

# Extended donor criteria in heart transplantation: a retrospective study from a single Chinese institution

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**Background:** Heart donor selection criteria have been progressively widened due to increasing donor recipient mismatch. This study evaluates the outcomes of the use marginal donor hearts for orthotopic heart transplantation (OHT) based on a single center experience in China.

**Methods:** We retrospectively analyzed outcomes of patients undergoing OHT in our hospital between September 2008 and December 2015. All the donor hearts were from voluntary donation of brain-dead patients. The primary outcome was overall survival; secondary outcomes included cardiopulmonary bypass (CPB) time, ventilation time, post-operative mechanical support and medium-term complications.

**Results:** Overall, 278 patients with OHT were analyzed. Whereas 180 patients (64.7%) underwent OHT utilizing marginal donors (MD group), only 98 patients (35.3%) underwent OHT with standard donors (SD group). Compared to the SD group, the MD group had longer CPB time ( $P=0.001$ ), ventilation time ( $P=0.010$ ) and increased mechanical support rate ( $P=0.011$ ). Survival rates were comparable between the two groups at 30 days, 1 year, 3 years and 5 years (92.2%, 83.3%, 70.6%, 70.6% vs. 95.9%, 91.4%, 80.2%, 80.2% respectively). Multivariate Cox regression analysis revealed that female recipient gender [hazard ratio (HR) =2.632 (1.325–5.227),  $P=0.006$ ], diagnosis ( $P=0.014$ ) and abnormal donor heart structure [HR =3.638 (1.005–13.167),  $P=0.049$ ] were three predictors for 1-year all-cause mortality. The occurrence of complications in the recipients with more than 3-year follow-up did not differ between the two cohorts.

**Conclusions:** Marginal donor can be reasonably applied to expand the benefits of transplantation. Changing previous MD criteria to include donors with an age greater than 50 years, cold ischemic time less than 6 hours, donor/recipient weight ratio less than 0.8, compatible blood type, hepatitis virus seropositivity and MD used for male recipient will likely offer a good prognosis.

**Keywords:** Heart transplantation; marginal donors; survival analysis; complications

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## Introduction

Despite the rapid progress of mechanical circulation assistance, especially ventricular assist devices in heart failure, heart transplantation is still the optimal choice for patients with end-stage heart disease. Till 2014, 120,992 orthotropic heart transplantations have been registered worldwide; only 1,483 of these transplants were performed in mainland China (1).

However, the enormous discrepancy between the growing number of candidates and the limited availability of organs has led to the biggest problem in the transplantation system. More than 30% of the patients die on the waiting list for transplantation (2). A number of options have been proposed to expand the donor pool, including new areas of myocardial protection, advanced systems for organ allocation and social awareness of organ donation (3). Unfortunately, given the stage of development of mainland China, the use of hearts through the liberalization of donor acceptance criteria may be the most realistic method to overcome organ shortage.

Marginal organs are initially turned down by standard transplant recipient lists for left ventricle hypertrophy, structure abnormalities, high inotrope requirements, and positive hepatitis serologies but accepted by patients at risk of imminent death or those at high medical risk who would otherwise not have been offered heart transplantation (4). Nonetheless, different centers have dissimilar criteria (5,6) of marginal donors that focus on their own risk factors and are not in strict accordance with guidelines of the International Society for Heart and Lung Transplantation (ISHLT) (7). As representatives of the highest transplantation volume Chinese center in 2014 and 2015, we will briefly introduce the clinical effect of using marginal donors at our institute.

## Methods

This study was approved by the Ethics Committee of Tongji Medical College of Huazhong University of Science and Technology (IORG No. IORG0003571) and performed in accordance with the ethical statement of the Declaration of Helsinki and ISHLT.

### Study population

Data for all 278 adult (age  $\geq 18$ ) cardiac transplant recipients in our center from September 1, 2008 to December 31,

**Table 1** Donor characteristics for assignment to the marginal donor group

Variables	No. (%) (n=278)
Donor	
Age $\geq 50$ years old	25 (8.99)
Cold ischemic time $>360$ min	102 (36.69)
Donor/recipient weight ratio $<0.8$	51 (18.35)
Non-identical but compatible ABO/Rh blood type	44 (15.83)
Hepatitis virus seropositivity	14 (5.04)
CAD or ASD	7 (2.52)
High-dose inotropic support	4 (1.44)

CAD, coronary artery disease; ASD, atrial septal defect.

2015 were collected retrospectively from electronic medical records. All grafts listed in this study were procured from donors after brain death, not from executed prisoners. Patients who underwent cardiac retransplantation or multivisceral transplantation were excluded from this analysis. The recipient population was divided into 2 groups: the marginal donor group (MD, 180) and the standard donor (SD, 98) group.

