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Favourable mid-term outcome after heart transplantation for late Fontan failure

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CONGENITAL

Abstract

OBJECTIVES: Fontan failure (FF) represents a growing and challenging indication for paediatric orthotopic heart transplantation (OHT). The aim of this study was to identify predictors of the best mid-term outcome in OHT after FF.

METHODS: Twenty-year multi-institutional retrospective analysis on OHT for FF.

RESULTS: Between 1991 and 2011, 61 patients, mean age 15.0 ± 9.7 years, underwent OHT for failing atriopulmonary connection (17 patients = 27.8%) or total cavopulmonary connection (44 patients = 72.2%). Modality of FF included arrhythmia (14.8%), complex obstructions in the Fontan circuit (16.4%), protein-losing enteropathy (PLE) (22.9%), impaired ventricular function (31.1%) or a combination of the above (14.8%). The mean time interval between Fontan completion and OHT was 10.7 ± 6.6 years. Early FF occurred in 18%, requiring OHT 0.8 ± 0.5 years after Fontan. The hospital mortality rate was 18.3%, mainly secondary to infection (36.4%) and graft failure (27.3%). The mean follow-up was 66.8 ± 54.2 months. The overall Kaplan–Meier survival estimate was 81.9 ± 1.8% at 1 year, 73 ± 2.7% at 5 years and 56.8 ± 4.3% at 10 years. The Kaplan-Meier 5-year survival estimate was 82.3 ± 5.9% in late FF and 32.7 ± 15.0% in early FF ($P = 0.0007$). Late FF with poor ventricular function exhibited a 91.5 ± 5.8% 5-year OHT survival. PLE was cured in 77.7% of hospital survivors, but the 5-year Kaplan-Meier survival estimate in PLE was 46.3 ± 14.4 vs 84.3 ± 5.5% in non-PLE ($P = 0.0147$). Cox proportional hazards identified early FF ($P = 0.0005$), complex Fontan pathway obstruction ($P = 0.0043$) and PLE ($P = 0.0033$) as independent predictors of 5-year mortality.

CONCLUSIONS: OHT is an excellent surgical option for late FF with impaired ventricular function. Protein dispersion improves with OHT, but PLE negatively affects the mid-term OHT outcome, mainly for early infective complications.

Keywords: Fontan operation • Heart transplantation • Congenital heart disease • Failing Fontan • Heart failure

INTRODUCTION

Since its original description over 40 years ago, the Fontan operation [1] has undergone countless modifications, probably as no other procedure in paediatric cardiac surgery. Despite the excellent results that can be currently expected for modern Fontan completion [2, 3], there are still concerns regarding the early and long-term durability of a systemic and pulmonary in series circulation driven by a single ventricle [4]. Early Fontan failure (FF), although rare, is not a completely resolved clinical issue [5]. A large variety of other Fontan-specific complications including protein-losing enteropathy (PLE), plastic bronchitis, intractable arrhythmias, thrombosis or obstruction in the Fontan circuit, among others, can lead to the failure of the Fontan principle, even in the presence of a relatively normal function of the single ventricle [6]. Fontan revision or conversion can address residual anatomical lesions or control

focal atrial arrhythmias [7]. Catheter-based interventions and pharmacological manipulation of pulmonary vascular resistance [8] can provide additional treatments, which aim at the best energy preservation model. Nevertheless, primary myocardial dysfunction or intolerance of the Fontan circulation in the absence of correctable lesions represents a growing indication for orthotopic heart transplantation (OHT) [9]. A previous Fontan status has been associated with lower actuarial survival after OHT, compared with non-Fontan congenital heart disease [10, 11]. Single-centre experience with OHT for FF is limited, and random variations in small cohorts might explain the nonuniform results of OHT after FF, mainly related to differences in early OHT outcomes [11]. Therefore in 2012, the European Congenital Heart Surgery Association (ECHSA) conducted a study, merging the databases of the ECHSA centres. The objective of this paper was to review the ECHSA experience with OHT for FF, evaluating outcomes and possibly identifying the best candidates for OHT in FF.

