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ORIGINAL ARTICLE

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The presence of an additional ventricular chamber does not change the outcome of Fontan circulation: a comparative study

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Key question

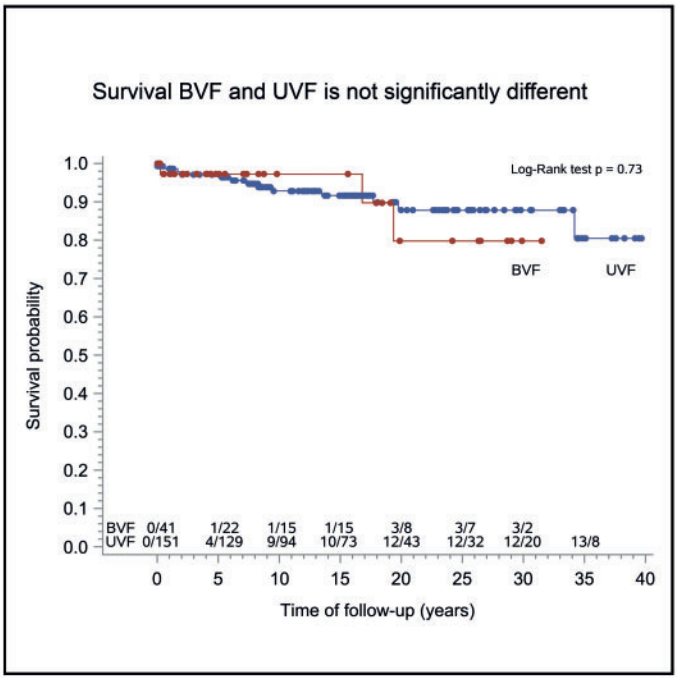
Is the presence of an additional ventricular chamber a prognostic risk factor for Fontan circulation?

Key finding(s)

We found no significant differences in clinical outcomes when an additional ventricle was present in Fontan circulation.

Take-home message

An additional ventricle in Fontan circulation is not significantly related to greater incidence of death or onset of complications.



Abstract

OBJECTIVES: The role of an additional ventricle in patients with a functional single ventricle undergoing the Fontan operation has been debated due to conflicting data. Our goal was to report our experience with Fontan circulation for complex congenital heart disease, with a focus on the influence that an additional ventricular chamber may have on early and long-term clinical outcomes.

METHODS: We performed a retrospective clinical study including all patients undergoing the Fontan procedure between 1978 and 2019. Clinical data were retrieved from our institutional database. A 'biventricular' Fontan (BVF) was defined as that performed in a patient with single ventricle anomaly where an additional diminutive ventricular cavity was present at echocardiographic evaluation.

RESULTS: A total of 210 consecutive patients with functional single ventricle were included. Among these, 46 had BVF (21.9%). Early complications occurred in 42 patients (20.0%; 11 in BVF vs 31 in univentricular Fontan; $P = 0.53$) There were 18 early deaths (8.6%) with no

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difference between the groups. At a median follow-up of 12.7 years (interquartile range 5.4–20.7), there were no significant differences in late mortality, whereas cardiac rhythm disturbances resulted more frequently in univentricular Fontan ($P = 0.018$). Statistical analysis showed an equal distribution of BVF across time ($P = 0.620$), and there were no significant differences in terms of early and late survival ($P = 0.53$ and $P = 0.72$, respectively) or morbidity ($P = 0.45$ and $P = 0.80$, respectively).

CONCLUSIONS: A secondary ventricle in Fontan circulation is not significantly related to any clinical disadvantage in terms of survival or onset of complications. However, the immediate postoperative course may be influenced negatively by the presence of an additional secondary ventricle.

Keywords: Fontan circulation • Single ventricle • Congenital heart disease • Ventricular morphology • Outcomes

ABBREVIATIONS

BVF	Biventricular Fontan
CHD	Congenital heart disease
CI	Confidence interval
FSV	Functionally single ventricle
RV	Right ventricle
UVF	Univentricular Fontan

INTRODUCTION

A 'functionally' single ventricle (FSV) is a complex congenital heart disease (CHD) in which only 1 ventricle is fully developed. It represents a complex clinical problem that entails different morphological diagnoses [1, 2]. Since 1971, the Fontan palliation has provided survival for patients with complex FSV who previously had no chance of survival [3]. Over the years, technical modifications of the original Fontan procedure have been introduced to improve clinical outcomes. Currently, patients undergoing the Fontan operation experience low perioperative mortality and good long-term survival [4]. In addition, originally created for the surgical treatment of tricuspid atresia, the Fontan operation has been gradually extended to all complex CHD with an FSV [5]. This heterogeneous group of patients has a great variety of complex CHD, which may have more than only 1 ventricle or even 2 ventricles of adequate size but not amenable to biventricular repair because of anatomical complexity that makes it a high-risk procedure [6].

