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Outcome of cardiac transplantation in patients requiring prolonged continuous-flow left ventricular assist device support

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OBJECTIVE: This study assessed the early and late outcomes after cardiac transplantation in patients receiving long-term continuous-flow left ventricular assist device (CF-LVAD) support.

METHODS: Between April 2004 and September 2013, 192 patients underwent HeartMate II (Thoratec, Pleasanton, CA) CF-LVAD placement as a bridge to transplant at our center. Of these, 122 (63%) successfully bridged patients were retrospectively reviewed. Patients were stratified into 2 groups according to their waiting time with CF-LVAD support of <1 year or ≥ 1 year.

RESULTS: The study cohort was a mean age of 54 $\pm$ 13 years, 79% were male, and 35% had an ischemic etiology. The mean duration of CF-LVAD support before transplantation was 296 days (range, 27–1,413 days). The overall 30-day mortality was 4.1%. Overall post-transplant survival was 88%, 84%, 78% at 1, 3, and 5 years, respectively. The 32 patients (26%) with ≥ 1 year of CF-LVAD support (mean, 635 days) were more likely to have blood type O, a larger body size, and to have been readmitted due to recurrent heart failure and device failure requiring exchange than those with <1 year of CF-LVAD support. Patients who required prolonged support time also had worse in-hospital mortality (16% vs 6.7%, $p = 0.12$) and significantly lower survival at 3 years after transplantation (68% vs 88%, $p = 0.049$).

CONCLUSIONS: The overall short-term and long-term cardiac transplant outcomes of patients supported with CF-LVAD are satisfactory. However, patients who require prolonged CF-LVAD support may have diminished post-transplant survival due to adverse events occurring during device support.

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Continuous-flow left ventricular assist devices (CF-LVADs) have rapidly become standard care for advanced heart failure patients.[1,2] The bridge-to-transplant (BTT) strategy is especially reasonable in patients listed for transplantation who are expected to have an extended waiting time due to blood type, a large body size, or a high degree of allosensitization. However, in contrast to the increasing number of CF-LVADs being implanted, there are a limited number of donors, which remains a nationwide issue. This discrepancy has led to longer waiting times to transplant spent on CF-LVAD support.[3] Currently, almost 50% of BTT patients are alive and on CF-LVAD support after 1 year.[4]

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Transplant outcomes in patients bridged with CF-LVAD appear similar to those of patients bridged with pulsatile-flow LVAD or who receive an allograft without BTT.[5]

However, limited data are available on the post-transplant outcomes of patients receiving CF-LVAD support for more than 1 year. There have been concerns regarding the negative effects of post-transplant hemodynamics in patients who required longer durations of CF-LVAD support.[6] Moreover, such patients can be exposed to an increased risk of device-related morbidities, including infection and device thrombosis, before transplantation.[3,7–9] These factors may affect short-term and long-term post-transplant outcomes. Given the continuously improving outcomes achieved with CF-LVADs as destination therapy,[10] the optimal timing of cardiac transplantation after the initiation of LVAD support requires clarification. In this long-term follow-up study, we reviewed our single-center experience of BTT with CF-LVAD.

Methods

The Columbia Presbyterian Medical Center Institutional Review Board approved this study. We retrospectively reviewed our experiences with CF-LVAD at the Columbia Presbyterian Medical Center between April 2004 and September 2013. During this period, 192 consecutive patients with advanced heart failure underwent the insertion of a HeartMate II (Thoratec, Pleasanton, CA) as a BTT, and 122 (63%) of these successfully bridged patients were included in this study. Patients were stratified by waiting time with CF-LVAD support into 2 groups: Group 1, support <1 year or Group 2, support ≥ 1 years.

Device implantation

All patients received the HeartMate II LVAD at our center. The details of the device and surgical implantation have been described before.[1,2]

Post-implant device management

After device implantation, all patients received a standardized medical regimen, including a neurohormonal antagonist, diuretics, and anti-arrhythmic agents, if needed. Anti-coagulation therapy with aspirin and warfarin was implemented. The target international normalized ratio range was 2 ± 0.5. After discharge, anti-coagulation was managed by nurse practitioners with the repeat testing frequency dictated by the ease or difficulty of maintaining the patient within the target range. Anti-coagulation therapy was withheld in the event of bleeding and resumed once bleeding stopped. Patients were followed up at 1 week after the initial discharge and monthly thereafter unless an issue necessitating more frequent visits arose. The frequency of clinic visits varied among patients depending on individual medical issues and travel distances. A shared-care program was established in 2012, and currently, 2 community health care providers are available for sharing patient care.

Desensitization therapy

The panel reactive antibody (PRA) test was used to screen for allosensitization. Patients with global sensitization, defined as a PRA greater than 10%, were treated with intravenous immunoglobulin (IVIg) therapy, with or without cyclophosphamide, before transplantation.[11]

Transplant procedures and post-operative immunosuppression

All patients underwent cardiac transplantation with bicaval anastomosis. All patients received standard therapy with calcineurin inhibitors, cyclosporine or tacrolimus, mycophenolate mofetil, and prednisone. Patients received 4 mg/kg azathioprine pre-operatively, and 500 mg Solu-Medrol (Pfizer, New York, NY) intraoperatively. Post-operatively, patients received 125 mg Solu-Medrol every 8 hours for 3 doses. Mycophenolate mofetil was started at a dose of 1,500 mg twice daily. High-dose oral prednisone was started at 100 mg daily and tapered to 30 mg daily by 2 weeks. Induction therapy using interleukin-2 receptor antagonists was administered within 24 hours after transplantation.[12] Patients with active infections did not receive induction therapy. Patients who were highly sensitized pre-operatively received cyclophosphamide for 4 to 6 months after transplantation and then were treated with mycophenolate mofetil.[13]

Post-operative endomyocardial biopsy

Endomyocardial biopsies were performed regularly.[11] The degree of cellular rejection on the specimen was graded according to International Society for Heart Transplantation criteria.[14] Antibody-mediated rejection was defined as histologic evidence of acute capillary injury and Ig and/or C4d deposition identified by immunofluorescence.