MATERIALS AND METHODS

A retrospective multicentre review was conducted among 11 ECHSA centres in Europe and USA on the management of the FF circulation by OHT. Patients who developed FF after Fontan completion and underwent OHT as the ultimate surgical treatment of their FF status between 1991 and 2011 fulfilled the inclusion criteria and qualified for the present multicentre study. The closing date for follow-up was 31 December 2012. Review of medical records was approved by each local committee and single-institutional review board on clinical investigation. Individual patients were not identified, and the need for patient consent was waived. The contribution of individual centres over time is outlined in Supplementary Fig. 1. A common ECHSA database was created summarizing baseline anatomical and demographic data of OHT recipients, technical details of previous palliative procedures, type of original Fontan operation, presence of fenestration, strategy of staged versus direct Fontan completion, previous Fontan conversion or take-down, timing of Fontan completion, timing and mechanism of FF and haemodynamic and echocardiographic data. Pretransplant ventricular function was systematically evaluated by 2D echocardiography, and graded in a semi-quantitative fashion as normal, moderately impaired or poor. This assessment was necessary due to the well-known variability in ventricular morphology of single ventricles, which prevented a systematic quantitative evaluation of ventricular function. Preoperative, intraoperative and postoperative variables, including pre- and post-OHT use of assist devices or extracorporeal membrane oxygenation (ECMO) were acquired. Early FF was prespecified and defined as the need for OHT within 2 years after the original Fontan completion. All FF requiring OHT later than 2 years after Fontan completion were defined as late FF. The 2-year time interval was selected to avoid colinearity with acute FF and emergency OHT. The primary end-points of the study were death and reintervention after OHT for FF. The secondary end-points related to quality of life in terms of functional class and major transplant-specific morbidity. Hospital chart review was conducted for each transplant recipient and donor at the local Institution. The University Medical Center of Groningen coordinated the study, collected the data, maintained the database and performed all the data analysis.

Statistical analysis

Standard summary statistics were reported as mean and standard deviation for normally distributed continuous variables, while medians with range were used for skewed continuous variables. Categorical analysis was conducted by Fisher's exact testing, while continuous variables were compared by unpaired *t*-testing. Analysis of freedom from events (death and reintervention) was conducted by the Kaplan–Meier technique at 3 months, 1 year, 5 years and 10 years after OHT; Wilcoxon and log-rank testing were utilized to compare event-free survival between subgroups. Cumulative hazards were calculated for each event-free survival. All potential risk factors for 5-year mortality were first assessed by logistic regression analysis and then entered into a multivariate Cox proportional hazard model to identify independent predictors of 5-year mortality, checking for the proportionality assumption. Statistical analysis was conducted with the SAS-Statview 1998 statistical software, SAS Institute, Inc., NC, USA.

RESULTS

Between 1991 and 2011, 61 patients underwent OHT for FF at 11 ECHSA centres. The cohort includes 51 primary OHT for FF, 6 OHT for FF after Fontan conversion and 4 OHT after Fontan

Table 1: Anatomical diagnosis

Anatomy in 61 patients	Patients (%)	Heterotaxy syndrome	Situs inversus with dextrocardia
Tricuspid atresia	10 (16.4%)		
Double inlet left ventricle	11 (18.0%)	1	
Pulmonary atresia with intact ventricular septum	4 (6.6%)		
HLHS and variants	16 (26.2%)		
Unbalanced atrioventricular septal defect	9 (14.8%)	8	2
Others (overall)	11 (18.0%)	3	2
Other description			
Double outlet right ventricle	(6)	(3)	(2)
Criss-cross, TGA, PS/PA	(3)		
cTGA PS/PA	(2)		
Total	61 (100%)	12 (19.7%)	4 (6.6%)

HLHS: hypoplastic left heart syndrome; TGA: transposition of great arteries; PS: pulmonary stenosis; PA: pulmonary atresia.

take-down. The mean age at OHT was 15.0 ± 9.7 years. Seven patients (11.4%) were younger than 6 years of age at OHT. Male gender was prevalent (39 patients, 63.9%). The majority of OHT were performed after 2001 (46 OHT = 75.4%). The total follow-up was 339.7 patient/years. The mean follow-up was 66.8 ± 54.2 months (range: 12.1–254 months) and was 100% complete and updated.

