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The Korean Organ Transplant Registry (KOTRY): Third Official Adult Heart Transplant Report

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AUTHOR'S SUMMARY

This study examines 709 heart transplants from the Korean Organ Transplant Registry, highlighting the rising utilization of mechanical support and its clinical impact. With expanded data, we identify factors influencing survival, rejection, and cardiac allograft vasculopathy (CAV). Notable findings include higher mortality with pre-transplant extracorporeal membrane oxygenation support, predicted heart mass mismatch, and age over 70, increased CAV with high-risk donors and elevated acute rejection with pre-transplantation antibody levels. Our study suggests statins and mammalian target of rapamycin inhibitors may prevent rejection and CAV. Additionally, we compare the characteristics and clinical outcomes of left ventricular assist device-assisted recipients.

ABSTRACT

Background and Objectives: The Korean Organ Transplant Registry (KOTRY) provided data for this third official report on adult heart transplantation (HT), including information from 709 recipients.

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

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
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Methods: Data from HTs performed at seven major centers in Korea between March 2014 and December 2020 were analyzed, focusing on immunosuppression, acute rejection, cardiac allograft vasculopathy (CAV), post-transplant survival, and mechanical circulatory support (MCS) usage.

Results: The median ages of the recipients and donors were 56.0 and 43.0 years, respectively. Cardiomyopathy and ischemic heart disease were the most common preceding conditions for HT. A significant portion of patients underwent HT at waiting list status 1 and 0. In the multivariate analysis, a predicted heart mass mismatch was associated with a higher risk of 1-year mortality. Patients over 70 years old had a significantly increased risk of 6-year mortality. The risk of CAV was higher for male donors and donors older than 45 years. Acute rejection was more likely in patients with panel reactive antibody levels above 80%, while statin use was associated with a reduced risk. The employment of left ventricular assist device as a bridge to transplantation increased from 2.17% to 22.4%. Pre-transplant extra-corporeal membrane oxygenation was associated with worse post-transplant survival.

Conclusions: In this third KOTRY report, we analyzed changes in the characteristics of adult HT recipients and donors and their impact on post-transplant outcomes. The most notable discovery was the increased use of MCS before HT and their impact on post-transplant outcomes.

Keywords: Heart transplantation; Heart failure; Registries

INTRODUCTION

In Korea, the first heart transplantation (HT) was conducted in 1992, marking the beginning of nearly three decades of significant progress in this field. Since that initial procedure, the annual incidence of HT has consistently increased, reaching a plateau in recent years.[1] Various advancements, such as improved recipient selection criteria, enhanced surgical technologies, and standardized protocols,[2] have contributed to better short- and long-term outcomes.[3] Recently, the median survival time for individuals who survive the immediate postoperative period has extended to approximately 15 years.[3]

Founded by the Korean Society of Transplantation and the Korea Disease Control and Prevention Agency in 2014, the Korean Organ Transplant Registry (KOTRY) serves as the primary nationwide registry for organ transplantation in Korea.[4] Its primary objective is to collect extensive data on various aspects of transplantation, including recipient, donor, and transplant characteristics, as well as post-transplant morbidity and mortality outcomes. This third biannual KOTRY report includes data from 709 HT procedures performed on adult recipients between March 2014 and December 2020. A focused analysis of left ventricular assist devices (LVADs), a type of durable mechanical circulatory support (MCS), was conducted. This analysis examines the characteristics and post-transplant outcomes of patients who received LVADs before HT as bridge therapy, providing a comprehensive assessment of current trends, challenges, and future directions of HT in Korea.

METHODS

As detailed in previous annual reports from the KOTRY,[1)5)] patients undergoing HT were enrolled from seven nationally representative medical centers and followed up longitudinally.

Follow-up assessments were planned at intervals of 1-, 6-, and 12-month post-transplant, and yearly thereafter. Data relevant to transplant-related events such as episodes of acute rejection, infection, and overall survival were systematically recorded. Written informed consent was obtained from the recipients themselves or from their legal representatives when patients were unable to provide consent due to medical severity. Clinical research coordinators, assisting attending physicians, completed a web-based case report form through the Clinical Data Management System administered by the Korea National Institute of Health. Individuals who had received multi-organ transplants were excluded from the primary dataset.

Data summaries, coupled with trend-focused analyses, were provided for the entire cohort. Adult HT patients were categorized into 4 cohorts: 2014–2015, 2016–2017, 2018–2019, and 2020. Each timeframe had a comparable number of transplants. The first confirmed case of coronavirus disease 2019 (COVID-19) in Korea was reported on January 20, 2019, indicating that the final cohort corresponded to the COVID-19 pandemic. Changes in Korea's HT waiting list criteria were adopted since 2017, which defined the additional regional bonus points, and reclassification of mechanical ventilation (MV) due to heart failure (HF) as status 0 (**Supplementary Table 1**) along with the onset of the COVID-19 pandemic in 2019 should be considered for interpretation. In our study, we defined a cardiac allograft vasculopathy (CAV) event as the occurrence of CAV graded 1 or higher according to the International Society of Heart and Lung Transplantation (ISHLT) guidelines.[6] Rejection was defined as treatment for rejection regardless of histologic grade or a biopsy result of grade 2 or higher regardless of treatment. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate consistently below 60 mL/min for at least three months before transplantation. We collected data on total panel reactive antibody (PRA), PRA1, and PRA2 levels and categorized them into 0% (non-sensitized), 1–79% (moderately sensitized), and >80% (highly sensitized) groups for analysis within each respective PRA category.[7] Owing to the high prevalence of missing data and insufficient information on PRA2, we used the PRA1 data for the analysis. We categorized patients based on MCS support immediately before transplantation, assigning cases where LVAD was implemented following extracorporeal membrane oxygenation (ECMO) to the LVAD group.

Calculation of predicted heart mass

Predicted heart mass (PHM) was calculated using published equations for left and right ventricular PHMs provided by the Multi-Ethnic Study of Atherosclerosis.[8]

(1) Predicted Left Ventricular Mass (g) = $\alpha \times Height^{0.54}$ (m) $\times Weight^{0.61}$ (kg), where $\alpha = 6.82$ for women and 8.25 for men

(2) Predicted Right Ventricular Mass (g) = $\alpha \times Age^{0.32}$ (years) $\times Height^{1.135}$ (m) $\times Weight^{0.315}$ (kg), where $\alpha = 10.59$ for women and 11.25 for men

(3) PHM (g) = Predicted Left Ventricular Mass (g) + Predicted Right Ventricular Mass (g)

(4) PHM Mismatch (%) = $\left[\dfrac{Donor\ PHM - Recipient\ PHM}{Recipient\ PHM} \right] \times 100$

Donor-recipient size and sex matching

In a previous study, the effect of size match on mortality after HT was assessed by classifying participants into seven groups using the donor-recipient size metric.[9] Considering the design of this study and similar previous studies,[10] we categorized participants based on

donor-recipient PHM mismatch: <−30% and −30% to −20% (under-sized), −20% to +20% (size-matched), +20% to +30%, and >+30% (over-sized). In subsequent analyses, we further grouped the undersized and oversized groups into a 'mismatched,' while designating the size-matched group as 'matched.' Sex matching was classified into 4 groups according to recipient and donor sex.

