Role of QRS Fragmentation for Risk Stratification in Adults With Tetralogy of Fallot

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Background—Patients with tetralogy of Fallot (TOF) remain at risk for cardiovascular events despite successful repair. Some of the current risk stratification tools require advanced imaging and invasive studies, and hence are difficult to apply to routine patient care. A recent study showed that QRS fragmentation (QRS-f) is predictive of mortality in patients with TOF. The current study aims to validate this result by assessing whether severity of QRS-f could predict all-cause mortality in a different TOF population.

Methods and Results—The authors reviewed the Mayo Adult Congenital Heart Disease database for patients with TOF who had ECG from 1990–2017. QRS-f was defined as notches in QRS complex in ≥ 2 contiguous leads on ECG, not related to bundle branch block, and classified as none, mild (≤ 3 leads), moderate (4 leads), or severe (≥ 5 leads). Of 465 patients (age 37 ± 14 years) in the study, QRS-f was present in 161 (35%): mild (n=43, 9%), moderate (n=77, 17%), and severe (n=41, 9%). There were 55 deaths (12%) during 13.6 ± 8.2 years of follow-up. Severity of QRS-f remained an independent predictor of all-cause mortality after adjustment for other ECG parameters, patient demographics, and atrial and ventricular arrhythmia (hazard ratio, 1.74 per class; 95% confidence interval, 1.08–2.93 [*P*=0.041]).

Conclusions—The presence of severe QRS-f may be used as complementary data to the usual clinical indices to determine whether interventions such as invasive electrophysiology study should be performed in patients with nonsustained ventricular tachycardia or to proceed with pulmonary valve replacement in patients with severe pulmonary regurgitation with ventricular volumes below the guideline-directed threshold for intervention. (*J Am Heart Assoc*. 2018;7:e010274. DOI: 10.1161/JAHA.118.010274.)

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease,[1] and despite improvement in medical and surgical management of this disease, adults with repaired TOF remain at risk for cardiovascular morbidity and mortality.[2–4] Patients with repaired TOF have reduced survival compared with the general population, with a 30-year survival of $\approx$85% to 90%.[2,4,5] As a result, risk stratification is important in this population to identify and treat patients at high risk for cardiovascular death.

Several studies have described risk factors for mortality in adults with repaired TOF.[3,5–10] The proposed risk factors include patient demographics such as age at time of TOF repair, left and right ventricular (RV) dysfunction, RV fibrosis, RV hypertrophy, ventricular arrhythmia, and increased left ventricular end-diastolic pressure.[3,5–10] Unfortunately, some of the available risk scores include variables derived from magnetic resonance imaging (MRI) and cardiac catheterization, and such tests are not routinely performed during annual evaluation. ECG, on the other hand, is inexpensive, noninvasive, readily available, and routinely performed during annual evaluation of patients with TOF.[11] In a recent study, Bokma et al[12] reported that QRS fragmentation (QRS-f), assessed using a standard 12-lead ECG, could reliably predict mortality in this population. The purpose of our study was to determine whether QRS-f derived from a standard 12-lead ECG could independently predict mortality in a different population of adult patients with TOF.

Methods

Patient Selection

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure. The data will be made available for requests made to corresponding author

via e-mail. We reviewed the Mayo Adult Congenital Heart Disease database and identified patients (age ≥18 years) with repaired TOF that had at least 1 ECG in the electronic health records between January 1, 1990, and December 31, 2017. The patients with pulmonary atresia were excluded. The Mayo Clinic's institutional review board approved this study and waived informed consent for patients who provided research authorization.

Data Collection

The following electronic health records were reviewed in detail: clinical notes, ECG, Holter monitor, transthoracic echocardiogram, cardiopulmonary exercise test, surgical records, and cardiac MRI. The first standard 12-lead ECG (25 mm/s, 10 mm/mV) obtained during the study period was considered the baseline ECG and was used for the assessment of QRS-f. The clinical data obtained within 12 months of the baseline ECG were analyzed as the baseline characteristics of the cohort. All-cause mortality was ascertained using the Mayo Clinic registration database and Accurint, an institutionally approved location service.