The group with 'more than 1 ventricle' is a particular population of Fontan patients in whom the role of the additional secondary ventricle is not clear. In particular, it is not clear if this accessory ventricle may interfere with cardiac function and Fontan circulation haemodynamics, affecting early and long-term outcomes. Several hypotheses can be made, but few studies in the literature have focused on this specific topic. Also, most reports are about patients with only 2 adequate ventricles, not counting those with an additional diminutive one [7–9].

We report our experience of 40 years with Fontan circulation in complex CHD with FSV to evaluate whether an additional ventricular chamber of any size may influence significantly early and long-term outcomes.

MATERIALS AND METHODS

We performed a single-centre retrospective, observational, longitudinal study including patients with FSV undergoing the Fontan procedure between November 1980 and March 2019. A review of medical records was approved by the hospital committee for clinical investigation (prot. number 75n/AO/2020). Individual patients were de-identified, and the need for patient consent was waived. We excluded those patients for whom sufficient information about the additional ventricle was not available. Preoperative data included demographics, anatomical variants, associated cardiac and non-cardiac disease and basic imaging (echocardiography, cardiac catheterization); cardiopulmonary bypass times, association with fenestration, onset of major postoperative complications, early (within 30 days after the operation or during hospitalization) death or complications.

Follow-up information collected between March 2019 and March 2020 included clinical status (New York Heart Association functional class > II) and adverse events as follows: death; surgical or interventional cardiology procedures; clinically significant arrhythmias (when treated with antiarrhythmic drug therapy, pacemaker placement or electrical/pharmacological cardioversion); pulmonary hypertension (when on pulmonary vasodilator therapy); protein-losing enteropathy, if there was evidence of enteric loss of alpha-1-antitrypsin or a low level of serum total protein/albumin; liver disease (based on liver characteristics on ultrasound and transient elastography evaluation).

All patients underwent a preoperative 2-dimensional echocardiography and Doppler study and cardiac catheterization to measure pulmonary artery pressure and pulmonary vascular resistance. Standardized 2-dimensional and Doppler echocardiograms were performed in our hospital by the same group of paediatric cardiologists; the ejection fraction of the dominant systemic ventricle was obtained with the biplane Simpson method.

The patients were classified into 2 groups: biventricular Fontan (BVF), when any additional ventricular cavity was evidenced at imaging; univentricular Fontan (UVF), when an additional ventricular cavity was absent, virtual or extremely hypoplastic. It is of note that the additional ventricular cavities might also have adequate dimensions that preclude anatomical biventricular repair during decision-making for reasons other than ventricular size.

The 'dominant ventricle' or 'primary ventricle' was designated as such because of its larger size and because it received most of the ventricular inflow [10]. The smaller ventricle was defined as the 'secondary ventricle'. When the ventricles were similar in size, the classification of primary and secondary was adjudicated according to each ventricle's contribution to the systemic output (patent connection to the aorta directly or through a ventricular septal defect).

This 'functional' differentiation (BVF vs UVF) was made by our cardiologists after they examined available images and records, combining preoperative imaging findings with intraoperative anatomical surgical observations on the surgical report. Patients with atrioventricular valve atresia were included.

The primary outcomes were assessment of (i) overall mortality and morbidity in the entire population, (ii) evaluation of any significant difference in mortality and morbidity in BVF versus UVF

and (iii) any significant differences in mortality and morbidity between patients with dominant anatomical right versus left ventricles.

Surgical evolution

Technical changes are described in detail in Supplementary Material, Appendix S1.

Statistical analyses

The results for categorical variables are presented as the number and percentage of patients in each category, as the mean and standard deviation and as the median and interquartile range in the case of quantitative variables. The normality of quantitative variables was checked graphically with a *Q*–*Q* plot and with the Shapiro–Wilk test. Categorical variables were analysed with the Fisher's exact test and quantitative variables, with the Mann–Whitney test. We performed logistic regression for early mortality and morbidity and presented the results as *P*-value, odds ratio and 95% confidence interval (CI). Cox regression was applied to late mortality and morbidity; results are expressed as *P*-value, hazard ratio and 95% CI.

When the number of events considered was consistent with the '1 in 10' rule of thumb, we introduced the group factor (BVF/UVF) in the multivariable model, and those variables resulted in statistically significant values at the 5% level in the univariate models.

Event-free survival was estimated with the Kaplan–Meier method, and the numbers of patients who survived were compared with the log-rank test. Survival was estimated with the 95% CI at specific time points (every 5 years). The follow-up period was calculated from the operation to the event considered or to the last follow-up for those who survived the event.