Table 2: Surgical history of 61 patients undergoing heart transplantation for Fontan failure

Previous surgical history in 61 patients	Patients
Palliative procedures prior to Fontan	
PA banding	12 (19.7%)
mBT shunt	38 (62.3%)
No PA banding or mBTS	11 (18%)
Fontan completion strategy	
Fontan staging with BDG	39 (63.9%)
Direct Fontan	22 (36.1%)
Fontan completion technique	
Atriopulmonary connection	17 (27.8%)
TCPC	44 (72.2%)
Fenestration	24 (39.3%)
Post-Fontan interventions	28 (45.9%)
Fontan take-down prior to OHT	4
Fontan conversion to TCPC prior to OHT	6
Surgical revision of Fontan	3
PA branch stenting prior to OHT	6
Other catheter intervention prior to OHT	9

First palliative procedure, Fontan staging, technique of Fontan completion and post-Fontan interventions prior to heart transplantation are reported.
PA: pulmonary artery; mBTS: modified Blalock–Taussig shunt; BDG: bidirectional Glenn; TCPC: total cavopulmonary connection; OHT: orthotopic heart transplantation.

Baseline anatomy and surgical history

The anatomical details of the cohort are depicted in Table 1. Hypoplastic left heart syndrome (HLHS) and variants represented the most frequent anatomical subtype (26.2%). Previous surgical history is depicted in Table 2. Bidirectional Glenn (BDG) staging to Fontan completion was preferred in 39 patients (63.9%). Fontan completion was performed at a mean age of 4.3 ± 1.6 years by atriopulmonary connection (17 patients = 27.8%), or total cavopulmonary connection (TCPC) (44 patients = 72.2%). Fontan completion by TCPC included the lateral tunnel variant (16 patients = 36%), intracardiac tube graft placement (3 patients = 7%) and extracardiac TCPC (25 patients = 57%). A fenestration had been accomplished in 24 (39.3%) patients at the time of Fontan completion. Conversion of an atriopulmonary Fontan to an extracardiac Fontan had been accomplished in 6 patients 3.7 ± 0.9 years prior to OHT, surgical revision of a suboptimal Fontan pathway had been performed in 3 patients 2.6 ± 1.1 years prior to OHT, while Fontan take-down had been necessary in 4 patients 10.1 ± 6.6 months prior to OHT. The mean time interval between Fontan completion and OHT was 10.7 ± 6.6 years. Early FF represented the indication for OHT in 11 patients (18%). The mean time interval between Fontan completion and OHT was 0.8 ± 0.5 years in early FF and 10.5 ± 6 years in late FF ($P < 0.001$). Table 3 summarizes the baseline characteristics of early and late FF subgroups. There was no significant difference between early FF and late FF according to sex, primary diagnosis, BDG staging, age at Fontan, presence of fenestration, indication for OHT, time on waiting list, need for pretransplant ICU admission, mechanical ventilation, dialysis or mechanical support.

Table 3: Baseline demographics in early and late Fontan failure

	Early FF ($n = 11$)	Late FF ($n = 50$)	P value
Time between Fontan completion and OHT (years)	0.8 ± 0.5	10.5 ± 6.0	<0.001
Sex (male)	8 (72.7%)	31 (62%)	0.73
Diagnosis of HLHS and variants	3 (27.3%)	13 (26%)	0.93
BDG staging to Fontan	9 (81.9%)	30 (60%)	0.17
Age at Fontan completion (years)	4.6 ± 1.2	4.1 ± 0.9	0.82
Fontan completion by TCPC	11 (100%)	33 (66%)	0.025
Fenestration	6 (55%)	28 (56%)	0.92
Conversion to TCPC pre-OHT	0 (0%)	6 (12%)	0.58
Days on OHT waiting list	32.5 ± 7	55.9 ± 5.6	0.056
PLE	2 (18%)	10 (20%)	0.88
Intractable arrhythmia	0 (0%)	9 (18%)	0.10
Poor ventricular function	3 (27.3%)	40 (80%)	0.0014
Mean PAP pre-OHT	18.4 ± 3.6	20.3 ± 4.1	0.14
Mean transpulmonary gradient	7.9 ± 2.1	6.7 ± 1.7	0.08
Mean EDVP	10.5 ± 1.3	13.6 ± 1.0	<0.001
ICU admission pre-OHT	5 (45.4%)	12 (24%)	0.26
Mechanical ventilation pre-OHT	2 (18.2%)	4 (8%)	0.29
Mechanical circulatory support pre-OHT	0 (0%)	2 (4%)	0.99
Dialysis pre-OHT	1 (9%)	2 (4%)	0.10
Dialysis post-OHT	3 (27.2%)	5 (10%)	0.14

FF: Fontan failure; BDG: bidirectional Glenn; TCPC: total cavopulmonary connection; PAP: pulmonary artery pressure; EDVP: end-diastolic ventricular pressure; PLE: protein-losing enteropathy; OHT: orthotopic heart transplantation.