All ECGs were analyzed by 2 observers (N.M., M.F.) blinded to patients' characteristics and clinical data. Standard ECG voltages and intervals were collected and analyzed. In cases of discordant assessments, a third observer (A.D.) provided adjudication. The severity of QRS-f was assessed using similar methods as described by Bokma et al.[12] QRS-f was defined as an additional R wave (R′) or notch in the nadir of the S wave in ≥2 contiguous leads (right-sided/septal: aVR, V1, V2; anterior: V2–V5; lateral: I, aVL, V5, V6; or inferior: II, aVF, III) in patients with QRS duration <120 ms. In patients with right bundle branch block, QRS-f was defined as ≥3 R waves/notches in

the R/S complex (more than typical 2 in right bundle branch block) in ≥2 contiguous leads. In patients with paced QRS and premature ventricular complexes, QRS-f was defined as ≥3 notches in the R/S complex (Figure 1). The severity of QRS-f was classified based on the number of leads with QRS-f: none, mild (≤3 leads), moderate (4 leads), and severe (≥5 leads) (Figure S1). The severity of QRS-f (number of leads with QRS-f) was verified in a randomly selected sample (50% of the cohort) by one of the investigators (A.C.E.). To assess for the progression of QRS-f, we reviewed ECGs performed in patients who had at least 5 years of follow-up (ie, ECGs performed 5 years from the baseline ECG).

Statistical Analysis

Categorical variables were reported as counts (percentages), and continuous variables were reported as means±SDs or medians (interquartile ranges) for skewed data. Intraclass correlation coefficient was used to determine interobserver variability in the observed number of leads with QRS-f. Survival curves were constructed by the Kaplan–Meier method and compared by log-rank test using the time of baseline ECG as "time zero." Incremental Cox proportional hazards models were used to assess the relationship between severity of QRS-f and all-cause mortality, and the strength of association is expressed as hazard ratio (HR) and 95% CI. The Schoenfeld residual method was used for testing proportional hazard assumption. Incremental models were constructed as follows: model 1 was a univariable analysis showing the association between QRS-f and all-cause mortality (unadjusted risk). Model 2 included all variables in model 1 plus adjustment for the following ECG parameters: QRS duration, JT interval, and rhythm (sinus, paced rhythm, atrial fibrillation, and atrial flutter/tachycardia). Model 3 included all variables in model 2 plus adjustment for patient demographic

Figure 1. Top, Right bundle branch block with QRS fragmentation. The arrows are pointing at the third R-wave/notch. Bottom, Right bundle branch block without QRS fragmentation.

characteristics (current age, sex, age at the time of TOF repair, and type of TOF repair [transannular patch versus nontransannular patch]). Model 4 included all variables in model 3 plus adjustment for history of sustained ventricular tachycardia and/or defibrillator implantation, moderate RV dysfunction by qualitative assessment, and left ventricular ejection fraction <40%.

We also performed separate analyses using the severity of QRS-f as a categorical variable. Univariable analyses were performed using the patients without QRS-f as the reference group to compare the risk of all-cause mortality for the mild, moderate, and severe QRS-f groups. Multivariable analyses were then performed for each QRS-f group by adjusting for all of the potential confounders described above. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc). $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 465 patients were selected for the study (Figure S2). The age at the time of baseline ECG was 37 ± 14 years, age at the time of TOF repair was 5 (3–10) years, and 223 (48%) were men. The baseline characteristics and hemodynamic data of the cohort are shown in Tables 1 and 2, respectively. There were 41 (9%) patients with pacemakers, 58 (13%) patients with defibrillators, and 100 (22%) patients with history of ventricular tachycardia.