To adjust for possible confounders, we weighted the univariate logistic and Cox regression for the group effect (unibiventricular). Weights were calculated with propensity scores using the inverse probability weighting method and considering the following as confounding variables: sex (male/female), age at surgery, time of surgery (1981–1990/1991–2000, >2000), type of Fontan and systemic right ventricle (RV). Tables are presented for unweighted/weighted standardized differences and the BVF/UVF ratio. We judged that we had obtained the right balance when the weighted standardized difference was <0.25 and the weighted ratio ranged from 0.5 to 2.

The analyses were exploratory in nature, so there was no prespecified plan to adjust *P*-values and CIs for multiple comparisons. A *P*-value <0.05 was indicative of statistical significance. Data were analysed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for Windows.

RESULTS

A total of 210 patients undergoing the Fontan procedure between June 1978 and March 2019 were included in the study. Among these patients, 46 had BVF. Complete preoperative and postoperative patient characteristics are shown in Table 1. In the BVF group, the most frequent diagnoses were double-outlet RV (15 patients, 32.6%) and unbalanced common atrioventricular septal defect (8 patients, 17.4%).

A dominant RV was present in 78 patients, a left ventricle in 115 and undetermined in 17. Of note, a dominant RV and undetermined ventricles were significantly more frequent in the BVF group.

Levocardia was present in 196 patients (92.9%). The prevalence of dextrocardia/mesocardia and heterotaxy syndrome was significantly higher in the BVF group ($P = 0.016$ and $P < 0.001$, respectively) (Table 1). The age at surgery was significantly higher in the BVF group ($P = 0.001$). Associated surgery was higher in the UVF group (65 patients, 39.6%; $P = 0.036$), and the most frequent procedures were atrioventricular valve plasty and surgery on the pulmonary branches.

Postoperatively, patients with a BVF had a longer stay in the intensive care unit (4.0 ± 6.3 vs 6.4 ± 10.7 days; $P = 0.004$) and longer chest tube drainage time (6.6 ± 7.7 vs 9.5 ± 8.7 days; $P = 0.038$). However, onset of postoperative low cardiac output syndrome and of arrhythmias at discharge was not significantly different between the 2 groups (Table 2).

Overall, logistic regression analysis confirmed that the staged approach ($P = 0.004$), most recent surgical era ($P = 0.015$), fenestration ($P = 0.007$) and total cavopulmonary connection technique ($P = 0.006$) were predictors of better early survival (Table 3). Interestingly enough, BVF was not significantly associated with early mortality ($P = 0.53$).

At a median follow-up of 12.7 years (interquartile range 5.4–20.7), there were 16 late deaths, with no significant difference between BVF and UVF ($P = 0.72$; Table 2). It is of note that 23 patients (11.9%) after an atriopulmonary connection underwent a Fontan revision (22 in the UVF group and 1 in the BVF group) and 4 required heart transplants (2 patients in each group). Rhythm disturbances at follow-up were more frequent in the UVF group ($P = 0.018$).

Cox regression analysis (Table 4) showed that predictors of late mortality were heart failure ($P = 0.002$), liver disease ($P = 0.019$) and pulmonary hypertension ($P = 0.030$), whereas the presence of an additional ventricular chamber was not significant ($P = 0.72$). As shown in Table 2, we could not find any significant difference in the incidence of late heart failure, liver disease or pulmonary hypertension between the 2 groups. Furthermore, there were no significant differences between UVF and BVF in the incidence of early ($P = 0.45$) (Table 5) and late morbidity ($P = 0.80$) (Table 6). Multivariate analyses confirmed that UVF and BVF were not statistically different as far as early and late morbidity are concerned (Tables 5 and 6).

Last, using inverse probability weighting propensity, we obtained a reasonable balance in the selected confounders that we considered (Supplementary Material, Appendices S2 and S3). It is of note that this method showed that only late mortality was significantly higher in the BVF group ($P = 0.036$; hazard ratio = 2.00, 95% CI 1.05–3.85). Long-term survival and freedom from adverse events are shown in Figs 1 and 2.

DISCUSSION

We evaluated our experience with the long-term clinical outcomes of Fontan patients, focusing on demonstrating any influence of any additional ventricular chamber on clinical outcomes. Based on our data, the presence of an additional ventricular chamber does not seem to be a significant adjunctive risk factor.

