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Heart transplantation with super-aged donors older than 65 years

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KEYWORDS:
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donor evaluation;
cardiac function

BACKGROUND: This study elucidated the clinical outcomes and serial allograft function of heart transplant (HTx) recipients who received hearts from super-aged donors (SAD) ≥65 years of age.
METHODS: Adult HTx recipients between 1999 and 2022 were retrospectively reviewed and divided into 2: donor age ≥65 years [SAD group (n = 12)] and donor age <65 years [younger donor, YD group (n = 140)]. The primary end-point was 3-year all-cause deaths after HTx. Secondary end-points included all-cause death, hospitalization due to heart failure, acute cellular rejection, coronary intervention, and electronic device implantation. Serial cardiac function was assessed using echocardiography and right heart catheterization.
RESULTS: Compared with the recipients in the YD group, those in the SAD group were older [age, 60 (interquartile range (IQR): 46-63) vs 42 (IQR: 31-52) years, $p < 0.001$], had a higher E/e' and lower cardiac index (CI) 1 month after HTx [E/e', 12.5 (IQR: 9.0-16.8) vs 9.5 (IQR: 7.5-11.9), $p = 0.026$; CI, 2.8 (IQR: 2.4-3.2) liter/min/m² vs 3.3 (IQR: 2.9-3.9) liter/min/m², $p = 0.014$], and a comparable CI with higher E/e' 1 year after HTx [E/e', 12.0 (IQR: 8.6-13.3) vs 7.9 (IQR: 6.6-10.6), $p = 0.007$; CI, 3.6 (IQR: 3.2-4.3) liter/min/m² vs 3.6 (IQR: 3.3-4.2) liter/min/m², $p = 0.99$]. The 3-year overall survival was lower in the SAD group than in the YD group (81.5% vs 97.8%, $p = 0.006$), whereas the secondary end-points were comparable.
CONCLUSION: SAG hearts at ≥65 years can be used for HTx with acceptable outcomes and feasible allograft function in relatively older recipients.
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Background

Heart transplantation (HTx) is an established therapeutic option for patients with advanced heart failure refractory to conventional guideline-directed treatments.[1] Despite the evolution of the medical management of patients with HTx, various issues remain unresolved.[2] Donor shortage is the most critical issue in HTx worldwide; however, the ratio of transplants performed to available donors has decreased in the United States—the country with the highest number of HTx procedures performed.[3] Therefore, various approaches have been proposed to address this issue.[4-8]

Accepting marginal donor hearts has been recognized as an effective way to expand the potential donor pool.[9,10] We previously reported that our program aggressively accepted marginal donor hearts with acceptable clinical outcomes.[11] In this report, over 80% of HTx in our program were conducted after accepting donor hearts with at least one conventional marginal factor, such as advanced age, small left ventricle, reduced left ventricular function, left ventricular hypertrophy, lower donor-to-recipient weight ratio, and the use of high-dose inotropes at procurement. There is currently no standard approach for evaluating and managing donor risk factors in HTx. Moreover, the impact of donor risk factors may change depending on the recipient's risk factors in each case.[12] Given this background and an extremely long average waiting time of over 3 years in our country, our program has been accepting hearts from super-aged donors (SAD) aged over 65 years as selected recipients.[13-15]

This study aimed to evaluate the clinical outcomes, including allograft function, of patients who received SAD hearts and assess the applicability of old donor hearts in current HTx clinical practice.