Electrocardiography

The baseline ECG showed the following rhythm: sinus, 407 (88%); atrial fibrillation, 17 (4%); atrial flutter/tachycardia, 20 (4%); and atrial and/or ventricular paced rhythm, 21 (5%). Heart rate was 74 ± 9 beats per minute, QRS duration was 148 ± 33 ms, and QRS morphology were as follows: normal, 9 (2%); incomplete right bundle branch block, 102 (22%) and right bundle branch block, 354 (76%). QRS-f was present in 161 (35%) patients, and severity of QRS-f was as follows: mild (QRS-f in ≤3 leads) in 43 (9%), moderate (QRS-f in 4 leads) in 77 (17%), and severe (QRS-f in ≥5 leads) in 41 (9%). The interobserver intraclass correlation coefficient for QRS-f was 0.81 (95% CI, 0.68–0.90) (Table S1). The patients with QRS-f had longer QRS durations (167 ± 31 versus 126 ± 24 ms, $P=0.001$) and were older at the time of TOF repair (7 ± 6 versus 4 ± 3 years, $P=0.023$) and at the beginning of the study period (40 ± 14 versus 32 ± 11 years, $P<0.001$). Of the 465 patients, 371 (80%) had ECG at 5 years of follow-up. Of these 371 patients, 39 (11%) showed progression of QRS-f, and these progressions were from no QRS-f to mild QRS-f in 34 patients and mild QRS-f to moderate QRS-f in 5 patients.

Outcomes

There were 55 deaths (12%) during a follow-up period of 13.6 ± 8.2 years. Among the 55 patients who died, the cause of death was congestive heart failure, 13 (24%); arrhythmic/sudden death, 11 (20%); postoperative death after cardiac surgery, 3 (6%); multisystem organ failure caused by sepsis, 4 (7%); malignancy, 5 (9%); gastrointestinal bleeding, 1 (2%); stroke, 2 (4%); and unknown/mixed, 16 (29%). The 20-year survival differed based on the severity of QRS-f (Figure 2). The 20-year survival in the patients without QRS-f was 97%, and using the group without QRS-f as the reference, the 20-year survival was similar in patients with mild QRS-f (97% versus 93%, $P=0.643$) but significantly lower in the groups with moderate QRS-f (97% versus 82%, $P=0.031$) and severe QRS-f (97% versus 33%, $P<0.001$), respectively. The severity of QRS-f was a risk factor (unadjusted risk) for all-cause mortality (HR, 2.72 per class [ie, degree of severity]; 95% CI, 2.11–3.56 [$P<0.001$]). The severity of QRS-f remained an independent predictor of all-cause mortality after adjustment for other ECG parameters, patient demographics, ventricular function, and history of atrial or ventricular arrhythmia (HR, 1.74 per class; 95% CI, 1.08–2.93 [$P=0.041$]) (Table 3). Separate models were constructed for subgroup analyses for patients with cardiac MRI data (Table S2) and patients with cardiac catheterization data (Table S3).

Using the group without QRS-f as the reference group, there was a significant difference in the unadjusted risk for all-cause mortality for the patients in the moderate QRS-f group (HR, 2.63; 95% CI, 1.73–3.64) and for the patients in the severe QRS-f group (HR, 3.29; 95% CI, 2.55–3.94) but not in the mild QRS-f group (HR, 1.65; 95% CI, 0.89–3.16). After multivariable adjustments, having moderate QRS-f (HR, 1.62; 95% CI, 1.13–2.98) and severe QRS-f (HR, 3.03; 95% CI, 1.96–5.11) remained significant risk factors for all-cause mortality.

Discussion

In this study we reviewed a cohort of 465 adult patients with TOF and showed that the severity of QRS-f, assessed using a standard 12-lead ECG, was an independent predictor of mortality. The importance of QRS duration in the risk stratification of patients with repaired TOF was described more than 2 decades ago, and QRS duration >180 ms is, almost universally, adopted as a risk factor for sudden death in the TOF population.[7,8] In the recent study, Bokma et al[12] reported that QRS-f was superior to QRS duration in the prediction of all-cause mortality in patients with TOF. We sought to validate this result by testing the ability of QRS-f to predict all-cause mortality in a different population of adult patients with TOF. The current study shows that QRS-f remained an independent risk factor for all-cause mortality, even after adjusting for QRS duration, patient demographics, and arrhythmia. The patients

