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Pre- and Post-operative determinants of transplantation-free survival after Fontan. The Australia and New Zealand experience

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ABSTRACT

Background: This review identifies the predictors of late mortality and heart transplantation that remain relevant in the contemporary population of patients with a Fontan circulation, focusing on the potential impact of post-Fontan morbidities on the late outlook of these patients.

Methods and Results: A total of 1561 patients who had survived the Fontan operation in Australia or New Zealand from 1975 to 2018 were included in this review. Over a median duration of 11.4 years, there was a total of 117 deaths (7%) and 32 heart transplantations (2%). Freedom from death and heart transplantation at 10, 20 and 35 years post Fontan surgery were 94% (95% CI 93–95%), 87% (95 %CI 85–90%) and 66% (95 %CI 57–78%) respectively. Being male, having an atriopulmonary Fontan, pre-Fontan atrioventricular valve intervention, or prolonged pleural effusions post Fontan were predictive of late death or heart transplantation. However, time-dependent variables such as the development of atrial arrhythmia, protein/losing enteropathy or late ventricular dysfunction were stronger predictors of the same outcome. Patients who developed a time-dependent risk factor had a freedom from death and heart transplantation rate of 54% (95 %CI 43–66) at 15 years and 44% (95 %CI 33–57) at 25 years post Fontan. However, 95% (95 %CI 91–99) of patients without any of the identified risk factors were free from death or heart transplantation rate at 25 years post Fontan.

Conclusion: In conclusion, the occurrence of post-operative complications such as PLE, arrhythmia and ventricular dysfunction will likely precede the late demise of these patients.

1. Introduction

The Fontan Procedure has provided survival odds beyond that originally conceived by Professor Fontan in 1990, when he first described his outcomes after a "perfect" Fontan in patients who were identified to have the best candidates to undergo the procedure [1]. At the time, the authors could not identify any risk factor

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for the late mortality or decline in functional status other than older age at surgery. They concluded that " . . .*the premature decline in survival and functional status . . .. are from the Fontan state per se and that the Fontan operation is, therefore, palliative but not curative*". Thirty years later, this procedure should certainly still be considered as palliative. With longer follow-up and a larger surviving population, we are now recognising that the factors most predictive of adverse outcomes are likely the late sequelae that occur after surgery, such as protein-losing enteropathy, pleural effusions and the need for a pacemaker [2]. The Australia and New Zealand Fontan Registry has been set up in 2009 and has accumulated serial data in this population for the last decade. We investigated this large contemporary dataset to identify the predictors of mortality and heart transplantation after Fontan surgery that remain relevant today.

2. Methods

All patients who had undergone a Fontan Procedure in Australia or New Zealand from 1975 to present are recruited for surveillance as part of the Australia and New Zealand Fontan Registry. At the data census timepoint of 1st January 2018, 1561 patients who have

Table 1
Baseline characteristics of 1561 patients.

