Right and left ventricular assist devices are an option for bridge to heart transplant

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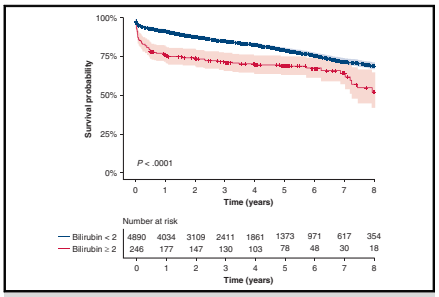
ABSTRACT

Background: Patients with a left ventricular assist device with right ventricular failure are prioritized on the heart transplant waitlist; however, their post-transplant survival is less well characterized. We aimed to determine whether pretransplant right ventricular failure affects postoperative survival in patients with a left ventricular assist device as a bridge to transplant.

Methods: We performed a retrospective review of the 2005-2018 Organ Procurement and Transplantation Network/United Network for Organ Sharing registry for candidates aged 18 years or more waitlisted for first-time isolated heart transplantation after left ventricular assist device implantation. Candidates were stratified on the basis of having right ventricular failure, defined as the need for right ventricular assist device or intravenous inotropes. Baseline demographic and clinical characteristics were compared among the 3 groups, and post-transplant survival was assessed.

Results: Our cohort included 5605 candidates who met inclusion criteria, including 450 patients with right ventricular failure, 344 patients with a left ventricular assist device and intravenous inotropes as a bridge to transplant, 106 patients with a left ventricular assist device and right ventricular assist device, and 5155 patients with a left ventricular assist device as a bridge to transplant without the need for right side support. Compared with patients without right ventricular failure, patients with a left ventricular assist device as a bridge to transplant with right ventricular failure were younger (median age 51 years, 55 vs 56 years, $P < .001$) and waited less time for organs (median 51 days, 93.5 vs 125 days, $P < .001$). These patients also had longer post-transplant length of stay (median 18 days, 20 vs 16 days, $P < .001$). Right ventricular failure was not associated with decreased post-transplant long-term survival on unadjusted Kaplan–Meier analysis ($P = .18$). Neither preoperative right ventricular assist device nor intravenous inotropes independently predicted worse survival on multivariate Cox proportional hazards analysis. However, pretransplant liver dysfunction (total bilirubin >2) was an independent predictor of worse survival (hazard ratio, 1.74; 95% confidence interval, 1.39-2.17; $P < .001$), specifically in the left ventricular assist device group and not in the left ventricular assist device + right ventricular assist device/intravenous inotropes group.



Kaplan–Meier analysis of long-term survival of recipients after heart transplantation in the LVAD group segregated by their bilirubin level; number at risk table is shown at the bottom. A significant reduction in survival is demonstrated once the bilirubin level is above 2 (95% confidence limits Kaplan–Meier analysis is presented).

CENTRAL MESSAGE

Patients with LVADs with RV failure supported by RVAD or IV inotropes before heart transplant have reduced short-term but not long-term post-transplant survival.

PERSPECTIVE

Patients with biventricular failure are prioritized on the waiting list because their critical pretransplant condition has no impact on their long-term survival but rather on their short-term survival. Liver dysfunction (a surrogate marker of RVF) was found to affect long-term survival in patients with LVADs; thus, the recipient's RV function optimization is suggested pretransplant.

See Commentary on page 160.

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The study was deemed exempt by our Institutional Review Board, IRB N. Pro00073879 approved on 5/29/16; informed consent was waived.

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Abbreviations and Acronyms

BTT = bridge to transplant
CI = confidence interval
ECMO = extracorporeal membrane oxygenation
HR = hazard ratio
IV = intravenous
LVAD = left ventricular assist device
RV = right ventricle
RVAD = right ventricular assist device
RVF = right ventricular failure
TAH = total artificial heart
UNOS = United Network for organ Sharing

Conclusions: Patients with biventricular failure are prioritized on the waiting list, because their critical pretransplant condition has limited impact on their post-transplant survival (short-term effect only); thus, surgeons should be confident to perform transplantation in these severely ill patients. Because liver dysfunction (a surrogate marker of right ventricular failure) was found to affect long-term survival in patients with a left ventricular assist device, surgeons should be encouraged to perform transplantation in these severely ill patients after a recipient's optimization by inotropes or a right ventricular assist device because even when the bilirubin level is elevated in these patients (treated with right ventricular assist device/inotropes), their long-term survival is not affected. Future studies should assess recipients' optimization before organ acceptance to improve long-term survival. (JTCVS Open 2022;9:146-59)

Left ventricular assist device (LVAD) implantation and heart transplantation continue to be delivered to an increasing number of patients, and the number of patients with an LVAD at the time of transplant has almost doubled in the last decade.[1–3]

Although heart transplant is the gold standard therapy for advanced heart failure, it is limited by an insufficient donor supply. As such, LVAD support is used in a growing number of patients with heart failure, including a significant number of patients who receive implants as a bridge to transplant (BTT). Although LVADs support the left side of the heart, after surgery, the right ventricle is challenged and exposed to the risk of right ventricular failure (RVF).[4,5] There are several causes of RVF after LVAD implantation, including left ventricle decompression causing a leftward shift of the interventricular septum, which changes the shape of the right ventricle and impairs its contractility. Furthermore, LVAD support may result in increased right ventricle (RV) volume load. Thus, some LVAD recipients experience RVF requiring a right ventricular assist device (RVAD) or intravenous (IV) inotropic support; these patients are given priority for transplant.[6] We specifically focused on an intermediate subpopulation of LVAD recipients with RVF, not the patients with chronic biventricular failure with a total artificial heart (TAH) or durable biventricular assist device and not the acute patients crashing on extracorporeal membrane oxygenation (ECMO).

