Protein-losing enteropathy and plastic bronchitis after the Fontan procedure

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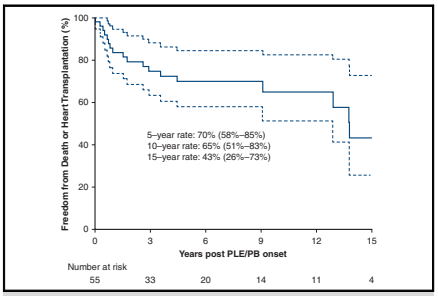
ABSTRACT

Objectives: Protein losing enteropathy and plastic bronchitis are severe complications in Fontan circulation, with 5-year survival ranging from 46% to 88%. We report risk factors and outcomes of protein losing enteropathy and plastic bronchitis in patients undergoing the Fontan.

Methods: We performed a retrospective analysis of 1561 patients from the Australia New Zealand Fontan Registry. Two end points were death and cardiac transplantation examined with Cox regression (if no competing risks) or cumulative incidence curves and cause-specific Cs regression.

Results: A total of 55 patients with protein losing enteropathy/plastic bronchitis were included. Their median age at the Fontan was 5.7 years, and time to onset after the Fontan for protein losing enteropathy was 5.0 years and plastic bronchitis was 1.7 years. Independent predictors for developing protein losing enteropathy/plastic bronchitis were right-ventricular morphology with hypoplastic left-heart syndrome (hazard ratio, 2.30; confidence interval, 1.12-4.74), older age at Fontan (hazard ratio, 1.13; confidence interval, 1.03-1.23), and pleural effusions after Fontan (hazard ratio, 2.43; confidence interval, 1.09-5.41); left-ventricular morphology was protective (hazard ratio, 0.36; confidence interval, 0.18-0.70). In the protein losing enteropathy/plastic bronchitis population, freedom from death or transplantation after protein losing enteropathy/plastic bronchitis diagnosis at 5, 10, and 15 years was 70% (confidence interval, 58-85), 65% (confidence interval, 51-83), and 43% (confidence interval, 26-73), respectively; only older age (hazard ratio, 1.23; confidence interval, 1.01-1.52) was an independent predictor. Twenty-six surgical interventions were performed in 20 patients, comprising Fontan revisions (n = 5), fenestrations (n = 11), Fontan conversions (n = 5), atrioventricular valve repairs (n = 3), and hepatic vein diversion (n = 2).

Conclusions: Protein losing enteropathy and plastic bronchitis remain severe complications, preferably affecting patients with dominant right single ventricle, with older age at Fontan being a predictor of developing protein losing enteropathy/plastic bronchitis and poorer prognosis. Heart transplantation remains the ultimate treatment, with 30% dying or requiring transplantation within 5 years, and the remaining being stable for long periods. (J Thorac Cardiovasc Surg 2020;■:1-8)



Kaplan–Meier curve showing freedom from death or transplantation after developing PLE or PB.

CENTRAL MESSAGE

Prevalence of PLE and PB is 4.9% at 30 years and 7.4% at 35 years, with freedom from death or transplantation at 5, 10, and 15 years at 70% (95% CI, 58-85), 65% (95% CI, 51-83), and 43% (95% CI, 26-73), respectively.

PERSPECTIVE

PLE and PB are typical complications of the Fontan circulation, and outcomes of these complications have changed in recent times. We investigate these complications in the ANZFR. We identified that these patients have improved survival compared with those previously reported, a notable change that will likely be of interest to the readers of the *Journal*.

See Commentary on page XXX.

CONG

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Abbreviations and Acronyms

ANZFR = Australia and New Zealand Fontan Registry
AV = atrioventricular
CI = confidence interval
HLHS = hypoplastic left heart syndrome
HR = hazard ratio
IQR = interquartile range
PB = plastic bronchitis
PLE = protein losing enteropathy
RV = right ventricular

Scanning this QR code will take you to the article title page to access supplementary information.

Protein losing enteropathy (PLE) and plastic bronchitis (PB) are among the more severe complications that can be encountered in patients with a Fontan circulation.[1] PLE and PB occur in 3% to 18% of patients at an average time of 2 to 4 years after the Fontan operation.[2,3] They carry a high mortality rate, with a wide range of 5-year survivals from 46% in early studies to 88% in the current era.[2,4,5]

The cause is uncertain; nevertheless, it is thought that an elevated systemic pressure and decreased systemic output result in inflammation and protein leakage at the gastrointestinal tract (PLE) or bronchi (PB). Current treatments are aimed locally at reducing protein loss (budesonide and heparin) or improving cardiac function by decreasing afterload (angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and diuretics) and increasing ventricular function (spironolactone and digoxin) and pulmonary vasodilation (sildenafil).[6,7] It is still unclear whether in the present era these new adjunctive treatments have improved the expected survival.

We have identified in a retrospective study of the Australia and New Zealand Fontan Registry (ANZFR) that the occurrence of PLE and PB was one of the most important predictive factors of death and transplantation in the patients who survived with a Fontan circulation. We wanted to further define outcomes of PLE and PB in patients with a Fontan circulation. In particular, we aim to identify (1) risk factors for PLE/PB after Fontan; (2) risk factors for death or transplant after PLE/PB; and (3) potential treatment strategies to minimize the clinical consequences of patients with PLE/PB.

PATIENTS AND METHODS

All patients who underwent a Fontan procedure in Australia or New Zealand from 1975 to the present are recruited for surveillance as part of the ANZFR. At present, 1561 patients who have survived to hospital discharge after Fontan completion are included. The initiation of this registry has been described[8] and currently includes comprehensive information regarding peri-Fontan characteristics and surgical and long-term follow-up clinical data gathered via prospective and retrospective data collation. The Australian National Death Index 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 (HREC Ethics Number 36260).

