Int J Heart Fail. 2023 Apr;5(2):91-99
https://doi.org/10.36628/ijhf.2023.0013
pISSN 2636-154X·eISSN 2636-1558

International Journal of Heart Failure
IJHF

Original Article

Direct Extracorporeal Membrane Oxygenation Bridged Heart Transplantation: The Importance of Multi-Organ Failure

Ji Hoon Lim, MD[1], Soo Yong Lee, MD, PhD[1], Min Ho Ju, MD[2], Seok Hyun Kim, MD[1], Jin Hee Choi, MD, PhD[1], Min Ku Chon, MD, PhD[1], Sang Hyun Lee, MD, PhD[1], Ki Won Hwang, MD, PhD[1], Jeong Su Kim, MD, PhD[1], Yong Hyun Park, MD, PhD[1], Junehong Kim, MD, PhD[1], Kook Jin Chun, MD, PhD[1], Mi Hee Lim, MD, PhD[2], Chee-hoon Lee, MD[2], and Hyung Gon Je, MD, PhD[2]

[1]Division of Cardiology, Department of Internal Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Yangsan, Korea
[2]Department of Cardiovascular Surgery and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea

Received: Feb 27, 2023
Revised: Apr 24, 2023
Accepted: Apr 26, 2023
Published online: Apr 28, 2023

Correspondence to
Soo Yong Lee, MD, PhD
Division of Cardiology, Department of Internal Medicine, Pusan National University School of Medicine, Pusan National University Yangsan Hospital, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea.
Email: shonge0906@gmail.com

Min Ho Ju, MD
Department of Thoracic and Cardiovascular Surgery, Pusan National University Yangsan Hospital, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea.
Email: deicidepan@naver.com

ABSTRACT

Background and Objectives: Recently, approximately 40% of all heart transplantation (HTx) in South Korea are performed using the direct extracorporeal membrane oxygenation (ECMO) bridging method. We conducted a study to examine the clinical outcome of direct ECMO-bridged HTx and to investigate the impact of multi-organ failure (MOF).
Methods: From June 2014 to September 2022, a total of 96 adult patients who underwent isolated HTx at a single tertiary hospital were included in the study. The patients were sub-grouped into ECMO (n=48) and non-ECMO group (n=48), and the ECMO group was subdivided into awake (n=22) and non-awake (n=26) groups based on mechanical ventilator (MV) dependency. Baseline characteristics, 30-day, and 1-year mortality were analyzed retrospectively.
Results: The 1-year survival rate was significantly lower in the ECMO group (72.9% vs. 95.8%, p=0.002). There was a significant difference in the 30-day survival rate between the awake and non-awake ECMO groups (81.8% vs. 65.4%, p=0.032). In the univariate analysis of logistic regression for 1-year mortality, the odds ratio was 8.5 for ECMO bridged HTx compared to the non-ECMO group, 12.3 in patients who required MV (p=0.003), and 23 with additional hemodialysis (p<0.001).
Conclusions: Patients who required MV in ECMO bridged HTx showed higher preoperative MOF rates and early mortality than those extubated. When considering ECMO bridged HTx, the severity of MOF should be thoroughly investigated, and careful patient selection is necessary.

Keywords: Mechanical ventilation; Hepato-renal failure; Extracorporeal membrane oxygenation; Heart transplantation

INTRODUCTION

Venoarterial extracorporeal membrane oxygenation (ECMO) is increasingly used worldwide as a short-term circulatory support in patients with refractory cardiogenic shock. And it bridges patient to recovery, decision, or transplantation.[1] Heart transplantation (HTx) in patients supported by ECMO which represented only 1% of ISHLT registry.[2] Similar to the United Network for Organ Sharing (UNOS) criteria revised in 2018, ECMO patients in South Korea are registered as status 0 and classified as the highest priority for HTx.[3] According to the annual report of Korean Network for Organ Sharing (KONOS), among 367 cases of total HTx during 2019-2020, 166 cases (45.2%) were status 0, which implies significantly high proportion of direct ECMO bridged HTx were done in South Korea recently.[4] In the unique situation in Korea where the proportion of ECMO bridged HTx is particularly high, preoperative risk assessment and management of ECMO bridged recipients become even more important.

In general, ECMO bridged HTx is known to have poor survival than non-ECMO bridged transplant even including other types of mechanical circulatory systems (MCS) bridged transplants.[2,5,6] The most frequent causes of death in patients bridged to HTx with VA ECMO are multi-organ failure (MOF).[7,8] However, recent research on direct ECMO bridged HTx suggested, highly selected recipients could have similar clinical outcomes compared with non-ECMO bridged recipients when minimized pre-transplant organ failure state.[9]

This study aimed to identify favorable patient groups who should undergo HTx bridged by ECMO, focusing on specifying the risk factors associated with preoperative MOF.