Methods

Study design

This retrospective, single-center, observational study was conducted to assess and compare the impact of SAD hearts (from donors over 65 years of age) on post-HTx outcomes. The primary end-point of this study was the 3-year all-cause deaths during the follow-up period after HTx. The secondary end-points were all-cause death; hospitalization due to heart failure; acute cellular rejection (ACR) greater than International Society for Heart and Lung Transplantation (ISHLT) grade 2R; donor-transmitted atherosclerosis defined as a maximal intimal thickness of 0.5 mm or greater at baseline; cardiac allograft vasculopathy (CAV) greater than ISHLT grade 1 for up to 1 and 3 years; coronary intervention, such as percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG); and electronic device implantation, such as pacemakers and implantable cardioverter defibrillators. This study was approved by the Institutional Research Board of our center (approval number: M30-026-6, ver.1.0, approval date: July 18, 2018, ver.1.5, approval date: March 31, 2022). The need for informed consent was waived because of the retrospective nature of this study. We also obtained approval from the Japan Organ Transplant Network to disclose donor information for analytical purposes.

Study participants and variables assessed

Consecutive patients who underwent isolated HTx between 1999 and 2022 at the National Cerebral and Cardiovascular Center were enrolled. Patients who were ≤18 years of age at HTx were excluded, and no patients received re-transplantation. The patients' medical records were retrospectively reviewed. The recipients' characteristics (age, sex, weight, ischemic etiology, waiting period as status 1, left ventricular assist device [LVAD] implantation), donors' characteristics (age, sex, weight, risk factors for coronary artery disease, echocardiographic parameters before procurement, history of cardiac arrest, and high-dose use of inotropic agents), and HTx-related parameters, including recipient-to-donor matching (donor-offered rank, and donor-to-recipient weight ratio) were recorded. Perioperative and postoperative characteristics included cold ischemic time, induction therapy, intra-aortic balloon pump (IABP), venoarterial extracorporeal membrane oxygenation (ECMO), inotropic agent, and length of intensive care unit stay. Allograft function, including hemodynamic parameters (mean blood pressure, mean pulmonary artery wedge pressure, mean pulmonary artery pressure, mean right atrial pressure, and cardiac index [CI]) and echocardiographic parameters, were also collected 1 month and 1 year after HTx. Data collection was censored in May 2023. The follow-up period was from the date of HTx to the date of last confirmed survival until May 2023.

Medical consultant system

The medical consultant (MC) doctor system is the second evaluation of the potential donor organ status. This evaluation follows the initial assessment performed by the donor hospital and is managed in collaboration with all transplant centers in our country by the Japan Organ Transplant Network.[16] With respect to HTx, when potential donors were identified after first being declared brain dead, registered transplant cardiologists or transplant surgeons were consulted as MCs. Their role was to determine the status of potential donor hearts and assess the eligibility of potential donor heart function for cardiac allografts. They were also involved in donor management. Clinical information, such as medical history, vital signs, blood examinations, chest radiography, electrocardiogram (ECG), and echocardiogram, are generally provided, whereas hemodynamics and coronary angiograms are typically not available in most cases. Whole-body computed tomography (CT) images were available in limited cases; however, coronary artery calcium score could not be obtained. If the dosage of inotropic drugs is high at this stage, antidiuretic hormones can be used to reduce the dosage of inotropic drugs as much as possible. If the MCs approve the transplant eligibility of the potential donor's heart, a second evaluation of brain death is performed.

Selection of potential recipients

After the second declaration of the potential donor as brain dead, matched recipients were selected. The urgency tier system is applied to the allocation system in Japan, where listed candidates are classified into 3 tiers according to their urgency: Status 1, active candidates requiring inotropic support at the intensive care unit, mechanical ventilation, or mechanical circulatory support, including IABP, ECMO, and LVAD; Status 2, active candidates other than those classified as Status 1; and Status 3, inactive candidates from any causes. Candidates at Status 1 are prioritized, and within the same tier, candidates are selected on a first-come, first-served basis with matched blood type and negative prospective cytotoxic crossmatch test. If the higher-ranked candidate declines the donor offer, the offer is sequentially extended to the next-ranked candidate. Since the upper age limit of donors is not defined, the decision to accept SAD hearts is made through shared decision-making considering the balance between risk and benefit.

