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ORIGINAL RESEARCH

High-Performing Fontan Patients

A Fontan Outcome Registry by Cardiac Magnetic Resonance Imaging Study

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ABSTRACT

BACKGROUND Fontan patients exhibit decreased exercise capacity. However, there is a subset of high-performing Fontan (HPF) patients with excellent exercise capacity.

OBJECTIVES This study aims to: 1) create a Fontan-specific percent predicted peak VO_2 tool using exercise data; 2) examine clinical factors associated with HPF patients; and 3) examine late outcomes in HPF patients.

METHODS Patients in the multi-institutional Fontan Outcomes Registry Using CMR Examination above the age of 8 years who had a maximal exercise test were included. An HPF patient was defined as a patient in the upper Fontan-specific percent predicted peak VO_2 quartile. Multivariable logistic regression was employed to investigate factors associated with the HPF and Cox regression was used to examine the association between HPF patients and late outcomes (composite of death or listing for cardiac transplant).

RESULTS The study included 813 patients (mean age: 20.2 ± 8.7 years). An HPF patient was associated with left ventricular morphology (OR: 1.50, $P = 0.04$), mixed morphology (OR: 2.23, $P < 0.001$), and a higher ejection fraction (OR: 1.31 for 10% increase, $P = 0.01$). Patients with at least moderate atrioventricular valve regurgitation, protein-losing enteropathy, or who were using psychiatric medications, were less likely to be an HPF patient. After a mean follow-up of 3.7 years, 46 (5.7%) patients developed a composite endpoint. HPF had a lower risk of death or listing for cardiac transplant (HR: 0.06 [95% CI: 0.01-0.25]).

CONCLUSIONS Patients with HPF have more favorable outcomes when compared to patients with lower exercise capacity. This large registry data highlights the role of exercise testing in providing personalized care and surveillance post-Fontan. (JACC Adv. 2024;3:101254) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AVVR = atrioventricular valve regurgitation

CMR = cardiac magnetic resonance imaging

EDV = end-diastolic volume

EF = ejection fraction

FppVO$_2$ = fontan-specific percent of predicted peak VO$_2$

HPF = high-performing Fontan

PLE = protein-losing enteropathy

RV = right ventricular

While the Fontan procedure has greatly improved the survival and quality of life of patients with single ventricle congenital heart disease, many patients still experience significant morbidity and have reduced exercise capacity compared to the general population.[1-3] This is likely multifactorial due to the inability to increase stroke volume at peak exercise, chronotropic impairment, diastolic dysfunction, and inherent power loss in the Fontan circulation.[2,3] A minority of high-performing Fontan (HPF) patients have "supranormal" exercise capacity compared to other Fontan patients. There is limited understanding of the factors associated with HPF and if this increased exercise capacity predicts better outcomes.[4,5] Cardiac magnetic resonance imaging (CMR) is an important tool for surveillance and management after the Fontan operation.[6] CMR is the gold standard to evaluate ventricular volume, mass, and function and is valuable in predicting adverse clinical outcomes in Fontan patients.[7-10] Delineation of associations of HPF may identify modifiable risk factors to improve exercise capacity in patients with subnormal performance.

The Fontan Outcomes Registry using CMR Examinations (FORCE) consortium is a network of 35 centers across the Americas and Europe with data from over 3,500 unique Fontan patients. Patients must have at least technically adequate CMR examination to be included in this registry. FORCE also collects clinical history, surgical history, testing data (exercise, catheterization, echocardiography), and clinical outcomes. The objective of this study was to use the FORCE data set to create a Fontan-specific percent predicted peak VO$_2$ (FppVO$_2$) tool using exercise data and characterize the clinical and CMR associations of HPF. Additionally, the study aimed to identify the associations of HPF with clinical outcomes.

METHODS

PATIENTS. This study was performed using data from the retrospective FORCE registry. This retrospective study was approved by each participating institution's committee on clinical investigations/institutional review board or via a reliance institutional review board agreement with Boston Children's Hospital. This study proposal and this manuscript were also approved by the FORCE Data Governance and Publications Committee. This analysis included data received by the FORCE registry as of May 2023. Patients were included in this study if they had a maximal effort cardiopulmonary exercise testing (at >8 years of age) and a CMR examination within 2 years of each other. If patients had multiple pairs of exercise testing and CMR examinations, the most recent pair was included in the study.

CARDIOPULMONARY EXERCISE TESTING. Exercise testing was performed using a calibrated cycle ergometer or treadmill per each institution's standard protocol.[11] Gas exchange at rest, during exercise, and during recovery was analyzed to determine peak VO$_2$.[12] Peak VO$_2$ was indexed to weight.[13] Maximal effort exercise test was defined as a respiratory exchange ratio of ≥1.1 or percent of predicted heart rate ≥80%. As institutions use different equations to calculate the percent of predicted peak VO$_2$, a Fontan-specific equation was created to calculate FppVO$_2$, as a weighted measure of exercise capacity by gender, age, and weight. It was defined by the ratio of actual VO$_2$ to Fontan-specific predicted VO$_2$ by gender, age, and weight. This approach was chosen a priori at the time of the study proposal and was approved by the FORCE Data Governance and Publication Committee. Sixty percent of the data was used to train a prediction model of VO$_2$, including gender, age, and weight as predictors. Based on the relationships between VO$_2$ and predictors that were visualized in scatter plots, polynomial and piecewise regressions were considered. The remaining 40% of the data was used for performance evaluation and model selection, as well as for determining the thresholds for different levels of exercise capacity: the lowest quartile (Q1) defined subnormal performance; the highest quartile (Q4) defined HPF.

