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Atrioventricular Valve Failure in Fontan Palliation

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ABSTRACT

BACKGROUND Atrioventricular valve failure (moderate or greater regurgitation, or valve operation) is a risk factor for adverse outcomes in patients undergoing Fontan palliation.

OBJECTIVES This study determined the incidence of atrioventricular valve failure and its clinical impact on patients undergoing Fontan palliation.

METHODS A retrospective cohort longitudinal study was conducted using patient data extracted from an existing bi-national, population-based registry.

RESULTS A total of 1,468 patients who underwent Fontan palliation were identified; complete follow-up data were available for 1,199 patients. Six hundred eighty-six patients had 2 atrioventricular valves, 286 had a single mitral valve, 130 had a common atrioventricular valve, and 97 had a single tricuspid valve. A total of 132 repairs were performed in 110 patients, and 15 replacements were performed in 13 patients. The cumulative incidence of atrioventricular valve failure at 25 years of age for patients with a common atrioventricular, single tricuspid, single mitral, and 2 atrioventricular valves was 56% (95% confidence interval [CI]: 46% to 67%), 46% (95% CI: 31% to 61%), 8% (95% CI: 4% to 12%), and 26% (95% CI: 21% to 30%), respectively. In patients without valve failure, freedom from Fontan failure at 10 and 20 years post-Fontan palliation was 91% (95% CI: 89% to 93%) and 77% (95% CI: 73% to 81%), respectively, compared with 77% (95% CI: 69% to 85%) and 54% (95% CI: 42% to 68%), respectively, in patients with valve failure (hazard ratio: 2.43; 95% CI: 1.74 to 3.39; $p < 0.001$).

CONCLUSIONS Atrioventricular valve failure occurs frequently in patients undergoing Fontan palliation. Patients with valve failure are twice as likely to have their Fontan circulation fail than those without valve failure.
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An increasing number of patients with Fontan circulation are surviving well into adulthood (1). Atrioventricular valve regurgitation is known to adversely affect outcomes in these patients (2,3). The rate at which atrioventricular valve regurgitation occurs in patients undergoing Fontan palliation is not clearly elucidated, nor are the factors that predict which patients will experience atrioventricular valve regurgitation or require intervention. Furthermore, the impact of moderate to

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severe regurgitation on long-term outcomes has not been quantified. We decided to review the data of the Australian and New Zealand Fontan Registry to determine the rate of atrioventricular valve regurgitation or intervention during the lifetime of patients who underwent Fontan palliation and the impact that this had on their long-term outcomes.

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METHODS

The Australian and New Zealand Fontan Registry, which was created in 2008, includes patients who had their Fontan procedure in either country, as well as patients who had their Fontan procedure overseas who are followed up within the region. When the Registry was created, all Fontan procedures were audited retrospectively, and this information was entered into the database. Prospective follow-up information continued to be collected annually for patients who consented to participate in the Registry. The design, structure, and protocol of the Fontan Registry were previously described (4). The degree of atrioventricular regurgitation was graded on an ordinal scale of 0 to 3 based on available echocardiography reports and clinical correspondence from initial and pre-Fontan presentation, and during follow-up (0 = none/trivial, 1 = mild, 2 = moderate, 3 = severe). A total of 1,521 Fontan operations, excluding Bjork procedures, were recorded between January 1975 and April 2016. A total of 53 patients were excluded because they had early Fontan takedown (n = 7) or died in hospital (n = 46). For the remaining 1,468 patients, follow-up data were extracted from the Registry and were based on clinical summaries that provided detailed echocardiography reports, outpatient appointments, and hospital admissions. Two hundred sixty-nine patients (269 of 1,468) had inadequate follow-up information (258 had echocardiographic follow-up of <2 years, 10 had no information recorded regarding the Fontan procedure, and 1 had no date of birth recorded). The remaining 1,199 patients constitute the cohort of this study.

DEFINITIONS. Fontan failure. The composite endpoint of Fontan failure was defined as death, heart transplantation, Fontan takedown, Fontan conversion, plastic bronchitis, protein-losing enteropathy, or New York Heart Association (NYHA) functional class III or IV at follow-up.

Atrioventricular valve failure. The composite endpoint of atrioventricular valve failure was defined as atrioventricular valve repair, or replacement or development of moderate or greater atrioventricular valve regurgitation.

Atrioventricular valve repair failure. The composite endpoint of atrioventricular valve repair failure was defined as atrioventricular valve re-intervention (re-repair or replacement) or the presence of recurrent moderate or greater atrioventricular valve regurgitation at follow-up post-initial repair.

For patients who experienced >1 of these endpoints, the date of Fontan failure, atrioventricular valve failure, or atrioventricular valve repair failure was the date of the earliest endpoint.

STATISTICAL ANALYSES. All statistical analyses were performed in R Version 3.4.4 software (R Foundation, Vienna, Austria). Patient baseline characteristics were summarized using median and the interquartile range (IQR) or range (minimum and maximum) for continuous variables, and counts and percentages for categorical variables. Unless stated otherwise, the calculation of percentages did not include the missing category. Time to events were depicted with Kaplan-Meier curves, or if competing risks (heart transplantation or death) were present, the cumulative incidence curve. The extended Kaplan-Meier method was used to illustrate the effect of a single time-varying covariate (5). Time-varying covariate analyses were used to depict the rate of Fontan failure in patients who experienced atrioventricular valve failure. Gray's test was used to compare the cumulative incidence curves. The censoring distribution was used to estimate the median follow-up time with the Kaplan-Meier method. Cox proportional hazard models and likelihood ratio tests were used to test the association between potential predictors and time-to-event endpoints. Variables with a $p < 0.05$ were considered in the multivariable analysis. Backward selection was used to reduce the number of variables, but if there was >1 possible multivariable model in which the included variables had a $p < 0.05$, then the model with the highest c-index was chosen as the final model. Collinearity of the variables was tested in the multivariable models using the variance inflation factor, and if >2, the variable was excluded. Competing risks regression methods were used for outcomes subjected to competing risks. The proportional hazards assumption was assessed based on the method of Fine and Gray (6).

