kcj

Korean Circulation Journal

Original Research

Check for updates

The Clinical Outcomes of Marginal Donor Hearts: A Single Center Experience

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

[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 Thoracic and Cardiovascular Surgery and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea

OPEN ACCESS

Correspondence to
Min Ho Ju, MD
Department of Thoracic and Cardiovascular Surgery and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, 20, Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea.
Email: deicidepan@naver.com

ORCID iDs
Soo Yong Lee (ID)
https://orcid.org/0000-0003-2616-1294
Seok Hyun Kim (ID)
https://orcid.org/0000-0003-4389-684X
Min Ho Ju (ID)
https://orcid.org/0000-0001-7839-8598
Mi Hee Lim (ID)
https://orcid.org/0000-0002-0167-7836
Chee-hoon Lee (ID)
https://orcid.org/0000-0002-0456-225X
Hyung Gon Je (ID)
https://orcid.org/0000-0003-4713-2898
Ji Hoon Lim (ID)
https://orcid.org/0000-0002-8201-1517
Ga Yun Kim (ID)
https://orcid.org/0000-0001-9901-0038

AUTHOR'S SUMMARY

This study aimed to report the outcomes of a single tertiary transplantation center that actively uses marginal donors (MDs). Consecutive 73 heart transplantation (HTx) cases were analyzed retrospectively and 43.8% of donor hearts met the MD criteria. There was no statistically significant difference in primary graft dysfunction (PGD), 30-day mortality and long-term survival between MD and non-MD groups. Notably, HTx using MDs in low-risk recipients showed excellent outcome. These results suggest appropriately selected donor hearts declined as MDs may increase organ utilization without an increase in post-transplant mortality or PGD.

ABSTRACT

Background and Objectives: Although the shortage of donor is a common problem worldwide, a significant portion of unutilized hearts are classified as marginal donor (MD) hearts. However, research on the correlation between the MD and the prognosis of heart transplantation (HTx) is lacking. This study was conducted to investigate the clinical impact of MD in HTx.
Methods: Consecutive 73 HTxs during 2014 and 2021 in a tertiary hospital were analyzed. MD was defined as follows; a donor age >55 years, left ventricular ejection fraction <50%, cold ischemic time >240 minutes, or significant cardiac structural problems. Preoperative characteristics and postoperative hemodynamic data, primary graft dysfunction (PGD), and the survival rate were analyzed. Risk stratification by Index for Mortality Prediction after Cardiac Transplantation (IMPACT) score was performed to examine the outcomes according to the recipient state. Each group was sub-divided into 2 risk groups according to the IMPACT score (low <10 vs. high ≥10).
Results: A total of 32 (43.8%) patients received an organ from MDs. Extracorporeal membrane oxygenation was more frequent in the non-MD group (34.4% vs. 70.7, p=0.007) There was no significant difference in PGD, 30-day mortality and long-term survival between

Ji Soo Oh (ID)
https://orcid.org/0000-0001-8992-0871
Jeong Su Kim (ID)
https://orcid.org/0000-0001-6877-4289

groups. In the subgroup analysis, early outcomes did not differ between low- and high-risk groups. However, the long-term survival was better in the low-risk group (p=0.01).

Conclusions: The outcomes of MD group were not significantly different from non-MD group. Particularly, in low-risk recipient, the MD group showed excellent early and long-term outcomes. These results suggest the usability of selected MD hearts without increasing adverse events.

Keywords: Heart transplantation; Transplant donors; Selection; Survival

INTRODUCTION

Donor shortage for heart transplantation (HTx) is a global phenomenon, including South Korea.[1)2)] As of 2020, only 174 of 774 (22.5%) waitlisted patients have received donor hearts.[3)] Even in status 0 patients with the highest priority, defined as receiving an extracorporeal membrane oxygenation (ECMO) or mechanical ventilator defined by the Korean Network for Organ Sharing, only 40–60% were allocated with donor hearts.[4)] This implies that lower priority patients in South Korea do not have a legitimate chance of receiving a heart until mechanical circulatory support is necessary. The high waitlist mortality rate of 15% may indeed be related to donor shortages in South Korea.

There are numerous ways to expand the donor pool: improvement of the conception through nationwide organ donation campaigns, modification of the law and system on organ donation as France, modification of the definition of brain death, or utilization of donors after circulatory death by the organ care system.[5)] However, these systematic changes are extremely challenging, for its time-consuming logistics and the necessity of astronomical figures of budget. Clinicians must accordingly devise rapid solutions within the system to save lives. Use of donor hearts classified as "marginal," which has been conventionally abandoned, can be a practical way to expand the donor pool.

A marginal donor (MD) is one with medical conditions not optimal for organ donation which may be related with poor post-transplantation outcomes. A significant numbers of donor hearts have been abandoned for their marginality, especially in South Korea: donor heart utilization rate is 30–40%.[6)] However, we question whether such donors were truly marginal and doomed to translate into poor outcomes. Herein, we report outcomes of HTx using MD hearts.

METHODS

Ethical statement
The study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (05-2021-209). The requirement for informed consent was waived owing to the retrospective nature of the study.

Study design and population
This retrospective observational study included patients who underwent HTx at a single center between June 2014 and March 2021. All data were collected from an institutional prospective surgical database and electronic charts. During the study period, 89 patients underwent HTx at a single institution. Of these, 77 (86.5%) cases of HTx were conducted in adult recipients,
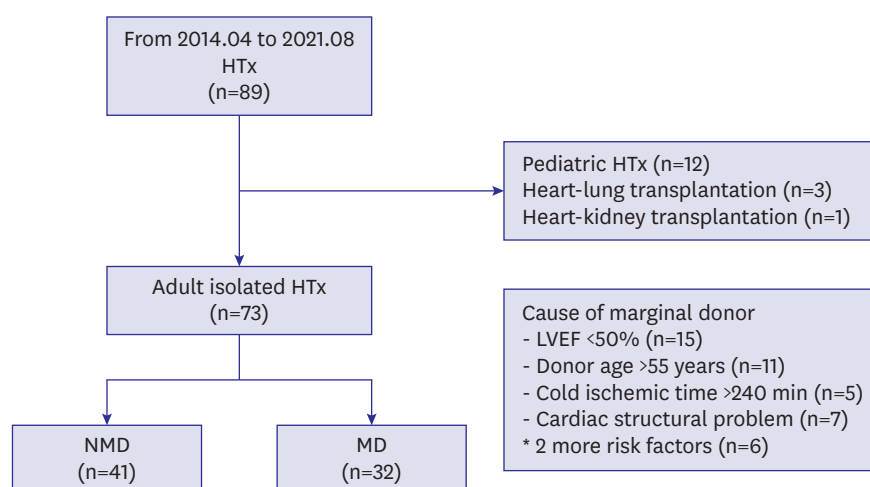
Figure 1. Inclusion criteria and classification of each group by definition of marginal donor.
HTx = heart transplant; LVEF = left ventricular ejection fraction; MD = marginal donor; NMD = non-marginal donor.

and 73 patients were included in present study after excluding four multiorgan transplantation cases. MD was defined as based on the following criteria: donor age >55 years, left ventricular ejection fraction (LVEF) <50% on preoperative echocardiography, cold ischemic time >240 minutes, or significant cardiac structural problems on any imaging study. Thirty-two (43.8%) recipients were classified into the MD group, and the remaining 41 (56.2%) were included in the non-marginal donor (NMD) group (**Figure 1**).