Conflicting evidence regarding the post-transplant survival of this population has been published. A recent publication by Grimm and colleagues reviewed United Network for Organ Sharing (UNOS) records between 2004 and 2012 and found that patients with a TAH or biventricular assist device had worse short- and long-term survival compared with patients with LVADs. Conversely, a smaller study by Urban and colleagues[7] reviewed single-institution data from the Czech Republic and demonstrated that no difference exists between patients bridged to transplant with an LVAD or an LVAD in addition to an RVAD regarding rates of early graft loss, post-transplant renal failure, stroke rate, and 3-year survival.[8] Carter and colleagues[9] reviewed UNOS records between 1999 and 2018 and found that the survival of patients on ECMO (status 1 on the waiting list) post-transplant was reduced in comparison with LVAD BTT recipients.

Previously, these patients were prioritized as 1A on the Heart Transplant Allocation system. According to the New Heart Transplant Allocation system,[10] patients with an LVAD + RVAD are prioritized as status 1 and patients with an LVAD + IV inotropes are prioritized as status 3. Thus, although patients with an LVAD and RVF are prioritized on the heart transplant waiting list, their post-transplant survival is not well characterized. Consequently, we used the UNOS registry to determine whether the post-operative survival of patients with an LVAD as BTT is affected by the presence of pretransplant RVF for an intermediate time interval.

MATERIALS AND METHODS

Data Source

A retrospective cohort analysis was performed using the United Network of Organ Sharing (UNOS) Standard Analysis and Research database. The UNOS administers the Organ Procurement and Transplantation Network (OPTN) under contract with the US Department of Health and Human Services. This database contains data on all transplant candidates undergoing listing for solid organ transplantation in the United States since October 1987. The dataset used for this investigation included all candidates listed for heart transplantation between 2005 and 2018. The study was deemed exempt by our Institutional Review Board (N. Pro00073879, approved on 5/29/16). Informed consent was waived.

Study Design and Outcomes

All first-time adult candidates undergoing isolated heart transplantation during the study dates were included. Exclusion criteria included candidates aged less than 18 years, patients using old versions of LVAD (other than HeartMate 2/3 (HM 2/3 HeartMate LVAD, Abbott) and HeartWare (HW HeartWare HVAD, Medtronic); those undergoing simultaneous lung, liver, or abdominal transplantation; those supported with ECMO at

the time of transplant; those who did not have an LVAD at the time of transplant, and those with TAHs at the time of transplant. Patients with LVADs with RV support of some kind who did not undergo transplantation were also not included in the study (Figure 1).

The Interagency Registry for Mechanically Assisted Circulatory Support definition for severe RVF for LVAD recipients was used, for example, the need for inotropes at any time since last surveillance period or requiring RVAD support at any time after hospital discharge.

The study population was then stratified by the existence of severe RVF,[11] which was defined as having a simultaneous temporary RVAD support or on a continuous IV inotropes drip before heart transplant. Because the study cohort comprised LVAD recipients who underwent transplantation, we assumed that if inotropes were used, the reason was RVF due to cardiogenic shock and not septic shock (because the patients underwent transplantation). The primary outcome was recipient long-term survival.

Statistical Analysis

Demographic data were compiled and described. Baseline characteristics and outcomes were compared between groups using the Kruskal–Wallis test for continuous variables and Pearson's chi-square test for categorical variables. Basic characteristics were compared between the 2 groups separately using the Mann–Whitney test.

Post-transplant survival was estimated for those candidates in each group who underwent heart transplantation using the Kaplan–Meier method. The log-rank test was used to determine statistical significance. Kaplan–Meier analysis was used to estimate survival post-transplant.

Cox proportional hazards modeling was performed to identify independent factors associated with survival. Statistical and clinically significant variables from the univariate analysis were chosen for the Cox multivariate analysis. The selection of variables is shown in Tables E1and E2.

We used a complete case method because of the small amount of missing data. We have performed a landmark analysis at 100 days to explore earlier versus later effects of different groups in survival. Kaplan–Meier survival curves and hazard ratios (HRs) were computed for each period. Conditional survival after 100 days was analyzed with a new time zero at 101 days. To avoid bias, the landmark was chosen before data analysis began and corresponded to a clinically meaningful period of time. The transplant literature has established "day 100" as a demarcation point for distinguishing early from late transplant-related events.

Missing values (<4%) were imputed as missing and were not calculated. Analyses were performed using SPSS Version 25 for Mac (IBM).

RESULTS

Demographic Characteristics

A total of 5605 LVAD recipients met the inclusion criteria for analysis. Of these, 5155 recipients (91.9%) had no RVF and 450 recipients (8.1%) had RVF. The LVAD + RVAD group included 106 patients, and the LVAD + inotropes group included 344 patients. At the time of transplant, the LVAD + RVAD group and LVAD + IV inotropes group were younger (48 years, 50 vs 54 years, $P < .001$) and had a lower body mass index (26.3 kg/m^2, 28.8% vs 28.8%, $P < .001$). The LVAD + RVAD and LVAD + inotropes groups had a higher level of total bilirubin (mean 0.9 mg/dL, 0.7 vs 0.6, $P < .001$). A higher percentage of the LVAD + RVAD and LVAD + inotropes groups were on IV antibiotics in the 2 weeks before transplant (29.0%, 18.3% vs 13.3%, $P < .001$), and their median waitlist time was substantially lower (51, 93 days vs 125 days, $P < .001$) (Tables 1 and 2).

The LVAD + RVAD group donors had lower BMI (26 kg/m^2, vs 27, 27, $P = .03$) compared with the LVAD + inotropes group and LVAD group donors. No other significant differences were found in relation to age, gender, or ischemic time between the groups (Table 3).