METHODS

Study design and population

This retrospective cohort study enrolled patients who underwent HTx at a single tertiary medical center between June 2014 and September 2022. During the study period, 103 cases of adult HTx were performed, and the present study included 96 patients (59 males and 37 females), excluding seven cases of multi-organ transplantation. Among the 96 patients who received HTx, 48 (29 males and 19 females) were supported with venoarterial ECMO (VA-ECMO) as a pre-transplant bridge therapy. Of these 48 patients, 22 were non-intubated or extubated while on VA-ECMO support before HTx, while the other 26 patients required ventilator support. (**Figure 1**). The "Awake-ECMO group" consisted of recipients on VA-ECMO who did not receive ventilator support until the day of transplantation, regardless of sedative use. On the other hand, the "Non-Awake ECMO group" was defined as recipients who received ventilator support prior to anesthesia.

All data were collected prospectively and analyzed retrospectively. Preoperative recipient risk was assessed using the Index for Mortality Prediction after Cardiac Transplantation (IMPACT) score and the Model for End-stage Liver Disease eXcluding International normalized ratio (MELD-XI) score.[11,12] Peripheral type VA-ECMO was applied to all patients who underwent HTx under ECMO support. This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (05-2023-034). The requirement for informed consent was waived due to the retrospective nature of the study.

Protocol for the management of patients on ECMO-bridged transplantation

The management of ECMO at our center followed the general guidelines of the Extracorporeal Life Support Organization (ELSO).[10] We routinely inserted a 5-6 Fr distal perfusion catheter in all patients on peripheral ECMO, and dorsal artery doppler flow sound was checked at every nurse duty. We maintained ECMO flow as low as possible while ensuring sufficient tissue perfusion monitoring and maintaining lactate levels under 2 mmol/L. The target activated partial thromboplastin time was usually maintained at 50–60 seconds using unfractionated heparin or argatroban. Optimal inotropic support was provided to help open the aortic valve and minimize ECMO flow, thus avoiding two circulation syndromes. Starting from 2019, we made a concerted effort to extubate all patients who were waiting for a transplant

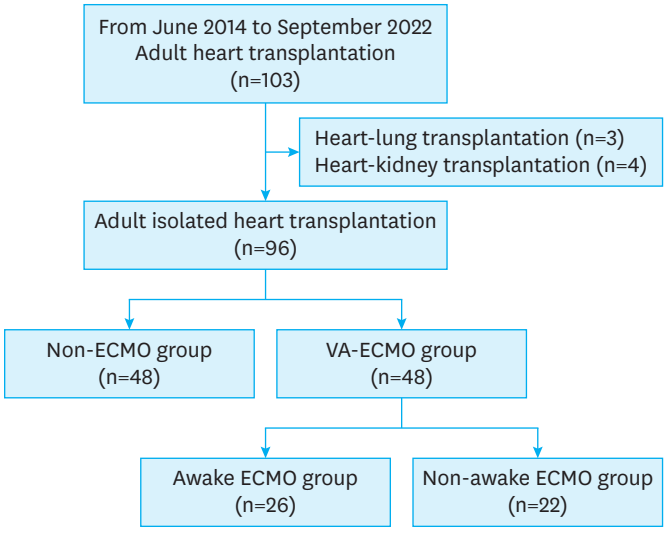


Figure 1. Flow chart of the study.
ECMO = extracorporeal membrane oxygenation; VA = veno-aterial.

https://doi.org/10.36628/ijhf.2023.0013

under VA ECMO by performing rapid left atrial (LA) venting using inter-atrial septostomy with a balloon size of ≥2.5 cm or direct LA cannulation for drainage immediately after detecting aortic valve closure. Consecutive rapid extubation was performed when the patient was alert, and attempts were made to initiate oral feeding. Since fever can be masked by the large volume of extracorporeal circulation, routine blood cultures were obtained via the central catheter to screen for bloodstream infections.

Surgical procedures

We performed a conventional median sternotomy with bicaval cannulation for HTx. The inferior vena cava was drained via cannulation through femoral vein access. Recipients who underwent preoperative ECMO were switched to cardiopulmonary bypass (CPB) using existing cannulas. In such cases, cannulation of the superior vena cava was performed before aortic cross-clamping (ACC). For patients without ECMO, arterial cannulation was routinely performed in the distal aorta. The standard bicaval anastomosis technique was used, and the superior vena cava anastomosis was performed after release of the ACC. Details surgical procedures have been previously described.[11]

Multi-organ failure assessment: liver, kidney and ventilator

Irreversible brain damage is an absolute contraindication for most organ transplantation. However, there is still debate regarding transiently deteriorated liver and kidney function during the waiting list. Therefore, the MELD-XI, which assesses both kidney and liver function at the same time, has been suggested to evaluate potential recipients. The MELD-XI score was calculated using the following formula as previously reported: 11.76 × ln (Creatinine [mg/dL]) + 5.11 × ln (Total Bilirubin [mg/dL]) + 9.44.[12] In addition, we used the preoperative recipient risk scoring system, Index for Mortality Prediction after Cardiac Transplantation (IMPACT), which includes age, sex, hepato-renal function, heart failure etiology, type of MCS, and ventilator status.[13,14] The details of the IMPACT score are described in **Supplementary Table 1.**