The primary and secondary endpoints were mortality and primary graft dysfunction (PGD), respectively. The definition of PGD was any graft dysfunction that occurs within 24 hours of HTx, and complies with the International Society for Heart and Lung Transplantation (ISHLT) meeting in 2014 (**Supplementary Table 1**).[7] Graft function after HTx was evaluated based on vasoactive inotropic score (VIS). VIS was derived from summing of inotropic dose rates: Dopamine Dose (µg/kg/min) + Dobutamine Dose (µg/kg/min) + 100 × Epinephrine Dose (µg/kg/min) + 10 × Milrinone Dose (µg/kg/min) + 10,000 × Vasopressin Dose (unit/kg/min) + 100 × Norepinephrine Dose (µg/kg/min).

Additionally, to quantify preoperative recipient risk, we employed the Index for Mortality Prediction after Cardiac Transplantation (IMPACT) score.[8][9] The details of IMPACT score ere described in **Supplementary Table 2**.

Surgical procedures

We performed a conventional median sternotomy with selective vena caval cannulation for HTx. Inferior vena cava was drained cannulation via the femoral vein access. A recipient who underwent preoperative ECMO was converted 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 who did not receive ECMO, arterial cannulation was routinely performed in the distal aorta. To minimize the CPB time, the heart of the recipient was explanted just before the donor heart arrived. Donor hearts were protected with infusion of a 4°C HTK solution (Custodiol®; Köhler Chemie GmbH, Bensheim, Germany) for 8 minutes before harvesting. The harvested heart was washed with the HTK solution and transported using an ice package. The standard bicaval anastomosis technique was routinely performed.

Management in the intensive care unit during the early period

A Swan-Ganz catheter was inserted in the operating room. All patients were transferred to the cardiac intensive care unit (ICU) after surgery. The postoperative target ranges of the monitoring indicators were as follows: cardiac output, 4–7 L/min; target heart rate, 95–110 beats/min; pulmonary capillary wedge pressure (PCWP), 15–20 mmHg; central venous pressure, <15 mmHg; <1/3 of pulmonary arterial pressure over systemic arterial pressure; lactate level, <2.0 mmol/L; mixed venous oxygen, >70 mmHg; pulmonary partial pressure of oxygen, > 100 mmHg; urine output >100 mL/hr; and potassium level >4.0 mmEq. Low dose dobutamine and norepinephrine were the most frequently used agents to maintain vital signs. If the patient's demand for inotropes increased and isolated pulmonary arterial hypertension was detected, milrinone was given, and if decreased systemic vascular resistance was detected with norepinephrine demand >0.2 mcg/kg/min, vasopressin was administered. Isoproterenol was used to achieve the target heart rate in cases of poor response to chronotropic drugs or complete atrioventricular block, and temporary or epicardial pacing was applied. After confirming consciousness and controlled bleeding, the patients were extubated. They were sent to the general ward from 3 days after the operation according to their medical conditions. Cardiac rehabilitation was started after chest tube removal and continued until discharge.

Immunosuppression protocol

An anti-interleukin-2 receptor monoclonal antibody (basiliximab) was used for induction from June 2014 to July 2018. Antithymoglobulin (rabbit) was replaced with basiliximab from August 2018. However, in cases of recipients older than 65 years of age or those with a high risk of infection, induction therapy was omitted. A bolus of 500 mg of methylprednisolone was administered when allograft left atrial anastomosis was initiated. The initial postoperative dose of prednisolone for maintenance therapy was 1 mg/kg/day, which was tapered to 0.25 mg/kg/day at 1 month and then to 2.5–5 mg/day at 1 year. Prednisolone was discontinued at approximately 1 year after HTx, except in the patients who experienced any type of rejection. Maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil (500–1,000 mg), and corticosteroids. Twelve months postoperatively, tacrolimus and everolimus, with or without prednisolone, were administered. In cases of cross-matching positive transplantation, pre-/post-desensitization with plasma pheresis and intravenous immunoglobulin (total, 1 mg/kg for 3 days) were administered. Rituximab, with or without bortezomib, was used to prevent antibody-mediated rejection.

Statistical analysis

Variables were summarized by frequency and percentage for categorical data and mean ± standard deviation and median (range) for numeric data. Group differences were tested using the χ^2 test or Fisher's exact for categorical data and independent t-test or Mann-Whitney U test for numeric data as appropriate. To check if its distribution is normal, we used Shapiro-Wilk's test.

Univariate and multivariate logistic regression analysis were performed to identify prognostic factors which are independently related to event. Due to the small number of deaths, risk factor analysis for the primary endpoint has been judged to be inappropriate and was not described. Instead, risk factor analysis was performed on the PGD, a secondary endpoint. Variables for analysis were selected as factors considered clinically meaningful, including MD. And variables known as risk factors in previous reports were also included.[7][10] Variables that were too small to be suitable for analysis were excluded (such as race, weight mismatch ≥30%, etc.) To check the multicollinearity problem, the variance inflation factor (VIF) was also estimated. VIF quantifies the severity of multicollinearity in regression analysis

and VIF less than 10 indicated that there was no problematic multicollinearity among the independent variables (VIF <10).

Overall survival and PGD-free survival were estimated using Kaplan-Meier curve. Survival curves were compared between groups using the log-rank test. Univariate and multivariate analyses, using Cox proportional hazard regression analysis, were performed to identify prognostic factors which are independently related to time to event (death or PGD).