Patients were included in the study if their referring clinicians diagnosed them with this complication. PLE diagnosis was made using an elevated α-1 antitrypsin clearance in a 24-hour stool collection or an elevated α-1 antitrypsin level in a single stool sample together with the presence of serum hypoalbuminemia and symptoms of edema without another identified cause, as defined by Rychik and colleagues' statement[1] from the American Heart Association. The diagnosis of PB was made by expectoration of casts, bronchoscopy, and histologic examination. Patients with PLE and PB were pooled for analysis of their outcomes and the prediction of their occurrence. We examined 2 end points: death and cardiac transplantation.

Statistical Analysis

Patient baseline characteristics were summarized using proportions for categoric variables and mean ($\pm$ standard deviation) or median (interquartile range [IQR]) for continuous variables. Percentages were calculated using nonmissing data. The end points examined were the onset of PLE or PB post-Fontan (with death as a competing risk) and freedom from death or heart transplantation post-PLE or PB onset. End points not subjected to competing risks were examined using Kaplan–Meier analysis, and risk factors were examined as predictors using Cox regression analysis. End points subjected to competing risks were examined using cumulative incidence curves and risk factors were examined using cause-specific Cs regression. All factors with adequate evidence against the null hypothesis ($P < .1$) were included in a multivariable model that was then reduced using stepwise elimination to obtain a model with all factors having strong evidence against the null hypothesis ($P < .05$). The proportional hazards assumption was assessed on the basis of the method of Harrell-Lee and via diagnostic plots. Data analysis was performed using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Risk Factors of Developing Protein Losing Enteropathy/Plastic Bronchitis After Fontan

From the registry of 1561 patients (Table 1), we identified a total of 55 patients with PLE or PB. Forty-eight had PLE only, 4 had PB only, and 3 had both. In these patients, the median age at Fontan was 5.7 years (IQR, 4.3-8.0 years), and the median time from Fontan operation to the onset of PLE was 5.0 years (IQR, 1.0-7.8 years) and PB was 1.7 years (IQR, 0.8-4.5 years). The most common encountered diagnoses were hypoplastic left heart syndrome (HLHS), double inlet left ventricle, and atrioventricular (AV) septal defect, which accounted for the underlying pathology in more than half of the patients with PLE or PB (Table 1).

Independent predictors for the risk of developing PLE or PB were right ventricular (RV) morphology with HLHS (hazard ratio [HR], 2.30; 95% CI, 1.12-4.74), older age at Fontan (HR, 1.13 for each 2-year increase in age; 95%

TABLE 1. Baseline characteristics of the 1561 patients from the Fontan Registry

Variable	Level	n = 1561 (%)	No PB or PLE after Fontan N = 1506	PB or PLE after Fontan N = 55	PLE after Fontan N = 51	PB after Fontan N = 7
Gender	Female	669 (42.9%)	644 (42.8%)	25 (45%)	24 (47%)	2 (29%)
	Male	892 (57.1%)	862 (57.2%)	30 (55%)	27 (53%)	5 (71%)
Ventricle morphology	Left	897 (58.2%)	878 (59.0%)	19 (35%)	19 (38%)	0 (0%)
	Right	512 (33.2%)	480 (32.3%)	32 (59%)	29 (58%)	6 (86%)
	Biventricular	94 (6.1%)	91 (6.1%)	3 (6%)	2 (4%)	1 (14%)
	Indeterminate	38 (2.5%)	38 (2.6%)	0 (0%)	0 (0%)	0 (0%)
	Unknown	20 (1.3%)	19 (1.2%)	1 (0.1%)	0 (0%)	0 (0%)
Primary diagnosis	Tricuspid atresia	346 (22.3%)	341 (22.8%)	5 (9%)	5 (10%)	0 (0%)
	DILV	261 (16.8%)	252 (16.8%)	9 (16%)	4 (8%)	0 (0%)
	DORV	210 (13.5%)	205 (13.7%)	5 (9%)	9 (18%)	0 (0%)
	AV canal or AVSD	121 (7.8%)	114 (7.6%)	7 (13%)	6 (12%)	1 (14%)
	Pulmonary atresia (with VSD)	33 (2.1%)	33 (2.2%)	0 (0%)	0 (0%)	0 (0%)
	Pulmonary atresia (no VSD)	127 (8.2%)	124 (8.3%)	3 (5%)	3 (6%)	0 (0%)
	HLHS	201 (13.0%)	186 (12.4%)	15 (27%)	13 (25%)	4 (57%)
	Ebstein's anomaly	14 (0.9%)	14 (0.9%)	0 (0%)	0 (0%)	0 (0%)
	ccTGA	96 (6.2%)	92 (6.1%)	4 (7%)	4 (8%)	0 (0%)
	Other	143 (9.2%)	136 (9.1%)	7 (13%)	7 (14%)	1 (14%)
	Unknown	9	9	0	0	0
Isomerism	Yes	109 (9.0%)	104 (7.0%)	5 (9%)	5 (10%)	1 (14%)
Dextrocardia	Yes	137 (8.8%)	135 (9.2%)	2 (4%)	2 (4%)	0 (0%)
No. of palliations	Mean (SD)	2.0 (1.0)	2.0 (1.0)	2.1 (1.3)	2.1 (1.3)	1.9 (1.2)
Prior aortic-arch intervention	Yes	80 (5.2%)	76 (5.1%)	4 (7%)	3 (6%)	1 (14%)
Prior PA banding	Yes	367 (24.0%)	353 (23.9%)	14 (25%)	13 (25%)	2 (29%)
Prior staging BCPS	Yes	1004 (64%)	974 (66.0%)	30 (55%)	27 (53%)	6 (86%)
Bilateral BCPS	Yes	115 (8%)	108 (7.3%)	7 (13%)	7 (14%)	0 (0%)
Age at first BCPS	Median (IQR)	0.7 (0.3-1.4)	0.7 (0.3-1.4)	0.6 (0.3-1.0)	0.6 (0.3-0.9)	0.3 (0.2-0.5)
PA reconstruction	Yes	102 (6.5%)	100 (6.6%)	2 (4%)	2 (4%)	0 (0%)
Pre-Fontan PA pressure	Mean (SD)	11.5 (3.5)	11.5 (3.6)	11.9 (2.4)	11.9 (2.4)	12.8 (1.3)
Preoperative elevated PAP	Yes	107 (9.1%)	105 (9.3%)	2 (5%)	2 (5%)	0 (0%)
Aortic pulmonary/venous collaterals	Yes	345 (29.5%)	335 (29.7%)	10 (24%)	9 (24%)	2 (40%)
Prior AV valve repair	Yes	77 (5.0%)	71 (4.8%)	6 (11%)	6 (12%)	0 (0%)
Pre-Fontan arrhythmia	Yes	22 (1.4%)	20 (1.3%)	2 (4%)	2 (4%)	0 (0%)
Pre-Fontan ventricular dysfunction	Yes	36 (6.1%)	32 (5.7%)	4 (15%)	3 (12%)	1 (20%)
Pre-Fontan thromboembolism	Yes	15 (1.0%)	14 (0.9%)	1 (2%)	1 (2%)	0 (0%)
Preoperative regurgitation	Yes	116 (9.4%)	111 (9.4%)	5 (10%)	5 (11%)	0 (0%)
Pre-Fontan pacemaker	Yes	6 (0.4%)	4 (0.3%)	2 (4%)	2 (4%)	0 (0%)
Age at Fontan (2-y increase)	Median (IQR)	4.6 (3.6-6.1)	4.6 (3.6-6.0)	5.7 (4.3-8.0)	5.6 (4.3-8.7)	4.6 (4.3-5.9)
Fontan type	AP	230 (14.7%)	218 (14.5%)	12 (22%)	12 (24%)	0 (0%)
	LT	286 (18.3%)	276 (18.3%)	10 (18%)	10 (20%)	0 (0%)
	ECC	1045 (66.9%)	1012 (67.2%)	33 (60%)	29 (57%)	7 (100%)
Year Fontan operation	1975-1989	192 (12.3%)	182 (12.1%)	10 (18%)	10 (20%)	0 (0%)
	1990-1999	359 (23.0%)	348 (23.1%)	11 (20%)	10 (20%)	1 (14%)
	2000-2009	525 (33.6%)	505 (33.5%)	20 (36%)	20 (39%)	0 (0%)
	2010-2017	485 (31.1%)	471 (31.3%)	14 (25%)	11 (22%)	6 (86%)