Statistical analysis

Continuous variables are presented as mean ± standard deviation, while categorical variables are described by frequency and proportion. Statistical methods were tailored to the distribution of each variable. Survival analysis was conducted using the Kaplan-Meier estimator and the log-rank test to compare survival curves across different groups. For comparisons involving three or more groups, adjustments were made using the Benjamini-Hochberg method. The Benjamini-Hochberg method was applied to control the false discovery rate in multiple comparisons. Multivariable analysis was performed using significant variables identified through univariate analysis. Cox proportional hazards regression was employed to assess patient survival and survival outcomes for each specific event, adjusting for these significant variables. Multivariable proportional hazards regression analyses were used to identify independent risk factors for clinical events occurring during the follow-up period post-transplant, though causality cannot be established and interpretations should be approached with caution. The covariates in these models are listed in **Supplementary Table 2**. In our multivariate analysis, we utilized stepwise selection with the following detailed settings: the entry p value threshold was set at 0.20, and the removal p value threshold was set at 0.15. Statistical analyses were performed using R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Transplant trends and recipient characteristics

Following the publication of the second annual report from KOTRY,[1] an additional 309 HT were added up to December 2020. A total of 1,146 HTs were conducted nationally between 2014 and 2020, and the present study incorporated data from approximately 61.9% of these cases. Stabilization in the annual volume of HT has been observed over the past 4 years, largely attributable to limitations in donor availability. **Table 1** shows the baseline recipient characteristics according to the transplant era. The age profile of HT recipients showed an upward trend from 2014–2015 period to 2020, with the median age increasing from 53 to 60 years. The sex distribution among HT recipients remained constant, with males constituting approximately 70% of the total. The number of comorbidities among transplant recipients has increased. The prevalence of CKD among HT recipients has shown an upward trend in recent eras. The prevalence of diabetes and hypertension among HT recipients has increased. Cardiomyopathy and ischemic heart disease (IHD) were the most common indications for transplantation, followed by valvular heart disease. Donor-recipient sex matching has remained consistent over time, with male-to-male transplantations continuing as the predominant pairing. A noteworthy observation is the substantial increase in the incidence of heart re-transplantation, from 3.3% during the initial period to 9.2% in the most recent period. The pre-transplant PRA levels among recipients have significantly increased over time, particularly those with PRA ≥80%, indicating a rise in highly sensitized individuals among transplant recipients.

Table 1. Baseline characteristic according to transplant era

Characteristics	Total (n=709)	2014–2015 (n=184)	2016–2017 (n=217)	2018–2019 (n=210)	2020 (n=98)	Overall p value	p value for trend
Recipient characteristics							
Age (years)	56.0 [45.0, 62.0]	53.0 [41.8, 61.0]	56.0 [43.0, 61.0]	56.0 [48.3, 63.0]	60.0 [50.0, 65.0]	0.001	<0.001
Sex, male	492 (69.4)	123 (66.8)	149 (68.7)	151 (71.9)	69 (70.4)	0.732	0.333
Height (cm)	166±8.55	166±8.47	166±8.49	166±8.63	166±8.78	0.832	0.742
Weight (kg)	62.3±12.1	60.9±11.6	62.6±12.5	63.0±12.2	63.0±11.9	0.281	0.094
BMI (kg/m²)	22.6±3.55	22.1±3.39	22.8±3.79	22.7±3.47	22.9±3.43	0.147	0.07
Cigarette smoking						0.074	0.215
Current	74 (10.5)	13 (7.10)	32 (14.7)	22 (10.5)	7 (7.37)		
Former	217 (30.8)	67 (36.6)	63 (29.0)	63 (30.0)	24 (25.3)		
Never	414 (58.7)	103 (56.3)	122 (56.2)	125 (59.5)	64 (67.4)		
ABO						0.257	0.568
A	248 (35.0)	71 (38.6)	80 (36.9)	60 (28.6)	37 (37.8)		
B	184 (26.0)	47 (25.5)	55 (25.3)	64 (30.5)	18 (18.4)		
O	169 (23.8)	42 (22.8)	50 (23.0)	55 (26.2)	22 (22.4)		
AB	108 (15.2)	24 (13.0)	32 (14.7)	31 (14.8)	21 (21.4)		
Comorbidities							
Diabetes	210 (29.6)	40 (21.7)	67 (30.9)	76 (36.2)	27 (27.6)	0.017	0.047
Hypertension	215 (30.3)	55 (29.9)	68 (31.3)	61 (29.0)	31 (31.6)	0.948	0.956
Chronic kidney disease	124 (17.5)	24 (13.1)	34 (15.7)	41 (19.5)	25 (25.5)	0.048	0.006
Renal replacement therapy	126 (17.8)	23 (12.5)	38 (17.5)	43 (20.5)	22 (22.4)	0.110	0.017
Creatinine (mg/dL)	1.30±0.99	1.23±0.87	1.31±1.03	1.25±0.72	1.52±1.46	0.101	0.089
Cancer history	53 (7.48)	15 (8.15)	14 (6.45)	16 (7.62)	8 (8.16)	0.914	0.954
HBs Ag	28 (4.01)	8 (4.44)	11 (5.14)	6 (2.87)	3 (3.12)	0.652	0.351
HBs Ab	464 (66.6)	126 (70.0)	138 (65.1)	135 (64.6)	65 (67.7)	0.664	0.516
Anti-HCV Ab	7 (1.00)	2 (1.10)	2 (0.95)	3 (1.44)	0 (0.00)	0.841	0.643
CMV IgG	650 (96.9)	166 (96.5)	199 (97.1)	195 (97.5)	90 (95.7)	0.816	0.958
EBV IgG	645 (97.4)	160 (96.4)	194 (96.5)	200 (99.5)	91 (96.8)	0.091	0.248
LVEF (%)	26.4±13.0	25.6±12.2	27.0±14.0	25.6±12.1	28.3±14.1	0.293	0.335
RVSP (mmHg)	40.9±16.4	42.6±16.9	41.1±17.7	39.8±14.9	39.0±15.3	0.339	0.069
Transplant characteristics							
Etiology for heart failure							
Cardiomyopathy	408 (57.5)	126 (68.5)	129 (59.4)	96 (45.7)	57 (58.2)	<0.001	0.001
Ischemic heart disease	150 (21.2)	26 (14.1)	46 (21.2)	63 (30.0)	15 (15.3)	0.001	0.067
Valvular heart disease	31 (4.37)	7 (3.80)	8 (3.69)	10 (4.76)	6 (6.12)	0.738	0.334
Restrictive cardiomyopathy						0.764	0.365
Cardiac amyloidosis	17 (68.0)	5 (62.5)	4 (57.1)	7 (77.8)	1 (100)		
Cardiac sarcoidosis	8 (32.0)	3 (37.5)	3 (42.9)	2 (22.2)	0 (0.00)		
Re-transplantation	29 (4.09)	6 (3.26)	8 (3.69)	6 (2.86)	9 (9.18)	0.091	0.093
Waiting list status							<0.001
0	220 (31.0)	24 (13.0)	74 (34.1)	91 (43.3)	31 (31.6)		
1	428 (60.4)	130 (70.7)	135 (62.2)	103 (49.0)	60 (61.2)		
2	34 (4.80)	15 (8.15)	4 (1.84)	10 (4.76)	5 (5.10)		
3	27 (3.81)	15 (8.15)	4 (1.84)	6 (2.86)	2 (2.04)		
Sex matching						0.903	0.674
Female to female	96 (13.5)	27 (14.7)	26 (12.0)	30 (14.3)	13 (13.3)		
Female to male	106 (15.0)	25 (13.6)	36 (16.6)	31 (14.8)	14 (14.3)		
Male to female	121 (17.1)	34 (18.5)	42 (19.4)	29 (13.8)	16 (16.3)		
Male to male	386 (54.4)	98 (53.3)	113 (52.1)	120 (57.1)	55 (56.1)		
Assisting device							<0.001
No	446 (62.9)	149 (81.0)	145 (66.8)	99 (47.1)	53 (54.1)		
ECMO	205 (28.9)	29 (15.8)	71 (32.7)	82 (39.0)	23 (23.5)		
IABP	2 (0.28)	2 (1.09)	0 (0.00)	0 (0.00)	0 (0.00)		
LVAD	56 (7.90)	4 (2.17)	1 (0.46)	29 (13.8)	22 (22.4)		
Mechanical ventilation	161 (22.7)	30 (16.3)	57 (26.3)	57 (27.1)	17 (17.3)	0.020	0.345
IV inotropes	596 (84.1)	172 (93.5)	197 (90.8)	156 (74.3)	71 (72.4)	<0.001	<0.001
PRA group						0.528	0.287
0%	446 (63.6)	118 (64.8)	136 (64.2)	134 (63.8)	58 (59.8)		
1–79%	216 (30.8)	55 (30.2)	65 (30.7)	67 (31.9)	29 (29.9)		
≥80%	39 (5.56)	9 (4.95)	11 (5.19)	9 (4.29)	10 (10.3)		