RESULTS

PATIENT BASELINE CHARACTERISTICS. Patient characteristics are displayed in Table 1. The median length of follow-up was 11.7 years (range 1.2 to 37.7 years). The median age at Fontan palliation was

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

NYHA = New York Heart Association

TABLE 1 Patient Baseline Characteristics

	Included (n = 1,199)	Excluded (n = 269)
Sex		
Female	512 (43)	113 (42)
Male	687 (57)	155 (58)
Missing information	0	1
Age at Fontan, yrs		
Mean ± SD	5.76 ± 4.09	5.42 ± 2.86
Median (range)	4.63 (0.28–40.94)	4.64 (0–20.45)
Fontan type		
AP	211 (18)	10 (4)
ECC	719 (60)	222 (88)
LT	267 (22)	21 (8)
Missing	2	16
Fontan fenestration		
No	745 (62)	154 (62)
Yes	436 (36)	94 (38)
Missing	18	21
Primary diagnosis		
CAVC-DORV	35 (3)	0 (0)
ccTGA	78 (7)	16 (7)
DILV	213 (18)	32 (13)
DORV	165 (14)	26 (11)
HLHS	128 (11)	44 (18)
Mitral atresia	6 (1)	1 (0)
PA-IVS	95 (8)	21 (9)
Pulmonary atresia with VSD	24 (2)	6 (2)
TGA	28 (2)	0 (0)
Tricuspid atresia	272 (23)	58 (24)
Ebstein's Anomaly	1 (0)	1 (0)
uAVSD	96 (8)	17 (7)
Other	58 (5)	22 (9)
Missing	0	25
Valve morphology		
Common AV valve	130 (11)	18 (7)
Mitral atresia	97 (8)	17 (6)
Tricuspid atresia	286 (24)	59 (22)
Two AV valves	686 (57)	175 (65)
Dominant ventricle		
Biventricular	81 (7)	20 (9)
Indeterminate	27 (2)	6 (3)
Left	716 (60)	124 (54)
Right	375 (31)	79 (35)
Missing	0	40
Isomerism		
Left	33 (3)	6 (3)
None	1,111 (93)	215 (94)
Right	55 (5)	7 (3)
Missing	0	41
Dextrocardia	102 (9)	22 (10)
Normal	1,097 (91)	200 (90)
Missing	0	47
Extracardiac syndrome		
No	1,045 (87)	246 (91)
Yes	154 (13)	23 (9)

Values are n (%) or n, unless indicated otherwise.

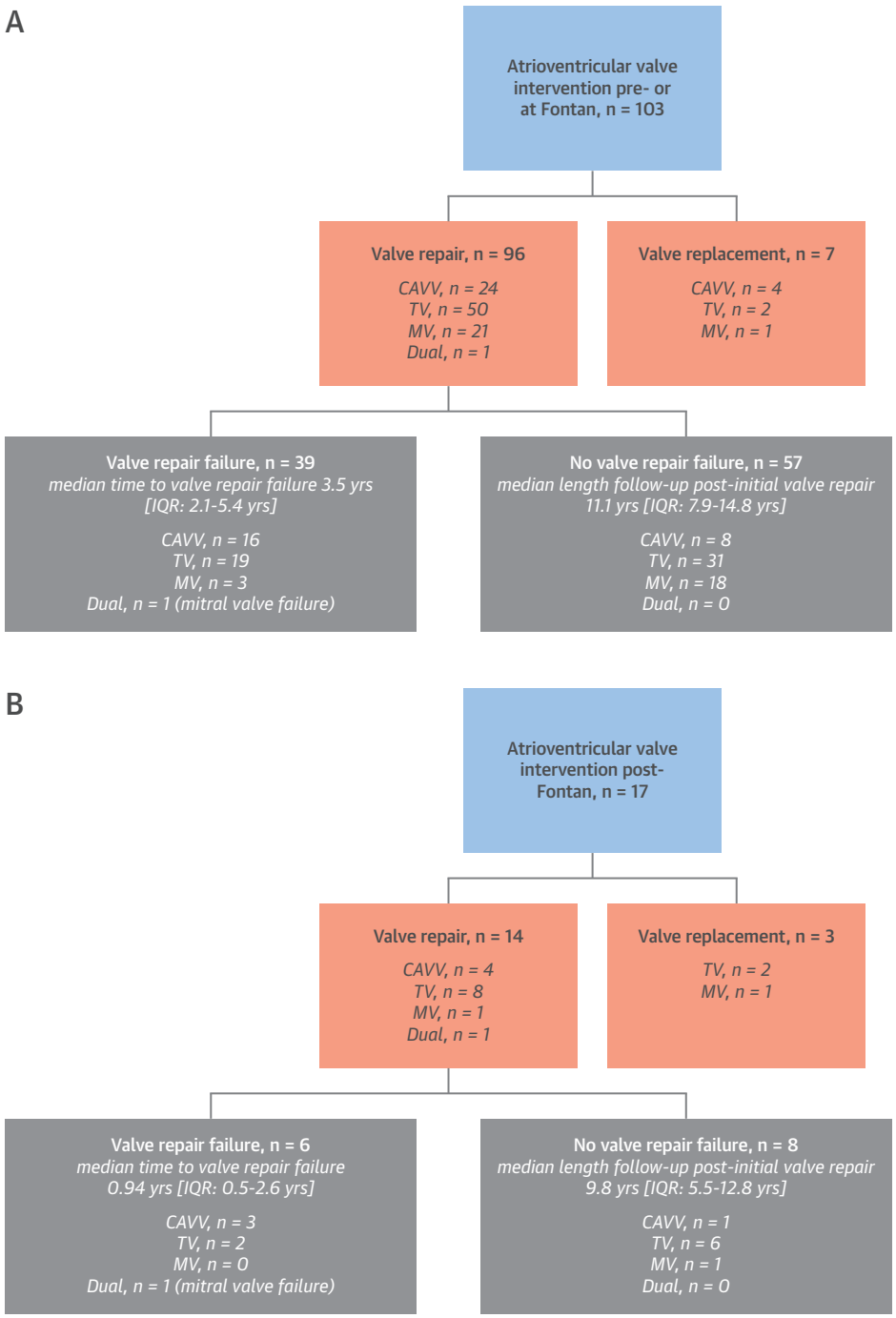
AP = atriopulmonary; AV = atrioventricular; CAVC-DORV = common atrioventricular canal-double outlet right ventricle; ccTGA = congenitally corrected transposition of the great arteries; DILV = double inlet left ventricle; DORV = double outlet right ventricle; ECC = extra-cardiac conduit; HLHS = hypoplastic left heart syndrome; LT = lateral tunnel; PA-IVS = pulmonary atresia-intact ventricular septum; TGA = transposition of the great arteries; uAVSD = unbalanced atrioventricular septal defect;VSD = ventricular septal defect.