Combining the experience of Massad (8), Lima *et al.* (5) and Taghavi *et al.* (9), donors were considered marginal if they met any of the following criteria: (I) advanced age ( $\geq 50$  years old and  $\leq 60$  years old); (II) long cold ischemic time ( $>360$  min); (III) donor/recipient size mismatch ( $0.6 <$  donor: recipient weight ratio  $<0.8$ ); (IV) non-identical but compatible ABO/Rh blood type; (V) hepatitis C seropositivity or hepatitis HBsAg, HBeAb and HBcAb positive simultaneously; (VI) coronary artery disease (CAD, any coronary artery stenosis evident on coronary angiogram or greater than mild calcified plaque) or repairable atrial septal defect (ASD); (VII) requiring high-dose inotropic support defined as the administration of dopamine or dobutamine ( $\geq 15$   $\mu\text{g}/\text{kg}/\text{min}$ ), epinephrine or norepinephrine ( $\geq 0.5$   $\mu\text{g}/\text{kg}/\text{min}$ ) (Table 1).

### Organ preservation and operation technique

A uniform method of preservation was applied to all donor hearts and consisted of 1 L of cold (4 °C) histidine-tryptophan-ketoglutarate (HTK) solution during transport. Additionally, 500 mL of HTK solution was perfused before implantation, and a typical biatrial or bicaval procedure with

moderate hypothermia (28 °C) was performed. A total of 5 donor allografts were identified with CAD and subsequently underwent coronary artery bypass graft (CABG). Two additional ASD hearts were repaired using patches. The need for post-transplant mechanical [intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO)] or inotropic support was determined by the surgeon on the basis of intraoperative transesophageal echocardiography (TEE), visualization of the heart and hemodynamic monitoring.

### *Post-transplantation treatment*

Basiliximab (20 mg) was administered intraoperatively and on the 4<sup>th</sup> day post-operation by intravenous pump for induction immunotherapy. This mediation was followed by a standard triple-drug immunosuppression regimen, including cyclosporine A (CsA)/tacrolimus, mycophenolate mofetil and prednisone. Prophylactic antibiotic therapy was discontinued in patients who exhibited no sign of infection seven days after transplantation. Patients with elevated pulmonary pressure after operation were prescribed iloprost by inhaler and a 3-month course of oral sildenafil (10). Followed by endomyocardial biopsy, acute cellular rejection exceeding grade 2R according to the ISHLT criteria (11) was treated by administering 500 mg of methylprednisolone for three days and increasing the doses of immunosuppressive drugs.

### *Outcome measures*

Demographic and clinical characteristics of all heart transplant donors and recipients were examined. After being discharged from our hospital, all patients were admitted to the outpatient department weekly for the 1<sup>st</sup> month, biweekly until the 3<sup>rd</sup> month, monthly from the 4<sup>th</sup> to 12<sup>th</sup> month, and twice for one year thereafter.

Immunosuppressant treatment failure resulted in switching to another primary immunosuppressive drug (CsA to tacrolimus or adding sirolimus) due to the obvious adverse effect and the occurrence of acute or chronic rejection. Acute rejection could be noted under surveillance through outpatient review. In contrast, chronic rejection, often with the manifestation of chronic allograft vasculopathy (CAV), which accounts for one-third of all-cause mortality at 5 years (12), might occur in the first half of the postoperative year. CAV was diagnosed if any coronary plaque or stenosis was found on computed

tomography angiograph (CTA) image, which was suggested to be conducted annually (13).

The patients who died or received heart retransplantation were included in the main outcome measures. Specifically, we selected 68 recipients from September 1, 2008 to March 1, 2013 with sufficient follow-up time to make a detailed analysis of immune inhibitor-related and unrelated complications.

March 1, 2016 was set as the end point of this study. The mean follow-up duration was 15.54 (6.98–28.73) months, and 269/278 (96.76%) patients completed followed-up.

### *Statistical analysis*

Unless otherwise stated, continuous variables conforming to a normal distribution were expressed as a mean ± standard deviation and analyzed by a 2-sample *t*-test. Variables fitting a skewed distribution, which were reported as the median [inter-quartile range (IQR)], were analyzed by the Mann-Whitney test. Categorical variables were presented as counts followed by percentages in parentheses and analyzed by the Chi-square test. The time to event analysis was estimated by the Kaplan-Meier method using the log-rank test. Univariate survival and mechanical support analysis were conducted using the Cox proportional hazard model and logistic regression, respectively. Covariates with *P*<0.05 in univariate analysis were then analyzed by stepwise multivariate regression with a probability of 0.05 and an elimination probability of 0.10. All tests were two-tailed with a 5% significance level. Statistical analysis was performed with SPSS version 21.0 (IBM corporation, Armonk, NY, USA).

## **Results**

### *Baseline characteristic*

Among the total 180 marginal donors listed in *Table 1*, there were 122 with only one marginal donor criterion, 50 with two marginal donor criteria, 7 with three marginal donor criteria and 1 with four marginal donor criteria. Baseline characteristics are presented in *Table 2*. The MD group was heavier than the SD group (66.11±14.41 *vs.* 60.21±9.79 kg, *P*<0.001) and included more patients with high blood pressure (20.00% *vs.* 10.20%). Perioperative data are recorded in *Table 3*. The MD group had longer Intra-operative cardiopulmonary bypass (CPB) time [104.00 (90.00–130.00) *vs.* 97.00 (86.00–107.00) min, *P*=0.001] and