Orthotopic heart transplantation indication and haemodynamics

The main indication for OHT included intractable arrhythmias (9 patients = 14.8%), complex obstruction of the Fontan circuit up to the level of the pulmonary veins (10 patients = 16.4%), PLE (14 patients = 22.9%), primary chronic ventricular failure (19 patients = 31.1%) or a combination of the above (9 patients = 14.8%). Arrhythmias included atrial fibrillation (7 patients) and non-sustained ventricular tachycardia (2 patients) refractory to medical therapy and/or catheter intervention. Arrhythmias were significantly more common in atriopulmonary Fontan (6 of 17 patients = 35.2%) than in TCPC (3 of 44 patients = 6.8%) ($P = 0.010$). Two patients with Fontan pathway obstruction presented with concomitant aortic arch obstruction resilient to catheter intervention. Severe AV valve insufficiency was diagnosed in 16 patients (26.2%). Ventricular function by 2D echocardiographic evaluation was defined as 'poor' in 43 patients (70.5%), while normal or moderate dysfunction was detected in 18 patients (29.5%). Table 3 shows that impaired ventricular function was diagnosed in 80% late FF (40 of 50 patients) and in only 27.2% early FF (3 of 11 patients) ($P = 0.0014$). The mean pretransplant pulmonary artery pressure (PAP) of the overall cohort was 19.7 ± 3.7 mmHg with a mean transpulmonary gradient of 7.1 ± 1.2 mmHg and a mean end-diastolic ventricular pressure (EDVP) of 12.6 ± 1.1 mmHg. The PVR index was measured in 11 patients (18%) prior to OHT and calculated to be equal to 2.96 ± 0.99 Wood Units/m^2; however, in the setting of extensive aortopulmonary collateral flow, this calculation should be considered with caution.

Status at orthotopic heart transplantation

The mean number of days on the waiting list was 51.6 ± 37.0. Prior to OHT, 31 patients (51%) were in NYHA Class III and 30 (49%) in NYHA Class IV. Seventeen patients (27.8%) were in high-urgency status, all admitted in the ICU on inotropic support for a mean of 33.6 ± 12.6 days. Prior to OHT, mechanical ventilation was necessary in 6 (9.8%) and haemodialysis in 3 (4.9%). Two patients were successfully bridged to OHT by a paracorporeal ventricular assist device (Berlin Heart EXCOR Pediatric VAD, Berlin, Germany) either as an LVAD interposed between the common atrium and the neoaorta (1 patient) or as an RVAD interposed between the systemic venous return and the pulmonary arteries (1 patient). The first patient received an OHT 2 days after LVAD implant while the latter was bridged to OHT for 408 days and is currently alive and well 5 years after transplant.

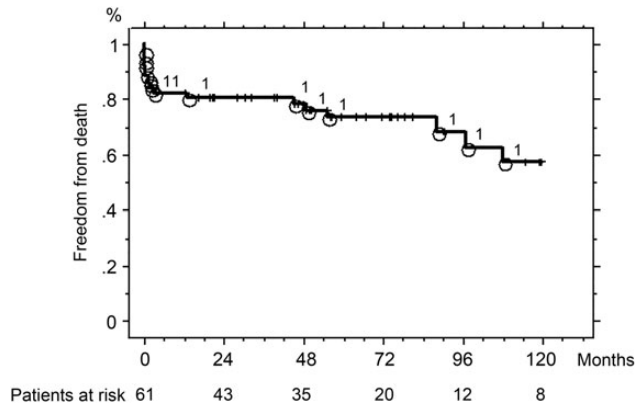

Figure 1: Kaplan–Meier freedom from death with patients at risk in the overall cohort.

Operative technique

Bicaval OHT technique was performed in all patients. Reconstruction of systemic venous return was necessary in 12 (19.6%) by rerouting a left-sided IVC (3) or unifocalizing a left SVC using the donor innominate vein (9). Reconstruction of the PA branches was very common (51 = 83.6%) including extensive hilum-to-hilum reconstruction in 12 (19.6%). Two patients required aortic arch reconstruction with a donor aortic arch. Donor tissue (either pulmonary artery bifurcation, innominate vein, pericardium or aorta) was preferentially used for reconstruction. The median number of sternotomies prior to OHT was 3.9 (range 2–9). The mean cardiopulmonary bypass time was 284 ± 125 min, the cross-clamp time 113.3 ± 66.9 min and the mean ischaemic time of the graft 227.2 ± 98.9 min. Circulatory arrest was necessary in 10 patients (16.4%) for 31.2 ± 12.9 min to control excessive collateral circulation or accomplish systemic arterial reconstruction.