CMR ACQUISITION. CMR studies were performed on various vendor magnets (Philips Healthcare; Siemens Healthineers; and GE Medical Systems). Protocols varied by institution and were generally consistent with the published CMR guidelines.[14,15] Ventricular size and function assessment was performed by an electrocardiographically gated steady-state free precession imaging in ventricular short-axis planes, encompassing the cardiac apex through the atria, reconstructed 20 to 30 phases per cardiac cycle.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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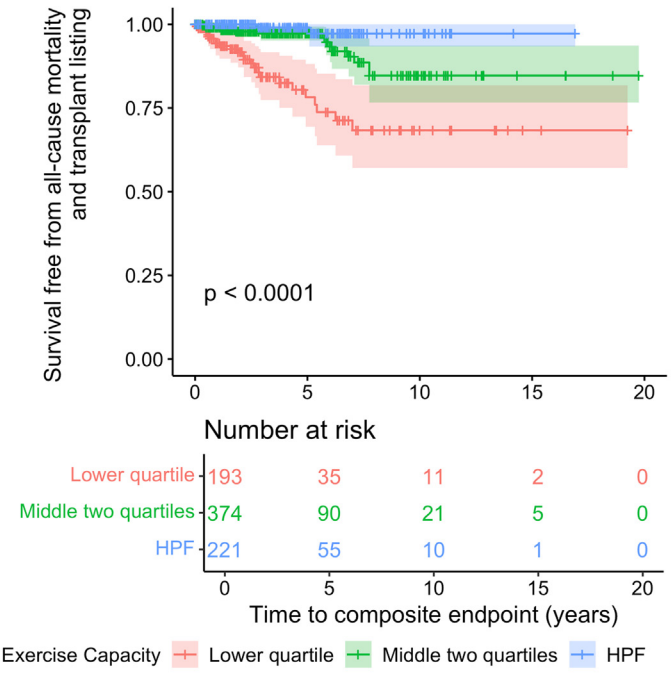
Quantitative CMR parameters were abstracted from the clinical reports and data entered into the FORCE registry by the sites. Ventricular volumes were measured by manual tracing of endocardial and epicardial borders at end-diastole (maximal volume) and end-systole (minimal volume) as previously described and were recorded in the registry.[8,15] In patients with 2 identifiable ventricles, if both ventricles contributed to the systemic circulation, their volumes and masses were summated, consistent with prior publications.[15] To better account for differences in body size, single ventricle end-diastolic volume (EDV), end-systolic volume, and stroke volume measurements were indexed to body surface area. Body surface area was calculated using the Mosteller equation.[8,16] Severe ventricular dysfunction was defined as an ejection fraction of <35%. Ascending aortic flow measured through 2-dimensional phase contrast was also reported. The flow was indexed to body surface area. In patients with aortopulmonary anastomosis (eg, Damus Kaye Stansel) with antegrade native aortic flow, the ascending aorta flow was obtained above the level of the anastomosis or the sum of the native and neoaorta flow was used. The ventricular morphology was defined as right ventricular (RV) dominant, left ventricular dominant, or mixed morphology. Mixed morphology was defined as a priori if the smaller ventricle contributes to the systemic circulation and if the smaller ventricle EDV is ≥25% of the combined ventricular EDV. Patients were considered to have ≥ moderate atrioventricular valve regurgitation (AVVR) if reported as at least moderate in the CMR report or if the regurgitant fraction calculated as (ventricular stroke volume-ascending aorta flow)/ventricular stroke volume was >20%. Maldistribution of pulmonary blood flow is defined as more than 20% difference between the branch pulmonary artery flow.

CARDIAC CATHETERIZATION AND ECHOCARDIOGRAPHY DATA. The data from the cardiac catheterization and echocardiographic clinic reports were recorded. These tests were performed per each institution's protocol.

CLINICAL DATA. Clinical history, surgical history, testing data (exercise, catheterization, echocardiography), and clinical outcomes data were abstracted from the medical records. Other variables included a medication treatment, plastic bronchitis, or protein-losing enteropathy (PLE).

OUTCOMES. The composite endpoint was the time to death or listing for heart transplantation. These data were obtained by a detailed chart review of every patient and was entered to the FORCE registry.

FIGURE 1 Association of Peak VO_2 in Males and Females With Age and Weight



Ex. Cap.	HR (95%CI)	p
Lower quartile	Ref.	-
Middle two quartiles	0.27 (0.14,0.50)	<0.001
HPF	0.06 (0.01,0.25)	<0.001

In the upper panel, the peak VO_2 increased with age and peaked around the age of 22 years in males and age of 18 years in females before starting to decline as the patients got older.

As mentioned previously, using the prediction model for $FppVO_2$, the lowest quartile (Q1) defined subnormal exercise performance and the highest quartile (Q4) defined HPF.

STATISTICAL METHODS

Descriptive analysis was performed for the demographic characteristics and medical history of patients included in the study cohort. For continuous variables, the mean ± SD, or median (IQR) were reported as appropriate. For categorical variables, chi-square or Fisher exact were used and frequencies and percentages are reported.

Multivariable logistic regression was employed to investigate the factors associated with the HPF. Variables were chosen using stepwise selection. Variables that were significant at $P < 0.05$ in descriptive

TABLE 1 Clinical Characteristics of the Study Population Stratified by Fontan-Specific Percent Predicted VO_2 Quartiles