Post-operative management and immunosuppression protocol

After surgery, all patients were transferred to the cardiac intensive care unit (ICU). In the operating room, a Swan-Ganz catheter was inserted to monitor cardiac output, pulmonary capillary wedge pressure, and pulmonary arterial pressure. Inotropics and vasopressors were routinely administered based on the patients' cardiac output and heart rate. After confirming consciousness and controlled bleeding, the patients were extubated within three days of the operation based on their medical condition. A bolus of 500 mg of methylprednisolone was administered during allograft LA anastomosis initiation. Basilixiamb or antithymoglobulin antibody were used for induction, but for ECMO patients at high risk of infection, induction therapy was either omitted or delayed. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and corticosteroids. Details regarding changes in the immunosuppression regimen have been previously described.[11]

Statistical analysis

Categorical variables were presented as numbers (percentage), and continuous variables were presented as mean and standard deviation. An independent samples test using Levene's test for equality of variances and t-test were performed to verify the significance of asymmetric differences in the average value of each group, and the chi-square test was used to compare categorical variables when appropriate. Time-to-event analyses were represented by constructing cumulative survival curves using the Kaplan-Meier method and comparing them with the log-rank test. Statistical analysis was conducted using SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA), with p values less than 0.05 considered statistically significant.

A risk factor analysis was conducted for one-year mortality after surgery due to the majority of deaths occurring within one year of HTx. However, since the number of events at one year was insufficient, a multivariable analysis was deemed inappropriate and was not performed. Instead, we examined the odds ratios (ORs) of promising predictors through univariable analysis of logistic regression.

To assess the discriminatory function of laboratory tests and associated clinical scores such as MELD-XI and IMPACT score for one-year postoperative mortality, receiver operating characteristic (ROC) curve analysis was performed, and the optimal cutoff value was obtained using the Youden index method.

RESULTS

Baseline characteristics

Non ECMO vs. ECMO group

The mean age of all patients was 54.4±12.5, and there was no significant age difference between the ECMO group and the non-ECMO group. In comparison with the non-ECMO group, patients bridged with VA-ECMO had lower hemoglobin levels and platelet count, higher bilirubin concentration, and elevated liver enzyme levels. Additionally, the high-sensitivity C-reactive protein (hs-CRP) level was higher in the VA-ECMO group. The mean IMPACT

Table 1. Preoperative characteristics

Variables	Non ECMO group (n=48)	ECMO group (n=48)	p value*	ECMO group		
				Awake group (n=22)	Non-awake group (n=26)	p value†
Age (years)	55.3±11.5	53.4±13.5	0.460	60.2 [50.0–64.5]	53.9 [43.6–60.0]	0.226
Sex (male)	30 (62.5)	29 (60.4)	>0.99	13 (59.1)	16 (61.5)	>0.99
BMI (kg/m^2)	23.1±3.4	22.6±3.4	0.505	22.2±3.6	22.9±3.3	0.498
DM	15 (31.2)	14 (29.2)	>0.99	7 (31.8)	7 (26.9)	0.958
Hypertension	33 (68.8)	28 (58.3)	0.396	16 (72.7)	12 (46.2)	0.117
DCMP	31 (64.6)	13 (27.1)	<0.001	11 (50.0)	2 (7.7)	0.003
CRRT	1 (2.1)	20 (41.7)	<0.001	2 (9.1)	18 (69.2)	<0.001
Intubation at ECMO insertion		26 (54.2)		9 (40.9)	17 (65.4)	0.160
Left heart venting		22 (45.8)		4 (18.2)	18 (69.2)	0.001
Hemoglobin (g/dL)	11.5±2.0	9.2±1.4	<0.001	9.1±1.7	9.4±1.2	0.509
Platelet count (10^3/uL)	212.4±69.9	103.6±49.7	<0.001	105.0 [85.0–158.0]	80.0 [62.0–120.0]	0.024
AST (IU/L)	32.6±28.6	220.5±606.1	0.037	42.5 [27.0–66.0]	86.5 [59.0–230.0]	0.001
ALT (IU/L)	34.5±58.0	138.4±278.5	0.015	49.0 [17.0–79.0]	47.0 [33.0–137.0]	0.301
Total bilirubin (mg/dL)	1.2±1.2	3.9±5.1	0.001	1.9 [1.3–3.5]	2.3 [1.5–5.0]	0.494
Albumin (g/dL)	3.8±0.5	3.0±0.3	<0.001	3.0±0.3	3.0±0.4	0.768
PT INR	1.4±0.4	1.5±0.6	0.323	1.3 [1.2–1.4]	1.4 [1.2–1.6]	0.370
hs-CRP (mg/dL)	2.1±4.0	9.8±8.9	<0.001	4.8 [3.0–9.2]	9.9 [4.2–16.9]	0.048
Waiting days (days)	35.6±51.8	7.7±7.9	0.001	7.0±5.9	8.2±9.3	0.607
Euroscore II	11.8±11.4	25.8±17.9	<0.001	24.0 [15.3–41.9]	21.2 [12.2–29.8]	0.501
MELD-XI score	12.6±4.1	21.8±10.2	<0.001	15.9±6.7	26.7±10.1	<0.001
IMPACT score	5.7±5.3	18.5±5.6	<0.001	14.1±3.7	22.2±3.9	<0.001
Prior cardiac surgery	7 (14.6)	15 (31.2)	0.089	7 (31.8)	8 (30.8)	>0.99

Categorical variables were presented as numbers (percentage), and continuous variables were presented as mean and standard deviation or median [interquartile range].
ECMO = extracorporeal membrane oxygenation; BMI = body mass index; DM = diabetes mellitus; DCMP = dilated cardiomyopathy; CRRT = continuous renal replacement therapy; AST = aspartate aminotransferase; ALT = alanine aminotransferase; PT = prothrombin time; INR = international normalized ratio; hs-CRP = high-sensitivity C-reactive protein; MELD-XI = model for end-stage liver disease excluding INR; IMPACT = index for mortality prediction after cardiac transplantation.
*p value: between non-ECMO group and all ECMO group, †p value: between awake group and non-awake group.

and MELD-XI scores of the VA-ECMO group were 18.5 and 21.8, respectively, which were significantly higher than those of the non-ECMO group. Other details are described in **Table 1**.