Variable		n = 1561 (%)	Patients alive free from Tx (n = 1421)	Patients dead/Tx (n = 140)
Gender	Female	669 (43%)	619 (44%)	50 (36%)
	Male	892 (57%)	802 (56%)	90 (64%)
Ventricle Morphology	Left	897 (58%)	814 (58%)	83 (60%)
	Right	512 (33%)	465 (33%)	47 (34%)
	Biventricular	94 (6%)	87 (6%)	7 (5%)
	Indeterminate	38 (3%)	37 (3%)	1 (1%)
Morphological Group	Tricuspid Atresia	346 (22%)	308 (22%)	38 (27%)
	Double Inlet Left Ventricle	261 (17%)	241 (17%)	20 (14%)
	Double Outlet Right Ventricle	210 (14%)	184 (13%)	26 (19%)
	Atrioventricular Canal or AVSD (aka unbalanced AVSD or common AV valve)	121 (8%)	112 (8%)	9 (7%)
	Pulmonary Atresia with VSD	33 (2%)	32 (2%)	1 (1%)
	Pulmonary Atresia with Intact Ventricular Septum	127 (8%)	118 (8%)	9 (7%)
	HLHS	201 (13%)	189 (13%)	12 (9%)
	Ebstein's Anomaly	14 (1%)	11 (1%)	3 (2%)
	ccTGA (VA discordance and AV discordance)	96 (6%)	88 (6%)	8 (6%)
	Other	143 (9%)	130 (9%)	13 (9%)
	Unknown	9	8	1
Isomerism	Yes	109 (7%)	97 (7%)	12 (9%)
Dextrocardia	Yes	137 (9%)	123 (9%)	14 (10%)
Number of Palliations	Mean (SD)	2.0 (1.0)	2.0 (1.0)	1.4 (1.1)
Prior aortic arch intervention	Yes	80 (5%)	77 (6%)	3 (2%)
Prior pulmonary artery banding	Yes	367 (24%)	333 (24%)	34 (25%)
Prior staging BCPS	Yes	1004 (66%)	964 (69%)	40 (29%)
Bilateral BCPS	Yes	115 (8%)	110 (8%)	5 (4%)
Age at first BCPS	Median (IQR)	0.7 (0.3–1.4)	0.7 (0.3–1.4)	1.0 (0.4–1.8)
Pulmonary artery reconstruction	Yes	102 (7%)	99 (7%)	3 (2%)
Pre Fontan O^2 saturation	Mean (SD)	82.2 (6.8)	82.3 (6.8)	80.8 (6.8)
Pre Fontan pulmonary artery pressure (mm Hg)	Mean (SD)	11.5 (3.5)	11.4 (3.0)	12.0 (3.0)
Preoperative elevated PAP (>15)	Yes	107 (9%)	95 (9%)	12 (12%)
Aortic pulmonary or venous Collaterals	Yes	345 (30%)	333 (31%)	12 (14%)
Prior atrioventricular valve repair	Yes	77 (5%)	67 (5%)	10 (7%)
Pre Fontan Arrhythmia	Yes	22 (1%)	16 (1%)	6 (4%)
Pre Fontan ventricular dysfunction	Yes	36 (6%)	27 (5%)	9 (19%)
Pre Fontan Thromboembolism	Yes	15 (1%)	12 (1%)	3 (2%)
Pre-operative regurgitation	Yes	116 (9%)	103 (9%)	13 (11%)
Pre Fontan pacemaker	Yes	5 (0.3%)	4 (0.3%)	1 (0.7%)
Age at Fontan	Median (IQR)	4.6 (3.6 – 6.1)	4.6 (3.6 – 5.8)	5.6 (3.8 – 10.1)
Fontan type	AP	230 (15%)	158 (11%)	72 (51%)
	LT	286 (18%)	257 (18%)	29 (21%)
	ECC	1045 (67%)	1006 (71%)	39 (28%)
Year Fontan operation	1975–1989	192 (12%)	131 (9%)	61 (44%)
	1990–1999	359 (23%)	314 (22%)	45 (32%)
	2000–2009	525 (34%)	500 (35%)	25 (18%)
	2010–2017	485 (31%)	476 (34%)	9 (6%)
Concomitant procedures	Yes	446 (29%)	402 (28%)	44 (31%)
Arch intervention	Yes	80 (5%)	77 (6%)	3 (2%)
Fenestration	Yes	573 (37%)	536 (38%)	37 (27%)
Concomitant Pulmonary artery reconstruction	Yes	91 (6%)	82 (6%)	9 (6%)
Concomitant atrioventricular valve repair	Yes	32 (2%)	30 (2%)	2 (1%)
Prolonged pleural effusions	Yes	88 (6%)	73 (5%)	15 (11%)

survived to hospital discharge after Fontan completion are included. The initiation of this registry has been previously described [3] and currently includes comprehensive information regarding *peri*-Fontan characteristics, surgical and long-term follow-up clinical data gathered via prospective and retrospective data collation. Informed consent was obtained from patients prior to registry inclusion. The Australian National Death Registry is reviewed biannually, with all information fed back to the registry to ensure data regarding late deaths are complete. All deaths in New Zealand are automatically reported to the principal treating hospital, which are noted by site representatives for the registry. Approval for this study was obtained as part of ongoing ethical approval for the registry at the respective sites and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in a priori approval by the institution's human research committee.