Considering the nature of the repeated measured data of echocardiography (LVEF), a generalized linear mixed model (GLMM) with random intercepts was used to fit a model. The GLMM model included repeated measures of numeric variables as dependent variables; group, time, and group × time interaction as fixed effects; and subject as a random effect. To avoid making any assumptions about the covariance structure, we used an unstructured covariance matrix that was allowed to differ across groups for the GLMM analysis.

All statistical analyses were carried out using SPSS 26.0 statistical software (IBM Corp. Released 2019, IBM SPSS Statistics for Windows, version 26.0; IBM Corp., Armonk, NY, USA) and R statistical software (version 3.4.0; R Foundation, Vienna, Austria, http://www.r-project.org/). The p values less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics
Donors in the MD group were older than those in the NMD group. LVEF was significantly lower in the MD group (**Table 1**). Twenty-five percent of patients in the MD group were rejected more than 5 times by other hospitals with a higher HTx allocation priority. Sex and medical history were not significantly different between the two groups. However, the rates of preoperative ECMO and ICU admission, the degree of emergency were higher in the NMD group. Although the preoperative creatinine level was higher in the NMD group than in the MD group, other laboratory results were comparable between the groups. Donor and recipient characteristics are described in detail in **Table 1**.

Perioperative clinical results
Cold ischemic and total ischemic times were numerically longer in the MD group. The ACC and CPB times in the recipients were also similar. There was one case of early mortality in each group. The incidence of other adverse events during the perioperative period between the groups. The surgical and perioperative details are presented in **Table 2**.

Immediate postoperative, 30-day, and long-term clinical results
Immediate postoperative creatine kinase-MB isoenzyme levels were similar between the two groups, and vasoactive inotropic scores were not different within 24 hours (**Figure 2A**). The cardiac index showed a slightly lower trend in the MD group compared to the NMD group without a statistical difference immediately postoperatively; however, it became similar between groups after 24 hours (**Figure 2B**). Moderate or higher grade PGD developed in 13 (17.8%) patients during the perioperative period, and there was no difference in the incidence of PGD between the groups. On the first echocardiography performed 1 week postoperatively, there was no difference in the LVEF between groups (**Table 2**). The 30-day and 1-year survival rates were 97.6±2.4% and 90.2±4.6% in the NMD group and 96.9±3.0% and 87.5±5.9% in

Table 1. Preoperative characteristics of donor and recipient

Variables	NMD group (n=41)	MD group (n=32)	p value
Donor profiles			
Age (years)	38.0 (25.5–43.5)	45.5 (34.5–56.0)	0.002[†]
Male	29 (70.7)	21 (65.6)	0.641[‡]
Height (cm)	168.1±7.2	169.3±7.1	0.493[*]
Weight (kg)	67.0 (60.0–76.3)	68.5 (61.5–86.0)	0.191[†]
LVEF (%)	60.0 (57.0–64.5)	53.0 (47.0–61.5)	0.001[†]
Diabetes mellitus	2 (4.9)	3 (9.4)	0.648[§]
Hypertension	3 (7.3)	4 (12.5)	0.692[§]
Cause of marginal donor	0	32	
Age >55 years	0 (0.0)	11 (34.4)	
LVEF <50%	0 (0.0)	15 (46.9)	
Cold ischemic time >240 min	0 (0.0)	5 (15.6)	
Significant structural problem	0 (0.0)	7 (21.9)	
More than 2 risk factors	0 (0.0)	6 (18.8)	
History of CPR	19 (46.3)	11 (34.4)	0.302[‡]
Inotropic agent except NE	10 (24.4)	10 (31.3)	0.514[‡]
Refuse more than 5 times	0 (0.0)	8 (25.0)	0.001[§]
Cause of brain death			0.253[§]
CVA	16 (38.1)	19 (59.4)	
Drowning	3 (7.1)	0 (0.0)	
Hypoxia	14 (34.1)	8 (25.0)	
Trauma	8 (19.5)	5 (15.6)	
Distance between institutions			1.000[§]
Same place	4 (9.8)	2 (6.2)	
Within 100km	15 (36.6)	12 (37.5)	
100 to 200 km	2 (4.9)	2 (6.2)	
200 to 300 km	5 (12.2)	4 (12.5)	
More than 300km	15 (36.6)	12 (37.5)	
Recipient profiles			
Age (years)	53.0 (44.5–63.0)	59.0 (50.5–63.0)	0.185[†]
Male	26 (63.4)	16 (50.0)	0.250[‡]
Height, cm	164.7±8.5	163.8±8.9	0.654[*]
Weight (kg)	60.0 (53.9–69.0)	60.3 (51.7–68.6)	0.841[†]
Diabetes mellitus	12 (29.3)	13 (40.6)	0.310[‡]
Hypertension	23 (56.1)	23 (71.9)	0.166[‡]
COPD	1 (2.4)	1 (3.1)	1.000[§]
History of CVA	2 (4.9)	5 (15.6)	0.228[§]
Prior cardiac surgery	10 (24.4)	5 (15.6)	0.358[‡]
ECMO support	29 (70.7)	11 (34.4)	0.004[‡]
Admission of ICU	30 (73.2)	11 (34.4)	0.001[‡]
KONOS status			0.004[§]
0	29 (70.7)	11 (34.4)	
1	11 (26.8)	15 (46.9)	
2	1 (2.4)	4 (12.5)	
3	0 (0.0)	2 (6.2)	
Cause of transplantation			0.358[§]
DCM	18 (43.9)	17 (53.1)	
ICM	15 (36.6)	11 (34.4)	
HCM	2 (4.9)	3 (9.4)	
Other	6 (14.6)	1 (3.1)	
Hemoglobin (gm/dL)	10.4±1.9	10.2±1.7	0.678[*]
Total bilirubin (mg/dL)	1.7 (1.1–2.8)	1.0 (0.6–1.7)	0.013[†]
Creatinine (mg/dL)	1.2 (0.8–4.0)	1.0 (0.7–1.4)	0.154[†]
Albumin	3.3 (3.0–3.8)	3.6 (3.1–4.0)	0.194[†]
CRP	3.3 (0.4–9.0)	2.1 (0.2–6.6)	0.203[†]
IMPACT score	14.0 (6.5–21.5)	6.5 (3.0–15.0)	0.009[†]

Values are presented as number (%), mean ± standard deviations, or median (interquartile range).

COPD = chronic obstruction pulmonary disease; CPR = cardiopulmonary resuscitation; CRP = C-reactive protein; CVA = cerebrovascular accident; DCM = dilated cardiomyopathy; ECMO = extracorporeal membrane oxygenation; HCM = hypertrophic cardiomyopathy; ICM = ischemic cardiomyopathy; ICU = intensive care unit; IMPACT = The Index for Mortality Prediction After Cardiac Transplantation; KONOS = Korean Network for Organ Sharing; LVEF = left ventricular ejection fraction; MD = marginal donor; NE = norepinephrine; NMD = non-marginal donor.