Table 1: Preoperative and postoperative patient characteristics

		UVF (*N* = 164)	BVF (*N* = 46)	*P*-value	Total (*N* = 210)
Year of surgery, *n* (%)	1978–1990	38 (22.2)	8 (17.4)	0.62[2]	46 (21.9)
	1991–2000	39 (23.8)	10 (21.7)		49 (23.2)
	2001–2019	87 (53.0)	28 (60.9)		115 (54.8)
Sex, *n* (%)	Male	103 (62.8)	25 (54.3)	0.40[2]	128 (60.9)
Ventricle morphology, *n* (%)	Left	108 (65.8)	7 (15.2)	**<0.0012**	115 (54.8)
	Right	52 (31.7)	26 (56.5)		78 (37.1)
	Indeterminate	4 (2.4)	13 (28.3)		17 (8.1)
Cardiac position, *n* (%)	Normal	157 (95.7)	39 (84.8)	**0.016[2]**	196 (92.9)
	Dextrocardia/mesocardia	7 (4.3)	7 (15.2)		15 (7.1)
Isomerism (heterotaxy), *n* (%)	None	159 (97.0)	30 (65.2)	**<0.0012**	189 (90.0)
	Left	1 (0.6)	7 (15.2)		8 (3.8)
	Right	4 (2.4)	9 (19.6)		13 (6.2)
Primary diagnosis, *n* (%)	Tricuspid atresia	57 (34.8)	0 (0.0)	**<0.0012**	57 (27.1)
	HLHS	35 (21.3)	0 (0.0)		35 (16.7)
	Double-inlet left ventricle	29 (17.7)	1 (2.2)		18 (8.6)
	DORV/CAVSD	5 (3.0)	7 (15.2)		12 (5.7)
	Double-outlet right ventricle	3 (1.8)	15 (32.6)		30 (14.3)
	Unbalanced CAVSD	1 (0.6)	8 (17.4)		9 (4.3)
	Mitral atresia	9 (5.5)	5 (10.9)		14 (6.7)
	PA/IVS	19 (11.6)	1 (2.2)		20 (9.5)
	Other	6 (3.7)	9 (19.6)		15 (7.1)
Age (months) at surgery		**58.7 (69.9)**	**71.2 (51.0)**	**0.001a**	61.6 (66.4)
Mean (SD)		**39.5 (29–55)**	**60.5 (39–75)**		41.5 (29–64)
Median (IQR)					
Surgery, *n* (%)	Atriopulmonary	38 (23.2)	7 (15.2)	0.33[2]	45 (21.4)
	Lateral tunnel	45 (27.4)	9 (19.6)		54 (25.7)
	Extracardiac tunnel	79 (48.2)	30 (65.2)		109 (51.9)
	Other	2 (1.2)	0 (0.0)		2 (1.0)
Fenestration, *n* (%)		104 (63.8)	30 (65.2)	1.00[2]	134 (64.1)
Associated surgery, *n* (%)		**65 (39.6)**	**10 (21.7)**	**0.036[2]**	75 (35.7)
ICU stay (days)		**4.0 (6.3)**	**6.4 (10.7)**	**0.004a**	4.5 (7.5)
Mean (SD)		**2 (1–4)**	**3.0 (2–5)**		2 (2–4)
Median (IQR)					
Chest tube drain (days)		**6.6 (7.7)**	**9.5 (8.7)**	**0.038a**	7.2 (8.0)
Mean (SD)		**4 (2–8)**	**6 (5–12)**		5 (2–8)
Median (IQR)					
Arrhythmia, *n* (%)		23 (15.0)	6 (14.3)	1.00[b]	29 (14.9)
Postoperative low cardiac output syndrome, *n* (%)		15 (11.9)	5 (19.2)	0.34[b]	20 (13.2)
Early death, *n* (%)		13 (7.9)	5 (10.9)	0.55[b]	18 (8.6)
Overall early morbidity, *n* (%)		31 (18.9)	11 (23.9)	0.53[b]	42 (20.0)

[a]Wilcoxon test.

[b]Fisher's exact test.

BVF: biventricular Fontan; CAVSD: common atrioventricular septal defect; DORV: double-outlet right ventricle; HLHS: hypoplastic left heart syndrome; ICU: intensive care unit; IQR: interquartile range; IVS: intact ventricular septum; PA: pulmonary atresia; SD: standard deviation; UVF: univentricular Fontan.

Boldface are those values which are statistically significant.

The Fontan principle was first applied to patients with tricuspid atresia and subsequently extended to patients with complex CHD with FSV, in which only 1 ventricle is adequate to sustain cardiac output, even when another diminutive ventricular chamber is present [6, 8, 11–13]. Also, the Fontan principle may be pursued even when the ventricles are adequately developed, and a biventricular repair is not feasible because the anatomical complexity makes it impossible to separate the 2 circulations or because the surgical risk is exceedingly high [6, 8, 11–13].

Several patients currently have an additional ventricular chamber, which is included in the Fontan circuit, and cardiac output is propelled by more than 1 ventricle. However, the effective role of such a secondary ventricle in the Fontan circulation has long been debated due to conflicting data emerging from the literature [7, 8, 11–13]. It has been speculated that through ventricle–ventricle interaction, a large secondary ventricle may impair the function of the primary ventricle. Using tagged cardiac magnetic resonance imaging, Kurotobi *et al.* [14] showed that a larger secondary ventricle was associated with impaired regional shortening, asynchronous contraction and greater end-diastolic pressure of the primary ventricle. Fogel *et al.* [15] also used tagged cardiac magnetic resonance imaging to demonstrate that in patients with a hypoplastic RV, left ventricular strain, radial motion and twisting were abnormal.

