

# Improving outcomes for transplantation in failing Fontan—what is the next target?



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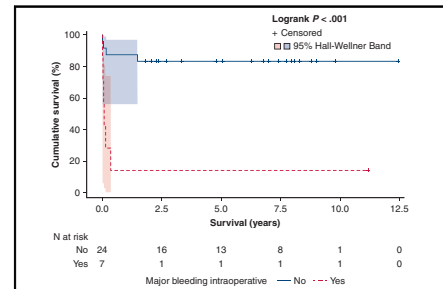
## ABSTRACT

**Objective:** To identify the key contributors to postoperative mortality in patients undergoing orthotopic heart transplantation (OHT) for late Fontan failure.

**Methods:** This retrospective review of failing Fontan patients who underwent OHT in our tertiary care center between 2007 and 2019 included adult patients with congenital heart disease and single ventricle physiology who were palliated with a Fontan circulation for >1 year. We excluded patients undergoing combined heart-liver transplantation.

**Results:** The study cohort comprised 31 patients, including 18 males (58.1%), with a mean weight of 58.4 kg, median age at Fontan of 6.9 years (interquartile range [IQR], 2-38 years), and a median age at OHT of 27.1 years (IQR, 16.7-53.3). Almost all (93.5%) of the patients were in New York Heart Association class III-IV, and the majority (74.2%) were in Interagency Registry for Mechanically Assisted Circulatory Support class 3. Overall survival at 30 days, 1 year, and 5 years after OHT was 81%, 71%, and 67%, respectively. Major intraoperative bleeding was associated with increased mortality after OHT (odds ratio, 30; 95% confidence interval, 2.8-322;  $P = .002$ ). Neither preoperative systemic ventricular function nor the development of primary graft dysfunction (PGD) was significantly associated with postoperative death. Nevertheless, PGD determined significant morbidity of this population.

**Conclusions:** In our cohort, major intraoperative bleeding was the key factor associated with mortality after OHT for late Fontan failure. Novel strategies for the prevention and management of postoperative bleeding will improve outcomes in this group of patients. (JTCVS Open 2021;8:565-73)



Kaplan-Meier survival curve according to major intraoperative bleeding (time in years).

## CENTRAL MESSAGE

Major intraoperative hemorrhage was the key factor associated with post-heart transplantation mortality in an adult failing Fontan population. This was reflected in a 30-day mortality rate of 57%.

## PERSPECTIVE

Heart transplantation for patients with failing Fontan circulation is a high-risk procedure. Major intraoperative hemorrhage was the key factor associated with post-transplantation mortality in our population. Novel strategies to improve the outcomes of this growing patient population are needed and should target the prevention and management of this complication.

See Commentaries on pages 574 and 576.

The Fontan procedure is the final stage in a series of palliative procedures that make it possible to extend the survival of children with univentricular circulation into adulthood.<sup>1</sup>

Nonetheless, over time, a significant proportion of Fontan recipients will ultimately develop circulatory failure. The estimated rate of Fontan failure is 7% by age 20 years

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**Abbreviations and Acronyms**

CHD	= congenital heart disease
CPB	= cardiopulmonary bypass
ECMO	= extracorporeal membrane oxygenation
EF	= ejection fraction
ICU	= intensive care unit
IVF	= impaired ventricular function
LV	= left ventricular
MELD-XI	= model for end-stage liver disease score excluding the international normalized ratio
OHT	= orthotopic heart transplantation
PGD	= primary graft dysfunction
PVF	= Preserved ventricular function
RV	= right ventricular

 Video clip is available online.

and increases by >5-fold to 38% by age 40 years.<sup>2</sup> Thus, increasing numbers of end-stage failing Fontan patients present for cardiac transplantation as they age.<sup>3</sup>

Heart transplantation is a high-risk procedure for failing Fontan patients compared with patients with other congenital heart diseases (CHDs).<sup>4-6</sup> However, the composition of patient populations and different clinical thresholds for transplantation can influence the identification of risk factors when single-center cohorts are interrogated, and contradictory findings have been reported.<sup>7</sup>

The aim of this study was to describe the contemporary perioperative management of adult patients with late failing Fontan undergoing heart transplantation in our tertiary care center and to identify key contributors to their postoperative mortality.

**METHODS****Study Design and Patient Selection**

This is a single-center retrospective cohort study of late failing Fontan patients who underwent orthotopic heart transplantation (OHT) at our tertiary care center between January 2007 and June 2019. This timeframe was selected for convenience, since electronic patient records were introduced in our Trust in 2007. Furthermore, it represents a contemporary cohort and reflects these patients' current management in our center. The patient population described in this article overlaps with the cohort described by Murta and colleagues.<sup>8</sup>

We included adult patients (age >16 years) with CHD and single ventricle physiology palliated with a Fontan circulation for >1 year. We excluded patients in other stages of the single ventricle palliation and those undergoing combined heart–liver transplantation. Data were collected from the patients' electronic records, case notes, and anesthetic charts.

This study was reviewed and a waiver of requirement for approval by a National Health Service Research Ethics Committee was confirmed by the chair of the Northeast Tyne and Wear South Research Ethics Committee.

Requirement for the patients' written consent for publication of the study data was waived. The Caldicott principles of patient information and confidentiality were respected (Caldicott application 6916; December 12, 2018).