Unadjusted Outcomes and Survival Analysis

The LVAD + RVAD and LVAD + inotropes groups had a longer length of stay from transplant to discharge in an unadjusted analysis (median 18 days, 20 vs 16 days, $P < .001$), but no difference was found between the groups in primary graft dysfunction and acute or chronic rejection (Table 4). Long-term post-transplant survival was estimated using the Kaplan–Meier method. The LVAD + RVAD and

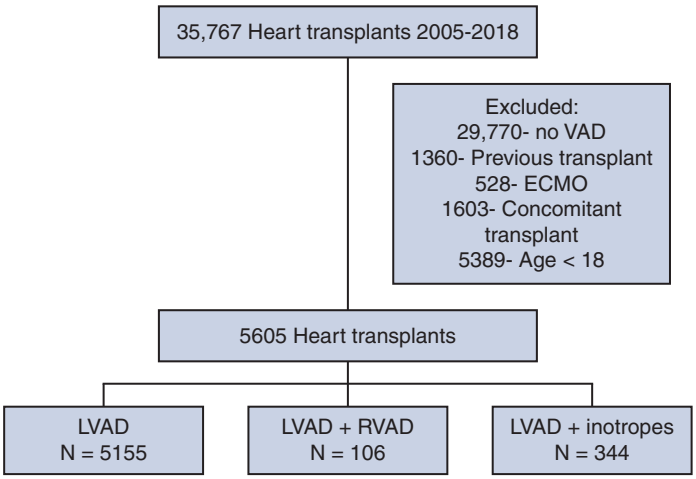

FIGURE 1. Patient cohort flowchart: study inclusions and exclusions. of 35,767 heart transplants performed in the study time period, only 5605 patients with an LVAD were included in the final cohort. *VAD,* Ventricular assist device; *ECMO,* extracorporeal membrane oxygenation; *LVAD,* left ventricular assist device; *RVAD,* right ventricular assist device.

TABLE 1. Recipient characteristics

Variable	LVAD N = 5155	LVAD + RVAD N = 106	LVAD + inotropes N = 344	*P* value	Missing values
Female gender	1010 (19.6%)	26 (24.5%)	64 (18.6%)	.40	0
Age (median, IQR), y	56 (48-63)	51 (38-58)	55 (42-61)	<.001	0
BMI (median, IQR) kg/m^2	29 (25-32)	26 (22-30)	29 (25-33)	<.001	0
Ethnicity/Race					
White	3374 (65.5%)	67 (63.2%)	224 (65.1%)	.80	0
Black	1228 (23.8%)	25 (23.6%)	89 (25.9%)		
Hispanic	354 (6.9%)	8 (7.5%)	22 (6.4%)		
Other	199 (3.9%)	6 (5.7%)	9 (2.6%)		
History					
Diabetes	1626 (31.6%)	34 (32.1%)	113 (33.0%)	.85	7
Malignancy	396 (7.7%)	6 (5.7%)	30 (8.7%)	.57	0
Cerebrovascular disease	335 (6.6%)	7 (6.7%)	19 (5.5%)	.75	58
Creatinine (median, IQR)	1.2 (0.9-1.4)	1.1 (0.8-1.5)	1.2 (0.9-1.5)	.52	2
Bilirubin (median, IQR)	0.6 (0.4-1)	0.9 (0.6-1.6)	0.7 (0.5-1.2)	<.001	20
Medical therapy					
IV antibiotics 2 wk from transplant	669 (13.3%)	29 (29.0%)	62 (18.3%)	<.001	123
IV inotropes at transplant	0 (0.0%)	17 (16.0%)	344 (100%)	<.001	0
Ventilator support at transplant	13 (0.3%)	3 (2.8%)	22 (6.4%)	<.001	0
ABO blood type					
A	2022 (39.2%)	39 (36.8%)	144 (41.9%)	.53	0
B	755 (14.6%)	13 (12.3%)	38 (11.0%)		
AB	215 (4.2%)	6 (5.7%)	13 (3.8%)		
O	2163 (42.0%)	48 (45.3%)	149 (43.3%)		
Days on waitlist (h, median, IQR)	125 (42-301)	51 (17.75-158.0)	93.5 (26.0-262.0)	<.001	0

Recipients' characteristics before heart transplantation, segregated by RV dysfunction. *LVAD,* Left ventricular assist device; *RVAD,* right ventricular assist device; *BMI,* body mass index; *IQR,* interquartile range; *IV,* intravenous.

LVAD + inotropes groups had reduced short-term survival: at 1 year: 86.6%, 88.6% versus 91.6% ($P = .03$, Figure 2, *A*); at 3 years: 75.8%, 82.0% versus 84.9% ($P = .02$); at 5 years: 69.3%, 76.4% versus 79.1% ($P = .03$). However, at 8 years, there was no difference in survival between the groups: 65.9%, 71.5% versus 60.6% ($P = .18$; Figure 2, *B*). Landmark analysis for short-term survival (100 days) and long-term survival (beyond the first 100 days) is presented in Figure 2, *B*. Although a significant difference was seen between the LVAD groups in the first 100 days, no statistically significant difference was observed between the LVAD groups for long-term survival. Next, a Kaplan–Meier survival analysis was done to explore the impact of liver dysfunction on survival. Although elevated bilirubin had no impact on survival in the LVAD + RVAD and LVAD + IV inotropes groups, it had a negative impact on survival in the LVAD group ($P < .001$) (Figure 3, *A-C*). Furthermore, we performed a multivariable Cox analysis on each group individually and found that bilirubin was associated with mortality only in the LVAD group (HR, 1.97; $P < .001$), but not in the RVAD or inotropes groups ($P = .98$, $P = .67$, respectively).

TABLE 2. Post hoc analysis

Variable	LVAD	LVAD + RVAD
Age		
LVAD + RVAD	<0.001	–
LVAD + inotropes	<0.001	0.04
Creatinine		
LVAD + RVAD	0.24	–
LVAD + inotropes	0.31	0.15
BMI		
LVAD + RVAD	<0.001	–
LVAD + inotropes	0.94	<0.001
Bilirubin		
LVAD + RVAD	<0.001	–
LVAD + inotropes	<0.001	0.02
Days on waitlist		
LVAD + RVAD	<0.001	–
LVAD + inotropes	<0.001	0.01

Intergroup comparisons for Table 1, univariate analysis. *LVAD,* Left ventricular assist device; *RVAD,* right ventricular assist device; *BMI,* body mass index.