We wanted to identify the predictors of a poorer long-term prognosis following Fontan completion. The principal endpoint was therefore defined as the need for heart transplantation or death. Our experience with heart transplantation in the Australia and New Zealand Fontan Registry has been described in detail in previous publications [4,5]. Referral criteria for heart transplantation is variable amongst the 6 transplant centres, but the primary indications for transplantation are chronic heart failure, intractable cardiac arrhythmia and protein losing enteropathy. The majority of patients with a Fontan circulation who undergo a heart transplantation are perceived to be at a continued high risk of attrition and were therefore assimilated to those who died. An extensive analysis was performed to identify significant predictors of this endpoint. This included baseline demographics and perioperative characteristics of their Fontan procedure. Patients who underwent Fontan surgery between 1975 and 1989 received the atriopulmonary Fontan and were segregated into 1 surgical era. The remaining patients received either the lateral tunnel or extracardiac conduit and were divided into surgical eras by decade. Features of late morbidity were also included in the analysis, with the inclusion of sequelae previously identified to have a potential impact on the long-term outcome of these patients [2,11]. This included the onset of atrial arrhythmia, plastic bronchitis, protein losing enteropathy, and significant systemic ventricular dysfunction. Significant late systemic ventricular dysfunction was defined as moderate or severe dysfunction diagnosed on follow-up cardiac investigations. A pulmonary artery pressure above 15 mmHg preceding Fontan surgery was defined to be elevated. The development of late atrioventricular valve dysfunction was identified when it was classified as moderate or severe regurgitation on transthoracic or transesophageal echocardiography. Prolonged pleural effusions post Fontan completion was defined as effusions lasting longer than 30 days post-op. Atrial arrhythmia was defined as the onset of supraventricular tachycardia including atrial flutter or atrial fibrillation.

3. Statistical analysis

Patient baseline characteristics were summarised using proportions (based on non-missing data) for categorical variables and mean (±standard deviation (SD)) or median (±interquartile range) for continuous variables. The endpoint examined was the onset of death or heart transplantation post Fontan completion. Freedom from death and heart transplantation were examined using Kaplan-Meier analysis. The censoring distribution with the Kaplan-Meier method was used to estimate the median follow-up time. All risk factors were examined as predictors for the primary endpoint using univariable Cox regression models and the Likelihood Ratio Test (LRT), as time-dependent or time-independent covariates accordingly. The proportional hazards assumption was assessed based on the method of Harrell-Lee [6] and via diagnostic plots. If the assumption was violated, an interaction term with the exposure time was added to the regression model to satisfy the assumption. Factors with adequate evidence ($p < 0.1$) against the null hypothesis with univariable modelling were included in the multivariable model. Stepwise selection was used to reduce the number of factors such that all remaining factors had a $p < 0.05$. The discrimination power of the multivariable model was assessed using the c-index. Data analysis was performed using R version 3.6.1 software (R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org).

4. Results

Between 1975 and 2018, a total of 1561 patients underwent and survived Fontan surgery in Australia and New Zealand. The baseline characteristics of the 1561 patients included in the review are described in Table 1. Hypoplastic left heart syndrome (HLHS) was the primary diagnosis in 201 patients (13%). Prior staging with bi-directional cavopulmonary shunt surgery was completed for 1004 patients (66%). The predominant type of Fontan procedure performed was the extra-cardiac conduit (ECC) as of 2007, and predictably made up two thirds of the total cohort at 67%. Mean age at Fontan completion was 5.7 ± 3.8 years old.

