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ORIGINAL ARTICLE

Use of Extracorporeal Membrane Oxygenation as Bridge to Replacement Therapies in Cardiogenic Shock: Insights From the Extracorporeal Life Support Organization

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BACKGROUND: There has been increasing use of extracorporeal membrane oxygenation (ECMO) as bridge to heart transplant (orthotopic heart transplant [OHT]) or left ventricular assist device (LVAD) over the last decade. We aimed to provide insights on the population, outcomes, and predictors for the selection of each therapy.

METHODS: Using the Extracorporeal Life Support Organization Registry between 2010 and 2019, we compared in-hospital mortality and length of stay, predictors of OHT versus LVAD, and predictors of in-hospital mortality for patients with cardiogenic shock that were bridged with ECMO to OHT or LVAD. One hundred sixty-seven patients underwent LVAD versus 234 patients who underwent OHT.

RESULTS: The overall use of ECMO has increased from 1.7% in 2010 to 22.2% in 2019. Mortality was similar between groups (LVAD: 28.7% versus OHT: 29.1%) while length of stay was longer for OHT (LVAD: 49.6 versus OHT: 59.5 days, *P*=0.05). Factors associated with OHT included prior transplant (odds ratio [OR]=31.26 [CI, 3.84–780.5]), use of a temporary pacemaker (OR=6.5 [CI, 1.39–50.15]), and increased use of inotropes on ECMO (OR=3.77 [CI, 1.39–11.07]), whereas LVAD use was associated with weight (OR=0.98 [CI, 0.97–0.99]), cardiogenic shock presentation (OR=0.40 [CI, 0.21–0.78]), previous LVAD (OR=0.01 [CI, 0.0001–0.22]), respiratory failure (OR=0.28 [CI, 0.11–0.70]), and milrinone infusion (OR=0.32 [CI, 0.15–0.67]). Older age (OR=1.07 [CI, 1.02–1.12]), cannulation bleeding (OR=26.1 [CI, 4.32–221.3]), and surgical bleeding (OR=6.7 [CI, 1.26–39.9]) in patients receiving LVAD and respiratory failure (OR=5 [CI, 1.17–23.1]) and continuous renal replacement therapy (OR=3.82 [CI, 1.28–11.9]) in patients receiving OHT were associated with increased mortality.

CONCLUSIONS: ECMO use as a bridge to advanced therapies has increased over time, with more patients undergoing LVAD than OHT. Mortality was equal between the 2 groups while length of stay was longer for OHT.

Key Words: extracorporeal membrane oxygenation ■ heart-assisted devices ■ length of stay ■ mortality ■ shock, cardiogenic ■ transplant

Despite the historical use of extracorporeal membrane oxygenation (ECMO) for refractory respiratory failure, its use for cardiac indications, including multifactorial cardiogenic shock (CS), cardiac arrest, and postcardiotomy shock, has become increasingly common in the last decade.[1] Recent data from the Extracorporeal Life Support Organization (ELSO) demonstrate that the use of ECMO for cardiac indications has rapidly increased by 1180% over the past 15 years.[1] In addition, the number of ECMO centers has seen a parallel increase from 135 in 2007 to

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WHAT IS NEW?

- There is increased use of extracorporeal membrane oxygenation as bridged to heart replacement therapies in recent years.
- Mortality appears equal between the 2 groups around 30% and different predictors are associated for each subgroup.
- Length of stay was shorter for left ventricular assist device recipients despite being sicker before left ventricular assist device implantation.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Heart replacement therapies from extracorporeal membrane oxygenation support are feasible and have recently increased. Outcomes are comparable between the 2 strategies.
- Careful selection of these patients is needed as overall mortality still remains high despite advances in cardiogenic shock management.
- Prospective studies are needed; however, it is unlikely to occur due to the severity of the patient's disease.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
CS	cardiogenic shock
ECMO	extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
ICD	*International Classification of Diseases*
LOS	length of stay
LVAD	left ventricular assist device
OHT	orthotopic heart transplant
OR	odds ratio

463 centers in 2019 representing a 242% increase.[2] Yet, it remains a complex, expensive therapy and is associated with high rates of detrimental complications.[3] In addition, it requires significant technical expertise and personnel infrastructure for its successful deployment and maintenance. This is important since ECMO does not provide etiologic treatment for the underlying condition; rather, it provides a bridge to patient recovery or to a more definite solution. This notion of a bridge therapy is highlighted in a recent scientific Expert Panel.[1]

Previous studies have shown an increased risk of in-hospital and long-term mortality in patients that are bridged to orthotopic heart transplant (OHT) with ECMO (28.8% at 1 year) or percutaneous temporary left ventricular assist devices (LVADs; 20.1% at 1 year).[4,5] Given existing concerns related to resource utilization and timing in an ECMO to transplant strategy, the alternative ECMO to LVAD strategy has arisen as a plausible option. There is a scarcity of descriptive data for this critically ill cohort of patients despite the rise in ECMO as an option for profound CS. Thus, the aim of this study is to describe the demographics, comorbidities, initial presentation (CS, acute coronary syndrome [ACS], cardiac arrest, etc), hemodynamics, ECMO-related complications, and outcomes for patients with CS treated with ECMO that ultimately go onto OHT versus LVAD.

METHODS

Data Source

ELSO is an organization committed to the advancement and optimal use of extracorporeal life support therapies across international member centers. ELSO maintains a patient registry with clinical and outcome data for the purposes of quality improvement and research, available to member centers and contains data for >125 000 patients worldwide.[6,7] A map of the participating centers for ELSO can be found at https://www.elso.org/Membership/CenterMap.aspx. Institutional review board approval was waived due to the nature of the study. The data are collected by a standardized collection form that includes demographic and clinical information, hemodynamics, diagnoses by means of *International Classification of Diseases, Ninth and Tenth Revisions* (*ICD-9* and *ICD-10*), procedures coded by Current Procedures Terminology codes, ECMO indications, ECMO-related information, pre-ECMO medical and mechanical support, ECMO-related complications, duration of hospital stay, and in-hospital mortality. The authors declare that all supporting data are available within the article.

Patient Population

For this study, we queried the ELSO Registry between 2010 and 2019 to identify adult patients (≥18 years of age) with CS treated with ECMO as a bridge to OHT or durable LVAD (Figure 1). Four patients that received both OHT and LVAD during the same admission were excluded from the analysis. For patients with 2 ECMO runs in 2 separate hospitalizations (7 unique IDs in the data set) during the study period, we included only the hospitalization leading to advances therapies. Nine patients had 2 runs of ECMO during the same hospitalization (either before, during, or after LVAD/OHT) for which we included only one run was included. Finally, 4 for patients with duplicate entries only one entry was used.

Outcomes and Statistical Analysis

Descriptive statistics were provided for all variables: mean and SD for continuous variables, frequency, and percentage for categorical variables. We compared demographics, comorbid conditions, hemodynamics, pre-ECMO support, ECMO-related information, ECMO complications, in-hospital mortality, and length of stay (LOS) between the 2 groups using Student *t* tests (continuous variables) and Pearson χ^2 tests (categorical variables). Hemodynamic parameters were available for a fraction of patients.

