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Integrated Clinical and Magnetic Resonance Imaging Assessments Late After Fontan Operation

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ABSTRACT

BACKGROUND Several clinical and cardiac magnetic resonance (CMR)-derived parameters have been shown to be associated with death or heart transplant late after the Fontan operation.

OBJECTIVES The objective of this study was to identify the relative importance and interactions of clinical and CMR-based parameters for risk stratification after the Fontan operation.

METHODS Fontan patients were retrospectively reviewed. Clinical and CMR parameters were analyzed using univariable Cox regression. The primary endpoint was time to death or (listing for) heart transplant. To identify the patients at highest risk for the endpoint, classification and regression tree survival analysis was performed, including all significant variables from Cox regression.

RESULTS The cohort consisted of 416 patients (62% male) with a median age of 16 years (25th, 75th percentiles: 11, 23 years). Over a median follow-up of 5.4 years (25th, 75th percentiles: 2.4, 10.0 years) after CMR, 57 patients (14%) reached the endpoint (46 deaths, 7 heart transplants, 4 heart transplant listings). Lower total indexed end-diastolic volume (EDV_i) was the strongest predictor of transplant-free survival. Among patients with dilated ventricles ($EDV_i \geq 156$ ml/$BSA^{1.3}$), worse global circumferential strain (GCS) was the next most important predictor (73% vs. 44%). In patients with smaller ventricles ($EDV_i < 156$ ml/$BSA^{1.3}$), New York Heart Association functional class ≥II was the next most important predictor (30% vs. 4%).

CONCLUSIONS In this cohort of patients late after Fontan operation, increased ventricular dilation was the strongest independent predictor of death or transplant (listing). Patients with both ventricular dilation and worse GCS were at highest risk. These data highlight the value of integrating CMR and clinical parameters for risk stratification in this population. (J Am Coll Cardiol 2021;77:2480–9) © 2021 by the American College of Cardiology Foundation.

Patients with a functional single ventricle are usually palliated with the Fontan procedure, whereby the systemic venous return is directly routed to the pulmonary circulation without the benefit of a subpulmonary ventricle (1). Despite important improvements in mortality and morbidity over the years, adverse outcomes are increasingly common as Fontan patients enter adulthood (2,3). Several risk factors for death or heart transplant have been identified, including clinical parameters, such as history of protein-losing enteropathy (3) and congestive heart failure (4,5). Reported ventricular parameters associated with this endpoint include right-dominant ventricular morphology (6,7), increased indexed end-diastolic volume (EDV_i) of the functional single ventricle (8), increased ventricular mass, worse ventricular strain (9), and worse functional single ventricle global function index (SVGFI) (10). Cardiac magnetic resonance (CMR) remains the preferred modality for the assessment of ventricular

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size and function in these patients (11). Although some risk factors for death or heart transplant have been identified, information is lacking on their relative importance and how these variables relate to different subgroups.

Classification and regression tree (CART) analysis is a statistical tree-building technique, with the potential to yield clinically practical information for risk stratification (12). CART analysis allows identification of patient characteristics at highest risk for the endpoint without any prespecification of the variable interactions. Creation of more accurate risk stratification models for death or transplant after Fontan is critical to identify patients who need early intervention, more intense monitoring, or early consideration of heart transplantation. The aim of this study was to identify the relative importance and interactions of clinical and CMR parameters for risk of death or transplant after the Fontan operation using CART analysis.

SEE PAGE 2490

METHODS

PATIENTS. All Fontan patients who had a postoperative CMR study at Boston Children's Hospital between March 2019 and January 2002 were retrospectively reviewed. Patients were included for analysis if they had a minimum of 1 year of follow-up since the CMR or if they reached the defined endpoint. Patients were excluded from analysis if steady-state free precession (SSFP) cine imaging was not performed or if technical limitations precluded reliable measurements of ventricular size and function parameters. The Boston Children's Hospital Committee on Clinical Investigation approved this retrospective study and waived the requirement for informed consent.

CLINICAL PARAMETERS. Demographic and clinical data, including underlying diagnoses, were abstracted from the medical records. The type of surgical palliation was classified as lateral tunnel, right atrium-to-pulmonary artery, right atrium-to-right ventricle, or extracardiac conduit. Additional parameters included age at Fontan, time from Fontan to CMR, duration of post-CMR follow-up, history of Fontan revision, and number and type of surgical and catheterization interventions before CMR, including age at volume-unloading surgery (e.g., bidirectional Glenn). Arrhythmia history was compiled by review of Holter monitors, electrocardiograms, electrophysiology catheterizations, and clinic notes. Episodes of atrial ectopy, atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular ectopy, nonsustained ventricular tachycardia (≥3 beats lasting <30 s), sustained ventricular tachycardia (lasting ≥30 s), and arrhythmia-related cardiac arrest were recorded. Other clinical variables included New York Heart Association (NYHA) functional class and history of protein-losing enteropathy, stroke, thrombus, seizures, and liver disease.