Post-transplant follow-up

Patients were regularly monitored by a cardiologist after transplantation. The follow-up examinations were completed on September 30, 2013, and the follow-up period lasted from 0.025 to 8.1 years (median, 2.1 years; interquartile range, 0.98–3.6 years). Clinical follow-up was completed in 98% of patients.

Data collection

All clinical data were collected thorough a review of electronic medical records. For each patient, pre-operative variables that might correlate with survival were retrospectively collected for each procedure (i.e., LVAD implantation and transplantation). These data included baseline demographics, medical histories, laboratory values, hemodynamic parameters, medications, and donor demographics.

Intraoperative variables included concomitant procedures at the time of LVAD implantation and ischemic time, cardiopulmonary bypass time, blood product use, dosage of vasoactive drugs, and nitric oxide use at the time of transplantation. Early post-operative data included complications that occurred between the operation and hospital discharge. Severe primary graft dysfunction (PGD) was defined as a need for mechanical circulatory support within 24 hours of completion of surgery.[15]

Major adverse events requiring readmission during the waiting time on LVAD support were also recorded. These included major bleeding events, such as gastrointestinal tract bleeding and significant epistaxis; device-related events, such as pump malfunction, thrombi, and infection; and major cerebral events, recurrent

heart failure, cardiac arrhythmia, infections not related to LVAD support, and various other reasons.

Post-transplant hemodynamic parameters, left ventricular function on transthoracic echocardiogram, and end-myocardial biopsy specimen data at 1 week and 1 year after transplantation were also collected to assess early and late graft function and the degree of rejection.

Statistical analysis

The data for categoric variables are presented in frequencies and percentages. Continuous variables are expressed as mean ± standard deviation and were compared using 2-sample *t*-tests. Categoric variables were compared using the chi-square test or Fisher's exact test. Kaplan-Meier curves were used to represent survival and were compared using the log-rank test. Cox proportional hazard regression was used to derive hazard ratios and 95% confidence intervals after testing for proportional hazard assumption using Schoenfeld residuals. Multivariable analysis was performed to assess the predictors of 3-year mortality, which included baseline variables, duration of LVAD support, adverse events during LVAD support, and pre-transplant laboratory values. All covariates with $p < 0.2$ were considered in the multivariable model. For all analyses, $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics at the time of LVAD implantation

Patient operative characteristics before, during, and after LVAD implantation are reported in Table 1. The patients were a mean age of 54 years. The cohort included 96 men (79%) and 79 patients (65%) with a non-ischemic etiology.

Patients in Group 2 were more likely to have a larger body mass index (BMI) and a pre-operative implantable cardioverter-defibrillator compared with those in Group 1. No significant between-group differences were observed in pre-operative comorbidities, hemodynamic parameters, laboratory data, concomitant surgeries, and post-operative morbidity rates.

Patient characteristics between LVAD implantation and transplantation

Table 2 reports baseline characteristics at the time of transplantation. The overall mean duration of LVAD support was 0.81 years (range, 0.074–3.9 years). The mean age at transplantation was 54 years. Sixty percent of patients had blood type O. A total of 78 patients (64%) were readmitted because they experienced adverse events during LVAD support. The leading causes of readmission included major bleeding events, recurrent heart failure, infection (including device infection), and cardiac arrhythmia. Nine patients (7.4%) required device exchange due to device thrombosis. Fourteen patients underwent desensitization with IVIg therapy for elevated PRA levels.

The mean duration of LVAD support was 0.48 years in Group 1 and 1.7 years in Group 2. The recipient and donor ages were similar between the 2 groups. Patients in Group 2 and their donors were both more likely to have blood type O and a larger body size (BMI and body surface area). The mean percentage change in BMI during LVAD support was 4.1% in Group 1 and 6.1% in Group 2 ($p = 0.53$). Compared with patients in Group 1, Group 2 patients were readmitted more frequently for heart failure and device failure requiring device exchange during LVAD support. The number of readmissions during LVAD support was 1.0 ± 0.12 in Group 1 and 1.8 ± 0.26 in Group 2 ($p = 0.0019$). With the exception of platelet count, which was lower in Group 2, pre-operative laboratory values did not differ significantly between the 2 groups.

Intraoperative and early post-operative outcomes

Table 3 summarizes intraoperative and post-operative outcomes. The cardiopulmonary bypass time was significantly longer in Group 2, but the total ischemic time was similar in both groups. When we excluded the patients who required additional pump time to place mechanical support for PGD, cardiopulmonary bypass time was similar between the 2 groups (165 ± 36 vs 178 ± 37 minutes, $p = 0.14$). No significant differences were found in the amount of blood products used, frequency of nitric oxide use, and the dosage of vasoactive drugs used in the operating room as represented by the vasoactive-inotropic score.[16] Eleven in-hospital deaths occurred. The causes of death were multisystem organ failure/sepsis in 9 patients, stroke in 1, and sudden death in 1. In-hospital mortality was higher in Group 2, although the difference did not reach statistical significance. Patients in Group 2 had significantly longer hospital stays than those in Group 1. There was a tendency in Group 2 toward an increased rate of post-operative morbidities, including sepsis/bacteremia and renal failure. Severe PGD developed in 12 patients (9.8%) within 24 hours of transplantation. Despite mechanical circulatory support, 5 (42%) died during the hospital stay. The incidence of severe PGD was significantly higher in Group 2.

