Mechanism and Risk Factors for Death in Adults With Tetralogy of Fallot

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One of the goals of lifelong care in adults with tetralogy of Fallot (TOF) is early identification and treatment of patients at high risk for adverse events. Clinical risk stratification tools are critical for achieving this goal. We reviewed the *M*ayo *A*dult *C*ongenital *H*eart *D*isease database and identified 465 TOF patients (age 37 ± 14 years, men 223 [48%]) seen at Mayo Clinic Rochester between 1990 and 2017. The aim was to determine the risk factors for death and/or heart transplant through a comprehensive analysis of 8 groups of variables (demographics, co-morbidities, medications, heart rhythm, echocardiography, cardiac magnetic resonance imaging, cardiac catheterization, and cardiopulmonary exercise test data) using univariable and multivariable Cox proportional hazard models. The end point of death and/or transplant occurred in 57 (12%) patients during a follow-up of 13.6 ± 8.2 years, yielding an event rate of 0.9% per year. Independent risk factors were age >42 years, atrial fibrillation, ≥moderate QRS fragmentation, left ventricular ejection fraction <50%, right ventricular end-diastolic pressure >16 mm Hg, and left ventricle end-diastolic pressure >16 mm Hg. There is nearly a twofold increase in the risk of death and/or transplant per unit increase in number of risk factors (hazard ratio 1.92, 95% confidence interval 1.62 to 2.27, p <0.001). In conclusion, the current study provides risk stratification indices based on a comprehensive risk model of all clinical variables in an unselected TOF population. Further studies are required to determine whether interventions targeted at modifying these risk factors will alter the annual event rate. **(Am J Cardiol 2019;124:803−807)**

The elevated mortality in the tetralogy of Fallot (TOF) population is attributed to residual hemodynamic lesions and arrhythmogenic substrates present in some of these patients.[1−4] The goal of lifelong care in these patients is to facilitate early identification and treatment of residual/recurrent hemodynamic lesions, ventricular dysfunction, and arrhythmias.[5,6] Unfortunately the therapies required to address these lesions often carry some risk of complications, and some of the lesions tend to reoccur even after successful therapy, hence increasing the cumulative lifetime risk of procedural complications in these patients.[4,7] As a result, risk stratification is important in order to identify high-risk patients, in whom the benefit of therapy outweighs the potential risks of intervention.[8,9] A comprehensive risk model that can be applied to any TOF population is therefore important to mitigate this heterogeneity. The purpose of the study was to determine the risk factors for death and/or heart transplant based on a comprehensive analysis of demographic, clinical, electrophysiologic, and hemodynamic variables.

Methods

The Mayo Adult Congenital Heart Disease database was queried for patients (age ≥18 years) with repaired TOF that received care at Mayo Clinic Rochester, Minnesota from January 1, 1990 through December 31, 2017. The patients with pulmonary atresia were excluded. The Mayo Clinic Institutional Review Board approved this study and waived informed consent for patients that provided research authorization.

The following electronic health records were reviewed in details: clinical notes, electrocardiogram, Holter monitor, cardiac implantable electronic device interrogation reports, transthoracic echocardiograms, cardiac catheterization procedures, cardiopulmonary exercise test, surgical records, and cardiac magnetic resonance imaging reports.

The study end point was the occurrence of death (all-cause mortality) and/or heart transplant. The occurrence of heart transplant was ascertained by review of clinical notes, whereas all-cause mortality was ascertained using Mayo Clinic registration database and Accurint, an institutionally approved location service. Vital status was ascertained in 100% of the patients as of December 31, 2017.