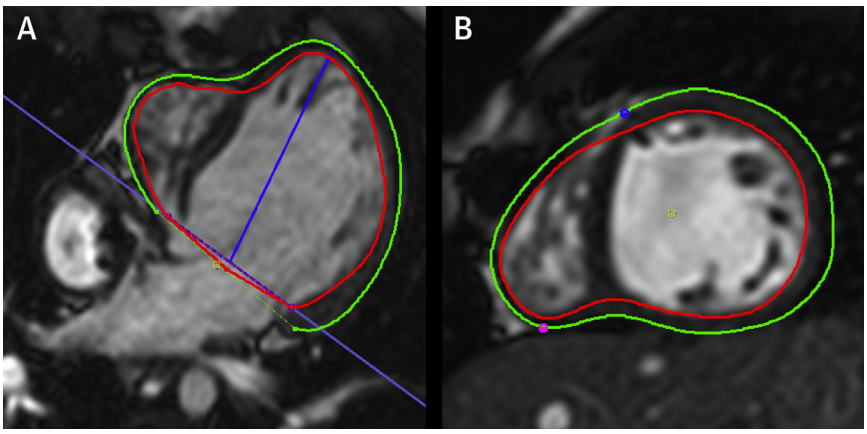
CMR TECHNIQUES. CMR studies were performed with 1.5-Tesla scanners (GE Medical Systems, Milwaukee, Wisconsin, and Philips Healthcare, Best, the Netherlands). The details of the CMR protocols used in our unit for assessment of patients after the Fontan operation have been published previously (13,14). Briefly, ventricular assessment was performed by an electrocardiogram-gated, SSFP cine imaging in a ventricular long- and short-axis planes encompassing the atrioventricular junction through the cardiac apex.

CMR DATA ANALYSIS. If a patient had multiple CMR studies, the earliest technically adequate study was used for analysis to maximize follow-up duration. All CMR data were abstracted from the clinical reports. Ventricular volumes and function were measured by manual tracing of endocardial and epicardial borders on each short-axis slice at end-diastole (maximal area) and end-systole (minimal area) as previously described by our institution (14). Ventricular morphology was classified as left ventricular, right ventricular, or biventricular according to previously published criteria (15). Ventricular type was classified as biventricular if the smaller ventricle contributed to the systemic circulation, defined as EDV ≥25% of combined ventricular EDV or EDV Z-score ≥−4. Published normative data from Alfakih et al. (16) were used for ventricular Z-score calculations. Regardless of the ventricular morphology type, when 2 ventricles contributed to the systemic circulation, ventricular volumes and mass were summated to allow for calculation of total functional EDV, end-systolic volume (ESV), ejection fraction, stroke volume, ventricular mass, and mass/volume ratio. Due to the known nonlinear associations of volumetric parameters to body surface area (BSA), EDV, ESV, stroke volume, and ventricular mass were indexed to BSA raised to the 1.3 power (8,17). Assessment of atrioventricular valve and aortic valvar regurgitation by phase-contrast imaging was performed using QFlow (Medis Medical Imaging Systems, Leiden, the Netherlands). The degree of regurgitation was categorized as significant (greater than or equal to moderate or a

ABBREVIATIONS AND ACRONYMS

BSA = body surface area
CART = classification and regression tree
CMR = cardiac magnetic resonance
EDV = end-diastolic volume
ESV = end-systolic volume
GCS = global circumferential strain
GLS = global longitudinal strain
NYHA = New York Heart Association
SSFP = steady-state free precession
SVGFI = single ventricle global function index

FIGURE 1 Fontan Strain Measurement Technique



(A and B) The contours for analysis for longitudinal and circumferential strain, respectively. In patients with smaller or 2 ventricles, contours were drawn along the ventricle free wall, therefore including both ventricles.

regurgitation fraction ≥20%) and not significant (mild or lower). All analyses were performed using commercially available software (QMass, Medis Medical Imaging Systems, and cvi42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). Internal reproducibility studies showed that identical contours imported across the 2 software programs produced no statistically significant differences.

STRAIN AND OTHER VENTRICULAR FUNCTION ANALYSES. Global circumferential strain (GCS) and global longitudinal strain (GLS) were re-measured and calculated on the SSFP ventricular mid-cavity short-axis, and 4-chamber images using feature tracking analysis (cvi42, Circle Cardiovascular Imaging Inc.). Details of the strain analysis methodology and reproducibility in our laboratory have been published (18). The endocardial border of the combined ventricular unit including both the dominant and hypoplastic ventricle was manually traced (19), and the software automatically tracked the border throughout the cardiac cycle (**Figure 1**). If tracking was judged to be suboptimal by visual inspection, the endocardial border was retraced until satisfactory tracking was accomplished. GCS and GLS have negative numeric values. Throughout the article, a numerically more negative value represents greater shortening and signifies better GCS/GLS, whereas a numerically less negative value signifies worse GCS/GLS.

The SVGFI was calculated as: (ventricular stroke volume × 100) / (ventricular mean cavity volume + total ventricular myocardial volume) (10). Ventricular mean cavity volume was defined as ([end-diastolic volume + end-systolic volume] /2). The ventriculoarterial coupling ratio was calculated as the ratio of arterial elastance (E_a) to ventricular end-systolic elastance (E_{es}), where E_a = mean arterial blood pressure/ventricular stroke volume and E_{es} = mean arterial blood pressure/end-systolic volume) (20). Two measures of myocardial stress were calculated: end-systolic wall stress and global average midwall end-systolic fiber stress (9).

STUDY ENDPOINT. The primary clinical endpoint was time to all-cause mortality and listing for or receiving a heart transplant. For survival analyses, follow-up was measured from the date of CMR to either the first occurrence of the endpoint or the last known follow-up date with documentation of transplant-free survival. Any reference in this manuscript to transplant-free survival or death/transplant includes patients who met any of the 3 criteria of our composite endpoint (listing for heart transplant, receiving a heart transplant, or death).