Late clinical outcomes

Among hospital survivors, 10 patients died during a mean follow-up of 2.5 years. The causes of death were pneumonia in 5, graft failure related to chronic rejection in 2, gastroenteritis in 1, and an unknown cause in 2. The overall post-transplant survival rates were 88%, 84%, and 78% at 1, 3, and 5 years, respectively (Figure 1). Post-transplant survival at 3 years was significantly worse in Group 2 than in Group 1 (68.4% vs 88.3%; $p = 0.049$; Figure 2).

Risk factors for 3-year mortality were analyzed by univariate and multivariable analyses (Table 4). Multivariable analysis found a longer duration of LVAD support and higher alanine aminotransferase and blood urea nitrogen levels at the time of transplantation were significant predictors.

Graft function and rejection

Post-transplant right heart catheterization was performed in 113 patients (93%) at 1 week and in 97 (80%) at 1 year. Early

Table 1 Baseline Characteristics at the Time of Left Ventricular Assist Device Implantation

Variable[a]	All ($N = 122$)	Group 1 ($n = 90$)	Group 2 ($n = 32$)	p-value
Age at LVAD implant, years	53.8 ± 13.2	54.5 ± 13.5	51.8 ± 12.2	0.33
Body mass index, kg/m^2	26.3 ± 4.98	25.7 ± 5.00	27.8 ± 4.66	0.050
Body surface area, m^2	1.92 ± 0.237	1.90 ± 0.229	1.97 ± 0.258	0.19
Male gender	96 (78.7)	71 (78.9)	25 (78.1)	0.93
Hypertension	60 (49.2)	42 (46.7)	18 (56.3)	0.35
Diabetes mellitus	37 (30.3)	24 (26.7)	13 (40.6)	0.14
Hyperlipidemia	42 (34.4)	31 (34.4)	11 (34.4)	0.99
Etiology of heart failure				0.42
Idiopathic cardiomyopathy	72 (59.0)	52 (57.8)	20 (62.5)	
Ischemic cardiomyopathy	43 (35.3)	34 (37.8)	9 (28.1)	
Others	7 (5.74)	4 (4.44)	3 (9.34)	
ICD	116 (82.9)	70 (77.8)	30 (93.8)	0.044
Reoperative surgery	30 (24.6)	25 (27.8)	5 (15.6)	0.63
Pre-operative support				
Inotropic drugs	105 (86.1)	77 (85.6)	28 (87.5)	0.79
Intraaortic balloon pump	35 (28.7)	26 (28.9)	9 (28.1)	0.93
Mechanical circulatory device	8 (6.56)	6 (6.67)	2 (6.25)	0.93
Ventilator	6 (4.92)	4 (4.44)	2 (6.25)	0.69
LVEF, %	15.8 ± 7.24	16.5 ± 7.76	13.9 ± 5.40	0.11
CVP, mm Hg	11.1 ± 5.38	11.2 ± 4.98	10.8 ± 6.42	0.77
Mean PAP, mm Hg	35.2 ± 9.98	35.1 ± 9.06	35.3 ± 12.2	0.95
PCWP, mm Hg	24.5 ± 8.42	24.8 ± 7.20	23.6 ± 11.0	0.53
Cardiac output, liters/min	3.22 ± 1.08	3.20 ± 1.15	3.28 ± 0.844	0.72
PVR, Wood units	3.88 ± 2.62	3.82 ± 2.80	3.99 ± 2.16	0.78
Sodium, mmol/liter	134 ± 4.09	133 ± 3.89	134 ± 4.71	0.81
Blood urea nitrogen, mg/dl	32.0 ± 16.2	31.8 ± 17.3	32.5 ± 12.6	0.83
Creatinine, mg/dl	1.43 ± 0.547	1.38 ± 0.520	1.55 ± 0.613	0.15
Albumin, g/dl	3.58 ± 0.436	3.55 ± 0.427	3.66 ± 0.460	0.26
AST, IU/liter	38.1 ± 63.7	42.8 ± 73.2	25.0 ± 12.5	0.18
ALT, IU/liter	59.5 ± 187	71.3 ± 217	26.2 ± 19.7	0.25
Total bilirubin, mg/dl	1.46 ± 1.16	1.58 ± 1.25	1.16 ± 0.791	0.080
White blood cells, ×1,000/ml	8.83 ± 3.32	8.95 ± 3.53	8.50 ± 2.65	0.52
Hemoglobin, g/dl	11.0 ± 1.84	10.9 ± 1.77	11.2 ± 2.04	0.54
Hematocrit, %	33.6 ± 5.00	33.5 ± 4.87	34.0 ± 5.42	0.58
Platelets, ×1000/ml	217 ± 69.6	222 ± 72.1	200 ± 60.2	0.13
International normalized ratio	1.37 ± 0.394	1.37 ± 0.407	1.38 ± 0.358	0.89
Concomitant valve surgery				
Tricuspid valve repair	31 (25.4)	24 (26.7)	7 (21.9)	0.59
Tricuspid valve replacement	1 (0.820)	1 (1.11)	0 (0)	0.55
Aortic valve repair	17 (13.9)	15 (16.7)	2 (6.25)	0.14
Prosthetic aortic valve closure	3 (2.46)	2 (2.22)	1 (3.13)	0.78
Mitral valve repair	5 (4.10)	4 (4.44)	1 (3.13)	0.75
Post-operative ICU stay, days	8.92 ± 8.70	9.06 ± 8.06	8.52 ± 6.17	0.75
Post-operative morbidity				
Ventricular arrhythmia	30 (24.6)	23 (25.6)	7 (21.9)	0.68
Sepsis/bacteremia	7 (5.74)	6 (6.67)	1 (3.13)	0.46
Chest reexploration for bleeding	16 (13.1)	13 (14.4)	3 (9.38)	0.47
Renal failure requiring dialysis	9 (7.38)	6 (6.67)	3 (9.38)	0.61
Stroke	4 (3.28)	3 (3.33)	1 (3.13)	0.95
RVAD use	5 (4.1)	5 (5.56)	0 (0)	0.17

Group 1, LVAD support of <1 year; Group 2, LVAD support ≥ 1 year. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVP, central venous pressure; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; INR, international normalized ratio; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RVAD, right ventricular assist device.

