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.

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.
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).1,5 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).

Conflict 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 colleagues7 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 colleagues9 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 postoperative 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 study population was then stratified by the existence of severe RVF,11 which was defined as having a simultaneous temporary RV AD 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 E1 and 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/m², 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/m², 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](image-url)

**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/m²           | 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%)               | 0       | 0             |
| Hispanic                          | 354 (6.9%)    | 8 (7.5%)            | 22 (6.4%)                | 0       | 0             |
| Other                             | 199 (3.9%)    | 6 (5.7%)            | 9 (2.6%)                 | 0       | 0             |
| 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%)               | 0       | 0             |
| AB                                | 215 (4.2%)    | 6 (5.7%)            | 13 (3.8%)                | 0       | 0             |
| O                                 | 2163 (42.0%)  | 48 (45.3%)          | 149 (43.3%)              | 0       | 0             |
| 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). 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                               | <.001       | –               |
| LVAD + RVAD                       | <.001       | 0.04            |
| Creatinine                        | 0.24        | –               |
| LVAD + inotropes                  | 0.31        | 0.15            |
| BMI                               | <.001       | –               |
| LVAD + RVAD                       | <.001       | –               |
| LVAD + inotropes                  | 0.94        | <.001           |
| Bilirubin                         | <.001       | –               |
| LVAD + RVAD                       | <.001       | –               |
| LVAD + inotropes                  | <.001       | 0.02            |
| Days on waitlist (h, median, IQR) | <.001       | –               |
| LVAD + RVAD                       | <.001       | –               |
| LVAD + inotropes                  | <.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...
and having diabetes (HR, 1.31; 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 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%)               | .66          | 90            |
| Hispanic                              | 700 (13.6%)   | 19 (17.9%)          | 52 (15.1%)               | .32          | 109           |
| Other                                 | 132 (2.6%)    | 7 (6.6%)            | 6 (1.7%)                 | .86          | 27            |
| 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%)               | .61          | 17            |
| Head trauma                           | 2629 (51.0%)  | 59 (55.7%)          | 174 (50.6%)              | .13          | 24            |
| CNS tumor                             | 22 (0.4%)     | 2 (1.9%)            | 1 (0.3%)                 | .86          | 27            |
| Other                                 | 98 (1.9%)     | 0 (0.0%)            | 6 (1.7%)                 | .86          | 27            |
| 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%)                | .37          | 627           |
| AB                                    | 77 (1.5%)     | 1 (0.9%)            | 3 (0.9%)                 | .37          | 627           |
| O                                     | 2659 (51.6%)  | 60 (56.6%)          | 178 (51.7%)              | .19          | 42            |
| 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%)                 | .37          | 627           |
| 2                                     | 135 (3.0%)    | 2 (2.0%)            | 12 (3.8%)                | .37          | 627           |
| 3+                                    | 4399 (96.4%)  | 99 (98.0%)          | 300 (94.9%)              | .19          | 42            |
| 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.
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. Moreover, RVF in LVAD recipients is associated with increased gastrointestinal bleeding and associated liver dysfunction. 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. 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.

Thus, while trying to predict which LVAD recipient will experience RVF postimplant remains the holy grail of treating patients with heart failure, 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.
bleeding, neurologic events, and device failure). Unfortunately, current mechanical support options for the right heart are limited. Most commonly, a durable LVAD is combined with extracorporeal RVAD support (eg, Centri
cmag RVAD, Abbott Inc). This form of support may predis
pose 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 strat-
egy. 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 addi-
tion, 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 conse-
sequently 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 pa-
tients 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).
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 RV AD 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 editors and reviewers of this article have no conflicts of interest.

References

1. Colvin M, Smith JM, Hadley N, Skeans MA, Carrico R, Uccellini K, et al. OPTN/SRTR 2016 annual data report: heart. Am J Transplant. 2018;18(Suppl 1): 291-362.
2. Kirklin JK, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, et al. Eighth annual INTERMACS report: special focus on framing the impact of adverse events. J Heart Lung Transplant. 2017;36:1080-6.
3. Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes D Jr, Kucheryavaya AY, et al. International society for heart and lung transplantation. The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-fifth adult heart transplantation report-2018; focus theme: multiorgan transplantation. J Heart Lung Transplant. 2018;37:1155-68.
4. Pagani FD, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, et al. HeartMate II investigators. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. J Am Coll Cardiol. 2009;54:312-21.
5. Harjola VP, Melbzaaz A, Čelutkiene J, Bettes D, Bueno H, Chioncel O, et al. Contemporary management of acute right ventricular failure: a statement from the heart failure association and the working group on pulmonary circulation and right ventricular function of the European Society of Cardiology. Eur J Heart Fail. 2016;18:226-41.
6. Criteria for medical urgency status, heart. 2018. Accessed January 16, 2019. https://optn.transplant.hrsa.gov/media/2414/adult_heart_infographic.pdf
7. Urban M, Pirk J, Szarszoi O, Besik J, Netuka I. Post-heart transplantation outcome of HeartMate II-bridged recipients requiring unplanned concomitant temporary right ventricular mechanical support. *Interact Cardiovasc Thorac Surg*. 2015;20:372-8.