**Baseline, Management, and Outcome Variables**

Recorded patient baseline characteristics included age, sex, weight, cardiac diagnosis, preoperative systemic ventricular systolic function, previous cardiac surgeries, comorbidities, and pretransplantation clinical status. Management was divided into preoperative, intraoperative, and postoperative stages.

Preoperative cardiac function data were collected from the last echocardiographic report before transplantation. Ventricular systolic function was classified as preserved (ejection fraction [EF] >55%), mildly impaired (EF 45%–54%), moderately impaired (EF 30%–44%) or severely impaired (EF <30%), according to the 2005 European Society of Cardiology/American Society of Echocardiography guidelines.<sup>9</sup>

Patients with preserved or mildly impaired function were included in the preserved ventricular function (PVF) group, and those with moderate to severe systolic impairment were included in the impaired ventricular function (IVF) group. Right ventricular (RV) function was assessed according to tricuspid annular plane systolic excursion and RV fractional area change and classified as severely impaired at a tricuspid annular plane systolic excursion <1 cm and an RV fractional area change ≤17%.<sup>9</sup> Preoperative hemodynamic data were collected from the report of the patient's last cardiac catheterization before transplantation.

Major outcomes included survival (30 days, 6 months, 1 year, and 5 years), development of primary graft dysfunction (PGD), and occurrence of major intraoperative bleeding. PGD was diagnosed within 24 hours of cardiac transplantation, whenever a discernible etiology could not be found. PGD was divided into left ventricular (LV) PGD and RV-PGD. Severe LV-PGD was defined as dependence on LV or biventricular mechanical support (extracorporeal membrane oxygenation [ECMO], LV assist device, biventricular assist device, or percutaneous LV assist device) and excluded a requirement for an intra-aortic balloon pump. RV-PGD was defined by any of the following criteria: right atrial pressure >15 mm Hg, pulmonary capillary wedge pressure <15 mm Hg, cardiac index <2.0 L/min/m<sup>2</sup>, transpulmonary gradient <15 mm Hg, and/or pulmonary artery systolic pressure <50 mm Hg or the need for an RV assist device.<sup>10</sup>

In this work, we have used the universal definition for perioperative bleeding in adult cardiac surgery proposed by Dyke and colleagues.<sup>11</sup> The authors divide perioperative bleeding into 4 categories, from 0 (insignificant) to 4 (massive). We have defined patients with major hemorrhagic events as those meeting the criteria for class 3 (severe) or class 4 (massive) bleeding. Criteria for severe bleeding included (1) delayed sternal closure; (2) chest reexploration, and (3) administration of 5 to 10 units of packed red blood cells or fresh frozen plasma. Criteria for massive bleeding included the administration of >10 units of packed red blood cells or fresh frozen plasma. According to Dyke and colleagues,<sup>11</sup> the presence of the worst single predefined attribute is sufficient to place a patient in a particular bleeding class; the presence of all attributes within a class is not necessary.

The secondary outcomes were post-OHT complications, duration of mechanical ventilation, and intensive care unit (ICU) length of stay. Furthermore, we compared these outcomes among the subgroups of patients who developed PGD and those who developed major intraoperative bleeding.

Complications were subdivided into reoperation at <48 hours after index surgery for mediastinal exploration, acute kidney failure, neurologic complications, sepsis, bowel resection, and limb amputation. Acute kidney failure was defined as an abrupt loss of renal function developing within 7 days of surgery and necessitating renal replacement therapy. Neurologic complications included ischemic stroke and intracranial hemorrhage, defined as a new acute neurologic deficit of any duration, associated with imaging findings corresponding anatomically to the clinical deficit. Sepsis was defined as a clinical infection treated with antimicrobial agents in

nonprophylactic dosage, with the presence of a positive culture from the infected site or organ unless strong clinical evidence indicated the need for treatment despite negative cultures.

### Statistical Analysis

The distribution of data was assessed using the Shapiro–Wilk test. Continuous variables were reported as mean  $\pm$  standard deviation if normally distributed (weight, body surface area, time from Fontan, resting peripheral oxygen saturation, main pulmonary artery pressure, systemic ventricular end-diastolic pressure, preoperative platelet count, model for end-stage liver disease score excluding the international normalized ratio [MELD-XI] score, estimated glomerular filtration rate, donor age, and donor–recipient weight ratio) and as median and interquartile range (IQR)/range if non–normally distributed. Categorical data were expressed as absolute number and percentage. Univariate analysis was performed using the  $\chi^2$  or Fisher exact test for categorical variables and the independent-samples *t* test or Mann–Whitney test for continuous variables. Kaplan–Meier analysis was used for survival, with the log-rank test used to determine significant differences. In all analyses, a *P* value  $<$  .05 was considered statistically significant. Statistical analyses were performed using SPSS version 20.0 (IBM, Armonk, NY).

## RESULTS

### Baseline Characteristics and Pretransplantation Management

The study cohort comprised 31 patients, including 58.1% males, with a median age of 27.1 years (IQR, 16.7–53.3 years) and a mean weight of 58.4 kg. All patients

had pre-Fontan univentricular circulations, with a systemic left ventricle in 71% of cases. The patients' median age at Fontan completion was 6.9 years (IQR, 2–38 years). Diagnoses according to type of pre-Fontan circulation are detailed in Table 1.