Procurement, heart transplantation, and immunosuppression

The institutional procurement team conducts a final evaluation of potential donor hearts immediately before procurement, in addition to the second evaluation performed by the MCs. The hearts were directly evaluated by transplant cardiologists and echosonographers from our institution using transthoracic echocardiography.[17] Donor heart procurement was performed according to standard procedures; 2,000 to 2,500 ml of Celsior or St. Thomas solution at 4°C was administered to preserve the donor heart.[18] All HTx procedures were performed using a modified bicaval method, except in 1 recipient with dilated cardiomyopathy complicated by dextrocardia, and the Lower-Shumway method was used in 1 recipient.[19] Regarding immunosuppression, a standard triple-drug regimen, including a calcineurin inhibitor (cyclosporine or tacrolimus) in combination with an antimetabolite (mycophenolate mofetil or azathioprine) and a corticosteroid (prednisone), was used.[20] Induction therapy with monoclonal or polyclonal antibodies, such as murine monoclonal CD3 antibody or interleukin-2 monoclonal antibody (basiliximab), was used in patients with renal dysfunction during the perioperative period. The indications for basiliximab induction therapy are older donors and recipients, initially without tacrolimus or with a reduced dosage for renal protection. Everolimus with a reduced tacrolimus regimen has not been used immediately after HTx but has been used since 2007 in patients with renal dysfunction and CAV.[21]

Statistical analysis

The baseline characteristics of the study population were described as median (interquartile range [IQR]) or mean ± standard deviation for continuous variables and as numbers (percentages) for categorical variables. For continuous data, groups were compared using the Wilcoxon rank-sum test. All categorical variables were compared using the Pearson's chi-square test. The log-rank test was employed, and the Kaplan-Meier method was used to estimate the cumulative event-free survival. Survival curves were then compared between the 2 groups. All p-values were 2-sided, and $p < 0.05$ was considered statistically significant. All analyses were performed using the statistical software program JMP version 16 (SAS Institute Inc., Cary, NC).

Results

Patient enrollment and preoperative characteristics

A total of 152 adult patients who underwent HTx were enrolled in this study. The patients were divided into 2 groups according to the age of the donors; 12 patients received hearts from SAD who were ≥65 years of age (SAD group), while 140 patients received hearts from donors who were < 65 years of age (younger donor, YD group) (Figure 1).

The scatter plots of donor and recipient ages are shown in Figure 2. The highest donor and recipient ages were 76 and 68 years, respectively. The recipients' characteristics before HTx are shown in Table 1. The recipient's age was higher in the SAD group than in the YD group [60 (46-63) vs 42 (31-52), $p < 0.001$], and the prevalence of the male sex was lower in the SAD group than in the YD group (42% vs 76%, $p = 0.009$). No significant differences were observed between the 2 groups in etiology, waiting period, LVAD implantation, complications, or laboratory data before HTx.

Donor characteristics before HTx are shown in Table 2. The prevalence of hypertension was higher in the SAD group than in the YD group (50% vs 20%, $p = 0.017$), whereas the prevalence of other coronary risk factors was

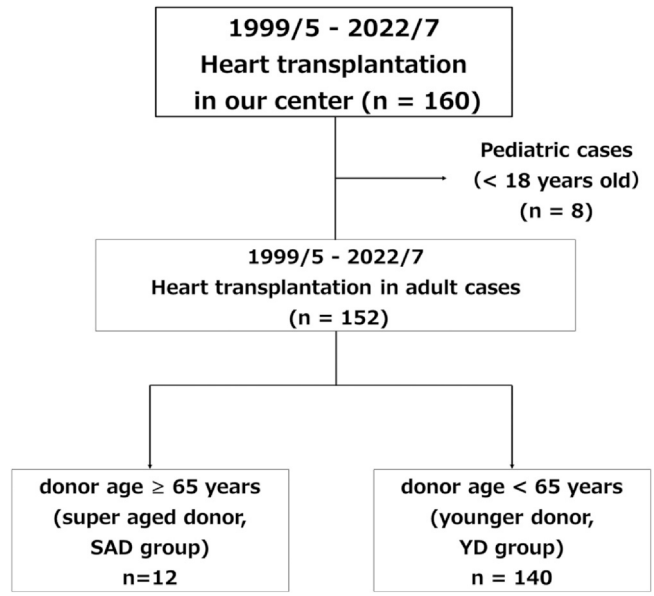

Figure 1 Flowchart of the study population.