[a]Continuous data are shown as mean ± standard deviation and categoric data as number (%).

Table 2 Patient Characteristics Between Left Ventricular Assist Device Implantation and Transplantation

Variable[a]	All ($N = 122$)	Group 1 ($n = 90$)	Group 2 ($n = 32$)	p-value
Age at transplantation, years	54.3 ± 13.3	54.7 ± 13.8	54.5 ± 12.0	0.67
Age groups				0.95
≤45 years	31 (25.4)	23 (18.9)	8 (25.0)	
>45 to ≤65 years	66 (54.1)	48 (39.3)	18 (56.3)	
>65 to ≤75 years	25 (20.5)	19 (15.6)	6 (18.8)	
Blood type				0.0012
O	73 (59.8)	46 (51.1)	27 (84.4)	
A	39 (31.9)	35 (38.9)	4 (12.5)	
B	9 (7.38)	8 (8.89)	1 (3.13)	
AB	1 (0.82)	1 (1.11)	0 (0)	
Body mass index, kg/m^2	27.3 ± 4.72	26.5 ± 4.37	29.5 ± 5.03	0.0020
Body surface area, m^2	1.96 ± 0.3	1.92 ± 0.305	2.07 ± 0.247	0.016
LVAD duration of support, years	0.81 ± 0.71	0.479 ± 0.249	1.74 ± 0.742	<0.0001
UNOS status				0.12
1A	86 (70.5)	60 (66.7)	26 (81.3)	
1B	36 (29.5)	30 (33.3)	6 (18.8)	
Readmission during LVAD support				
Bleeding	24 (19.7)	19 (21.1)	5 (15.6)	0.50
Any infection	22 (18.0)	14 (15.6)	8 (25.0)	0.23
Device infection	13 (10.7)	8 (8.89)	5 (15.6)	0.26
Heart failure	14 (11.5)	6 (6.67)	8 (25.0)	0.011
Arrhythmia	14 (11.5)	11 (12.2)	3 (9.38)	0.66
Stroke	10 (8.2)	4 (4.44)	2 (6.25)	0.69
Device exchange	9 (7.38)	4 (4.44)	5 (15.6)	0.038
IVIg therapy	14 (11.5)	8 (8.89)	6 (18.8)	0.24
Medication during LVAD support				
β-Blocker	105 (86.1)	75 (83.3)	30 (93.4)	0.14
ACE inhibitor	50 (41.0)	32 (35.6)	18 (56.3)	0.041
Diuretics	82 (67.2)	58 (64.4)	24 (75.0)	0.28
Amiodarone	46 (37.7)	33 (36.7)	13 (40.6)	0.69
Aspirin	100 (82.0)	72 (80.0)	28 (87.5)	0.34
Coumadin	111 (91.0)	81 (90.0)	30 (93.8)	0.53
Sildenafil	17 (13.9)	13 (14.4)	4 (12.5)	0.79
Milrinone	10 (8.20)	6 (6.67)	4 (12.5)	0.30
Laboratory data at transplantation				
Sodium, mmol/liter	137 ± 3.12	137 ± 2.89	137 ± 3.74	0.84
Blood urea nitrogen, mg/dl	25.1 ± 11.7	25.3 ± 12.8	24.3 ± 8.41	0.65
Creatinine, mg/dl	1.37 ± 0.69	1.35 ± 0.744	1.43 ± 0.532	0.55
Albumin, g/dl	4.02 ± 0.59	4.02 ± 0.508	4.01 ± 0.778	0.97
AST, IU/liter	29.5 ± 11.6	29.2 ± 12.8	30.3 ± 7.74	0.66
ALT, IU/liter	24.6 ± 15.7	24.6 ± 17.1	24.7 ± 11.3	0.98
Total bilirubin, mg/dl	0.81 ± 0.41	0.821 ± 0.424	0.763 ± 0.366	0.49
White blood cells, ×1,000/ml	7.33 ± 2.1	7.41 ± 2.08	7.13 ± 2.16	0.52
Hemoglobin, g/dl	11.4 ± 1.8	11.2 ± 1.83	11.8 ± 1.54	0.11
Hematocrit, %	35.1 ± 4.8	34.8 ± 4.89	36.0 ± 4.41	0.20
Platelets, ×1,000/ml	208 ± 62.1	216 ± 63.0	185 ± 54.8	0.014
International normalized ratio	1.96 ± 0.65	1.98 ± 0.673	1.91 ± 0.566	0.69
Echocardiographic data at transplantation				
LVEDD, mm	58.8 ± 12.7	58.8 ± 11.8	58.7 ± 15.2	0.96
Moderate to severe				
Reduced RV systolic function	39 (32.0)	29 (32.2)	10 (31.3)	0.92
Tricuspid regurgitation	13 (10.7)	8 (8.89)	5 (15.6)	0.29
Donor variables				
Age, years	31.9 ± 11.6	32.0 ± 12.3	31.5 ± 9.63	0.84
Blood type				0.02
O	80 (65.6)	52 (57.8)	28 (87.5)	

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Table 2 (*Continued*)

Variable[a]	All ($N = 122$)	Group 1 ($n = 90$)	Group 2 ($n = 32$)	p-value
A	34 (27.9)	30 (33.3)	4 (12.5)	
B	7 (5.74)	7 (7.78)	0 (0)	
AB	1 (0.82)	1 (1.11)	0 (0)	
Body mass index, kg/m^2	26.9 ± 5.21	26.2 ± 5.11	28.8 ± 5.07	0.014
Body surface area, m^2	1.91 ± 0.24	1.88 ± 0.232	2.01 ± 0.224	0.0046

Group 1, LVAD support of <1 year; Group 2, LVAD support ≥1 year. ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IVIg, intravenous immunoglobulin; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic dimension; RV, right ventricle; UNOS, United Network for Organ Sharing;

[a]Continuous data are shown as mean ± standard deviation and categoric data as number (%).

and late hemodynamic indices and left ventricular ejection fractions were similar between the 2 groups (Table 5).