Early postoperative outcome

The Kaplan-Meier 90-day survival estimate was 81.9 ± 1.81% and was equal to hospital survival. The overall hospital mortality rate was 18.3% (11 patients). There was a trend towards lower hospital mortality in recent years, which did not reach statistical significance (5 of 24 patients = 20.8% before 2005 and 6 of 37 patients = 16.2% after 2005) ($P = 0.73$). No early or late mortality occurred after OHT in all 6 patients with previous conversion of an atriopulmonary Fontan to TCPC. Previous take-down Fontan was associated with 25% hospital mortality after OHT (1 of 4 patients). The hospital mortality rate in OHT for late FF was 12% (6 of 50 patients) and 45.5% for early FF (5 of 11 patients) ($P = 0.02$). The hospital mortality rate for OHT in PLE was 35.7% (5 of 14 patients) and 12.7% in non-PLE (6 of 47 patients) ($P = 0.028$). Causes of early death included bleeding in 2, graft failure with predominant RV dysfunction in 3, multiorgan failure with stroke in 2 and infection in 4 patients. Intractable bleeding was the cause of intraoperative death in 2 patients with known coagulopathy secondary to hepatic dysfunction and cachexia. Stent removal from the right (1) and left (1) pulmonary artery resulted in suboptimal reconstruction of the pulmonary arterial tree in 2 patients and contributed to early fatal RV failure. The third graft failure was secondary to inadequate graft myocardial protection in a patient with a pulmonary vascular resistance index of 3.8 U/m^2. Multiorgan failure with associated stroke was the cause of early death in 2 patients. One of them had been bridged to transplant by LVAD (Berlin Heart EXCOR). He developed a stroke with left hemiplegia after OHT; an intestinal perforation with Gram-negative peritonitis represented the final cause of death 16 days after OHT. A disseminated CMV infection with positive blood cultures for coagulase-negative *Staphylococcus* was the source of lethal infection in 1 patient on plasmapheresis treatment, 45 days after OHT. Gram-negative sepsis (*Pseudomonas aeruginosa* and/or *Serratia marcescens*) was the source of lethal infection in 3 patients between 16 and 90 days after OHT. Gram-negative sepsis was associated with gastrointestinal bleeding in 2 patients. Mechanical circulatory support after OHT was accomplished by veno-arterial ECMO in 5 patients for a median period of 16 days (range 8–53 days) with three deaths. Haemodialysis was necessary in 8 patients after OHT with four early deaths, all due to infective complications in patients with PLE.

Plasmapheresis was used in 15 patients (24.5%) in the treatment of antibody-mediated rejection and combined with immunoadsorption in 4 cases with elevated panel reactive antibody. The mean time of mechanical ventilation after OHT was 8.2 ± 2.7 days in the overall cohort, and 4.8 ± 1.9 days in hospital survivors. The mean ICU stay was 22.6 ± 6.8 days and the mean hospital stay was 45.7 ± 9.6 days.