4.1. Death and transplantation

Patients were followed up over a median duration of 11.4 years (range 6 days to 40.2 years). There was a total of 117 deaths (7%) and 32 heart transplantations (2%) at median duration of 10.8 (IQR 4.4–18.8) and 8.4 (IQR 4.2 – 14.6) years post Fontan completion. Of the 32 patients who underwent heart transplantation, 9 died (28%), making a total number of 141 events. The date of death of 1 patient was unknown and hence excluded from the analysis. Freedom from death and heart transplantation at 10, 20 and 35 years post Fontan surgery were 94% (95% CI 93–95%), 87% (95 %CI 85–90%) and 66% (95 %CI 57–78%) respectively (Fig. 1).

During the follow-up period, 207 patients (13%) developed atrial arrhythmia at a median time of 10.2 years (IQR 1.9 – 18.0) post Fontan surgery. Fifty-four patients (3%) were diagnosed with protein losing enteropathy or plastic bronchitis at a median time of 4.5 years (IQR 1.0 – 7.9) post Fontan completion. A total of 252 patients (16%) developed moderate or severe atrioventricular

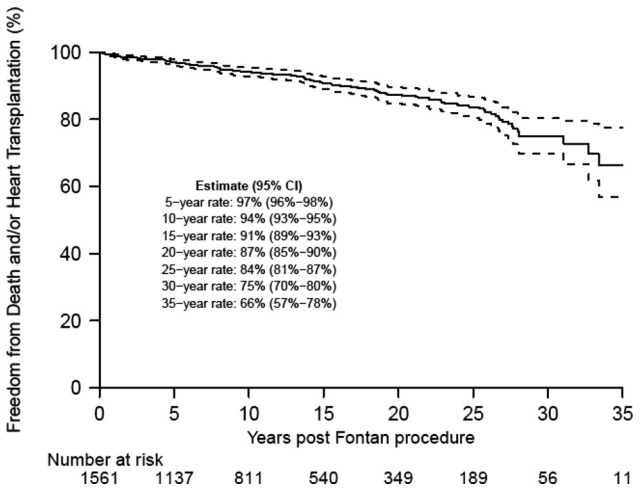

Fig. 1. Kaplan Meier curve of freedom from death and transplantation for total patient cohort (n = 1561).

valve regurgitation at a median time of 8.6 years (IQR 3.8–16.1) post Fontan completion. Only 148 patients (9.5%) had significant systemic ventricular dysfunction at latest follow-up. The development of late sequelae including atrial arrhythmia, protein-losing enteropathy (PLE)/ plastic bronchitis (PB), or significant systemic ventricular dysfunction were found to be predictive of late death

Table 2
Univariable analysis of predictors of death and heart transplantation.