Endomyocardial biopsy was performed in 118 patients (97%) at 1 week after transplantation. Significant acute rejection was noted in 7 (5.9%), comprising grade 2R cellular rejection in 5 and antibody-mediated rejection in 2. Acute rejection developed in 2 of 14 patients (14%) who underwent desensitization therapy before transplantation. The incidence of significant cellular rejection and antibody-mediated rejection was significantly higher in Group 2 (2.3% vs 17%; $p = 0.015$). Two patients who developed antibody-mediated rejection were successfully treated with plasmapheresis and enhanced immunosuppression therapy.

Effect of adverse events during CF-LVAD support on outcomes

Post-transplant mortality was stratified according to adverse events during LVAD support (Table 6). In-hospital mortality was significantly higher in patients who required more than 2 readmissions than in those with 0 or 1 readmission. Similarly, patients who experienced bleeding events had higher early mortality compared with those who did not. The 1-year post-transplant survival did not differ significantly between the groups.

Patients were further stratified according to both the duration of CF-LVAD support (<1 year or ≥1 year) and the

Table 3 Intraoperative and Early Post-operative Outcomes

Variables[a]	All ($N = 122$)	Group 1 ($n = 90$)	Group 2 ($n = 32$)	p-value
Intraoperative variables				
Cardiopulmonary bypass time, min	180 ± 52.7	173 ± 50.0	197 ± 56.3	0.025
Ischemic time, min	189 ± 47.9	191 ± 48.6	183 ± 46.2	0.40
Transfusion				
Packed red blood cells, units	3.30 ± 3.15	3.19 ± 3.00	3.58 ± 3.55	0.56
Fresh frozen plasma, units	5.67 ± 3.67	5.69 ± 3.42	5.59 ± 4.31	0.90
Platelets, units	13.2 ± 6.81	13.6 ± 6.56	12.1 ± 7.45	0.31
Nitric oxide use	44 (36.1)	34 (27.9)	10 (31.3)	0.51
Vasoactive-inotropic score[b]	21.6 ± 13.4	22.5 ± 1.53	19.0 ± 1.80	0.21
Early mortality and morbidity				
30-day mortality	5 (4.1)	3 (3.33)	2 (6.25)	0.48
In-hospital mortality	11 (9.02)	6 (6.67)	5 (15.6)	0.12
Hospital stay, days	25.8 ± 29.4	20.9 ± 10.1	36.7 ± 53.0	0.0016
Major morbidity				
Stroke	5 (4.10)	3 (3.33)	2 (6.25)	0.48
Sepsis/bacteremia	19 (15.6)	11 (12.2)	8 (25.0)	0.087
Chest reexploration for bleeding	22 (18.0)	14 (15.6)	8 (25.0)	0.23
Renal failure requiring dialysis	16 (13.1)	9 (10.0)	7 (21.9)	0.087
Arrhythmia	16 (13.1)	13 (14.4)	3 (9.38)	0.47
Severe primary graft dysfunction	12 (9.84)	5 (5.56)	7 (21.9)	0.0078
Intraaortic balloon pump support	4 (3.28)	1 (1.11)	3 (9.38)	
VAD support	8 (6.56)	4 (4.44)	4 (12.5)	
Deep sternal wound infection	7 (5.74)	5 (5.56)	2 (6.25)	0.89

Group 1, LVAD support of <1 year; Group 2, LVAD support ≥1 year. IABP, intraaortic balloon pump; VAD, ventricular assist device.

[a]Continuous data are shown as mean ± standard deviation and categoric data as number (%).

[b]Vasoactive-inotropic score[11] = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (μ/kg/min) + 100 × norepinephrine dose (μg/kg/min).

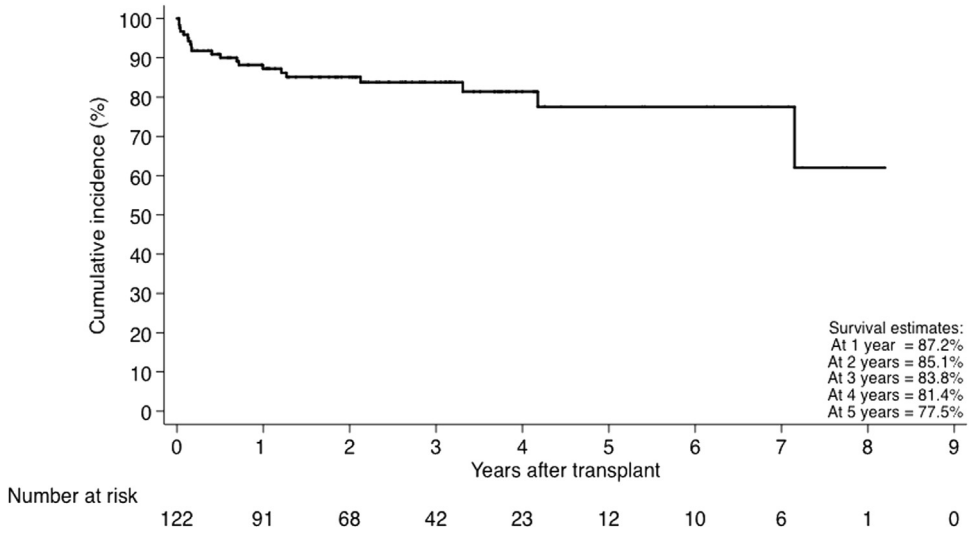

Figure 1 Overall survival after transplantation.

number of readmissions (0–1 or ≥2). Kaplan-Meier curves constructed for these 4 groups showed that patients having shorter support duration and fewer readmissions (Group a) had better post-transplant survival (Figure 3).