In contrast, Wisler *et al.* [16] did not find a consistent correlation between the size of the hypoplastic left ventricle and the echocardiographic measurements of global RV function in patients with hypoplastic left heart syndrome. Although these studies have shown that the secondary ventricle can affect the regional functioning of the primary ventricle, the effects of such ventricle–ventricle interactions on global cardiovascular performance are still unclear. Also, the presence of an accessory ventricular chamber may bring with it the potential disadvantage of flow dynamics, i.e. conflicting flow turbulence that can be created

Table 2: Patient characteristics at follow-up

		UVF (n = 151)	BVF (n = 41)	P-value	Total (N = 192)
Follow-up time (years)		15.3 (10.7)	10 (10.3)		14.1 (10.8)
Mean (SD)		13.5 (7.3–23.1)	5.2 (1.1–18.4)		12.7 (5.4–20.7)
Median (IQR)					
Late death, n (%)		13 (8.6)	3 (7.3)	0.72[b]	16 (8.3)
Overall morbidity, n (%)		70 (46.4)	13 (31.7)	0.80[b]	83 (43.2)
Late cardiac failure, n (%)		12 (10.2)	4 (14.3)	0.51[a]	16 (11.0)
Liver disease, n (%)		9 (7.6)	0 (0.0)	0.21[a]	9 (6.2)
Pulmonary hypertension, n (%)		11 (9.3)	4 (14.3)	0.49[a]	15 (10.3)
Protein-losing enteropathy, n (%)		7 (6.3)	1 (3.8)	1.00[a]	8 (5.8)
Cardiac rhythm, n (%)	Sinus	84 (63.2)	31 (88.6)	**0.018**[a]	115 (68.4)
	Pacemaker	28 (21.0)	1 (2.9)		29 (17.3)
	Arrhythmias necessitating direct-current shock	7 (5.3)	1 (2.9)		8 (4.8)
	Atrial-junctional rhythm	14 (10.5)	2 (5.7)		16 (9.5)
Surgical reoperations, n (%)		26 (17.2)	4 (9.8)	0.33[a]	30 (15.6)

[a]Fisher's exact test.
[b]Cox regression.
BVF: biventricular Fontan; IQR: interquartile range; SD: standard deviation; UVF: univentricular Fontan.
Boldface are those values which are statistically significant.

Table 3: Summary statistics of potential predictors of late mortality and univariate Cox regression results

Variables		Early deaths		OR (95% CI)	P-value
		Yes (n = 18)	No (n = 192)		
Year of surgery, n (%)	2001–2019	5 (27.8)	110 (57.3)	1	0.015
	1991–2000	4 (22.2)	45 (23.4)	1.96 (0.50–7.62)	
	1978–1990	9 (50.0)	37 (19.3)	5.35 (1.69–16.98)	
Age at surgery (months)		57.6 (52.5)	62.0 (67.6)	1.00 (0.99–1.01)	0.79
Mean (SD)		31.5 (25–86)	43 (29.5–64)		
Median (IQR)					
Systemic RV, n (%)		9 (50.0)	69 (35.9)	1.78 (0.68–4.70)	0.24
Staged Fontan, n (%)		8 (44.4)	146 (77.2)	**0.24 (0.09–0.63)**	**0.004**
Fenestration, n (%)		6 (33.3)	128 (67.0)	**0.25 (0.09–0.69)**	**0.007**
TCPC versus atriopulmonary, n (%)		9 (50.0)	154 (80.2)	**0.25 (0.09–0.66)**	**0.006**
Associated surgery, n (%)		9 (50.0)	66 (34.4)	1.91 (0.72–5.04)	0.19
ICU stay (days)		4.1 (3.1)	4.6 (7.8)	0.99 (0.91–1.08)	0.82
Mean (SD)		3 (2–5)	2 (2–4)		
Median (IQR)					
Missing, 9					
Chest tube drainage (days)		16.0 (16.8)	6.6 (6.9)	**1.09 (1.03–1.16)**	**0.005**
Mean (SD)		6.5 (3–35)	5 (2–8)		
Median (IQR)					
Rhythm disturbances, n (%)		4 (57.1)	25 (13.3)	8.69 (1.84–41.16)	**0.006**
Low cardiac output syndrome, n (%)		9 (52.9)	11 (8.1)	**12.68 (4.08–39.44)**	**<0.001**
BVF, n (%)		5 (27.8)	41 (21.3)	1.42 (0.48–4.20)	0.53

BVF: biventricular Fontan; CI: confidence interval; ICU: intensive care unit; IQR: interquartile range; OR: odds ratio; RV: right ventricle; SD: standard deviation; TCPC: total cavopulmonary connection.
Boldface are those values which are statistically significant.

inside the ventricular cavities, which may affect the cardiac output bloodstream line [7]. Additionally, this turbulence may cause consumption of blood factors [17] and coagulation problems, which often cause substantial morbidity in Fontan patients [18].