At the time of transplantation, 29 patients (93.5%) were in New York Heart Association NYHA class III–IV with 23 (74.2%) in Interagency Registry for Mechanically Assisted Circulatory Support class 3.<sup>12</sup> Nineteen patients (61.3%) had moderate to severe IVF. At the time of the last hemodynamic study before transplantation, their mean pulmonary artery pressure was  $15 \pm 5.4$  mm Hg and median transpulmonary gradient was 4 mm Hg (IQR, 2.3 mm Hg). Seven of the 11 patients with aortopulmonary collaterals (64%) had undergone preoperative percutaneous embolization.

The patients' mean MELD-XI score<sup>13</sup> was  $12 \pm 3.8$ , and their mean estimated glomerular filtration rate was  $82.8 \pm 28.3$  mL/min/1.73 m<sup>2</sup>. Only 1 patient had renal replacement therapy. Seven patients (22.6%) had protein-losing enteropathy. Pretransplantation status and comorbidities are detailed in Table 2.

Most of the patients (77.4%) were admitted to hospital and received inotropic support (74.2%); they were listed as urgent transplantation candidates. The patients' pretransplantation management is detailed in Table 2.

TABLE 1. Demographics and baseline characteristics according to patient group

Characteristic	Patients with		<i>P</i> value	Patients with		<i>P</i> value
	major intraoperative bleeding (N = 7)	Other patients (N = 24)		primary graft dysfunction (N = 8)	Other patients (N = 23)	
Male sex, n (%)	4 (57.1)	14 (58.3)	.99	6 (75)	12 (52.2)	.41
Weight, kg, mean $\pm$ SD	63.8 (7.7)	58.7 (9.0)	.18	64 (10)	58.4 (8.2)	.13
BSA, m <sup>2</sup> , mean $\pm$ SD	1.7 (0.1)	1.7 (0.1)	.23	1.7 (0.15)	1.6 (0.13)	.09
Original diagnosis, n (%)			.28			.11
ARVC post–right ventriculectomy	1 (14.3)	0 (0)		1 (12.5)	0 (0)	
HLHS	0 (0)	1 (4.2)		0 (0)	1 (4.3)	
DILV + associated lesions	2 (28.6)	6 (25)		2 (25)	6 (26.1)	
Tricuspid atresia	3 (42.9)	7 (29.2)		1 (12.5)	9 (39.1)	
Unbalanced CAVSD + associated lesions	1 (14.3)	1 (4.2)		2 (25)	0 (0)	
DORV + associated lesions	0 (0)	7 (29.2)		2 (25)	5 (21.7)	
Pulmonary atresia	0 (0)	2 (8.3)		0 (0)	2 (8.7)	
Systemic ventricle, n (%)						.66
Left ventricle	6 (85.7)	16 (66.7)	.64	5 (62.5)	17 (73.9)	
Right ventricle	1 (14.4)	8 (33.3)		3 (37.5)	6 (26.1)	
Previous thoracotomies, n, median (range)	1 (0–2)	1 (0–2)	.37	0 (1)	1 (1)	.15
Previous sternotomies, n, median (range)	3 (1–4)	2 (1–5)	.73	2.5 (1.8)	2 (1)	.67
Type of Fontan, n (%)			.83			.71
Atriopulmonary	1 (14.3)	3 (12.5)	.39	0 (0)	4 (17.4)	
Lateral tunnel	1 (14.3)	8 (33.3)		3 (37.5)	6 (26.1)	
Extracardiac	5 (71.4)	13 (54.2)		5 (62.5)	13 (56.5)	
Fenestrated Fontan, n (%)	2 (28.6)	12 (52.2)	.99	6 (75)	8 (36.4)	.10
Time from Fontan to OHT, y, mean $\pm$ SD	14.2 (9.97)	19.9 (6.43)	.08	14.5 (9.5)	20 (6.4)	.07

SD, Standard deviation; BSA, body surface area; ARVC, arrhythmogenic right ventricular cardiomyopathy; HLHS, hypoplastic left heart syndrome; DILV, double-inlet left ventricle; CAVSD, complete atrioventricular septal defect; DORV, double-outlet right ventricle; OHT, orthotopic heart transplantation.

**Intraoperative Management**

Patients underwent cardiac transplantation after a median time on the transplantation list of 45 days (IQR, 92 days). The mean donor age was 32 ± 12.4 years, median donor weight was 79.6 kg (IQR, 15 kg), and median donor–recipient weight ratio was 1.4. The majority of donors were male (77.4%), and there were 10 (32.3%) sex-mismatched transplantations. The median donor ischemic time was 182 minutes (IQR, 111 minutes), and the median warm ischemic time was 46.5 minutes (IQR, 12.5 minutes).

Anesthesia was maintained with total intravenous anesthesia in 16.1%, sevoflurane in 9.7%, and isoflurane in 71% of cases. Patients received antibiotic prophylaxis and immunosuppressive therapy based on local institutional guidance. In addition to standard American Society of Anesthesiologists monitoring, bilateral regional brain perfusion was monitored using cerebral oximetry (INVOS; Medtronic, Minneapolis, Minn).

Femoral bypass was instituted in 2 patients due to major bleeding—right atrial tear and ascending aorta injury—during preliminary dissection. In 2 other patients, the femoral vein was electively cannulated because of interrupted inferior vena cava anatomy.

The complexity of the repair required in some patients dictated an early start of cardiopulmonary bypass (CPB) to address any required arterial or venous reconstruction before the graft’s arrival in the operating theatre. On completion of vascular reconstruction, the graft was brought to the field, a dose of cardioplegia was given, and an interatrial communication was created to aid left side decompression, should ECMO be required later. The anastomoses were performed in the following order: left atrium, pulmonary artery, aorta, inferior vena cava, and superior vena cava. The pulmonary arterial anastomosis was performed prior to the aortic anastomosis because pulmonary artery interventions are often required in these patients.