We performed multivariable logistic regression to find predictors of undergoing OHT (versus LVAD) with predictors identified with $P<0.05$ from univariate logistic regression.

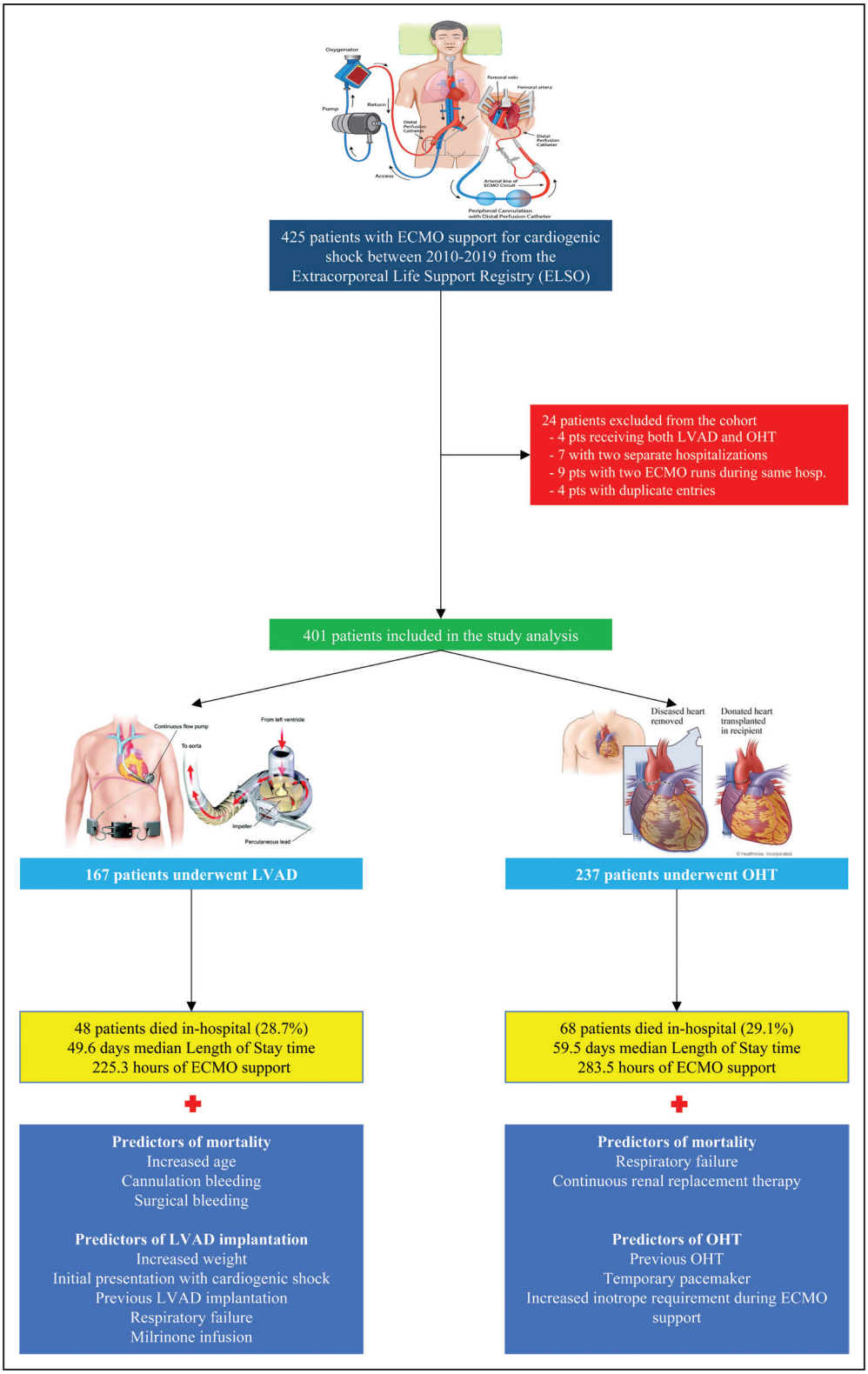

Figure 1. Patients from the Extracorporeal Life Support Organization (ELSO) registry undergoing orthotopic heart transplant (OHT) vs left ventricular assist device (LVAD) implantation: study flow, outcomes, and predictors.
ECMO indicates extracorporeal membrane oxygenation.

We also performed logistic regression analysis to identify predictors of survival within each isolated group (LVAD and OHT). To address missing values, we used imputation with 5 nearest neighbors and excluded predictor variables with >20% missing from the analyses. Sensitivity analysis was conducted to examine the effect of imputation using

unimputed data to ensure the direction and significance of the findings were unchanged. As a secondary analysis, we limited to patients with no missing data for the variables cardiac index, mean blood pressure, mean pulmonary artery pressure, and pH and performed a penalized regression (Least Absolute Shrinkage and Selection Operator) to select features that had a significant relationship with OHT versus LVAD.[8] We then performed logistic regression analysis using the selected features to interpret the predictors of getting OHT versus LVAD within this subgroup. All statistical tests are 2 sided and at a significance level of 0.05. All analyses were conducted with R software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The initial registry query yielded 425 patients with a diagnosis of CS bridged with ECMO to either OHT or LVAD between the years 2010 and 2019. After exclusions, our final data set included 401 patients. Among these, 167 patients underwent LVAD implantation, and 234 underwent OHT during their hospitalization (Figure 1). Among the total number of ECMOs in our study, most cases occurred between the years 2016 to 2019. Of the 401 patients, only 1.7% had received ECMO support in 2010 with that percentage increasing to 22.2% in 2019 ($P<0.01$; Figure 2). Similar trends have been observed for each strategy individually with increased utilization as bridging strategy towards OHT (from 3% to 15.4%) and LVAD (from 0% to 31.7%) groups over the last decade. While the percentage of OHTs occurring from 2010 until 2016 was higher than LVADs, there was an abrupt increase in the percentage of LVADs implants between 2017 and 2019 surpassing the numbers of OHTs performed.

Demographics and Comorbidities at Baseline

The mean cohort age was 47.8±14.1 years, mean weight was 82.8±21.9 kg, 29.2% were women, and 56.4% were Whites. Overall, 10.4% had prior history of CAD, 44.4% history of previous cardiomyopathy diagnosis, 4.7% with myocarditis, 3% with LVAD presence, and 7.6% history of prior heart transplant. The full set of demographic differences are presented in Table 1. Compared with OHT patients, those who underwent LVAD implantation were more likely to be older (50.5 versus 42.7 years; $P<0.01$) and have increased weight (88.8 versus 78.3 kg; $P<0.01$). In addition, they were more likely to have a history of previous LVAD implantation (6.5% versus 0.4%; $P<0.01$), coronary artery disease (14.9% versus 7.5%; $P=0.02$), tobacco abuse (3.6% versus 0%; $P=0.01$), and malnutrition (3% versus 0%; $P=0.03$). In contrast, patients that received OHT were more likely to have a history of previous cardiomyopathy diagnosis (49.2% versus 37.5%, $P=0.01$) and history of cardiac transplantation (12.5% versus 0.6%; $P<0.01$).