[*]p values were derived from independent t-test. [†]p values were derived from Mann-Whitney's U test. [‡]p values were derived from χ^2 test. [§]p values were derived from Fisher's exact test. Shapiro-Wilk's test was employed for test of normality assumption.

Table 2. Surgical and perioperative profiles

Variables	NMD group (n=41)	MD group (n=32)	p value
Cold ischemic time (min)	106.0 (70.0–198.0)	134.5 (78.5–204.0)	0.427[†]
Warm ischemic time (min)	68.5±18.5	69.3±22.2	0.873[*]
Total ischemic time (min)	197.7±70.8	213.0±74.6	0.374[*]
Recipient cross clamp time (min)	97.0 (79.5–114.0)	92.0 (75.0–119.5)	0.681[†]
Cardiopulmonary bypass time (min)	149.0 (126.0–172.0)	153.5 (125.8–187.5)	0.450[†]
30-days mortality	1 (2.4)	1 (3.1)	1.000[§]
Postoperative ECMO support	2 (4.9)	1 (3.1)	1.000[§]
Primary graft dysfunction	6 (14.6)	7 (21.9)	0.422[‡]
ICU stay (hours)	179.0 (101.0–365.5)	152.0 (97.0–227.0)	0.192[†]
Amount of bleeding for 12 hours	730.0 (316.5–1,253.5)	632.5 (394.8–1,212.8)	0.996[†]
Reoperation for bleeding	4 (10.0)	3 (9.4)	1.000[§]
Cerebrovascular accident	1 (2.5)	0 (0.0)	1.000[§]
Postoperative CRRT	13 (31.7)	4 (12.5)	0.054[‡]
New onset CRRT	2 (4.9)	2 (6.3)	1.000[§]
Pneumonia	3 (7.3)	0 (0.0)	0.251[§]
Prolonged ventilation >24 hours	16 (39.0)	9 (28.1)	0.330[‡]
1st LVEF during hospitalization (%)	61.7±8.0	63.7±5.5	0.200[*]
LVEF ≥60%	27 (65.9)	27 (84.4)	
50% ≤LVEF <60%	12 (29.3)	4 (12.5)	
LVEF <50%	2 (4.9)	1 (3.1)	

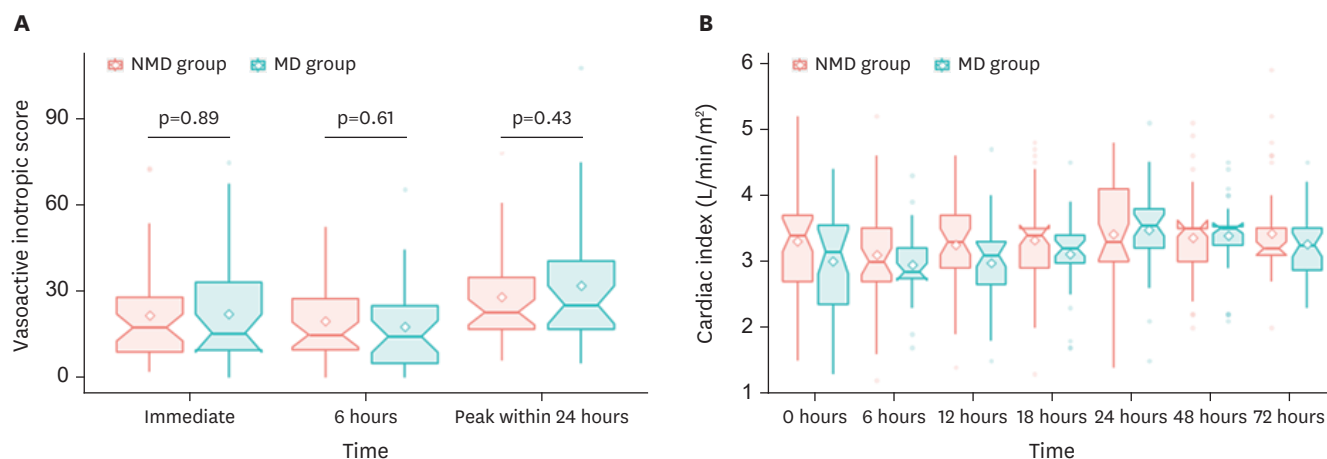Values are presented as number (%), mean ± standard deviations, or median (interquartile range).
CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; LVEF = left ventricular ejection fraction; MD = marginal donor; NMD = non-marginal donor.
[*]p values were derived from independent t-test. [†]p values were derived from Mann-Whitney's U test. [‡]p values were derived from χ² test. [§]p values were derived from Fisher's exact test. Shapiro-Wilk's test was employed for test of normality assumption.

the MD group (p=0.87, 0.73 respectively). There was no difference in the long-term mortality rate between groups: 12.5% vs. 9.8% in MD vs. NMD during follow up (mean 26.3±24.6 vs. 29.1±17.6 months, p=0.75; **Figure 3A**). The LVEF on serial echocardiography showed no difference between 2 groups during long-term follow-up (**Figure 3B**).

Risk factor analysis of primary graft dysfunction

In the multivariate logistic regression analysis for PGD, there were no meaningful predictors. MD hearts or IMPACT scores were not significant predictors of PGD. Logistic regression analysis failed to converge since there was no case of PGD in female to male transplantation. The detailed values of the univariate analysis are shown in **Table 3**.