Continued in the next column

4.6 years (interquartile range [IQR]: 3.5 to 6.2 years), and 687 of the 1,199 included patients were male. Fontan type consisted of 719 extracardiac conduits, 267 lateral tunnel, 211 atriopulmonary connections and 2 missing. Six hundred eighty-six patients had 2 atrioventricular valves, 286 had a single mitral valve, 130 had a common atrioventricular valve, and 97 had a single tricuspid valve. Three-hundred seventy-five patients had a dominant right ventricle. Thirty-three patients had left atrial isomerism, and 55 patients had right atrial isomerism. One hundred fifty-four patients had extracardiac anomalies.

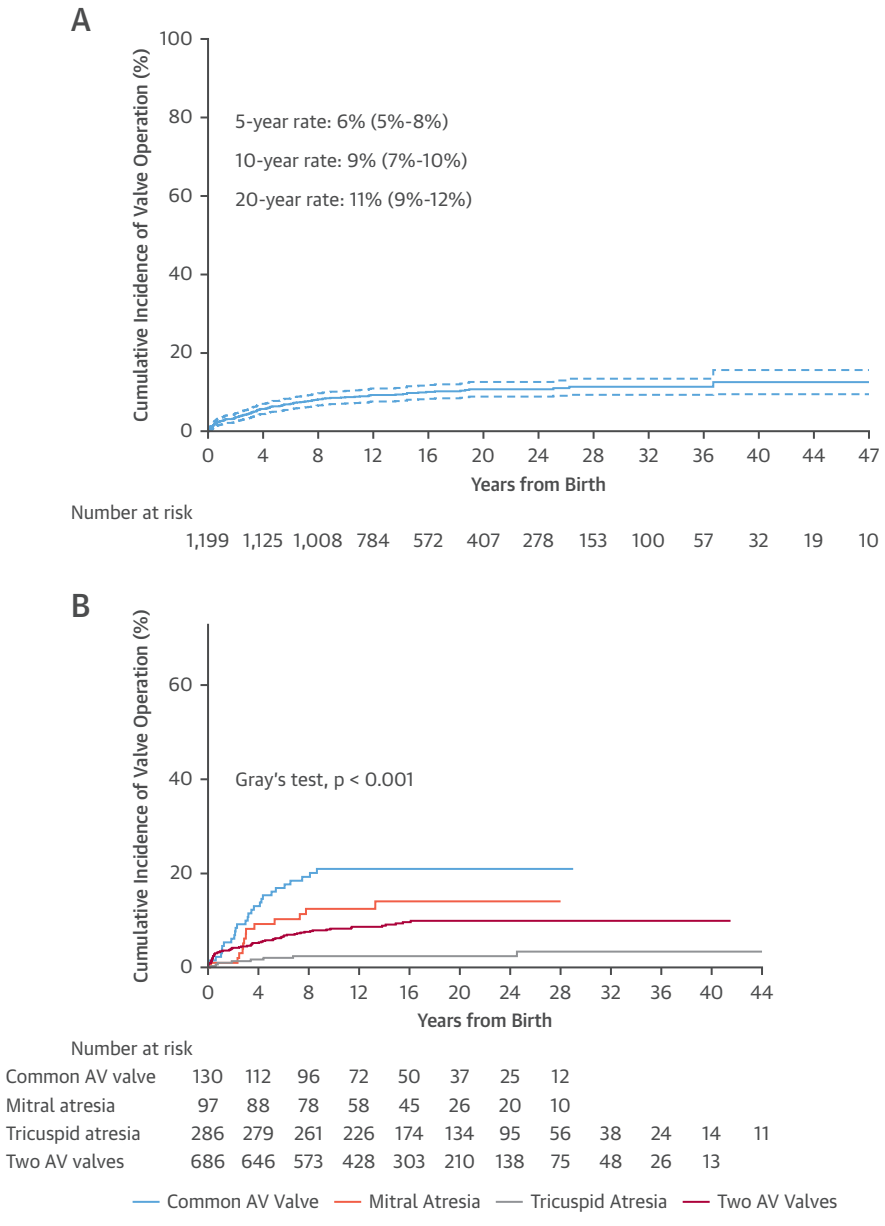
ATRIOVENTRICULAR VALVE INTERVENTION. A total of 120 patients underwent at least 1 atrioventricular valve operation. The median age at first atrioventricular valve operation was 3.4 years (IQR: 1.9 to 6.9 years). First atrioventricular valve operation consisted of 110 repairs and 10 replacements. With regard to timing of the index operation, 103 patients underwent intervention at or pre-Fontan completion, whereas 17 patients underwent intervention post-Fontan completion. The median age of the 110 patients who underwent initial valve repair was 3.1 years (IQR: 0.7 to 6.1 years). The median age of the 13 patients who underwent initial atrioventricular valve replacement, 3 of whom underwent previous valve repair, was 7.8 years (IQR: 3.8 to 14.2 years). The index atrioventricular operation consisted of 62 tricuspid valve operations (58 repairs, 4 replacements), 32 common atrioventricular valve operations (28 repairs, 4 replacements), 24 mitral valve operations (22 repairs, 2 replacements), and 2 dual mitral and tricuspid valve repairs (Figures 1A and 1B). In total, 132 repairs were performed on 110 patients, and 15 replacements were performed on 13 patients. The cumulative incidence of atrioventricular valve intervention at 5, 10, and 20 years of age was 6% (95% confidence interval [CI]: 5% to 8%), 9% (95% CI: 7% to 10%), and 11% (95% CI: 9% to 12%), respectively (Figure 2A). Figure 2B illustrates the cumulative incidence of atrioventricular valve intervention stratified by valve morphology. The cumulative incidence of atrioventricular valve

FIGURE 1 **Timing of Atrioventricular Valve Intervention**



Flow diagram illustrating the number of patients with atrioventricular valve intervention **(A)** before or at time of Fontan completion and **(B)** post-Fontan completion and the subsequent number of valve repair failures. CAVV = common atrioventricular valve; Dual = mitral and tricuspid valve; IQR = interquartile range; MV = mitral valve; TV = tricuspid valve.