Table 1. (Continued) Baseline characteristic according to transplant era

Characteristics	Total (n=709)	2014–2015 (n=184)	2016–2017 (n=217)	2018–2019 (n=210)	2020 (n=98)	Overall p value	p value for trend
Donor characteristics							
Donor age (years)	43.0 [31.0, 49.0]	40.0 [28.8, 46.0]	43.0 [34.0, 50.0]	43.0 [33.0, 50.0]	43.5 [34.0, 50.0]	0.002	0.009
Donor sex, male	507 (71.5)	132 (71.7)	155 (71.4)	149 (71.0)	71 (72.4)	0.994	0.984
Donor height (cm)	169±7.41	169±7.58	169±7.18	170±7.74	169±6.95	0.664	0.388
Donor weight (kg)	67.5±12.1	67.4±11.9	66.9±11.5	67.7±12.9	68.5±11.9	0.710	0.407
Donor BMI (kg/m²)	23.5±3.56	23.6±3.62	23.4±3.33	23.4±3.66	23.9±3.75	0.724	0.651
Donor hypertension	99 (14.6)	25 (13.9)	28 (13.5)	34 (17.1)	12 (12.9)	0.690	0.737
Donor diabetes	34 (4.97)	6 (3.31)	9 (4.33)	18 (9.00)	1 (1.05)	0.015	0.529

Continuous variables are presented as mean ± standard deviation or median with range, categorical variables are described by number (%).
Ab = antibody; Ag = antigen; BMI = body mass index; CMV = cytomegalovirus; EBV = Ebstein-Barr virus; ECMO = extracorporeal membrane oxygenation; HBs = hepatitis B surface; HCV = hepatitis C virus; IABP = intraaortic balloon pump; IgG = immunoglobulin G; IV = intravenous; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; PRA = panel reactive antibody; RVSP = right ventricular systolic pressure.

Immunosuppression

The immunosuppressive drugs administered to patients at the time of discharge are shown in **Supplementary Table 3**. The most commonly used induction therapy was basiliximab, which was prescribed to 83.9% of patients, typically followed by a maintenance regimen consisting of calcineurin inhibitors (CNIs), mycophenolate, and corticosteroids. Tacrolimus has been increasingly prescribed as the primary CNI over cyclosporine. During the study period, everolimus was the only mammalian target of rapamycin (mTOR) inhibitor prescribed at discharge. Most patients (94.5%) were prescribed corticosteroids at the time of discharge. After discharge, the corticosteroid prescription rates at 6 months, 1 year, 3 years, and 5 years were 76.6%, 72.7%, 38.6%, and 37.4%, respectively.

Survival analysis

The overall survival curve showed that the one-year post-transplant survival rate was 89%. The 2-, 3-, 4-, 5-, and 6-year survival rates were 86%, 85%, 84%, 82%, and 80%, respectively. No significant variations were observed in the survival curves across different transplantation eras (**Figure 1A**). Survival rates differed according to the age group of the recipients, with those aged ≥70 years exhibiting significantly lower survival rates (p<0.0001; **Figure 1B**, **Supplementary Table 4**). The recipient sex did not have an impact on short- and long-term survival rates (**Figure 1C**). The survival rate varied depending on the underlying disease leading to transplantation (**Figure 1D**), with patients transplanted for cardiomyopathy demonstrating the most favorable survival outcomes. The difference in PHM influenced short-term survival at one year (**Supplementary Figure 1A**) but did not have a significant effect on long-term (6-year) survival (**Supplementary Figure 1B**). In survival analysis, higher pre-transplant PRA was shown to be associated with poorer patient survival (**Supplementary Figure 2**).

Regression analysis

One-year mortality

Univariate Cox regression analysis identified multiple significant predictors of 1-year mortality following HT (**Supplementary Table 5**). Recipients aged 70 years and above had a significantly increased risk of one-year mortality, with a hazard ratio (HR) of 2.41 (95% confidence interval [CI], 1.10–5.24; p=0.027). Both IHD and CKD were significant risk factors for 1-year mortality, with IHD having an HR of 1.71 (95% CI, 1.05–2.81; p=0.033) and CKD an HR of 2.19 (95% CI, 1.33–3.62; p=0.002). MV prior to transplantation was associated with a significantly increased HR of 3.56 (95% CI, 2.25–5.63; p<0.001). PHM mismatch significantly increased the risk of 1-year mortality, as indicated by an HR of 2.10 (95% CI, 1.32–3.33; p=0.002). Recipients with elevated PRA levels also had a higher mortality risk (HR, 1.66; 95%
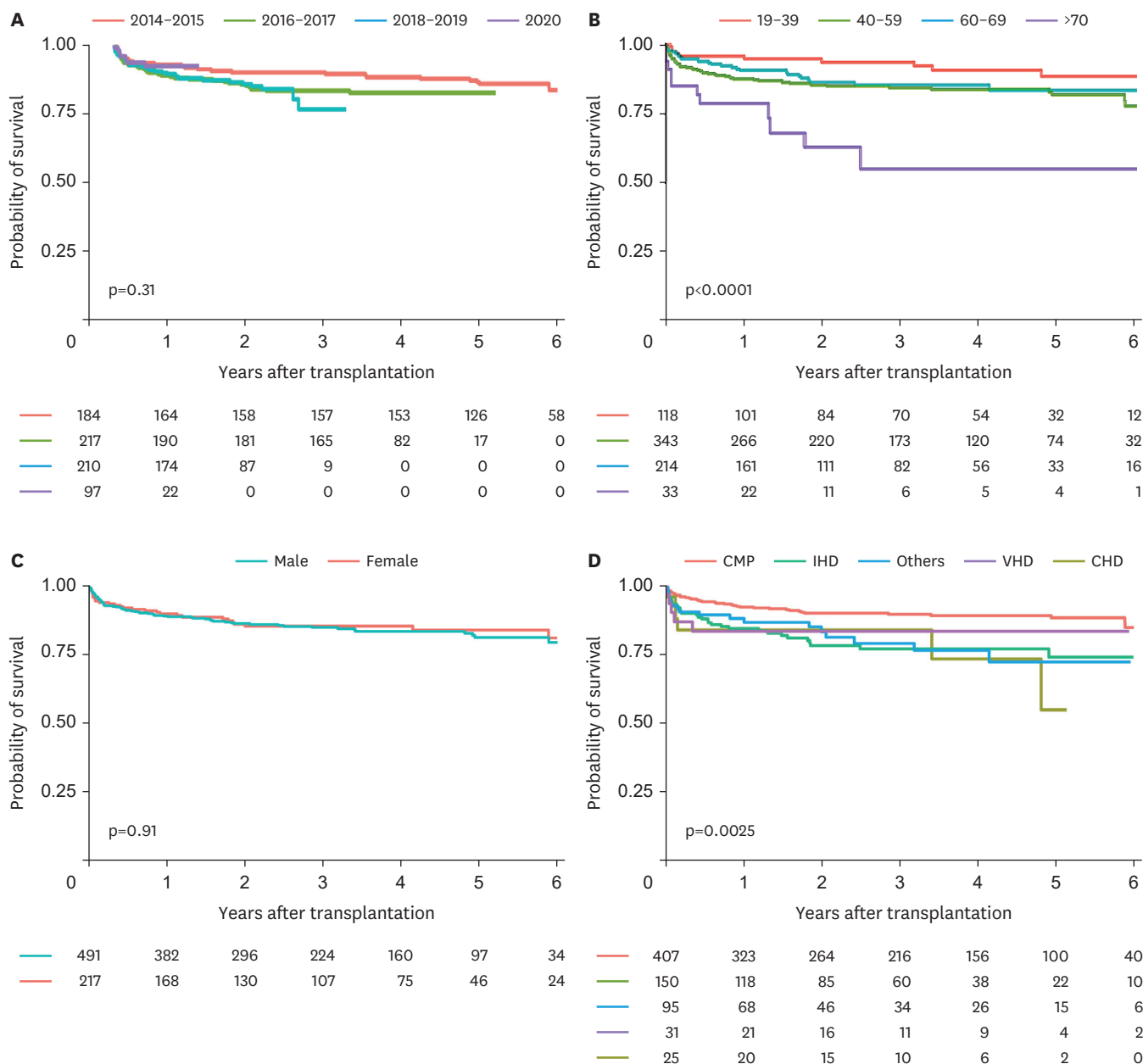
Figure 1. Kaplan-Meier survival curves. (A) By year of transplantation, (B) recipient age, (C) recipient sex, and (D) etiology of heart failure.
CHD = congenital heart disease; CMP = cardiomyopathy; IHD = ischemic heart disease; VHD = valvular heart disease.