STATISTICAL ANALYSIS. Continuous variables were summarized as median (25th, 75th percentiles) or mean ± SD. Comparison between those who reached the endpoint and those who did not was done using a Mann-Whitney *U* test for continuous variables. Categorical data were summarized using frequencies and percentages, and comparisons were performed using the chi-square or Fisher exact test. All statistical tests were 2-sided and results were considered statistically significant if $p < 0.05$.

CART survival analysis was performed using the rpart package in R (i386 version 3.6.2) to determine which variables, when considered simultaneously, place a patient at higher risk for death or heart transplant or listing (12). All parameters with a $p < 0.1$ by univariable Cox regression analysis were included as candidate predictors in the CART model. All parameters were selected ahead of time. CART begins by partitioning data into smaller sections to provide a clearer view of interactions among variables (21,22). The algorithm selects the predictor that provides the best or "optimal" split, such that each of the 2 subgroups is more homogeneous with respect to the outcome. For continuous variables, the algorithm selects the cutoff value that best discriminates between outcomes. This process was repeated on each derived subset in an iterative manner (i.e., recursive partitioning) without bagging. In addition, multivariate Cox regression analysis was performed including all parameters with $p < 0.1$ by univariable analysis. Backward selection was used with $p > 0.05$ as removal criterion. The accuracy of the 2 models was compared using the area under the receiver operating characteristic curve.

Cutoff values established with CART analysis were used to construct binary variables for the most important predictors. Cumulative survival functions were made with Kaplan-Meier estimates using the variables from the final CART model and event times were compared with the log rank test. Data analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago, Illinois) and R i386 version 3.6.2 (R Foundation, Vienna, Austria).

RESULTS

PATIENT CHARACTERISTICS AND CMR DATA. A total of 599 patients met the initial screening criteria. Of these, 111 (19%) patients were excluded because they did not have a fully measurable quantitative assessment of ventricular size and function, mostly due to metallic implant-related artifacts. An additional 72 patients were excluded due to a follow-up time of <1 year. The final cohort consisted of 416 Fontan patients. The excluded versus included patient groups were similar with regard to demographic and clinical parameters, except that the prevalence of protein-losing enteropathy was higher among excluded patients (11% vs. 5%, $p = 0.009$). The demographic and clinical characteristics of the study cohort are summarized in Table 1. The patients had a

TABLE 1 Demographic and Clinical Characteristics

	All Patients (N = 416)	Transplant-Free Survival (n = 359)	Death or Transplant (n = 57)	p Value
Male	257 (62)	224 (62)	33 (57)	0.42
Age at Fontan, yrs	2.9 (2.2, 4.5)	2.8 (2.1, 4.2)	3.8 (2.4, 11.3)	0.007
Age at CMR, yrs	15.6 (10.8, 22.3)	15.6 (11.2, 22.0)	15.6 (8.1, 28.6)	0.52
Time from Fontan to CMR, yrs	12.6 (7.9, 17.2)	12.7 (8.3, 17.0)	12.0 (4.2, 18.0)	0.15
Body surface area at CMR, m^2	1.5 (1.1, 1.8)	1.5 (1.1, 1.8)	1.5 (0.9, 1.9)	0.94
Weight, kg	52.9 (31.0, 68.0)	53.0 (31.9, 67)	48.9 (22.6, 74.2)	0.23
Height, cm	157 (135, 167)	157 (138, 166)	157 (121, 169)	0.70
Heart rate, beats/min	82 (70, 93)	81 (69, 92)	88 (73, 101)	0.001
MAP, mm Hg	77 (69, 85)	78 (69, 85)	74 (66, 84)	0.02
Cardiac diagnosis				0.14
HLHS	109 (26)	88 (25)	21 (36)	
Tricuspid atresia	75 (18)	63 (18)	12 (21)	
Double-inlet left ventricle	54 (13)	50 (14)	4 (7)	
Double-outlet right ventricle	53 (13)	50 (14)	3 (5)	
Unbalanced AV canal	35 (8)	29 (8)	6 (11)	
Complex 2 ventricle	29 (7)	27 (8)	2 (3)	
Hypoplastic TV/RV	26 (6)	23 (6)	3 (5)	
Pulmonary atresia/IVS	19 (5)	17 (5)	2 (3)	
Mitral atresia with VSD	16 (4)	12 (3)	4 (7)	
Heterotaxy	54 (13)	45 (13)	9 (16)	0.34
Ventricular morphology				0.14
Left ventricle	150 (36)	136 (38)	14 (25)	0.03
Right ventricle	161 (39)	136 (38)	25 (44)	0.07
Biventricular	105 (25)	87 (24)	18 (32)	0.73
Surgical history				
Neonatal surgery	282 (68)	248 (69)	34 (60)	0.39
Bidirectional Glenn	294 (71)	256 (71)	38 (67)	0.61
Fontan revision (post CMR)	30 (7)	20 (6)	10 (17)	0.03
Intervention for non-neonatal aortic arch obstruction	56 (14)	50 (14)	6 (11)	0.75
Fontan Type				0.004
Lateral tunnel	300 (72)	263 (73)	37 (64)	0.01
Extracardiac conduit	57 (14)	51 (14)	6 (11)	0.14
RA-PA	49 (12)	40 (11)	9 (16)	0.07
RA-RV	10 (2)	5 (1)	5 (9)	0.18
Morbidity				
Liver disease	113 (27)	94 (26)	19 (33)	0.90
NYHA functional class ≥II	101 (24)	62 (17)	39 (68)	<0.001
Thrombus	80 (19)	58 (16)	22 (39)	<0.001
Seizures	50 (12)	41 (12)	8 (14)	0.92
Stroke	69 (17)	52 (15)	17 (30)	0.02
Protein-losing enteropathy	21 (5)	10 (3)	11 (20)	<0.001
Atrial flutter/fibrillation	96 (23)	72 (20)	24 (42)	0.04
Nonsustained VT	54 (13)	40 (11)	14 (25)	0.12
Sustained VT	11 (3)	4 (1)	7 (12)	<0.001
Pacemaker (post MRI)	51 (12)	39 (11)	12 (21)	0.454

Values are n (%) or median (25th, 75th percentile). p values represent univariable Cox regression analysis.