Late outcome

The late mortality (after hospital discharge) rate was 14% (7 of 50 patients) and occurred between 1.1 and 19.1 years after OHT. Four deaths (57.1%) supervened between 0.6 and 26.4 months after re-OHT. Causes of late death included cancer (2), mycotic infections (2), acute rejection (1), chronic rejection (1) and multiorgan failure after re-OHT (1). Lymphoproliferative disorder was the cause of death in 1 patient 55 months after OHT. This patient had developed recurrent PLE 33 months after OHT and was bridged by ECMO to successful re-OHT, but eventually died 22 months later from B-cell lymphoma. Uterine cancer was the cause of death in 1 patient 19.1 years after OHT and 3.2 years after re-OHT for chronic rejection. Two lethal mycotic infections occurred at 47 and 97 months after OHT. An *Aspergillus fumigatus* brain abscess was the cause of death in 1 patient 8.1 years after ABO-incompatible OHT, treated until then with column-based immunoadsorption, exchange plasmapheresis, C1 inhibitor infusion and a subsequent triple immunosuppressive regimen. A Candida septicaemia was the cause of death in another patient 1.1 month after re-OHT, performed 3.9 years after OHT. Acute rejection with severe myocardial necrosis was the cause of death in 1 patient 45 months after OHT, while chronic rejection determined the death of a patient 9.1 years after OHT. Graft failure with subsequent multiorgan failure was the leading cause of death in the last patient, 18 days after re-OHT performed 88 months after his initial OHT. The overall Kaplan-Meier survival estimate was 81.9 ± 1.8% at 1 year, 73 ± 2.7% at 5 years and 56.8 ± 4.3% at 10 years after OHT (Fig. 1). Supplementary Fig. 2 depicts the cumulative hazard plot for 10-year follow-up with early and late phase of hazard. Supplementary Table 1 shows 1- and 5-year Kaplan-Meier survivals after OHT according to mutually exclusive subgroups. Poor ventricular function represented the best indication for OHT, with 87.4 ± 5.3% 5-year Kaplan-Meier survival ($P = 0.0252$). The Kaplan-Meier 5-year OHT survival estimate was 82.3 ± 5.9% in late FF and 32.7 ± 15.0% in early FF ($P = 0.0007$) (Fig. 2). When timing to FF was stratified by pre-OHT ventricular function, late FF with poor ventricular function exhibited the best mid-term outcome for OHT in FF, with 91.5 ± 5.8% 5-year survival ($P = 0.0010$) (Fig. 3). The mid-term outcome in PLE was suboptimal, with a Kaplan-Meier 5-year survival of 46.3 ± 14.4 vs 84.30 ± 5.5% in non-PLE ($P = 0.0147$) (Fig. 4). Logistic regression identified potential risk factors for mortality that are outlined in Supplementary Table 2. When all potential risk factors for death ($P < 0.10$) were entered in a Cox proportional hazard model, early FF ($P = 0.0005$), complex obstruction of Fontan pathway ($P = 0.0043$) and PLE ($P = 0.0033$) were identified as independent predictors of 5-year mortality (Table 4).

Reintervention and major morbidity

Ten patients underwent major reinterventions between 0.4 and 180 months after OHT. Early graft failure (1), recurrent PLE (1) and chronic rejection (6) represented the indication for re-OHT in 8 patients. Candida mediastinitis with aortic penetration resulted in massive mediastinal bleeding in 1 patient who required multiple sternal revisions, excision of the infected tissue and patch reconstruction of the ascending aorta, 25 days after OHT. The last patient required stenting of the right pulmonary artery to correct a critical stenosis 13 days after OHT. Additional reinterventions included re-exploration for bleeding (4), wound debridement (1) and embolization of a residual AV fistula (1). The Kaplan-Meier freedom estimate from major reintervention was 82.2 ± 7% at 10 years. Five non-fatal but life-threatening infections were successfully treated during follow-up, including Toxoplasma myocarditis (2), Candida mediastinitis (1), respiratory syncytial virus pneumonia with bilateral alveolo-interstitial infiltrate (1) and hepatitis C (1). PLE was cured in seven of nine hospital survivors (77.7%). PLE relapsed in 2 patients at 33 months and 10 years after OHT; it was treated by re-OHT in the first case and by medical therapy in the other. Ultimately, 43 hospital survivors are currently alive (86%) and 35 of them (81.4%) are in NYHA Class 1 or 2 at the last follow-up. Four patients (9.3%) are currently under evaluation for the development of accelerated coronary artery disease.

DISCUSSION

In recent years, there has been growing interest in the challenging management of FF circulation, which is expected to become

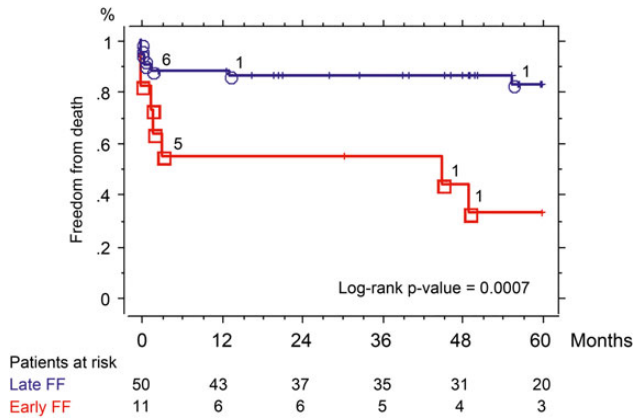

Figure 2: Kaplan–Meier 5-year freedom from death after orthotopic heart transplantation in late and early Fontan failure (FF) with the number of patients at risk.