In order to determine the risk factors for death and/or heart transplant, we performed a comprehensive analysis of 8 domains of clinically obtained variables: patient demographics, co-morbidities, medications, heart rhythm, echocardiograms, cardiac magnetic resonance imaging, cardiac catheterization, and cardiopulmonary exercise test data. For the patients with multiple visits and tests, we used data from

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the first visit and test/procedure as the baseline variable for analysis. QRS fragmentation was one of the heart rhythm variables analyzed, and QRS fragmentation was assessed using standard 12-lead electrocardiogram as previously described by Bokma et al.[10] QRS fragmentation was defined as an additional R wave (R') or notch in the nadir of the S wave in ≥2 contiguous leads 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 (i.e., more than 2 typically seen in right bundle branch block) in ≥2 contiguous leads. The extent 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).[10]

Data were presented as mean ± standard deviation, median (interquartile range) or number (%). Unpaired *t* test, Wilcoxon rank sum test, chi-square or Fisher's exact test were used as appropriate to compare between-group differences. First, we performed univariable analyses using a univariable Cox proportional hazard model that incorporated all 8 domains of clinically obtained variables (Supplementary Table 1). The association between variables and end point was expressed as hazard ratio (HR) and 95% confidence interval (CI). A p <0.050 was considered statistically significant, and the variables that reached statistical significance were then incorporated into a multivariable Cox model (Table 3). The single conditional imputation method was used to correct for missing data. The continuous variables used in the multivariable model were dichotomized using optimal cutoff points derived from receiver operating characteristic curve analyses. Again the variables with p <0.050 on multivariable analysis were considered statistically significant.

We assigned 1-point to each of the multivariable predictors based on HR. We then grouped all patients into subcategories based on the number of points (risk factors), and these groups were low risk (1 or 2 points), intermediate risk (3 or 4 points), and high risk (5 or 6 points). The patients without risk factors (no points) were used as the reference group. Transplant-free survival for the different groups was assessed by Kaplan-Meier method using the first clinic visit (baseline data) as the "time zero," and compared using log-rank test. All statistical analyses were performed with JMP software (version 13.0; SAS Institute Inc, Cary, North Carolina).

Results

A total of 465 patients were selected for the study. The age at baseline was 37 ± 14 years, 223 (48%) were men, and the age at the time of TOF repair was 5 (3 to 10) years of which 174 (37%) patients had transannular patch repair. The baseline characteristics, cardiac structure and function,

Table 1
Baseline characteristics

Variables	All (n = 465)	Alive (n = 408)	D/T (n = 57)	p
Age at beginning of study (years)	37 ± 14	35 ± 13	47 ± 15	<0.001
Male	223 (48%)	187 (46%)	36 (63%)	0.014
Body mass index (kg/m^2)	27 ± 6	27 ± 6	28 ± 6	0.168
Body surface area (m^2)	1.9 ± 0.3	1.8 ± 0.2	1.9 ± 0.2	0.475
Age at TOF repair (years)	5 (3−10)	5 (2−8)	14 (5−34)	<0.001
Prior palliative shunt	181 (39%)	149 (37%)	32 (56%)	0.004
Atrial fibrillation	118 (25%)	82 (20%)	36 (63%)	<0.001
Atrial flutter/tachycardia	100 (22%)	79 (19%)	21 (37%)	0.003
Hypertension	125 (27%)	102 (25%)	23 (40%)	0.014
Hyperlipidemia	193 (42%)	162 (40%)	31 (42%)	0.060
Coronary artery disease	57 (12%)	39 (10%)	18 (32%)	0.001
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 (14%)	0.999
NYHA III/IV	73 (16%)	59 (15%)	14 (25%)	0.002
Non-sustained ventricular tachycardia	100 (22%)	79 (19%)	21 (37%)	0.003
Sustained ventricular tachycardia	43 (9%)	35 (9%)	8 (14%)	0.242
Pacemaker implantation	41 (9%)	41 (10%)	10 (18%)	0.138
Defibrillator implantation	67 (14%)	53 (13%)	14 (25%)	0.049
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
Diuretics	84 (18%)	63 (15 %)	21 (37%)	<0.001
Beta blockers	106 (23%)	76 (19%)	30 (53%)	<0.001
Calcium channel blockers	59 (13%)	39 (10%)	20 (35%)	<0.001
RAAS antagonist	87 (19%)	68 (17%)	19 (33%)	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

D/T = death and/or heart transplant; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York heart Association; RAAS: renin angiotensin aldosterone system; TOF = tetralogy of Fallot.