8. Grimm JC, Sciortino CM, Magruder JT, Dungan SP, Valero V III, Sharma K, et al. Outcomes in patients bridged with univentricular and biventricular devices in the modern era of heart transplantation. *Ann Thorac Surg*. 2016;102:102-8.

9. Carier KT, O’Brien R, Larson SB, Creswell LL, Katcher M, Baran DA, et al. Veno-arterial extracorporeal membrane oxygenation is a viable option as a bridge to heart transplant. *J Thorac Cardiovasc Surg*. 2022;163:e140-7-e4.

10. Pisters A, Smith J, Hess T, Pham D, Baber A, Fiedler A, et al. Abstract 14118: new heart transplant allocation tier system and clinical outcomes. *Circulation*. 2019;140:A14118.

11. INTERMACS adverse event definitions: adult and pediatric patients, manual of operations version 5.0, appendix A: adverse event definitions. Accessed January 1, 2020. https://www.uab.edu/medicine/intermacs/intermacs-documents

12. Maltais S, Stulak JM. Right and left ventricular assist devices support and liver dysfunction: prognostic and therapeutic implications. *Curr Opin Cardiol*. 2016;31:287-91.

13. Sparrow CT, Nassif ME, Raymer DS, Novak E, LaRue SJ, Schilling JD. Preoperative right ventricular dysfunction is associated with gastrointestinal bleeding in patients supported with continuous-flow left ventricular assist devices. *JACC Heart Fail*. 2015;3:956-64.

14. Deo SV, Daly RC, Altarabsheh SE, Hasin T, Zhao Y, Shah IK, et al. Predictive value of the model for end-stage liver disease score in patients undergoing left ventricular assist device implantation. *ASAIO J*. 2013;59:57-62.

15. Youm GL, Coyle L, Bhat G, Tatoolees AJ. Model for end-stage liver disease in patients with left ventricular assist devices. *J Artif Organs*. 2016;19:21-8.

16. Majumder K, Spratt JR, Holley CT, Roy SS, Cogswell RJ, Liao K, et al. Impact of postoperative liver dysfunction on survival after left ventricular assist device implantation. *Ann Thorac Surg*. 2017;104:1556-62.

17. Yang JA, Kato TS, Shulman BP, Takayama H, Farr M, Jorde UP, et al. Liver dysfunction as a predictor of outcomes in patients with advanced heart failure requiring ventricular assist device support: use of the model of end-stage liver disease (MELD) and MELD excluding INR (MELD-XI) scoring system. *J Heart Lung Transplant*. 2012;31:601-10.

18. Bellavia D, Iacovoni A, Scardulla C, Moja L, Filato M, Kushwaha SS, et al. Prediction of right ventricular failure after ventricular assist device implant: systematic review and meta-analysis of observational studies. *Eur J Heart Fail*. 2017;19:926-46.

19. Cleveland JC Jr, Naftel DC, Reece TB, Murray M, Antaki J, Pagani FD, et al. Survival after biventricular assist device implantation: an analysis of the interagency registry for mechanically assisted circulatory support database. *J Heart Lung Transplant*. 2011;30:862-9.

20. Fitzpatrick JR III, Frederick JR, Hiesinger W, Hsu VM, McCormick RC, Kozin ED, et al. Early planned institution of biventricular mechanical circulatory support results in improved outcomes compared with delayed conversion of a left ventricular assist device to a biventricular assist device. *J Thorac Cardiovasc Surg*. 2009;137:971-7.

21. Shah P, Hu R, Singh R, Cotts W, Adler E, Kiernan M, et al. Multicenter experience with durable biventricular assist devices. *J Heart Lung Transplant*. 2018;37:1093-101.

22. Cheng A, Trivedi JR, Van Berkel VH, Massey HT, Slaughter MS. Comparison of total artificial heart and biventricular assist device support as bridge-to-transplantation. *J Card Surg*. 2016;31:648-53.

23. Levin AP, Jaramillo N, Garan AK, Takeda K, Takayama H, Yuzefpolskaya M, et al. Outcomes of contemporary mechanical circulatory support device configurations in patients with severe biventricular failure. *J Thorac Cardiovasc Surg*. 2016;151:530-5.e2.

24. Creaser JW, Rourke D, Vandenbogaart E, Chaker T, Nsair A, Cheng R, et al. Outcomes of biventricular mechanical support patients discharged to home to await heart transplantation. *J Cardiovasc Nurs*. 2015;30:E13-20.

25. Holman WL, Kormos RL, Naftel DC, Miller MA, Pagani FD, Blume E, et al. Predictors of death and transplant in patients with a mechanical circulatory support device: a multi-institutional study. *J Heart Lung Transplant*. 2009;28:44-50.

26. Cheng RK, Deng MC, Tseng CH, Shemin RJ, Kubak BM, MacLellan WR. Risk stratification in patients with advanced heart failure requiring biventricular assist device support as a bridge to cardiac transplantation. *J Heart Lung Transplant*. 2012;31:831-8.

**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              |         |          |
| 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.
| Predictor                                | HR   | 95% CI Lower | 95% CI Upper | P value |
|-----------------------------------------|------|--------------|--------------|---------|
| **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 | Lower 95% CI | Upper 95% CI | P value |
|----------------------------------------|----|--------------|--------------|---------|
| **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.