Initial Presentation and Hemodynamics

Overall, 53.6% of the cohort presented with CS, 22.4% with cardiac arrest, 15% with ACS, 19.2% with acute kidney injury, and 5.9% with cardiac transplant complications (Tables 1 and 2). Patients that underwent LVAD implantation were more likely to present with ACS (24.4% versus 7.9%, $P<0.01$), acute kidney injury (25% versus 15%; $P=0.02$), cardiac arrest (28.6% versus 17.5%; $P=0.01$), cardiogenic (73.8% versus 37.9%; $P<0.01$) or septic shock (4.8% versus 0.4%; $P=0.01$), and respiratory failure (32.7% versus 14.6%; $P<0.01$), whereas patients that received OHT were more likely to

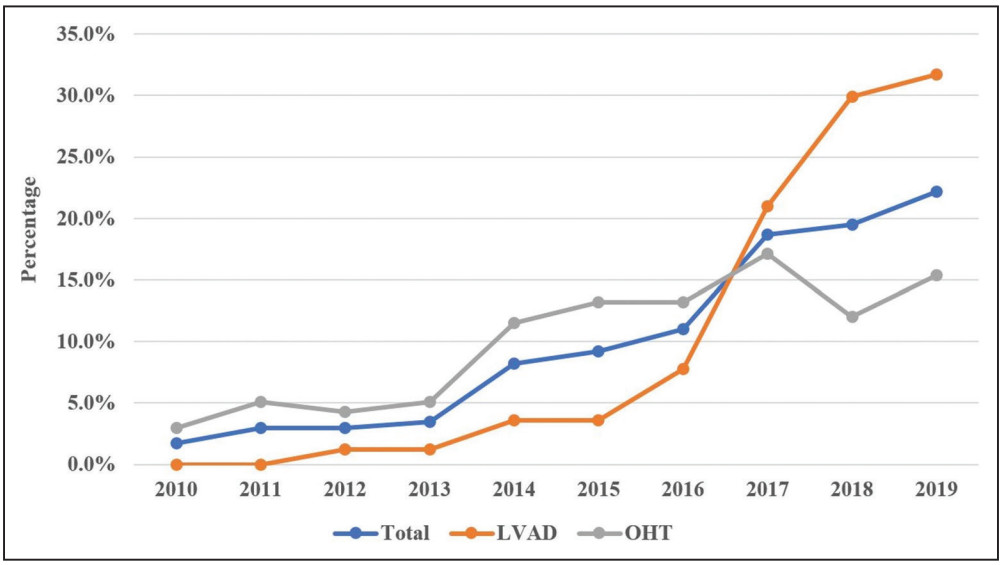

Figure 2. Yearly distribution (%) of extracorporeal membrane oxygenation (ECMO) use (1) in all ECMO patients and (2) by strategy group (left ventricular assist device [LVAD] vs orthotopic heart transplant [OHT]).
The diagram demonstrates that the majority of ECMO cases in the cohort occurred in recent years.

Table 1. Baseline Demographic and Clinical Characteristics

Demographics/characteristics	All ECMO, N=401	LVAD, N=167	Transplant, N=234	*P* value
Demographics				
Age, y (SD)	47.8±14.1	50.5±14.1	42.7±13.8	<0.01
Weight, kg (SD)	82.8±21.9	88.8±22.5	78.3±20.3	<0.01
Female	117 (29.2)	44 (26.3)	73 (31.2)	0.26
Race and ethnicity				<0.01
White	226 (56.4)	106 (63.5)	120 (51.3)	
Black	42 (10.5)	22 (13.2)	20 (8.5)	
Asian	64 (16.0)	11 (6.6)	53 (22.6)	
Hispanic	19 (4.7)	6 (3.6)	13 (5.6)	
Comorbidities				
Coronary artery disease	42 (10.4)	25 (14.9)	18 (7.5)	0.02
Cardiomyopathy	178 (44.4)	60 (37.5)	118 (49.2)	0.01
Myocarditis	19 (4.7)	6 (3.6)	13 (5.4)	0.52
Valvular disease	21 (5.2)	10 (6)	11 (4.7)	0.73
Congenital heart disease	7 (1.7)	0 (0)	7 (2.9)	0.06
Arrhythmias	58 (14.5)	24 (14.3)	34 (14.2)	NS
AF/flutter	33 (8.2)	16 (9.6)	17 (7.3)	
Bradycardia	1 (0.2)	1 (0.6)	0 (0)	
Atrioventricular block	4 (1)	1 (0.6)	3 (1.3)	
Supraventricular tachycardia	8 (2)	2 (1.2)	6 (2.6)	
NSVT	7 (1.7)	2 (1.2)	5 (2.1)	
Hx of heart transplant	31 (7.6)	1 (0.6)	30 (12.5)	<0.01
LVAD presence	12 (3)	11 (6.5)	1 (0.4)	<0.01
Hx of ECMO	3 (0.7)	3 (1.8)	0 (0)	0.13
Endocarditis	4 (1)	0 (0)	4 (1.7)	0.24
Hypertension	22 (5.5)	11 (6.6)	11 (4.7)	0.55
Hyperlipidemia	18 (4.5)	8 (4.8)	10 (4.3)	0.99
Diabetes	39 (9.7)	21 (12.5)	18 (7.5)	0.12
CKD/ESRD	33 (8.1)	15 (8.9)	18 (7.5)	0.50
COPD	11 (2.)	7 (4.2)	4 (1.7)	0.22
Encephalopathy/neurological disorder	28 (7)	14 (8.4)	14 (5.9)	0.45
Cerebrovascular accident	6 (1.5)	2 (1.2)	4 (1.7)	NS
Anemia	24 (6)	10 (6)	14 (5.8)	0.98
Thrombocytopenia	13 (3.2)	7 (4.2)	6 (2.5)	0.51
Coagulopathy	17 (4.2)	8 (4.8)	10 (4.2)	0.96
Bleeding	19 (4.7)	6 (3.6)	13 (5.4)	0.53
Cancer	10 (2.2)	7 (4.2)	3 (1.2)	0.38
Malnutrition	5 (1.2)	5 (3)	0 (0)	0.03
Drug abuse	3 (0.7)	3 (1)	0 (0)	0.14
Tobacco abuse	6 (1.5)	6 (3.6)	0 (0)	0.01
Alcohol abuse	2 (0.5)	2 (1.2)	0 (0)	0.34
Initial presentation				
Acute coronary syndrome	60 (15)	41 (24.4)	19 (7.9)	<0.01
Cardiogenic shock	215 (53.6)	124 (73.8)	91 (37.9)	<0.01
Cardiac arrest	90 (22.4)	48 (28.6)	42 (17.5)	0.01
Cardiac transplant rejection/complication	24 (5.9)	0 (0)	24 (9.8)	<0.01

AF indicates atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; Hx, history; LVAD, left ventricular assist device; NS, nonsignificant; and NSVT, nonsustained ventricular tachycardia.