**Table 2** Baseline characteristics of marginal donor group and standard donor group

Variables	MD (n=180)	SD (n=98)	P value
<b>Donor</b>			
Gender male (%)	160 (88.89)	89 (90.82)	0.615
Age (years)	35.30±12.30	35.30±8.23	1.000
Body weight (kg)	60.00 (55.00–70.00)	65.00 (60.00–70.00)	0.054
Cold ischemic time (min)	382.00 (156.00–455.00)	150.00 (123.00–283.50)	<0.001
Donor/recipient weight ratio	0.92 (0.77–1.14)	1.05 (0.93–1.17)	<0.001
<b>Recipient</b>			
Gender, male (%)	144 (80.00)	78 (79.59)	0.935
Age (years)	45.77±12.76	46.60±12.40	0.604
Body weight (kg)	66.11±14.41	60.21±9.79	<0.001
BMI (kg/m <sup>2</sup> )	23.48±4.03	21.51±2.67	<0.001
Diagnosis			0.190
ICM (%)	126 (70.00)	79 (80.61)	
CAD (%)	29 (16.11)	9 (9.18)	
VHD (%)	8 (4.44)	5 (5.10)	
Others (%)	17 (9.44)	5 (5.10)	
High blood pressure history (%)	36 (20.00)	10 (10.20)	0.036
Diabetes history (%)	31 (17.22)	15 (15.31)	0.681
Renal impairment (%)	36/179 (20.11)	20/97 (20.62)	0.920
Liver impairment (%)	46/179 (25.70)	24/97 (24.74)	0.862
Neurological impairment (%)	10/179 (5.59)	11/97 (11.34)	0.085
PRA ≥10% (%)	1 (0.56)	3 (3.06)	0.251
LCM (%)	7.00 (5.00–8.00)	6.00 (5.00–8.00)	0.298
Preoperative MPAP (mmHg)	38.49±13.85	38.96±12.84	0.796
Preoperative LVEF (%)	27.00 (21.00–32.00)	27.00 (21.00–31.00)	0.584

Continuous data of normal distribution expressed as a mean ± standard deviation, and the rest presented as median (IQR 25–75); Categorical data as number (percentage). Renal impairment stands for renal insufficiency, hydronephrosis, hyperuricemia, kidney stone and cyst of kidney. Liver impairment stands for medical history of liver disease including fatty liver, gall-stone, hypohepatia etc. Neurological impairment stands for any neurosurgery, vertebrobasilar insufficiency, lacunar or cerebral infarction, encephalatrophy and epilepsy. BMI, body mass index; ICM, idiopathic cardiomyopathy including dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; VHD, valvular heart disease; PRA, panel reactive antibody; LCM, lymphocyte cross matching; MPAP, mean pulmonary artery pressure; LVEF, left ventricle ejection fraction.

postoperative ventilation time [28.00 (20.00–42.00) *vs.* 22.00 (17.75–35.25) min, *P*=0.010]. The SD group exhibited more blood drainage [385.00 (265.00–505.00) *vs.* 450.00 (330.00–550.00) mL, *P*=0.020]. Consistent with preferred use of mechanical support [50 (27.78%) *vs.* 14 (14.29%), *P*=0.011 for IABP or ECMO and 46 (25.56%) *vs.* 12 (12.24%),

*P*=0.009 for IABP usage], dobutamine use rate was higher in the MD group (*P*<0.001). The number of patients with postoperative complications and treatment rejection [11 (6.11%) *vs.* 3 (3.06%), *P*=0.730] did not vary considerably before discharge from our hospital, and hospital mortality did not vary [7 (3.89%) *vs.* 2 (2.04%), *P*=0.623].

**Table 3** Perioperative data of marginal donor group and standard donor group

Variables	MD (n=180)	SD (n=98)	P value
CPB time (min)	104.00 (90.00–130.00)	97.00 (86.00–107.00)	0.001
ICU length of stay (d)	6.00 (5.00–8.00)	6.00 (5.00–11.83)	0.219
Blood drainage (mL)	385.00 (265.00–505.00)	450.00 (330.00–550.00)	0.020
Peak of CVP (mmHg)	14.53±3.50	14.78±4.96	0.626
Ventilation time (h)	28.00 (20.00–42.00)	22.00 (17.75–35.25)	0.010
PO mechanical support			
IABP (%)	46 (25.56)	12 (12.24)	0.009
ECMO (%)	11 (6.11)	5 (5.10)	0.730
PO inotropic support			
Using time for epinephrine (d)	1.00 (0.00–3.00)	1.00 (0.00–2.00)	0.143
Epinephrine at 24 h (µg/kg/min)	0.00 (0.00–2.00)	0.00 (0.00–1.00)	0.029
Using time for dopamine (d)	5.00 (3.00–8.00)	4.00 (3.00–7.00)	0.217
Dopamine at 24 h (µg/kg/min)	5.00 (3.00–6.00)	4.00 (3.00–5.00)	0.072
Use of dobutamine (%)	87 (48.33)	23 (23.47)	< 0.001
PO LVEF (%)	66.14±6.12	66.24±4.96	0.894
Reoperation for bleeding (%)	6 (3.33)	2 (2.04)	0.810
PO ≥2 TI (%)	17/116 (12.07)	2/34 (5.88)	0.289
CRRT (%)	16 (8.89)	6 (6.12)	0.414
PO neurological impairment (%)	11 (6.11)	3 (3.06)	0.410
PO infection (%)	51 (28.33)	25 (25.51)	0.614
PO hospitalization duration (d)	25.00 (21.00–32.00)	25.00 (22.00–32.00)	0.436
PO treated rejection (%)	11 (6.11)	5 (5.10)	0.730
PO mortality (%)	7 (3.89)	2 (2.04)	0.623

