Relationship of Ventricular Morphology and Atrioventricular Valve Function to Long-Term Outcomes Following Fontan Procedures

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ABSTRACT

BACKGROUND The influence of ventricular morphology on Fontan outcomes is controversial.

OBJECTIVES This study hypothesized that dysfunction of the single right ventricle (RV) and right atrioventricular valve regurgitation (AVVR) increases over time and adversely impacts late outcomes following a Fontan operation. A single-center retrospective study was performed.

METHODS From 1985 through 2018, 1,162 patients underwent the Fontan procedure at our center and were included in this study. Transplant and takedown free survival, ventricular, and atrioventricular valve dysfunction after Fontan were analyzed. Death or heart transplantation information was obtained from the National Death Index and the Scientific Registry of Transplant Recipients.

RESULTS The follow-up rate was 99%. Morphologic RV was present in 58% of patients. Transplant and takedown free survival were 91%, 75%, and 71% at 10 years, 20 years, and 25 years, respectively. Morphologic RV was an independent risk factor for transplant, takedown free survival (hazard ratio: 2.4; p = 0.008). The AVVR, which preceded ventricular dysfunction in most cases, was associated with the development of ventricular dysfunction after Fontan (odds ratio: 4.3; 95% confidence interval: 2.7 to 6.7; p < 0.001). Furthermore, AVVR and ventricular dysfunction progressed over time after Fontan, especially in the RV (AVVR: p < 0.0001, ventricular dysfunction: p < 0.0001).

CONCLUSIONS Morphologic RV is negatively associated with the long-term survival following the Fontan, possibly due to a tendency toward progressive AVVR and deterioration of the single ventricle function. Additional volume overload caused by AVVR may be one of the main factors accelerating the dysfunction of the single RV, implying that early valve intervention may be warranted. (J Am Coll Cardiol 2020;76:419–31) © 2020 by the American College of Cardiology Foundation.

S ingle ventricle heart disease comprises a wide variety of critical heart defects that result in 1 dominant single ventricle to provide systemic cardiac output and requires staged surgical palliation that culminates in the Fontan circulation (1). The single ventricle can be distinguished as having a left ventricle (LV) or right ventricle (RV) morphology, and in rare cases, the morphology is indeterminate (2). Morphologic left and right ventricles differ in their embryological origin, anatomy, and associated atrioventricular valves (3,4). Further, the RVs and LVs are generally subjected to different afterload conditions; the single RV being systemic and thereby pressure-overloaded (5,6). In congenitally corrected transposition of the great arteries, a defect of atrioventricular and ventriculoarterial discordance that places the RV in the systemic circulation, and the LV in the pulmonary circulation, the systemic RV and tricuspid valve are prone to failure (7).

With these considerations in mind, we hypothesized that patients with single RVs would have worse outcomes as compared with patients with single LVs due to early ventricular dysfunction. Existing clinical data regarding this has been conflicting. In a previous study of the outcomes following a Fontan procedure performed at our institution, ventricular morphology had no impact on survival with a mean follow-up of 50 months (8). More recent studies have also demonstrated that ventricular morphology does not influence 8 to 10 years of survival (9,10). However, Oster and colleagues (11) demonstrated that patients with a single RV had worse survival after Fontan, but could only speculate the cause of this was due to deteriorating function of the single RV. Further, insufficiency of the systemic tricuspid valve is also found in a substantial number of patients with hypoplastic left heart syndrome (HLHS) who have a single RV (12), and tricuspid valve regurgitation has been attributed to be secondary to annular dilation and poor function (13) or intrinsic anatomical abnormalities of the tricuspid valve (13-15).

To evaluate our hypothesis and to address these controversies, we performed a detailed analysis of the Fontan experience at our center. We specifically evaluated the effect of ventricular morphology on survival and Fontan takedown and its impact on the function of the atrioventricular valve and the single ventricle. This study also allowed us to perform a secondary analysis of the data to determine the

TABLE 1 Anatomic Diagnosis in Fontan Patients

Diagnosis	Patients	Ventricle Morphology	
		RV	LV
HLHS	484 (42)	484	0
TA	181 (16)	0	181
DILV	159 (14)	0	159
DORV/MA	94 (8)	94	0
Heterotaxy	84 (7)	66	18
PAIVS	78 (7)	0	78
uAVSD	41 (4)	26	15
Others	41 (4)	8	33
Total	1,162	678	484

Values are n (%) or n. The most common diagnosis was HLHS (n = 484, 42%). Fifty-five of 84 patients with heterotaxy had common atrioventricular valve morphology. A total of 96 patients with common atrioventricular valve morphology were detected, with 71 having a right dominant valve and 25 having a left dominant valve. Other diagnoses included variant HLHS, d-transposition of great arteries, truncus arteriosus, and Ebstein anomaly.

DILV = double inlet left ventricle; DORV = double outlet right ventricle; HLHS = hypoplastic left heart syndrome; MA = mitral atresia; PAIVS = pulmonary atresia with intact ventricular septum; TA = tricuspid atresia; uAVSD = unbalanced atrioventricular septal defect.

overall long-term outcomes of the Fontan as well as perform an accompanying risk factor analysis.

METHODS

DATA COLLECTION AND PATIENT SELECTION. A single-center retrospective cohort study of 1,162 patients who underwent Fontan completion at the University of Michigan, from January 1985 through March 2018 was performed. This cohort included the patients previously reported (8), albeit with a shorter follow-up and less detail. Baseline morphology (**Table 1**) and demographics as well as pre-, intra-, and post-operative data (**Table 2**) were collected by electronic and paper chart review for each patient. The most current vital status was obtained from our internal clinical database and electronic medical records, as well as the National Death Index (Centers for Disease Control and Prevention, National Center for Health Statistics). This study also used data from the SRTR (Scientific Registry of Transplant Recipients) (Minneapolis, Minnesota). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. Institutional review board approval was obtained before the initiation of this study, and the need for informed consent was waived.