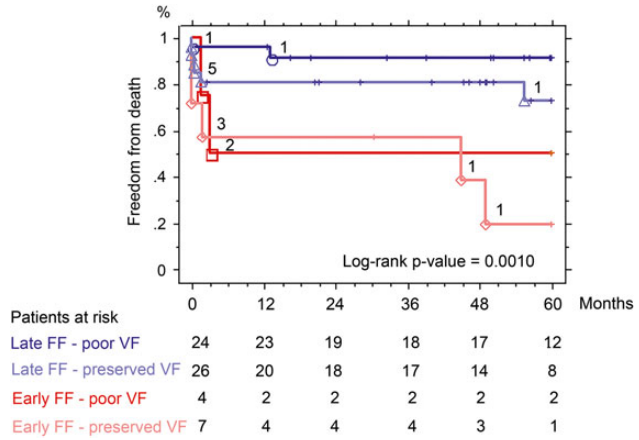

Figure 3: Kaplan–Meier 5-year freedom from death after orthotopic heart transplantation (OHT) in early and late Fontan failure (FF) stratified by pre-OHT ventricular function (VF) with the number of patients at risk.

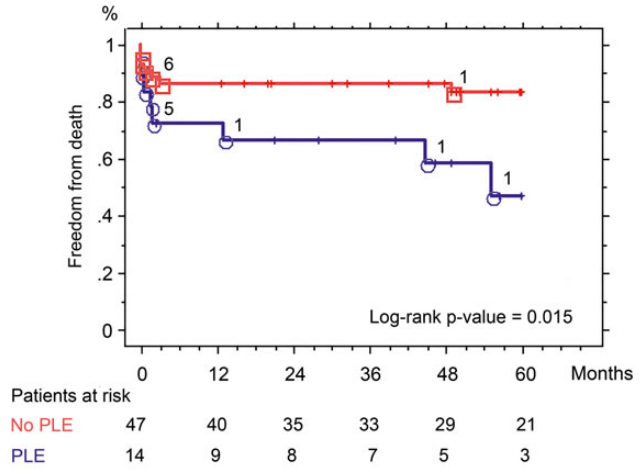

Figure 4: Kaplan–Meier 5-year freedom from death after orthotopic heart transplantation in protein-losing enteropathy (PLE) and non-PLE with the number of patients at risk.

Table 4: Independent predictors of 5-year mortality after heart transplantation by Cox proportional hazard multivariate analysis

	Hazard ratio	95% Lower CI	95% Upper CI	*P*-value
Early Fontan failure	7.02	2.36	21.14	0.0005
Fontan failure for PLE	5.32	1.74	16.23	0.0033
Fontan failure for obstruction	5.57	1.71	18.17	0.0043

Censor variable: status at 5 years.
Model: proportional hazards.