	Lowest $FppVO_2$ Quartile (n = 198)	Middle 2 $FppVO_2$ Quartile (n = 388)	Highest $FppVO_2$ Quartile (High Performing Fontan Patients) (n = 227)	*P* Value
Age at exercise test (y)	20.4 ± 8.25	19.6 ± 8.88	21.3 ± 8.76	0.062
Age at Fontan (y)	4.48 ± 3.90	4.04 ± 3.75	4.38 ± 5.20	0.440
Gender (female %)	88 (44%)	152 (39%)	95 (42%)	0.459
Body surface area	1.64 ± 0.35	1.62 ± 0.36	1.68 ± 0.29	0.092
Weight (kg)	60.5 ± 20.0	59.6 ± 21.1	61.8 ± 16.9	0.411
Body mass index (kg/m^2)	23.4 ± 6.02	22.3 ± 5.45	22.4 ± 4.52	0.062
Cardiac diagnosis				
Hypoplastic left heart syndrome	72 (37.7%)	112 (30.9%)	45 (21.6%)	<0.001
Tricuspid atresia	27 (14.1%)	82 (22.7%)	47 (22.6%)	
Double outlet right ventricle	34 (17.8%)	44 (12.2%)	27 (13.0%)	
Atrioventricular canal	18 (9.4%)	22 (6.1%)	10 (4.8%)	
Double inlet left ventricle	14 (7.3%)	50 (13.8%)	36 (17.3%)	
Pulmonary atresia with intact septum	12 (6.3%)	25 (6.9%)	18 (8.7%)	
Ebstein anomaly	1 (0.5%)	1 (0.3%)	6 (2.9%)	
Single ventricle morphology				<0.001
Right	106 (54.1%)	151 (39.3%)	65 (28.8%)	
Left	58 (29.6%)	169 (44.0%)	109 (48.2%)	
Balanced or mixed	32 (16.3%)	64 (16.7%)	52 (23.0%)	
Fontan type				0.347
Lateral tunnel	95 (49.0%)	176 (46.1%)	104 (47.5%)	
Extracardiac conduit	76 (39.2%)	176 (46.1%)	91 (41.6%)	
Patent fenestration at exercise test	32 (22.4%)	55 (17.3%)	24 (12.5%)	0.058
Protein-losing enteropathy	12 (6.1%)	20 (5.2%)	2 (0.9%)	0.012
Medications				
Angiotensin-converting enzyme inhibitors	123 (62.1%)	204 (52.6%)	104 (46.2%)	0.005
Diuretics	89 (45.2%)	91 (23.5%)	40 (18.1%)	<0.001
Beta blocker	58 (29.4%)	74 (19.1%)	35 (15.8%)	0.001
Psychiatric medication	38 (19.4%)	65 (16.9%)	22 (9.8%)	0.016
Pulmonary vasodilators	13 (6.7%)	19 (5.0%)	13 (5.9%)	0.683
History of thrombosis	39 (19.9%)	44 (11.4%)	16 (7.2%)	<0.001
History of atrial tachyarrhythmias/atrial fibrillation/atrial flutter/atrial tachycardia	60 (30.6%)	86 (22.3%)	47 (21.2%)	0.044
History of pacemaker placement	20 (10.2%)	21 (5.4%)	10 (4.4%)	0.034

Values are mean ± SD or n (%).
$FppVO_2$ = Fontan-specific percent of predicted peak VO_2.

analysis were added to the multivariable analysis. Candidate variables included single ventricle morphology, AVVR, protein-losing enteropathy, history of atrial tachyarrhythmias/atrial fibrillation/atrial flutter/atrial tachycardia, history of post-Fontan electrophysiologic study, history of pacemaker placement, medication of angiotensin converting enzyme inhibitors, diuretic, Beta blocker, psychiatric medication, history of thrombosis, indexed EDV, and EF. Cardiac diagnosis was not considered for the model due to the collinearity with single ventricle morphology. The multicollinearity assumption was inspected using variance inflation factor, and variables that caused multicollinearity in the regression model were removed.[17,18]

Catheterization variables were not included due to missing values in >50%. To further explore the relationship between exercise capacity and clinical outcomes, a Kaplan-Meier curve was drawn of the composite outcome of death or listing for transplantation. Log-rank test was performed to compare the survival probability among patients with different exercise capacity and the hazard ratio was estimated using a univariate Cox model. Data management and statistical analysis were completed using R, version 4.3.1.

TABLE 2 Exercise and Catheterization Data Stratified by Fontan-Specific Percent Predicted VO_2 Quartiles

	Lowest $FppVO_2$ Quartile (n = 198)	Middle 2 $FppVO_2$ Quartile (n = 388)	Highest $FppVO_2$ Quartile (High-Performing Fontan Patients) (n = 227)	*P* Value
Exercise data				
Peak VO_2 (ml/kg/min)	18.9 ± 4.74	26.6 ± 5.74	33.4 ± 6.58	<0.001
Fontan Specific Percent of predicted VO_2 (%)	70.5 ± 11.0	97.4 ± 8.2	128.0 ± 14.8	NA
Saturation at baseline (%)	90.7 ± 5.87	92.3 ± 8.62	93.8 ± 3.85	<0.001
Saturation at peak exercise (%)	88.3 ± 6.01	90.1 ± 6.90	90.3 ± 5.57	0.003
VE/VCO_2 slope	38.0 ± 8.60	34.1 ± 8.57	31.2 ± 10.2	<0.001
VO_2 at anaerobic threshold (mL/kg/min)	13.4 ± 4.25	17.8 ± 6.20	21.7 ± 11.5	<0.001
Heart rate at peak exercise (beats/min)	149 ± 29.0	162 ± 22.1	170 ± 19.1	<0.001
Stress test modality (treadmill)	71 (35.9%)	178 (46.2%)	131 (58.2%)	<0.001
Catheterization data				
Fontan pressure (mm Hg)	14.6 ± 3.65	13.1 ± 3.45	12.4 ± 2.83	<0.001
Ventricular end-diastolic pressure (mm Hg)	10.2 ± 10.4	8.93 ± 3.79	7.86 ± 3.02	0.049
Pulmonary vascular resistance (indexed WU)	1.94 ± 0.86	1.63 ± 0.88	1.54 ± 0.79	0.003
Systemic cardiac index (indexed WU)	2.91 ± 0.94	3.26 ± 1.23	3.08 ± 0.79	0.016

Values are mean ± SD or n (%).
$FppVO_2$ = Fontan-specific percent of predicted peak VO2; NA = not applicable.