Awake ECMO group vs. non-awake ECMO group

There were no significant differences in sex, age, or body mass index between the awake and non-awake groups. The proportion of patients with dilated cardiomyopathy was higher in the awake group, while the proportion of patients receiving continuous renal replacement therapy (CRRT) or left heart venting was higher in the non-awake group. In nine out of 22 patients, intubation was performed at the time of ECMO insertion, but extubation was performed prior to transplantation, resulting in inclusion in the awake group. Platelet count was higher in the awake group, while aspartate aminotransferase and hs-CRP were higher in the non-awake group. There were no significant differences in other blood test results between the two groups. In terms of preoperative risk scoring systems, Euroscore II did not differ between the groups, but the MELD-XI and IMPACT score were significantly higher in the non-Awake group. Further details are described in **Table 1**.

Early clinical outcomes

In all groups, there were no differences in ischemic time or CPB time. The length of ICU stay was longer in the ECMO group compared to the non-ECMO group, but there was no significant difference between the awake and non-awake groups. All cases that required VV ECMO after surgery were in the non-awake group, and the proportion was significantly higher. Conversely, the proportions of other complications did not differ significantly. However, the proportion of major complications, which is a composite outcome of complications, was higher in the ECMO group than in the non-ECMO group, and in the non-awake group than in the awake group. There were five early deaths, all of which occurred in the non-awake group (**Table 2**). The detailed information of those 5 patients is described in **Supplementary Table 2**. The early (30-day) survival rate exhibited a significant difference between the awake ECMO group and non-awake ECMO group, with survival rates of 100% and 80.8%, respectively (p=0.032) (**Figure 2**).

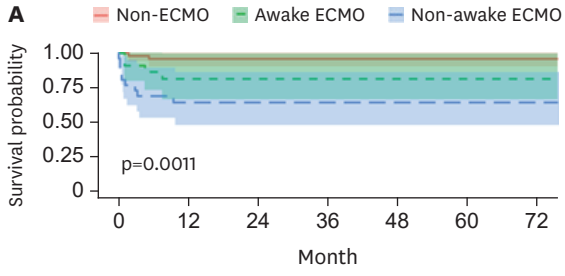
1 year mortality predictive value of organ failure in ECMO-bridged HTx

There were significant differences in 1-year survival rates between the non-ECMO group and the VA-ECMO group (95.7%

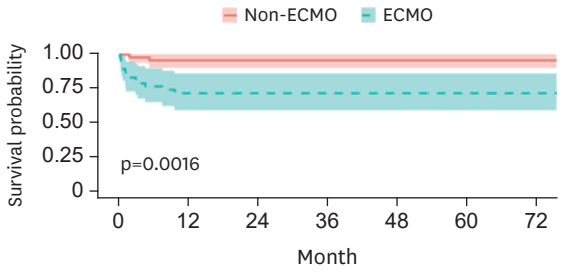
Table 2. Surgical profiles and early clinical outcomes

Variables	Non ECMO group (n=48)	ECMO group (n=48)	p value*	ECMO group		
				Awake group (n=22)	Non-awake group (n=26)	p value†
Total ICT (min)	199.8±72.9	218.3±73.6	0.219	212.4±81.5	223.3±67.4	0.614
Cold ICT (min)	116.5±72.7	131.2±64.5	0.298	132.4±71.8	130.2±59.0	0.905
CPB time (min)	149.1±36.3	165.1±53.7	0.091	160.3±65.5	169.3±42.2	0.583
ICU stay (hours)	141.8±83.0	362.5±429.2	0.001	269.5±240.7	441.1±532.5	0.149
VV ECMO support	0 (0.0)	8 (16.7)	0.010	0 (0.0)	8 (30.8)	0.014
VA ECMO support	1 (2.1)	6 (12.5)	0.116	2 (9.1)	4 (15.4)	0.827
Reoperation for bleeding control	4 (8.3)	6 (12.5)	0.738	4 (18.2)	2 (7.7)	0.511
New onset dialysis	8 (16.7)	3 (6.2)	0.200	2 (9.1)	1 (3.8)	0.881
Pneumonia	1 (2.1)	6 (12.5)	0.116	1 (4.5)	5 (19.2)	0.274
CVA	0 (0.0)	2 (4.2)	0.475	0 (0.0)	2 (7.7)	0.546
Death within 30 days	0 (0.0)	5 (10.4)	0.066	0 (0.0)	5 (19.2)	0.089
Major complication‡	8 (16.7)	21 (43.8)	0.008	5 (22.7)	16 (61.5)	0.016