Furthermore, postoperative diastolic dysfunction after the Fontan procedure may be acutely increased by the presence of an additional hypertrophic cardiac chamber that, instead of contributing to the antegrade blood flow of the cardiac output, on the contrary, may affect it adversely. The potential conflicting intraventricular bloodstream lines may cause an intracardiac blood flow vortex that can sharpen the postoperative cardiac dysfunction and contribute to the onset of postoperative low cardiac output [13, 14, 19]. These hypotheses may explain why patients with BVF in our series showed a more extended stay in the intensive care unit and a longer time with chest tube drainage, because having a larger myocyte mass could lead to more significant transitional diastolic impairment and higher pressure in the Fontan circuit in the immediate postoperative period.

This analysis of long-term experience with Fontan circulation has confirmed the improved early and late results over the decades (Tables 3–6). Specifically, in our series the presence of an additional ventricular chamber is not a convincing predictor of worse outcome (Tables 3–6), which confirms the report by Marathe *et al.* [8], who investigated the role of BVF with 2 fully

Table 4: Summary statistics of potential predictors of late mortality and univariate Cox regression results

		Late mortality		HR (95% CI)	*P*-value
		Yes (*n* = 16)	No (*n* = 176)		
Year of surgery, *n* (%)	2001–2019	2 (12.5)	108 (61.4)	1	0.19
	1991–2000	7 (43.7)	38 (21.6)	4.37 (0.87–22.03)	
	1978–1990	7 (43.7)	30 (17.1)	3.87 (0.73–20.38)	
Age at surgery (months)		91.9 (93.3)	59.3 (64.5)	**1.00 (1.00–1.01)**	**0.057**
Mean (SD)		36 (26.5–150.5)	43.5 (30.5–63.5)		
Median (IQR)					
Systemic RV, *n* (%)		4 (25.0)	65 (36.9)	0.75 (0.24–2.35)	0.62
Staged Fontan, *n* (%)		10 (62.5)	136 (78.6)	0.99 (0.34–2.87)	0.99
Fenestration, *n* (%)		5 (31.2)	123 (70.3)	0.43 (0.14–1.33)	0.14
Heart failure, *n* (%)		5 (83.3)	11 (7.9)	**28.69 (3.27–251.62)**	**0.002**
Liver disease, *n* (%)		3 (50.0)	6 (3.7)	**8.01 (1.42–45.27)**	**0.019**
Pulmonary hypertension, *n* (%)		2 (33.3)	13 (9.3)	**6.47 (1.16–36.16)**	**0.030**
BVF, *n* (%)		3 (18.7)	38 (21.6)	1.25 (0.35–4.46)	0.72

BVF: biventricular Fontan; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; RV: right ventricle; SD: standard deviation.
Boldface are those values which are statistically significant.

Table 5: Summary statistics of potential predictors for early morbidity and univariate and multivariate logistic regression results

Univariate analysis results					
		Early morbidity		OR (95% CI)	*P*-value
		Yes (*n* = 42)	No (*n* = 168)		
Year of surgery, *n* (%)	2001–2019	17 (40.5)	20 (17.3)	1	0.007
	1991–2000	8 (19.0)	41 (24.4)	1.12 (0.45–2.81)	
	1978–1990	17 (40.5)	29 (17.3)	3.38 (1.53–7.44)	
Age at surgery (months)		71.6 (68.2)	59.1 (65.8)	1.00 (1.00–1.01)	0.28
Mean (SD)		41 (27.0–86.0)	41.5 (29.5–61.5)		
Median (IQR)					
Systemic RV, *n* (%)		15 (35.7)	63 (37.5)	0.93 (0.46–1.87)	0.83
Staged Fontan, *n* (%)		24 (57.1)	130 (78.8)	**0.36 (0.17–0.73)**	**0.005**
Fenestration, *n* (%)		16 (38.1)	118 (70.7)	**0.26 (0.13–0.52)**	**<0.001**
TCPC versus atriopulmonary, *n* (%)		25 (59.5)	138 (82.1)	**0.32 (0.15–0.66)**	**0.002**
Associated surgery, *n* (%)		22 (52.4)	53 (31.5)	**2.39 (1.20–4.75)**	**0.013**
BVF, *n* (%)		11 (26.2)	35 (20.8)	1.35 (0.62–2.95)	0.45
Multivariate analysis results					
Year of surgery, *n* (%)		2001–2019		**1**	**0.73**
		1991–2000		**0.77 (0.27–2.23)**	
		1978–1990		**1.68 (0.15–18.46)**	
Staged Fontan, *n* (%), 3 missing				**1.05 (0.31–3.52)**	**0.94**
Fenestration, *n* (%), 1 missing				**0.33 (0.12–0.93)**	**0.0361**
TCPC versus atriopulmonary, *n* (%)				**1.33 (0.14–12.93)**	**0.81**
Associated surgery, *n* (%)				**1.75 (0.80–3.83)**	**0.16**
BVF, *n* (%)				1.58 (0.67–3.69)	0.29