RESULTS

PATIENT CHARACTERISTICS. The study cohort consisted of 813 unique Fontan patients from 23 institutions. The mean age at exercise testing was 20.2 ± 8.7 years and 335 (41%) were females. The most common diagnosis was hypoplastic left heart syndrome in 229 (28%) followed by tricuspid atresia (19%). The most common type of Fontan was lateral tunnel in 375 (46%) followed by extracardiac conduit in 343 (42%) Fontan.

Percent of predicted VO_2 equations. Figure 1 and Supplemental Figure 1 depict the associations of weight and age with peak VO_2 in males and females. In Figure 1, the locally estimated scatterplot smoothing lines clearly show the quadratic relationship between predicted VO_2 and age in both genders. The predicted VO_2 increases with age and then decreases, suggesting the addition of a quadratic term for age in the regression model. Based on the validated model created in this study, the predicted VO_2 equations for both genders are summarized below.

- For male:

$$\widehat{VO_2} = -191.32 + 26.32 \cdot Weight + 79.93 \cdot Age - 1.35 \cdot Age^2 - 0.78 \cdot Age \cdot Weight + 0.01 \cdot Age^2 \cdot Weight$$

- For female:

$$\widehat{VO_2} = -549.68 + 39.35 \cdot Weight + 107.68 \cdot Age - 1.83 \cdot Age^2 - 2.17 \cdot Age \cdot Weight + 0.03 \cdot Age^2 \cdot Weight$$

The $FppVO_2$ was calculated as: predicted VO_2/actual VO_2. Based on the equation, the HPF (higher quartile) had $FppVO_2$ ≥113%, the lowest quartile had $FppVO_2$ less than or equal to 83%, and the middle 2 quartiles were >83% and <113%.

Clinical characteristics of the high performers. The HPF had an age, body surface area, and gender similar to the middle and low quartile groups (Table 1). There was no difference in age at Fontan procedure between the groups. HPF were more likely to have a diagnosis of tricuspid atresia and less likely to have hypoplastic left heart syndrome compared to the other 2 groups (Table 1). Similarly, HPF were less likely to have right ventricular morphology and more likely to have left or mixed morphologies. There was no difference in the rate of fenestration at the time of the exercise test (Table 1). Patients with HPF were less likely to have a history of PLE or thrombosis, and less likely to be taking diuretics, beta-blockers, or psychiatric medications (antidepressants, antianxiety, stimulants, antipsychotics, and/or mood stabilizers).

TABLE 3 Imaging data Stratified by Fontan-specific Percent Predicted VO_2 Quartiles

	Lowest $FppVO_2$ Quartile (n = 198)	Middle 2 $FppVO_2$ Quartile (n = 388)	Highest $FppVO_2$ Quartile (High-Performing Fontan Patients) (n = 227)	*P* Value
CMR data				
Single ventricle end-diastolic volume (ml/m^2)	113.6 ± 49.7	103.9 ± 35.1	103.3 ± 29.6	0.007
Single ventricle end-systolic volume (ml/m^2)	59.9 ± 38.1	52.7 ± 26.6	49.0 ± 20.2	<0.001
Single ventricle ejection fraction (%)	49.4 ± 11	51.2 ± 9.8	53.7 ± 8.4	<0.001
Single ventricle mass (gram/m^2)	59.5 ± 28.7	58.3 ± 25.9	56.3 ± 23.4	0.561
Ascending aorta flow (L/m^2)	3.0 ± 1.2	3.0 ± 0.7	3.1 ± 0.7	0.439
Caval flow (superior plus inferior vena cava flow) (L/m^2)	3.1 ± 1.7	3.0 ± 1.7	3.1 ± 1.6	0.740
Qp:Qs[b]	1.10 ± 0.24	1.05 ± 0.22	1.03 ± 0.21	0.065
Visible venovenous collaterals	27 (19.1%)	45 (14.8%)	33 (18.9%)	0.380
Aorto pulmonary collateral burden (%)	11 ± 13	14 ± 26	16 ± 20	0.296
Maldistribution of pulmonary blood flow[a]	54/138 (39.1%)	107/275 (38.9%)	49/153 (32.0%)	0.314
≥Moderate AVVR	39 (19.7%)	49 (12.6%)	12 (5.3%)	<0.001
Echo data				
Patent fenestration	111 (77.6%)	263 (82.7%)	168 (87.5%)	0.058
≥Moderate AVVR	25 (13.7%)	44 (12.0%)	13 (6.0%)	0.027
≥Moderate ventricular dysfunction	17 (9.2%)	23 (6.3%)	9 (4.2%)	0.123
Arch obstruction by echo	7 (4.7%)	7 (2.2%)	4 (2.1%)	0.253

Values are mean ± SD or n (%). [a]Maldistribution of pulmonary blood flow is defined as more than 20% difference between the branch pulmonary artery flow. [b]Qp:Qs pulmonary flow to systemic flow. This was reported by the center based on 1 of 3 methods. 1) Comparison of the aortic flow and pulmonary artery flow; 2) pulmonary artery and caval flow; and 3) pulmonary vein and caval flow.

AVVR = atrioventricular valve regurgitation; $FppVO_2$ = Fontan-specific percent of predicted peak VO_2.

TESTING CHARACTERISTICS OF THE HPF PATIENTS. Patients with HPF had higher oxygen saturation at baseline and at peak exercise and had a lower VE/VCO_2 slope (Table 2). The median time between the exercise test and cardiac catheterization was 2.3 years (IQR: 0.5-6.8). At cardiac catheterization, HPF had lower Fontan pressure, lower ventricular end-diastolic pressures, lower pulmonary vascular resistance, and higher cardiac index.