Continuous data of normal distribution expressed as a mean ± standard deviation, and the rest presented as median (IQR 25–75); Categorical data as number (percentage). CPB, cardiopulmonary bypass; ICU, intensive care unit; CVP, central venous pressure; PO, postoperative; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; TI, tricuspid insufficiency; CRRT, continuous renal replacement therapy.

Given 30% 30-day mortality and 34.6% (14) 1-year mortality in recipients with primary graft dysfunction (PGD), logistic regression models were utilized to determine the predictors listed in *Tables 2* and *3*. After univariate analysis, only cold ischemic time ( $P=0.012$ ) was found to be independent predictor of hospital mechanical support (*Table 4*). Of note, times greater than 8 hours [OR =3.617 (1.496–8.750), ≤4 hours as reference,  $P=0.004$ ] and time between 6 and 8 hours [OR =1.758 (0.894–3.460), ≤4 hours as reference,  $P=0.102$ ] were both associated with high risk of it. Other donor characteristics, such as compatible but non-

identical ABO type, low donor/recipient weight ratio, older donor, donor hepatitis virus seropositive, donor CAD or ASD and high-inotropic support donor did not significantly predict mechanical support.

#### **Short and intermediate-term survival rates**

Excluding 1 patient who died on the operating table, the remaining 277 recipients were followed to track survival rates (*Figure 1A*). The SD group had higher survival rate than the MD group [95.9% vs. 92.2% in 30 days, 91.4% vs.

**Table 4** Univariate logistic regression of primary graft dysfunction requiring mechanical support

Variables	Odds ratio (95% CI)	P value
Cold ischemic time		
≤4	Ref.	0.012
[4, 6]	0.791 (0.315–1.988)	0.619
[6, 8]	1.758 (0.894–3.460)	0.102
>8	3.617 (1.496–8.750)	0.004
ABO type compatible not same (vs. ABO type same)	0.706 (0.310–1.608)	0.408
Donor/recipient weight ratio <0.8 (vs. ≥0.8)	1.056 (0.515–2.165)	0.882
Donor age ≥50 years old (vs. <50 years old)	0.975 (0.371–2.560)	0.959
Donor weight	0.994 (0.965–1.024)	0.684
Donor female gender (vs. male gender)	1.587 (0.684–3.683)	0.282
Donor infectious status (hepatitis virus seropositive vs. seronegative)	0.923 (0.249–3.415)	0.904
Donor CAD or ASD (vs. normal)	1.348 (0.255–7.121)	0.725
Donor high-dose inotropic support (vs. normal)	0.286 (0.040–2.075)	0.216
Recipient female gender (vs. male gender)	0.676 (0.320–1.431)	0.306
Recipient age	1.006 (0.984–1.029)	0.615
Recipient weight	1.013 (0.993–1.035)	0.207
Recipient BMI	1.053 (0.976–1.136)	0.179
Diagnosis		
ICM	Ref.	0.256
CAD	1.895 (0.877–4.094)	0.104
Others	1.264 (0.533–2.886)	0.579
High blood pressure (vs. normal blood pressure)	1.138 (0.539–2.405)	0.734
Diabetes mellitus (vs. no diabetes mellitus)	0.784 (0.342–1.794)	0.564
Renal impairment (vs. no renal impairment)	1.472 (0.758–2.858)	0.253
Liver impairment (vs. no liver impairment)	1.372 (0.735–2.558)	0.320
Neurological impairment (vs. no neurological impairment)	1.061 (0.373–3.021)	0.911

CAD, coronary artery disease; ASD, atrial septal defect; ICM, idiopathic cardiomyopathy.