Cox Proportional Hazards

To account for potential confounders and to identify independent factors associated with recipient survival, a Cox proportional hazard model was created. Independent factors associated with reduced recipient survival included

TABLE 3. Donor/graft characteristics

Variable	LVAD N = 5155	LVAD + RVAD N = 106	LVAD + inotropes N = 344	*P* value	Missing values
Female gender	1224 (23.7%)	25 (23.6%)	87 (25.3%)	.81	0
Gender mismatch	1042 (20.2%)	21 (19.8%)	83 (24.1%)	.22	0
Age (median, IQR)	30 (23-39)	31 (22-40)	31 (23-40)	.46	0
BMI (median, IQR)	27 (24-31)	26 (23-30)	27 (24-32)	.03	1
Ethnicity/Race					
White	3411 (66.2%)	67 (63.2%)	219 (66.0%)	.06	0
Black	912 (17.7%)	13 (12.3%)	67 (19.5%)		
Hispanic	700 (13.6%)	19 (17.9%)	52 (15.1%)		
Other	132 (2.6%)	7 (6.6%)	6 (1.7%)		
History					
Cigarette use	585 (11.5%)	18 (17.1%)	40 (12.0%)	.20	77
Cocaine use	1027 (20.2%)	25 (23.8%)	69 (20.5%)	.66	90
Alcohol use	855 (16.9%)	18 (17.0%)	46 (13.7%)	.32	109
Diabetes	180 (3.5%)	0 (0.0%)	10 (2.9%)	.13	24
Hypertension	821 (16.0%)	13 (12.5%)	49 (14.5%)	.48	32
Cancer	73 (1.4%)	1 (1.0%)	4 (1.2%)	.86	27
Donor cause of death					
Anoxia	1514 (29.4%)	34 (32.1%)	102 (29.7%)	.21	2
Cerebrovascular/stroke	892 (17.3%)	11 (10.4%)	61 (17.7%)		
Head trauma	2629 (51.0%)	59 (55.7%)	174 (50.6%)		
CNS tumor	22 (0.4%)	2 (1.9%)	1 (0.3%)		
Other	98 (1.9%)	0 (0.0%)	6 (1.7%)		
ABO blood type					
A	1838 (35.7%)	39 (36.8%)	136 (39.5%)	.17	0
B	581 (11.3%)	6 (5.7%)	27 (7.8%)		
AB	77 (1.5%)	1 (0.9%)	3 (0.9%)		
O	2659 (51.6%)	60 (56.6%)	178 (51.7%)		
HLA mismatch level					
0	7 (0.2%)	0 (0.0%)	0 (0.0%)	.37	627
1	20 (0.4%)	0 (0.0%)	4 (1.3%)		
2	135 (3.0%)	2 (2.0%)	12 (3.8%)		
3+	4399 (96.4%)	99 (98.0%)	300 (94.9%)		
Graft ischemic time (h, median, IQR)	3.13 (2.51-4.02)	3.26 (2.51-4.02)	3.13 (2.45-3.68)	.19	42

LVAD, Left ventricular assist device; *RVAD,* right ventricular assist device, *IQR,* interquartile range; *BMI,* body mass index; *CNS,* central nervous system; *HLA,* human leukocyte antigen.

the following: donor characteristics: older donor age (HR, 1.01; 95% confidence interval [CI], 1.00-1.02; $P = .001$), black race (HR, 1.26; 95% CI, 1.07-1.48; $P = .005$), and ischemic time (HR, 1.1; 95% CI, 1.04-1.17; $P = .001$); recipient characteristics: receiving antibiotics in the 2 weeks pretransplant (HR, 1.18; 95% CI, 1.00-1.40; $P = .05$), having a higher BMI (HR, 1.03; 95% CI, 1.01-1.04; $P < .001$), and having diabetes (HR, 1.31; 95% CI, 1.14-1.5; $P < .001$). Pretransplant RVAD or IV inotropes were not factors associated with post-transplant survival; however, recipient pretransplant total bilirubin greater than 2 mg/dL was found to be independently associated with reduced survival (HR, 1.74; 95% CI, 1.39-2.17; $P < .001$) (Table 5). Additionally, once the cohort was segregated by their liver function above and below 2 mg/dL of total bilirubin, a significant difference was found in terms of long-term survival, for example, the patients with elevated bilirubin had reduced long-term survival (Figure 3, *A*). Elevated total bilirubin was more common among the LVAD + RVAD group (17%) and the LVAD + IV inotropes group (10.5%) than within the LVAD group (4.8%). Landmark analysis of the entire cohort at the first 100 days after transplantation and beyond reinforces the results of the study. In the first 100 days post-transplant RVAD, IV inotropes and bilirubin greater than 2 mg/dL are found to be factors associated with reduced survival, whereas they were not found as factors associated

TABLE 4. Unadjusted outcomes

Variable	LVAD N = 5155	LVAD + RVAD N = 106	LVAD + inotropes N = 344	*P* value	Missing values
Length of stay, d (IQR)	16 (11-23)	18 (13-32)	20 (13-33)	<.001	65
Death during first 100 d	293 (5.7%)	11 (10.4%)	30 (8.7%)	.01	0
Recipient cause of death					
Primary failure	51 (5.3%)	2 (7.1%)	4 (5.8%)	.89	0
Acute rejection	37 (3.8%)	0 (0.0%)	1 (1.4%)	.35	
Chronic rejection	19 (2.0%)	2 (7.1%)	0 (0.0%)	.07	
Infection	133 (13.7%)	3 (10.7%)	8 (11.6%)	.8	
Cardiovascular	160 (16.5%)	4 (14.3%)	16 (23.2%)	.34	
Pulmonary	70 (7.2%)	2 (7.1%)	3 (4.3%)	.66	
Cerebrovascular	65 (6.7%)	2 (7.1%)	2 (2.9%)	.46	
Hemorrhage	29 (3.0%)	1 (3.6%)	0 (0.0%)	.34	
Malignancy	79 (7.9%)	1 (3.6%)	5 (7.2%)	.70	
Liver failure	3 (0.3%)	0 (0.0%)	0 (0.0%)	.86	
Renal failure	14 (1.4%)	0 (0.0%)	1 (1.4%)	.81	
Multiple organ failure	86 (8.9%)	4 (14.3%)	5 (7.2%)	.54	

LVAD, Left ventricular assist device; *RVAD,* right ventricular assist device; *IQR,* interquartile range.

with reduced survival beyond the first 100 days post-transplant (Tables E3 and E4).