FIGURE 2 Atrioventricular Valve Intervention



(A) Cumulative incidence curve for estimated incidence of atrioventricular valve intervention (repair or replacement) in patients who underwent Fontan palliation and **(B)** cumulative incidence curve for estimated incidence of atrioventricular valve intervention (repair or replacement) stratified by valvular morphology for patients who underwent Fontan palliation. **Dashed lines** denote 95% confidence intervals.

intervention at 25 years of age for patients with a common atrioventricular valve, mitral atresia, 2 atrioventricular valves, and tricuspid atresia was 25% (95% CI: 17% to 33%), 19% (95% CI: 9% to 28%), 10% (95% CI: 8% to 13%), and 3% (95% CI: 1% to 6%), respectively. Univariable analysis revealed a dominant right ventricle ($p < 0.001$), common atrioventricular valve, mitral atresia ($p < 0.001$), atrial isomerism ($p < 0.001$) and the diagnosis of an extracardiac syndrome ($p < 0.001$) to be predictors of atrioventricular valve intervention (Table 2). Using the variables identified in the univariable analysis, the multivariable model showed a dominant right ventricle ($p < 0.001$) and right atrial isomerism ($p = 0.002$) as independent predictors of atrioventricular valve intervention.

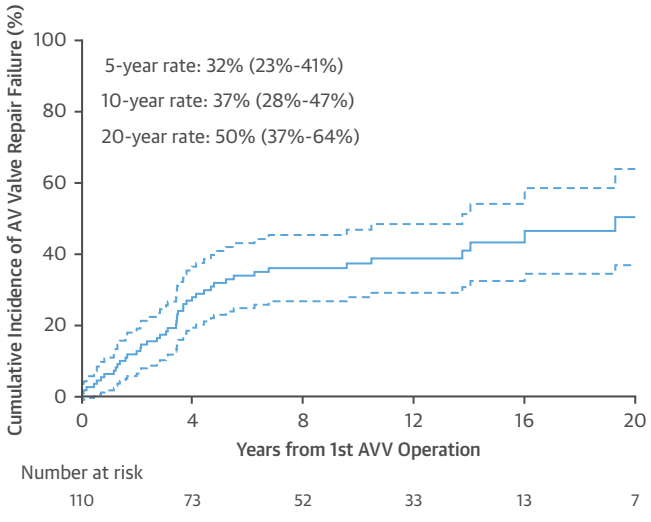
TABLE 2 Competing Risks Regression Models for Cumulative Incidence of AV Valve Intervention

	Patients (N = 1,199)	Events (N = 120)	Univariable Analyses HR (95% CI)	p Value	Multivariable Analyses HR (95% CI)	p Value
Sex						
Female	512	42	1.00	0.06		
Male	687	78	1.43 (0.98–2.08)			
Valve morphology*						
Common AV valve	130	32	1.00	<0.001		
Mitral atresia	97	15	0.60 (0.33–1.10)			
Tricuspid atresia	286	8	0.10 (0.05–0.21)			
Two AV valves	686	65	0.36 (0.24–0.55)			
Isomerism						
None	1,111	98	1.00	<0.001	1.00	0.002
Left	33	7	2.48 (1.16–5.30)		1.98 (0.91–4.31)	
Right	55	15	3.31 (1.96–5.60)		2.87 (1.64–5.02)	
Dextrocardia						
No	1,079	104	1.00	0.60		
Yes	99	11	1.18 (0.65–2.12)			
Dominant ventricle						
Right	375	57	1.00	<0.001	1.00	<0.001
Biventricular	81	11	0.87 (0.46–1.66)		0.82 (0.43–1.57)	
Indeterminate	27	2	0.46 (0.11–1.89)		0.34 (0.08–1.40)	
Left	716	50	0.42 (0.29–0.61)		0.46 (0.31–0.68)	
Extracardiac syndrome						
No	1,045	92	1.00	<0.001		
Yes	154	28	2.19 (1.44–3.34)			

Values are n unless otherwise indicated. *Omitted from the multivariable analysis due to collinearity (variance inflation factor >2).
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

DURABILITY OF VALVE REPAIR. Of the 110 patients who underwent repair as the index atrioventricular valve operation, the repair failed in 45 patients. Of the 28 index common atrioventricular valve repairs, 19 failed, including 9 re-interventions (7 re-repairs and 2 replacements). Of the 22 index mitral valve repairs, 3 failed, including 2 re-interventions (2 re-repairs). Of the 58 index tricuspid valve repairs, 21 failed, including 11 re-interventions (11 re-repairs). Of the 2 patients who underwent index dual mitral and tricuspid valve repairs, their mitral valve repairs failed with no re-interventions (Figures 1A and 1B). The median time to failure of initial valve repair was 3.4 years (IQR: 1.6 to 4.8 years). The 5-year, 10-year, and 20-year cumulative incidence of valve failure following initial valve repair was 32% (95% CI: 23% to 41%), 37% (95% CI: 28% to 47%), and 50% (95% CI: 37% to 64%), respectively (Figure 3). Univariable analysis revealed valve morphology (p = 0.001) and a dominant ventricle (p = 0.001) as predictors of atrioventricular valve repair failure (Table 3). Using the variables identified in the univariable analysis, a multivariable model was not obtained.

FIGURE 3 Durability of AV Valve Repair



Cumulative incidence curve for estimated incidence of atrioventricular (AV) valve repair failure (re-repair or replacement or recurrent moderate or greater regurgitation) following initial atrioventricular valve repair in patients who underwent Fontan palliation. **Dashed lines** denote 95% confidence intervals.