AV = atrioventricular; CMR = cardiac magnetic resonance; HLHS = hypoplastic left heart syndrome; IVS = intact ventricular septum; MAP = mean arterial blood pressure; MRI = magnetic resonance imaging; NYHA = New York Heart Association; PA = pulmonary artery; RA = right atrium; RV = right ventricle; TV = tricuspid valve; VSD = ventricular septal defect; VT = ventricular tachycardia.

TABLE 2 Comparison of CMR Parameters Between Patients With and Without the Endpoint

	All Patients (N = 416)	Transplant-Free Survival (n = 359)	Death or Transplant (n = 57)	p Value
EDV_i, ml/BSA$^{1.3}$	97 (78, 121)	95 (78, 116)	126 (88, 169)	<0.001
ESV_i, ml/BSA$^{1.3}$	45 (33, 62)	44 (33, 58)	55 (37, 96)	<0.001
SV_i, ml/BSA$^{1.3}$	56 (47, 66)	55 (47, 64)	63 (53, 79)	<0.001
CI, l/min/BSA$^{1.3}$*	2.67 (2.2, 3.3)	2.67 (2.2, 3.9)	2.54 (1.9, 3.7)	0.83
EF, %	54 (47, 59)	54 (47, 59)	50 (39, 59)	<0.001
$Mass_i$, g/BSA$^{1.3}$	50 (42, 64)	49 (41, 61)	67 (46, 91)	<0.001
M/V ratio, g/ml	0.52 (0.43, 0.65)	0.53 (0.44, 0.65)	0.49 (0.40, 0.64)	0.74
≥Moderate AVVR	58 (14)	45 (13)	13 (23)	0.03
≥Moderate AR	13 (3)	10 (3)	3 (5)	0.33
GLS, %†	−13.5 (−15.9, −11.0)	−13.7 (−16.0, −11.4)	−12.5 (−15.7, −9.3)	0.05
GCS, %†	−13.1 (−15.4, −10.7)	−13.2 (−15.7, −11.1)	−11.7 (−14.6, −7.5)	<0.001
ESWS, kPa	16.0 (12.5, 21.9)	15.9 (12.5, 21.6)	16.3 (12.4, 24.6)	0.05
$ESFS_{ga}$, kPa	21.0 (17.2, 26.8)	21.0 (17.3, 26.5)	21.2 (16.5, 29.0)	0.10
VAC ratio	0.85 (0.69, 1.13)	0.84 (0.59, 1.11)	1.0 (0.71, 1.58)	<0.001
SVGFI, %	42 (36, 49)	42 (37, 49)	38 (28, 49)	<0.001

Values are median (25th, 75th percentile) or n (%). p values represent univariate Cox regression analysis. *n = 290. †n = 395.

AR = aortic or neo-aortic valve regurgitation; AVVR = atrioventricular valve regurgitation; BSA = body surface area; CI = cardiac index; EDV = end-diastolic volume; ESFSga = global average midwall end-systolic fiber stress; ESV = end-systolic volume; ESWS = end-systolic wall stress; SV = stroke volume; SVGFI = single ventricle global function index; VAC ratio = ventriculoarterial coupling ratio.

median age at CMR of 15.6 years (25th, 75th percentiles: 10.8, 22.3 years) and a median interval between Fontan surgery and CMR of 12.6 years (25th, 75th percentiles: 7.9, 17.2 years). The most common type of Fontan operation was lateral tunnel (72%). The CMR data are summarized in Table 2.