The median time between CMR and exercise test was 0.25 years (IQR: 0-0.75). By CMR, patients with HPF had lower indexed end-diastolic volumes, lower end-systolic volumes, higher ejection fraction, and were less likely to have ≥ moderate AVVR (Table 3). There was no difference in ascending aorta flow or ventricular mass between the groups. By echocardiography, patients with HPF were less likely to have ≥ moderate AVVR.

On multivariate analyses, patients with left morphology (OR: 1.50, $P = 0.04$), or mixed morphology (OR: 2.23, $P < 0.001$) and a higher ejection fraction (OR: 1.31 for 10% increase, $P = 0.01$) were more likely to be HPF. Patients with a history of ≥ moderate AVVR by CMR (OR: 0.37, $P < 0.001$), use of psychiatric medicines (OR: 0.50, $P = 0.01$), or history of PLE (OR: 0.11, $P = 0.03$) were less likely to be HPF (Table 4, Figure 2).

TABLE 4 Clinical, Anatomic and Cardiac Imaging Variables Association of High-Performing Fontan Patients (Highest Quartile of Fontan-Specific Percent of Predicted VO_2)

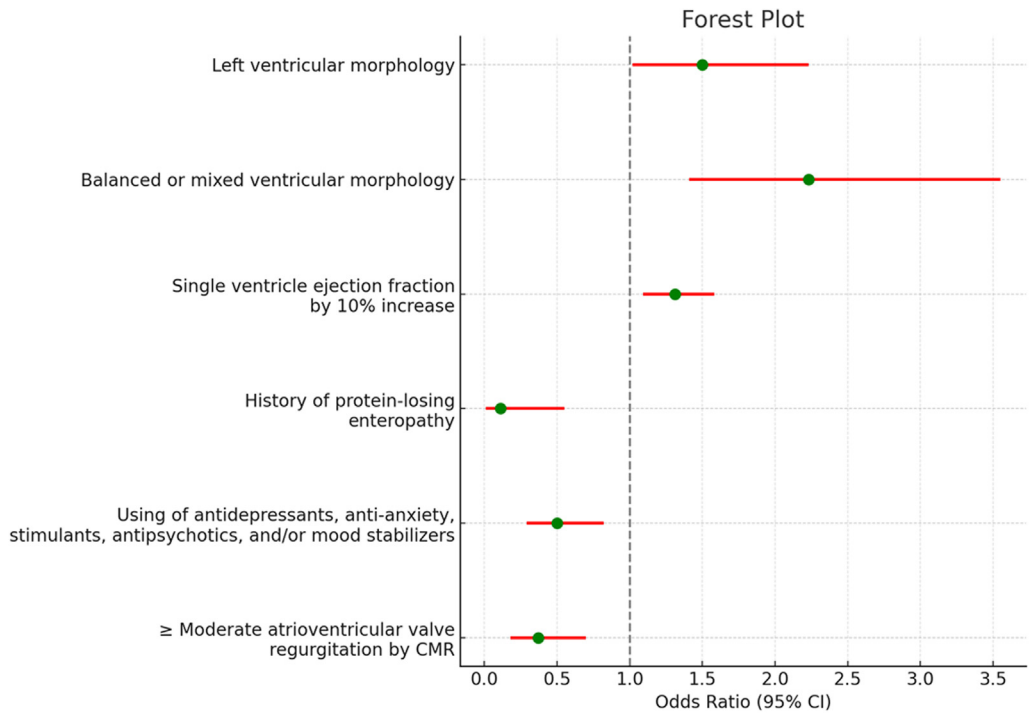
	Odd Ratio	95% CI	*P* Value
Morphology			
Left	1.50	1.02-2.23	0.04
Balanced or mixed	2.23	1.41-3.55	<0.001
History of protein-losing enteropathy	0.11	0.01-0.55	0.03
Using of antidepressants, antianxiety, stimulants, antipsychotics, and/or mood stabilizers	0.50	0.29-0.82	0.01
Single ventricle ejection fraction by 10% increase	1.31	1.09-1.58	0.01
≥Moderate atrioventricular valve regurgitation by CMR	0.37	0.18-0.70	<0.001

$FppVO_2$ = Fontan-specific percent of predicted peak VO_2.

HPF AND CLINICAL OUTCOMES. After a mean follow-up of 3.7 ± 3.4 years, there were 46 (5.7%) patients who met the composite endpoint for death or listing for heart transplantation (28 deaths, 23 transplant listings). Among patients who met this endpoint, 2 (4.3%) were HPF (Table 5).

Time to event analysis showed that HPF had a significantly lower hazard for death/listing for transplantation (HR: 0.06 [95% CI: 0.01-0.25]). The middle two-quartile group also had significantly lower hazards for death/listing for transplantation compared to the lower quartile group (Figure 3, Central Illustration).

FIGURE 2 Forest Plot: ORs of Factors Associated With High-Performing Fontan Patients (Highest Quartile of Fontan-Specific Percent of Predicted VO_2)



DISCUSSION

In this large multicenter study involving 813 unique Fontan patients, we identified distinct clinical, exercise, hemodynamic, and imaging characteristics of HPF patients. Notably, HPF demonstrated associations on multivariable analysis with left or mixed ventricular morphology, higher ejection fraction and were less likely to have significant AVVR, take psychiatric medications and have PLE. HPF was associated with a notably low hazard for adverse outcomes.