TABLE 3 Cox Regression Models for Freedom From AV Repair Failure

	Patients (N = 110)	Events (N = 45)	Univariable Analyses HR (95% CI)	p Value
Sex				
Female	37	14	1.00	0.50
Male	73	31	1.22 (0.65-2.30)	
Age at Fontan, yrs				
Per unit increase	110	45	1.01 (0.96-1.06)	0.80
Fontan fenestration				
No	51	19	1.00	0.20
Yes	67	25	1.46 (0.80-2.66)	
Valve morphology				
Common AV valve	28	19	1.00	0.001
Mitral atresia	12	8	0.88 (0.41-1.91)	
Tricuspid atresia	7	1	0.14 (0.02-1.09)	
Two AV valves	63	17	0.31 (0.16-0.60)	
Dominant ventricle				
Right	53	28	1.00	0.001
Biventricular	9	3	0.38 (0.14-1.04)	
Indeterminate	2	2	6.52 (3.44-12.4)	
Left	46	12	0.39 (0.20-0.78)	
Isomerism				
None	92	33	1.00	0.10
Left	7	6	2.67 (1.32-5.38)	
Right	11	6	1.63 (0.68-3.91)	
Dextrocardia				
No	100	39	1.00	0.10
Yes	10	6	1.87 (0.83-4.22)	
Extracardiac syndrome				
No	86	34	1.00	0.80
Yes	24	11	1.09 (0.58-2.04)	

Values are n unless otherwise indicated. Abbreviations as in Tables 1 and 2.

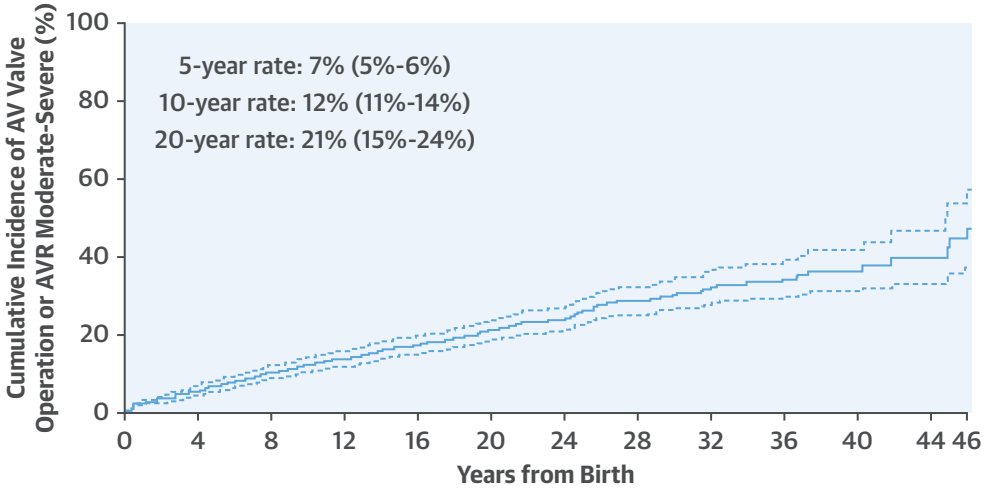
VALVE REPLACEMENT. A total of 15 valve replacements were performed on 13 patients. There were 10 valve replacements (4 common atrioventricular valves, 4 tricuspid valves, 2 mitral valves) as initial atrioventricular valve interventions. Seven of the index valve replacements occurred at or before Fontan completion (4 common atrioventricular valves, 2 tricuspid valves, 1 mitral valve) and 3 occurred post-Fontan (2 tricuspid valves, 1 mitral valve). Of the 4 patients who underwent common atrioventricular valve replacement as the initial intervention, 2 required re-replacement of the valve (12 and 6 years post-initial replacement, respectively). None of the patients who underwent tricuspid or mitral valve replacement as the initial intervention required re-replacement of the valve. Of the 13 patients who underwent valve replacement, 5 required heart transplantation and 5 died (2 who underwent transplantation and subsequently died).

ATRIOVENTRICULAR VALVE FAILURE. A total of 261 patients reached the composite endpoint of atrioventricular valve failure during their lifetime. The median age of atrioventricular valve failure was 8.6 years (IQR: 3.6 to 17.5 years). Of the 103 patients in whom the atrioventricular valve failed before or at Fontan completion, all of them reached the endpoint by way of atrioventricular valve operation. Of the 158 patients in whom the atrioventricular valve fail post-Fontan, 17 reached the endpoint by way of atrioventricular valve operation and 141 by way of echocardiographic degree of valve regurgitation. The cumulative incidence of atrioventricular valve failure at 5, 15, 30, and 45 years of age was 7% (95% CI: 5% to 8%), 17% (95% CI: 15% to 19%), 30% (95% CI: 27% to 34%), and 45% (95% CI: 36% to 54%), respectively (Central Illustration). The Central Illustration illustrates the cumulative incidence of atrioventricular valve failure stratified by valve morphology. The cumulative incidence of atrioventricular valve failure at 25 years of age for patients with a common atrioventricular valve, mitral atresia, 2 atrioventricular valves, and tricuspid atresia was 56% (95% CI: 46% to 67%), 46% (95% CI: 31% to 61%), 26% (95% CI: 21% to 30%), and 8% (95% CI: 4% to 12%), respectively. Univariable analysis revealed a dominant right ventricle ($p < 0.001$), a common atrioventricular valve, mitral atresia ($p < 0.001$), atrial isomerism ($p < 0.001$), and diagnosis of an extracardiac syndrome ($p < 0.001$) as predictors of atrioventricular valve failure. Using the variables identified in the univariable analysis, the multivariable model showed a dominant right ventricle ($p < 0.001$) and right atrial isomerism ($p = 0.005$) as independent predictors of atrioventricular valve failure (Table 4).