CI, 1.02–2.70; p=0.04). While the 1-year mortality risk was not significantly elevated among those bridged to transplant with LVADs (HR, 0.94; 95% CI, 0.28–3.08; p=0.912), the use of ECMO prior to transplantation was associated with a heightened risk of 1-year mortality (HR, 3.55; 95% CI, 2.20–5.73; p<0.001).

In multivariate Cox regression analysis (**Figure 2A**), one-year mortality was significantly associated with CKD and MV prior to transplantation, with HRs of 2.34 (95% CI, 1.41–3.88; p=0.001) and 2.38 (95% CI, 1.26–4.52; p=0.008), respectively. Age over 70 also heightened the risk (HR, 2.22; 95% CI, 1.00–4.91; p =0.049). A PHM mismatch significantly increased 1-year mortality risk (HR, 1.99; 95% CI, 1.25–3.19; p=0.004). ECMO use was moderately

A

Forest plot of hazard ratio
(1-year survival)

Recipient age >70 years	2.22 (1.00–4.91)
Congenital heart disease	2.78 (0.99–7.80)
Mechanical ventilation	2.38 (1.26–4.52)
Chronic kidney disease	2.34 (1.41–3.88)
LVAD vs. No assist device	0.82 (0.25–2.76)
ECMO vs. No assist device	1.99 (1.02–3.88)
PHM mismatched	1.99 (1.25–3.19)

Hazard ratio

B

Forest plot of hazard ratio
(overall survival)

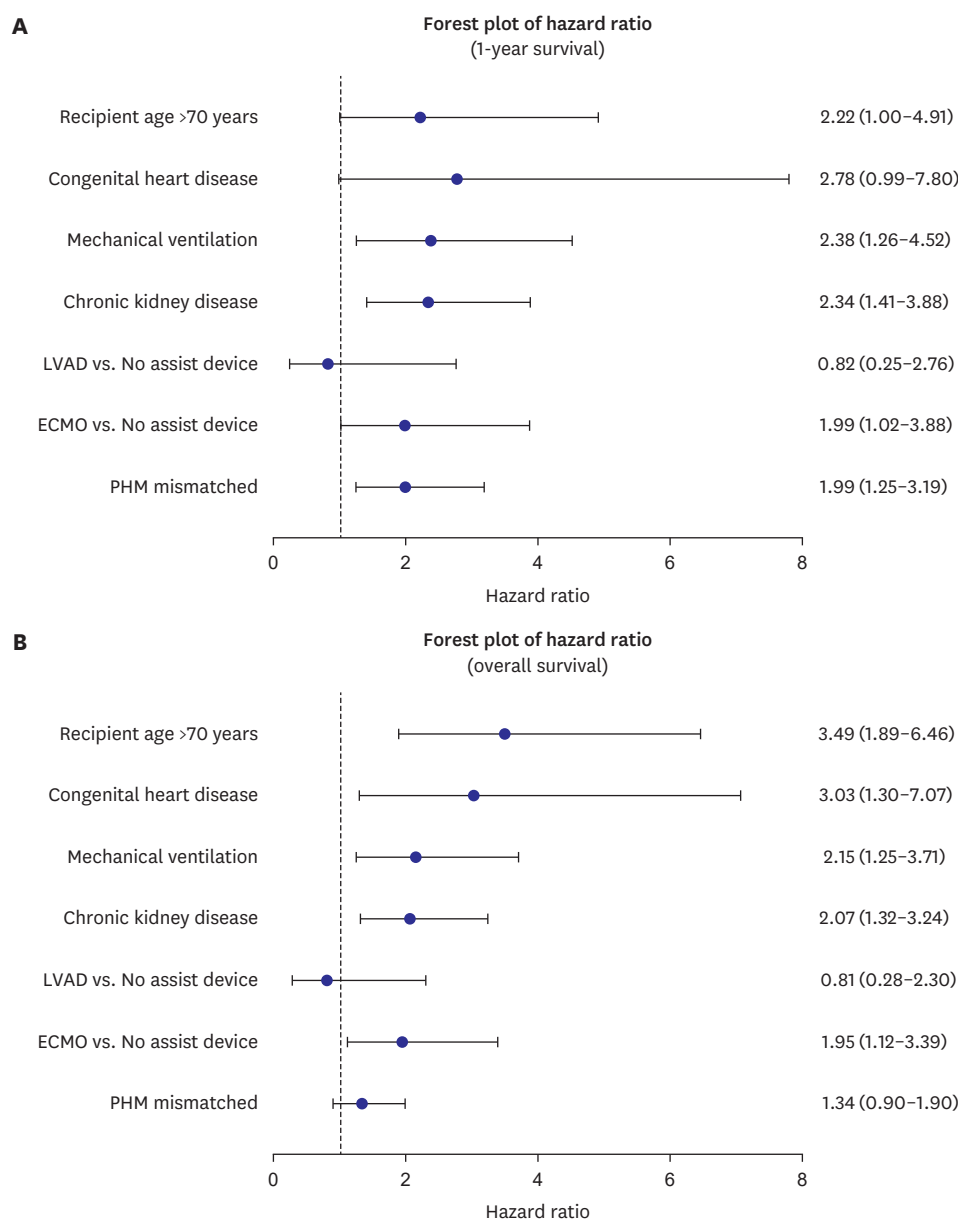|	
Recipient age >70 years	3.49 (1.89–6.46)
Congenital heart disease	3.03 (1.30–7.07)
Mechanical ventilation	2.15 (1.25–3.71)
Chronic kidney disease	2.07 (1.32–3.24)
LVAD vs. No assist device	0.81 (0.28–2.30)
ECMO vs. No assist device	1.95 (1.12–3.39)
PHM mismatched	1.34 (0.90–1.90)

Hazard ratio

Figure 2. Forest plot of hazard ratio for (A) 1-year and (B) overall survivals.
ECMO = extracorporeal membrane oxygenation; LVAD = left ventricular assist device; PHM = predicted heart mass.

associated with increased risk (HR, 1.99; 95% CI, 1.02–3.88; p=0.043). Notably, LVAD use did not significantly impact one-year mortality (HR, 0.82; 95% CI, 0.25–2.76; p=0.755).