Time-independent variables		N	No. of events	HR (95% CI)	p value
Gender	Female	669	50	1	**0.009**
	Male	892	90	1.58 (1.11–2.24)	
Ventricle morphology	Left	897	83	1	0.1
	Right	512	47	1.52 (1.06–2.18)	
	Biventricular	94	7	1.22 (0.56–2.65)	
	Indeterminate	38	1	0.44 (0.06–3.19)	
HLHS	No	1352	128	1	0.2
	Yes	209	12	1.55 (0.84–2.85)	
Isomerism	No	1423	126	1	0.3
	Yes	109	12	1.39 (0.77–2.51)	
Dextrocardia	No	1377	123	1	0.5
	Yes	137	14	1.20 (0.69–2.09)	
Fontan type	AP	230	72	1	**<0.001**
	LT	286	29	0.47 (0.30–0.73)	
	ECC	1045	39	0.43 (0.27–0.67)	
Year Fontan operation	1975–1989	192	61	1	**0.01**
	1990–1999	359	45	0.61 (0.41–0.93)	
	2000–2009	525	25	0.43 (0.25–0.72)	
	2010–2017	485	9	0.49 (0.22–1.06)	
Number Palliations	Per unit increase	1531	138	0.84 (0.71–1.00)	**0.05**
Prior aortic arch intervention	No	1451	135	1	0.6
	Yes	80	3	0.74 (0.24–2.35)	
Prior pulmonary artery banding	No	1164	104	1	0.8
	Yes	367	34	1.04 (0.71–1.54)	
Prior staging BCPS	No	527	98	1	**0.002**
	Yes	1004	40	0.53 (0.36–0.79)	
Bilateral BCPS	No	1416	133	1	0.8
	Yes	115	5	0.89 (0.36–2.18)	
Age at first BCPS	Per unit increase	971	38	0.99 (0.84–1.16)	0.9
Pulmonary artery reconstruction	No	1459	137	1	0.1
	Yes	102	3	0.44 (0.14–1.38)	
Pre Fontan O^2 saturation	Per unit increase	1145	78	0.98 (0.95–1.01)	0.3
Pre Fontan pulmonary artery pressure (mmHg)	Per unit increase	1172	99	0.99 (0.95–1.04)	0.8
Aortic pulmonary or venous Collaterals	No	825	72	1	0.4
	Yes	345	12	0.76 (0.41–1.42)	
Preoperative elevated PAP (>15)	No	1065	87	1	0.5
	Yes	107	12	0.81 (0.44–1.48)	
Pre Fontan Arrhythmia	No	1539	134	1	0.02
	Yes	22	6	3.04 (1.34–6.91)	
Pre-operative atrioventricular regurgitation	No	1116	103	1	**0.05**
	Yes	116	13	1.88 (1.05–3.36)	
Pre Fontan Atrioventricular valve repair	No	1454	128	1	**0.002**
	Yes	77	10	3.31 (1.71–6.39)	
Pre Fontan pacemaker	No	1555	139	1	0.8
	Yes	6	1	1.32 (0.19–9.47)	
Arch intervention	No	1451	135	1	0.6
	Yes	80	3	0.74 (0.24–2.35)	
Age at Fontan	Per unit increase	1561	140	1.05 (1.02–1.08)	**0.001**
Fenestration	No	967	102	1	0.9
	Yes	573	37	1.02 (0.69–1.50)	
Concomitant procedures	No	1115	96	1	0.2
	Yes	446	44	1.27 (0.89–1.82)	
Concomitant Pulmonary artery reconstruction	No	1470	131	1	0.4
	Yes	91	9	1.34 (0.68–2.63)	
Concomitant atrioventricular valve repair	No	1529	138	1	0.6
	Yes	32	2	0.71 (0.18–2.87)	
Prolonged pleural effusions post-Fontan	No	1473	125	1	**0.005**
	Yes	88	15	2.34 (1.37–4.01)	

Time-dependent variables		N	No. of events	HR (95% CI)	p value
Arrhythmia (Flutter, SVT or Fibrillation)	No	1354	92	1	**<0.001**
	Yes	207	48	2.99 (1.99–4.48)	
				3.49 (2.21–5.49)*	
PLE/plastic bronchitis	No	1506	121	1	**<0.001**
	Yes	55	19	7.46 (4.41–12.6)	
Atrioventricular valve regurgitation	No	1309	131	1	0.9
	Yes	252	9	1.04 (0.50–2.13)	
Late ventricular dysfunction	No	1413	86	1	**<0.001**
	Yes	148	54	15.8 (10.7–23.1)	

* Fitted with time-dependent variable × time interaction to adjust for proportional hazards assumption violation.

Table 3
Multivariable time-dependent and independent regression models for death and/or heart transplantation.