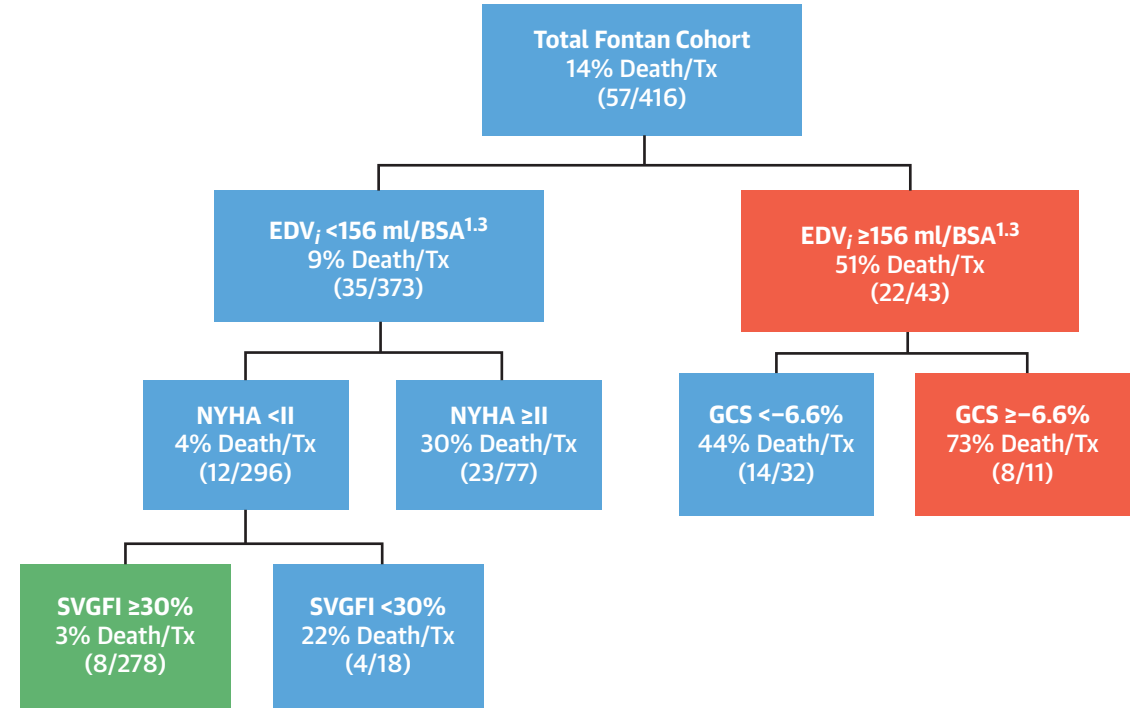
DEATH OR TRANSPLANT. Of the 416 patients, 57 (14%) reached an endpoint (death 46, heart transplant 7, and heart transplant listing 4) during a median follow-up of 5.4 years (25th, 75th percentiles: 2.4, 10.0 years). Causes of death included heart failure (n = 15), presumed arrhythmia-related cardiac arrest (n = 13), complications immediately after surgical procedures (n = 5), complications after heart transplantation (n = 4), sepsis (n = 3), unknown (n = 2), embolic stroke (n = 1), cerebral hemorrhage (n = 1), pulmonary hemorrhage (n = 1), and trauma (n = 1). Cumulative freedom from the endpoint after CMR for the entire cohort was 96% at 1 year and 89% at 5 years.

In Table 1, patient characteristics and clinical variables are compared between patients who did and did not meet the endpoint. Age at Fontan completion, heart rate, Fontan type, NYHA functional class ≥II, history of thrombus, stroke, protein-losing enteropathy, atrial arrhythmia, and sustained ventricular tachycardia were associated with the endpoint by univariable Cox analysis. Era testing was performed for decade of Fontan procedure and for 5-year intervals of date of CMR. Fontan era was significant at a univariable level ($p < 0.007$); however, CMR era was not. Comparisons of CMR parameters between patients with and without the endpoint are shown in Table 2. The following CMR variables were associated with the endpoint: higher EDV_i, ESV_i, stroke volume, indexed ventricular mass, and ventriculoarterial coupling ratio, as well as lower ejection fraction, GLS, GCS, end-systolic wall stress, and SVGFI. An overview of all variables significantly associated with the endpoint is shown in Supplemental Table 1.

Using the CART method, ventricular dilation, with a cutoff of EDV_i ≥156 ml/BSA$^{1.3}$, emerged as the strongest predictor of death or transplant in this population (Central Illustration). In patients with dilated ventricles, worse GCS, defined as worse than −6.6%, was the next most important predictor. Overall, 73% of the patients with dilated ventricles and worse GCS died, underwent or were listed for heart transplantation. In patients with smaller ventricles (EDV_i <156 ml/BSA$^{1.3}$), NYHA functional class ≥II was the next most important discriminator. Asymptomatic (NYHA functional class I) patients with smaller ventricles had only a 4% incidence of death, transplantation, or listing for transplant during the follow-up period. The Kaplan-Meier plot showing freedom from death or (listing for) heart transplant stratified by EDV_i ≥156 ml/BSA$^{1.3}$ (representing the first level of the CART model) is shown in Figure 2. Kaplan-Meier survival curves using the second-level subgroups informed by the CART model are shown in Figure 3.

Among the asymptomatic patients with no or mild ventricular dilation (n = 296), SVGFI was the next most important discriminator (Central Illustration). Asymptomatic patients with smaller ventricles and

CENTRAL ILLUSTRATION Classification and Regression Tree



Meyer, S.L. et al. J Am Coll Cardiol. 2021;77(20):2480–9.

This diagram depicts the risk stratification for death or heart transplant for Fontan patients on the basis of the cutoff values that have been established through classification and regression tree analysis. Values are expressed as number of patients with death or need for transplant/all patients in subgroup. The **red boxes** indicate the patient groups that are at high risk for death or transplant, whereas the **green box** indicates the patient group at low risk. BSA = body surface area; EDV$_i$ = indexed end-diastolic volume; GCS = global circumferential strain; NYHA = New York Heart Association; SVGFI = single ventricle global function index; Tx = Transplant (listing for or receiving)

better SVGFI (≥30%) had only a 3% (8 of 278) incidence of death, transplantation, or listing for transplant during the follow-up period.