Table 1. Baseline Characteristics

	All (N=465)	Alive (n=410)	Dead (n=55)	*P* Value
Age at the beginning of study, y	37±14	35±13	47±15	<0.001
Men, No. (%)	223 (48)	186 (45)	37 (67)	0.004
Body mass index, kg/m²	27±6	27±6	28±6	0.168
Body surface area, m²	1.9±0.3	1.8±0.2	1.9±0.2	0.475
Age at TOF repair, y	5 (3–10)	5 (2–8)	14 (5–34)	<0.001
Prior palliative shunt, No. (%)	181 (39)	148 (37)	33 (60)	0.004
Comorbidities, No. (%)				
Atrial fibrillation	118 (25)	82 (20)	36 (55)	<0.001
Atrial flutter/tachycardia	100 (22)	79 (19)	21 (38)	0.002
Hypertension	125 (27)	102 (25)	23 (42)	0.004
Hyperlipidemia	193 (42)	162 (40)	31 (56)	0.060
Coronary artery disease	57 (12)	38 (9)	19 (35)	0.011
Current or prior smoker	93 (20)	77 (18)	18 (32)	0.064
Diabetes mellitus	72 (16)	59 (15)	13 (23)	0.117
Sleep apnea	130 (28)	109 (27)	21 (38)	0.155
Prior stroke	41 (9)	33 (8)	8 (15)	0.943
NYHA class III/IV	73 (16)	59 (15)	14 (25)	0.002
Down syndrome	9 (2)	8 (2.0)	1 (1.8)	0.914
22q11 deletion	7 (1.5)	6 (1.5)	1 (1.8)	0.943
Laboratory tests				
Hemoglobin, g/dL	14.1±2.5	14.0±2.6	13.4±2.1	0.018
Creatinine, mg/dL	1.0±0.3	0.9±0.2	1.3±0.5	<0.001
NT-proBNP, pg/mL	255 (123–720)	223 (112–813)	313 (146–481)	0.348
Medications, No. (%)				
Diuretics	84 (18)	63 (15)	21 (38)	<0.001
β-Blockers	106 (23)	76 (19)	30 (54)	<0.001
Calcium channel blockers	59 (13)	39 (10)	20 (36)	<0.001
RAAS antagonist	87 (19)	68 (17)	19 (34)	0.002
Warfarin	41 (9)	29 (7)	12 (21)	0.001
Direct oral anticoagulants	3 (0.7)	2 (0.5)	1 (0.7)	0.330
Aspirin	116 (25)	97 (24)	19 (33)	0.118

Values are expressed as mean±SD or median (interquartile range) unless otherwise indicated. NT-proBNP indicates N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; RAAS, renin-angiotensin-aldosterone system; TOF, tetralogy of Fallot.

with moderate (or greater) QRS-f had reduced 20-year survival, and there was a 2-fold increase in the risk of all-cause mortality per unit increase in the severity of QRS-f (mild versus moderate versus severe fragmentation).

QRS Fragmentation as a Marker of Ventricular Dysfunction

Previous studies have shown that QRS-f involving the left precordial leads was associated with myocardial scar and left ventricular aneurysm in patients with coronary artery disease.[13,14] One of the studies evaluated 479 patients with coronary artery disease who underwent nuclear stress test and showed that the presence and severity of QRS-f correlated with the presence and extent of myocardial scar.[13] Similarly, QRS-f in the anterior leads has been shown to be associated with RV dysfunction and RV outflow tract aneurysm in patients with TOF.[15,16] It is postulated that QRS-f is a marker of myocardial fibrosis based on the observation of late gadolinium enhancement on cardiac MRI