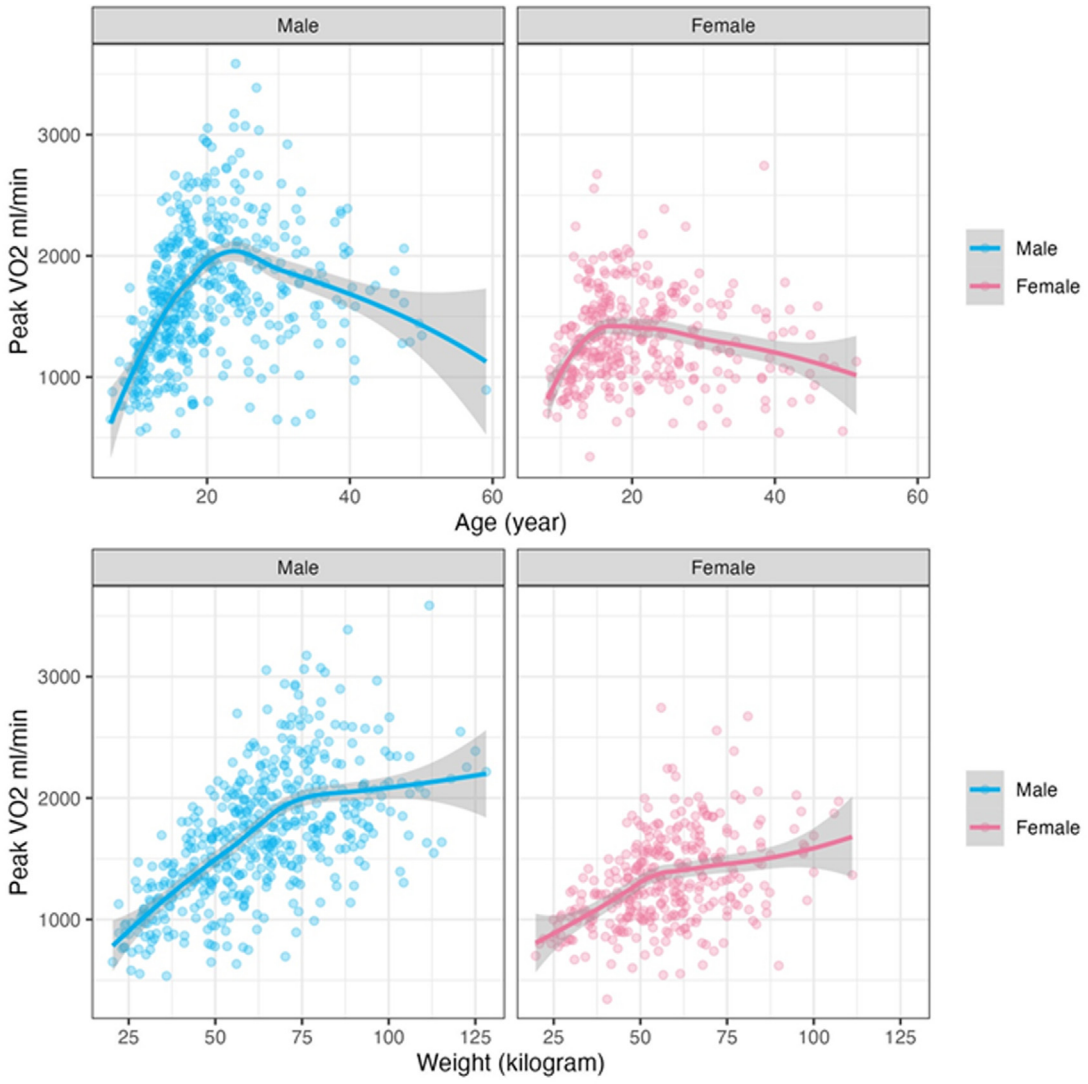
HPF AND CMR PARAMETERS. Our findings underline the importance of specific cardiac morphologies and their associations with HPF. Patients with HPF typically had a higher ejection fraction, a crucial determinant of cardiac efficiency and output. This is a somewhat intuitive finding that stresses the importance of a healthy myocardium to achieve high exercise performance.[5] Ventricular function has been shown to be association with the "super-Fontan" or HPF in multiple previous studies.[18] Ejection fraction was also the primary outcome of previous clinical trials including the single ventricle reconstruction III trial given its association with exercise capacitance, morbidity, and mortality.[19] The lower incidence of significant AVVR in the HPF is also not a surprising

TABLE 5 Clinical Outcomes and Exercise Capacity Stratified by Fontan-Specific Percent Predicted VO_2 Quartiles

	Lowest $FppVO_2$ Quartile (n = 198)	Middle 2 $FppVO_2$ Quartile (n = 388)	Highest $FppVO_2$ Quartile (High-Performing Fontan Patients) (n = 227)	*P* Value
Death (n = 28)	16 (8.2%)	11 (2.9%)	1 (0.5%)	<0.001
Listed for transplantation (n = 23)	14 (7.1%)	8 (2.1%)	1 (0.4%)	<0.001
Received transplantation (n = 13)	8 (4.0%)	4 (1.0%)	1 (0.4%)	0.006
NYHA functional class >II (n = 42)	21 (11.2%)	20 (5.6%)	1 (0.5%)	<0.001

Values are n (%).