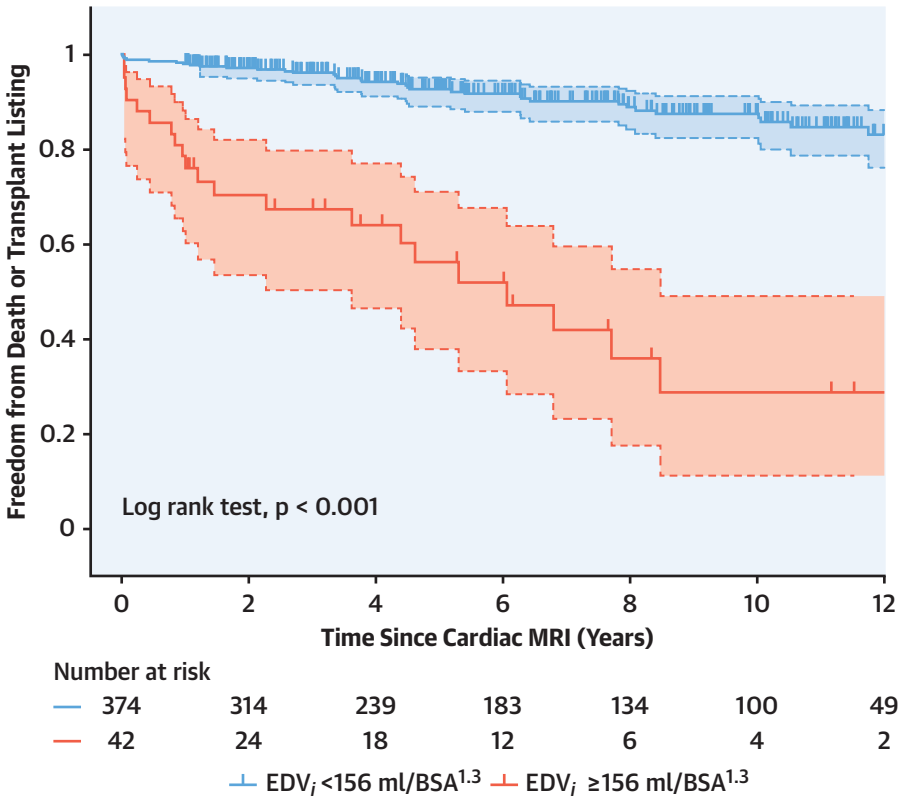
For sake of comparison of statistical approach, a multivariate Cox model was also performed showing the independent associations of EDV$_i$, ESV$_i$, GCS, ventriculoarterial coupling ratio, protein-losing enteropathy, and NYHA functional class ≥II as shown in Supplemental Table 2. Both the CART model as well as the multivariate Cox model showed good predictability (area under the curve 0.819; 95% confidence interval [CI]: 0.747 to 0.891; $p < 0.001$, and 0.829; 95% CI 0.761 to 0.897; $p<0.001$, respectively).

DISCUSSION

In this large cohort of patients late after the Fontan operation, lower CMR-derived EDV$_i$ emerged as the strongest independent predictor of transplant-free survival. Furthermore, in patients with moderate or worse ventricular dilation, worse GCS had additional discriminating power for predicting death, heart transplant, or listing for transplant. Asymptomatic patients with smaller ventricles had the highest transplant-free survival. These data introduce important interactions between ventricular dilation, measures of systolic function, and symptoms in this population and highlight the utility of CMR for risk stratification.

To date, only a few studies have examined imaging parameters and their predictive value for clinical outcomes in Fontan patients. This study integrated CMR and clinical parameters in a large cohort of Fontan survivors and created a practical decision tree to predict adverse clinical outcomes using CART analysis. CART models identify the relative importance of various risk factors without prespecification of possible interactions and are preferable to

FIGURE 2 Kaplan-Meier Survival Curves Stratified by EDV_i

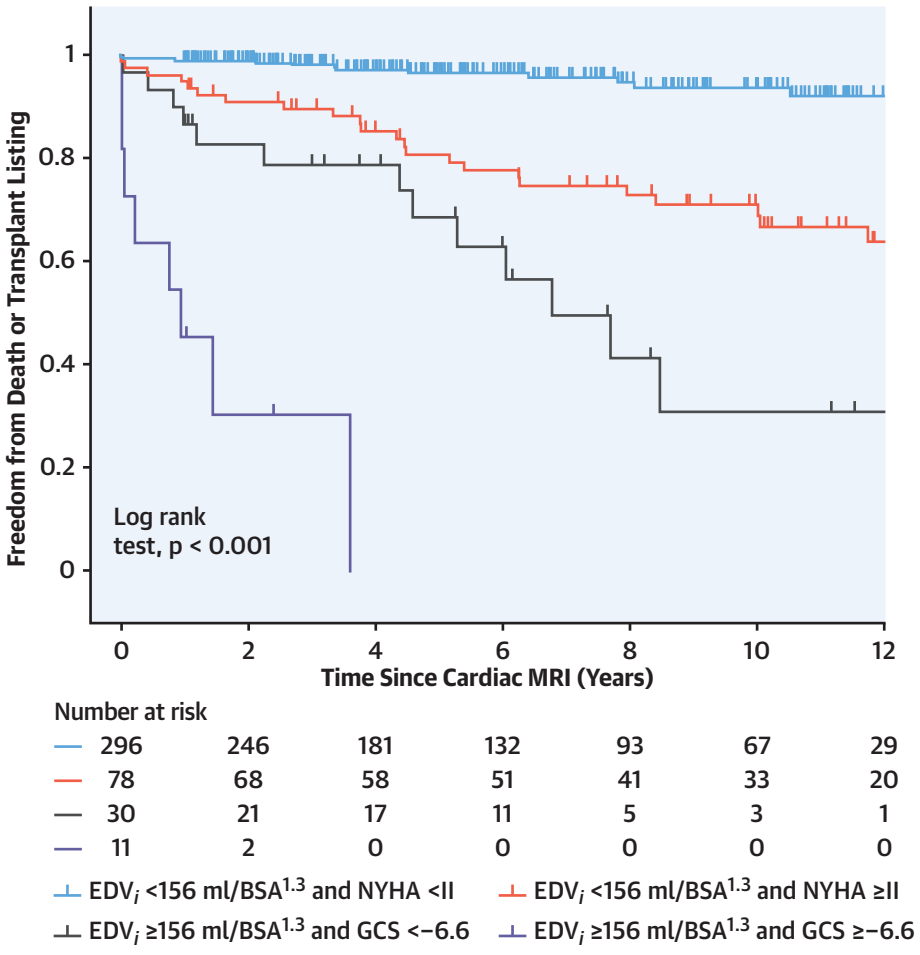


Patients are stratified by indexed end-diastolic volume equal/higher or lower than 156 ml/$BSA^{1.3}$. BSA = body surface area; EDV_i = indexed end-diastolic volume.