Long-term mortality
In the univariate Cox regression analysis (**Supplementary Table 6**) evaluating 6-year mortality post-HT, IHD was associated with an increased risk (HR, 1.75; 95% CI, 1.15–2.65; p=0.009). Recipients aged over 70 had higher mortality (HR, 5.66; 95% CI, 2.48–12.91; p<0.001) compared to those <40. CKD (HR, 1.87; 95% CI, 1.20–2.91; p=0.006) and MV prior to transplantation (HR, 3.12; 95% CI, 2.12–4.60; p<0.001) were also significant predictors of 6-year mortality. However, a PHM mismatch (HR, 1.40; 95% CI, 0.95–2.07; p=0.092) does not increase long-term mortality. ECMO use before transplantation substantially increased

long-term mortality (HR, 3.14; 95% CI, 2.11–4.67; p<0.001), whereas LVAD use did not significantly affect long-term mortality (HR, 0.98; 95% CI, 0.35–2.72; p=0.965).

In the multivariate Cox regression analysis (**Figure 2B**), age over 70 years was associated with increased long-term mortality risk (HR, 3.50; 95% CI, 1.89–6.46; p<0.001). Additionally, congenital heart disease (HR, 3.03; 95% CI, 1.30–7.07; p=0.010), MV before transplantation (HR, 2.15; 95% CI, 1.25–3.71; p=0.006), and CKD (HR, 2.07; 95% CI, 1.32–3.24; p=0.002) were all associated with increased long-term mortality risk. The use of ECMO before transplantation substantially raised the risk of mortality (HR, 1.95; 95% CI, 1.12–3.39; p=0.018). However, a PHM mismatch and pre-transplant LVAD use did not significantly impact long-term mortality outcomes, with HRs of 1.34 (95% CI, 0.90–1.99; p=0.147) and 0.81 (95% CI, 0.28–2.30; p=0.693), respectively.

Rejection

The incidence rates of acute rejection, as defined by our study, were highest in the first year, with rates of 10.9%, 30.1%, and 33.7% at 1, 6, and 12 months, respectively. Highly sensitized recipients exhibited a significantly higher incidence of acute rejection compared to non-sensitized patients (**Figure 3A**). Patients prescribed statins at discharge experienced fewer acute rejection episodes than those not prescribed statins (**Figure 3B**). Pre-transplant MCS, such as ECMO or LVAD, was associated with a higher incidence of acute rejection than in patient groups without MCS support (**Figure 4**). Transplants conducted in 2020 appeared to have a lower rate of acute rejection compared to previous periods; however, this may be attributed to the shorter follow-up duration and the impact of the COVID-19 pandemic.

In the univariate analysis, pre-transplant ECMO use, cold ischemic time over 2 hours, and PRA levels ≥80% were associated with an increased risk of acute rejection, while transplantation in 2020 and statin prescriptions at discharge were associated with a reduced risk of acute rejection (**Supplementary Table 7**). In the multivariate Cox regression analysis (**Figure 5A**), transplants performed in 2020 still demonstrated a lower risk of CAV (HR, 0.40; 95% CI, 0.24–0.69;
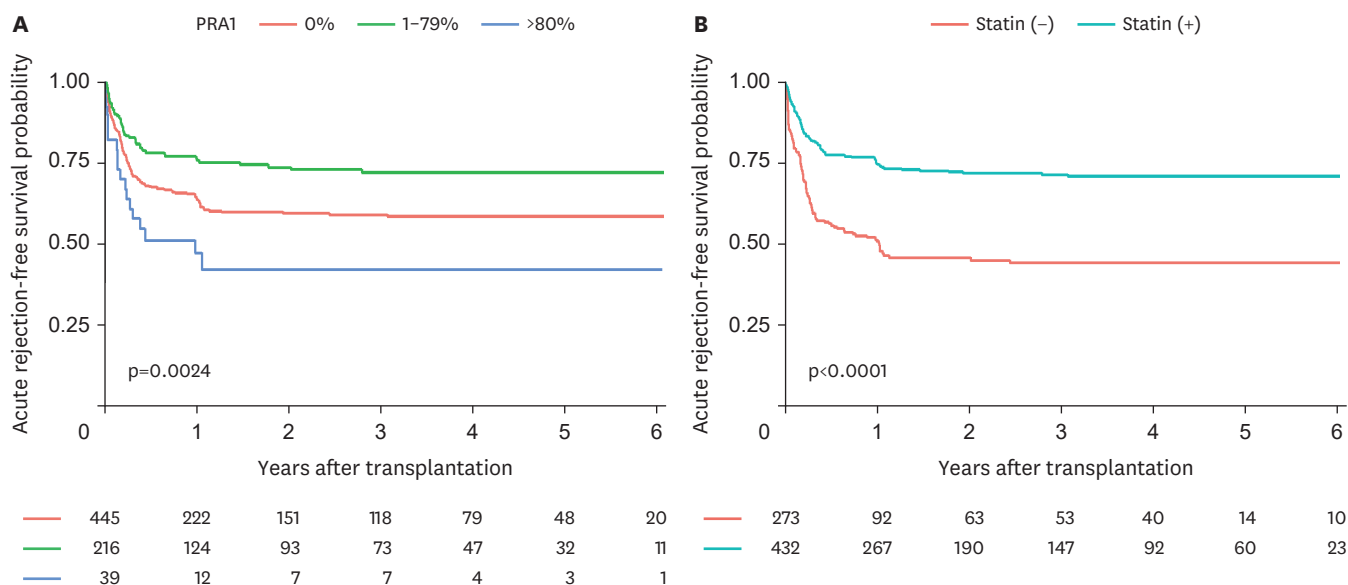

Figure 3. Kaplan-Meier analysis of acute rejection-free survival according to (A) pre-transplant PRA levels and (B) statin prescription at discharge.
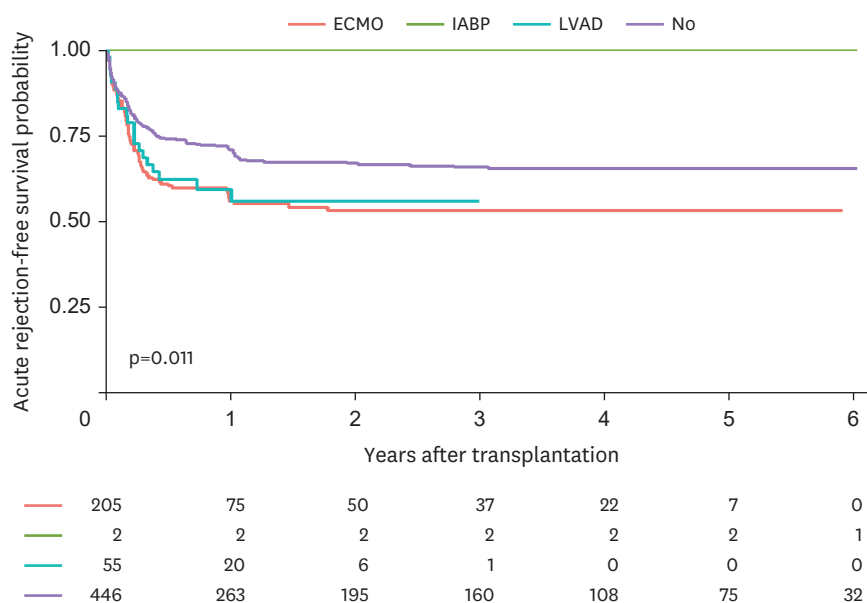PRA = panel reactive antibody.

Figure 4. Kaplan-Meier analysis of acute rejection-free survival according to pre-transplant assist device type. ECMO = extracorporeal membrane oxygenation; IABP = intraaortic balloon pump; LVAD = left ventricular assist device.

p<0.001). Pre-transplant ECMO support was associated with an increased risk of acute rejection (HR, 1.53; 95% CI, 1.14–2.06; p=0.004). An extended cold ischemic time exceeding 2 hours was also associated with heightened acute rejection risk (HR, 1.31; 95% CI, 1.01–1.70; p=0.040). PRA levels above 80% substantially increased the risk of acute rejection (HR, 2.18; 95% CI, 1.32–3.59; p=0.002). The prescription of statins at discharge was significantly reduced risk of acute rejection, with an HR of 0.43 (95% CI, 0.32–0.56; p<0.001). The use of an LVAD prior to transplantation, did not showed a significant impact on the risk of developing rejection.