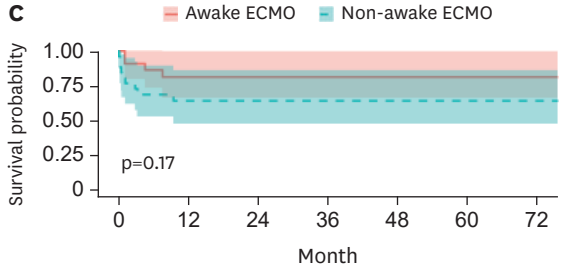
Categorical variables were presented as numbers (percentage), and continuous variables were presented as mean and standard deviation.
ECMO = extracorporeal membrane oxygenation; ICT = ischemic time; CPB = cardiopulmonary bypass; ICU = intensive care unit; VV = veno-venous; VA = veno-aterial; CVA = cerebrovascular accident.
*p value: between non-ECMO group and all ECMO group, †p value: between awake group and non-awake group.
‡Major complication = composite of death, CVA, new onset dialysis, any ECMO support and pneumonia.



No. at risk							
Non-ECMO	48	37	30	25	15	11	6
Awake ECMO	22	14	10	5	2	1	1
Non-awake ECMO	26	14	13	10	9	6	5



No. at risk							
Non-ECMO	48	37	30	25	15	11	6
ECMO	48	28	23	15	11	7	6



No. at risk							
Awake ECMO	22	14	10	5	2	1	1
Non-awake ECMO	26	14	13	10	9	6	5

D

% ± SD	30-day	6-month	12-month
Non-ECMO	100	95.7 ± 3.0	95.7 ± 3.0
VA-ECMO	89.6 ± 4.4	76.9 ± 6.1	71.9 ± 6.7
p value	0.022	0.007	0.002

% ± SD	30-day	6-month	12-month
Awake ECMO	100	86.4 ± 7.3	81.3 ± 8.5
Non-awake ECMO	80.8 ± 7.7	69.0 ± 9.1	64.4 ± 9.6
p value	0.032	0.110	0.164

Figure 2. Survival outcome after HTx. (A) Kaplan-Meier curve of all adult isolated HTx recipients divided by non-ECMO, awake ECMO and non-awake ECMO group. (B) Survival curve of non-ECMO and ECMO group. (C) Survival curve of awake-ECMO and non-awake ECMO group. (D) Survival rate of 30-day, 6-month, 12-month post HTx comparing each group. VA-ECMO, venoaterial extracorporeal membrane oxygenation.
ECMO = extracorporeal membrane oxygenation; SD = standard deviation; HTx = heart transplantation; VA = veno-aterial.

vs. 71.9%, p=0.002) (**Figure 2**). There were no significant differences in 1-year survival rates between the awake and non-awake ECMO groups (81.3% vs. 64.4%, p=0.164).

In the univariate analysis of logistic regression for 1-year mortality, the ECMO group demonstrated an OR of 8.5 compared to the non-ECMO group, but without statistical significance (p=0.073).

https://doi.org/10.36628/ijhf.2023.0013

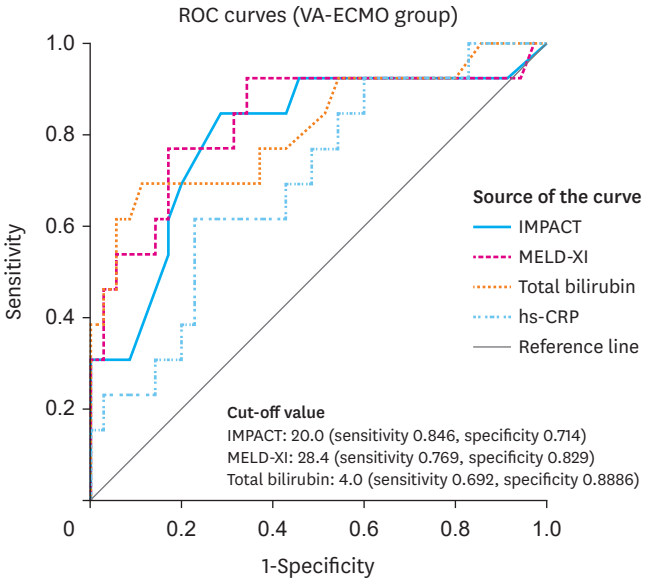
Table 3. Univariable analysis of logistic regression analysis for 1 year mortality

Predictor	OR (95% CI)	p value
VA ECMO (vs. non-ECMO)	8.54 (2.18–56.93)	0.007
ECMO only	5.11 (0.92–39.26)	0.073
ECMO + vent	12.28 (2.80–85.42)	0.003
ECMO + vent + CRRT	23 (4.96–169.01)	<0.001
Bilirubin per 1 increase	1.68 (1.29–2.33)	<0.001
CRP per 1 increase	1.11 (1.04–1.19)	0.002
MELD-XI score per 1 increase	1.2 (1.11–1.31)	<0.001
IMPACT score per 1 increase	1.29 (1.16–1.50)	<0.001

OR = odds ratio; CI = confidence interval; VA = veno-aterial; ECMO = extracorporeal membrane oxygenation; vent = mechanical ventilator; CRRT = continuous renal replacement therapy; CRP = C-reactive protein; MELD-XI = model for end-stage liver disease excluding international normalized ratio; IMPACT = index for mortality prediction after cardiac transplantation.

