was found between the percentage of fibrosis and LVEF in patients operated for isolated severe AS.[17,18] Patients with severe AS or AR show different adaptive responses to pressure (concentric LV hypertrophy in AS) or volume (eccentric LV hypertrophy in AR) overload. However, in both situations increased LV wall stress causes myocardial fibrosis and LV systolic dysfunction.[17,19]

After successful AVR, the functional capacity of the patients increases and generally the LVEF improves.[20] However, not all patients respond positively to AVR, and in some patients, LVEF does not not improve after AVR. Therefore, we investigated the association of the presence of F-QRS on surface ECG before AVR,

a possible marker of myocardial fibrosis, with postoperative LV systolic dysfunction (LVEF <50%). We detected that the presence of F-QRS was significantly associated with postoperative LV systolic dysfunction (LVEF <50%). Although preoperative LVEF was similar between the two groups, postoperative LVEF was much worse in patients with F-QRS. We suggest that, in patients with F-QRS and LV systolic dysfunction LVEF does not improve after AVR due to the irreversible myocardial damage caused by subendocardial fibrosis. On the other hand, in other patients with lower LVEF but without F-QRS, LV systolic function responds favorably to AVR. Similarly, Azevedo et al.[7] found that the increase in the amount of myocardial fibrosis (evaluated by using delayed contrast-enhanced cardiac magnetic resonance and histological analysis of myocardial samples) was associated with poor improvement of LV systolic function after AVR. Also, Villari et al.[8] revealed that the higher myocardial fibrosis (demonstrated by endomyocardial biopsy) was inversely correlated with postoperative LVEF.[8]

Along with the myocardial fibrosis, various factors; including preoperative low LVEF, prolonged LV systolic dysfunction, decreased preoperative dp/dt, stroke volume or cardiac index, increased preoperative LVEDDI, and LVESDI have been associated with postoperative LV systolic dysfunction.[7,8,21,22]

Preoperative LVEF is an important predictor of postoperative prognosis, so the degree of LV systolic dysfunction is critical in determining the optimal timing for surgery.[11] In the same line, Klodas et al.[5] found that preoperative EF was the only independent predictor for postoperative LVEF in patients with chronic severe AR.[5] Besides, doppler-derived dp/dt (if ≤700 mmHg/s) and preoperative LVEF (if ≤45%) were found as significant predictors for LV systolic dysfunction after AVR.[22] Similarly, in our study, lower preoperative LVEF was found to be associated with postoperative LV systolic dysfunction. Furthermore, in this study, preoperative lower LVEF was detected as the most powerful predictor for postoperative LV systolic dysfunction. Hiroyuki saisho et al.[23] also revealed that, depressed preoperative LVEF (<50.2%) with increased LVESDI (≥26.7 mm/m$^2$), and decreased cardiac index (<2.71 L/min/m$^2$) were associated with poor LV systolic function after AVR.[23] On the contrary, in a study by Bonow et al.[20] postoperative LVEF was not associated with preoperative LVEF in patients with severe AR and LV systolic dysfunction. That study showed that prolonged LV systolic dysfunction was significantly correlated with poor recovery of LV systolic function after AVR. This result may be explained by the fact that, patients with prolonged LV systolic dysfunction may have been exposed to negative LV remodelling for longer periods, which causes myocardial fibrosis. In the same line, we found that F-QRS was associated with postoperative LV systolic dysfunction, regardless of preoperative LVEF. In light of these results, we can conclude that LVEF could not improve significantly after AVR in patients with F-QRS since myocardial fibrosis may have caused irreversible LV systolic dysfunction.

Previous studies have also showed that LVEF does not improve after AVR in patients with impared LV systolic function and significantly dilated ventricle.[5,24] Besides, in a study by Ho Cho et al. increased LVESDI (>35.32 mm/m$^2$) and LVEDDI (>44.42 mm/m$^2$) was associated with poor LV systolic function early after AVR.[25] Similarly, in our study, increased LVEDDI was inversely correlated with postoperative LVEF.

The present study has several limitations. First, this study was a single-center experience and included a relatively small number of patients. The retrospective nature of the study was another shortcoming. Moreover, the follow-up period after AVR was relatively short, and it might have been important to identify additional changes in LVEF after a longer follow-up period. Finally, myocardial fibrosis was not confirmed by cardiac MRI in patients with F-QRS. Therefore, a prospective study including MRI to compare the fibrosis determination through MRI and F-QRS and use of myocardial strain or CMR as reference for LV systolic function will be more valuable in determining the association between F-QRS and postoperative LV systolic dysfunction.