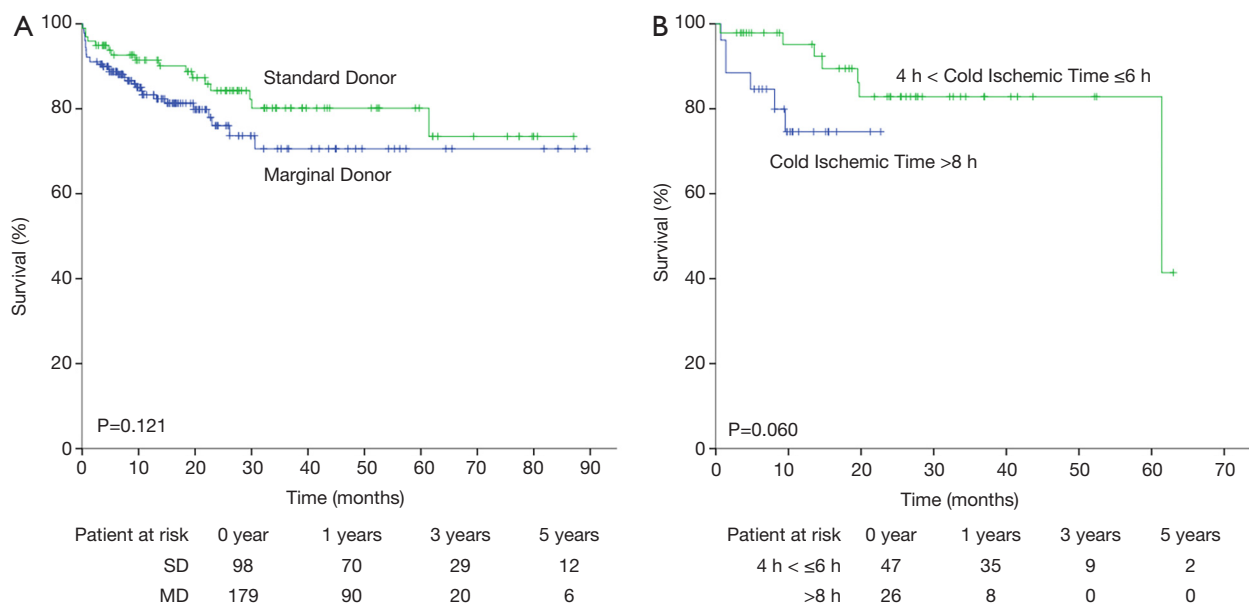
83.3% in 1 year, 80.2% vs. 70.6% in 3 years and 80.2% vs. 70.6% in 5 years], however, no significant differences in the endpoints were noted (overall  $P=0.121$ ).

#### *Predictors of survival outcomes*

Donor and recipient predictive factors of death or retransplantation are presented in *Table 5*. According to the univariate analysis, female recipient gender, recipient

weight, recipient diagnosis and recipient liver impairment were independent predictors of main outcomes in the cohort. After multivariate analysis, only female recipient gender [HR =2.861 (1.609–5.088),  $P<0.001$ ] persisted. Kaplan-Meier analysis also revealed that cold ischemic time greater than 8 hours resulted in worse survival outcomes than cold ischemic time between 4 and 6 hours at a marginally significant level ( $P=0.060$ , *Figure 1B*).

Furthermore, 1-year Cox analysis was also performed to



**Figure 1** Kaplan-Meier curve of mortality after heart transplantation for recipients still alive after operation stratified by (A) standard donor (green line) and marginal donor (blue line); (B) cold ischemic time less or equal than 6 hours but above 4 hours (green line) and cold ischemic time above 8 hours (blue line). Log-rank test was used for analysis.

evaluate the predictors for short-term outcomes (*Table 6*). In addition to female recipient gender, donor CAD or ASD and recipient disease other than idiopathic cardiomyopathy (ICM) and CAD also became risk factors in the final model.

Finally, the risk factors listed above were considered in determining whether marginal donors could be used in these situations. Considering the overall survival curve for female recipients, marginal donors exhibited relatively high mortality compared with standard donors ( $P=0.052$ , *Figure 2A*). No difference was observed for male recipients ( $P=0.601$ , *Figure 2B*). However, there was no significant difference for ICM, CAD recipients utilizing marginal donors (data not shown). The 1- and 3-year survival rates for ICM were 88.1% and 71.5% for the MD group and 92.2% and 82.4% for the SD group, respectively.

### Intermediate-term complications

From the information obtained through the outpatient department and telephone calls, immunosuppressant usage was recorded for 160 MD recipients and 92 SD recipients. For the typical triple-drug immunosuppression regimen, the SD group had an increased CsA utilization rate (15.22% *vs.* 3.75%) and immunosuppressant treatment failure (8.70% *vs.* 3.13%).

Specifically, of the 68 patients who were discharged from the hospital before March 1, 2013 (*Table 7*), 15 suffered from death or retransplantation and 6 patients were lost to follow-up. Immune inhibitor-related and -unrelated complications were comparable between the groups except that SD patients were more likely to experience  $\geq$  grade 2 tricuspid insufficiency (15,16) (29.73% *vs.* 6.45%).

### Discussion

Since the advent of cardiac transplantation as an effective solution for advanced heart failure in the 1960s, physicians have made considerable efforts to expand donor pool due to the high demand and comparatively low supply of available organs. Numerous modified protocols regarding the suitability of potential cardiac donors have been published over recent decades (17-20). Although common guidelines for donor selection are proposed according to the United Network for Organ Sharing (UNOS) database (7), different institutes should have their own criteria for donor allocation given that higher volume centers have prior experience focusing on complex donor management and higher baseline recipient risk (6). Considering the principles proposed by Duke University Medical Center (5) and University of Illinois (8), including single vessel CAD,