FIGURE 3 Time to Event Analysis: Composite Outcome of Death or Heart Transplant Listing Stratified by Fontan-Specific Percent of Predicted VO_2 Quartiles

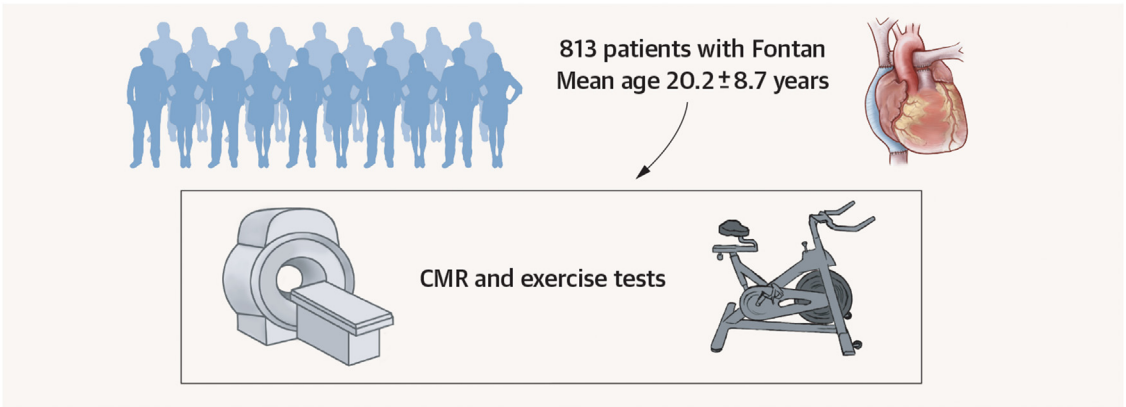


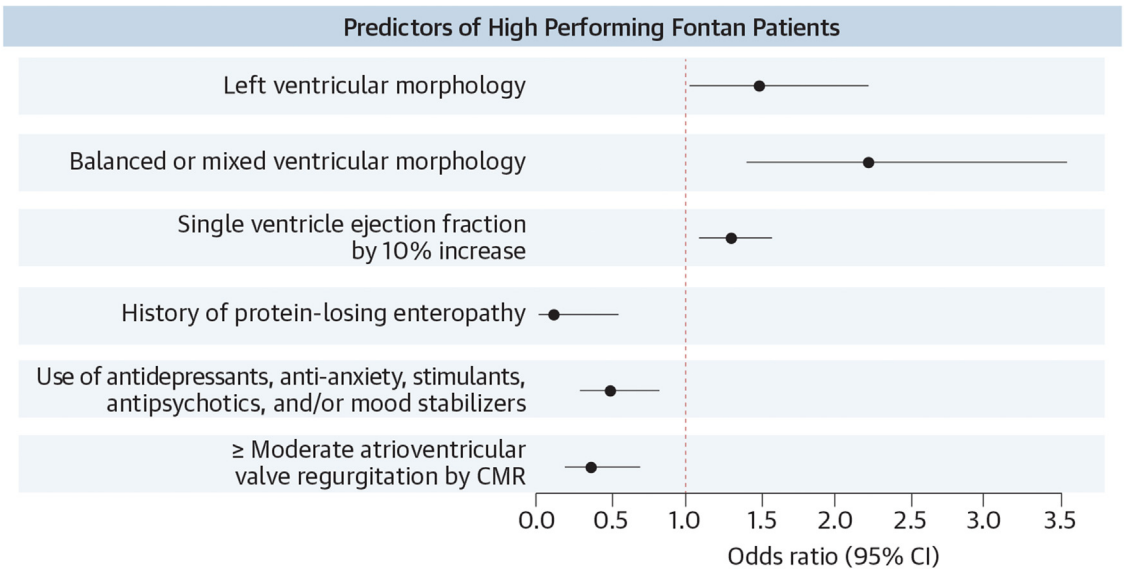
The high-performing fontan (HPF) group had lower hazard for the composite outcome. HPF = high-performing Fontan.

finding. AVVR in single-ventricle patients is associated with higher atrial pressure, lower cardiac output with lower flow to skeletal muscles which likely results in lower exercise capacity.[20]

Patients with HPF also demonstrated predominantly left or mixed morphology, pointing toward a possible structural advantage in these phenotypes when it comes to exercise capacity. This fits with previous data showing that right ventricular morphology is disadvantageous. Previous studies have highlighted that right ventricular morphology in Fontan patients is associated with worse exercise capacity.[21] Sano et al.[22] showed that the RV does not adapt as well as the left ventricular, with less thickening when subjected to systemic workloads. This can lead to challenges in managing increased blood flow during physical activity and restricted cardiac output enhancement, especially during intense exercise.[22] Additionally, the systemic RV typically has more dilation as noted in previous echocardiographic studies.[23,24] The risk factors of right ventricular morphology and significant AVVR highlight the importance of the interplay between ventricular morphology and AVVR. The single

CENTRAL ILLUSTRATION **Predictors of High-Performing Fontan Patients and Their Outcomes: The FORCE Study**





Alsaied T, et al. JACC Adv. 2024;3(10):101254.

Summary of the study in patients with fontan who had a cardiac MRI and an exercise stress test. High-performing fontan (HPF) is associated with significantly lower risk for death or transplant. The predictors of HPF by multivariable analysis are shown.

tricuspid valve is more likely to develop at least moderate regurgitation, and moderate AVVR is associated with poor outcomes only in RV dominant Fontans.[25,26] Having a morphologic RV has itself been shown to be a risk factor for poor Fontan outcomes.[27]

CATHETERIZATION AND EXERCISE TEST ASSOCIATIONS OF HPF BY UNIVARIATE ANALYSIS. By cardiac catheterization, patients with HPF had lower Fontan pressure and lower pulmonary vascular resistance (PVR). Fontan pressure and PVR are critical factors influencing exercise capacity in patients with Fontan physiology. Studies have shown that patients with reduced Fontan pressure and PVR tend to have better exercise tolerance and overall cardiovascular health. Egbe et al. demonstrated that individuals with lower PVR during exercise exhibited better pulmonary endothelial function and higher peak VO_2.[28] Goldstein et al. corroborated these findings by showing that higher PVR at peak exercise was associated with decreased exercise performance in Fontan patients.[29] Additionally, computational models have highlighted that high PVR significantly impairs cardiac output during exercise in Fontan, further limiting exercise capacity.[30]