CPB prime contained fresh frozen plasma in 26 patients (83.9%), mannitol in 20 (64.5%) and aprotinin in 23 (74.2%). All patients received heparin 400 IU/kg before initiation of CPB, and an activated clotting time >600 seconds was maintained. Supernormal flows were used aiming for 125% to 130% of the calculated normal flow of 2.4 L/min/m<sup>2</sup>. The CPB strategy included maintaining the hematocrit level around 30%. Patients were cooled down to 32°C, and a pH strategy was used. A warm dose of cardioplegia was administered before removal of the aortic

**TABLE 2. Pretransplantation status, comorbidities, and management according to patient group**

Parameter	Patients with major intraoperative bleeding (N = 7)		P value	Patients with primary graft dysfunction (N = 8)		P value
	Other patients (N = 24)	Other patients (N = 23)				
<b>Cardiac function</b>						
NYHA class III-IV, n (%)	7 (100)	22 (91.6)	.62	8 (100)	21 (91.3)	.21
Resting SpO <sub>2</sub> (%), mean ± SD	87 (9)	89.5 (5.4)	.09	89 (8.3)	89 (5.6)	.99
Systemic ventricular function, n (%)			<b>.007</b>			.99
Preserved ventricular function	6 (85.7)	6 (25)		3 (37.5)	9 (39.1)	
Impaired ventricular function	1 (14.3)	18 (75)		5 (62.5)	14 (60.9)	
AV valve regurgitation, n (%)			.39			.22
Trivial to mild	5 (71.4)	11 (45.8)		6 (75)	10 (43)	
Moderate to severe	2 (28.6)	13 (54.2)		2 (25)	13 (56.5)	
<b>Hemodynamic data</b>						
MPA pressure, mm Hg, mean ± SD	17.3 (4.3)	14.0 (5.5)	.21	13.9 (4.5)	15 (5.7)	.62
TPG, mm Hg, median (IQR)	4.0 (2.0)	4.0 (3.0)	.63	4 (1)	4 (3)	.43
Systemic ventricle EDP, mm Hg, mean ± SD	12.5 (5.0)	10.4 (5.1)	.76	8.9 (3.8)	11.7 (5.3)	.22
<b>Liver function</b>						
MELD-XI, mean ± SD	12.4 (3.5)	13.0 (3.6)	.56	11.7 (2.1)	13.4 (3.9)	.30
<b>Renal function</b>						
eGFR, mL/min/1.73 m <sup>2</sup> , mean ± SD	81.4 (25.1)	70.1 (39.0)	.41	84.1 (43.9)	68.6 (33.3)	.31
Protein-losing enteropathy, n (%)	2 (28.6)	5 (20.8)	.64	1 (12.5)	6 (26.1)	.64
Plastic bronchitis, n (%)	0 (0)	0 (0)		0 (0)	0 (0)	
<b>Pretransplantation management</b>						
Inpatient at time of transplantation, n (%)	5 (71.4)	19 (79.2)	.64	7 (87.5)	17 (73.9)	.64
Inotropic support, n (%)	5 (71.4)	18 (75)	.99	7 (87.5)	16 (69.6)	.64
Time on transplant list, d, median (IQR)	45 (99.0)	47 (90.5)	.91	61.5 (70)	45 (127)	.86

Significant P values are in bold type. NYHA, New York Heart Association; SpO<sub>2</sub>, peripheral oxygen saturation; SD, Standard deviation; AV, atrioventricular; MPA, main pulmonary artery; TPG, transpulmonary gradient; IQR, interquartile range; EDP, end-diastolic pressure; MELD-XI, model for end-stage liver disease score excluding international normalized ratio; eGFR, estimated glomerular filtration rate.

cross-clamp to ensure even rewarming of the donor heart. The median time on CPB was 241 minutes (IQR, 100 minutes). Inotropic support while coming off bypass typically included milrinone, vasopressin, and/or noradrenaline and adrenaline.

Coagulation management was a major aspect of anesthesia. Patients who had been on warfarin received vitamin K on induction (35.5%) or prothrombin complex concentrate (19.4%; Beriplex P/N; CSL Behring, King of Prussia, Pa). Most patients (87.1%) received a continuous infusion of aprotinin, and 29% received tranexamic acid. Baseline and post-protamine thromboelastography were used to guide transfusion therapy.

### Posttransplantation Management and Complications

Seven patients (22.6%) required chest reexploration less than 48 hours after their primary surgery due to bleeding; nine patients (29%) had delayed chest closure. Nine patients (29%) required postoperative veno-arterial ECMO (3 with LV-PGD, 4 with RV-PGD, and 1 with cardiopulmonary resuscitation with cannulation onto ECMO) for a median of 2.4 days (IQR, 1-26 days). Seven patients (22.6%) developed a postoperative neurologic complication; of these, 6 had received ECMO. Overall, the median duration of mechanical ventilation was 12 hours (IQR, 28 hours), and the median duration of inotropic support was 8 days (IQR, 7.5 days). The majority of patients (77.4%) developed posttransplantation kidney injury necessitating renal replacement therapy for a median of 10 days (IQR, 24 days). Nine patients (29%) developed postoperative sepsis. One patient (3.2%) required bowel resection due to acute ischemia, and 3 patients (9.7%) underwent limb amputation. The median ICU length of stay was 11 days (IQR, 25 days), and the median total hospital length of stay was 60 days (IQR, 72 days).