**Table 5** Univariate and multivariate cox regression analysis for overall survival outcomes

Variables	Hazard ratio (95% CI)	P Value
Univariate		
Cold ischemia time		
≤4	Ref.	0.429
[4, 6]	0.777 (0.335–1.805)	0.558
[6, 8]	1.117 (0.555–2.245)	0.757
>8	1.922 (0.768–4.812)	0.163
ABO type compatible not same (vs. ABO type same)	1.226 (0.596–2.523)	0.580
Donor/recipient weight ratio <0.8 (vs. ≥0.8)	0.402 (0.145–1.119)	0.081
Donor age ≥50 years old (vs. <50 years old)	0.797 (0.246–2.581)	0.705
Donor weight	1.018 (0.987–1.050)	0.265
Donor female gender (vs. male gender)	1.839 (0.862–3.925)	0.115
Donor infectious status (hepatitis virus seropositive vs. seronegative)	1.339 (0.416–4.306)	0.625
Donor CAD or ASD (vs. normal)	2.766 (0.857–8.927)	0.089
Donor high-dose inotropic support (vs. normal)	1.380 (0.190–10.036)	0.751
Recipient female gender (vs. male gender)	2.773 (1.565–4.915)	<0.001
Recipient age	0.995 (0.972–1.017)	0.639
Recipient weight	0.971 (0.949–0.994)	0.012
Recipient BMI	0.946 (0.866–1.034)	0.220
Diagnosis		
ICM	Ref.	0.037
CAD	1.276 (0.532–3.061)	0.585
Others	2.461 (1.236–4.900)	0.010
High blood pressure (vs. normal blood pressure)	0.866 (0.367–2.042)	0.742
Diabetes mellitus (vs. no diabetes mellitus)	0.640 (0.254–1.612)	0.343
Renal impairment (vs. no renal impairment)	1.608 (0.852–3.037)	0.143
Liver impairment (vs. no liver impairment)	1.859 (1.027–3.364)	0.041
Neurological impairment (vs. no neurological impairment)	1.800 (0.765–4.235)	0.178
Multivariate		
Recipient female gender	2.861 (1.609–5.088)	<0.001

CAD, coronary artery disease; ASD, atrial septal defect; ICM, idiopathic cardiomyopathy.

higher inotrope requirement, smaller donor, older donor, positive hepatitis serologies, we developed marginal donor criteria at our institute.

Based on the fact that the MD group had a lower weight ratio than the SD group when donor body weight was similar, we concluded that an overweight recipient was

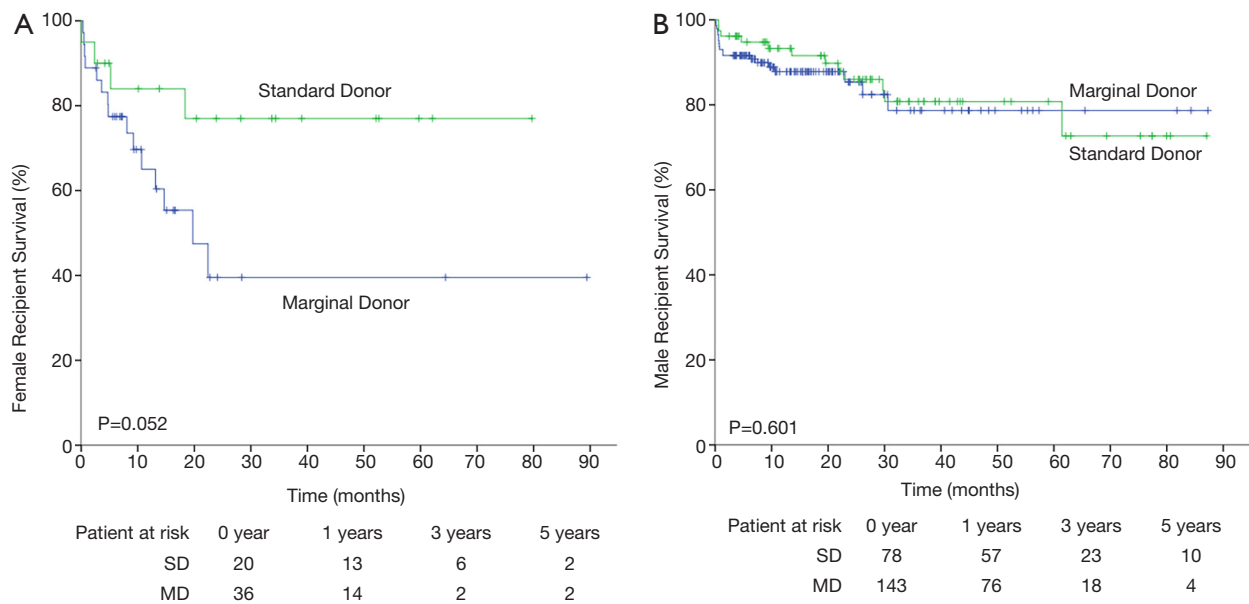
the main cause of the donor-recipient size mismatching. The internal relationship between body weight and high blood pressure history might also be explained the fact that more recipients suffered from high blood pressure in the MD group. Unlike the disease distribution of the ISHLT annual report (1), more idiopathic cardiomyopathy (74% vs.