## 5 | CONCLUSION

As a possible marker of myocardial fibrosis on the 12-lead ECG, F-QRS was associated with postoperative LV systolic dysfunction. Patients with severe AR and depressed LVEF are at greater risk of heart failure, and some of these patients are not operated due to the high mortality risk. Consequently, as a simple and convenient clinical parameter, F-QRS, may be used to predict poor recovery of LV systolic function after surgery.

### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;368(9540):1005-1011.
2. Siu SC, Silversides CK. Bicuspid aortic valve disease. *J Am Coll Cardiol*. 2010;55(25):2789-2800.
3. Fielitz J, Hein S, Mitrovic V, et al. Activation of the cardiac renin-angiotensin system and increased myocardial collagen expression in human aortic valve disease. *J Am Coll Cardiol*. 2001;37(5):1443-1449.
4. Tornos P, Sambola A, Permanyer-Miralda G, Evangelista A, Gomez Z, Soler-Soler J. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. *J Am Coll Cardiol*. 2006;47(5):1012-1017.
5. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Aortic regurgitation complicated by extreme left ventricular dilation: long-term outcome after surgical correction. *J Am Coll Cardiol*. 1996;27(3):670-677.

6. Amano M, Izumi C, Imamura S, et al. Pre- and postoperative predictors of long-term prognosis after aortic valve replacement for severe chronic aortic regurgitation. *Circ J*. 2016;80(12):2460-2467.
7. Azevedo CF, Nigri M, Higuchi ML, et al. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. *J Am Coll Cardiol*. 2010;56(4):278-287.
8. Villari B, Sossalla S, Ciampi Q, et al. Persistent diastolic dysfunction late after valve replacement in severe aortic regurgitation. *Circulation*. 2009;120(23):2386-2392.
9. Das MK, Suradi H, Maskoun W, et al. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. *Circ Arrhythm Electrophysiol*. 2008;1(4):258-268.
10. Das MK, Maskoun W, Shen C, et al. Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. *Heart Rhythm*. 2010;7(1):74-80.
11. Baumgartner H, Falk V, Bax JJ, et al. ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2017;38(36):2739-2791.
12. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39.
13. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the american society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr*. 2017;30(4):303-371.
14. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. *Anatomic validation of the method. Circulation*. 1977;55(4):613-618.
15. Perazzolo Marra M, De Lazzari M, Zorzi A, et al. Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. *Heart Rhythm*. 2014;11(5):856-863.
16. Açıkgöz E, Yaman B, Açıkgöz SK, Topal S, Tavil Y, Boyacı NB. Myocardial fibrosis is the key component of hypertrophied myocardium that cause fragmented qrs in aortic stenosis. *Ann Noninvasive Electrocardiol*. 2015;20(5):513.
17. Hein S, Arnon E, Kostin S, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation*. 2003;107(7):984-991.
18. Carabello BA. Clinical practice. *Aortic stenosis. N Engl J Med*. 2002;346(9):677-682.
19. Krayenbuehl HP, Hess OM, Monrad ES, Schneider J, Mall G, Turina M. Left ventricular myocardial structure in aortic valve disease before, intermediate, and late after aortic valve replacement. *Circulation*. 1989;79(4):744-755.
20. Bonow RO, Dodd JT, Maron BJ, et al. Long-term serial changes in left ventricular function and reversal of ventricular dilatation after valve replacement for chronic aortic regurgitation. *Circulation*. 1988;78(5 Pt 1):1108-1120.
21. Sénéchal M, Bernier M, Dagenais F, Dubois M, Dubois-Sénéchal IN, Voisine P. Usefulness of preoperative stroke volume as strong predictor of left ventricular remodeling and outcomes after aortic valve replacement in patients with severe pure aortic regurgitation. *Am J Cardiol*. 2011;108(7):1008-1013.
22. Kang HJ, Kim YJ, Sohn DW, et al. Prediction of postoperative left ventricular systolic function with Doppler-derived dP/dt in patients with chronic aortic regurgitation. *J Am Soc Echocardiogr*. 2003;16(11):1111-1115.
23. Saisho H, Arinaga K, Kikusaki S, et al. Long term results and predictors of left ventricular function recovery after aortic valve replacement for chronic aortic regurgitation. *Ann Thorac Cardiovasc Surg*. 2015;21(4):388-395.
24. Hirooka K, Yasumura Y, Tsujita Y, et al. Enhanced method for predicting left ventricular reverse remodeling after surgical repair of aortic regurgitation: application of ultrasonic tissue characterization. *J Am Soc Echocardiogr*. 2002;15(7):695-701.
25. Cho SH, Byun CS, Kim KW, Chang BC, Yoo KJ, Lee S. Preoperative indexed left ventricular dimensions to predict early recovery of left ventricular function after aortic valve replacement for chronic aortic regurgitation. *Circ J*. 2010;74(11):2340-2345.

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