Figure 2. Trend of postoperative vasoactive inotropic scores and cardiac index in each group.
(A) Vasoactive inotropic score of immediate, 6 hours and peak value within 24 hours post operation. (B) Serial cardiac index within 72 hours post operation. MD = marginal donor; NMD = non-marginal donor.
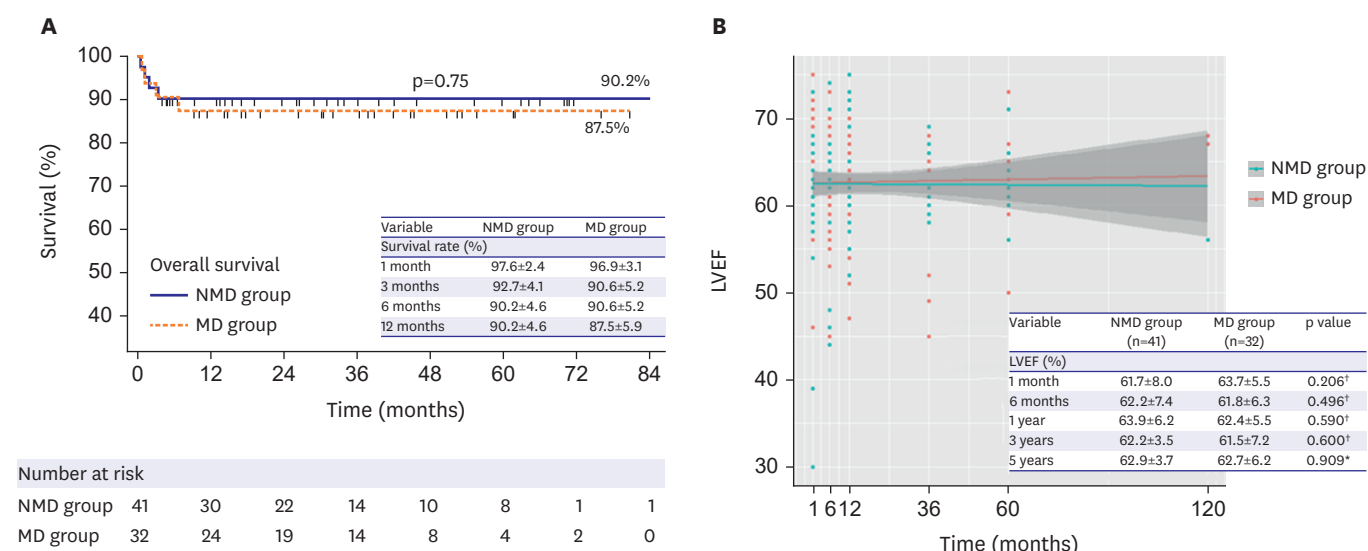
Figure 3. Overall survival and left ventricular function during follow up period.
(A) Overall long-term survival between groups. (B) Long-term follow-up LVEF between groups.
LVEF = left ventricular ejection fraction; MD = marginal donor; NMD = non-marginal donor.
*p values were derived from independent t-test. †p values were derived from the Mann-Whitney test. Shapiro-Wilk's test was employed for the test of the normality assumption.

Table 3. Risk factor analysis for primary graft dysfunction

Variables	Univariate			Multivariate			
	OR	95% CI	p	OR	95% CI	p	VIF
Recipient age	1.02	(0.97 to 1.07)	0.552	1.01	(0.95 to 1.07)	0.751	1.435
Recipient DM	1.25	(0.36 to 4.32)	0.724				
Prior cardiac surgery	1.20	(0.29 to 5.05)	0.804				
Preoperative ECMO support	0.48	(0.14 to 1.63)	0.239	0.44	(0.05 to 4.17)	0.473	3.417
Preoperative hemodialysis	0.33	(0.04 to 2.82)	0.313	0.41	(0.03 to 6.05)	0.514	2.163
Bilirubin	0.94	(0.71 to 1.26)	0.695	1.04	(0.73 to 1.47)	0.846	1.601
No DCM (vs. DCM)	0.75	(0.23 to 2.50)	0.639				
Use of amiodarone	0.81	(0.16 to 4.19)	0.801				
Female to male transplantation	0.16	(0.0 to 2.88)	0.232				
Marginal donor	1.63	(0.49 to 5.45)	0.425	1.19	(0.32 to 4.37)	0.797	1.199
IMPACT risk score increase	0.96	(0.89 to 1.04)	0.358	1.02	(0.86 to 1.22)	0.784	5.743

CI = confidence interval; DCM = dilated cardiomyopathy; DM = diabetes mellitus; ECMO = extracorporeal membrane oxygenation; IMPACT = The Index for Mortality Prediction After Cardiac Transplantation; LVEF = left ventricular ejection fraction; OR = odds ratio; VIF = variance inflation factor.

Sub-group analysis: clinical impact of marginal donor according to recipient's status

Of the MD group, 19 recipients (59.3%) were classified as low-risk groups (IMPACT Risk Score <10) and 13 as high-risk groups (IMPACT Risk Score ≥10). There was no difference in donor characteristics or surgical profiles between the low- and high-risk groups (**Table 4**). The high-risk group showed higher incidence of prolonged ICU stay (**Table 4**). Other clinical outcomes were not different between two groups. However, the low-risk group showed better long-term survival than high-risk group (**Figure 4**). Particularly, there was no mortality in low-risk group during follow-up regardless of donor's marginality (**Figure 4A**). On the other hand, high-risk recipients transplanted with marginal donor showed lower survival during follow up period (**Figure 4B**). In the NMD group, recipient risk status did not affect the survival (low-risk vs. high-risk recipient group, 100% vs. 86.2%, p=0.19; **Figure 4C**). However, in the MD group, the survival was significantly different according to the recipient risk status (low-risk group vs. high-risk group, 100% vs. 69.2%, p=0.01; **Figure 4D**).

Table 4. Major outcomes according to risk stratification of recipient

Variables, N (%), mean±SD	IMPACT score <10			IMPACT score ≥10			NMD group			MD group		
	NMD group (n=12)	MD group (n=19)	p value	NMD group (n=29)	MD group (n=13)	p value	IMPACT <10 (n=12)	IMPACT ≥10 (n=29)	p value	IMPACT <10 (n=19)	IMPACT ≥10 (n=13)	p value
Postoperative ECMO support	1 (8.3)	1 (5.3)	1.000‡	1 (3.4)	0 (0.0)	1.000‡	0 (0.0)	1 (3.4)	1.000‡	1 (5.3)	0 (0.0)	1.000‡
ICU stay (hours)	142.5±71.8	129.6±39.3	0.593*	433.6±542.2	271.3±196.4	0.571†	142.5±71.8	433.6±542.2	0.028†	129.6±39.3	271.3±196.4	0.024*
Reoperation for bleeding	0 (0.0)	1 (5.3)	1.000‡	4 (13.8)	2 (15.4)	1.000‡	0 (0.0)	4 (13.8)	0.560‡	1 (5.3)	2 (15.4)	0.552‡
Cerebrovascular accident	0 (0.0)	0 (0.0)		1 (3.4)	0 (0.0)	1.000‡	0 (0.0)	1 (3.4)	1.000‡	0 (0.0)	0 (0.0)	
New onset CRRT	0 (0.0)	1 (5.3)	1.000‡	2 (6.9)	1 (7.7)	1.000‡	0 (0.0)	2 (6.9)	1.000‡	1 (5.3)	1 (7.7)	1.000‡
Pneumonia	0 (0.0)	0 (0.0)		3 (10.3)	0 (0.0)	0.540‡	0 (0.0)	3 (10.3)	0.543‡	0 (0.0)	0 (0.0)	
Primary graft dysfunction	1 (8.3)	6 (31.6)	0.201‡	5 (17.2)	1 (7.7)	0.647‡	1 (8.3)	5 (17.2)	0.651‡	6 (31.6)	1 (7.7)	0.195‡
30-days mortality	0 (0.0)	0 (0.0)		1 (3.4)	1 (7.7)	0.528‡	0 (0.0)	1 (3.4)	1.000‡	0 (0.0)	1 (7.7)	0.406‡