Table 2
Hemodynamic data

Echocardiography	All (n = 465)	Alive (n = 408)	D/T (n = 57)	p
≥Moderate RV enlargement*	318 (68%)	278 (68%)	40 (70%)	0.887
≥Moderate RV systolic dysfunction*	137 (30%)	113 (28%)	24 (42%)	0.025
≥Moderate tricuspid regurgitation*	92 (20%)	75 (18%)	17 (30%)	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
Mitral medial E/e'	10 ± 4	10 ± 3	10 ± 4	0.788
Mitral lateral E/e'	7 ± 3	10 ± 3	10 ± 4	0.788
LV ejection fraction (%)	58 ± 8	58 ± 8	54 ± 10	0.020
Magnetic resonance imaging	(n = 164)			
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 (ml/m^2)	44 ± 10	44 ± 10	36 ± 10	0.101
Catheterization	(n = 154)			
Right atrial pressure (mmHg)	11 ± 6	10 ± 5	16 ± 7	<0.001
RVEDP (mm Hg)	14 ± 5	13 ± 5	19 ± 7	0.004
Mean PA pressure (mmHg)	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 = 181)			
Peak VO_2 (ml/kg/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

EDP = end-diastolic pressure; FAC = fractional area change; LV = left ventricle; PA = pulmonary artery; PVR = pulmonary vascular resistance; RV = right ventricle; RVEDV = right ventricular end-diastolic volume; RVESV = right ventricular end-systolic volume; TAPSE = tricuspid annular plane systolic excursion; WU × m^2 = Wood units × meter squared.

*Quantitative assessment; VO_2 = oxygen consumption; VE/VCO_2 = ventilatory equivalent for carbon dioxide.

exercise capacity and hemodynamic data of the cohort are shown in Tables 1 and 2.

The end point of death and/or transplant occurred in 57 (12%) patients during a follow-up of 13.6 ± 8.2 years. There were 54 deaths and the age at the time of death was 57 ± 15 years. The cause of death was congestive heart failure in 23 (43%) patients, arrhythmic/sudden death in 14 (26%) patients, postoperative death following cardiac surgery in 3 (6%) patients, multisystem organ failure due to sepsis in 4 (7%) patients, malignancy in 5 (9%) patients, stroke in 2 (4%) patients, gastrointestinal bleeding in 1 (2%) patient, and unknown/mixed in 3 (6%) patients. Three patients underwent heart transplant for end-stage heart failure and the average age at the time of transplant was 54 ± 5 years. One of the patients transplanted at age 55 years died 13 months later from suspected rejection and sepsis resulting in multisystem organ failure. In comparison to the rest of the cohort, the patients that reached end point of death and/or transplant were older, had more co-morbidities, were more likely to be on cardiac medications, and had worse invasive hemodynamic data (Tables 1 and 2).

Supplementary Table 1 shows a comprehensive univariable analysis incorporating all 8 domains of clinically obtained variables. Based on the results of univariable analysis, we constructed a multivariable risk model and the following risk factors for death and/or transplant were identified (Table 3): age >42 years (HR 1.86, 95% CI 1.24 to 2.03), atrial fibrillation (HR 1.84, 95% CI 1.06 to 3.17), ≥moderate QRS fragmentation (HR 1.92, 95% CI 1.47 to 2.81), left ventricular ejection fraction <50% (HR 1.39, 95% CI 1.08 to 2.31), right ventricular end-diastolic pressure >16 mm Hg (HR 1.41, 95% CI 1.02 to 1.22), and left ventricle end-diastolic pressure >16 mm Hg (HR 1.32, 95% CI 1.11 to 1.89).

We assigned 1-point per risk factors as described in the Methods section. Of the 465 patients in the study, 208 (45%) had no risk factors (0 point), 191 (41%) were classified as low risk (1 or 2 points/risk factors), 59 (13%) were classified as intermediate risk (3 or 4 points/risk factors), and 7 (1.5%) were classified high risk (5 or 6 points/risk factors). The 20-year transplant-free survival differed between the different risk groups: 98% versus 81% versus 55% versus 22%, respectively, p <0.001 (Figure 1). The event (death and/or transplant) rate for the entire cohort was 0.9% per year. Using the patients without risk factors as the reference group, the annual event rate was higher in the low risk group (0.2% vs 1.0% per year, p <0.001), intermediate risk group (0.2% vs 2.7% per year, p <0.001), and the high risk groups (0.2% vs 4.6% per year, p <0.001). There is nearly a twofold increase in the risk of death and/or transplant per unit increase in number of risk factors/points (HR 1.92, 95% CI 1.62 to 2.27, p <0.001).