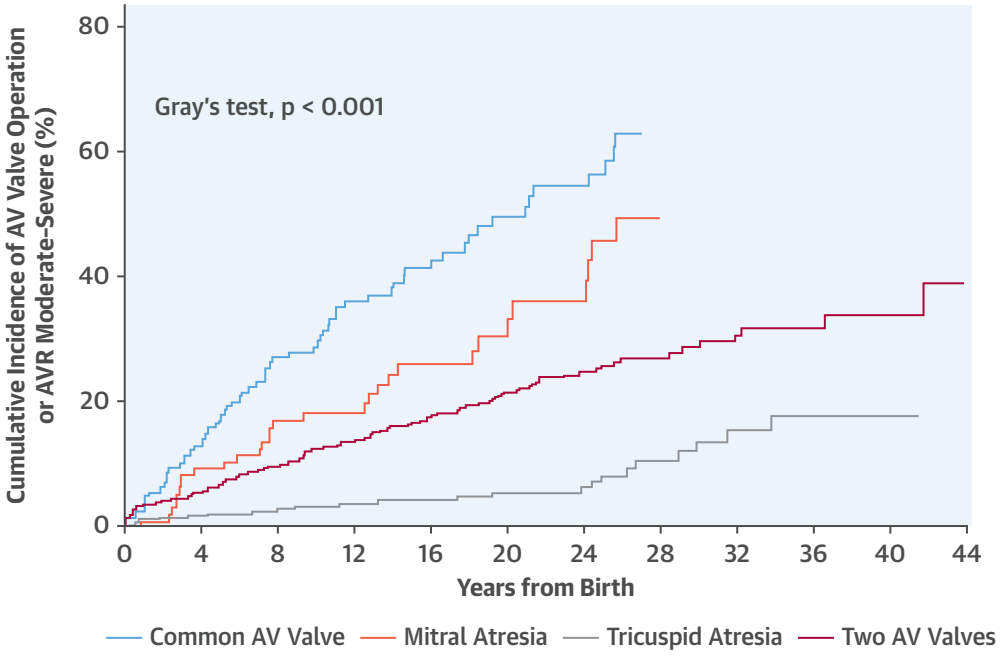
ATRIOVENTRICULAR VALVE FAILURE AT OR PRE-FONTAN COMPLETION. Valve failure occurred in 103 patients before or at the time of Fontan operation. As alluded to earlier, all of these patients underwent atrioventricular valve intervention (96 repairs, 7 replacements) at or before Fontan completion. Of these patients, Fontan failures occurred in 19 patients (12 deaths, 5 transplantations, 2 takedowns, 1 conversion, 4 patients developed protein-losing enteropathy, 1 patient developed plastic bronchitis, and 6 patients were classified as NYHA functional class III or higher during follow-up). The median time to Fontan failure was 2.7 years (IQR: 1.2 to 8.5 years). Of the 96 patients who underwent valve repair, repair failed in 39 patients. The median time to valve repair failure was 3.5 years (IQR: 2.1 to 5.4 years) (Figure 4A).

CENTRAL ILLUSTRATION **Atrioventricular Valve Failure**

A **Cumulative Incidence of Atrioventricular Valve Failure Entire Cohort**



B **Cumulative Incidence of Atrioventricular Valve Failure Stratified by Valvular Morphology**



King, G. et al. J Am Coll Cardiol. 2019;73(7):810–22.

(A) Cumulative incidence curve for estimated incidence of atrioventricular (AV) valve failure (moderate or greater regurgitation, or valve intervention) in patients who underwent Fontan palliation and **(B)** cumulative incidence curve for estimated incidence of AV valve failure (moderate or greater regurgitation, or valve intervention) stratified by valvular morphology for patients who underwent Fontan palliation. **Dashed lines** denote 95% confidence intervals. AVR = atrioventricular regurgitation.

TABLE 4 Competing Risks Regression Models for Cumulative Incidence of AV Valve Failure

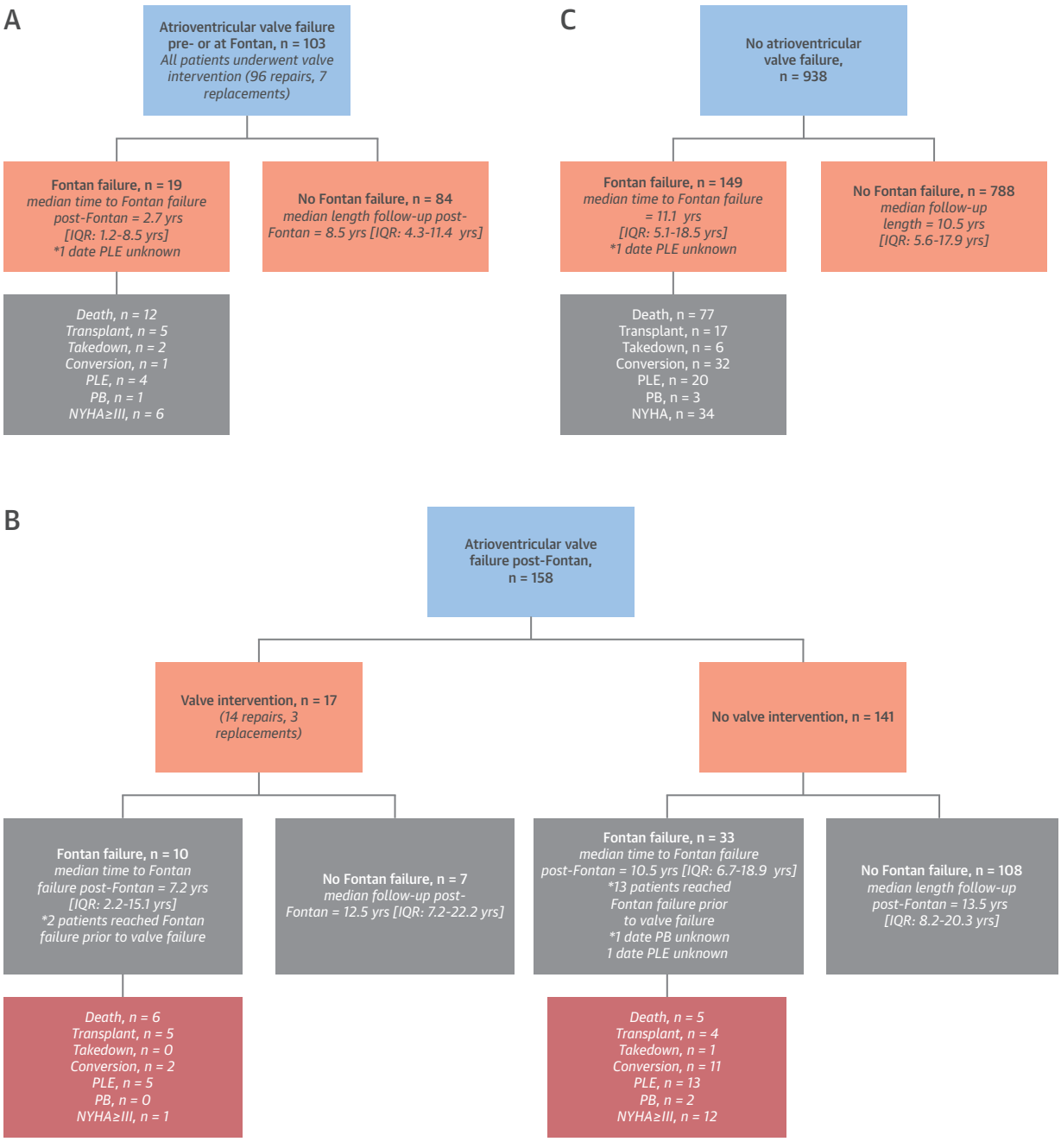
	Patients (N = 1,199)	Events (N = 261)	Univariable Analyses HR (95% CI)	p Value	Multivariable Analyses HR (95% CI)	p Value
Sex						
Female	512	115	1.00	0.90		
Male	687	146	1.02 (0.8–1.3)			
Valve morphology*						
Common AV valve	130	66	1.00	<0.001		
Mitral atresia	97	33	0.64 (0.43–0.96)			
Tricuspid atresia	286	23	0.11 (0.07–0.17)			
Two AV valves	686	139	0.35 (0.26–0.47)			
Isomerism						
None	1,111	221	1.00	<0.001	1.00	0.005
Left	33	13	1.99 (1.13–3.50)		1.44 (0.82–2.55)	
Right	55	27	2.92 (1.95–4.37)		2.02 (1.33–3.06)	
Dextrocardia						
No	1,097	236	1.00	0.70		
Yes	102	25	1.09 (0.73–1.64)			
Dominant ventricle						
Right	375	133	1.00	<0.001	1.00	<0.001
Biventricular	81	20	0.67 (0.42–1.09)		0.71 (0.44–1.14)	
Indeterminate	27	4	0.38 (0.14–1.07)		0.36 (0.13–0.96)	
Left	716	104	0.32 (0.24–0.41)		0.34 (0.26–0.44)	
Extracardiac syndrome						
No	1,045	210	1.00	<0.001		
Yes	154	51	1.94 (1.43–2.64)			