TABLE 2 Baseline Cohort Characteristics With Morphologic Single Ventricle Comparison

	Total Cases	RV	LV	p Value
Cases/Patients	1,162	678 (58)	484 (42)	
Female	457	240 (53)	217 (47)	0.02
Age at Fontan, yrs	2.2 (1.8–3.1)	2.1 (1.7–2.8)	2.3 (1.8–3.7)	<0.001
BW at Fontan, kg	11.8 (10.3–13.8)	11.3 (10.1–13.0)	12.4 (10.6–14.9)	<0.001
Stage I	1,015	631 (62)	384 (38)	
Norwood	582	512 (88)	70 (12)	<0.001
SP shunt	330	80 (24)	250 (76)	<0.001
PAB	103	39 (38)	64 (62)	<0.001
Stage II	1,007	644 (64)	363 (36)	
HFP	745	506 (68)	239 (32)	<0.001
BDG	262	138 (53)	124 (47)	0.03
Pre-Fontan evaluation	1,125	667 (59)	458 (41)	
SVEDP, mm Hg	8.0 (6.0–10.0)	8.0 (6.0–10.0)	8.0 (6.0–10.0)	0.75
Mean PAP, mm Hg	12.0 (10.0–14.0)	12.0 (10.0–14.0)	12.0 (10.0–14.0)	0.21
PVR, Wood U × m²	1.8 (1.3–2.4)	1.9 (1.4–2.4)	1.7 (1.1–2.3)	0.006
Dysfunction ≥ moderate	24	19 (79)	5 (21)	0.04
AVVR ≥ moderate	144	114 (79)	30 (21)	<0.001
LT Fontan	957	601 (63)	356 (37)	<0.001
ECC Fontan	123	66 (54)	57 (46)	0.23
APC/Bjork	82	10 (12)	72 (88)	<0.001
CPB time, min	67 (54–93)	64 (54–87)	72 (56–102)	<0.001
Cross clamp time, min	29 (22–40)	29 (23–37)	30 (22–47)	0.20
Fenestration	929	668 (74)	452 (36)	<0.001
Concomitant procedures				
AVV repair/replacement	89	75 (84)	14 (16)	<0.001
Fontan pathway	77	45 (58)	32 (42)	1.0
Rhythm surgery	27	13 (48)	14 (52)	0.3
Systemic obstruction	21	7 (33)	14 (67)	0.02
Others	25	13 (52)	12 (48)	0.5
Median follow-up, yrs	8.3 (2.0–15.4)	7.9 (2.1–14.0)	9.9 (1.9–19.0)	0.06

Values are n, n (%) or median (interquartile range). The normality of data was assessed with the Shapiro-Wilk test, and all variables were found to be non-normally distributed and were reported as median with interquartile range. Difference analysis was conducted by the chi-square test and Mann-Whitney *U* test. Concomitant procedures included: 1) atrioventricular valve repair or replacement; 2) patch augmentation of pulmonary arteries, superior vena cava or inferior vena cava stenosis as "Fontan pathway"; 3) surgical ablation or pacemaker implantation as "Rhythm surgery"; 4) re-coarctation repair, bulboventricular foramen/ventricular septal defect enlargement or sub-aortic stenosis repair as "Systemic obstruction"; and 5) atrial septectomy, pulmonary vein stenosis repair, collateral vessels ligation or diaphragm plication as "others." The number of patients available of SVEDP, mean PAP, PVR was 1,123 (99%), 1,125 (99%), and 747 (66%), respectively.

APC = atriopulmonary connection; AVVR = atrioventricular valve regurgitation; BDG, bidirectional Glenn; BW = bodyweight; CPB = cardiopulmonary bypass; ECC = extracardiac conduit; HFP = Hemi-Fontan procedure; IQR = interquartile range; LT = lateral tunnel; PAB = pulmonary artery banding; PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; SP = systemic pulmonary; SVEDP = systemic ventricle end-diastolic pressure.

TABLE 3 Variables for Risk Factor Analysis

Category	Specific Factors
Patient demographics	Age at Fontan, era
Morphologic factors	Hypoplastic left heart syndrome, heterotaxy, morphologic right ventricle
Interstage factors	Norwood procedure, primary Fontan
Pre-Fontan evaluation	Mean pulmonary artery pressure ≥15 mm Hg, systemic ventricle end-diastolic pressure ≥10 mm Hg, atrioventricular valve regurgitation ≥ moderate, ventricular dysfunction ≥ moderate
Intraoperative factors	Cardiopulmonary bypass time, cross clamp time, concomitant procedure at Fontan, type of Fontan (lateral tunnel and the others)
Post-operative factors	Chest tube drainage ≥ 2 weeks, length of hospital stay, atrioventricular valve regurgitation ≥ moderate, ventricular dysfunction ≥ moderate

Risk factors were selected from clinical experience and previous reports.

TABLE 4   Risk Analysis of In-Hospital Death and/or Takedown

	Univariable		Multivariable	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Heterotaxy	2.9 (1.5–5.8)	0.003	1.8 (0.7–4.3)	0.21
PAP ≥15 mm Hg	2.1 (1.2–3.8)	0.01	1.5 (0.7–3.0)	0.28
SVEDP ≥10 mm Hg	2.1 (1.2–3.5)	0.007	1.5 (0.8–2.9)	0.20
Dysfunction ≥ moderate	6.0 (2.3–15.6)	<0.001	2.2 (0.6–8.2)	0.25
AVVR ≥ moderate	2.6 (1.5–4.7)	0.01	1.4 (0.7–3.1)	0.36
CPB time, min	1.02 (1.01–1.03)	<0.001	1.01 (1.005–1.02)	0.001
Concomitant procedure	2.5 (1.5–4.2)	0.001	2.1 (1.07–4.1)	0.03
Era				
1985–1997	9.9 (3.1–32.7)	<0.001	6.1 (1.7–21.7)	0.005
1998–2007	6.3 (1.9–21.0)	<0.001	6.9 (2.0–24.2)	0.003
2008–2018	1.0		1.0	
LT Fontan	0.3 (0.2–0.5)	<0.001	0.5 (0.3–1.1)	0.12

A binary logistic regression model was used for risk factor analysis. The era was divided into 3 periods. The earlier era was from 1985 to the end of 1997, the second era was 1998 to the end of 2007, and the latest era was from 2008 to March 2018.

AVVR = Atrioventricular valve regurgitation; CI = confidence interval; CPB = cardiopulmonary bypass; LT = lateral tunnel; OR = odds ratio; PAP = pulmonary artery pressure; SVEDP = systemic ventricle end-diastolic pressure.