Table 2. End-Organ Function on Presentation

End-organ function on presentation	All ECMO, N=401	LVAD, N=167	Transplant, N=234	*P* value
AKI	77 (19.2)	42 (25)	35 (15)	0.02
AKI requiring replacement therapy	21 (5.2)	13 (7.8)	8 (3.4)	0.08
Respiratory failure	90 (22.4)	55 (32.7)	35(14.6)	<0.01
Acid base disturbances	17 (4.2)	11 (6.5)	6 (2.5)	0.08
Liver injury	22 (5.5)	12 (7.1)	10 (4.2)	0.28

AKI indicates acute kidney injury; ECMO, extracorporeal membrane oxygenation; and LVAD, left ventricular assist device.

present with cardiac transplant rejection/complications (9.8% versus 0%; *P*<0.01).

With regards to hemodynamic parameters on presentation, the mean systolic pulmonary arterial pressure was 41.9±13.4 mm Hg, the mean pulmonary artery pressure was 31.5±9.2 mm Hg, the pulmonary artery wedge pressure was 22.6±9.2 mm Hg, and cardiac index was 2.16±1.7 L/min per m^2. Hemodynamic parameters did not differ significantly between the 2 groups with the exception of lower diastolic blood pressure (53.9 versus 58.6 mm Hg; *P*<0.05) and mean arterial pressure (63.2 versus 69.2 mm Hg; *P*<0.01) which were lower in the transplant group. The hemodynamic profile differences on presentation (before ECMO) are shown in Table 3.

Pre-ECMO Support, ECMO Specifications, and Complications

Pre-ECMO medical and mechanical support is illustrated in Table 4. Patients who underwent LVAD implantation were more likely to require to be supported with milrinone (34.7% versus 19.7%; *P*=0.01), norepinephrine (45.5% versus 32.5%; *P*=0.01), vasopressin (16.8% versus 5.6%; *P*<0.01), and percutaneous LVAD (21.6% versus 3%; *P*<0.01). Conversely, patients that received OHT were more likely to be supported with dopamine infusion (21.8% versus 10.8%; *P*<0.01) and receive a temporary pacemaker (12% versus 5.4%; *P*=0.04) compared with their counterparts. There were no differences between when we compared the groups ≥2 pressors infusions (*P*=0.13), ≥2 inotropes (*P*=0.20), and ≥3 vasoactive medications (*P*=0.80).

Veno-arterial ECMO was the most common configuration used (88%) in the cohort, whereas conversion from veno-venous to veno-arterial configuration was the second most frequent (6%). Importantly, 27.4% of patients had cardiac arrest before deployment (whether on presentation or in-hospital), more commonly occurring in the LVAD group as compared to OHT (35.3% versus 21.8%, *P*<0.01). Advanced therapies (OHT and LVAD) during ECMO support (80.5%) were more frequent than those after ECMO wean (19.5%), as shown in Table 5. Finally, there were 9 patients that required ECMO support after OHT. Of those, 2 patients were decannulated before OHT. There were no patients that were supported with ECMO post-LVAD implantation.

Renal replacement therapy (23.4%), surgical site bleeding (14.7%), worsening kidney function (14.7%),

Table 3. Hemodynamics, Cardiac Indices, and Related Labs

Hemodynamics/labs	All ECMO, N=401	LVAD, N=167	Transplant, N=234	*P* value
Systolic blood pressure, mm Hg	87.1±21.8	89.4±21.9	85.2±21.6	0.12
Diastolic blood pressure, mm Hg	56.0±15.5	58.6±17.5	53.9±13.4	0.01
Mean blood pressure, mm Hg	65.7±16.8	69.2±17.9	63.2±15.6	0.01
Systolic pulmonary artery pressure, mm Hg	41.9±13.4	43.8±12.9	39.7±13.8	0.12
Diastolic pulmonary artery pressure, mm Hg	25.0±8.1	25.7±7.9	24.2±8.3	0.33
Mean pulmonary artery pressure, mm Hg	31.5±9.2	32.9±9.1	29.8±9.2	0.11
Pulmonary capillary wedge pressure, mm Hg	22.6±9.2	24.9±8.6	20.0±9.6	0.18
Cardiac index, L/min per m^2	2.16±1.7	1.9±0.68	2.4±2.5	0.40
SvO_2, %	55.7±19.3	53.9±18.2	57.1±20.2	0.50
pH (initial)	7.33±0.15	7.32±0.17	7.34±0.14	0.24
pH (24 h)	7.45±0.07	7.45±0.07	7.45±0.08	0.88
HCO_3 (initial), mEq/L	21.0±6.0	20.2±5.7	21.5±6.2	0.10
HCO_3 (24 h), mEq/L	25.8±4.3	26.2±3.7	25.6±4.7	0.20
Sao_2 (initial), %	92.1±14.2	92.6±13.8	91.8±14.7	0.68
Sao_2 (24 h), %	97.7±5.9	97.7±2.2	97.8±2.6	0.88

ECMO indicates extracorporeal membrane oxygenation; HCO_3, serum bicarbonate level; LVAD, left ventricular assist device; Sao_2, arterial oxygen saturation; and SvO_2, pulmonary artery oxygen saturation.

Table 4. Pre-ECMO Support

Support	All ECMO, N=401	LVAD, N=166	Transplant, N=234	*P* value
Inotropes/pressors				
Dobutamine	107 (27.0)	41 (24.6)	66 (28.2)	0.48
Dopamine	69 (17.2)	18 (10.8)	51 (21.8)	<0.01
Milrinone	104 (25.9)	58 (34.7)	46 (19.7)	0.01
Norepinephrine	152 (37.9)	76 (45.5)	76 (32.5)	0.01
Epinephrine	162 (40.3)	71 (42.5)	91 (38.9)	0.53
Phenylephrine	17 (4.2)	17 (10.2)	0 (0)	<0.01
Vasopressin	41 (10.2)	28 (16.8)	13 (5.6)	<0.01
≥2 inotropes	57 (14.2)	20 (12.0)	37 (15.8)	0.20
≥2 pressors	138 (34.4)	66 (39.8)	72 (30.8)	0.13
≥3 vasoactive medication	142 (35.4)	62 (37.3)	80 (34.2)	0.80
Additional medical support				
Nitroprusside	9 (2.2)	5 (3)	4 (1.7)	0.60
Nitroglycerin	6 (1.4)	4 (2.4)	2 (0.9)	0.40
Nitric oxide	26 (6.5)	8 (4.8)	18 (7.7)	0.33
Inhaled epoprostenol	7 (1.7)	3 (1.8)	4 (1.7)	NS
Prostacyclin analogues	4 (1)	2 (1.2)	2 (0.9)	NS
Neuromuscular blockers	51 (12.7)	24 (14.4)	27 (11.5)	0.49
Intravenous systemic steroids	20 (5.0)	6 (3.6)	14 (6)	0.39
Intravenous bicarbonate	43 (10.7)	22 (13.2)	21 (9)	0.23
Temporary pacemaker	37 (9.2)	9 (5.4)	28 (12)	0.04
Mechanical circulatory support				
IABP	88 (21.9)	23 (23.4)	65 (27.8)	0.37
Percutaneous LVAD	43 (10.7)	36 (21.6)	7 (3)	<0.01
Cardiopulmonary bypass	54 (13.4)	13 (7.8)	41 (17.5)	0.01
LVAD	29 (7.2)	14 (8.4)	15 (6.4)	0.58
RVAD	3 (0.7)	1 (0.6)	2 (0.9)	NS
BiVAD	6 (1.4)	2 (1.2)	4 (1.7)	NS