BVF: biventricular Fontan; CI: confidence interval; ICU: intensive care unit; IQR: interquartile range; OR: odds ratio; RV: right ventricle; SD: standard deviation; TCPC: total cavopulmonary connection.
Boldface are those values which are statistically significant.

developed ventricles. After comparing patients with UVF and those with BVF, they found no significant difference in global clinical outcomes. Our study confirms that conclusion, even including patients in the BVF group with an accessory diminutive ventricular chamber that was not adequately formed. We speculate that, despite having a more powerful pumping chamber with 2 'engines' instead of 1, the diastolic dysfunction affects both ventricles (chronically overloaded and hypertrophic). Thus, the pulmonary venous pressures do not change, and the Fontan circuit does not benefit, which confirms that the factors that most contribute to Fontan circulation attrition are those causing increased pressure in the Fontan circuit [20, 21].

Interestingly, Prakash *et al.* [10] demonstrated that exercise capacity was greater in subjects with a larger, and less hypertrophied secondary ventricle, that was able to make a greater contribution to stroke volume. These data strongly challenge the hypothesis that a larger secondary ventricle impairs the function of the primary ventricle in the Fontan circulation. In contrast, they support the intuitive feeling that a secondary ventricle might contribute by augmenting the work performed by the primary ventricle in the long term. An additional chamber that works together with the main one may lower end-diastolic pressures, resulting in lower Fontan pressure and fewer late complications. We could not evaluate stress tests in all our patients, and we

Table 6: Summary statistics of potential predictors for late morbidity and univariate logistic regression results and multivariate cox regression results

		Late morbidity		HR (95% CI)	*P*-value
		Yes (*n* = 83)	No (*n* = 109)		
Univariate logistic regression results					
Year of surgery, *n* (%)	2001–2019	34 (41.0)	76 (69.7)	1	0.022
	1991–2000	22 (26.5)	23 (21.1)	0.45 (0.24–0.85)	
	1978–1990	27 (32.5)	10 (9.2)	0.48 (0.26–0.88)	
Age at surgery (months)		63.0 (67.5)	62.2 (68)	1.00 (1.00–1.00)	0.63
Mean (SD)		40 (29–64)	45 (31–64)		
Median (IQR)					
Systemic RV, *n* (%)		27 (32.5)	42 (38.5)	1.14 (0.72–1.81)	0.58
Staged Fontan, *n* (%)		57 (70.4)	89 (82.4)	**1.89 (1.12–3.17)**	**0.017**
Fenestration, *n* (%)		43 (52.4)	85 (78.0)	**1.43 (0.89–2.32)**	0.14
TCPC versus atriopulmonary, *n* (%)		55 (66.3)	99 (90.8)	1.39 (0.85–2.29)	0.19
Associated surgery, *n* (%)		35 (42.2)	31 (28.4)	0.97 (0.62–1.52)	0.90
BVF, *n* (%)		13 (15.7)	28 (25.7)	0.92 (0.51–1.68)	0.80
Multivariate Cox regression results					
Year of surgery, *n* (%)	2001–2019			**1**	**0.15**
	1991–2000			**0.55 (0.30–1.02)**	
	1978–1990			**0.77 (0.34–1,73)**	
Staged Fontan, *n* (%), 3 missing				**1.87 (0.92–3.80)**	**0.082**
BVF, *n* (%)				1.05 (0.57–1.92)	0.88

BVF: biventricular Fontan; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; RV: right ventricle; SD: standard deviation; TCPC: total cavopulmonary connection.
Boldface are those values which are statistically significant.