Survival and risk factor analyses were performed. Primary endpoints for survival were Fontan takedown, heart transplant, and death. Covariates for risk factor analysis were selected based on clinical experience and previous reports (8,16-19) regarding survival outcomes after Fontan (**Table 3**). Survival and

FIGURE 1   Fontan Cohort for Long-Term Analysis

From January 1985 through 2018, a total of 1,162 Fontan patients were included in this study. Patients who had in-hospital death or takedown after Fontan, as well as unidentified vital status, were excluded from the long-term analysis. A total of 1,083 patients were included in our downstream analyses.

risk factor analyses were also performed in those who were discharged with an intact Fontan circulation to obtain conditional survival. Atrioventricular valve regurgitation (AVVR) and ventricular dysfunction analyses after Fontan procedure were obtained using data from post-operative echocardiogram studies, which were performed at the time of patient discharge as well as 3, 5, 10, 15, and 20 years after Fontan. Atrioventricular valve regurgitation and ventricular dysfunction data were graded and recorded as nominal with the following order: 1 = none or trivial dysfunction, 2 = mild dysfunction, 3 = moderate dysfunction, and 4 = severe dysfunction. Primary endpoints for AVVR and ventricular dysfunction analyses were at least moderate AVVR censored by atrioventricular valve replacement or repair and at least moderate ventricular dysfunction. In addition, competing risk analyses with cumulative incidence functions were performed for AVVR and ventricular dysfunction after Fontan and was stratified by ventricular morphology and atrioventricular valve morphology. Death, transplant, and Fontan takedown were defined as a competing risk.

SURGICAL TECHNIQUE/STRATEGY. The Hemi-Fontan procedure (HFP) and the bidirectional Glenn (BDG) procedure were used for stage 2 palliation. Our surgical technique of HFP, followed by lateral tunnel Fontan, was described in the previous report (20). The HFP maintains continuity between the superior vena cava and right atrium, and the pulmonary arteries are augmented with a pulmonary homograft patch. In the BDG, the superior vena cava is transected and then directly connected to the right pulmonary artery. The HFP requires cardioplegic arrest as well as a more prolonged cardiopulmonary bypass (CPB) time compared with the BDG procedure. However, the HFP permits the creation of a lateral tunnel at the time of the Fontan (stage 3 palliation), which requires less dissection and CPB time than the extracardiac Fontan procedure that is typically performed after BDG. We also prefer the HFP because it results in widely patent pulmonary arteries and minimizes the development of restriction in the Fontan pathway after stage 3 palliation (20,21).

We usually perform the HFP at age 3 to 6 months, followed by a lateral tunnel Fontan procedure (8) at 2 to 3 years of age. In patients with systemic or pulmonary venous anomalies that preclude a lateral tunnel Fontan, the BDG procedure followed by an extracardiac conduit Fontan is used. The BDG
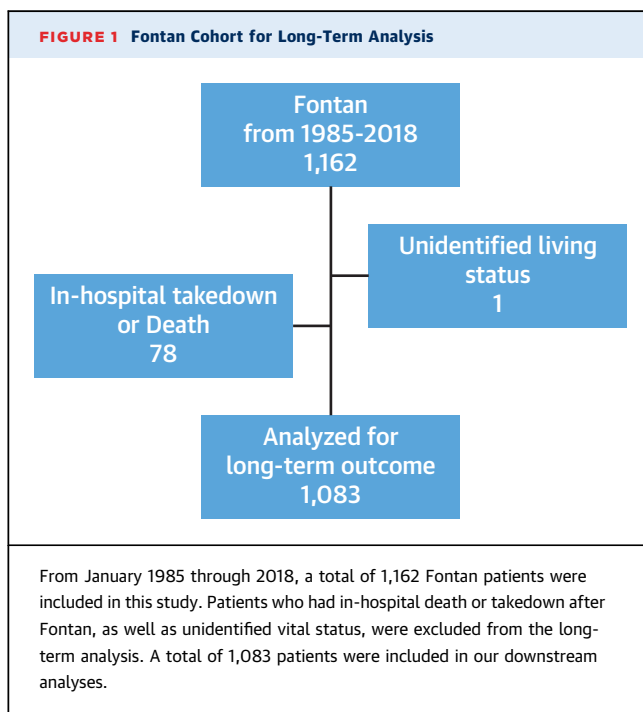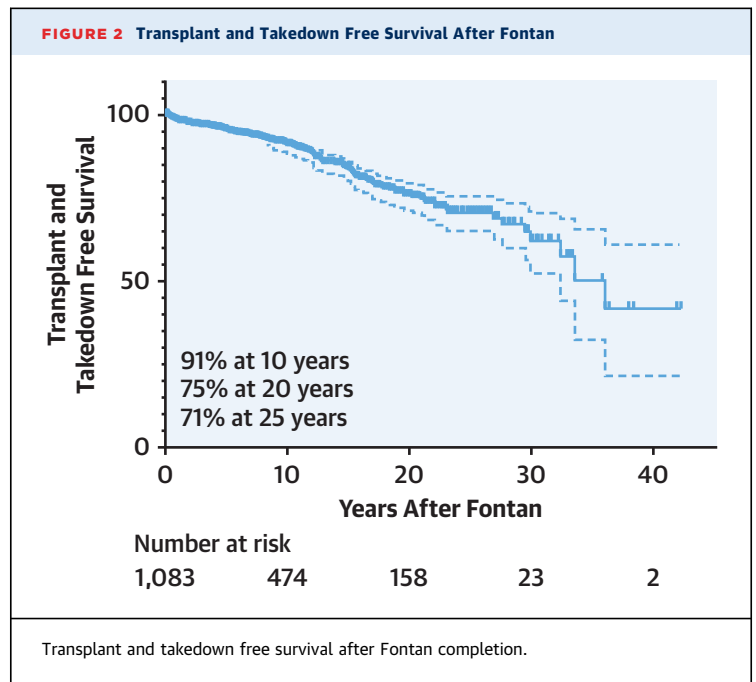
procedure is also chosen for pulmonary atresia with intact ventricular septum with RV-dependent coronary circulation to avoid coronary ischemia by decompression of the RV that would potentially occur during the HFP. Contraindications for Fontan completion include severe diastolic or systolic dysfunction of the single ventricle and severe pulmonary hypertension that is nonresponsive to supplemental oxygen and nitric oxide.

DATA ANALYSIS. Data analysis was performed using SPSS 26 software (SPSS, Inc, Chicago, Illinois) and SAS 9.4 (SAS Institute Inc., Cary, North Carolina). Nonnormally distributed variables were reported as median with interquartile range (IQR). The Student's *t*-test, chi-square test, and Mann-Whitney *U* test were used for characteristics comparison. Binary logistic regression was used for risk factor analysis of in-hospital death or takedown. Kaplan-Meier curves were created to estimate long-term survival. A Cox regression model was used for risk factor analysis of transplant and Fontan takedown free survival. For time-dependent covariates (at least moderate AVVR and single ventricular dysfunction after Fontan), time-varying covariates were created and analyzed. A nonparametric repeated measurement test (Cochran's Q test) was used to conduct a comparative analysis for AVVR and ventricular dysfunction after Fontan and was performed for patients who had consistent data across each time point. The dichotomous variables are defined as AVVR < moderate versus AVVR ≥ moderate and ventricular dysfunction < moderate versus ventricular dysfunction ≥ moderate. A p value was calculated with Fine and Gray's test for the cumulative incidence function of AVVR and ventricular dysfunction analysis. The ASSESS statement in PROC PHREG by SAS was used to examine Schoenfeld residuals for the assumption of proportional hazards. Nonviolation of assumptions was confirmed for the survival analyses as well as atrioventricular valve and ventricular function analyses. Statistical significance was considered as p < 0.05.