DISCUSSION

Patients with LVADs represent a growing number of patients undergoing transplantation worldwide. A small percentage of them undergo transplantation while having RVF and thus are supported by RVAD or IV inotropes. This added RV support increases their status on the heart waitlist to 1 or 3 of 7 categories, and they are prioritized for transplant (previously status 1A). We have used the UNOS registry to decipher whether their pretransplant condition affects their post-transplant long-term survival. We have demonstrated that their short-term survival is reduced compared with LVAD recipients without RVF, and that their postoperative hospitalization is also prolonged. However, neither RVAD nor IV inotropes were found to be an independent predictor of long-term reduced survival. Of note, the LVAD group with liver dysfunction was shown to have reduced long-term survival; the primary driver of difference in survival appears to be short-term, and long-term outcomes may be similar, although more data are needed. One should bear in mind that patients with LVAD + RVAD/IV inotropes with liver dysfunction who did not survive to transplant were not included in the cohort. This analysis suggests that although these patients are not optimal heart transplant candidates (reduced short-term survival), their long-term survival is not affected by their RVAD or IV inotropes or by their liver dysfunction; thus, their prioritization on the waiting list is justified and a good viable option. However, our analysis shows that LVAD recipients with liver failure should not be rushed to transplant because they have reduced long-term survival. Thus, future transplants in these patients should be performed following the recipient's optimization by inotropes or RVAD or using other means that will ameliorate liver dysfunction (future studies should verify this suggestion).

Liver dysfunction and increased bilirubin are considered risk factors for early death post-LVAD implantation and heart transplantation.[1,12] Moreover, RVF in LVAD recipients is associated with increased gastrointestinal bleeding and associated liver dysfunction.[13] Likewise, the significance of liver dysfunction in RV failure post-LVAD implantation was reemphasized when reports were published on the ability of the Model for End-Stage Liver Disease score to predict postoperative right heart failure and the necessity for RVAD implantation and increased postoperative mortality.[14,15] Although liver dysfunction can predict reduced survival post-LVAD implantation, if it improves during ventricular assist device support, postimplant survival is similar to that of patients without prior liver dysfunction.[16,17]

Thus, while trying to predict which LVAD recipient will experience RVF postimplant remains the holy grail of treating patients with heart failure,[18] our results show that if a BTT LVAD recipient experiences RVF and is in need for advanced support as inotropes or RVAD, the post-transplant long-term survival is not affected even if the patient has liver dysfunction. However, LVAD recipients with liver dysfunction should be optimized pretransplant to prevent long-term reduced survival.

Severe RVF requiring an RVAD occurs in 6% to 11% of LVAD recipients. These patients are more critically ill and have reduced short- and long-term survivals than patients supported with LVAD alone; furthermore, they have a higher rate for adverse events (eg, infection,