**Table 6** Univariate and multivariate cox regression analysis for 1-year survival outcomes

Variables	Hazard ratio (95% CI)	P value
Univariate		
Cold ischemic time		
≤4	Ref.	0.184
[4, 6]	0.311 (0.072–1.348)	0.119
[6, 8]	0.986 (0.439–2.215)	0.973
>8	1.823 (0.718–4.629)	0.207
ABO type compatible not same (vs. ABO type same)	0.925 (0.359–2.384)	0.872
Donor/recipient weight ratio <0.8 (vs. ≥0.8)	0.416 (0.127–1.361)	0.147
Donor age ≥50 years old (vs. <50 years old)	0.951 (0.290–3.116)	0.934
Donor weight	1.012 (0.976–1.048)	0.528
Donor female gender (vs. male gender)	2.189 (0.956–5.012)	0.064
Donor infectious status (hepatitis virus seropositive vs. seronegative)	1.905 (0.583–6.221)	0.286
Donor CAD or ASD (vs. normal)	3.413 (1.045–11.148)	0.042
Donor high-dose inotropic support (vs. normal)	2.616 (0.353–19.381)	0.347
Recipient female gender (vs. male gender)	2.838 (1.443–5.584)	0.003
Recipient age	1.005 (0.978–1.032)	0.737
Recipient weight	0.959 (0.933–0.987)	0.004
Recipient BMI	0.904 (0.815–1.003)	0.057
Diagnosis		
ICM	Ref.	0.011
CAD	1.484 (0.557–3.955)	0.430
Others	3.232 (1.508–6.924)	0.003
High blood pressure (vs. normal blood pressure)	0.896 (0.348–2.310)	0.821
Diabetes mellitus (vs. no diabetes mellitus)	0.965 (0.374–2.487)	0.941
Renal impairment (vs. no renal impairment)	1.897 (0.929–3.873)	0.079
Liver impairment (vs. no liver impairment)	2.065 (1.050–4.061)	0.036
Neurological impairment (vs. no neurological impairment)	2.017 (0.783–5.201)	0.146
Multivariate		
Recipient female gender	2.632 (1.325–5.227)	0.006
Diagnosis		
ICM	Ref.	0.014
CAD	1.383 (0.485–3.947)	0.544
Others	3.133 (1.452–6.758)	0.004
Donor CAD or ASD (vs. normal)	3.638 (1.005–13.167)	0.049

CAD, coronary artery disease; ASD, atrial septal defect; ICM, idiopathic cardiomyopathy.



**Figure 2** Kaplan-Meier curve of mortality after heart transplantation for (A) female patients and (B) male patients receiving standard (green line) or marginal donor (blue line). Log-rank test was used for analysis.

55%) and less CAD (14% *vs.* 36%) were discovered at our institute. Patients who were designated marginal donors had increased CPB time and mechanical and inotropic support rates, suggesting a sicker status during the post-operation period. The MD group exhibited lower survival rate than the SD group, however, it offered a 70.6% 5-year survival rate to patients who would otherwise be expected to live 1 year. Moreover, intermediate term complications were similar except for  $\geq$  grade 2 tricuspid insufficiency in the SD group, which are worthy of further analysis. Due to the high cost required to diagnose CAV, despite it's the leading cause of late morbidity and mortality (21), only 14.3% of patients (34.7% recipients received CTA) were diagnosed with CAV in 5 years, compared with 32% when angiography was used in ISHLT data (22).

Assessing 7 marginal donor criteria separately could guide us in determining whether we should follow these criteria in the future. The 2010 guidelines recommended donor younger than 45 years or between 45 and 55 years but with a projected ischemic time  $\leq$ 4 hours (7). Hong *et al.* also regarded older age as an independent risk factor for 1-year mortality (23), but the upper limit of the acceptable age continued to increase as time progresses. In our study, age as a continuous variable or categorical variable with a cutoff of 50 years did not affect short and intermediate-term survival rates or the mechanical support

incidence rate. There were 25 patients with an average age of 49.3 years who received hearts from donors 50 years or older; the other group consisted of recipients who received hearts from younger donors with an average age of 45.7 years. Matching a younger donor with a young recipient may be basic principle of donor selection.

A 11,700 patients study showed ischemic time between 4 and 6 hours had an odds ratio of 1.4 (1.3–1.6) compared with a time of 2 to 4 hours when concerning 1-year outcomes (23). In our center, 4 to 6 hours resulted in a better outcome, though it made a rapid decline in the 5-year follow-up for lack of enough patients. Meanwhile, cold ischemic time between 6 and 8 hours and greater than 8 hours were predictors for mechanical support and had worse survival outcomes. In conclusion, cold ischemic within 6 hours without other risk factors was acceptable for recipients according to logistic and Cox models at our institute.