Values are n unless otherwise indicated. *Omitted from the multivariable analysis due to collinearity (variance inflation factor >2).
Abbreviations as in Tables 1 and 2.

ATRIOVENTRICULAR VALVE FAILURE POST-FONTAN COMPLETION. Of the 158 patients in whom valve failure occurred post-Fontan, 17 underwent valve intervention (14 repairs, 3 replacements). Fontan failure occurred in 10 of these patients (6 deaths, 5 transplantations, 2 conversions, 5 patients developed protein-losing enteropathy, and 1 patient was classified as NYHA functional class III or higher during follow-up). The median time to Fontan failure was 7.2 years (IQR: 2.2 to 15.1 years) (Figure 4B). Of the 14 patients who underwent valve repair, repair failed in 6 patients. Median time to valve repair failure was 0.94 years (IQR: 0.5 to 2.6 years) (Figure 1B). Of the 141 patients with moderate or greater regurgitation who did not undergo valve intervention, Fontan failures occurred in 33 patients (5 deaths, 4 transplants, 1 takedown, 11 conversions, 13 patients developed protein-losing enteropathy, 2 patients developed plastic bronchitis, and 12 patients were classified as NYHA functional class III or higher during follow-up). The median time to Fontan failure was 10.5 years (IQR: 6.7 to 18.9 years) (Figure 4B).

IMPACT OF ATRIOVENTRICULAR VALVE FAILURE ON FONTAN FAILURE. Three patients had protein-losing enteropathy, and 1 patient had plastic bronchitis; however, the date of onset was unknown. These patients were excluded from statistical analysis, bringing the total sample size to 1,195 and the number of patients in whom Fontan palliation failed to 208 patients. Of these 4 patients, 3 had reached the composite endpoint of atrioventricular valve failure and 1 did not. Of the 261 patients who had atrioventricular valve failure, the Fontan procedure failed in 59 patients. Of the 59 patients with atrioventricular valve failure in whom the Fontan procedure failed, 15 patients reached the endpoint of Fontan failure before failure of their atrioventricular valve. Of the 938 patients with no atrioventricular valve failure, the median follow-up length was 10.6 years (IQR: 5.6 to 18.0 years). Among these patients, Fontan failures occurred 149 patients (77 deaths, 17 transplantations, 6 takedowns, 32 conversions, 20 patients developed protein-losing enteropathy, 3 patients developed plastic bronchitis, and 34 patients were classified as NYHA functional class III or higher during follow-up). The median time to Fontan failure was 11.1 years (IQR: 5.1 to 18.5 years) (Figure 4C). Time-varying covariate analysis of

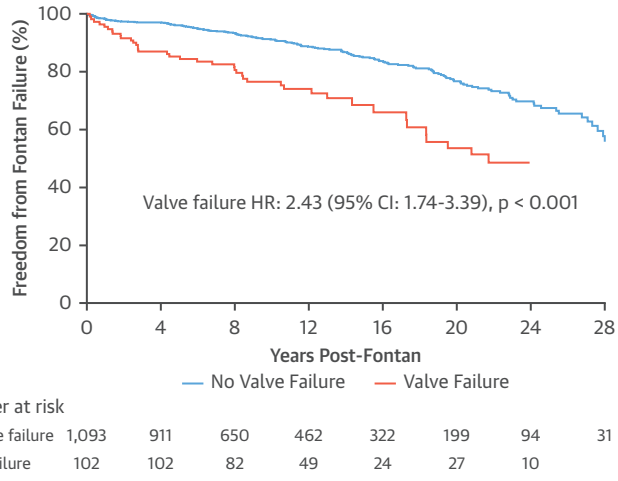
FIGURE 4 **AV Valve Failure and Fontan Failure**



Flow diagram illustrating the number of patients with AV valve failure **(A)** before or at time of Fontan completion and **(B)** post-Fontan completion, and **(C)** patients without AV valve failure and the subsequent number of Fontan failures. NYHA = New York Heart Association; PB = plastic bronchitis; PLE = protein losing enteropathy; other abbreviations as in Figures 1 and 3.

patients with atrioventricular valve failure and without atrioventricular valve failure is displayed in Figure 5. In patients without valve failure, freedom from Fontan failure at 10 and 20 years post-Fontan was 91% (95% CI: 89% to 93%) and 77% (95% CI: 73% to 81%), respectively. In patients with valve failure, freedom from Fontan failure at 10 and 20 years post-Fontan was 77% (95% CI: 69% to 85%)

FIGURE 5 AV Valve Function and Fontan Failure



Time-varying covariate Kaplan-Meier curve for estimated freedom from Fontan failure in patients with AV valve failure **(orange line)** and in patients without AV valve failure **(blue line)**. HR = hazard ratio; other abbreviation as in Figure 3.

and 54% (95% CI: 42% to 68%), respectively (HR: 2.43; 95% CI: 1.74 to 3.39; $p < 0.001$).