parametric approaches for identifying homogeneous subgroups due to greater resistance to the effects of multicollinearity, outliers, as well as their ability to examine higher-order interactions among predictors (21).

We have previously reported that dilation of the functional single ventricle and worse GCS are associated with adverse clinical outcomes in this population (8,9). The current study builds on these observations, and, to our knowledge, is the largest study using clinical and CMR parameters. It is interesting to note that GCS is associated with death, heart transplant, or listing for transplant, whereas GLS is less significant. One hypothesis to explain this distinction may be due to sphericity, as qualitatively many functional single ventricles are more globular in shape. Unfortunately, those measurements were not in this data set and could be evaluated in future studies. This is also the first study highlighting the hierarchy of these parameters and doing this type of cohort subgroup analysis for risk stratification late after Fontan. Ventricular dilation likely is the result of a combination of multiple detrimental characteristics of the Fontan circulation. From prenatal life onward, the systemic ventricle is exposed to hemodynamic stress. Furthermore, volume overload, valve regurgitation, aortopulmonary collateral burden, and electrophysiological abnormalities may play a role in the pathophysiology of ventricular dilation. Interestingly, other markers of systolic function, such as ejection fraction, were not associated with the endpoint by CART analysis. Although commonly used as an imaging biomarker, ejection fraction may be less useful for risk stratification in Fontan patients, as it does not account for ventricular dilation. For example, 2 patients with significantly different ventricular volumes might have the same ejection fraction, but will have drastically different stroke volumes and cardiac outputs. GCS measures deformation over multiple smaller segments, therefore it may reflect a better biomarker of systolic function or contractility in this patient population. Interestingly,

FIGURE 3 Kaplan-Meier Survival Curves Stratified By End-Diastolic Volume, Strain, and NYHA



Patients with EDV$_i$ higher/equal or lower than 156 ml/BSA$^{1.3}$ are further stratified by their NYHA functional class (class I vs. class II to IV) and GCS better than −6.6% versus equal/worse than −6.6%. EDV$_i$ = indexed end-diastolic volume; GCS = global circumferential strain; NYHA = New York Heart Association.

in asymptomatic patients with smaller ventricles, SVGFI, a parameter combining ventricular volumes, mass, and systolic function, was also a more important discriminator than ejection fraction. These data suggest that reliance on ejection fraction in patients with Fontan circulation may not be an adequate prognostic biomarker.

Clinical parameters previously shown to be associated with mortality include arrhythmias, thromboembolic events, and protein-losing enteropathy (2,3). In our model, however, NYHA functional class emerged as the most important clinical predictor of adverse outcome, particularly in those patients with no more than mild ventricular dilation. The association between worse NYHA functional class and adverse outcome has previously been described (23). Although NYHA functional class has known limitations given its somewhat subjective nature, the fact that it emerged as a predictive parameter emphasizes the importance of a thorough clinical history in this population.

Although multiple risk factors have been identified in the past, so far, a clear prioritization and appropriate metrics for stratification of Fontan patients at risk for Fontan failure and death is lacking. CART has the ability to demonstrate which factors are particularly important in a model with regard to explanatory power and variance. Furthermore, CART has advantages over more traditional methods, such as multivariate regression; it is inherently

nonparametric and does not require a priori categorization of the data. It explores datasets and identifies interactions among prognostic factors (21). This is especially useful in heterogeneous clinical datasets like our cohort.

STUDY LIMITATIONS. The cross-sectional, retrospective single-center design of this study has some inherent limitations. Patients with pacemakers and defibrillators were excluded from this study, as they remain a relative contraindication to CMR examination. This selection bias may result in underrepresentation of arrhythmia-related events that could result in poor outcomes. Referral bias for CMR testing may have led to overrepresentation of sicker and more symptomatic patients in this cohort. However, this bias is mitigated by our institutional practice of routine assessment of Fontan patients once they are old enough to cooperate with the examination. We also excluded patients who did not have an endpoint event with inadequate follow-up (<1 year), which may introduce a bias for patients with early event rates. Given the relatively small number of endpoints and the number of significant variables in the univariable analysis, there is a potential for overfitting, limiting the generalizability of the CART model. Future studies should validate this model against larger datasets. Although extensive, the available dataset was not comprehensive. Potentially interesting parameters, like oxygen saturation, hematocrit, and current fenestration status, were not available or not recorded in the medical record. This study focused on clinical and CMR parameters in the Fontan circulation and did not examine other biomarkers of organ dysfunction, such as myocardial fibrosis, liver damage, and exercise capacity. Further studies integrating and examining these elements are warranted. Contemporaneous catheterization data were also not available in this cohort given that invasive hemodynamic assessment is not routine clinical practice.