Values are presented as number (%) or mean ± standard deviations.
CRRT = continuous renal replacement therapy; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; IMPACT = Index for Mortality Prediction after Cardiac Transplantation; MD = marginal donor; NMD = non-marginal donor.
*p values were derived from independent t-test. †p values were derived from Mann-Whitney's U test. ‡p values were derived from Fisher's exact test. Shapiro-Wilk's test was employed for test of normality assumption.

Characteristics of donors declined >5 times

Like other donor allocation programs, Korean Network for Organ Sharing (KONOS) re-allocates declined donor heart to the patient with highest priority among the remaining candidates. We collected the specific reasons for turning down donor hearts among candidates with higher priority than our patients. We considered that if a donor heart was declined more than 5 times by other candidates due to the 'donor factor,' it was discerned as a marginal donor by other institutions meaningfully. **Supplementary Table 3** summarizes the characteristics and results of seven transplant cases utilizing donor hearts that were declined more than 5 times by other listed candidates. The specific reasons for 'medical unsuitability' of donor hearts were various, including old age (61 years), bradycardia, eccentric left ventricular (LV) hypertrophy, LVEF of 47% with regional wall motion abnormalities, right ventricular dysfunction (suspicious intracardiac right to left shunt), LVEF of 35% with global hypokinesia, and one case with an unidentifiable reason. In two donors whose donations were delayed for remnant electroencephalogram signals, the LVEF recovered to the normal range after transplantation. Donor #4, whose diastolic LV septal and posterior wall thicknesses exceeded 13 mm, required permanent pacemaker implantation for atrioventricular dyssynchrony despite 1 month of waiting for recovery after transplantation. Sinus rhythm was completely restored 2 weeks after permanent pacemaker insertion. All recipients had excellent 1-year survival rates.

DISCUSSION

In the present study, we compared the clinical outcomes MD and NMD hearts. Early outcomes including PGD, 30-day and long-term mortality were comparable between groups. Notably, the clinical status (emergency status) of the recipients of MD group was better. In addition, even the donor hearts declined by more than 5 candidates of higher priority on the waiting list showed excellent short and long-term outcomes. To our knowledge, this is the first MD heart utilization report in South Korea.
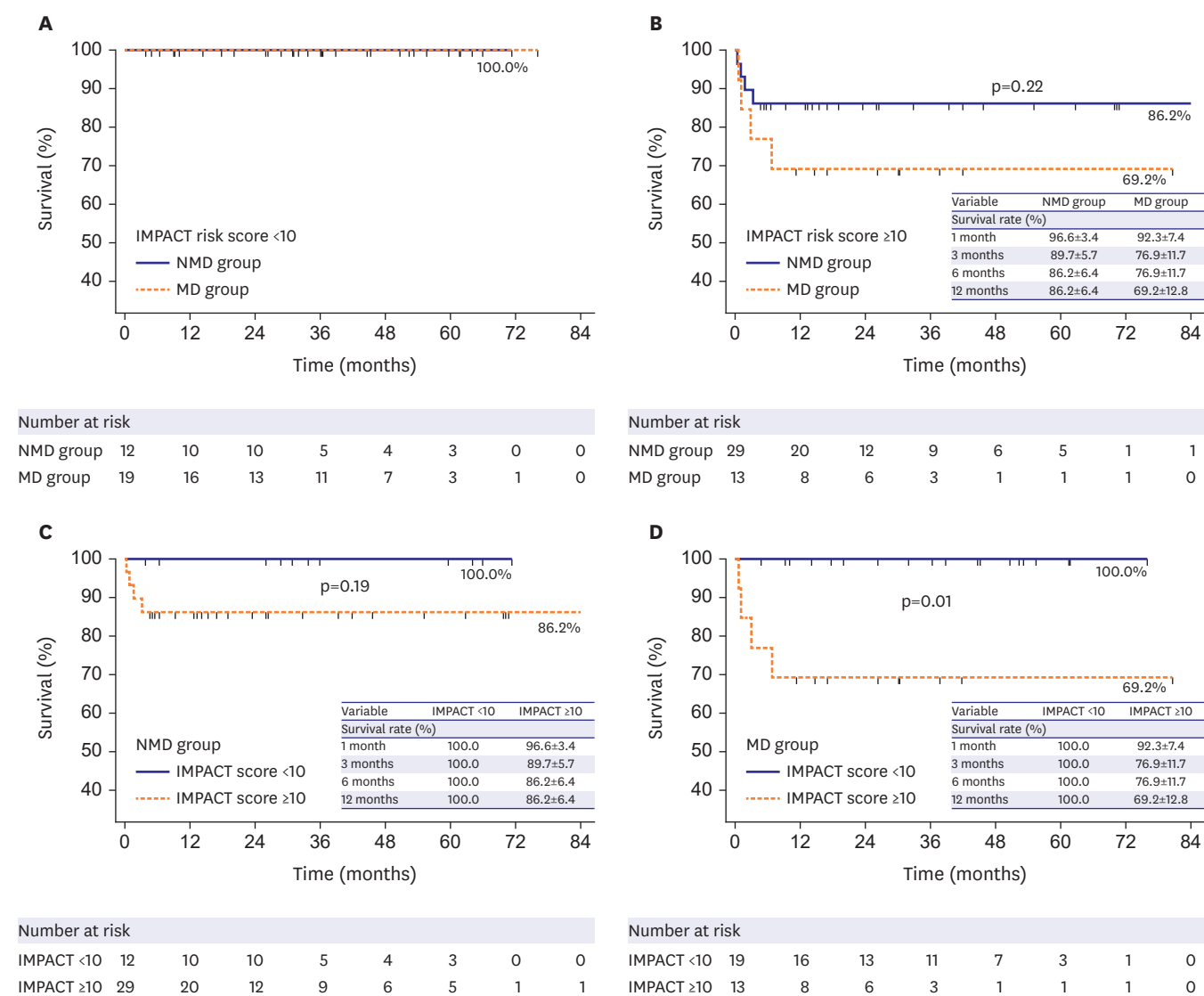
Figure 4. Kaplan–Meier survival curve by donor and recipient medical status.
(A) Survival rate in the low-risk recipient (IMPACT score <10) group. (B) Survival rate in the high-risk recipient (IMPACT score ≥10) group. (C) Survival rate in NMD group. (D) Survival rate in MD group.
IMPACT = Index for Mortality Prediction after Cardiac Transplantation; MD = marginal donor; NMD = non-marginal donor.