(Continued)

TABLE 1. Continued

Variable	Level	n = 1561 (%)	No PB or PLE after Fontan N = 1506	PB or PLE after Fontan N = 55	PLE after Fontan N = 51	PB after Fontan N = 7
Concomitant procedures	Yes	446 (28.6%)	428 (28.4%)	18 (33%)	16 (31%)	4 (57%)
Arch intervention	Yes	80 (5.2%)	76 (5.1%)	4 (7%)	3 (6%)	1 (14%)
Fenestration	Yes	573 (37.2%)	546 (36.8%)	27 (49%)	25 (49%)	4 (57%)
Concomitant PA reconstruction	Yes	91 (5.8%)	87 (5.8%)	4 (7%)	4 (8%)	1 (14%)
Concomitant AV valve repair	Yes	32 (2.0%)	31 (2.1%)	1 (2%)	1 (2%)	0 (0%)
Prolonged pleural effusions	Yes	88 (5.6%)	81 (5.4%)	7 (13%)	7 (14%)	1 (14%)

PB, Plastic bronchitis; *PLE*, protein losing enteropathy; *DILV*, double inlet left ventricle; *DORV*, double outlet left ventricle; *AV*, atrioventricular; *AVSD*, unbalanced atrioventricular septal defect; *VSD*, ventricular septal defect; *HLHS*, hypoplastic left heart syndrome; *ccTGA*, congenitally corrected transposition of great arteries; *SD*, standard deviation; *PA*, pulmonary artery; *BCPS*, bidirectional cavopulmonary shunt; *IQR*, interquartile range; *PAP*, pulmonary arterial pressure; *AP*, atriopulmonary; *LT*, lateral tunnel; *ECC*, extracardiac conduit.

CI, 1.03-1.22), and prolonged pleural effusions after Fontan (HR, 2.39; 95% CI, 1.07-5.31). Left ventricular morphology was protective (HR, 0.36; 95% CI, 0.18-0.70) (Table 2 and Table E1).

Clinical Course and Treatment Strategies

Patients were followed up over a median duration of 11.3 years (range, 6.0 days to 40.2 years). The majority of patients with PLE (n = 45) and PB (n = 5) presented symptomatically to the hospital at the time of their primary diagnosis, but thereafter management was largely on an outpatient basis. Readmissions were rare; among patients with PLE, 5 had a second readmission and 1 had 2 readmissions. These occurred at a median time of 371 days (IQR, 356-1057 days) from the previous episodes. In patients with PB, 1 had 1 recurrent episode (at 1095 days after the initial episode) and 1 had 2 recurrent episodes (at 659 and 1736 days after the initial episode). Outpatient medical treatments were budesonide (n = 14), sildenafil (n = 9), furosemide (n = 31), spironolactone (n = 22), angiotensin-converting enzyme inhibitor (n = 29), and antiarrhythmic agents (n = 14).

TABLE 2. Multivariable model for the development of protein losing enteropathy and plastic bronchitis using hazard ratios

Variable	HR (95% CI)	*P* (Wald)
Right ventricle morphology and non-HLHS (reference category)	1.00	
Right ventricle morphology and HLHS	2.30 (1.12-4.74)	.024
Left ventricle morphology	0.36 (0.18-0.70)	.003
Biventricular/indeterminate	0.49 (0.14-1.70)	.26
Age at Fontan (per 2-y increase)	1.13 (1.03-1.23)	.007
Pleural effusions (postoperative complication)	2.43 (1.09-5.41)	.03

HR, Hazard ratio; *CI*, confidence interval; *HLHS*, hypoplastic left heart syndrome.