DISCUSSION

As patients with Fontan circulation continue to survive further into adulthood, it becomes increasingly important to understand factors that affect the durability of the Fontan circulation. This is particularly significant if we are able to identify risk factors that can be negated. A significant burden of morbidity and mortality post-Fontan is attributed to arrhythmias, protein-losing enteropathy, liver disease, thromboembolism, and reduced exercise tolerance (7–11). Previous studies have highlighted variables such as pre-operative ventricular dysfunction, pre-operative pulmonary artery pressures, right ventricular dominance, and atrioventricular valve regurgitation as predictors of poor outcomes for patients undergoing single ventricle palliation (3,12,13).

The rate of failure of the atrioventricular valve in Fontan palliation has not been clearly elucidated until now. Our results showed that nearly one-third of all patients who underwent Fontan palliation would have failure of their atrioventricular valve by 30 years of age. When divided into subgroups based upon valve morphology, we showed that approximately two-thirds of patients with a common atrioventricular valve and one-half of the patients with a single tricuspid valve would experience failure of their atrioventricular valve by 30 years of age. As was the case with our recent series that evaluated common atrioventricular valve function, these data showed no evidence of plateau in the rate of failure of the atrioventricular valve, which suggested that these valves would continue to fail as patients with a Fontan circulation live longer (14). Our results showed that isomerism and a dominant right ventricle were independent predictors of atrioventricular valve failure and valve intervention.

Such a high incidence of valve failure in patients with Fontan circulation was unanticipated, but its real impact remains difficult to determine at this stage. Valve regurgitation would undoubtedly negatively affect pulmonary blood flow; therefore, it would be expected to contribute to failure of the Fontan circulation. Our results showed that failure of the atrioventricular valve increased the rate of Fontan failure >2-fold. In approximately one-half of the patients with valve failure, the Fontan procedure failed within 20 years of Fontan completion.

Whether re-operation should be offered to these patients and at which stage remains unclear. Repair of these valves remains difficult, with a significant proportion of those undergoing repair experiencing a failure of the repair within 5 years. The results of valve replacement remain uncertain. In the Mayo Clinic experience, one-half of the patients who underwent atrioventricular valve surgery after Fontan palliation died within a decade of these operations (15). Our results showed that, in our region, the clinicians following these patients were reluctant to offer surgery in the setting of moderate or greater regurgitation post-Fontan. Of patients who experienced valve failure before Fontan completion, all underwent valve intervention. Our regional preference was to offer valve surgery before Fontan surgery as a separate, rather than a concomitant, procedure. Of patients who experienced moderate or greater regurgitation after Fontan completion, approximately 1 in 10 underwent valve intervention. At this stage, it remained difficult to assess the outcomes between patients with valve failure who underwent intervention before the Fontan procedure compared with those post-Fontan and those who did not receive intervention. Moderate regurgitation was likely well tolerated in those patients for several years, whereas valve intervention was likely associated with a clear mortality and uncertain outcomes. In the Mayo Clinic experience, the early mortality of valve surgery post-Fontan was 13%, and predictors of mortality were the degree of ventricular dysfunction and the presence of protein-losing enteropathy (15). To decrease mortality, the benefits of a lower threshold for intervention

should be explored. It is also possible that valve replacement should be favored over an unsatisfactory repair, as we discussed in response to the recent series that evaluated the experience of atrioventricular valve replacement in the Japan Cardiovascular Database (16,17). We are not yet in a position to determine whether re-operation would modify the final outcome of those with a Fontan circulation who develop valve regurgitation, especially when this regurgitation is only moderate.

STUDY LIMITATIONS. Grading the degree of atrioventricular valve regurgitation has an element of subjectivity, and, as such, patients deemed to have the same grade of regurgitation might, in reality, experience differing grades of regurgitation. Patients with atrioventricular valve regurgitation are less likely to reach Fontan completion. Data for this study were extracted from the Australia and New Zealand Fontan Registry. Entry criteria for this registry included survival after Fontan, and as such, the incidence of atrioventricular valve failure and the impact that this had on patients who underwent single ventricle and Fontan palliation was likely underestimated. Furthermore, estimates of the incidence of valve regurgitation might be imprecise because patients with incomplete echocardiographic follow-up were excluded. The study was not able to assess the impact of atrioventricular valve intervention on negating the impact of moderate or greater regurgitation due to the limited sample size of the study cohort. Future research should focus on how atrioventricular valve repair or replacement affects long-term outcomes for Fontan patients with moderate or greater regurgitation. This was a retrospective cohort study; therefore, it was limited in its ability to account for compounding variables that might have influenced results. For instance, mitral valve atresia and right ventricular dominance both conferred an increased risk of atrioventricular valve failure. Most patients with mitral atresia had a dominant right ventricle. This study could not isolate the impact of each variable as a predictor of atrioventricular valve failure.

CONCLUSIONS

Patients with Fontan circulation are facing an unexpected burden of valve disease that is likely to affect their outcomes. The question remains whether valve regurgitation warrants re-intervention and at what stage.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: There is a high incidence of atrioventricular valve failure in patients undergoing single ventricle palliation, particularly in those with a common atrioventricular valve or a single tricuspid valve, and this is associated with an increased risk of Fontan failure compared to patients with intact atrioventricular valves.

TRANSLATIONAL OUTLOOK: It remains unclear whether valve intervention in patients with regurgitation improves long-term outcomes, particularly when regurgitation is not severe.

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