	Baseline only		Time-varying only		Time-varying + baseline	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Gender = Male	1.71 (1.20–2.43)	0.003	–		1.40 (0.97–2.02)	0.071
Fontan type = ECC vs AP (reference)	0.36 (0.22–0.58)	<0.001	–		0.31 (0.19–0.51)	<0.001
Fontan type = LT vs AP (reference)	0.51 (0.32–0.81)	0.004	–		0.50 (0.31–0.80)	0.004
Age at Fontan (per year increase)	1.054 (1.024–1.086)	<0.001	–		1.028 (0.995–1.063)	0.098
Pre-Fontan Atrioventricular valve repair	4.37 (2.17–8.79)	<0.001	–		4.22 (2.09–8.51)	<0.001
Prolonged pleural effusions post Fontan	2.68 (1.51–4.79)	<0.001			2.45 (1.41–4.26)	0.002
Arrhythmia (Flutter, SVT or Fibrillation)*	–		2.82 (1.70–4.67)	<0.001	2.04 (1.20–3.46)	0.009
PLE/plastic bronchitis	–		3.66 (2.12–6.32)	<0.001	3.81 (2.19–6.62)	<0.001
Ventricular dysfunction	–		13.6 (9.08–20.3)	<0.001	13.9 (9.20–21.1)	<0.001
c-index	0.733		0.748		0.843	

or transplantation on univariable analysis. Of the total patient cohort, 336 patients (22%) developed at least 1 late sequelae that was predictive of a higher risk of late death or heart transplantation.

The risk factors identified on univariable analysis to predict for late death and heart transplantation are listed in Table 2. Having prior bi-directional cavopulmonary shunt (BCPS) was associated with a lower risk of the primary end-point of death or transplantation (HR 0.53 95 %CI 0.36–0.79, p = 0.002). The need for concomitant atrioventricular valve repair predicted for a higher likelihood of death or transplantation (HR 3.31 95 %CI 1.71–6.39, p = 0.002). All predictors identified on univariable analysis, except having a BCPS, remained significant on multivariable analysis (Table 3). Patients who needed atrioventricular valve intervention also continued to face a higher risk of death or heart transplantation at late follow-up (HR 3.76, 95 %CI 1.84–7.69, p < 0.001). Most prominently, having PLE or PB was strongly predictive of the outcome (HR 6.15, 95 %CI 3.58–10.56, p < 0.001). The development of systemic ventricular dysfunction and atrial arrhythmia similarly remained important predictors of death or heart transplantation (HR 5.54, 95 %CI 2.75–11.2, p < 0.001 and HR 2.25, 95 %CI 1.38–3.66, p = 0.001 respectively).

A sub-analysis was performed to review the outcomes of contemporary patients with either an LT or ECC Fontan. Patients without any risk factors identified in the multivariable analysis had a freedom from death or heart transplantation rate of 99% (95% CI 98–100) at 15 years and 95% (95 %CI 91–99) 25 years post Fontan. Patients with only time-independent risk factors (being male, atrioventricular valve repair at time of Fontan completion or prolonged pleural effusions post-Fontan) had a freedom from death or heart transplantation rate of 97% (95 %CI 95–99) at 15 years and 92% (95 %CI 87–98) at 25 years. However, for patients who had developed a time-dependent risk factor (ie atrial arrhythmia, systemic ventricular dysfunction, PLE or PB), only 54% (95 %CI 43–66) were alive and free from heart transplantation at 15 years and 44% (95 %CI 33–57) at 25 years post Fontan (Fig. 2). The c-index for the final multivariate model with addition of the time-dependent covariates to the baseline variables was satisfactory at 0.84.