With the ability of our experienced physicians to match donor judging from the recipients' preoperative general condition, infectious status and pulmonary artery pressure, ABO type compatibility, hepatitis virus seropositivity and undersized donors did not influence survival as others stated (9,24,25). Both CAD and repairable ASDs in the donor's heart undoubtedly lowered the 1-year survival rate. Thus, this metric should not be used, which is further supported by Grauhan *et al.* (26). There were 4 donors with high-dose

Table 7 Medium-term outcomes for 68 recipients

Variables	MD (n=31)	SD (n=37)	P value
Immune inhibitors related complications			
Renal insufficiency (% , SCr >133 $\mu$ mol/L)	12 (38.71)	14 (37.84)	0.941
Hepatic dysfunction (% , ALT >0.68 $\mu$ kat/L or TB >19.0 $\mu$ mol/L)	21 (67.74)	22 (59.46)	0.481
New-onset fast blood glucose abnormal (% , FBG >7.0 mmol/L)	2 (6.45)	4 (10.81)	0.840
Tchol abnormal (% , Tchol $\geq$ 5.2 mmol/L)	13 (41.94)	17 (45.95)	0.740
LDL-C abnormal (% , LDL-C $\geq$ 3.13 mmol/L)	12 (38.71)	10 (27.03)	0.305
New-onset UA abnormal (% , UA $\geq$ 420 $\mu$ mol/L)	16 (51.61)	21 (56.76)	0.671
Pathogenic infection (%)	9 (29.03)	9 (24.32)	0.661
Others (%)	7 (22.58)	8 (21.62)	0.924
Immune inhibitors unrelated complications			
Gastrointestinal symptom (%)	2 (6.45)	8 (21.62)	0.157
$\geq$ Grade 2 TI (%)	2 (6.45)	11 (29.73)	0.015
Moderate to massive pericardial effusion (%)	3 (9.68)	0 (0.00)	0.090
Pericardial adhesion (%)	1 (3.23)	2 (5.41)	1.000
Arrhythmia (%)	10 (32.26)	14 (37.84)	0.632
CAV (%)	1 (3.23)	5 (13.51)	0.289
LVEF, %	68.40 $\pm$ 4.31	65.61 $\pm$ 5.76	0.108
Blood test			
TB ( $\mu$ mol/L)	16.96 $\pm$ 9.97	18.90 $\pm$ 11.16	0.563
ALT ( $\mu$ kat/L)	0.41 $\pm$ 0.26	0.35 $\pm$ 0.26	0.476
BUN (mmol/L)	6.97 (6.43–9.52)	8.10 (5.85–9.93)	0.806
SCr ( $\mu$ mol/L)	99.60 (82.00–110.30)	86.50 (72.65–106.00)	0.145
UA ( $\mu$ mol/L)	350.52 $\pm$ 91.77	353.79 $\pm$ 90.70	0.979
LDL-C (mmol/L)	2.67 $\pm$ 0.86	2.15 $\pm$ 1.32	0.173
Tchol (mmol/L)	5.09 $\pm$ 1.12	4.80 $\pm$ 1.90	0.584
FBG (mmol/L)	6.31 $\pm$ 2.65	6.56 $\pm$ 1.62	0.751

Continuous data of normal distribution expressed as a mean  $\pm$  standard deviation, and the rest presented as median (IQR 25–75); Categorical data as number (percentage). Pathogenic infection stands for positive computed tomography scan or sputum culture. Other disease listed in the table stands for femoral head osteonecrosis, herpes zoster and neoplasm etc. Tchol, total cholesterol; LDL-C, low density lipoprotein cholesterol; UA, uric acid; CAV, cardiac allograft vasculopathy; TB, total bilirubin; ALT, alanine transaminase; BUN, blood urea nitrogen; SCr, serum creatinine; FBG, fasting blood glucose.

inotropic support before heart procurement, and only one of the matched recipient suffered from perioperative death due to acute rejection.

Multivariate analysis combining recipient characteristics could lower the effect of confounding factors and multicollinearity of covariates. Female recipient gender

exhibited a higher hazard ratio (HR) in the overall and 1-year Cox regression analysis than male recipient gender. We do not recommend marginal donors for female recipients because female patients may have lower survival rates than those who receive hearts from standard donors. Consistent with Sharven Taghavi's report of male recipient gender

with a 0.882 HR for 1-year mortality (9), the high risk of female recipients in our center would be accounted for by gender mismatching [47/56 (83.9%) mismatching in female recipient group *vs.* 20/222 (9.0%) in male recipient group], which was thought to increase early mortality (27).

This study is limited by its retrospective design using single center data. Another important limitation is the relatively subjective definition of marginal donors, introducing significant bias in the selection process. Not all marginal donors satisfying the 7 criteria were used considering the general condition of the patients, and donor status should be evaluated with respect to the corresponding recipient, which will cause non-randomized donor selection. In addition, a small number of total cases and low main outcome incidence rates will contribute to fewer covariates in each step of multivariate regression analysis, and this will also make clinically significant data like intermediate term survival rate and predictors for hospital mechanical support be marginally significant.

In conclusion, based on prior experience, standardized clinical pathways and dedicated perioperative staff at our institute, selecting marginal donors using previous criteria may be reasonably applied to expand the benefits of transplantation. Nonetheless the following criteria will likely offer a good prognosis: (I) 50 years old  $\leq$  age  $\leq$  60 years old; (II) cold ischemic time  $<$  6 hours; (III) 0.6  $<$  donor/recipient weight ratio  $<$  0.8; (IV) compatible ABO/Rh blood type; (V) hepatitis virus seropositivity; (VI) MD used for male recipient. These findings also suggest the need for developing a national marginal donors mechanism appropriate for Chinese patients to extend the donor pool. However, further studies including data from other centers and the evaluation of long-term outcomes should be performed.

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### Footnote

**Conflicts of Interest:** The authors have no conflicts of interest

to declare.

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