Optimal donor characteristics are defined as age <55 years, absence of significant structural abnormalities (wall thickness >13 mm on echocardiography and significant valvular, congenital, and coronary artery disease), adequate physiologic function (LVEF >45%, mean arterial pressure >60 mmHg; PCWP, 8–12 mmHg), no inotrope dependence, acceptable donor-recipient body size (20–30% of height and weight), negative hepatitis C virus (HCV) antibody, hepatitis B surface antigen, and human immunodeficiency virus (HIV) serology, and absence of active malignancy.[11] Although donors ineligible for these conditions may be classified as an MD, the specific criteria differ from one center to another, depending on the experiences of each center (**Supplementary Table 4**).[12-18] In an effort to guide clinicians, an integrative scoring system was suggested based on UNOS data.[19] Predictive risk models have been developed to optimize donor selection; however, they are not widely applicable or adopted in clinical practice.[20]

Around 40% of our HTxs were performed by hearts that met the MD criteria (**Supplementary Figure 1**). Individual donor selection requires detailed review and repeated discussion within the transplant team. From the accumulation of our experience and data, the consensus within our multidisciplinary HTx team for donor selection principles are as follows: donor age ≤65 years with the difference of donor and recipient age less than five years, LVEF ≥40% with reversibility (e.g., prominent stress-induced cardiomyopathy features in echocardiogram or documented improvement with serial follow-up echocardiogram), cold ischemic time >240 minutes without risk factors, structural heart disease that can be easily corrected or controllable with medical therapy and negative HCV and HIV serology. However, we would like to stress out "donor-recipient coupling" when considering utilization of MD from our experiences. As shown in **Figure 4**, low-risk recipients (IMPACT score <10) had excellent long-term outcome despite utilizing MD hearts. High-risk recipients (IMPACT score ≥10) matched with MD showed worst outcome. Based on such findings, our multidisciplinary HTx team no longer receive MD hearts in high-risk recipients.

The most frequently encountered medical conditions for MD in our study were old age and LV dysfunction. The ISHLT stresses the importance of donor age as an important predictor of early death in risk-adjusted models.[21] Advanced donor age is associated with increased mortality, although there is conflicting results.[22-24] However, with increased life expectancy, we can expect better medical outcomes from aged donors than in the previous era. Blanch et al. suggested that carefully selected donor hearts over 50 years of age may have similar long-term survival and related outcomes as younger donor organs.[22] It is widely accepted that life expectancy reported by the World Health Organization has increased. Between 2000 and 2019, global life expectancy at birth increased from 66.8 years in 2000 to 73.3 years in 2019, and healthy life expectancy increased from 58.3 to 63.7 years.[25] Indeed, recent ISHLT registry and Eurotransplant reports have shown an increase in the average recipient and donor age.[1)26]

During brain death, a surge in the adrenergic response results in pulmonary and systemic hypertension, which increases the afterload in both ventricles, causing myocardial ischemia and stress-induced cardiomyopathy.[10] Additionally, prolonged cardiopulmonary resuscitation or severe hypoxia induced by suicide deteriorates LV contractility. LV systolic dysfunction has been reported to occur in up to 42% of patients with brain death.[27] However, Madan et al.[28] reported that LVEF may frequently improve to the normal range on repeated transthoracic echocardiography (TTE) after brain death. Interestingly, hearts with improved systolic function over time (12–24 hours) showed clinical outcomes similar to those of hearts with an initially normal LVEF.[28] These data highlight the importance of a second or third TTE evaluation before procurement in patients with poor initial systolic function. The Korean Organ Donation Agency does not routinely assess the recovery of LVEF in donor hearts unless requested. We apply a watch-and-wait strategy for assessing donor hearts with low LVEFs but high chances for improvement, e.g., prolonged cardiopulmonary resuscitation and stress-induced cardiomyopathy, to acquire follow up TTE results. Such watch-and-waits were unfeasible in several of our patients because the donor care physician did not concur with the second TTE exam.

In addition, dysrhythmias are common (25–32%) in patients with brain damage due to activation of the hypothalamic–pituitary–adrenal axis.[29] Some cases are caused by extreme volume loss combined with disturbances in electrolytes and arterial gas disorders caused by central diabetes insipidus in brain-dead patients. However, most neurogenic arrhythmias are benign, and proper donor management with volume replacement along with serial

electrocardiogram tracings can save transplantable hearts.[29] In our experience, donor #3 showed junctional bradycardia with a heart rate of <50 beats/min and recovered normal sinus rhythm during donor management (**Supplementary Table 1**).

Actively using MD hearts could be an effective way to expand the donor pool and shorten waiting time. However, it is challenging because short- and long-term results should be guaranteed. Although this study included data from a single center, the results showed no significant statistical difference in PGD and long-term survival between the MD and NMD groups.

These findings indicate that carefully selected 'marginal' donor hearts could be used to address the donor shortage without increasing the risk of negative events and may actually result in optimal outcomes for HTx. Present study has all potential limitations inherent to retrospective/observational design. As the data were retrospectively collected from a single center, geographic and demographic biases could be present. Even with various customized analyses, several potential confounding factors may have influenced the study. The average follow-up duration was not sufficient for estimating coronary allograft vasculopathy, accounting for approximately 47.4% of post-transplant deaths at 10 years.[30] We conducted post-hoc power analysis and the observed power was calculated as 5.8% for mortality and 12.8% for the PGD. In this study, both the relatively small sample size and total number of events reduced the post-hoc power. For this reason, we could not statistically evaluate the risk factor of death, but instead evaluated the risk factors of PGD. Therefore, the further study with larger sample size is need. Follow-up was good, but there were deaths of various causes, which limit the clinical impact of MD on survival.