Table 2. Hemodynamic Data

Echocardiography	All (N=465)	Alive (n=410)	Dead (n=55)	P Value
≥Moderate RV enlargement, No. (%)*	318 (68)	278 (68)	40 (72)	0.887
≥Moderate RV systolic dysfunction, No. (%)*	137 (30)	113 (28)	24 (43)	0.025
≥Moderate tricuspid regurgitation, No. (%)*	92 (20)	75 (18)	17 (31)	0.042
Tricuspid regurgitation velocity, m/s	3.1±0.7	3.1±0.7	3.2±0.8	0.786
Pulmonary valve peak velocity, m/s	2.5±0.9	2.5±0.9	2.5±1.0	0.218
TAPSE, cm	18±4	18±4	18±3	0.793
FAC, %	40±10	39±6	33±11	0.048
RV S′, cm/s	10±2	11±8	9±3	0.210
Medial E/e′	10±4	10±3	10±4	0.788
Lateral E/e′	7±3	10±3	10±4	0.788
LV ejection fraction, %	58±8	58±8	54±10	0.020
Moderate LV dysfunction (<40%), No. (%)	62 (13)	50 (12)	12 (22)	0.031
Magnetic resonance imaging (n=157)				
RVEDV index, mL/m^2	140±48	142±47	150±78	0.808
RVESV index, mL/m^2	80±37	81±37	89±49	0.693
RV ejection fraction, %	44±10	44±10	36±10	0.101
Catheterization (n=148)				
Right atrial pressure, mm Hg	11±6	10±5	16±7	<0.001
RVEDP, mm Hg	14±5	13±5	19±7	0.004
Mean PA pressure, mm Hg	24±9	23±8	30±11	0.005
LVEDP, mm Hg	16±5	15±5	21±7	0.003
Mean arterial pressure, mm Hg	88±13	89±13	83±14	0.103
Cardiac index, L/min×m^2	2.3±0.6	2.3±0.7	2.1±0.4	0.072
PVR index (WU×m^2)	4.5±3.0	4.3±3.1	5.3±2.4	0.129
Cardiopulmonary exercise test (n=177)				
Peak VO$_2$, mL/kg per min	22±7	22±7	22±8	0.995
Peak VO$_2$, % predicted	63±17	63±16	64±23	0.956
VE/VCO$_2$ nadir	28±4	28±4	30±4	0.377

Values are expressed as mean±SD unless otherwise indicated.
FAC indicates fractional area change; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; PA, pulmonary artery; PVR, pulmonary vascular resistance; RV, right ventricular; RVEDP, right ventricular end-diastolic pressure; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; TAPSE, tricuspid annular plane systolic excursion; VE/VCO$_2$, ventilatory equivalent for carbon dioxide; VO$_2$, oxygen consumption; WU×m^2, Wood units times meters squared.
*Quantitative assessment.

in patients with TOF and QRS-f.[16] In a retrospective study of 37 patients with repaired TOF who underwent cardiac MRI, QRS-f was present in 20 of the patients, and the presence and severity of QRS-f (number of leads involved) correlated with extent of late gadolinium enhancement and RV dilation and dysfunction.[16]

Myocardial scar/fibrosis is known to occur in patients with repaired TOF, and the presence of fibrosis is associated with RV dysfunction and poor cardiovascular outcomes such as heart failure, arrhythmia, and death.[17,18] Myocardial fibrosis results in deterioration of myocardial contractility and relaxation, and

may serve as a substrate for arrhythmias.[17,18] The accurate identification of myocardial fibrosis by cardiac MRI is therefore important in risk stratification of patients with TOF. Previous studies suggest that QRS-f can be used as a surrogate for myocardial fibrosis based on the correlation between the extent and location of myocardial fibrosis and extent and location of QRS-f.[13,14,17,18] The current study shows that the presence and extent of QRS-f, a surrogate for myocardial fibrosis, was predictive of all-cause mortality even after adjustment for other ECG parameters, patient demographics, and arrhythmia history. Our finding is consistent with, and to a large extent
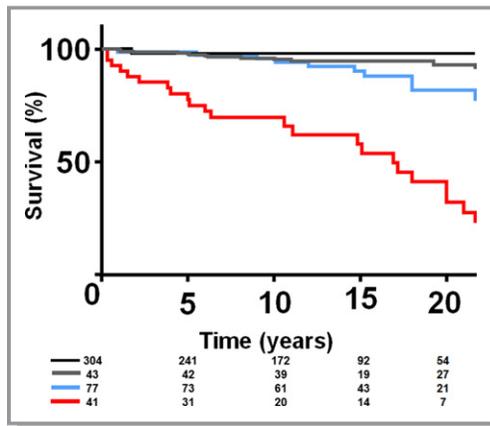
Figure 2. Kaplan–Meier curves comparing survival between patients without QRS fragmentation (QRS-f) (dark blue), mild QRS-f (red), moderate QRS-f (light blue), and severe QRS-f (green).