RESULTS

PATIENT CHARACTERISTICS. The anatomic diagnoses and baseline cohort characteristics are shown in **Tables 1 and 2.** The single ventricle morphology was RV in 678 (58%) and LV in 484 (42%), for a total of 1,162 patients. Hypoplastic left heart syndrome was the most common diagnosis (48%, n = 488). A Norwood procedure was performed in

FIGURE 2 Transplant and Takedown Free Survival After Fontan

91% at 10 years
75% at 20 years
71% at 25 years

Number at risk
1,083   474   158   23   2

Transplant and takedown free survival after Fontan completion.

57% (n = 582) and HFP was performed in 74% (n = 745). The median age and body weight at Fontan completion was 2.2 years (IQR: 1.6 to 3.1 years) and 11.8 kg (IQR: 10.3 to 13.8 kg). A lateral tunnel Fontan was performed in 82% (n = 957) and a fenestration in the lateral tunnel was created in 80% (n = 929).

IN-HOSPITAL DEATH OR TAKEDOWN RATE AND THE RISK FACTORS. There were 45 (3.9%) in-hospital deaths and 33 (2.8%) in-hospital takedowns after Fontan. There have been no in-hospital deaths since 2008, and these 78 patients were excluded from the long-term survival analysis. The risk factors for in-hospital death or takedown were Fontan CPB time (odds ratio [OR]: 1.01 per min; 95% confidence interval [CI]: 1.00 to 1.02; p = 0.001), a concomitant procedure at Fontan (OR: 2.1; 95% CI: 1.1 to 4.1; p = 0.03), and surgical era (1985 to 1997, OR: 6.1; 95% CI: 1.7 to 21.7; p = 0.005; 1998 to 2008, OR: 6.9; 95% CI: 2.0 to 24.2; p = 0.003) by multivariable analysis (**Table 4**).

DEATH, TAKEDOWN, AND HEART TRANSPLANT AFTER FONTAN. After linking our Fontan clinical database to the National Death Index, we determined, as of December 31, 2018, the vital status of 1,161 patients (99.9%). This vital status determination allowed us to analyze the entire cohort of Fontan

CENTRAL ILLUSTRATION Takedown and Transplant-Free Survival

LV: 78% at 25 years
RV: 63% at 25 years
p = 0.005

Years After Fontan

Number at risk

RV	631	250	66	4	
LV	452	224	92	19	2

Moon, J. et al. J Am Coll Cardiol. 2020;76(4):419–31.

Survival rate was significantly better in the left ventricle (LV) than in the right ventricle (RV) (LV: 92%, 82%, and 78% vs. RV: 90%, 68%, and 63% at 10, 20, and 25 years, respectively, p = 0.005). The **dashed lines** represent 95% CI for each RV and LV curve.

patients for long-term death, takedown, and transplant (**Figure 1**). A total of 123 (11%) deaths occurred after post-Fontan discharge. A total of 40 takedowns occurred, and 33 of them were during the same hospitalization as the Fontan procedure, as noted

previously (Supplemental Figure 1). Heart transplantation status was verified in 99% as of July 2019 by the SRTR. Seventy-five patients were listed for heart transplantation, and 43 patients underwent heart transplantation, including 16 at our center. Two of these 43 patients also underwent a second heart transplantation.

LONG-TERM SURVIVAL WITH INTACT FONTAN CIRCULATION AND RISK FACTORS FOR DEATH, TAKEDOWN, AND TRANSPLANT. The median follow-up rate was 8.3 years (IQR: 2.0 to 15.4 years), and at least 1 follow-up was obtained after hospital discharge in 90% of patients (n = 972). Transplantation and takedown free survival after Fontan was 91%, 75%, and 71% at 10, 20, and 25 years, respectively (**Figure 2**). An analysis of the impact of single ventricle morphology found that transplantation and takedown free survival was significantly superior in the patients with a single LV as compared with that in patients with a single RV (LV: 92%, 82%, and 78% vs. RV: 90%, 68%, and 63% at 10, 20, and 25 years, respectively, p = 0.005, **Central Illustration**).

Risk factors for death, takedown, and transplantation are presented in **Table 5**. Using a Cox regression model, the independent risk factors for

TABLE 5 The Risk Analysis of Transplant and Takedown Free Survival

	Univariable		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
HLHS	1.5 (1.1–2.1)	0.02	1.2 (0.7–2.3)	0.50
Heterotaxy	2.0 (1.2–3.3)	0.008	1.3 (0.6–2.5)	0.40
Morphologic RV	1.7 (1.2–2.4)	0.005	2.4 (1.3–4.6)	0.008
Age at Fontan, yrs	1.05 (1.03–1.08)	<0.0001	1.08 (1.03–1.1)	<0.001
PAP ≥15 mm Hg	1.7 (1.2–2.5)	0.004	1.6 (1.0–2.4)	0.03
CPB time (min)	1.01 (1.00–1.01)	0.007	1.0 (1.0–1.004)	0.60
Concomitant procedure	1.7 (1.2–2.4)	0.006	2.0 (1.3–3.0)	0.002
CT drain ≥2 weeks	2.4 (1.7–3.5)	<0.0001	2.1 (1.3–3.4)	0.006
LOS, days	1.02 (1.01–1.03)	<0.0001	1.01 (1.00–1.02)	0.001
Other than LT Fontan	2.3 (1.6–3.3)	<0.0001	2.0 (1.2–3.4)	0.006
AVVR ≥ moderate	1.8 (1.2–2.8)	0.006	2.4 (1.5–3.8)	<0.001

The risk analysis was performed using a Cox regression model with time-varying covariate for ventricular dysfunction and AVVR after Fontan. The reference groups of covariates are as follows: HLHS vs. non-HLHS, Heterotaxy vs. non-heterotaxy, morphologic RV vs. morphologic LV/2 ventricle morphology.