The OR significantly increased in patients who required mechanical ventilation or additional CRRT compared to those who only needed ECMO (12.3 [95% CI, 2.8–85.4; p=0.003] and 23.0 [95% CI, 5.0–169.0; p<0.001]). As the levels of bilirubin or hs-CRP increased, the odds ratio for 1-year mortality also increased, and this trend was observed in both MELD-Xi score and IMPACT score (**Table 3**).

To determine whether MELD-XI and IMPACT score have diagnostic value for prognosis compared to other indicators, we performed ROC analysis for all-cause 1-year mortality. The area under the curve (AUC) of the IMPACT score was 0.798 (p=0.002, 0.643–0.952), and the AUC of the MELDXI score was 0.830 (p=0.001, 0.680–0.980). These had higher AUC values compared to other indicators except for total bilirubin. The cut-off value of the IMPACT score was 20.0 (sensitivity 0.846, specificity 0.714), and that of the MELDXI score was 28.4 (sensitivity 0.796, specificity 0.829) (**Figure 3** and **Supplementary Table 3**).



Area under the curve					
Test result variable(s)		Area	p value	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
	IMPACT	0.798	0.002	0.643	0.952
	MELD-XI	0.830	0.001	0.680	0.980
	Total bilirubin	0.812	0.001	0.660	0.965
	hs-CRP	0.697	0.038	0.533	0.860

Figure 3. The ROC curves for predicting 1-year mortality in patient who received VA-ECMO support according to different variables.
ROC = receiver operating characteristic; VA = veno-aterial; ECMO = extracorporeal membrane oxygenation; IMPACT = index for mortality prediction after cardiac transplantation; MELD-XI = model for end-stage liver disease excluding international normalized ratio; hs-CRP = high-sensitivity C-reactive protein.

DISCUSSION

The prognostic value of concomitant pre-transplant organ failure during VA-ECMO support has been reported previously.[15-17] However, those studies evaluated only a single clinical variable with ECMO bridged transplants, such as ventilator, high MELD-XI, and CRRT respectively, not comprehensively. As these situations often occur in combination in real-world practice (e.g., ECMO and/or ventilator and/or hepatic dysfunction and/or CRRT), we needed to suggest an answer to how we could evaluate such a high-risk recipient when a transplant team decides whether to transplant or not.

In the present study, ECMO bridged HTx showed a trend of higher mortality and complication rates compared to the non-ECMO group, however this was mainly driven by the non-awake subgroup within the ECMO group. All five 30-day deaths occurred only in the non-awake group. The incidence of major complications was numerically similar between the awake ECMO group and the non-ECMO group, while it was significantly higher only in the non-awake group. The 30-day survival rate of non-awake ECMO group was significantly lower at 80.8% compared to the awake ECMO group (100%, p=0.032). The OR for 1-year mortality was 5.11 for the ECMO-only group (awake ECMO without CRRT) compared to the non-ECMO group, but this difference was not statistically significant (p=0.073). However, the OR increased to 12.28 when a ventilator was added, and even higher to 23 when a ventilator and CRRT were used simultaneously (p=0.03 and p=0.01 respectively, **Table 3**). These results suggest that coexisting MOF is strongly associated with poor prognosis, rather than ECMO itself.

Recently, French researchers have reported no significant difference in ECMO-bridged HTx outcomes compared with the no-pretransplant ECMO group, supporting the hypothesis that ECMO itself may not be an independent risk factor for post-HTx mortality.[9] This result is somewhat opposed to the numerous other reports on ECMO-bridged HTx.[6,7,17] Notably, the proportion of ventilator-dependent patients among those who received ECMO as a bridge to HTx was only 11% in the study, which was significantly lower than the 46% reported in a similar study that used data from the UNOS registry and was published in the same year. The French authors described that they kept the patients in a stable state of "isolated cardiac failure" before HTx, and one of the strategies they used was to keep the patients awake and not intubated while on ECMO support.[9] Our transplant team has a similar strategy for ECMO-bridged recipients. Since 2019, we have aggressively sought to maintain patients receiving VA ECMO in an awake and orally fed state (**Figure 4**). The awake ECMO strategy of our institution does not simply mean weaning off the mechanical ventilator. Rather, it implies a determination to prevent MOF and maintain isolated cardiac failure state. We have applied awake ECMO to all possible patients to maintain pulmonary preservation and identified hidden risk factors by performing computed tomography scans. LA decompression strategies were actively employed when necessary. As a result, nearly 40% of recipients were intubated at the time of VA ECMO but were kept awake (extubated) until the day of transplantation. The awake ECMO group had a significantly lower mortality rate compared to the non-awake ECMO group. The non-awake group had a higher illness severity, as indicated by higher rates of CRRT and a higher MELD-Xi score, reflecting MOF. Despite a much higher rate of LA venting strategy (69.2% vs. 18.2%), they could not be weaned from the ventilator. Therefore, recipients in non-awake group of current study were 'sickers' who could not be weaned from ventilator despite several trials and efforts, and could be interpreted as a surrogate marker of multi-organ failure.