BiVAD indicates biventricular assist device; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump; LVAD, left ventricular assist device; NS, nonsignificant; and RVAD, right ventricular assist device.

cardiac arrhythmias (14%), and circuit clots (10.5%) were the most common ECMO complications (Table 6). Patients who received OHT were more likely to require additional inotropic support after ECMO deployment (36.3% versus 9.6%; *P*<0.01), have more surgical site bleeding complications (19.2% versus 8.4%; *P*=0.004), culture proven infection (12.4% versus 3%; *P*=0.01), circuit clots (13.2% versus 6.6%; *P*=0.05), and continuous renal replacement therapy requirement (29.1% versus 15.6%; *P*=0.002), whereas patients that received LVAD were more likely to have more cannulation site bleeding (8.4% versus 1.3%; *P*=0.01).

Mortality, LOS, and Independent Predictors

All-cause in-hospital mortality was 28.9% and was not different between the groups ([28.7% versus 29.1%; *P*=0.24], Table 7). Figure 3 shows the temporal variation of in-hospital mortality throughout the study period. As the number of procedures increased overtime, combined in-hospital mortality ranged between 19% and 36% without significant differences between the 2 groups. However, there was a trend towards reduced mortality in the OHT group in 2019. In-hospital mortality for patients who underwent the procedure while on ECMO versus underwent the procedure after ECMO decannulation was similar (*P*=0.11). Total LOS was 55.3±49.9 days and was significant longer for patients that underwent OHT compared with those that received an LVAD (59.5 versus 49.6 days; *P*=0.05), as shown in Table 7. The ECMO therapy duration between the 2 groups did not differ significantly (225.3 versus 283.5 hours, *P*=0.13).

Using the modified imputed logistic regression analysis, we identified predictors of undergoing LVAD versus OHT. Higher weight (OR=0.98 [CI, 0.97–0.99]; *P*=0.01), CS presentation (OR=0.40 [CI, 0.21–0.78]; *P*=0.01), history of LVAD implantation (OR=0.01 [CI, 0.0001–0.22]; *P*=0.05), respiratory failure (OR=0.28 [CI, 0.11–0.70]; *P*=0.01), and milrinone infusion (OR=0.32 [CI, 0.15–0.67]; *P*=0.01) were independently associated

Table 5. ECMO Specifications/Information

	All ECMO, N=401	LVAD, N=167	Transplant, N=234	*P* value
ECMO mode				0.01
Venous-arterial	353 (88)	143 (85.6)	210 (89.7)	
Venous-venous to venous-arterial conversion	24 (6.0)	18 (10.8)	6 (2.6)	
Venous-venous-arterial	7 (1.7)	3 (1.8)	4 (1.7)	
Venous-venous	8 (2.0)	2 (1.2)	6 (2.6)	
Support type				0.18
Cardiac	360 (89.8)	150 (89.8)	210 (89.7)	
ECPR	33 (8.2)	16 (9.6)	17 (7.3)	
Pulmonary	8 (2.0)	2 (1.2)	6 (2.6)	
Procedure timing				0.05
On ECMO support	323 (80.5)	145 (85.6)	180 (77.0)	
After ECMO support	78 (19.5)	24 (14.4)	54 (22.6)	
Pre-ECMO cardiac arrest	110 (27.4)	59 (35.3)	51 (21.8)	0.01

ECMO indicates extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation; and LVAD, left ventricular assist device.

with LVAD implantation, whereas prior cardiac transplant (OR=31.26 [CI, 3.84–780.5]; *P*=0.01), use of a temporary pacemaker (OR=6.5 [CI, 1.39–50.15]; *P*=0.03), and increased requirement of inotropes during ECMO support (OR=3.77 [CI, 1.39–11.07]; *P*=0.01) were independently associated with undergoing OHT (Figure 4). These predictors were confirmed with logistic regression after Least Absolute Shrinkage and Selection Operator with the addition of pre-ECMO arrest (OR=0.5 [CI, 0.25–0.99]; *P*=0.05) as an additional predictor for LVAD implantation. In a secondary analysis incorporating hemodynamics in the predictive model, no additional independent predictors were identified. There were no significant differences in additional sensitivity analyses performed excluding patients with extracorporeal resuscitation and venous-venous ECMO indications (Tables S1 through S3).

Using a different model assessing survival for each group individually, while respiratory failure (OR=5 [CI, 1.17–23.1]; *P*=0.03) and continuous renal replacement therapy (OR=3.82 [CI, 1.28–11.9]; *P*=0.02) were associated with increased mortality, using ECMO to bridge to OHT in the most contemporary years (OR=0.023 [CI, 0.003–0.017]; *P*<0.01) and discontinuing ECMO before OHT (OR=0.015 [CI, 0.003–0.06]; *P*<0.01) were strongly related with improved in-hospital survival after heart transplantation (Figure 5). Furthermore, increasing age (OR=1.07 [CI, 1.02–1.12]; *P*=0.01), cannulation bleeding (OR=26.1 [CI, 4.32–221.3]; *P*=0.01), and surgical bleeding (OR=6.7 [CI, 1.26–39.9], *P*=0.03) were associated with increased mortality in patients that underwent LVAD implantation (Figure 6). There were no significant differences in additional sensitivity analyses performed excluding patients with extracorporeal resuscitation and venous-venous ECMO indications (Tables S1 through S3).

Supplemental Analyses

To address the impact of the heart transplant organ allocation policy changes in 2018, we performed additional analyses for OHT patients between 2011 to 2017 and 2019 periods (Tables S4 through S7). Patients that underwent OHT in 2019 had more frequently chronic kidney disease/end-stage renal disease (22.2% versus 5.9%), presented with CS (58.3% versus 35.3%), and underwent OHT on ECMO more commonly (94.4% versus70%) as compared to the 2011 to 2017 patients. However, in-hospital mortality was significantly lower in 2019 patients (5.6% versus 32.9). There were no other differences that were observed.

In addition, given that 20% of patients underwent advanced therapies after decannulation, we sought to identify predictors of decannulation. Overall, patients that were decannulated had ECMO circuit clots. There were no other differences that were observed. In-hospital mortality, LOS, and ECMO duration did not differ significantly. A discontinuation intent (OR=3.6; *P*=0.01), cardiac arrest presentation (OR=1.94; *P*=0.05), and intraaortic balloon pump support (OR=1.86; *P*=0.05) were predictive of decannulation before OHT/LVAD (Tables S8).