AVVR = atrioventricular valve regurgitation; BW = body weight; CI = confidence interval; CPB = cardiopulmonary bypass; CT = chest tube; HLHS = hypoplastic left heart syndrome; HR = hazard ratio; LOS = length of hospital stay; LT = lateral tunnel; PAP = pulmonary artery pressure; RV = right ventricle.

death, takedown, and transplant after Fontan that we identified were morphologic RV (HR: 2.4; 95% CI: 1.3 to 4.6; p = 0.008), >15 mm Hg of mean pulmonary artery pressure before Fontan (HR: 1.6; 95% CI: 1.0 to 2.4; p = 0.03), concomitant procedures at Fontan (HR: 2.0; 95% CI: 1.3 to 3.0; p = 0.002), a requirement of chest tube >2 weeks (HR: 2.1; 95% CI: 1.3 to 3.4; p = 0.006), length of hospital stay (HR: 1.01 per day; 95% CI: 1.00 to 1.02; p = 0.001), other than lateral tunnel Fontan (HR: 2.0; 95% CI: 1.5 to 3.8; p < 0.001), and at least moderate AVVR after Fontan (HR: 2.4; 95% CI: 1.5 to 3.8; p < 0.001). Although the age at Fontan was a statistically significant risk factor with our analysis, it may be biased by the clinical factors that drove the decision for the timing of Fontan.

PROGRESSION OF AVVR AND VENTRICULAR DYSFUNCTION AFTER FONTAN. A total of 5,140 (2,578 for ventricular dysfunction and 2,562 for AVVR) echocardiograms were reviewed for AVVR and ventricular dysfunction after the Fontan completion. The serial echocardiogram data revealed that atrioventricular valve and single ventricular dysfunction progressively increased after Fontan (**Figures 3A and 3B**). Morphological comparisons were then performed and demonstrated that progressive AVVR and ventricular dysfunction were more severe in patients with a single RV as compared with patients with a single LV (**Figures 3C to 3F**). Further, we found a significant correlation between AVVR and ventricular dysfunction (**Table 6**). In patients with AVVR ≥ moderate, 18% developed subsequent ventricular dysfunction. On the other hand, only 4.9% of patients with AVVR < moderate developed ventricular dysfunction (OR: 4.3; 95% CI: 2.7 to 6.7; p < 0.001). Importantly, AVVR preceded ventricular dysfunction in most cases, suggesting preceding AVVR may be associated with the progression of systemic ventricular dysfunction.

Cumulative incidence rates were calculated for AVVR ≥ moderate and ventricular dysfunction ≥ moderate after Fontan with competing risk analysis (**Figure 4**). The cumulative incidence rate of AVVR ≥ moderate after Fontan was 36% in the single RV group versus 13% in the single LV group at 20 years, respectively (**Figure 4A**) (HR: 3.4; 95% CI: 2.4 to 4.6; p < 0.0001). The cumulative incidence rate of ventricular dysfunction ≥ moderate after Fontan was 18% in the single RV group versus 5.8% in the single LV group at 20 years, respectively (**Figure 4B**) (HR: 3.2; 95% CI: 1.9 to 5.2; p < 0.0001). Taken together,
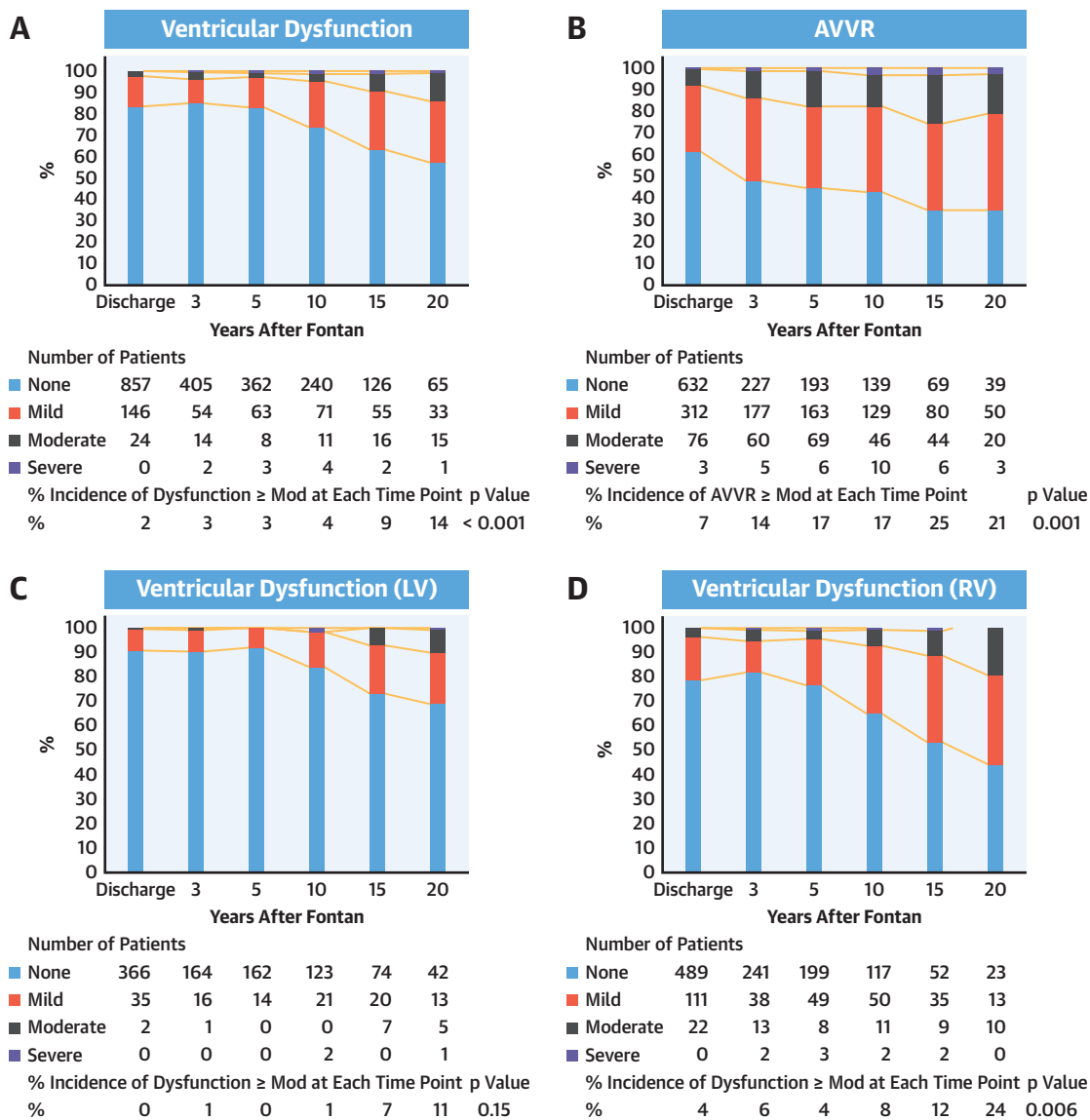
these results indicate that AVVR and ventricular dysfunction progressed more rapidly in patients with a single RV as compared with those with a single LV. Finally, the determined cumulative incidence rates stratified by the valve morphology demonstrated that the single ventricle and atrioventricular valve function rapidly deteriorated in the common atrioventricular valve and tricuspid valve as compared with the mitral valve (**Figures 4C and 4D**). However, when comparing the common atrioventricular valve with a single RV with the tricuspid valve (by definition, also with a single RV), there was no significant difference in the incidence rate of AVVR ≥ moderate (HR: 1.4; 95% CI: 0.9 to 2.0; p = 0.10).