In conclusion, HTx is expected to continue as an important option for treating advanced heart failure. Active use of the MD could be one of the solutions to the worldwide shortage of donors. Although this was an underpowered cohort, our findings suggest that the selected MD hearts can achieve comparable clinical outcomes to NMD hearts, especially in HTxs using MDs in low-risk recipients.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIALS

Supplementary Table 1
The definition of Primary graft dysfunction

Click here to view

Supplementary Table 2
The stratification of recipients: IMPACT score

Click here to view

Supplementary Table 3
Detailed characteristics and outcomes of the donors declined more than 5 times by other candidates on the waiting list

Click here to view

Supplementary Table 4
Previous research on clinical outcomes of the utilization of marginal donors

Click here to view

Supplementary Figure 1
Trends of marginal donor utilization in Pusan National University Yangsan Hospital, since 2014.

Click here to view

REFERENCES

1. Eurotransplant International Foundation. *Eurotransplant annual report 2020*. Leiden: Eurotransplant International Foundation; 2020.

2. Colvin M, Smith JM, Ahn Y, et al. OPTN/SRTR 2020 Annual Data Report: Heart. *Am J Transplant* 2022;22 Suppl:350-437.
   PUBMED | CROSSREF

3. Korea Organ Donation Agency. Report from Korean Organ Donation Agency [Internet]. Seoul: Korea Organ Donation Agency; 2020. Available from: https://www.koda1458.kr/info/transplant.do.

4. Korean Network for Organ Sharing. *2019 KONOS annual report*. Seoul: Korean Network for Organ Sharing; 2019.

5. Zaroff JG, Rosengard BR, Armstrong WF, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28-29, 2001, Crystal City, Va. *Circulation* 2002;106:836-41.
   PUBMED | CROSSREF

6. Kim JC, Youn JC, Lee SE, Jung SH, Kim JJ. Donor heart utilization in Korea. *Int J Heart Fail* 2020;2:254-63.
   PUBMED | CROSSREF

7. Kobashigawa J, Zuckermann A, Macdonald P, et al. Report from a consensus conference on primary graft dysfunction after cardiac transplantation. *J Heart Lung Transplant* 2014;33:327-40.
   PUBMED | CROSSREF

8. 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

9. 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

10. Singh SS, Dalzell JR, Berry C, Al-Attar N. Primary graft dysfunction after heart transplantation: a thorn amongst the roses. *Heart Fail Rev* 2019;24:805-20.
    PUBMED | CROSSREF

11. Choi JO. Use of organ from marginal donor in cardiac transplantation: is it ready for us? *Int J Heart Fail* 2020;2:244-6.
    PUBMED | CROSSREF

12. Aliabadi-Zuckermann AZ, Gökler J, Kaider A, et al. Donor heart selection and outcomes: an analysis of over 2,000 cases. *J Heart Lung Transplant* 2018;37:976-84.
    PUBMED | CROSSREF

13. Wang Y, Cai J, Sun Y, et al. Extended donor criteria in heart transplantation: a retrospective study from a single Chinese institution. *J Thorac Dis* 2018;10:2153-65.
    PUBMED | CROSSREF

14. Galeone A, Lebreton G, Coutance G, et al. A single-center long-term experience with marginal donor utilization for heart transplantation. *Clin Transplant* 2020;34:e14057.
PUBMED | **CROSSREF**

15. Bifulco O, Bottio T, Caraffa R, et al. Marginal versus standard donors in heart transplantation: proper selection means heart transplant benefit. *J Clin Med* 2022;11:2665.
PUBMED | **CROSSREF**

16. Lima B, Rajagopal K, Petersen RP, et al. Marginal cardiac allografts do not have increased primary graft dysfunction in alternate list transplantation. *Circulation* 2006;114:I27-32.
PUBMED | **CROSSREF**

17. Chen JM, Russo MJ, Hammond KM, et al. Alternate waiting list strategies for heart transplantation maximize donor organ utilization. *Ann Thorac Surg* 2005;80:224-8.
PUBMED | **CROSSREF**

18. Rajagopalan N, Shafii AE, Dennis DR, Charnigo R, Sekela ME. Increasing heart transplant volume by expansion of donor heart selection criteria: a single-center analysis. *Transplant Proc* 2020;52:949-53.
PUBMED | **CROSSREF**

19. Trivedi JR, Cheng A, Ising M, Lenneman A, Birks E, Slaughter MS. Heart transplant survival based on recipient and donor risk scoring: a UNOS database analysis. *ASAIO J* 2016;62:297-301.
PUBMED | **CROSSREF**

20. Sathianathan S, Bhat G. Heart transplant donor selection guidelines: review and recommendations. *Curr Cardiol Rep* 2022;24:119-30.
PUBMED | **CROSSREF**

21. Taylor DO, Edwards LB, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult heart transplant report--2008. *J Heart Lung Transplant* 2008;27:943-56.
PUBMED | **CROSSREF**

22. Blanche C, Kamlot A, Blanche DA, et al. Heart transplantation with donors fifty years of age and older. *J Thorac Cardiovasc Surg* 2002;123:810-5.
PUBMED | **CROSSREF**

23. Hong KN, Iribarne A, Worku B, et al. Who is the high-risk recipient? Predicting mortality after heart transplant using pretransplant donor and recipient risk factors. *Ann Thorac Surg* 2011;92:520-7.
PUBMED | **CROSSREF**

24. Daniel M, Chen C, Chung J, Goldberg L, Acker MA, Atluri P. Interaction of donor and recipient age: do older heart transplant recipients require younger hearts? *Ann Thorac Surg* 2019;107:62-6.
PUBMED | **CROSSREF**

25. World Health Organization. *World Health Statistics 2021*. Geneva: World Health Organization; 2021.

26. Khush KK, Cherikh WS, Chambers DC, et al. The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: thirty-fifth Adult Heart Transplantation Report-2018; Focus Theme: Multiorgan transplantation. *J Heart Lung Transplant* 2018;37:1155-68.
PUBMED | **CROSSREF**

27. Dujardin KS, McCully RB, Wijdicks EF, et al. Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. *J Heart Lung Transplant* 2001;20:350-7.
PUBMED | **CROSSREF**

28. Madan S, Saeed O, Vlismas P, et al. Outcomes after transplantation of donor hearts with improving left ventricular systolic dysfunction. *J Am Coll Cardiol* 2017;70:1248-58.
PUBMED | **CROSSREF**

29. Anwar AS, Lee JM. Medical management of brain-dead organ donors. *Acute Crit Care* 2019;34:14-29.
PUBMED | **CROSSREF**

30. 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**