Finally, we assessed the impact of ACS presentation in this population (Tables S9 through S12). Non-ACS OHT patients were more likely to be younger, have a history of cardiomyopathy, whereas non-ACS LVAD patients were more likely to be heavier, have a history of CAD, present with CS, and cardiac arrest. There were no differences in in-hospital mortality. Regarding ACS patients, ACS LVAD patient were more likely to be older, have increased weight, present with CS, have cardiac arrest and undergo on-pump LVAD compared with ACS OHT. ACS OHT patients have a greater LOS.

Table 6. ECMO Complications

Complications	All ECMO, N=401	LVAD, N=166	Transplant, N=234	*P* value
Hemorrhagic				
Cannulation site bleeding	32 (7.9)	9 (5.4)	23 (9.8)	0.15
DIC	9 (2.2)	1 (0.6)	8 (3.4)	0.12
GI hemorrhage	11 (2.7)	4 (2.4)	7 (3)	0.95
Hemolysis	14 (3.5)	3 (1.8)	11 (4.7)	0.19
Mediastinal cannulation site bleeding	6 (1.4)	5 (3.0)	1 (1.3)	0.39
Peripheral cannulation site bleeding	17 (4.2)	14 (8.4)	3 (1.3)	0.01
Surgical site bleeding	59 (14.7)	14 (8.4)	45 (19.2)	0.01
Infectious				
Culture proven infection	34 (8.5)	5 (3.0)	29 (12.4)	0.01
White blood cells <1500	9 (2.2)	5 (3.0)	4 (1.7)	0.60
Limb				
Fasciotomy	7 (1.7)	4 (2.4)	3 (1.3)	0.65
Compartment syndrome	1 (0.2)	1 (0.6)	0 (0)	0.86
Ischemia	14 (3.5)	6 (3.6)	8 (3.4)	NS
Mechanical				
Air in circuit	5 (1.2)	1 (0.6)	4 (1.7)	0.59
Cannular problems	11 (2.7)	5 (3.0)	6 (2.6)	NS
Circuit change	9 (2.2)	6 (3.6)	3 (1.3)	0.23
Clots and air emboli	1 (0.2)	0 (0)	1 (0.4)	NS
Circuit component clots	42 (10.5)	11 (6.6)	31 (13.)	0.05
Oxygenator failure	25 (6.2)	6 (3.6)	19 (8.1)	0.10
Pump failure	6 (1.5)	2 (1.2)	4 (1.7)	NS
Metabolic				
Serum glucose <40 mg/dL	2 (0.5)	1 (0.6)	1 (0.4)	NS
Serum glucose >240 mg/dL	34 (8.5)	9 (5.4)	25 (10.7)	0.09
Hyperbilirubinemia	37 (9.2)	17 (10.2)	20 (8.5)	0.70
Hemolysis	4 (1)	3 (1.8)	1 (0.4)	0.50
pH<7.2	15 (3.7)	8 (4.8)	7 (3)	0.50
pH>7.6	18 (4.5)	6 (3.6)	12 (5.1)	0.62
Neurological				
Brain death	3 (0.7)	1 (0.6)	2 (0.9)	NS
CNS hemorrhage	4 (1)	1 (0.6)	3 (1.3)	0.86
CNS infarction	11 (2.7)	4 (2.4)	7 (3)	0.95
Seizures	1 (0.2)	0 (0)	1 (0.4)	NS
Renal				
Creatinine 1.5–3	59 (14.7)	24 (14.4)	35 (15)	0.98
Creatinine >3	30 (7.5)	14 (8.4)	16 (6.8)	0.69
Renal replacement therapy	94 (23.4)	26 (15.6)	68 (29.1)	0.01

CNS indicates central nervous system; DIC, diffuse intravascular coagulation; ECMO, extracorporeal membrane oxygenation; GI, gastrointestinal; LVAD, left ventricular assist device; and NS, nonsignificant.

DISCUSSION

As the trend of ECMO use as intermediary to advanced heart failure therapies has been rising over the past several years, there has been an increased demand for evidence supporting these practices. In this present analysis, we sought to elucidate various aspects of patients bridged with ECMO towards either LVAD or OHT. Our findings from this analysis can be summarized as follows: (1) there has been an increase in use of ECMO as bridge to either therapy in the last decade, (2) the cumulative in-hospital mortality remains high at 28.9%, however, the temporal trends do not appear to differ between the 2 groups, (3) 80% of LVAD/OHT occurred during ECMO support with LVAD more than OHT, (4) patients that underwent OHT had significantly longer

Table 7. Outcomes

	Total	LVAD, N=167	Transplant, N=234	*P* value
Length of stay, d	55.3±49.9	49.6±52.6	59.5±47.5	0.05
In-hospital mortality	116 (28.9)	48 (28.7)	68 (29.1)	0.24
During ECMO support	100 (30.9)	43 (30.1)	57 (31.5)	0.88
After ECMO support	16 (20.8)	5 (20.8)	11 (20.8)	NS
ECMO support duration, h	259.2±381.7	225.3±182	283.5±474	0.13

ECMO indicates extracorporeal membrane oxygenation; LVAD, left ventricular assist device; and NS, nonsignificant.

stay in the hospital compared with LVAD, (5) increased weight, CS presentation, prior LVAD, respiratory failure, and milrinone infusion independently predicted LVAD implantation, whereas prior transplant, use of a temporary pacemaker, and increased requirement of inotropes on ECMO were independently associated with undergoing OHT, and (4) respiratory failure and continuous renal replacement therapy were associated with increased mortality in OHT, whereas age, surgical, and cannulation bleeding predicted mortality in LVAD.

Our cohort demographics are different than cohorts where ECMO has been used for a different indication such as postcardiotomy shock, CS, and cardiac arrest in which patients were older and had more comorbid conditions.[9–12] Hernandez-Montfort et al[13] using a contemporary cohort of CS patients, showed that patients receiving heart replacement therapies were younger, had lower weight, and had less comorbidities compared with those who recovered or died. Since all patients in our cohort received heart replacement therapies, these age and weight differences likely reflect the unique selection process in deploying ECMO for patients with reversible causes of cardiomyopathy (myocarditis) or those who are thought to be appropriate candidates for OHT/LVAD. In fact, the decision-making process early after deployment is identical as ECMO is not an etiologic treatment but merely a temporizing measure while more durable therapies (recovery, LVAD, OHT) can be considered. Of note, patients who received LVAD were older that those receiving OHT (50.5 versus 42.7 years; $P<0.001$) with increased number of comorbid conditions at the time of implantation.