Cardiac allograft vasculopathy

The incidence of CAV after HT rose from 1.42% at 1 year to 7.75% at 3 years and 15.68% at 5 years (**Supplementary Figure 3**). Non-sensitized recipients with a pre-transplant PRA of 0 had a lower incidence of CAV. The results of the univariate Cox regression analysis, as detailed in **Supplementary Table 8**, show that male donors have a significantly higher risk of CAV, with an HR of 2.84 (95% CI, 1.35–5.96; p=0.006). Donor age over 45 years, shows a trend towards marginal significance with an HR of 1.55 (95% CI, 0.94–2.55; p=0.087). However, the recipient's male sex does not significantly affect the risk of CAV (HR, 1.04; 95% CI, 0.60–1.78; p=0.769). The prescription of statins at discharge significantly increased the risk of CAV (HR, 3.84; 95% CI, 1.83–8.08; p<0.001). In contrast, the prescription of everolimus at discharge indicated a protective effect (HR, 0.40; 95% CI, 0.13–1.27, p=0.12). Regarding the incidence of CAV, there were no statistically significant differences based on the presence or type of pre-transplant assist devices (**Supplementary Figure 4**).

Multivariate Cox regression (**Figure 5B**) identified male donor sex (HR, 2.99; 95% CI, 1.42–6.28; p=0.004) and donor age over 45 (HR, 1.75; 95% CI, 1.06–2.89; p=0.029) as significant risk factors for CAV. mTOR inhibitor (everolimus) at discharge showed a protective trend (HR, 0.35; 95% CI, 0.11–1.11; p=0.075). However, it is important to acknowledge that these findings did not reach statistical significance likely due to the limitations of sample size and the relatively short follow-up duration. Interestingly, statins, commonly prescribed to reduce the risk of CAV, were associated with an increased risk of CAV (HR, 4.15; 95% CI, 1.97–8.74; p<0.001).

A

Forest plot of hazard ratio
(Acute rejection)

2016–2017 vs 2014–2015	0.74 (0.53–1.03)
2018–2019 vs 2014–2015	0.80 (0.57–1.14)
2020 vs 2014–2015	0.40 (0.24–0.69)
LVAD vs. No assist device	1.63 (0.98–2.71)
ECMO vs. No assist device	1.53 (1.14–2.06)
Cold ischemic time >2 hour	1.31 (1.01–1.70)
PRA 1–79%	0.73 (0.53–1.00)
PRA >80%	2.18 (1.32–3.59)
Statin at discharge	0.42 (−0.32–0.56)

Hazard ratio

B

Forest plot of hazard ratio
(Cardiac allograft vasculopathy)

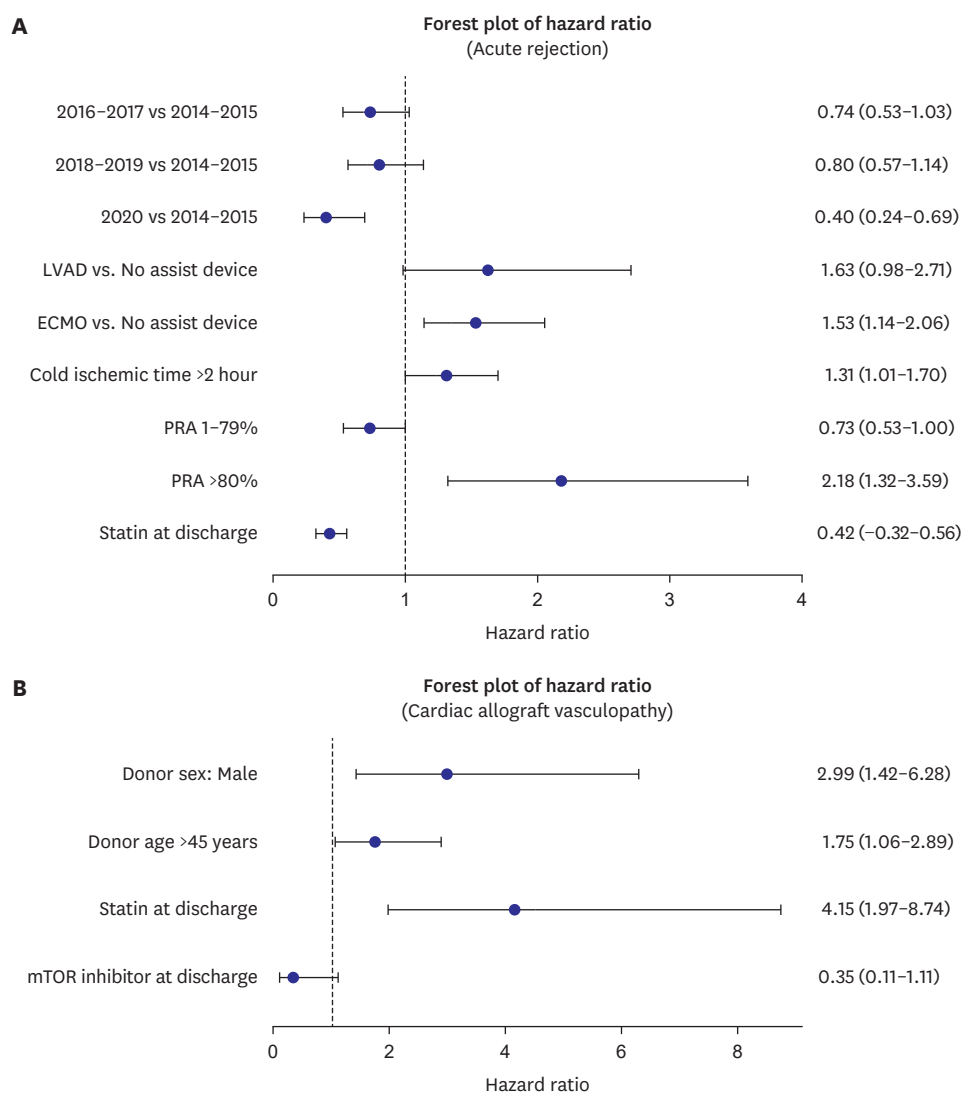|	
Donor sex: Male	2.99 (1.42–6.28)
Donor age >45 years	1.75 (1.06–2.89)
Statin at discharge	4.15 (1.97–8.74)
mTOR inhibitor at discharge	0.35 (0.11–1.11)

Hazard ratio

Figure 5. Forest plot of hazard ratios for (A) acute rejection and (B) cardiac allograft vasculopathy.
ECMO = extracorporeal membrane oxygenation; LVAD = left ventricular assist device; mTOR = mammalian target of rapamycin; PRA = panel reactive antibody.

Focused topic: Left ventricular assist device

Technological advancements and changes in Korean heart allocation criteria in 2017 led to increased MCS use as a bridge to transplantation (**Supplementary Figure 4**). Pre-transplant ECMO use increased from 15.8% to 23.5%, whereas the introduction of insurance coverage for LVADs in October 2018 led to an increase in their use from 2.17% to 22.4%. The ECMO group had a higher pre-transplant disease severity compared to the LVAD group (lower left ventricular ejection fraction, higher right ventricular systolic pressure [RVSP], greater use of renal replacement therapy, MV, intravenous inotropes, and a higher percentage on waiting list 0) (**Supplementary Table 9**). This shift from inotropic agents to LVADs likely reduced pre-transplant hospitalization from 60.7% to 44.6%. Patients in the LVAD-assisted group showed distinct demographic and clinical characteristics compared to those not receiving LVAD support (**Table 2**). Notably, these patients were significantly older, and significant variability in blood type distribution was observed, particularly with a higher prevalence of type O blood in the LVAD-assisted group (22.8% in non-LVAD assisted group vs. 35.7% in LVAD-assisted group). Prevalence

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Table 2. Baseline characteristics according to pre-transplant left ventricular assist device support