Twenty-six surgical interventions were performed in 20 patients (Table 3): These were defined as Fontan revisions (n = 5; n = 3 deaths, n = 1 transplant), Fontan fenestrations (n = 11; n = 1 transplant, n = 2 deaths), Fontan conversions (n = 5; n = 1 transplant, n = 2 deaths), AV valve repairs (n = 3; no transplants, n = 2 deaths), and hepatic vein diversion (n = 2; no death or transplants). Patients with hepatic vein diversion (n = 2) remain free of death or transplantation at 5.67 years and 10.86 years of follow-up, respectively, both at New York Heart Association II without recurrent episodes requiring hospital admission.

Budesonide, an emerging treatment that has shown promise in select patients,[1] was used in 14 patients. These patients had also been treated with pre-PLE/PB fenestration closure (n = 3), pacemakers (n = 2), and AV valve repair (n = 1). Three of these 14 patients died, 1 had a heart transplantation, 1 had recurrent episode at 2933 days, and the remaining 9 remained free of recurrence, death, or transplantation after a median average of 11.2 years (range, 0.7-24.7 years).

TABLE 3. Number of patients with surgical revision, transplantation, or death

Operative intervention	All patients (N = 1561)	No PB/PLE (N = 1506)	PB/PLE (N = 55)
Fontan revision	19	14	5
Fontan fenestration	21	10	11
Fontan conversion	52	47	5
AV valve repair	15	12	3
Hepatic vein diversion	3	1	2
Fontan takedown	10	7	3
Transplantation	32	26	6
Death	117	102	15

Some patients underwent multiple operative interventions (eg, initial Fontan revision but subsequent transplantation). *PB*, Plastic bronchitis; *PLE*, protein losing enteropathy; *AV*, atrioventricular.

Risk Factors for Death or Transplant After Protein Losing Enteropathy/Plastic Bronchitis

There were 117 deaths in the Fontan population, and 13 deaths in the PLE/PB population. There were 4 Fontan takedowns and 6 transplants. The competing risks plot in Figure 1 shows the incidence of PB and PLE, death, and those alive and PB/PLE free. By univariable analyses, being male (HR, 2.58; 95% CI, 0.85-7.86) and older age at Fontan completion (HR, 1.22; 95% CI, 0.99-1.49 per 2-year increase) had a trend for poorer outcomes in predicting death or transplantation ($P < .1$); in multivariable analysis, age (HR, 1.23; 95% CI, 1.01-1.52) but not sex (HR, 2.79; 95% CI, 0.91-8.55) were predictive (Tables E2 and E3).

In the PLE/PB population, the freedom from death or transplantation at 5, 10, and 15 years was 70% (95% CI, 58-85), 65% (95% CI, 51-83), and 43% (95% CI, 26-73), respectively (Figures 2 and 3). When stratified by era (pre-2000 vs post-2000), there is no difference in freedom from death and heart transplantation in the contemporary era at up to 9 years after follow-up (log-rank P value = .2); however, there appears to be a difference in the early portion of the curve, which may demonstrate significance with longer follow-up (Figure 2).

DISCUSSION

PLE and PB are poor prognostic factors after the Fontan procedure[4] and are one of the primary predictors of death and transplantation in our population from the ANZFR. There is a lack of data regarding the risk of their occurrence, predictors of adverse outcomes in affected patients, and optimal treatments. Best management practices are dictated by a series of case reports and isolated single-center studies. From the ANZFR, we report the prevalence of PLE/PB of 4.9% at 30 years and 7.4% at 35 years, with freedom from death or transplantation at 5, 10, and 15 years at 70% (95% CI, 58-85), 65% (95% CI, 51-83), and 43% (95% CI, 26-73), respectively (Figure 2).

We have previously reported outcomes after Fontan surgery in Australia and New Zealand that were superior to those previously published, a finding that we attribute to the fact that we started our experience late, at a time when contraindications for this surgery were already identified, and to a lower proportion of patients with HLHS (13.0% in overall population and 27.0% in the PLE/PB population).

Our incidence of PLE and PB is marginally lower than that of 8% at 15 years by Atz and colleagues[9] and significantly less than that of 13.4% at 10 years reported by Feldt