The same notion of selection bias is likely applicable for the characteristics of presentation for these patients. Overall, patients in the LVAD group were more critically ill on presentation as evidenced by the observation that they were more likely to present with CS, cardiac arrest, ACS, and acute kidney injury when compared with the OHT group. Although data regarding acute presentation of patients with CS that ended up undergoing OHT or LVAD have been scarce, the preponderance of more severe presentation in patients with LVAD is unlikely due to chance effect. Based on their risk profile and comorbid conditions, this group is more likely to exhibit a poor outcome posttransplantation. In addition, despite the improvement of neurologically favorable results post-extracorporeal resuscitation after cardiac arrest, overall outcomes are still meager. As such, physicians faced with an ethical dilemma of poor posttransplant outcome for a finite resource may opt for stabilization with durable LVADs. Of note, although ACS presentation was higher in LVAD group (24.4%

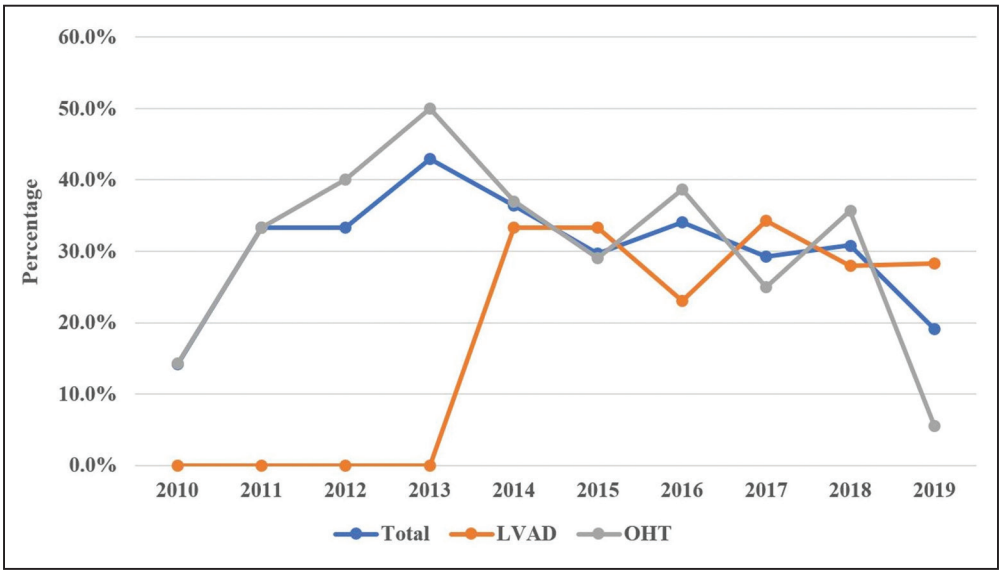

Figure 3. All-cause mortality temporal trends (1) in all extracorporeal membrane oxygenation (ECMO) patients and (2) by strategy group (left ventricular assist device [LVAD] vs orthotopic heart transplant [OHT]).

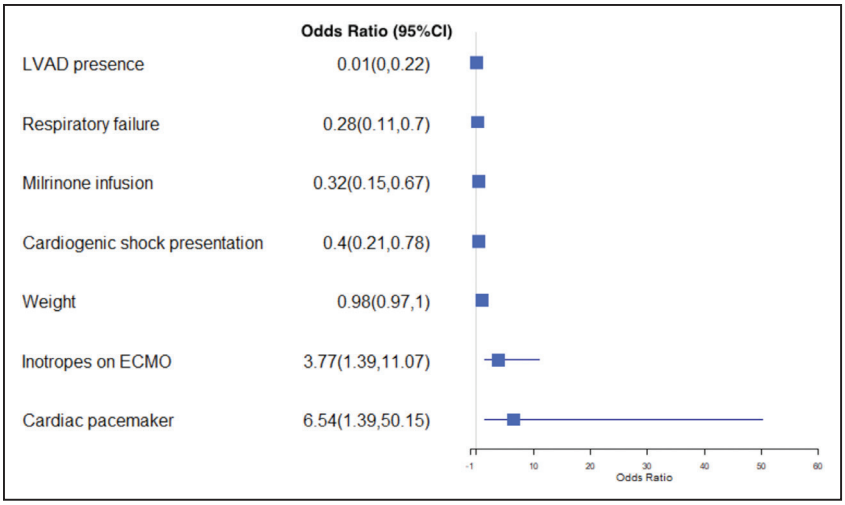

Figure 4. Predictors of undergoing left ventricular assist device (LVAD) vs orthotopic heart transplant (OHT). An odds ratio (OR) <1 denotes that an LVAD strategy is more likely, whereas an OR >1 denotes that an OHT strategy is more likely. ECMO indicates extracorporeal membrane oxygenation.

versus 7.9%, *P*<0.001), the overall ACS presentation was as low as 15% in our population. While this might seem counterintuitive, prior evidence shows that CS complicates about 5% to 10% of acute myocardial infarction.[14]

The use of ECMO as bridge to advanced therapies has increased in the last decade due to technological improvements, increasing availability and familiarity of medical staff, its ability to provide biventricular support and ease of implantation in the catheterization lab.[1] Interestingly, the cases of OHT after ECMO have recently decreased along with a concurrent increase in LVAD as shown in Figure 1. Similar declining ECMO to OHT trends have been observed in the United States.[15] These inversing trends have to be interpreted within the context of outcomes for this population. While superior to other ECMO populations, mortality in patients bridged to LVAD/OHT remains unacceptably high. We found a cumulative in-hospital mortality of ≈30% that was similar in both groups. A single-center experience from France had comparable in-hospital mortality of 38.5% and 29% in OHT and LVAD, respectively.[16] Contemporary data from the United Network for Organ Sharing and International Society for Heart and Lung Transplantation (ISHLT) databases found a 1-year survival rate of 68% and 71.2%, respectively, after OHT, with ECMO use independently associated with mortality.[4,15] However, patients who survive exhibit a superior long-term outcome after OHT showing an annual survival rate of 90%.[4] This latter finding may be partially responsible for the declining numbers of OHT.

Pulmonary artery pressure is an important determinant of future therapies (OHT versus LVAD) and long-term outcomes. OHT is avoided in patients with elevated pulmonary pressures given the high incidence of graft right ventricular failure postoperatively with a subsequent increase in mortality.[17] In that context, LVAD treatment is preferred as it has been shown to normalize pulmonary pressures re-introducing future eligibility for heart transplant.[18] In our cohort, the mean pulmonary artery pressure was elevated at 31.5 mm Hg. Although not statistically significant, mean pulmonary artery pressure was numerically higher in LVAD group (32.9 versus 29.8 mm Hg). Same trends are seen in wedge pressure (24.9 versus 20.0 mm Hg). Although numerically congruent with previous reports definite conclusions on the hemodynamic

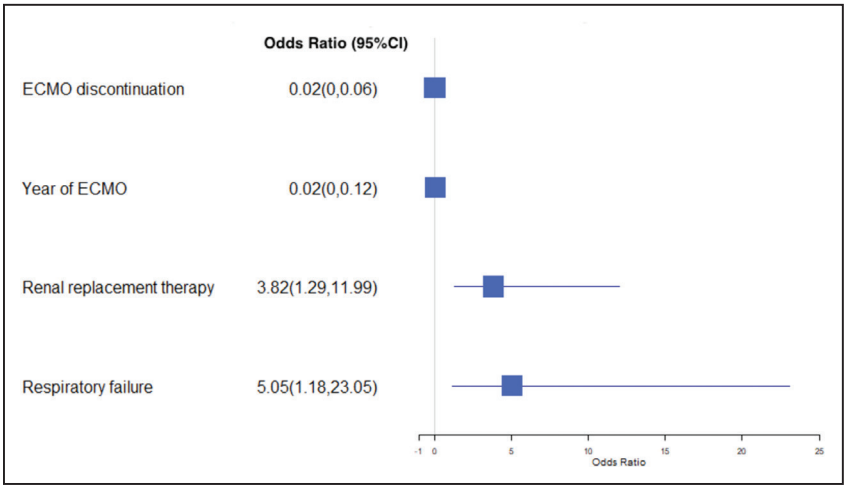

Figure 5. Predictors of mortality in the orthotopic heart transplant (OHT) group. An odds ratio (OR) >1 denotes increased mortality, whereas an OR <1 denotes decreased mortality. ECMO indicates extracorporeal membrane oxygenation.