Discussion

Major findings of this study are (1) overall short-term and long-term cardiac transplant outcomes for patients supported with CF-LVAD were satisfactory; and (2) patients who require prolonged CF-LVAD support had an increased risk of adverse events, such as bleeding, heart failure, and infection, which might lead to diminished post-transplant survival.

This study reported our single-center experience with CF-LVAD as a BTT in 122 patients. Satisfactory transplant survival rates of 88% at 1 year, 84% at 3 years, and 78% at 5 years were obtained after a mean of 296 days of CF-LVAD support. Recent smaller single-center experiences have also shown excellent outcomes.

Kamdar et al[17] reported the outcomes of their 77 BTT patients. After a mean support time of 310 days, post-transplant survival at 1, 3, and 5 years was 93%, 91%, and 88%, respectively. Deo et al[18] analyzed 37 BTT patients with a median support time of 227 days who achieved 1- and 3-year post-transplant survival rates of 90% and 83%, respectively. A comprehensive analysis of 250 patients from the multicenter HeartMate II trial found a 1-year survival of 87% after a median 151 days of support.[9] These reports along with our data suggest promising post-transplant outcomes after extended support with CF-LVADs.

However, the question of the optimal timing of transplantation after LVAD support still remains.[8,9,19] Current CF technology can provide a longer waiting time with favorable mortality and morbidity rates.[2,3,20] As reported by the Interagency Registry for Mechanically Assisted Circulatory Support, almost 50% of BTT patients are alive on CF-LVAD support after 1 year.[4] These data imply that patients on CF-LVAD support might receive preferred donor hearts, which may lead to improved post-transplant outcomes.

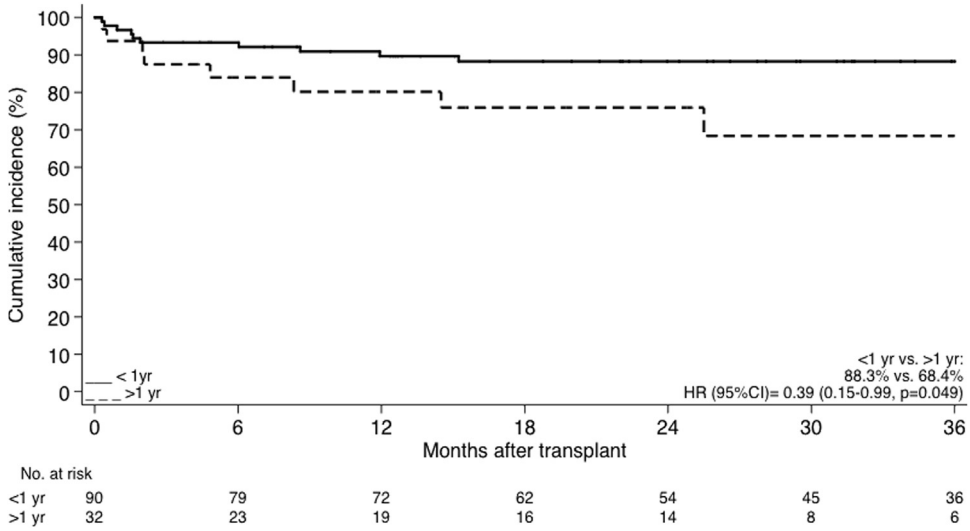

Figure 2 Comparison of survival according to waiting time on continuous flow-left ventricular assist device support. CI, confidence interval; HR, hazard ratio.

Table 4 Predictors of Mortality at 3 Years

	Crude		Multivariable	
Baseline variables	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Male	1.38 (0.40–4.78)	0.61		
Age at LVAD implantation	1.04 (0.99–1.08)	0.16	1.02 (0.96–1.07)	0.56
Hypertension	3.02 (1.07–8.50)	0.035	2.15 (0.69–6.69)	0.19
Diabetes	1.16 (0.44–3.10)	0.76		
Hyperlipidemia	1.24 (0.48–3.20)	0.65		
Etiology of heart failure		0.89		
Idiopathic cardiomyopathy	Reference			
Ischemic cardiomyopathy	1.07 (0.41–2.76)			
Others	…			
Central venous pressure	1.05 (0.97–1.14)	0.24		
Mean pulmonary artery pressure	1.01 (0.97–1.06)	0.56		
Pulmonary vascular resistance	0.99 (0.81–1.21)	0.94		
Months on LVAD	1.07 (1.03–1.11)	0.001	1.10 (1.04–1.16)	0.001
Adverse event during LVAD				
Bleeding	1.90 (0.67–5.33)	0.22		
Heart failure	3.47 (1.23–9.75)	0.018	1.14 (0.30–4.36)	0.85
Any infection	1.53 (0.50–4.65)	0.46		
Arrhythmia	1.59 (0.46–5.50)	0.46		
Readmission	1.88 (0.74–4.77)	0.18	0.89 (0.31–2.54)	0.82
Device exchange	0.99 (0.13–7.45)	0.99		
IVIg therapy	2.08 (0.48–9.04)	0.33		
Pre-transplant laboratory data				
White blood cells	1.13 (0.91–1.41)	0.27		
Hemoglobin	0.91 (0.70–1.19)	0.49		
Hematocrit	0.94 (0.85–1.04)	0.24		
Platelets	1.00 (0.99–1.01)	0.79		
Total bilirubin	0.53 (0.14–1.95)	0.34		
Aspartate aminotransferase	1.02 (0.98–1.05)	0.28		
Alanine aminotransferase	1.02 (1.00–1.04)	0.096	1.03 (1.00–1.06)	0.025
Albumin	1.34 (0.54–3.36)	0.53		
Sodium	0.90 (0.79–1.04)	0.15	0.95 (0.82–1.09)	0.46
Blood urea nitrogen	1.04 (1.01–1.07)	0.008	1.04 (1.01–1.08)	0.021
Creatinine	1.32 (0.79–2.21)	0.29		
International normalized ratio	1.10 (0.54–2.27)	0.79		