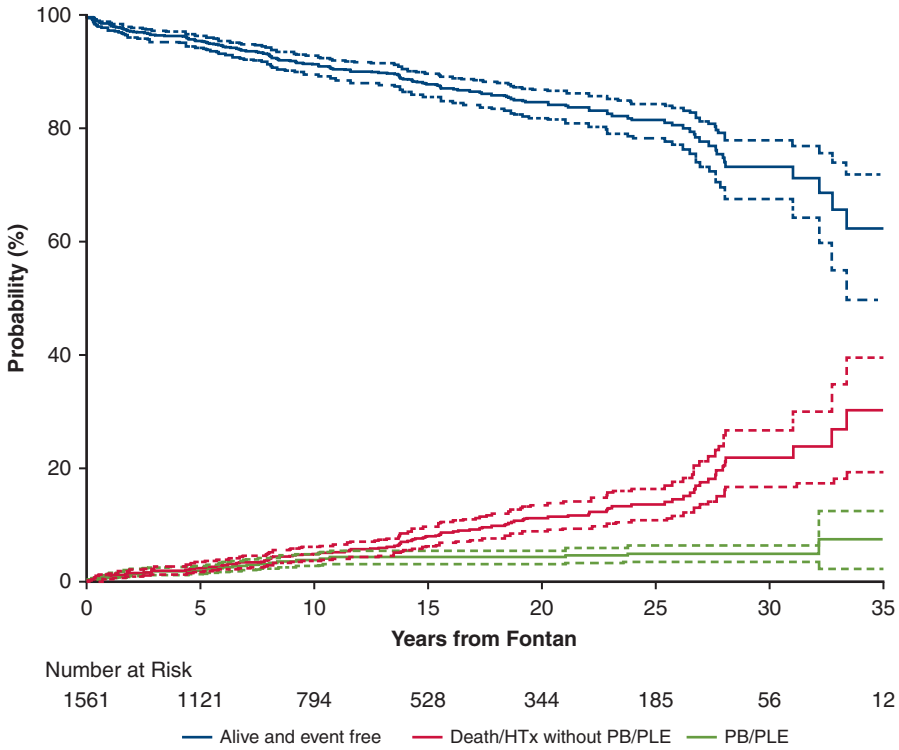
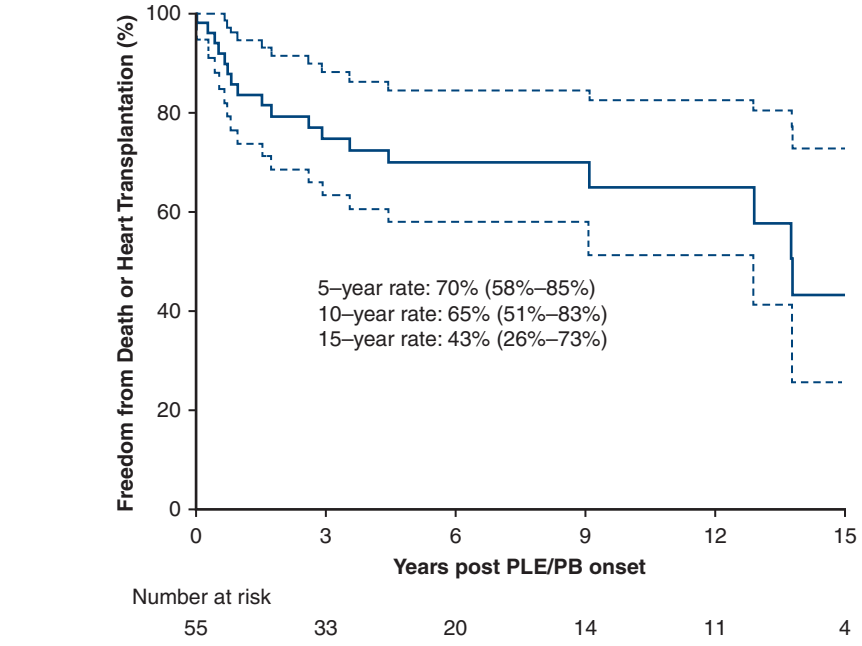


FIGURE 1. Competing risks plot shows probability of patients who received the Fontan remaining free of PLE and PB (*blue*). This is plotted against the probability of death before PLE or PB (*red*) and the probability of developing PLE or PB (*green*). The risk of developing PLE/PB increased up to 10 years from the Fontan, after which the risk plateaued. Conversely, there remains continuous risk of death from other causes. *HTx*, Heart transplantation; *PB*, plastic bronchitis; *PLE*, protein losing enteropathy.



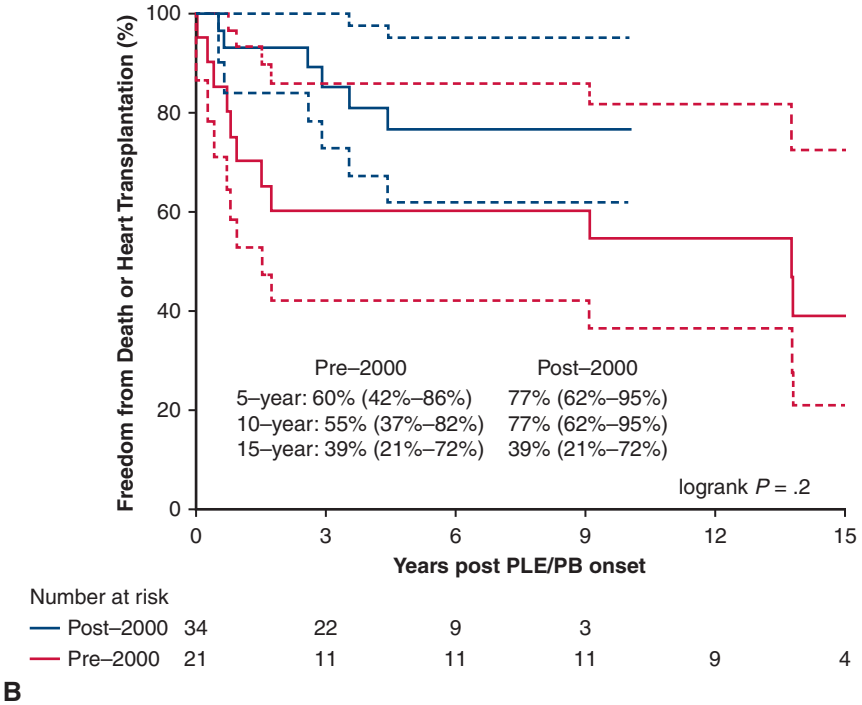


FIGURE 2. Kaplan–Meier examining freedom from (A) death or transplantation and (B) death or transplantation stratified by pre-2000 versus post-2000 (contemporary) group in the PLE/PB population. The freedom from death or transplantation at 5, 10, and 15 years was 70% (95% CI, 58-85), 65% (95% CI, 51-83), and 43% (95% CI, 26-73), respectively. When stratified by era (pre-2000 vs post-2000), there was no significant difference in freedom from death and heart transplantation in the contemporary era up to 9 years after follow-up. *PLE*, Protein losing enteropathy; *PB*, plastic bronchitis.

and colleagues.[10] It is likely that the incidence of PLE and PB reflects the health of a given population of patients with a Fontan circulation. Upon onset, the condition may have a protracted subclinical course. The majority of patients had 1 admission. Rehospitalization occurred in up to 10% within a median of 1.41 (IQR, 1.00-2.70) years after first diagnosis. The maximum number of hospital admissions for symptomatic flare-ups was 3.