Compared with the other patients, patients with major intraoperative bleeding and PGD required a longer duration of vasopressor and ECMO support, as well as of mechanical ventilation. They accrued significantly more morbidity in the form of neurologic complications and sepsis and had longer ICU stays (Table 3).

### Major Outcomes

Ten patients (32.3%) died after a median follow-up of 30.5 months (IQR, 84.9 months). In-hospital mortality was 29% (9 patients), at a median of 21 days post-OHT. One patient died at 2 years post-OHT.

In our study cohort, most of the deaths occurred early, with an overall 30-day survival of 80.6%. Survival of these patients plateaued at 6 months at 71%, with 1-year and 5-year survival rates of 71% and 67.2%, respectively (Figure 1). Seven patients (22.6%) had a major intraoperative hemorrhage, and 8 (25.8%) developed PGD (4 with LV-PGD and 4 with RV-PGD). Three patients had both of these complications.

### Predictors of Mortality

Major intraoperative bleeding (odds ratio, 30; 95% confidence interval [CI], 2.8-322;  $P = .002$ ) was associated with increased mortality after OHT. This group had a significantly higher mortality compared with their counterparts, with a 30-day-survival of only 43% ( $P < .001$ ) (Figure 2). Conversely, neither the occurrence of PGD ( $P = .683$ ) (Figure 3) nor preoperative systemic ventricle systolic function ( $P = .067$ ) (Figure 4) was associated with postoperative mortality in this cohort.

### Determinants of Bleeding

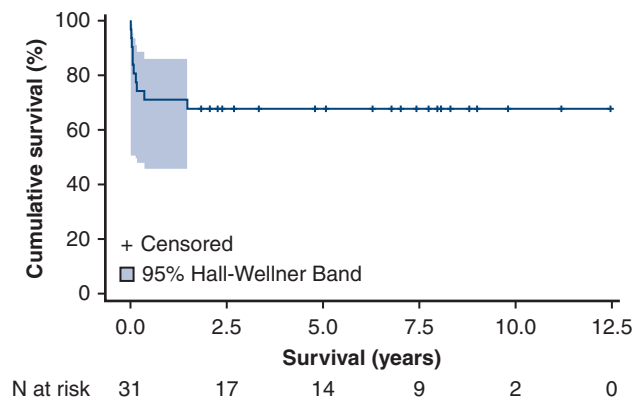
The occurrence of major intraoperative bleeding was significantly higher in patients with preoperative PVF

TABLE 3. Postoperative complications according to patient group

Complication	Patients with major intraoperative bleeding (N = 7)	Other patients (N = 24)	P value	Patients with primary graft dysfunction (N = 8)	Other patients (N = 23)	P value
Duration of vasopressors, d, median (IQR)	<b>26 (28)</b>	2 (5)	<b>&lt;.001</b>	<b>26 (28)</b>	2 (6)	<b>.003</b>
Postoperative ECMO, n (%)	4 (57.1)	5 (20.5)	.150	<b>7 (87.5)</b>	2 (8.7)	<b>&lt;.001</b>
Duration of ECMO, d, median (IQR)	<b>5 (19)</b>	0 (0)	<b>.014</b>	<b>5 (14.8)</b>	0 (0)	<b>&lt;.001</b>
Duration of ventilation, h, median (IQR)	<b>51 (40)</b>	5 (22.8)	<b>.005</b>	<b>42.5 (80.8)</b>	5 (20)	<b>.001</b>
AKF, n (%)	7 (100)	17 (70.8)	.161	8 (100)	16 (69.6)	.146
Duration of RRT, d, median (IQR)	<b>26 (49)</b>	<b>8.5 (23)</b>	<b>.043</b>	<b>39.5 (120.8)</b>	9 (21)	<b>.034</b>
Neurologic complications, n (%)	<b>4 (57.1)</b>	3 (12.5)	<b>.029</b>	<b>5 (62.5)</b>	2 (8.7)	<b>.006</b>
Sepsis, n (%)	<b>5 (71.4)</b>	4 (16.7)	<b>.012</b>	<b>5 (62.5)</b>	4 (17.4)	<b>.027</b>
Bowel resection, n (%)	1 (14.3)	0 (0)	.226	0 (0)	1 (4.3)	.99
Limb amputation, n (%)	2 (28.6)	1 (4.2)	.120	2 (25)	1 (4.3)	.156
ICU length of stay, d, median (IQR)	<b>26 (49)</b>	5 (13)	<b>.033</b>	<b>29.5 (59)</b>	<b>10 (15)</b>	<b>.030</b>

Significant values are in bold type. IQR, Interquartile range; ECMO, extracorporeal membrane oxygenation; AKF, acute kidney failure; RRT, renal replacement therapy; ICU, intensive care unit.





**FIGURE 1.** Kaplan–Meier survival curve for the overall population of adult failing Fontan patients undergoing heart transplantation (time in years).

compared with those with IVF (85.7% vs 14.3%;  $P = .007$ ). The intraoperative administration of vitamin K (28.6% vs 37.5%;  $P = .39$ ), Beriplex (14.3% vs 20.8%;  $P = .99$ ), aprotinin (85.7% vs 87.5%;  $P = .99$ ), and tranexamic acid (0% vs 37.5%;  $P = .13$ ) did not differ significantly between the 2 groups.