DISCUSSION

In this study, we report the long-term survival outcome after the Fontan procedure at our center with 25 years of follow-up (**Central Illustration**). The uniqueness of our cohort is the large proportion of single morphologic RV (58%) with hypoplastic left heart syndrome (n = 488, 42%) and >80% of lateral tunnel Fontan staged by the HFP. The HFP followed by the lateral tunnel Fontan completion has been our preferred stage 2 and stage 3 procedure for single ventricle palliation when anatomically feasible. The lateral tunnel Fontan had been primarily used since the mid-1990s; however, many institutions have begun to use the BDG and extracardiac Fontan since the late 1990s to the early 2000s (16,17,19,22). The consistent Fontan strategy over several decades in our institution provides the largest and longest follow-up of the lateral tunnel Fontan described to date. Any comparison between the lateral tunnel Fontan and the extracardiac Fontan in our study is inappropriate because there is a selection bias of the type of Fontan procedure based on anatomy. However, ease of Fontan completion, lower energy losses, more effective flow distribution to the pulmonary arteries (23), and growth potential of the Fontan pathway (24) provide practical and theoretical advantages of the HFP-lateral tunnel Fontan approach.

The early mortality rate of the Fontan has dramatically improved with staged surgical palliations as well as advances in peri-operative and intraoperative management. Reported mortality rates for the Fontan have been <2% from modern series (16,25). A total of 45 in-hospital deaths (3.9%) were demonstrated in our study. However, most of these in-hospital deaths occurred before 1998, and after

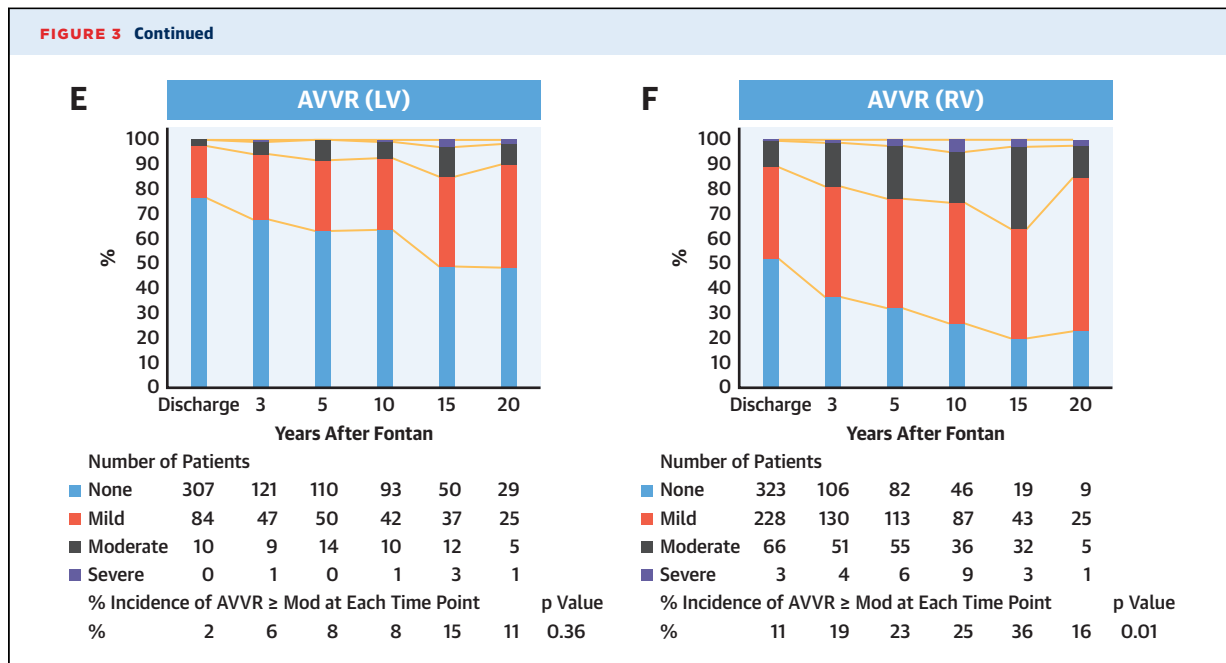**FIGURE 3   Progression of Ventricular Dysfunction and AVVR After Fontan**

A   Ventricular Dysfunction

Years After Fontan

Number of Patients

	Discharge	3	5	10	15	20
None	857	405	362	240	126	65
Mild	146	54	63	71	55	33
Moderate	24	14	8	11	16	15
Severe	0	2	3	4	2	1
% Incidence of Dysfunction ≥ Mod at Each Time Point						p Value
%	2	3	3	4	9	14	< 0.001

B   AVVR

Years After Fontan

Number of Patients

	Discharge	3	5	10	15	20
None	632	227	193	139	69	39
Mild	312	177	163	129	80	50
Moderate	76	60	69	46	44	20
Severe	3	5	6	10	6	3
% Incidence of AVVR ≥ Mod at Each Time Point						p Value
%	7	14	17	17	25	21	0.001

C   Ventricular Dysfunction (LV)

Years After Fontan

Number of Patients

	Discharge	3	5	10	15	20
None	366	164	162	123	74	42
Mild	35	16	14	21	20	13
Moderate	2	1	0	0	7	5
Severe	0	0	0	2	0	1
% Incidence of Dysfunction ≥ Mod at Each Time Point						p Value
%	0	1	0	1	7	11	0.15

D   Ventricular Dysfunction (RV)

Years After Fontan

Number of Patients

	Discharge	3	5	10	15	20
None	489	241	199	117	52	23
Mild	111	38	49	50	35	13
Moderate	22	13	8	11	9	10
Severe	0	2	3	2	2	0
% Incidence of Dysfunction ≥ Mod at Each Time Point						p Value
%	4	6	4	8	12	24	0.006

Progression of ventricular dysfunction **(A)** and AVVR **(B)** after Fontan by serial echocardiogram. Ventricular dysfunction **(C and D)** and AVVR **(E and F)** are worse in patients with a single RV **(C to F)**. Percent incidence of ventricular dysfunction ≥ moderate and AVVR ≥ moderate at each time point was compared using Cochran's Q test. AVVR = atrioventricular valve regurgitation; LV = left ventricle; Mod = moderate; RV = right ventricle.