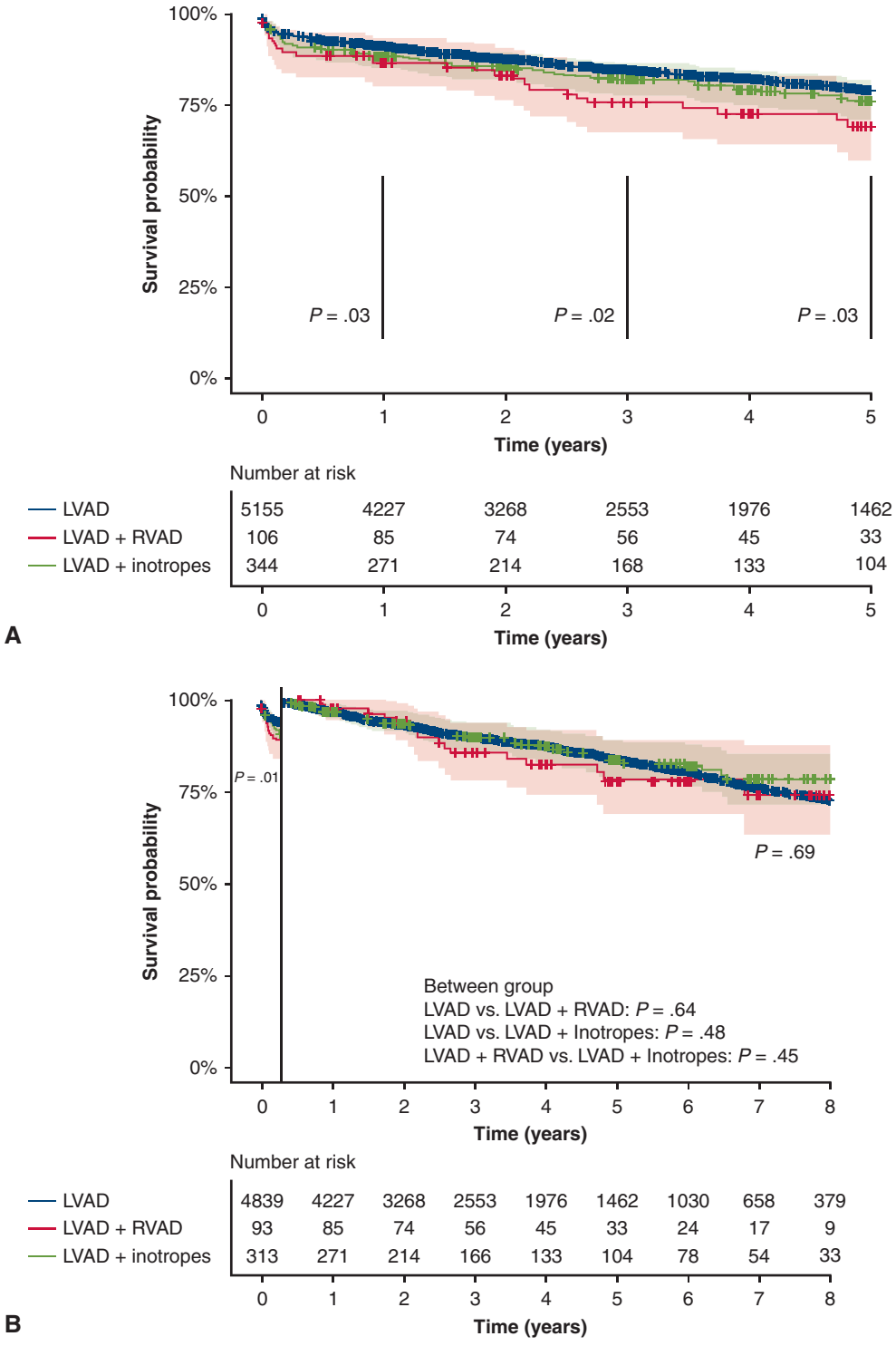

FIGURE 2. A, Kaplan–Meier analysis of short-term survival of recipients after heart transplantation in the entire cohort, stratified by the presence of RVAD/IV inotropes in a recipient with an LVAD. Number at risk table shown at the bottom. A significant survival difference is demonstrated between the groups. *P* value for the 3 groups' survival comparison at 1, 3, and 5 years is depicted (95% confidence limits Kaplan–Meier analysis is presented). B, Kaplan–Meier landmark analysis of long-term survival (the first 100 days and beyond) of recipients after heart transplantation in the entire cohort, stratified by the presence of RVAD/IV inotropes in a recipient with an LVAD. Number at risk table shown at the bottom. A significant survival difference can be seen between the groups in the first 100 days but not beyond (95% confidence limits Kaplan–Meier analysis is presented). *LVAD,* Left ventricular assist device; *RVAD,* right ventricular assist device.