Major intraoperative bleeding was significantly associated with longer total surgical duration (median, 12 hours vs 8 hours;  $P = .003$ ) and longer CPB time (median, 296 minutes vs 217 minutes;  $P = .011$ ).

**DISCUSSION**

In our single-center experience of OHT in adults with late Fontan failure, our main finding was the association of major intraoperative bleeding with increased postoperative mortality. Conversely, neither the occurrence of PGD nor

the preoperative systemic ventricular function correlated with the increased mortality of these patients. Nevertheless, PGD was associated with significant morbidity. Despite the increased early posttransplantation mortality, the medium-term survival of these patients was reasonable.

**Survival**

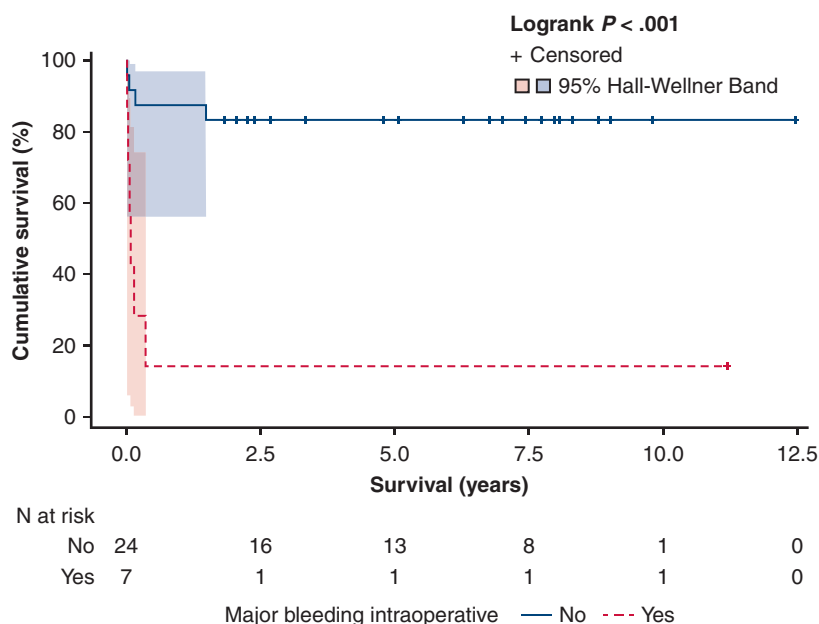
Multi-institutional studies have identified the Fontan procedure as a risk factor for early mortality after cardiac transplantation, with a similar long-term survival as that of other CHD patients.<sup>14,15</sup> Our observed in-hospital mortality of 29% compares favorably with the 26.3% reported by Hernandez and colleagues<sup>16</sup> in a US multi-institutional study spanning the last decade. In our cohort, mortality plateaued at 6 months, with good medium-term survival of 71% at 1 year and 67% at 5 years.

These findings are in line with the results of a recently published meta-analysis that included a total of 351 Fontan patients undergoing OHT and showed 1- and 5-year survival rates of 80.3% (95% CI, 75.9%-84.2%) and 71.2% (95% CI, 66.3%-75.7%), respectively.<sup>17</sup>

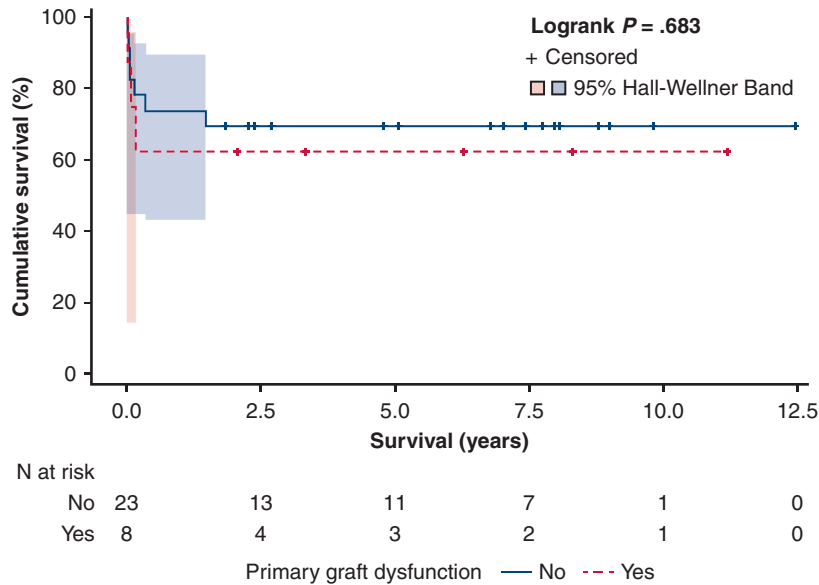
**Primary Graft Failure**

Primary graft failure is a known complication after OHT for failing Fontan circulation.<sup>18,19</sup> It may be attributed to allo-sensitization in the context of multiple reoperations, prolonged CPB time, elevated pulmonary vascular resistance that is unmasked after transplantation,<sup>20</sup> and comorbidities, such as renal and liver dysfunction.<sup>10</sup>

Our analysis did not show a significantly increased incidence of primary graft failure (26%) in our cohort, which lies at the upper end of that described in literature for non-CHD transplantation (2.3%-28.2%).<sup>10</sup> Postoperatively, this



**FIGURE 2.** Effect of major intraoperative bleeding on survival after heart transplantation in adult failing Fontan patients (time in years).