Characteristics	LVAD (−) (n=653)	LVAD (+) (n=56)	p value
Recipient characteristics			
Age (years)	52.0±13.0	59.9±11.1	<0.001
Sex, male	448 (68.6)	44 (78.6)	0.161
Height (cm)	166±8.59	166±8.13	0.694
Weight (kg)	62.2±12.2	64.0±11.6	0.280
BMI (kg/m²)	22.6±3.59	23.0±3.12	0.292
Cigarette smoking			0.794
Current	68 (10.5)	6 (10.9)	
Former	198 (30.5)	19 (34.5)	
Never	384 (59.1)	30 (54.5)	
ABO			0.029
A	228 (34.9)	20 (35.7)	
B	170 (26.0)	14 (25.0)	
O	149 (22.8)	20 (35.7)	
AB	106 (16.2)	2 (3.57)	
Comorbidities			
Diabetes	192 (29.4)	18 (32.1)	0.781
Hypertension	197 (30.2)	18 (32.1)	0.875
Chronic kidney disease	112 (17.2)	12 (21.4)	0.535
Renal replacement therapy	116 (17.8)	10 (17.9)	NS
Creatinine (mg/dL)	1.30±1.01	1.32±0.66	0.827
Cancer history	51 (7.81)	2 (3.57)	0.422
HBs Ag	26 (4.04)	2 (3.57)	NS
HBs Ab	424 (66.1)	40 (71.4)	0.512
Anti-HCV Ab	7 (1.09)	0 (0.00)	NS
CMV IgG	602 (96.9)	48 (96.0)	0.665
EBV IgG	595 (97.5)	50 (96.2)	0.636
LVEF (%)	26.7±13.4	23.3±6.33	0.002
RVSP (mmHg)	41.4±16.6	32.1±9.74	<0.001
Transplant characteristics			
Waiting time (days)	203±467	429±789	0.039
Etiology for heart failure			
Cardiomyopathy	382 (58.5)	26 (46.4)	0.107
Ischemic heart disease	123 (18.8)	27 (48.2)	<0.001
Valvular heart disease	30 (4.59)	1 (1.79)	0.502
Restrictive cardiomyopathy			NS
Cardiac amyloidosis	17 (68.0)	0 (0.0)	
Cardiac sarcoidosis	8 (32.0)	0 (0.0)	
Re-transplantation	29 (4.44)	0 (0.00)	0.158
Waiting list status:			0.027
0	207 (31.7)	13 (23.2)	
1	385 (59.0)	43 (76.8)	
2	34 (5.21)	0 (0.00)	
3	27 (4.13)	0 (0.00)	
Sex matching:			0.314
Female to female	90 (13.8)	6 (10.7)	
Female to male	99 (15.2)	7 (12.5)	
Male to female	115 (17.6)	6 (10.7)	
Male to male	349 (53.4)	37 (66.1)	
Mechanical ventilation	151 (23.1)	10 (17.9)	0.461
IV inotropes	578 (88.5)	18 (32.1)	<0.001
PRA group			0.750
0%	337 (51.8)	28 (50.0)	
1–79%	252 (38.8)	21 (37.5)	
≥80%	61 (9.38)	7 (12.5)	
Donor characteristics			
Donor age (years)	39.9±11.4	43.1±11.8	0.058
Donor sex, male	464 (71.1)	43 (76.8)	0.449
Donor height (cm)	169±7.40	171±7.44	0.065

(continued to the next page)

Table 2. (Continued) Baseline characteristics according to pre-transplant left ventricular assist device support

Characteristics	LVAD (−) (n=653)	LVAD (+) (n=56)	p value
Donor weight (kg)	67.5±12.2	67.6±10.5	0.953
Donor BMI (kg/m²)	23.5±3.58	23.1±3.38	0.378
Donor hypertension	88 (14.0)	11 (21.6)	0.206
Donor diabetes	29 (4.60)	5 (9.43)	0.174

Continuous variables are presented as mean ± standard deviation, categorical variables are described by number (%).
Ab = antibody; Ag = antigen; BMI = body mass index; CMV = cytomegalovirus; EBV = Ebstein-Barr virus; HBs = hepatitis B surface; HCV = hepatitis C virus; IgG = immunoglobulin G; IV = intravenous; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; NS = not significant; PRA = panel reactive antibody; RVSP = right ventricular systolic pressure.

of IHD was also notably higher among LVAD-assisted recipients. Additionally, most recipients in the LVAD-assisted group (81.2%) were listed as status 1, reflecting Korea's waiting list criteria, which prioritize LVAD patients for transplantation. The LVAD group had lower pre-transplant RVSP compared to the non-LVAD group, likely due to LV unloading secondary to the LVAD.

When comparing survival among patients with different pre-transplant assistive devices, those who underwent ECMO showed poorer outcomes, while those with an LVAD and those without any assistive device had similar survival rates (**Figure 6**). For both 1-year and 6-year mortality, LVAD showed no significant difference compared to patients without assist devices, with HRs of 0.82 (95% CI, 0.25–2.76; p=0.75) and 0.81 (95% CI, 0.28–2.30; p=0.69), respectively. However, ECMO showed a significant increase in mortality, with HRs of 1.99 (95% CI, 1.02–3.88; p=0.043) for 1-year mortality and 1.95 (95% CI, 1.12–3.39; p=0.018) for 6-year mortality. These results suggest that the pre-transplant assist device status may affect mortality rates in both the short and long term. Regarding acute rejection, pre-transplant LVAD showed a trend toward increased acute rejection with an HR of 1.63 (95% CI, 0.98–2.71; p=0.06), although this difference did not reach statistical significance. Conversely, the ECMO group was significantly associated with an increased risk of acute rejection, with an HR of 1.53 (95% CI, 1.14–2.06; p=0.004). The incidence of CAV was not significantly influenced by either LVAD or ECMO (**Supplementary Figure 5**).
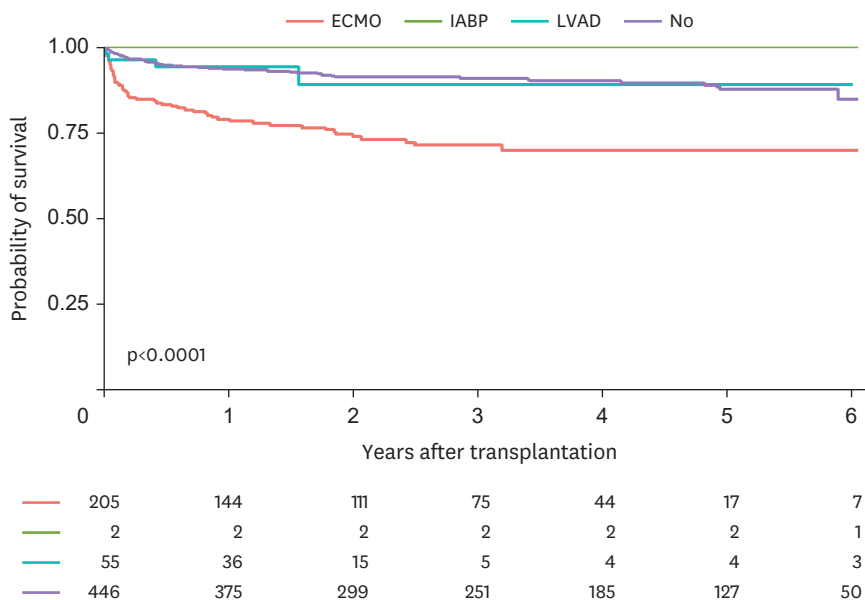

Figure 6. Kaplan-Meier analysis of survival stratified by pre-transplant assist device.
ECMO = extracorporeal membrane oxygenation; IABP = intraaortic balloon pump; LVAD = left ventricular assist device.