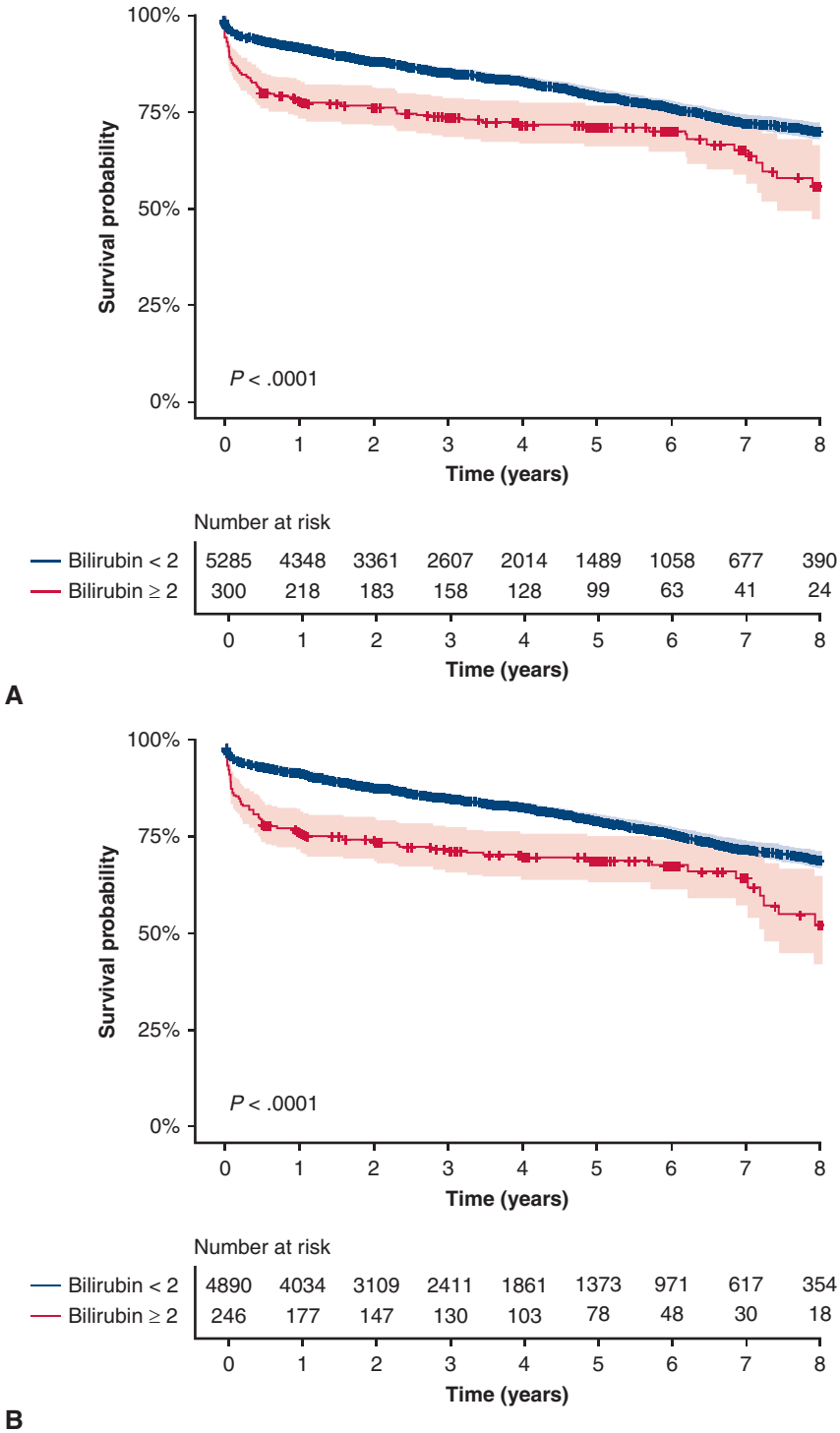

FIGURE 3. A, Kaplan–Meier analysis of long-term survival of recipients after heart transplantation in the entire cohort, segregated by their bilirubin level. Number at risk table shown at the bottom. A significant reduction in survival can be seen once the bilirubin level is above 2 (95% confidence limits Kaplan–Meier analysis is presented). B, Kaplan–Meier analysis of long-term survival of recipients after heart transplantation in the LVAD group segregated by their bilirubin level. Number at risk table shown at the bottom. A significant reduction in survival can be seen once the bilirubin level is above 2 (95% confidence limits Kaplan–Meier analysis is presented). C, Kaplan–Meier analysis of long-term survival of recipients after heart transplantation in the LVAD + RVAD and LVAD + IV inotropes groups. Number at risk table shown at the bottom (95% confidence limits Kaplan–Meier analysis is presented). No significant difference in survival was observed. *IV,* Intravenous; *LVAD,* left ventricular assist device; *RVAD,* right ventricular assist device.

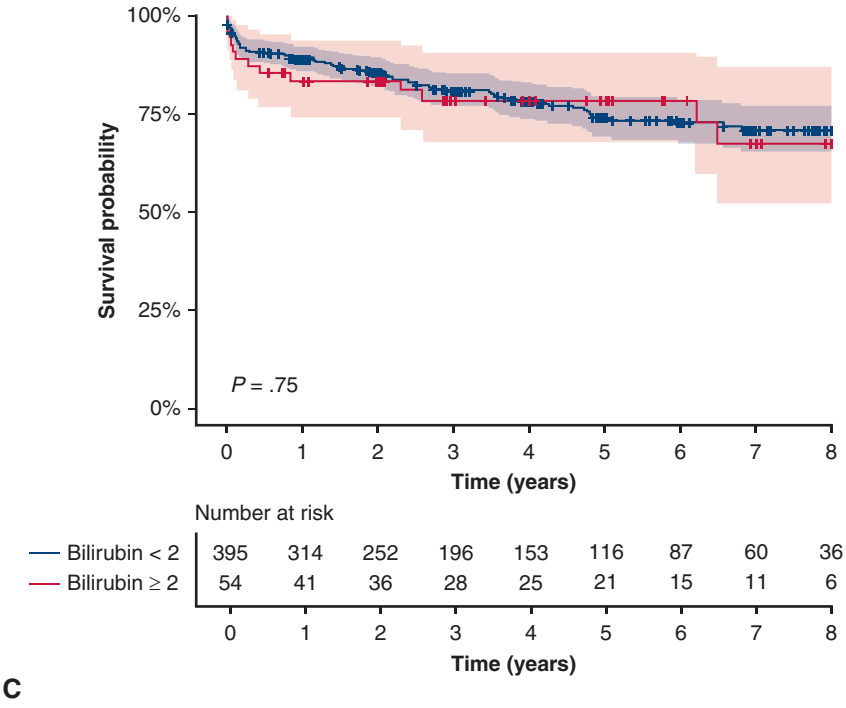

FIGURE 3. Continued.

bleeding, neurologic events, and device failure).[19] Unfortunately, current mechanical support options for the right heart are limited. Most commonly, a durable LVAD is combined with extracorporeal RVAD support (eg, Centrimag RVAD, Abbott Inc). This form of support may predispose patients to longer hospitalization because patients with these devices are not dischargeable. Furthermore, these extracorporeal devices may predispose the patient to infection because large cannulas exit the mediastinum. Previous reports are mixed as to the superiority of TAH or durable biventricular assist device as a treatment strategy.[20–26] In general, there is less experience with these forms of more durable right heart support. Nevertheless, efforts to develop more experience with right heart MCS, which enables hospital discharge and greater end-organ recovery, should be pursued and may lead to improved transplant outcomes.

Study Limitations

This study is limited because it is retrospective. In addition, we have no control over UNOS data quality. The UNOS registry also has some incomplete data in certain instances; however, because this is randomly scattered throughout both groups, it is unlikely to bias the results. Likewise, our study is limited by variables available in the UNOS registry. Primary graft dysfunction, for instance, is not reliably coded in the registry and consequently could not be used as an end point in our analysis, although this is of clinical interest. Furthermore, the time elapsed from the RVAD implant to the heart transplant and the timing of implant of the RVAD in regard to the LVAD implant are also missing. The UNOS database did not include information about right heart failure criteria, so we defined right heart failure according to strict criteria for the use of IV inotropes or RVAD. Our data uniquely reflect outcomes of those who survived until transplant; they do not reflect the validity of RVAD versus inotrope support as strategies for survival to transplantation. All patients in our cohort have undergone heart transplantation; thus, the comparison cannot predict a better BTT therapy. Moreover, this analysis considers only a highly selected group of patients and did not consider those on the waitlist who did not receive a transplant or those delisted.

Nevertheless, the UNOS registry contains information on 100% of organ transplants performed in the United States and therefore serves as a robust source of data. Finally, the Cox regression model is based on 2 smaller cohorts (LVAD + RVAD, LVAD + inotropes) and a larger cohort (LVAD); thus, it can lead to a type 2 error (failing to reject the null hypothesis of equal survival curves when in fact the curves are different).