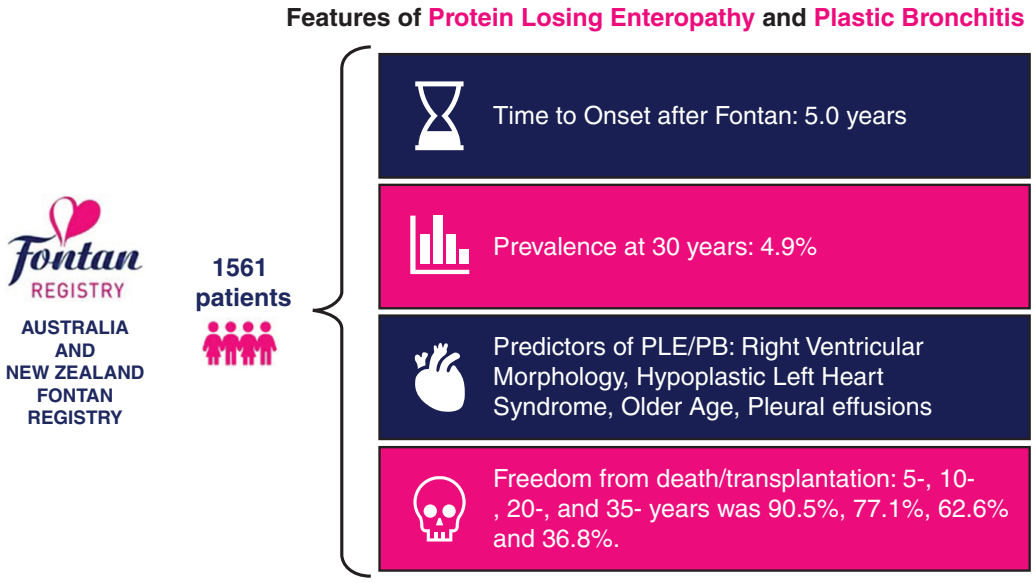


FIGURE 3. Our analysis of the ANZFR compromising of 1561 patients show the following features of PLE and PB: Average age of onset after the Fontan procedure is 5.0 years; the prevalence at 30 years among all patients who received the Fontan is 4.9%; the predictors of developing PLE or PB are RV morphology, HLHS, older age, and pleural effusions at the time of Fontan operation; and the freedom from death or transplantation among PLE/PB patients at 5, 10, and 15 years was 70% (95% CI, 58-85), 65% (95% CI, 51-83), and 43% (95% CI, 26-73), respectively. *PLE*, Protein losing enteropathy; *PB*, plastic bronchitis.

The risk factors for PLE/PB identified from multivariable regression were age at Fontan, RV morphology with HLHS, and pleural effusions. It was not surprising that risk factors for developing PLE or PB were RV with HLHS morphology, which are all likely associated with adverse outcomes. The association of prolonged postoperative pleural effusions with PLE and PB is consistent with etiological risk factors such as elevated venous pressure and decreased cardiac output. One could postulate that older age of Fontan may predispose to the development of systemic pulmonary collaterals, negatively affecting the Fontan circulation.

In the seminal article by Mertens and colleagues[4] from 1998 collecting the outcomes of 114 patients with PLE, the 5-year survival was 59%. A subsequent study by John and colleagues[5] in 2014 noted their 5-year survival at 88%. Compared with these studies, the ANZFR represents a larger cohort from a multicenter study, and although John and colleagues note an older mean age at PLE diagnosis (18.9 $\pm$ 11.0 years), their cohort had their initial Fontan operation performed at a later age (10.1 $\pm$ 10.8 years). It seems that we may now be evolving to a stage where we have a better control of these complications. Only 30% of the patients died or required heart transplantation in the 5 years after the diagnosis, with the remaining patients remaining relatively stable for long periods. The current literature describes these complications as a chronic indolent disease leading to morbidity in terms of wound healing, coagulopathies, bone hypodensity, immunocompromise, and growth stagnation.

It remains unclear what are the best interventions to offer to these patients and difficult to decide at what stage to offer them. The mainstay of treatment remains decreasing fluid overload through aggressive diuresis as noted by Mertens and colleagues.[4] Anecdotally, our results with budesonide (n = 14) have been favorable in protecting against death (n = 3/14) or transplant (n = 1/14). Transplant may offer a cure, but patients with this complication have been described to have a high early mortality after heart transplantation. Similar to the findings of Mertens and colleagues,[4] we found surgical intervention to be fraught by high risk. There have been promising reported results by interventional procedures blocking the lymphatics originating from the liver or the connections with the vessels responsible for spillage in the airways.[11,12] In expert hands, these are likely the most attractive interventions. In our series, patients who underwent hepatic vein diversion remained free of death or transplantation at 5 and 11 years of follow-up, respectively, both at New York Heart Association II without recurrent episodes requiring hospital admission. In patients who are fit for and managed to survive cardiac transplantation (n = 4), it proved to be the only cure for PLE or PB.

Study Limitations

Because this was a large retrospective study, with interventions dating back to 1977, there may be drastic differences in contemporary outcomes, but this is difficult to accurately identify because of a relatively large number of predictors compared with outcomes (n = 55). The 35-year

follow-up across 2 countries and 11 centers makes some specific hemodynamic data difficult to collect consistently. PLE and PB remain rare conditions, with each clinician seeing a few patients, rendering difficulty in creating diagnosis and management protocols. A strict diagnostic criterion should be set in place, with imaging of the lymphatic system for each patient. These should then correlate to strict medical and surgical intervention protocols (which at present remain speculative) and investigated through further prospective studies.