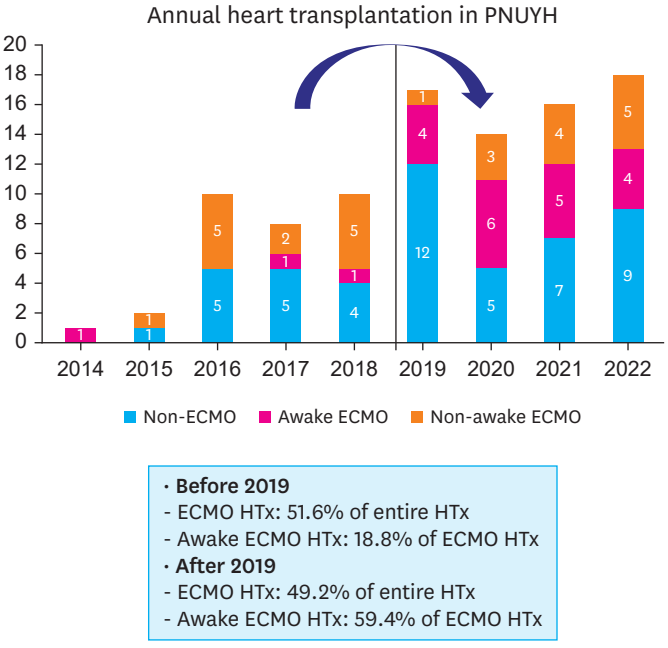


Figure 4. Annual adult isolated heart transplantation trends in our institution. There was strategy change in 2019 to manage the recipients who were waiting for transplant bridged with ECMO. Consequently, the rate of awake ECMO recipients increased from 18.8% to 59.4% among the entire VA-ECMO bridged HTx cases after 2019.
ECMO = extracorporeal membrane oxygenation; HTx = heart transplantation; VA = veno-aterial.

Additionally, we compared the MELD-XI and IMPACT scores, which summarize various risk factors including creatinine, total bilirubin, and ventilator status. In the all HTx patient group, the IMPACT score showed the best predictive value for 1-year mortality (AUC 0.901, p<0.001). However, in the VA ECMO group, the MELD-XI score showed the best predictive value (AUC 0.830, p=0.001).

After the change in UNOS allocation policy, ECMO and IABP bridged heart transplants have become more common.[18] This highlights the importance of the definition of urgency status in determining the recipient's health status when listed. As VA ECMO patients are defined as the highest priority group for allocation, the proportion of VA ECMO bridged HTx is likely to remain high in South Korea. In this situation, careful patient selection is necessary to reduce early mortality in VA ECMO bridged HTx. In the current study, an IMPACT score higher than 20 or a MELD-XI score over 28.4 would indicate a poor 1-year outcome, suggesting that cautious decision-making is necessary. Additionally, efforts should be made to reduce modifiable factors such as extubation (if possible), waiting until recovery of hepato-renal function, and controlling infection before allocation.

The present study has inherent limitations due to its retrospective and observational design. As the data were collected retrospectively from a single center, geographic and demographic biases may be present. It is important to note that the results may not be applicable to other institutions in South Korea and other countries due to regional variations in urgency status and policy differences. Specifically, as our transplant team gains more experience, patients with severe multi-organ dysfunction are now being excluded in advance, which could affect the cutoff value of certain parameters. Therefore, caution is warranted in interpreting the data. Additionally, the relatively small sample size and limited number of events may have reduced the post-hoc power. Therefore, further studies with larger sample sizes are needed.

In this study, significant differences in survival were observed between the ECMO-bridged HTx group and non-ECMO-bridged HTx group. However, among the ECMO bridged recipients, those who were non-awake (ventilator dependent) showed higher rate of MOF and mortality than the awake ECMO group. There was no significant difference in overall mortality between the non-ECMO and awake ECMO groups. This result suggests that the clinical outcome is affected by multi-organ failure, rather than ECMO itself. The high IMPACT score (>20) and MELD-XI (>28.4) could be used to select recipients or determine the timing of transplant in ECMO-bridged HTx.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

The stratification of recipients: IMPACT score

Click here to view

Supplementary Table 2

Baseline characteristics of 30-day survivals and deaths in non-awake ECMO group

Click here to view

Supplementary Table 3

The cut-off value of Variables in the VA-ECMO group

Click here to view

ORCID iDs
Ji Hoon Lim
https://orcid.org/0000-0002-8201-1517
Soo Yong Lee
https://orcid.org/0000-0003-2616-1294
Min Ho Ju
https://orcid.org/0000-0001-7839-8598
Seok Hyun Kim
https://orcid.org/0000-0003-4389-684X
Jin Hee Choi
https://orcid.org/0000-0002-3775-256X
Min Ku Chon
https://orcid.org/0000-0003-0183-6996
Sang Hyun Lee
https://orcid.org/0000-0001-7196-2643
Ki Won Hwang
https://orcid.org/0000-0002-1372-330X
Jeong Su Kim
https://orcid.org/0000-0001-6877-4289
Yong Hyun Park
https://orcid.org/0000-0001-6122-214X
Junehong Kim
https://orcid.org/0000-0003-0653-0929
Kook Jin Chun
https://orcid.org/0000-0002-6463-9407
Mi Hee Lim
https://orcid.org/0000-0002-0167-7836
Chee-hoon Lee
https://orcid.org/0000-0002-0456-225X
Hyung Gon Je
https://orcid.org/0000-0003-4713-2898

Funding
This study was supported by a 2023 research grant from Pusan National University Yangsan Hospital.