2008 there has been no in-hospital mortality. As early mortality after Fontan now appears to be a historical challenge, increased attention is now being given toward the long-term outcomes. The number of living Fontan patients continues to increase with an estimated number of 50,000 to 70,000 worldwide in 2018, of whom 40% of these patients are older than 18 years (26). Several investigators have recently reported long-term overall survival rates after Fontan, with approximately 90% to 95% survival at 10 years (8,18,19,27) and 61% to 90% survival at 20 years (16-18). Our survival rates at 10 years and 20 years in

FIGURE 3 Continued

	Discharge	3	5	10	15	20	
E AVVR (LV)							
Number of Patients							
None	307	121	110	93	50	29	
Mild	84	47	50	42	37	25	
Moderate	10	9	14	10	12	5	
Severe	0	1	0	1	3	1	
% Incidence of AVVR ≥ Mod at Each Time Point							p Value
%	2	6	8	8	15	11	0.36

	Discharge	3	5	10	15	20	
F AVVR (RV)							
Number of Patients							
None	323	106	82	46	19	9	
Mild	228	130	113	87	43	25	
Moderate	66	51	55	36	32	5	
Severe	3	4	6	9	3	1	
% Incidence of AVVR ≥ Mod at Each Time Point							p Value
%	11	19	23	25	36	16	0.01

this study were 91% and 75%, respectively, which were within the ranges reported in the aforementioned studies.

The various risk factors for long-term survival that we identified included the diagnosis of HLHS, pre-operative pulmonary hypertension, pre-operative AVVR, and prolonged post-operative chest tube drainage (8,17,18). Heterotaxy has been recognized as a risk factor for single ventricle palliation outcomes before and after the Fontan (17,28,29) and it was not found to be a significant risk factor for Fontan outcomes in our data. However, given the small numbers of patients with heterotaxy in our study, this result might have been because of the lack of statistical power. Yet another explanation for this result is that some patients with heterotaxy with a single ventricle died before Fontan and those who survived to Fontan at our center were a select group with favorable and yet-to-be-identified characteristics that led to non-inferior outcomes.

Although the poor late outcomes following an atrial switch operation for d-transposition of great arteries or after conventional repair of congenitally corrected transposition of great arteries are well known (30), the impact of single ventricle morphology has been controversial, with short- and mid-term studies demonstrating no effect (8-11), whereas a recent longer-term study demonstrated

worse outcomes with a single RV (11). Given the potential developmental and anatomic differences as well as the pressure-overloaded state that make the single RV prone to failure (31), we hypothesized that dysfunction of the single RV increases over time and adversely affects the clinical outcomes of Fontan. Our analysis demonstrated a superior survival rate in patients with a single LV as compared with those with a single RV (**Figure 2**), and we found a morphologic RV to be a significant independent risk factor for late survival.

Regurgitation of the systemic tricuspid valve is relatively common in patients with HLHS (12), and it has also been attributed to worsening single RV function (13). However, recent studies have also indicated that these valves may have intrinsic anatomic abnormalities predisposing them to failure (13). To address this controversy, we ascertained the temporal relationship between systemic AVVR and single ventricular dysfunction to provide insight into possible causative relationships. We found that AVVR and single ventricular dysfunction progressively worsened with time, and these were significantly worse in patients with a single RV (**Figures 3C to F**). Interestingly, single ventricle function tends to be preserved for a substantial amount of time in the presence of AVVR. However, our assessment of single ventricle function in the presence of AVVR may

TABLE 6   The Correlation Between AVVR and Ventricular Dysfunction

	AVVR < Moderate			AVVR ≥ Moderate		
	Total	RV	LV	Total	RV	LV
Dysfunction < moderate	843	442	401	198	125	37
Dysfunction ≥ moderate	42	31	11	36	31	5
% incidence of dysfunction ≥ moderate	4.8*	6.6	2.7	18*	20	12

The number and rate of developed ventricular dysfunction ≥ moderate are shown. The rate of ventricular dysfunction ≥ moderate was significantly higher in AVVR ≥ moderate group (18% vs. 4.8%, p < 0.001, odds ratio: 4.3; 95% confidence interval: 2.7 to 6.7). *p < 0.001.

AVVR = atrioventricular valve regurgitation; LV = left ventricle; RV = right ventricle.

underestimate the degree of ventricular dysfunction, as it has been well described in the estimation of LV function in the presence of mitral regurgitation (32). Nonetheless, we also demonstrated the cumulative incidence of 36% of AVVR ≥ moderate and 18% of ventricular dysfunction ≥ moderate at 20 years in patients with a single RV. In addition, when AVVR preceded the Fontan, this scenario was associated with worsening single ventricular dysfunction, suggesting that volume overload by AVVR will further impair the already pressure-overloaded single RV. The temporal relationship revealed by our analysis suggests that the development of AVVR in single RV may precede ventricular dysfunction, indicating that not only the annular dilation but also multiple factors may affect atrioventricular valve function, such as pre-existing anatomic abnormalities of valve morphology, or abnormal ventricular septum mechanics due to a diminutive LV. Indeed, tricuspid valve abnormalities have been identified in patients with HLHS, including 12% with bicuspid, 33% with moderate dysplasia, and 2% with severe dysplasia of the tricuspid valve (15).

Historically, our surgical preference is bicuspidization of the systemic tricuspid valve, which yields a 73% early and 63% late success rate (33). However, a more selective approach tailored to address the underlying tricuspid valve abnormality may be warranted. The timing and indication of the atrioventricular valve intervention after Fontan are still controversial. Although there are some reports about atrioventricular valve repair or replacement following Fontan (34-36), peri-operative risk and long-term outcomes remain unclear. Given the multiple risks, including redo sternotomy, significant collateral vessels, and limited CPB options, surgical atrioventricular valve intervention may have a high mortality and morbidity risk. Notwithstanding, our data revealed AVVR ≥ moderate after Fontan was a significant risk factor for long-term survival. Moreover, morphologic RV was associated with deteriorating atrioventricular valve and ventricular function. Therefore, particularly in patients with morphologic RV, early intervention for AVVR ≥ moderate might be beneficial for long-term Fontan outcomes if the risk for intervention is determined to be acceptable.