TABLE 5. Cox regression long-term survival analysis

Predictor	HR	95.0% CI		*P* value
		Lower	Upper	
Recipient characteristics				
Pretransplant assist device				
LVAD	Ref	Ref	Ref	Ref
LVAD + RVAD	1.34	0.91	1.97	.14
LVAD + inotropes	1.03	0.81	1.33	.79
Gender mismatch	1.05	0.90	1.23	.49
Age (y)	1.005	0.99	1.01	.08
Total bilirubin >2 mg/dL	1.74	1.39	2.17	<.001
Ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.10	0.95	1.27	.21
Hispanic	0.86	0.65	1.13	.27
other	0.80	0.55	1.16	.23
IV antibiotics in 2 wk before transplant	1.18	1.00	1.40	.05
Diabetes	1.31	1.14	1.50	<.001
BMI	1.03	1.01	1.04	<.001
Donor/graft characteristics				
Ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.26	1.07	1.48	.005
Hispanic	1.20	1.00	1.44	.05
other	1.11	0.76	1.63	.58
Age (y)	1.01	1.00	1.02	.001
Ischemic time (h)	1.10	1.04	1.17	.001

BMI, Body mass index; *CI,* confidence interval; *HR,* hazard ratio; *ICU,* intensive care unit; *IV,* intravenous; *LVAD,* left ventricular assist device; *RVAD,* right ventricular assist device.

CONCLUSIONS

Patients with biventricular failure are prioritized on the waiting list because their critical pretransplant condition has limited impact on their post-transplant survival (short-term effect only); thus, surgeons should be confident to perform transplantation in these severely ill patients. Because liver dysfunction (a surrogate marker of RV failure) was found to affect long-term survival in LVAD recipients, surgeons should be encouraged to perform transplantation in these severely ill patients after the recipient's optimization by inotropes or RVAD because even when the bilirubin level is elevated in these patients (treated with RVAD/inotropes), their long-term survival is not affected. Future studies should assess recipients' optimization before organ acceptance to improve long-term survival.

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: heart transplantation, LVAD, RV failure, UNOS

TABLE E1. Recipient-related variables chosen for the Cox regression analysis

Variable	*P* value	Included
Female gender	.40	
Age (median, IQR)	<.001	V
BMI (median, IQR)	<.001	V
Ethnicity/Race		
White	.80	V
Black		
Hispanic		
Other		
History		
Diabetes	.85	V
Malignancy	.57	
Cerebrovascular disease	.75	
Creatinine (median, IQR)	.52	
Bilirubin (median, IQR)	<.001	V
Medical therapy		
IV antibiotics 2 wk from transplant	<.001	V
IV inotropes at transplant	<.001	
Ventilator support at transplant	<.001	
ABO blood type		
A	.53	
B		
AB		
O		
Days on waitlist (h, median, IQR)	<.001	

IQR, Interquartile range; *BMI,* body mass index; *IV,* intravenous.

TABLE E2. Donor-related variables chosen for the Cox regression analysis

Variable	*P* value	Included
Female gender	.81	
Gender mismatch	.22	V
Age (median, IQR)	.46	V
BMI (median, IQR)	.03	
Ethnicity/Race		
White	.06	V
Black		
Hispanic		
Other		
History		
Cigarette use	.20	
Cocaine use	.66	
Alcohol use	.32	
Diabetes	.13	
Hypertension	.48	
Cancer	.86	
Donor cause of death		
Anoxia	.21	
Cerebrovascular/stroke		
Head trauma		
CNS tumor		
Other		
ABO blood type		
A	.17	
B		
AB		
O		
HLA mismatch level		
0	.37	
1		
2		
3+		
Graft ischemic time (h, median, IQR)	.19	V

IQR, Interquartile range; *BMI,* body mass index; *CNS,* central nervous system; *HLA,* human leukocyte antigen; *IV,* intravenous.

TABLE E3. Cox regression long-term survival analysis beyond the first 100 days post-transplant

Predictor	HR	95% CI		*P* value
		Lower	Upper	
Recipient characteristics				
Pretransplant assist device				
LVAD	Ref	Ref	Ref	Ref
LVAD + RVAD	1.07	0.65	1.79	.78
LVAD + inotropes	0.85	0.61	1.18	.32
Gender mismatch	1.08	0.90	1.29	.43
Age (y)	0.99	0.99	1.00	.21
Total bilirubin >2 mg/dL	1.20	0.88	1.65	.24
Ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.13	0.95	1.35	.17
Hispanic	0.74	0.52	1.06	.10
other	0.83	0.54	1.30	.42
IV antibiotics in 2 wk before transplant	1.33	1.09	1.61	.004
Diabetes	1.48	1.25	1.74	<.001
BMI	1.02	1.00	1.03	.03
Donor/graft characteristics				
Ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.30	1.07	1.58	.01
Hispanic	1.26	1.01	1.57	.04
other	1.19	0.74	1.89	.47
Age (y)	1.01	1.00	1.02	.001
Ischemic time (h)	1.04	0.97	1.11	.31

HR, Hazard ratio; *CI,* confidence interval; *BMI,* body mass index; *LVAD,* left ventricular assist device; *RVAD,* right ventricular assist device; *ICU,* intensive care unit; *IV,* intravenous.

TABLE E4. Cox regression 100 days post-transplant survival analysis

Predictor	HR	95% CI		*P* value
		Lower	Upper	
Recipient characteristics				
Pretransplant assist device				
LVAD	Ref	Ref	Ref	Ref
LVAD + RVAD	1.95	1.05	3.61	.03
LVAD + inotropes	1.47	1.00	2.17	.05
Gender mismatch	0.99	0.76	1.31	.99
Age (y)	1.03	1.02	1.04	<.001
Total bilirubin >2 mg/dL	3.02	2.21	4.14	<.001
Ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.06	0.81	1.39	.68
Hispanic	1.13	0.74	1.74	.57
other	0.75	0.37	1.53	.43
IV antibiotics in 2 wk before transplant	0.87	0.63	1.21	.41
Diabetes	1.03	0.81	1.31	.79
BMI	1.05	1.02	1.07	<.001
Donor/graft characteristics				
Ethnicity				
White	Ref	Ref	Ref	Ref
Black	1.16	0.87	1.54	.32
Hispanic	1.09	0.79	1.51	.59
other	1.00	0.51	1.96	.99
Age (y)	1.01	0.99	1.02	.16
Ischemic time (h)	1.24	1.13	1.37	<.001

HR, Hazard ratio; *CI,* confidence interval; *LVAD,* left ventricular assist device; *RVAD,* right ventricular assist device; *IV,* intravenous; *BMI,* body mass index.