CI, confidence interval; HR, hazard ratio; IVIg, intravenous immunoglobulin; LVAD, left ventricular assist device.

However, this assumption does not necessarily hold from the perspective of the recipient's condition. Smedira et al[8] showed that a longer duration of mechanical circulatory support before transplantation adversely affects post-transplant survival, although their study included only 11 patients supported by CF-LVADs. They concluded that early transplantation to avoid infection, sensitization, and neurologic complications may improve post-transplant

Table 5 Graft Function at 1 Week and 1 Year After Transplantation

	1 week				1 year			
	All	Group 1	Group 2		All	Group 1	Group 2	
Variable[a]	(*N* = 113)	(*n* = 86)	(*n* = 27)	*p*-value	(*N* = 97)	(*n* = 76)	(*n* = 21)	*p*-value
CVP, mm Hg	6.66 ± 4.37	6.73 ± 4.68	6.44 ± 3.23	0.77	4.98 ± 3.72	5.09 ± 3.62	4.57 ± 4.12	0.57
Mean PAP, mm Hg	19.8 ± 5.26	19.3 ± 4.99	21.5 ± 5.79	0.054	19.5 ± 5.82	19.1 ± 5.32	21.0 ± 7.30	0.18
PCWP, mm Hg	10.6 ± 4.91	10.4 ± 5.03	10.9 ± 4.58	0.66	9.67 ± 4.41	9.64 ± 4.54	9.76 ± 4.01	0.91
CO, liters/min	5.29 ± 1.53	5.27 ± 1.63	5.35 ± 1.22	0.81	5.29 ± 1.35	5.29 ± 1.31	5.30 ± 1.51	0.96
PVR, Wood units	1.93 ± 0.917	1.86 ± 0.866	2.12 ± 1.05	0.20	2.12 ± 1.09	2.06 ± 0.951	2.35 ± 1.49	0.28
LVEF, %	61.3 ± 9.17	61.3 ± 9.28	61.4 ± 9.04	0.95	60.5 ± 7.85	60.3 ± 8.24	61.2 ± 6.47	0.67

Group 1, LVAD support of <1 year; Group 2, LVAD support ≥1 year. CO, cardiac output; CVP, central venous pressure; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

[a]Data are shown as mean ± standard deviation.

Table 6 In-Hospital Mortality and 1-Year Post-transplant Survival Stratified by Adverse Event During Continuous-Flow Left Ventricular Assist Device Support

	Patients	In-hospital mortality		Survival at 1 year	
Variable	No. (%)	(%)	*p*-value	(%)	*p*-value
Readmissions, No.					
0 or 1	81 (66.4)	4.93	0.027	89.7	0.18
≥2	41 (33.6)	17.1		88.9	
Bleeding					
Yes	24 (19.7)	20.8	0.024	79.2	0.099
No	98 (80.3)	6.12		89.3	
Any infection					
Yes	22 (18.0)	18.2	0.097	81.8	0.27
No	100 (82.0)	7.00		88.6	
Heart failure					
Yes	14 (11.5)	21.4	0.085	78.6	0.20
No	108 (88.5)	7.41		88.4	
Arrhythmia					
Yes	14 (11.5)	14.3	0.46	78.6	0.26
No	108 (88.5)	8.33		88.4	
Device exchange					
Yes	9 (7.38)	11.1	0.82	88.9	0.96
No	113 (92.6)	8.85		87.1	
IVIg therapy					
Yes	14 (11.5)	7.14	0.79	92.9	0.58
No	108 (88.5)	9.26		86.5	

IVIg, intravenous immunoglobulin.

survival.[8] John et al[9] found a worse trend in 1-year survival among 14 patients supported for more than 12 months (79% at 1 year). They speculated that this trend could be due to sensitization.

The present data further illuminate the paucity of post-transplant outcomes after prolonged CF-LVAD support. Patients who required prolonged CF-LVAD support (mean duration of 1.7 years) had significantly worse early and late outcomes. The worse outcomes were likely related to a cumulative burden of adverse events during device support.

Although CF pumps have dramatically decreased overall complications compared with pulsatile pumps,[1,2] device-related or non-related complications have not been eliminated. Recent evidence reveals that readmissions due to