CONCLUSIONS

PLE and PB remain severe complications of the Fontan circulation that seem to preferably affect patients with a dominant right single ventricle. There is no significant improvement in transplant-free survival in the current era, with one-quarter dying or requiring a heart transplantation within a few years and the remaining being relatively stable for long periods. Heart transplantation remains the ultimate treatment for those the most severely affected by these complications.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: Fontan, protein-losing enteropathy, plastic bronchitis

TABLE E1. Univariable analysis of risk factors for the onset of protein losing enteropathy or plastic bronchitis

Variable	Level	N	Events	HR (95% CI)	*P* (Wald)
Gender	Female	669	25	1	.9
	Male	892	30	0.98 (0.57-1.67)	
Ventricle morphology	Left-biventricular or intdeterminate	1049	23	1	<.001
	Right	512	32	3.58 (2.07-6.17)	
Primary diagnosis	AV canal or AVSD	121	7	1	.003
	ccTGA	96	4	0.67 (0.20-2.30)	
	Double inlet left ventricle	261	9	0.51 (0.19-1.36)	
	Double outlet right ventricle	210	5	0.36 (0.11-1.13)	
	Ebstein's anomaly	14	0	Not estimable	
	HLHS	201	15	1.76 (0.71-4.33)	
	Other	143	7	0.85 (0.30-2.42)	
	PA with IVS	127	3	0.41 (0.11-1.58)	
	PA with VSD	33	0	Not estimable	
	Tricuspid atresia	346	5	0.16 (0.05-0.56)	
HLHS (primary diagnosis)	No	1351	40	1	<.001
	Yes	201	15	3.89 (2.12-7.15)	
HLHS (all patients)	No	1343	39	1	<.001
	Yes	209	16	4.14 (2.27-7.52)	
Fontan type	AP	230	12	1	.6
	ECC	1045	33	1.21 (0.58-2.52)	
	LT	286	10	0.86 (0.36-2.08)	
Year Fontan operation	1975-1989	192	10	1	.1
	1990-1999	359	11	0.80 (0.32-2.00)	
	2000-2009	525	20	1.19 (0.51-2.77)	
	2010-2017	485	14	2.33 (0.90-6.02)	
No. palliations	Per unit increase	1531	55	1.28 (1.01-1.62)	.04
	None, 1, or 2	1134	36	1	.04
	3-6	397	19	1.80 (1.03-3.16)	
Pre-Fontan aortic arch repair	No	1451	51	1	.3
	Yes	80	4	1.77 (0.64-4.92)	
Pre-Fontan PA banding	No	1164	41	1	.8
	Yes	367	14	1.08 (0.59-1.99)	
Prior staging BCPS	No	527	25	1	.8
	Yes	1004	30	0.94 (0.54-1.64)	
Prior staging bilateral BCPS	No	1416	48	1	.044
	Yes	115	7	2.28 (1.02-5.06)	
Age at first BCPS	Per unit increase	971	29	0.91 (0.69-1.21)	.5
AV valve repair	No	1454	49	1	.008
	Yes	77	6	3.18 (1.36-7.47)	
PA reconstruction	No	1459	53	1	.4
	Yes	102	2	0.56 (0.14-2.30)	
Pre-Fontan pulmonary artery pressure	Per unit increase	1172	44	1.02 (0.95-1.09)	.6
Atriopulmonary collaterals	No	825	31	1	.9
	Yes	345	10	1.03 (0.50-2.12)	
Aortic arch intervention	No	1451	51	1	.3
	Yes	80	4	1.77 (0.64-4.92)	
Fenestration	No	967	28	1	.01
	Yes	573	27	2.04 (1.19-3.52)	
Age at Fontan	Per 2-y increase	1561	55	1.10 (1.01-1.21)	.035
Concomitant procedure	No	1115	37	1	.3
	Yes	446	18	1.38 (0.78-2.42)	

(Continued)

TABLE E1. Continued

Variable	Level	N	Events	HR (95% CI)	*P* (Wald)
Concomitant PA reconstruction	No	1470	51	1	.5
	Yes	91	4	1.38 (0.50-3.83)	
Concomitant AV valve repair	No	1529	54	1	.9
	Yes	32	1	0.91 (0.13-6.56)	
Isomerism	No	1423	50	1	.8
	Yes	109	5	1.36 (0.54-3.41)	
Dextrocardia	No	1377	52	1	.2
	Yes	137	2	0.39 (0.10-1.62)	
Common AV valve	No	1424	47	1	.09
	Yes	137	8	1.93 (0.91-4.09)	
Pre-Fontan elevated PAP (>15)	No	1065	42	1	.2
	Yes	107	2	0.39 (0.09-1.60)	
Pleural effusions	No	1473	48	1	.015
	Yes	88	7	2.68 (1.21-5.92)	
Pre-Fontan arrhythmias	No	1539	53	1	.2
	Yes	22	2	2.63 (0.64-10.8)	
Pre-Fontan ventricular dysfunction	No	550	22	1	.06
	Yes	36	4	2.83 (0.97-8.26)	
Pre-Fontan thromboembolic events	No	1546	54	1	.3
	Yes	15	1	2.58 (0.36-18.7)	
Pre-Fontan AV valve regurgitation	No	1116	44	1	.6
	Yes	116	5	1.27 (0.50-3.20)	
Pre-Fontan pacemaker	No	1555	53	1	.002
	Yes	6	2	9.69 (2.36-39.8)	

HR, Hazard ratio; *CI*, confidence interval; *AV*, atrioventricular; *AVSD*, unbalanced atrioventricular septal defect; *ccTGA*, congenitally corrected transposition of great arteries; *HLHS*, hypoplastic left heart syndrome; *PA*, pulmonary artery; *IVS*, intact ventricular septum; *VSD*, ventricular septal defect; *AP*, atriopulmonary; *ECC*, extracardiac conduit; *LT*, lateral tunnel; *BCPS*, bidirectional cavopulmonary shunt; *PAP*, pulmonary arterial pressure.