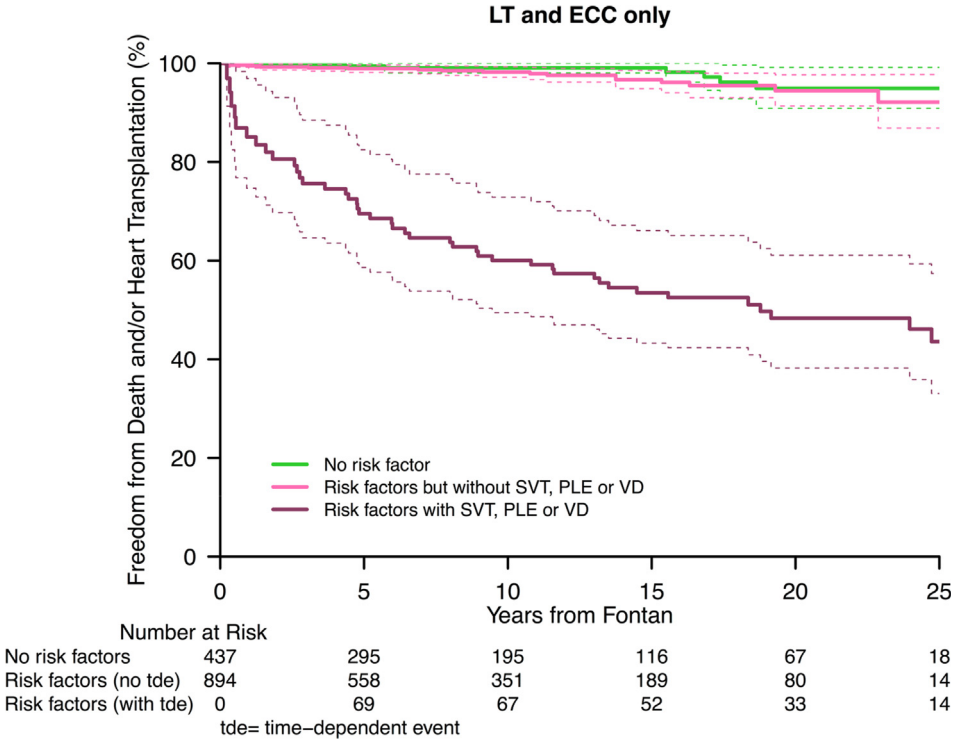

Fig. 2. Kaplan Meier curves of freedom from death and heart transplantation in patients with either a lateral tunnel (LT) or extracardiac conduit (ECC) Fontan. (Patients with no risk factors; patients with only time-independent risk factors; and patients with time-dependent risk factors).

5. Discussion

The Fontan operation represents 3% of all congenital cardiac operations today [7], and is now regarded as the treatment of choice for a wide spectrum of congenital cardiac defects that are not amenable to biventricular repair. Since its first iteration, the perioperative mortality of the Fontan procedure has decreased to 2–3% worldwide [7–9]. The Society of Thoracic Surgeons recently estimated the in-hospital mortality post Fontan surgery to be 1.4%, albeit significantly higher in the adult cohort at 7% [10].

The pre- and *peri*-operative predictors of mortality and transplantation identified in our patients are similar to those previously published. Male gender, older age at Fontan, having a "classical" atrio-pulmonary Fontan and prolonged pleural effusions at the time of Fontan surgery all remained predictive of late death and transplantation. However, as we continue to accumulate late post-operative data in our patients, we now see that the most important predictor identifying those at risk of premature death or failure are those who develop the late sequelae of the Fontan physiology. The onset of protein-losing enteropathy or ventricular dysfunction appears to be a precursor of a state of heightened risk for late death or need for cardiac transplantation. A recent review of a contemporary group of Fontan patients confirmed this by demonstrating a stark difference in 20-year survival free from Fontan failure in patients with and without late morbidity, such as tachyarrhythmia, thrombosis or PLE [11]. Optimal management of these complications needs to be prioritised as an area of focus in this current era, in order to maximise the life expectancy of the surviving patients.

6. Limitations

This study, albeit a large cohort study, remains a retrospective study in nature. It may be argued that the development of the time-dependent risk factors is merely part of the spectrum of time-related decline that ultimately leads to late Fontan failure and death. However, we believe this study identifies an important fact that patients who have developed Fontan related co-morbidities have a starkly different prognosis as compared to their counterparts spared of these sequelae, and need to be treated differently.

7. Conclusion

With a follow-up extending to 35 years, 22% of our patients develop co-morbidities impacting their survival. The likelihood of survival without transplantation for the remaining 78% remained excellent with or without the historical predictors of a high-risk Fontan state. We have recently identified that anatomical or technical factors may be contributing to the late demise of patients with contemporary Fontan circulations [12]. There is also some empirical evidence suggesting the detrimental impact of ventricular pacing on the Fontan circulation [13,14].