replicates, the results of the recent study by Bokma et al[12] despite differences in the demographic characteristics of both populations. In comparison to the Bokma et al cohort, the Mayo Clinic cohort had older patients with more comorbidities, which may explain the higher all-cause mortality (6% versus 12%). In spite of these differences in cohort characteristics and outcomes (mortality), both studies show that the severity of QRS-f was predictive of all-cause mortality in different populations of patients with TOF. Additionally, there was good interobserver correlation in the identification and quantification of the severity of QRS-f in both studies, which suggests that this technique can easily be integrated into daily clinical practice.

Clinical Impact and Future Directions

Several risk scores have been proposed for identifying patients with TOF at high risk for cardiovascular adverse events, and

Table 3. Incrementally Adjusted Risk for All-Cause Mortality

	HR (95% CI)	P Value
Model 1	2.72 (2.11–3.56)	<0.001
Model 2	2.67 (2.06–3.64)	<0.001
Model 3	2.22 (1.68–2.97)	0.014
Model 4	1.74 (1.08–2.93)	0.041

Model 1: unadjusted all-cause mortality risk based on the extent of QRS fragmentation (QRS-f). Model 2: includes all variables in model 1 plus adjustment for the following ECG parameters: QRS duration, JT interval, and rhythm (sinus, paced rhythm, atrial fibrillation, and atrial flutter/tachycardia). Model 3: includes all variables in model 2 plus adjustment for patient demographic characteristics (current age, sex, age at the time of tetralogy of Fallot [TOF] repair and type of TOF repair [transannular patch vs nontransannular patch]). Model 4: includes all variables in model 3 plus adjustment for history of sustained ventricular tachycardia and/or defibrillator implantation, moderate right ventricular dysfunction by qualitative assessment, and left ventricular ejection fraction <40%. Hazard ratio (HR) is expressed per incremental risk per class/extent of QRS-f (none, mild, moderate, severe).

some of these risk scores have good predictive value, at least in the population from which these variables were derived.[3,5–10] Unfortunately, some of the variables required to calculate these risk scores involve performing cardiac MRI and, sometimes, cardiac catheterization. Some of these tests are not performed during annual evaluation, making it difficult to provide ongoing risk stratification, which is important since patients' risk changes over time. ECG, on the other hand is inexpensive, readily available, easy to interpret by a general cardiologist (without any advanced training), and is recommended as part of routine annual evaluation in adults with congenital heart disease.[11,19] QRS-f from a standard ECG can therefore be applied for ongoing risk stratification in our patients, and may potentially be a trigger to prompt further investigation and treatment if progression of QRS-f is observed on serial ECGs.

Limitations

The major limitation of this study was that we used all-cause mortality instead of cardiovascular mortality as the primary end point. If QRS-f is postulated to be caused by myocardial fibrosis, which subsequently results in ventricular dysfunction and arrhythmia, then QRF-f should predict cardiovascular mortality without much association with noncardiovascular mortality. Unfortunately, the cause of death could not be reliably ascertained in ≈29% of the cohort because of the retrospective study design, and the small sample size prohibited more robust subgroup analysis. Another study limitation was that we did not correct for the length of time each patient had QRS-f before the initial ECG (thereby introducing lead time bias). In spite of these study limitations, findings from the current study and the prior study by Bokma et al show that the severity of QRS-f could independently predict all-cause mortality in different TOF populations.