Table 3
Multivariable analysis of risk factors for death and/or transplant

	HR (95% CI)	p
Age >42 years	1.86 (1.24−2.03)	0.002
Male gender	0.73 (0.41−1.26)	0.272
Age at TOF repair, >12 years	0.98 (0.96−1.01)	0.132
Prior palliative shunt	1.06 (0.61−1.85)	0.837
Atrial fibrillation	1.84 (1.06−3.17)	0.029
Coronary artery disease	1.40 (0.26−2.47)	0.254
NYHA III/IV	1.47 (0.81−2.57)	0.192
Diuretics	1.25 (0.71−2.16)	0.441
Beta and/or calcium channel blockers	1.66 (0.90−2.44)	0.269
RAAS antagonist	2.01 (0.62−6.32)	0.226
Warfarin	1.23 (0.61−2.28)	0.531
Heart rhythm		
Non-sustained ventricular tachycardia	0.86 (0.48−1.51)	0.615
QRS duration >180 ms	1.09 (0.68−1.98)	0.214
QRS fragmentation (≥moderate*)	1.92 (1.47−2.81)	0.001
FAC, <25%	0.98 (0.94−1.01)	0.098
LV ejection fraction, <50%	1.39 (1.08−2.31)	0.031
Right atrial pressure, >13 mmHg	1.03 (0.82−1.67)	0.241
RVEDP, >16 mm Hg	1.14 (1.02−1.22)	0.043
Mean PA pressure, >30 mmHg	0.97 (0.84−2.02)	0.432
LVEDP, >16 mm Hg	1.32 (1.11−1.89)	0.009

D/T = death and/or heart transplant; EDP = end-diastolic pressure; FAC = fractional area change; LV = left ventricle; NYHA = New York heart Association; PA = pulmonary artery; RAAS = renin angiotensin aldosterone system; RV = right ventricle; TOF = tetralogy of Fallot; ≥moderate × QRS fragmentation = QRS fragmentation in 3 or more leads of a standard electrocardiogram.

Discussion

In this retrospective study of 465 adult TOF patients, the event rate (death and/or transplant) was 0.9% per year. Based on a comprehensive analysis of patient demographics, comorbidities, medications, heart rhythm, echocardiography, cardiac magnetic resonance imaging, cardiac catheterization, and cardiopulmonary exercise test data, the study showed that age >42 years, atrial fibrillation, ≥moderate QRS fragmentation, left ventricular ejection fraction <50%, right ventricular end-diastolic pressure >16 mm Hg, and left ventricle end-diastolic pressure >16 mm Hg were independent risk factors for death and/or transplant.

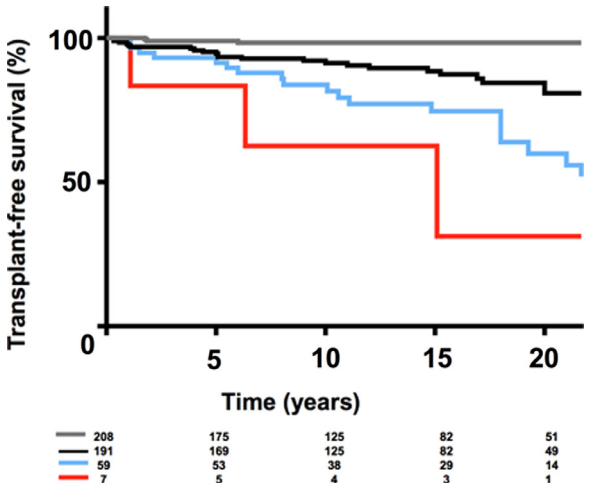

Figure 1. Kaplan-Meier curves comparing transplant-free survival between patients grouped according to number of risk factors/points: patients without risk factors (gray), low risk group (black), intermediate risk group (blue), and high risk group (red). Using the patients without risk factors as the reference group, survival is different between all the groups (p <0.001 for all comparisons). Color version of figure is available online.