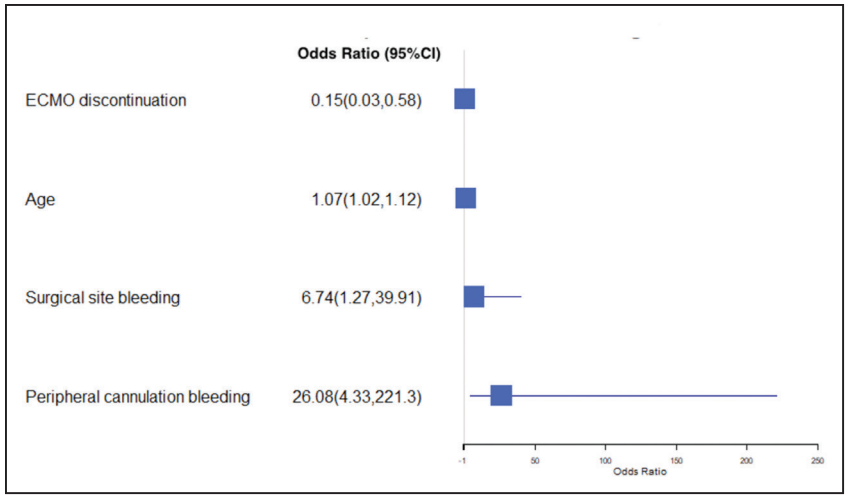

Figure 6. Predictors of mortality in left ventricular assist device (LVAD) group. An odds ratio (OR) >1 denotes increased mortality, whereas an OR <1 denotes decreased mortality. ECMO indicates extracorporeal membrane oxygenation.

profiling of the population cannot be made given the low numbers provided by the registry.[15,19,20]

Patients that underwent heart transplantation had significant longer hospital stay than those undergoing LVAD implantation (59.5 versus 49.6 days; *P*=005). The LVAD group exhibited a lower LOS despite higher age and more severe presentation. This finding could be attributed to a few plausible explanations. First, patients that underwent transplant may have to wait longer times until a suitable graft becomes available. Second, in our analysis, the OHT group experienced more complications, including worsening hemodynamic instability, surgical bleeding, circuit clots, and renal replacement, that could contribute to prolonged hospitalization. Third, this difference could reflect physician's practices and comfort leading to a more conservative management of the OHT group. In patients with ECMO, post-LVAD LOS was recently found to be 29 days, whereas for OHT could be up to 69 days.[21] Indeed, perioperative ECMO use has been found to be an independent predictor of prolonged LOS in both LVAD and OHT populations.[22,23]

Increased weight, CS presentation, respiratory failure, prior LVAD implantation, and milrinone infusion independently predicted LVAD implantation. While increased weight is likely the result of the selection process for heart transplant, CS presentation, and respiratory failure would suggest a relatively sicker subgroup of patients. As increased body mass index and mechanical ventilation has been previously identified as independent predictors of poor posttransplant outcomes, our findings appear rational.[15] CS in patients with previous LVAD is likely to result from LVAD malfunction or right ventricular failure. While there is no way to know that from our data, previous LVAD strongly predicted recurrent LVAD implantation. In this case, LVAD malfunction and surgical considerations may have impacted our results. On the contrary, prior heart transplant and the use of a temporary pacemaker predicted OHT. While the former appears a logical finding, the latter does not have a straightforward cause. A possible explanation could include cardiac sarcoidosis and giant cell myocarditis as concomitant causes of atrioventricular block and CS.[24] In the same context, use of a temporary pacemaker could be an indicator of a global biventricular cardiomyopathy that would favor transplant over LVAD.

Finally, we showed that respiratory failure and continuous renal replacement therapy conveyed a 5-fold and a 4-fold increase, respectively, in in-hospital mortality for OHT patients. Moonsamy et al[15] have confirmed our finding in a recent report where pretransplant dialysis and ventilator dependency conferred a 1.8- to 3-fold and 2- to 2.5-fold increase in posttransplant mortality, respectively.[15] Regarding LVAD, while increasing age weakly predicted in-hospital mortality (OR=1.07; *P*=0.003), cannulation bleeding and surgical site bleeding conferred an astounding 26- and 7-fold respective increase in in-hospital mortality. Saeed et al found that age among body mass index, sex, lactate, atrial fibrillation, and prior surgery has been an important predictor of mortality post-LVAD.[25–28] Congruent with our report, an ISHLT Mechanically Assisted Circulatory Support registry study found increased rates of bleeding, cerebrovascular accidents, and mortality after mechanical circulatory support in patients undergoing LVAD implantation.[29] Others have shown that ECMO duration >7 days has prognostic implications on mortality post-LVAD.[30] While this could be a reflection of ECMO-related complications due to prolonged therapy, it may represent a surrogate for peripheral vascular disease complications after LVAD implantation, although causal inferences cannot be made. Vascular disease has been found to be a strong predictor of mortality in this population.[31,32]

Limitations

The findings of our analysis should be interpreted within the context of its limitations. First, the ELSO database uses *ICD-9* and *ICD-10* for coding purposes from which most of our data regarding diagnoses and procedures are derived. Thus, the use of administrative data set for this study may make it prone to errors of coding, including miscoding, under coding, or over coding. However,

we think that such effect is negligible as much of our data match data from previous studies. Second, our ability to find differences or predictors in hemodynamic parameters might have been impacted by missing patient data in the ELSO database. To address this problem and increase the reliability of our findings, we have created a separate logistic regression model including only the population that had nonmissing hemodynamic data. Importantly, complete hemodynamic profiling that has been shown to predict outcomes before mechanical circulatory support initiation was not available on the basis of the ELSO database.[33] Third, the ELSO database does not provide the breadth, or the longitudinal outcomes provided by other databases. However, the goal of our study was to describe the ECMO population undergoing OHT/LVAD along with perioperative factors that affect in-hospital outcomes. We think that our study provides a distinct wealth of information that pertains to acute cardiovascular care physicians.

Conclusions

ECMO use has been increasing in the recent year as bridge to advanced therapies with LVAD case more than OHT. The LVAD group had a more severe presentation and comorbidities, but hemodynamics did not differ between the 2 groups. Mortality remains high overall, and OHT has longer LOS. Further studies are needed to confirm our results.

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Supplemental Material

Tables S1–S12

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