**FIGURE 3.** Effect of acute graft dysfunction on survival after heart transplantation in adult failing Fontan patients (time in years).

group of patients was successfully supported with ECMO until recovery of cardiac function, and this did not result in increased mortality. Nevertheless, these patients experienced significant postoperative morbidity. Notably, the majority (86%) of patients who developed a postoperative neurologic complication had undergone ECMO.

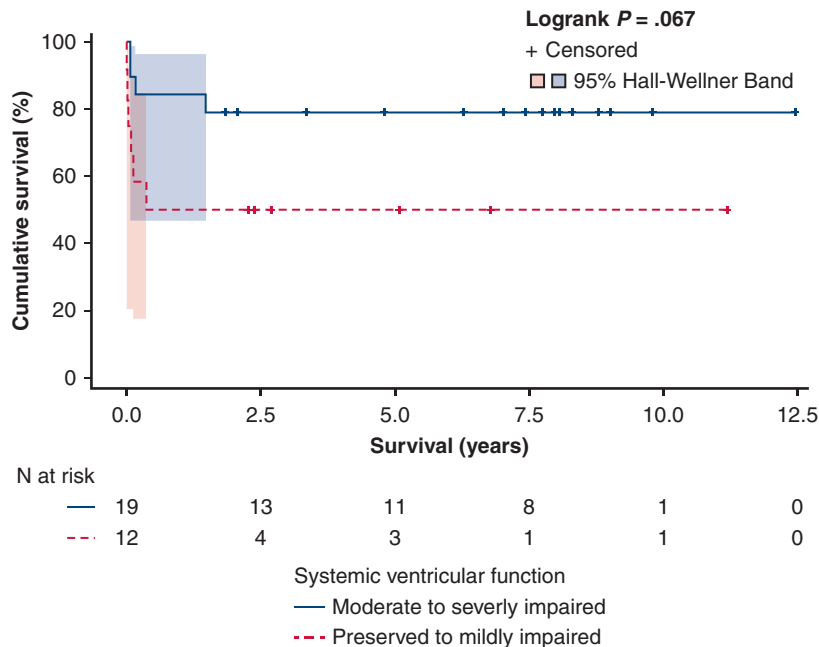
**Perioperative Bleeding**

Perioperative bleeding is another well-described complication in this group of patients. Miller and colleagues<sup>19</sup> reported a 50% incidence of significant postoperative bleeding in their cohort of failing Fontan patients undergoing OHT. Similarly, Hernandez and colleagues<sup>16</sup> reported a >5-fold higher risk

of post-OHT bleeding in Fontan patients compared with non-Fontan patients (odds ratio, 5.32; *P* = .015).

The etiology of bleeding in Fontan patients is multifactorial and includes thoracic collateralization, previous operations involving extensive adhesiolysis and long bypass times, preexisting liver disease and coagulopathy, the use of pretransplantation thromboprophylaxis, vasoplegia,<sup>21</sup> and endothelial dysfunction.<sup>22</sup>

Our key finding was the association of major intraoperative bleeding with increased postoperative mortality. In fact, the group with major intraoperative hemorrhage had a 30-day mortality rate of 57% (Figure 5). All these patients required early chest exploration for hemostasis. In our



**FIGURE 4.** Effect of acute graft dysfunction on survival after heart transplantation in adult failing Fontan patients (time in years).

cohort, this complication resulted from injury to cardiovascular structures during dissection (n = 2), bleeding from the anastomotic site (n = 1), and, in the remaining 4 patients, extensive adhesiolysis combined with coagulopathy secondary to a long bypass run. Not unexpectedly, bleeding was associated with longer total duration of surgery and time on CPB. Interestingly, preoperative PVF was associated with the occurrence of major intraoperative bleeding. However, preoperative collateral embolization did not significantly affect the occurrence of bleeding in our cohort, and neither did the use of intraoperative vitamin K, Beriplex, aprotinin, or tranexamic acid. Unfortunately, our study was insufficiently powered to detect statistically significant differences among these interventions.