CONCLUSIONS

This is the largest study, to our knowledge, to determine the relative importance and interactions of clinical and CMR parameters for risk of death, heart transplantation, or listing for transplant in a large cohort of patients late after the Fontan operation. The data highlight the importance of combining variables to identify clinically meaningful subgroups that are at highest or lowest risk for death and transplantation in patients late after the Fontan operation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with functional single ventricles late after Fontan operation, ventricular dilation and worsening ventricular strain predicts adverse outcomes. Asymptomatic patients with smaller ventricles have the highest survival rate.

TRANSLATIONAL OUTLOOK: Future studies are required to determine whether early intervention to reduce ventricular dilation following the Fontan procedure could prevent or delay deterioration of ventricular function and improve long-term outcomes.

REFERENCES

1. Gewillig M, Brown SC. The Fontan circulation after 45 years: update in physiology. Heart 2016;102:1081–6.

2. Khairy P, Fernandes SM, Mayer JE, et al. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. Circulation 2008;117:85–92.

3. Pundi KN, Johnson JN, Dearani JA, et al. 40-year follow-up after the Fontan operation long-term outcomes of 1,052 patients. J Am Coll Cardiol 2015;66:1700–10.

4. Atz AM, Zak V, Mahony L, et al. Longitudinal outcomes of patients with single ventricle after the Fontan procedure. J Am Coll Cardiol 2017;69:2735–44.

5. Diller GP, Giardini A, Dimopoulos K, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. Eur Heart J 2010;31:3073–83.

6. Oster ME, Knight JH, Suthar D, Amin O, Kochilas LK. Long-term outcomes in single-ventricle congenital heart disease. Circulation 2018;138:2718–20.

7. Liu MY, Zielonka B, Snarr BS, Zhang X, Gaynor JW, Rychik J. Longitudinal assessment of outcome from prenatal diagnosis through Fontan operation for over 500 fetuses with single ventricle-type congenital heart disease: The Philadelphia Fetus-to-Fontan cohort study. J Am Heart Assoc 2018;7:e009145.

8. Rathod RH, Prakash A, Kim YY, et al. Cardiac magnetic resonance parameters predict

transplantation-free survival in patients with Fontan circulation. Circ Cardiovasc Imaging 2014;7:502–9.

9. Ghelani SJ, Colan SD, Azcue N, et al. Impact of ventricular morphology on fiber stress and strain in Fontan patients. Circ Cardiovasc Imaging 2018;11:e006738.

10. Alsaied T, Critser PJ, Azcue N, St. Clair N, Powell AJ, Rathod RH. CMR-derived ventricular global function index in patients late after the Fontan operation. J Am Coll Cardiol Img 2020;13:2686–7.

11. Margossian R, Schwartz ML, Prakash A, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging measurements of functional single ventricular volumes, mass, and ejection fraction (from the Pediatric Heart Network Fontan Cross-Sectional Study). Am J Cardiol 2009;104:419–28.

12. Breiman L, Friedman J, Olshen R, Stone C. Classification and Regression Trees. 2nd ed. Pacific Grove, CA: Wadswort, 1984.

13. Prakash A, Rathod RH, Powell AJ, McElhinney DB, Banka P, Geva T. Relation of systemic-to-pulmonary artery collateral flow in single ventricle physiology to palliative stage and clinical status. Am J Cardiol 2012;109:1038–45.

14. Garg R, Powell AJ, Sena L, Marshall AC, Geva T. Effects of metallic implants on magnetic resonance imaging evaluation of Fontan palliation. Am J Cardiol 2005;95:688–91.

15. Anderson PAW, Sleeper LA, Mahony L, et al. Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study. J Am Coll Cardiol 2008;52:85–98.

16. Alfakih K, Plein S, Thiele H, Jones T, Ridgway JP, Sivananthan MU. Normal human left and right ventricular dimensions for MRI as assessed by turbo gradient echo and steady-state free precession imaging sequences. J Magn Reson Imaging 2003;17:323–9.

17. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. J Appl Physiol 2005;99:445–57.

18. Ghelani SJ, Harrild DM, Gauvreau K, Geva T, Rathod RH. Echocardiography and magnetic resonance imaging based strain analysis of functional single ventricles: a study of intra- and inter-modality reproducibility. Int J Cardiovasc Imaging 2016;32:1113–20.

19. Meyer SL, Ridderbos F-JS, Wolff D, et al. Serial cardiovascular magnetic resonance feature tracking indicates early worsening of cardiac function in Fontan patients. Int J Cardiol 2020;303:23–9.

20. Godfrey ME, Rathod RH, Keenan E, et al. Inefficient ventriculoarterial coupling in Fontan patients: a cardiac magnetic resonance study. Pediatr Cardiol 2018;39:763–73.

21. Lemon SC, Roy J, Clark MA, Friedmann PD, Rakowski W. Classification and regression tree analysis in public health: methodological review and comparison with logistic regression. Ann Behav Med 2003;26:172–81.

22. Siriopol D, Popa R, Mihaila M, et al. Application of survival classification and regression tree analysis for identification of subgroups of risk in patients with heart failure and reduced left ventricular ejection fraction. Int J Cardiovasc Imaging 2021 Jan 16 [E-pub ahead of print].

23. Driscoll DJ, Offord KP, Feldt RH, Schaff HV, Puga FJ, Danielson GK. Five- to fifteen-year follow-up after Fontan operation. Circulation 1992;85:469–96.

KEY WORDS CART analysis, CMR, Fontan circulation, strain

APPENDIX For supplemental tables, please see the online version of this paper.