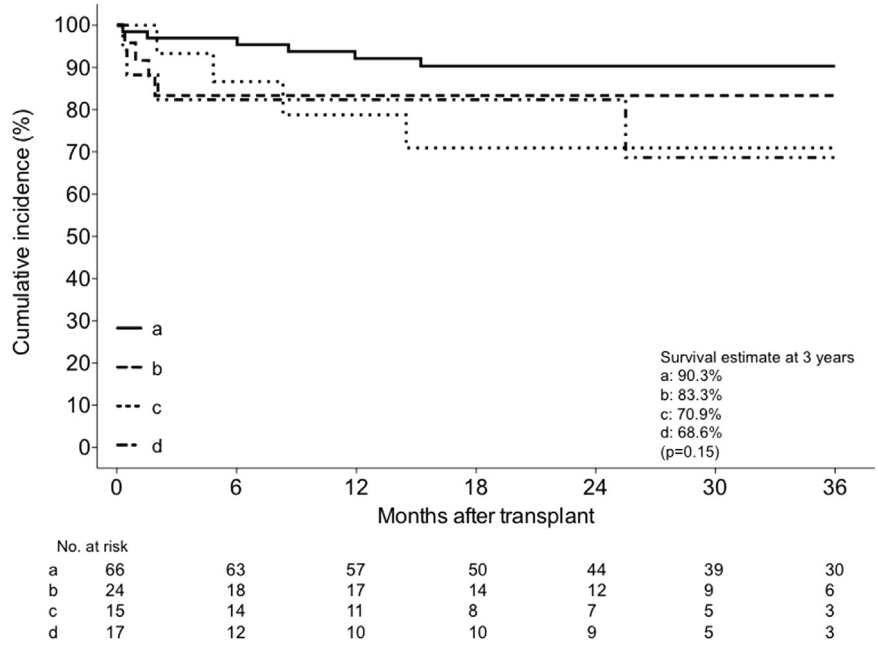

Figure 3 Post-transplant survival stratified by duration of continuous-flow left ventricular assist device support of <1 year or ≥1 year and the number of readmissions (0–1 or ≥2). a: support time <1 year, number of readmissions 0 or 1; b: support time <1 year, number of readmissions ≥2; c: support time ≥1 year, number of readmissions 0 or 1; d: support time ≥1 year, number of readmissions ≥2.

bleeding, infection, and cardiac pathology are quite common during long-term CF-LVAD support.[21,22] Furthermore, resource use for readmission increases rapidly after 1 year of support, and an increasing number of readmissions negatively affects survival on device.[22] Our study suggests that patients in Group 2 likely became compromised due to repeated adverse events that occurred during device support, resulting in increased early morbidity and mortality after transplantation. Although CF-LVADs can now provide excellent 1-year survival rates approaching 90% when used as a life support,[4] these data suggest that earlier transplantation within 1 year of support would reduce on-device and post-transplant mortality.

PGD is the most catastrophic complication after transplantation.[14] The need for pre-operative mechanical circulatory support, such as extracorporeal membrane oxygenation and extracorporeal LVAD, is known to be a risk factor for the development of PGD.[23] However, evidence is scarce in patients bridged with CF-LVADs. Our data showed that severe PGD occurred in 9.8% of bridged patients and that in-hospital mortality in these patients was extremely high. Interestingly, severe PGD was more frequently seen in patients who required prolonged CF-LVAD support. This finding provides additional evidence that we may need to pay special attention to PGD in recipients supported by CF-LVADs for a prolonged period. Further analyses in large series are advisable to examine our findings.

An increased incidence of allosensitization after LVAD placement negatively affects post-transplant outcomes.[11,24] The increased use of blood products consequent to bleeding events during LVAD support can be related to a further risk of sensitization.[9] The higher incidence of early rejection and the need for peri-operative circulatory support in Group 2 may be related to sensitization, although early and late graft function was similar in both groups. As demonstrated in our prior study,[11] patients who received desensitization therapy had an equivalent survival to those who did not. Routine monitoring of PRA levels and use of immunomodulatory therapy should be considered in patients requiring prolonged CF-LVADs support.

Under the current United Network of Organ Sharing (UNOS) allocation system, in several regions in the United States, most patients supported by LVADs are receiving transplants after being upgraded to status 1A due to device-related complications such as device infection, severe aortic insufficiency, or recurrent severe bleeding.[3,25] However, a multicenter study with the HeartMate II demonstrated decreased post-transplant survival in patients who received more than 2 units of packed red blood cells during LVAD support and those who had driveline infections.[9] Our analysis also suggests that patients who require multiple readmissions due to bleeding, any infection, or heart failure have a trend toward increased early mortality.

Although not all adverse events during LVAD support are equal in terms of adverse outcomes after transplantation, better strategies for managing these complicated patients to reduce post-transplant mortality are clearly needed to maximize the benefit of transplantation. We recently refined our strategies to improve outcomes in these high-risk BTT patients. These include better matching of recipients with donors in gender and size, earlier reperfusion to decrease ischemic time, decrease transfusion, and pressor requirements, and refinement of procurement technique.

The BTT strategy with CF-LVADs has become a standard option for patients with a goal of transplantation. Longer waiting times beyond 1 year can be expected concurrent with the evolution of device technology and improvements in patient management. However, the current study calls attention to the need for further refinements of long-term care, the timing of transplantation, and the selection of transplant candidates in patients supported by CF-LVADs for a prolonged period. The current study raises a question whether the patients with longer-term CF-LVAD support and multiple readmissions should receive a transplant more urgently or these patients rather should not receive a transplant in consideration of chronic donor shortage. Further multicenter studies including a larger population are warranted to answer this question.

This study has several limitations. First, it was a retrospective analysis of a single-center experience. However, the strength of the present single-center study was the large number of patients to whom consistent strategies were applied in terms of patient selection, operative procedure, and post-operative management. Furthermore, the present study included detailed analyses of longitudinal data from before device implantation to post-transplantation that could not be addressed in the multicenter studies. Second, the number of patients in Group 2 was low, thereby limiting statistical power.

In conclusion, overall short-term and long-term cardiac transplant outcomes of patients bridged with CF-LVAD are satisfactory. However, patients who require prolonged CF-LVAD support may become compromised due to adverse events occurring during device support, and therefore, have diminished post-transplant survival.

Disclosure statement

U.P.J. and Y.N. have received consulting fees from Thoratec Corp. None of the remaining authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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