**PVF**

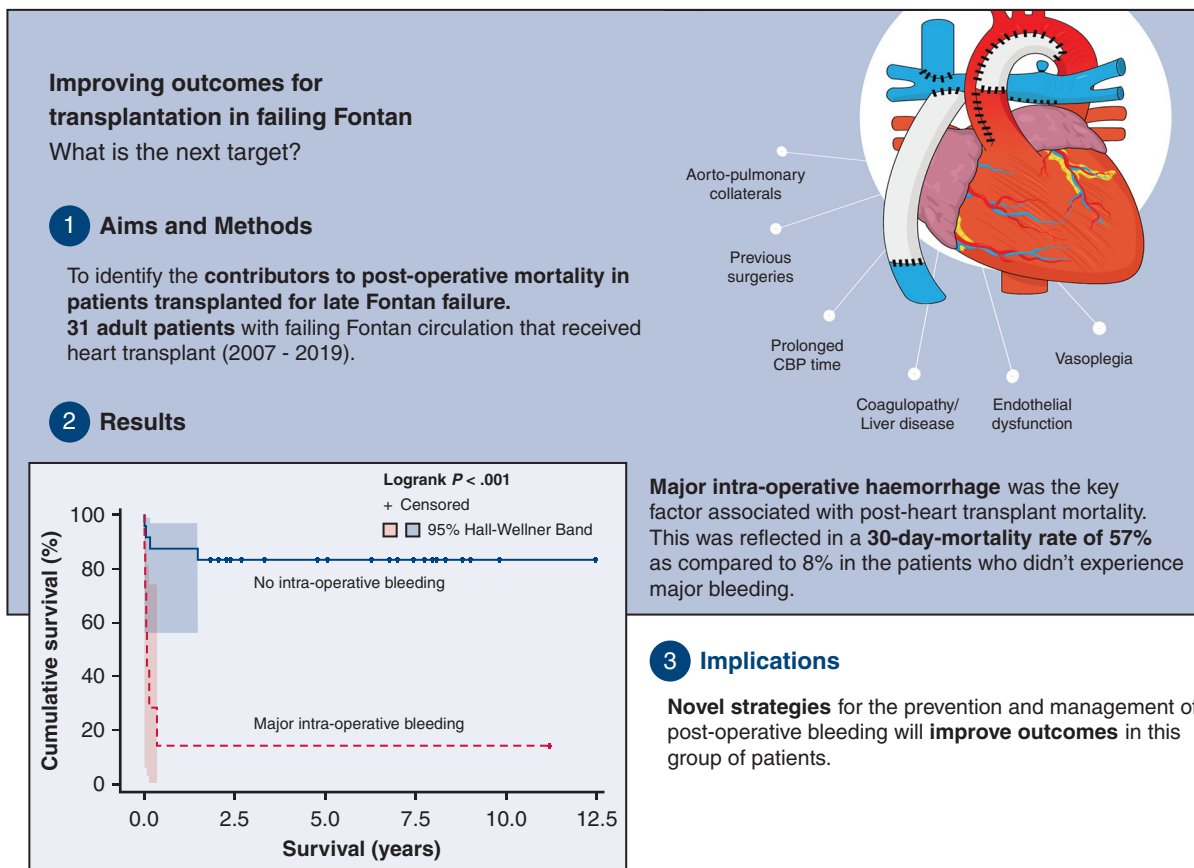
Controversy exists about the value of systemic ventricular function as a predictor of post-transplantation mortality in failing Fontan patients.<sup>23</sup> Several reports (including one from our group) have identified PVF as a risk factor for post-transplantation mortality and as a surrogate for failing Fontan physiology and increased pulmonary vascular resistance.<sup>8</sup> Interestingly, in our cohort, pretransplantation ventricular function did not significantly impact post-transplantation mortality.

In a recent study, Miller and colleagues<sup>19</sup> found that in the current era, patients with PVF had the most significant increase in post-transplantation survival, and that this could be attributable in part to modifications of risk factors specific to this population. We hypothesize that this also could have occurred in our cohort, and that our results potentially reflect the implementation of specific management strategies including preoperative cross-sectional imaging to plan for chest reentry and anatomic reconstruction, volume load reduction with AP collateral embolization, and a higher goal donor–recipient weight ratio. Furthermore, we targeted supranormal CPB flows to account for collateral flow, routinely used milrinone and inhaled nitric oxide, and aggressively monitored for and treated post-OHT vasoplegia.

That being said, however, the relationship of preoperative PVF and post-transplantation risk is complex, remains to be fully elucidated, and needs further study.

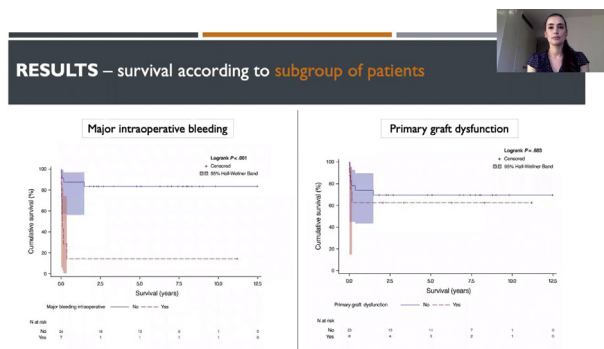
**Limitations**

This study has limitations that are inherent to its single-center and retrospective design. The sample size is small, and the overlap of outcomes precludes drawing strong conclusions despite the use of standard statistical methods and



**FIGURE 5.** Major intraoperative hemorrhage was the key factor associated with post–heart transplantation mortality in an adult failing Fontan population. This was reflected in a 30-day mortality rate of 57%.





**VIDEO 1.** Improving outcomes for transplantation in failing Fontan—what is the next target? Video available at: [https://www.jtcvs.org/article/S2666-2736\(21\)00233-3/fulltext](https://www.jtcvs.org/article/S2666-2736(21)00233-3/fulltext).

*P* values. Any inferences drawn from the present data should be validated in future larger, multicenter studies.

## CONCLUSIONS

Favorable outcomes may be achieved in adults with late failing Fontan circulation undergoing OHT. Early postoperative mortality remains concerning and is associated with the occurrence of major intraoperative bleeding. Although not associated with an increased risk of mortality, PGD was correlated with significant morbidity in this population. Contrary to previously published results, pretransplantation systemic ventricular function had no impact on post-transplantation survival in our cohort. We hypothesize that this may be attributable to the implementation of procedures targeted at reducing risk factors specific to this population. Novel strategies to improve outcomes in this group of patients are needed and should target the prevention and management of postoperative bleeding (Video 1). This should be the focus of future prospective studies.

## 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:** adult congenital heart disease, Fontan circulation, heart transplantation