STUDY LIMITATIONS. In this retrospective cohort study, one of the limitations was missing data, which included pre-Fontan echocardiogram and catheterization data. In particular, pulmonary vascular resistance data were missing in a substantial number of patients, and therefore, this parameter was excluded from the risk factor analysis. Because the definitions for indeterminant or 2-ventricle morphology are not standardized, we considered these few patients as having LV morphology. Another limitation was incomplete follow-up because a large number of patients live remotely from our center and receive their post-Fontan care elsewhere. However, survival and transplant follow-up data were obtained from our electronic medical records, the National Death Index, and SRTR, allowing us to achieve a 99.9% follow-up rate. Further, we were able to analyze a total of 5,140 post-Fontan echocardiogram reports, which yielded sufficient statistical power. Because of the incomplete follow-up of our cases, we were not able to perform analysis of the effects of post-Fontan comorbidities on the Fontan outcomes. Considering 63% undetected transplant (n = 27) occurred outside of our institution, other comorbidities may be underestimated as well. Not all patients with a single ventricle have achieved Fontan completion. Given the incidence of interstage death and failing Glenn physiology, there might be a selection bias for this cohort.

CONCLUSIONS

The single morphologic RV is negatively associated with long-term survival following the Fontan procedure, possibly due to a tendency toward progressive AVVR and deterioration of ventricular function. Additional volume overload caused by AVVR is not well-tolerated in the pressure-overloaded, single RV, and accelerates ventricular dysfunction, implying that valve intervention before deteriorating ventricular function might be beneficial, provided that such intervention can be performed with acceptable risk.

FIGURE 4 Cumulative Incidence Functions for AVVR ≥ Moderate and Ventricular Dysfunction ≥ Moderate
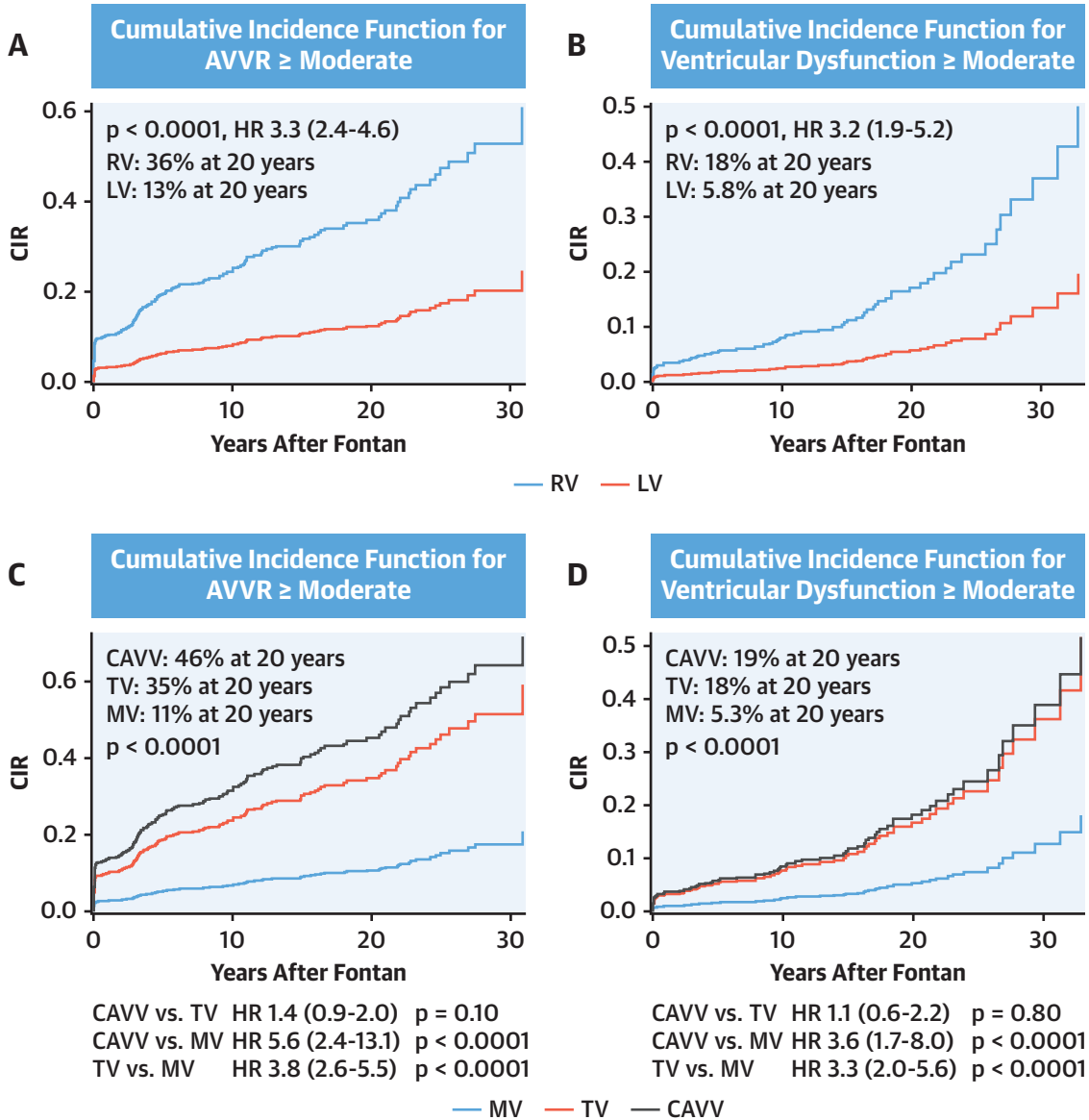
Death, transplant, and Fontan takedown were defined as a competing risk. The results were stratified by the single ventricle morphology **(A and B)**, and the atrioventricular valve morphology **(C and D)**. AVVR = atrioventricular valve regurgitation; CAVV = common atrioventricular valve; CIR = cumulative incidence rate; MV = mitral valve; TV = tricuspid valve.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE:
Following the Fontan operation for patients with single ventricle congenital defects, progressive AV valve regurgitation can lead to deterioration of morphological right ventricular function with an adverse impact on long-term survival.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether early intervention to reduce AV valve regurgitation following the Fontan procedure could prevent or retard deterioration of ventricular function and improve long-term outcomes.

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KEY WORDS atrioventricular valve regurgitation, Fontan, heart transplant, long-term outcome, systemic right ventricle

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