Conclusions

The assessment of the presence and severity of QRS-f was feasible in all patients with TOF, was reproducible based on good interobserver correlation, and was independently predictive of all-cause mortality. A standard 12-lead ECG is inexpensive, easy to interpret, readily available, and routinely obtained during annual cardiac evaluation for patients with repaired TOF. Putting all of these together, QRS-f can provide readily accessible risk stratification for patients with TOF that may be complementary to existing risk scores, especially when the other risk scores may not be feasible because of lack of data. Further studies are required to evaluate temporal changes in the extent of QRS-f, and whether timely intervention (medical or surgical) based on changes in extent of QRS-f will improve outcomes.

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Disclosures

None.

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Supplementary Table 1: Inter-observer correlation for diagnosis of QRS-f

	Observer #1	Observer #2	ICC (95% CI)
No QRS-f	304	307	0.82 (0.89-0.88)
Mild QRS-f	43	58	0.70 (0.54-0.86)
Moderate QRS-f	77	71	0.80 (0.69-0.89)
Severe QRS-f	41	39	0.94 (0.92-0.96)
All QRS-f	**161**	**168**	**0.81 (0.68-0.90)**

QRS-f: QRS fragmentation; ICC: interclass correlation coefficient; CI: confidence interval
Note: the numbers in the different cells represent the count of patients for each severity of QRS-f by each of the observers

Supplementary Table 2: Incrementally Adjusted Risk for All-cause Mortality for patients with Cardiac MRI (N=157)

	HR (95% CI)	p
Model 1	2.81 (2.16- 3.66)	<0.001
Model 2	2.61 (2.00 - 3.61)	<0.001
Model 3	1.96 (1.22 - 2.85)	0.022
Model 4	1.71 (1.14 – 2.99)	0.033
Model 5	1.63 (1.06-2.61)	0.048

Model 1: unadjusted all-cause mortality risk based on the extent of QRS-f

Model 2: includes all variables in Model 1 plus adjustment for the following ECG parameters: QRS duration, JT interval and rhythm (sinus, paced rhythm, atrial fibrillation, and atrial flutter/tachycardia).

Model 3: includes all variables in Model 2 plus adjustment for patient demographic characteristics (current age, gender, age at the time of TOF repair and type of TOF repair [transannular patch vs non-transannular patch])

Model 4: includes all variables in Model 3 plus adjustment for history of sustained ventricular tachycardia and/or defibrillator implantation, moderate right ventricular dysfunction by qualitative assessment, and left ventricular ejection fraction <40%.

Model 5: includes all variables in Model 4 plus adjustment for right ventricular end-diastolic volume index > 150 ml/m2, right ventricular ejection fraction <40%, and left ventricular ejection fraction <40%.

HR: Hazard ratio; CI: Confidence interval. HR is expressed per incremental risk per class/extent of QRS-f (none, mild, moderate, severe)

Supplementary Table 3: Incrementally Adjusted Risk for All-cause Mortality for patients with Cardiac catheterization data (N=148)

	HR (95% CI)	p
Model 1	2.06 (2.23- 3.69)	<0.001
Model 2	2.43 (191 - 3.13)	<0.001
Model 3	2.06 (1.17 – 3.06)	0.037
Model 4	1.87 (1.05 – 2.61)	0.046
Model 5	1.72 (0.98-2.81)	0.055

Model 1: unadjusted all-cause mortality risk based on the extent of QRS-f

Model 2: includes all variables in Model 1 plus adjustment for the following ECG parameters: QRS duration, JT interval and rhythm (sinus, paced rhythm, atrial fibrillation, and atrial flutter/tachycardia).

Model 3: includes all variables in Model 2 plus adjustment for patient demographic characteristics (current age, gender, age at the time of TOF repair and type of TOF repair [transannular patch vs non-transannular patch])

Model 4: includes all variables in Model 3 plus adjustment for history of sustained ventricular tachycardia and/or defibrillator implantation, moderate right ventricular dysfunction by qualitative assessment, and left ventricular ejection fraction <40%.

Model 5: includes all variables in Model 4 plus adjustment for right ventricular end-diastolic pressure >14 mm Hg and   left ventricular end-diastolic pressure >16 mm Hg

HR: Hazard ratio; CI: Confidence interval. HR is expressed per incremental risk per class/extent of QRS-f (none, mild, moderate, severe)