Also, we found that HPF exhibited higher peak heart rates during exercise. This observation points toward the critical role of chronotropic competency in this population.[31] Chronotropic incompetence has been identified as a limiting factor in exercise capacity for Fontan patients.[32-34] Effective heart rate response to exercise reflects better autonomic regulation and cardiovascular adaptation, which are essential for meeting the increased metabolic demands during physical activit.[35] This aligns with previous studies that underscore the importance of maintaining optimal heart rate dynamics and oxygen delivery in managing the unique physiological challenges faced by this population. Of note the FORCE registry includes only patients who had at least one CMR and thus our study would have excluded patients with severe chronotropic incompetence that required a pacemaker with epicardial lead placement before having a CMR.[36]

CLINICAL ASSOCIATIONS OF HPF. Patients with HPF were less likely to be on psychiatric medications. The need for psychiatric medicines could be a surrogate for psychological challenges or more severe systemic symptoms.[37] The lesser reliance on these psychiatric medications in the HPF group could be reflective of their overall better health status, both physically and mentally. It is possible that patients with worse hemodynamics who had worse exercise capacity will have more mental health issues and thus need psychiatric medications. Whether some psychiatric medications could have a more direct effect on exercise capacity, related to effects on the autonomic nervous system or other mechanisms, is not clear. We also found that patients with PLE are less likely to have HPF. While PLE can be found in patients with normal hemodynamics, it is usually associated with worse hemodynamics and is associated with mortality in patients with Fontan.[10,12] Some of the sequelae of PLE, such as ascites, could also directly impact on exercise performance. Therefore, it is not surprising that PLE is linked to diminished exercise capacity.

While many of the factors were previously shown to be associated with exercise capacity, to our knowledge this study is the first to show the association of HPF with significantly lower hazard of death or listing for transplantation.

LOW RISK AND IMPLICATIONS FOR SURVEILLANCE. The significantly lower risk for adverse outcomes in the HPF group cannot be understated. During follow-up, adverse outcomes were very unlikely in the HPF and the hazard ratios for adverse outcomes in HPF are markedly low. Given the challenges and complications that Fontan patients can face, identifying such a low-risk group has important clinical implications.[38,39] This revelation emphasizes the value of routine exercise testing to risk stratify patients in this population,[40] as is recommended in the 2018 American College of Cardiology/American Heart Association Guideline for Management of Adults with Congenital Heart Disease.[41] For HPF patients, an aggressive surveillance strategy might not be as crucial, leading to fewer invasive tests, less frequent monitoring, and potentially better quality of life.

STUDY LIMITATIONS. While this study has a relatively large number of patients compared to previous publication, there are inherent limitations. Despite pooling data from 23 institutions, there might be variations in data collection, management protocols, and patient demographics. To mitigate this limitation, we created a new equation for $FppVO_2$ in Fontan patients. Moreover, our conclusions are based on correlations and associations, and while robust, causal relationships need more in-depth exploration. Patients were included if they had maximal exercise testing within 2 years of their CMR; it is possible that some had changes in status in the time between those tests. CMR-based variables such as ejection fraction are taken from the measurements performed at individual centers; there may be variability in the technical performance of those measurements between centers. Furthermore, this paper did not compare the

Fontan specific equation we created with the available percent of predicted VO_2 equations and this will be the focus of a future project using the FORCE registry. Finally, as a CMR-centric study, some patients with pacemakers or defibrillators are excluded as these devices with epicardial leads are not compatible with CMR. The use of pacemakers and defibrillators is common, seen in ~13% of patients after the Fontan operatio.[36]

CONCLUSIONS

Patients with HPF had a significantly lower hazard ratio for death or listing for transplantation. This comprehensive analysis, derived from the large FORCE registry, underscores the value of exercise testing to risk stratify Fontan patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Understanding the clinical and CMR associations of high-performing Fontan patients enhances medical knowledge by identifying specific factors associated with improved exercise capacity and outcomes. This may inform the development of targeted surveillance, interventions and management strategies for Fontan patients.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Integrating exercise testing and CMR findings into the routine evaluation of Fontan patients enables clinicians to more accurately identify those at risk of adverse outcomes and tailor care accordingly, emphasizing the need for personalized management plans.

COMPETENCY IN INTERPERSONAL AND COMMUNICATION SKILLS: Effective communication about the benefits and limitations of exercise capacity assessments and the implication for long-term care is crucial in managing expectations and engaging Fontan patients in their care plans.

COMPETENCY IN SYSTEMS-BASED PRACTICE: Recognizing the role of multidisciplinary teams in the management of Fontan patients and the importance of integrating new diagnostic tools into clinical pathways can improve patient outcomes through a coordinated approach to care.

COMPETENCY IN PRACTICE-BASED LEARNING: The findings encourage clinicians to reflect on and potentially adjust their practice based on new evidence about predictors of better outcomes in Fontan patients, fostering a culture of continuous learning and improvement.

COMPETENCY IN PROFESSIONALISM: The study underscores the importance of commitment to patient-centered care through the adoption of evidence-based practices to enhance the well-being of Fontan patients.

TRANSLATIONAL OUTLOOK 1: Future research should explore interventions that could potentially modify the identified associations of HPF to improve outcomes. This includes investigating the impact of specific exercise programs, medical therapies, and surgical techniques on exercise capacity and long-term health.

TRANSLATIONAL OUTLOOK 2: There's a need for longitudinal studies to understand the evolution of exercise capacity and its associations over time in Fontan patients, which could lead to early identification of those at risk and timely intervention.

TRANSLATIONAL OUTLOOK 3: The application of novel imaging techniques and biomarkers to further refine the risk stratification of Fontan patients represents an area for future investigation, with the aim of enhancing personalized care strategies.

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KEY WORDS exercise testing, Fontan, single ventricle, univentricular heart

APPENDIX For additional FORCE investigators as well as supplemental figures, please see the online version of this paper.