Conflict of Interest
The authors have no financial conflicts of interest.

Author Contributions
Conceptualization: Lee SY; Data curation: Min Ho Ju, Lee SY; Formal analysis: Ji Hoon Lim, Min Ho Ju; Investigation: Ji Hoon Lim; Methodology: Min Ho Ju, Lee SY; Resources: Lee SY; Supervision: Lee SY; Validation: Lee SY; Writing - original draft: Ji Hoon Lim, Min Ho Ju, Lee SY; Writing - review & editing: Min Ho Ju, Seok Hyun Kim, Jin Hee Choi, Min Ku Chon, Sang Hyun Lee, Ki Won Hwang, Jeong Su Kim, Yong Hyun Park, Junehong Kim, Kook Jin Chun, Mi Hee Lim, Chee-Hoon Lee, Hyung Gon Je, Lee SY.

REFERENCES

1. Guglin M, Zucker MJ, Bazan VM, et al. Venoarterial ECMO for adults: JACC scientific expert panel. J Am Coll Cardiol 2019;73:698-716.
PUBMED | CROSSREF
2. Lund LH, Khush KK, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult heart transplantation report-2017; focus theme: allograft ischemic time. J Heart Lung Transplant 2017;36:1037-46.
PUBMED | CROSSREF
3. Kim IC, Youn JC, Kobashigawa JA. The past, present and future of heart transplantation. Korean Circ J 2018;48:565-90.
PUBMED | CROSSREF
4. Korean Network for Organ Sharing. KONOS Annual Report. Seoul: Korean Network for Organ Sharing; 2019.
5. Zalawadiya S, Fudim M, Bhat G, Cotts W, Lindenfeld J. Extracorporeal membrane oxygenation support and post-heart transplant outcomes among United States adults. J Heart Lung Transplant 2017;36:77-81.
PUBMED | CROSSREF
6. Moonsamy P, Axtell AL, Ibrahim NE, et al. Survival after heart transplantation in patients bridged with mechanical circulatory support. J Am Coll Cardiol 2020;75:2892-905.
PUBMED | CROSSREF
7. Montisci A, Donatelli F, Cirri S, Coscioni E, Maiello C, Napoli C. Veno-arterial extracorporeal membrane oxygenation as bridge to heart

transplantation: the way forward. Transplant Direct 2021;7:e720.
PUBMED | CROSSREF

8. Fukuhara S, Takeda K, Kurlansky PA, Naka Y, Takayama H. Extracorporeal membrane oxygenation as a direct bridge to heart transplantation in adults. J Thorac Cardiovasc Surg 2018;155:1607-1618.e6.
PUBMED | CROSSREF
9. Coutance G, Jacob N, Demondion P, et al. Favorable outcomes of a direct heart transplantation strategy in selected patients on extracorporeal membrane oxygenation support. Crit Care Med 2020;48:498-506.
PUBMED | CROSSREF
10. Lorusso R, Shekar K, MacLaren G, et al. ELSO interim guidelines for venoarterial extracorporeal membrane oxygenation in adult cardiac patients. ASAIO J 2021;67:827-44.
PUBMED | CROSSREF
11. Lee SY, Ju MH. The clinical outcomes of marginal donor hearts: a single center experience. Korean Circ J 2023;53:e17.
CROSSREF
12. Heuman DM, Mihas AA, Habib A, et al. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl 2007;13:30-7.
PUBMED | CROSSREF
13. Kilic A, Allen JG, Weiss ES. Validation of the United States-derived index for mortality prediction after cardiac transplantation (IMPACT) using international registry data. J Heart Lung Transplant 2013;32:492-8.
PUBMED | CROSSREF
14. Weiss ES, Allen JG, Arnaoutakis GJ, et al. Creation of a quantitative recipient risk index for mortality prediction after cardiac transplantation (IMPACT). Ann Thorac Surg 2011;92:914-21.
PUBMED | CROSSREF
15. Kim D, Choi JO, Cho YH, et al. Impact of preoperative renal replacement therapy on the clinical outcome of heart transplant patients. Sci Rep 2021;11:13398.
PUBMED | CROSSREF
16. Grimm JC, Shah AS, Magruder JT, et al. MELD-XI score predicts early mortality in patients after heart transplantation. Ann Thorac Surg 2015;100:1737-43.
PUBMED | CROSSREF
17. Khush KK, Hsich E, Potena L, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: thirty-eighth adult heart transplantation report - 2021; focus on recipient characteristics. J Heart Lung Transplant 2021;40:1035-49.
PUBMED | CROSSREF
18. Kilic A, Mathier MA, Hickey GW, et al. Evolving trends in adult heart transplant with the 2018 heart allocation policy change. JAMA Cardiol 2021;6:159-67.
PUBMED | CROSSREF