TABLE E2. Univariable analysis of factors predicting death or transplantation after protein losing enteropathy/plastic bronchitis onset

Variable	Level	N	Events	HR (95% CI)	*P* (Wald)
Gender	Female	25	5	1	.1
	Male	30	14	2.58 (0.85-7.86)	
Ventricle morphology	Left-biventricular or intdeterminate	23	10	1	.9
	Right	32	9	0.95 (0.36-2.53)	
Primary diagnosis	Tricuspid atresia	5	3	1	.9
	AV canal or AVSD	7	0	Not estimable	
	ccTGA	4	1	0.56 (0.05-6.26)	
	Double inlet left ventricle	9	6	1.68 (0.34-8.42)	
	Double outlet right ventricle	5	2	1.29 (0.17-9.62)	
	HLHS	15	5	1.44 (0.25-8.15)	
	Other	7	1	0.39 (0.03-4.54)	
	PA with IVS	3	1	0.75 (0.07-8.35)	
AV canal or AVSD	No	47	19		
	Yes	8	0	Not estimable	
HLHS (all patients)	No	39	14	1	.4
	Yes	16	5	1.65 (0.55-4.96)	
Ventricle morphology version2	Left	19	9	1	.5
	Right HLHS	16	5	1.46 (0.42-5.01)	
	Right non-HLHS	16	4	0.70 (0.20-2.43)	
Fontan type	AP	12	8	1	.3
	ECC	33	7	0.44 (0.15-1.36)	
	LT	10	4	0.50 (0.15-1.72)	
Year Fontan operation	1975-1989	10	5	1	.6
	1990-1999	11	7	0.85 (0.26-2.78)	
	2000-2009	20	5	0.47 (0.13-1.69)	
	2010-2017	14	2	0.46 (0.08-2.47)	
Year Fontan operation	Pre-2000	21	12	1	.2
	Post-2000	34	7	0.51 (0.19-1.40)	
No. palliations	Per unit increase	55	19	0.90 (0.62-4.14)	.6
	None, 1, or 2	36	14	1	.3
	3 to 6	19	5	0.60 (0.21-1.71)	
Pre-Fontan aortic arch repair	No	51	18	1	.9
	Yes	4	1	0.91 (0.12-6.92)	
Pre-Fontan PA banding	No	41	12	1	.3
	Yes	14	7	1.60 (0.62-4.14)	
Prior staging BCPS	No	25	13	1	.13
	Yes	30	6	0.45 (0.16-1.25)	
Prior staging bilateral BCPS	No	48	17	1	.95
	Yes	7	2	1.05 (0.24-4.63)	
Age at first BCPS	Per unit increase	29	6	0.86 (0.45-1.66)	.7
AV valve repair	No	49	18	1	.7
	Yes	6	1	0.63 (0.08-4.83)	
PA reconstruction	No	53	19		
	Yes	2	0	Not estimable	
Pre-Fontan pulmonary arterial pressure	Per unit increase	44	12	1.06 (0.82-1.37)	.6
Atriopulmonary collaterals	No	31	10	1	.95
	Yes	10	2	1.05 (0.22-4.94)	
Aortic arch intervention	No	51	18	1	.9
	Yes	4	1	0.91 (0.12-6.92)	

(Continued)

TABLE E2. Continued

Variable	Level	N	Events	HR (95% CI)	*P* (Wald)
Fenestration	No	28	11	1	.9
	Yes	27	8	0.96 (0.37-2.46)	
Age Fontan	Per 2-y increase	55	19	1.22 (0.99-1.49)	.06
Concomitant procedure	No	37	13	1	.3
	Yes	18	6	0.56 (0.20-1.60)	
Concomitant PA reconstruction	No	51	18	1	.5
	Yes	4	1	0.53 (0.07-3.99)	
Concomitant AV valve repair	No	54	19		
	Yes	1	0	Not estimable	
Isomerism	No	50	18	1	.6
	Yes	5	1	0.60 (0.08-4.60)	
Dextrocardia	No	52	18		
	Yes	2	0	Not estimable	
Common AV valve	No	47	19		
	Yes	8	0	Not estimable	
Pre-Fontan elevated PAP	No	42	11	1	.3
	Yes	2	1	2.94 (0.36-24.2)	
Pleural effusions	No	48	16	1	.2
	Yes	7	3	2.35 (0.65-8.50)	
Pre-Fontan arrhythmias	No	53	18	1	.5
	Yes	2	1	2.15 (0.28-16.5)	
Pre-Fontan ventricular dysfunction	No	22	7	1	.9
	Yes	4	2	1.12 (0.21-5.87)	
Pre-Fontan thromboembolic events	No	54	18	1	.3
	Yes	1	1	2.98 (0.39-22.8)	
Pre-Fontan AV valve regurgitation	No	44	16	1	.2
	Yes	5	3	2.46 (0.70-8.64)	
Pre-Fontan pacemaker	No	53	18	1	.8
	Yes	2	1	1.31 (0.17-9.99)	

HR, Hazard ratio; *CI*, confidence interval; *AV*, atrioventricular; *AVSD*, unbalanced atrioventricular septal defect; *ccTGA*, congenitally corrected transposition of great arteries; *HLHS*, hypoplastic left heart syndrome; *PA*, pulmonary artery; *IVS*, intact ventricular septum; *AP*, atriopulmonary; *ECC*, extracardiac conduit; *LT*, lateral tunnel; *BCPS*, bidirectional cavopulmonary shunt; *PAP*, pulmonary arterial pressure.

TABLE E3. Multivariable analysis of factors predicting death or transplantation after protein losing enteropathy/plastic bronchitis onset

Variable	HR (95% CI)	*P* (Wald)
Age at Fontan (per 2-y increase)	1.23 (1.01-1.52)	.04
Pleural effusions (postoperative complication)	2.79 (0.91-8.55)	.07

HR, Hazard ratio; *CI*, confidence interval.

000 Protein-losing enteropathy and plastic bronchitis after the Fontan procedure

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Prevalence of PLE and PB is 4.9% at 30 years and 7.4% at 35 years, with freedom from death or transplantation at 5, 10, and 15 years at 70% (95% confidence interval [CI], 58-85), 65% (95% CI, 51-83), and 43% (95% CI, 26-73), respectively.