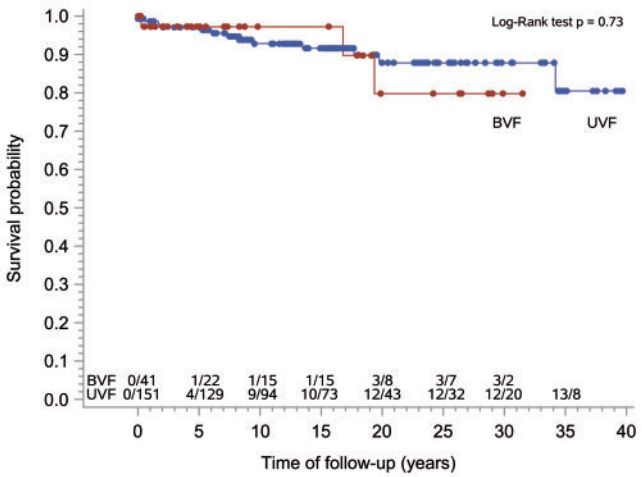

Figure 1: Kaplan–Meier curves showing that survival in the 2 different groups (BVF vs UVF) is not significantly different. For each group, numbers are events/patients at risk at specific times. BVF: biventricular Fontan; UVF: univentricular Fontan.

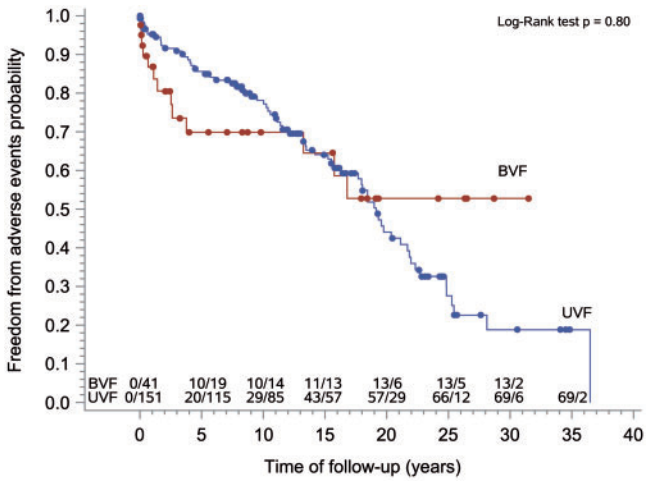

Figure 2: Kaplan–Meier curve showing that freedom from adverse events in the 2 different groups (BVF vs UVF) is not significantly different. For each group, numbers are events/patients at risk at specific times. BVF: biventricular Fontan; UVF: univentricular Fontan.

cannot support this finding. However, it is intuitive that ventricular remodelling and adaptation of Fontan circulation may justify this interesting finding.

Last, the role of anatomical morphology (left or right) of the dominant ventricle in clinical outcomes after Fontan palliation has been examined in the literature, with some reporting that RV dominant morphology results in poorer outcomes [18, 22]. Recent reports challenge this concept [18, 22], but there are few studies investigating the role of an additional chamber [18, 23, 24]. We could not find any significant difference in outcomes related to the presence of an anatomical right or left ventricle, even when an additional chamber was involved.

Of note, the inverse probability weighting method has shown that only late mortality may be influenced negatively by BVF (Supplementary Material, Appendix S3). This finding may be justified with the speculation mentioned above. However, it needs to be confirmed with more extensive experiences.

We believe that this study may be useful for various reasons. First, the evidence that we cannot expect better outcomes of the Fontan with a secondary ventricle should support the surgeon's goal of pursuing a more demanding biventricular repair for complex CHD, if the estimated surgical risk does not exceedingly overcome that of the Fontan procedure. In contrast, we were not able to demonstrate any significant risk for worse outcomes of a Fontan circulation when an accessory ventricle is present. This

information can help provide the parents with full evidence-based preoperative surgical counselling.

Limitations

Significant limitations of this study are its retrospective nature and the relatively small size of the sample. In addition, it is a single-centre analysis, the population is heterogeneous and, due to the long period considered, the effects of technological advantages and different eras cannot be excluded. Also, the surgical timing of Fontan completion has changed through the decades, based on different techniques, which may influence outcomes. Last, the volume of the additional ventricular chambers was not available for further analysis because magnetic resonance imaging data were not available for all patients.

CONCLUSIONS

The presence of a secondary ventricle of any size in Fontan palliation is not significantly related to any clinical disadvantage in terms of survival or morbidity. However, the immediate postoperative course may be influenced negatively by a secondary ventricle, which may sharpen the well-known postoperative diastolic dysfunction after the Fontan operation. Further investigation with magnetic resonance imaging and 3-dimensional echocardiographic flow dynamics may help clarify the effect of the additional chamber on Fontan circulation.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

Author contributions

Elena Rossi: Data curation; Formal analysis; Investigation; Writing—original draft. **Anna Chiara Frigo:** Formal analysis; Methodology; Software; statistics. **Elena Reffo:** Investigation; Supervision; Validation. **Giulio Cabrelle:** Data curation; Supervision. **Biagio Castaldi:** Data curation; Investigation; Supervision; Writing—review & editing. **Giovanni Di Salvo:** Conceptualization; Supervision; Validation; Visualization; Writing—review & editing. **Vladimiro L. Vida:** Supervision; Validation; Visualization; Writing—review & editing. **Massimo A. Padalino:** Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

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