a substantial cause of paediatric heart failure in the near future [12–14]. Several medical, surgical and catheter-based interventions have been introduced to improve FF circulation; nevertheless, OHT currently represents the ultimate surgical option in FF [15]. OHT in FF is still challenging for the complexity of preoperative, intraoperative and postoperative management. Our 18.3% early mortality favourably compares with the average early mortality on OHT for FF of most recent reports, which can vary from the outstanding 4% by the Atlanta group [16], to 24% in the St Louis report [17], or to 35% in the Columbia University experience [18]. Random variations in small and single-centre cohorts over a long time span may account for such a large variability in early outcome; nevertheless, a 22% mean early mortality for OHT in FF was confirmed in three multicentre studies in North America [10, 11, 19]. Surgical creativity has largely overcome the technical intraoperative issues related to abnormalities of cardiac position, situs and systemic or pulmonary venous connections. The extensive use of donor tissue has proved to be useful in compensating for recipient anatomical defects or distortions. This has been true in our experience as well, since virtually all our patients required extensive PA reconstruction and/or systemic venous reconnection or systemic arterial remodelling preferentially by donor tissue. Moreover, we verified that previous conversion of an atriopulmonary Fontan to TCPC did not carry any additional risk at OHT. Despite the undeniable technical challenges, demonstrated by longer ischaemic times and occasional need for circulatory arrest, careful surgical planning enables a successful OHT for FF. Advances in postoperative ICU care and immunosuppression therapies have further contributed to better survival trends in recent years [16–18]. These operative and postoperative improvements, however, did not translate into a statistically significant better early outcome in recent years, both in single-centre reports [18, 20] and in multicentre studies [13] including our ECHSA report (Supplementary Table 1). Bernstein *et al.* [10] described a significantly lower OHT actuarial survival in Fontan diagnosis versus non-congenital paediatric OHT, both at 1 year (77 vs 91%) and 5 years (67 vs 81%). In the combined Pediatric Transplant Study and Cardiac Transplant Registry Database, Lamour *et al.* [11] not only confirmed this finding, but also identified a significantly lower 5-year survival in OHT for FF compared with OHT for non-Fontan congenital heart disease (60 vs 74%). A previous Fontan status exhibited an 8.6-fold risk of death after OHT [11]. Nevertheless, this impact was completely neutralized when conditional freedom from death was analysed for 90-day survivors. We infer that substantial improvements in the early phase of hazard after OHT for FF might be achieved when properly addressing pretransplant issues, since operative and postoperative enhancements were not sufficient to abolish the gap with non-Fontan congenital OHT outcome. This issue thus guided the rationale of our European multicentre study, which was specifically designed to identify the best candidate for OHT in FF, in order to set the optimal standards for early and mid-term OHT survival. Our study proves that primary ventricular failure represents the best indication for OHT in FF, in agreement with the experience of Griffiths *et al.* [6]. Poor ventricular function was identified as an inverse risk factor of 5-year mortality. We could verify a strong correlation between late FF and impaired ventricular function. We observed that patients with late FF and poor ventricular function can benefit the most from OHT, exhibiting a 91.5 ± 5.8% 5-year OHT survival. These two last findings represent the novel message of this report, which centres on the domain of best graft allocation in OHT for FF. Referral for OHT in this setting should occur prior to the development of systemic hypoperfusion, severe malnutrition or cachexia. Conversely, several risk factors for OHT mortality have been suggested in previous studies. Bernstein *et al.* [10] identified younger age and need for mechanical ventilation at listing as significant preoperative risk factors for OHT in FF. Davies *et al.* [18] indicated higher creatinine levels prior to OHT as an independent predictor of mortality. In our study, age, anatomical diagnosis including heterotaxy, ICU admission with pre-OHT inotropic support and mechanical ventilation did not affect the OHT outcome, in agreement with the experience of Backer *et al.* [20]. High pre-OHT pulmonary artery pressures only marginally influenced 5-year OHT survival by univariate analysis. Need for dialysis after OHT was associated with a significant increase in 5-year mortality by univariate analysis, in agreement with Davies *et al.* [18]. Our multivariate analysis indicates early FF as the most powerful predictor of 5-year OHT mortality. Early FF was associated with a relatively preserved ventricular function. OHT for early FF and preserved ventricular function was not beneficial in our experience because the problem was not myocardial in origin. We believe that alternative options such as Fontan revision or take-down [5] should be pursued in this scenario. Moreover, we speculate that an RVAD could be considered in selected cases, as we could successfully bridge to OHT in early FF with preserved ventricular function, after resolution of PLE through an RVAD [21]. This study identified

PLE as an independent predictor of OHT mortality, mainly for infective complications, but we acknowledge that PLE was cured in the majority of our OHT survivors, as reported by Backer *et al.* [20].

One of the strengths of this study is its multi-institutional nature, which reflects a cross section of contemporary practice of OHT in FF, as demonstrated by the high percentage of HLHS and variants in the anatomical spectrum, by the mean age at Fontan completion, the high prevalence of TCPC as a technique for Fontan completion and the uniform bicaval technique used for OHT. Nevertheless, this is a retrospective study and selection bias related to indication for listing and transplant might have occurred among different institutions. Moreover, this report does not evaluate the morbidity and mortality that occurred on the waiting list, possibly introducing additional selection bias.

In conclusion, OHT is an excellent option for late FF with impaired ventricular function. Previous Fontan conversion does not jeopardize subsequent OHT. Early FF is the most powerful predictor of 5-year mortality after OHT. This finding underlines the magnitude of the decision-making process at the time of Fontan completion, since rescue OHT after early FF seems unwarranted. PLE improves in the majority of patients after OHT, but remains an independent predictor of mortality, mainly for the exposure to early infection hazard.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

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