In conclusion, we cannot precisely identify the patients who will fail in the long-term based solely on preoperative factors. However, the development of post-operative complications, PLE, arrhythmia and ventricular dysfunction will likely precede the demise of these patients. Hence, we need to confront the challenge of these late Fontan morbidities with the same fervour with which our predecessors tackled the limitations of Choussat's commandments four decades ago.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] F. Fontan, J. Kirklin, G. Fernandez, F. Costa, D. Naftel, F. Tritto, et al., Outcome after a "perfect" Fontan operation, Circulation 81 (1990) 1520–1536.
[2] C.L. Poh, Y. d'Udekem, Life After Surviving Fontan Surgery: A Meta-Analysis of the Incidence and Predictors of Late Death, Heart Lung Circ. 27 (2018) 552–559.
[3] A. Iyengar, D. Winlaw, J. Galati, T. Gentles, R. Weintraub, et al., The Australia and New Zealand Fontan Registry: description and initial results from the first population-based Fontan registry, Intern Med J. 44 (2) (2014) 148–155.
[4] W. Shi, M. Yong, D. McGiffin, P. Jain, P. Ruygrok, S. Marasco, et al., Heart transplantation in Fontan patients across Australia and New Zealand, Heart 102 (14) (2015) 1120–1126.
[5] A. Iyengar, V. Sharma, R. Weintraub, A. Shipp, C. Brizard, Y. d'Udekem, et al., Surgical strategies to facilitate heart transplantation in children after failed univentricular palliations: the role of advanced intraoperative surgical preparation†, Eur J Cardiothorac Surg. 46 (2014) 480–485.
[6] Harrell F, Lee K. Verifying the assumptions of the Cox proportional hazards model. Proceedings of the 11th Annual SAS User's Group International Conference Cary, North Carolina: SAS Institute; 1986:823-8.
[7] J. Jacobs, B. Maruszewski, Functionally Univentricular Heart and the Fontan Operation: Lessons Learned About Patterns of Practice and Outcomes From the Congenital Heart Surgery Databases of the European Association for Cardio-Thoracic Surgery and the Society of Thoracic Surgeons, Wolrd J Pediatr Congenit Heart Surg. 4 (4) (2013) 349–355.
[8] L. Rogers, A. Glatz, C. Ravishankar, T. Spray, S. Nicolson, J. Rychik, et al., 18 Years of the Fontan Operation at a Single Institution, J Am Coll Cardiol. 60 (2012) 1018–1025.
[9] d"Udekem Y, Iyengar A, Cochrane A, Grigg L, Ramsay J, et al. The Fontan Procedure: Contemporary Techniques Have Improved Long-Term Outcomes. Circulation. 2007;116(suppl 1):I-157-64.
[10] S. Fuller, X. He, J. Jacobs, S. Pasquali, J. Gaynor, C. Mascio, et al., Estimating Mortality Risk for Adult Congenital Heart Surgery: An Analysis of The Society of Thoracic Surgeons Congenital Heart Surgery Database, Ann Thorac Surg. 100 (2015) 1728–1736.
[11] K. Allen, T. Downing, A. Glatz, L. Rogers, C. Ravishankar, J. Rychik, et al., Effect of Fontan-Associated Morbidities on Survival With Intact Fontan Circulation, Am J Cardiol. 119 (2017) 1866–1871.
[12] C. Poh, T. Hornung, D. Celermajer, D. Radford, R. Justo, D. Andrews, et al., Modes of late mortality in patients with a Fontan circulation, Heart (2020).
[13] C.L. Poh, D. Celermajer, L. Grigg, J. Kalman, M. McGuire, T. Gentles, et al., Pacemakers are associated with a higher risk of late death and transplantation in the Fontan population, Int J Cardiol. 282 (2019) 33–37.
[14] J. Kochav, M. Rosenbaum, S. Kochav, E. Slater, N. Wassercug-Zemer, M. Lewis, Effect of Ventricular Pacing on Morbidity in Adults After Fontan Repair, Am J Cardiol (2020).