DISCUSSION

The continuous increase in the prevalence of HF,[11] driven by an aging society and improved survival following cardiovascular events such as myocardial infarction, has led to a growing demand for HT.[12] Our study revealed that the majority of HT recipients had significant comorbidities, including advanced age and the use of MCS, with an increasing number being classified as status 0 for urgency. Despite these challenges, post-transplant survival remained favorable, comparable to other countries. Older age and previous surgery were significant predictors of mortality, while PHM mismatch predicted 1-year mortality. Among pre-transplant MCS types, LVAD showed a better prognosis compared to ECMO and was comparable to patients not requiring MCS. Pre-transplant sensitization was identified as a risk factor for post-transplant acute rejection. Furthermore, mTOR inhibitors and statins demonstrated potential in reducing acute rejection and CAV.

There has been a notable increase in the median age of recipients, reflecting a trend where older populations are now considered suitable for transplantation. Specifically, recipients in their 70s comprised approximately 4.8% of the cohort. Concurrently, the number of recipients with complex comorbidities has increased, as evidenced by the higher incidences of diabetes, hypertension, and CKD. Another significant trend is the increased use of MCS as a bridge to transplantation. The increase in pre-transplant MCS support is due to changes in the waiting list criteria and the ongoing donor shortages.[13] Furthermore, the report indicated a significant rise in the proportion of highly sensitized recipients, as evidenced by elevated pre-transplant PRA levels. This increase in highly sensitized patients represents a substantial challenge, as these individuals are at a higher risk of transplant rejection and other complications.[14]

Our survival analysis identified several key factors that influence both short- and long-term post-transplantation mortality. Because the HR for mortality was higher in patients over 70 years,[15] meticulous selection is crucial for this age group. This balances the risks and benefits of transplantation in older patients, highlighting individualized assessment in an aging population.[16] CKD and the need for MV prior to transplantation have also emerged as critical predictors increasing both one-year and long-term mortality risks. A mismatch in PHM specifically elevates the risk of 1-year mortality but does not significantly affect long-term mortality.[17] PHM mismatch may affect early post-transplant survival, increasing initial mortality. Survivors beyond the first year are less affected, reducing its impact on long-term outcomes.

The time-dependent increase in CAV incidence underscores the necessity for continuous monitoring and proactive management strategies in the post-transplant period.[18] Our findings identify male sex and age over 45 as donor risk factors for CAV. Close monitoring of CAV and preventive measures are needed for recipients from high-risk donors. The potential protective role of mTOR inhibitors against CAV, as indicated in our analysis, aligns with the findings of previous randomized controlled trial[19] and registry study.[20] These studies have consistently shown that mTOR inhibitors such as everolimus have a protective effect against CAV.[21][22] These findings suggest that including everolimus or other mTOR inhibitors in immunosuppressive regimens may benefit patients at higher risk of developing CAV. Contrary to earlier studies showing statins reduce CAV post-transplant,[23] our research found a higher risk of CAV in statin users. This suggests a possible selection bias, with statins prescribed more often to high-risk patients, potentially confounding the analysis. In our study, the group prescribed statins at discharge showed a higher risk of CAV. The non-statin

group generally consisted of more critically ill patients with a higher mortality rate compared to the statin group. This higher mortality rate may explain the lower observed incidence of CAV in the non-statin group.

Our findings indicated that elevated PRA levels are associated with an increased risk of acute rejection after HT. Notably, the increased risk of rejection associated with pretransplant ECMO use may be due to the likelihood of increased blood transfusions and potential endothelial damage during ECMO, which could sensitize the immune system and increase the risk.[24] The analysis further indicated that extended cold ischemic times correlate with a higher risk of long-term rejection. This is likely due to the effects of prolonged ischemic injury on transplanted organs, which may increase immunogenicity and lead to organ rejection. Therefore, it is crucial to minimize ischemic times to reduce this risk. HT data from 2020 indicating a reduced rejection risk are intriguing and may reflect recent improvements in transplantation protocols, more effective management of sensitized patients, or the influence of a shorter follow-up period for these cases.[25] The protective role of statins at discharge against acute rejection highlights an important aspect of post-transplant care, likely due to their immunomodulatory effects. This finding enhances our understanding of the role of statins beyond lipid control and CAV management in transplant recipients.

Recent advancements in technology and changes in organ allocation guidelines have significantly influenced the deployment of MCS. The HT urgency criteria in the United States and South Korea are similar, with Status 1A in the United States corresponding to Urgency 0 in Korea, and Status 1B corresponding to Urgency 1, both reflecting comparable levels of clinical severity. With the evolution of reimbursement policies, the use of LVAD as a bridge to HT has markedly increased. Data show an increase in LVAD use before HT from 2.17% in the 2014–2015 era to 22.4% in the 2020 era, a substantial rise facilitated, in part, by insurance coverage. The KOTRY data analysis revealed distinctive demographic and clinical characteristics among patients receiving LVAD support. These individuals tended to be older than those in the non-LVAD supported group. Additionally, the prevalence of type O blood and IHD was higher in the LVAD group, suggesting that LVADs are used to safely support patients while waiting for HT. In Korea, most LVAD procedures employ the HeartMate 3 system. The HeartMate 3 LVAD has shown long-term survival rates of over 60% at five years, similar to HT recipients with a comparable risk profile.[26] However, while long-term outcome data for LVAD-assisted HT recipients are not yet available, the current analysis indicates that survival rates of LVAD recipients are not significantly worse than those of non-assisted patients.[27] This observation is crucial, as it suggests the viability of LVAD as a bridge to transplantation. In contrast, patients receiving ECMO prior to transplantation exhibited poorer outcomes, with a higher 1-year mortality rate and an increased likelihood of rejection compared to the non-ECMO bridged group.

This study has several limitations. First, although we used a well-maintained heart transplant cohort dataset supported by national funding, the data were collected only from seven major transplant centers in Korea, which may limit the generalizability of the findings to the entire Korean population. Second, the relatively short follow-up period results in insufficient data on post-transplant malignancies. However, this study has the strength of being a highly systematic and meticulously verified standard HT dataset from Korea.

In conclusion, our study provides a comprehensive overview of HT in Korea, highlighting significant changes in recipient demographics and clinical outcomes. We observed a trend

towards transplanting older recipients with more complex medical profiles, including CKD, prior cardiac surgery, and allosensitization. The increasing prevalence of heart re-transplantation and the rising use of MCS as a bridge to transplantation indicate growing challenges in the field. Our survival analysis revealed key factors influencing mortality, emphasizing the importance of meticulous patient selection and the need for ongoing monitoring of comorbidities. The increased use of LVAD as a bridge to HT, contrasted with poorer outcomes associated with pre-transplant ECMO, offers new insights into optimizing HT strategies.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Korean heart transplant urgency criteria

Supplementary Table 2
List of covariates considered in the multivariable models for adult heart

Supplementary Table 3
Immunosuppression at discharge

Supplementary Table 4
Results of multiple comparison test for survival analysis in multiple groups using the Benjamini-Hochberg method

Supplementary Table 5
Univariate and multivariate Cox regression analysis of 1-year survival post-transplant

Supplementary Table 6
Univariate and multivariate Cox regression analysis of overall survival post-transplant

Supplementary Table 7
Univariate and multivariate Cox regression analysis of acute rejection incidents

Supplementary Table 8
Univariate and multivariate Cox regression examination of cardiac allograft vasculopathy

Supplementary Table 9
Baseline characteristics according to pre-transplant mechanical circulatory support apply

Supplementary Figure 1
Kaplan-Meier survival curves based on predicted heart mass difference for (A) 1-year and (B) 6-tear overall survivals.

Supplementary Figure 2
Kaplan-Meier survival curves based on pre-transplant PRA levels.

Supplementary Figure 3
Incidence of CAV after transplantation.

Supplementary Figure 4
Number of transplants and use of pre-transplant assist devices by year of transplant.

Supplementary Figure 5
Kaplan-Meier analysis of cardiac allograft vasculopathy-free survival according to pre-transplant assist device type.

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