There are several studies about risk stratification in adults with repaired TOF.[2,10−16] The largest and the most robust of these studies involved 873 patients from the INDICATOR multicenter cohort.[15] Of these 873 patients, 32 patients reached the primary end point of death and/or sustained ventricular tachycardia, and the risk factors for adverse event were right ventricular hypertrophy, right ventricular hypertension, left ventricular dysfunction, and atrial arrhythmia. There are some differences between the INDICATOR study and the current study both in terms of cohort demographics and study design. The median age in the INDICATOR study was 24 years and the end point of death and/or sustained ventricular tachycardia occurred in 4%. In contrast, our study was based on an older cohort (mean age 37 years) with a higher percentage (12%) of the patients reaching the end point of death and/or heart transplant most likely due to more co-morbidities such as hypertension, hyperlipidemia, diabetes, and coronary artery disease. In contrast to the INDICATOR study, the current study incorporated invasive hemodynamic data in the risk model, hence providing a more comprehensive risk analysis. As the adult congenital heart disease population ages over time, we anticipate that the patient demographics in the current study will be more reflective of the general TOF population, making the new risk model more applicable to this population.

Additionally, several other studies have reported risk stratification indices based on review of specific subsets of TOF patients.[2,8,12] A single-center study of 220 patients who underwent pulmonary valve replacement identified preoperative peak oxygen consumption as risk factor of early and late mortality.[8] Another study of 121 TOF patients (median age 33 years) with implantable cardioverter defibrillator used appropriate defibrillator shock as surrogate end point for death, and identified nonsustained ventricular tachycardia and elevated left ventricular end-diastolic pressure as risk factors for appropriate defibrillator shock.[12] Two other studies involving 413 TOF patients (median age 36 years) and 170 patients (median age 38 years) reported left ventricular dysfunction and QRS duration >180 milliseconds as risk factors for death respectively.[2,14]

The data from these previous studies form the bedrock of modern day clinical practice and the basis for clinical decision-making for adults with repaired TOF.[5,6,17] However most of these studies were based on data from specific subsets of TOF patients such as patients with implantable cardioverter defibrillator or patients who underwent pulmonary valve replacement thereby introducing some selection bias.[8,12] Additionally, the risk models were based on some, but not all of the patient's clinical variables. These factors limit the clinical application of these risk models only to certain subset of patients depending on how closely the demographics of the population of interest mirror that of the population from which the risk models were derived. In the current study, we reviewed an unselected cohort of adults with repaired TOF followed in a single tertiary center for nearly 3 decades, and incorporated all clinical variables into

the risk model. Based on this design, we anticipate that the risk model is more applicable to any adult TOF cohort, and perhaps eliminate some of the heterogeneity in risk stratification of TOF patients.

This is a retrospective single-center study and hence has certain inherent limitations. Despite our effort to eliminate selection bias by including all patients, and to control for confounders through comprehensive multivariable risk models, the study is still limited by referral bias and other potential founding factors not completely eliminated by multivariable analysis. Although we included all clinical variables in the model, certain variables such as invasive hemodynamics, exercise data, and cardiac magnetic resonance imaging data were not available in all patients. We tried to correct for these missing variables using the single conditional imputation method in the multivariable model. Regardless of these potential limitations, the study provides a comprehensive risk model that should make it adaptable to different TOF populations.

In conclusion, based on a comprehensive review of all clinical variables, the present study showed that age >42 years, atrial fibrillation, ≥moderate QRS fragmentation, left ventricular ejection fraction <50%, right ventricular end-diastolic pressure >16 mm Hg, and left ventricle end-diastolic pressure >16 mm Hg were independent risk factors for death and/or transplant. In a TOF population with an annual event rate of 0.9% per year, these risk factors allow for cohort stratification into low-, intermediate-, and high risk subsets.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.048.

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