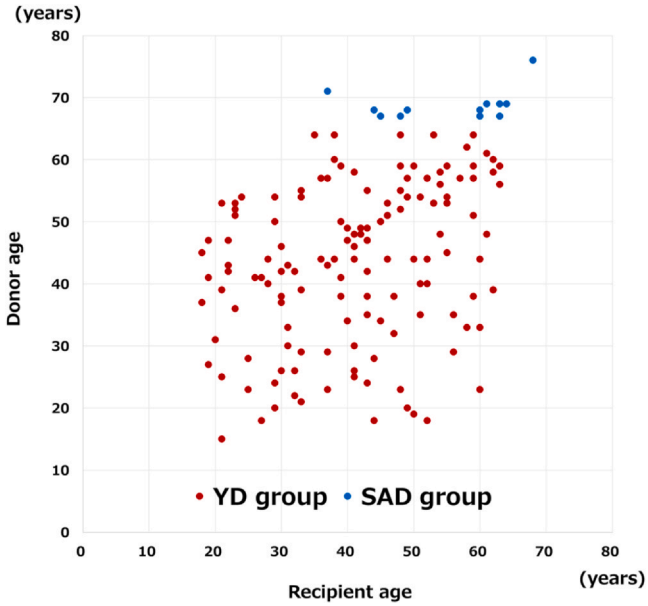

Figure 2 Scatter plot between donor and recipient ages. SAD, super-aged donor; YD, younger donor.

comparable between the groups. No significant difference was observed in donor cause of death between the 2 groups. Regarding the echocardiographic parameters of the donors before HTx, no significant differences were observed between the groups, including in left ventricular function and marginal factors.

Perioperative recipient and donor characteristics

Perioperative recipient and donor characteristics are shown in Table 3. No significant differences were found in the sex or weight mismatches between the 2 groups, except for the donor-offered rank. Donor-offered rank in the SAD group was significantly lower than that in the YD group [24 (11-32) vs 2 (1-7), $p < 0.001$]. Regarding postoperative characteristics, there were no significant differences in cold ischemic time, mechanical ventilation and mechanical circulatory support, or inotropic agents, except for the use of induction therapy, which was higher in the SAD group than in the YD group (100% vs 46%, $p < 0.001$).

Laboratory, echocardiographic, and hemodynamic variables after HTx

Echocardiographic and hemodynamic variables at 1 month and 1 year following HTx and laboratory data at 1 year after HTx are displayed in Table 4. Regarding echocardiographic parameters, the SAD group demonstrated a higher E/e' at both 1 month and 1 year after HTx [1 month after HTx, 12.5 (9.0-16.8) vs 9.5 (7.5-11.9), $p = 0.026$; 1 year after HTx, 12.0 (8.6-13.3) vs 7.9 (6.6-10.6), $p = 0.007$] than the YD group, whereas no significant differences were observed in left ventricular ejection fraction at 1 month and 1 year after HTx with all values within normal range (1 month after HTx, 58% ± 9% vs 60% ± 5%, $p = 0.76$; 1 year after HTx, 61% ± 2% vs 59% ± 4%, $p = 0.10$). Furthermore, the SAD group demonstrated a lower CI compared with the YD group 1 month after HTx, which was comparable at 1 year after HTx [SAD group vs YD group, 1 month after HTx, 2.8 (2.4-3.2) liter/min/m² vs 3.3 (2.9-3.9) liter/min/m², $p = 0.014$; 1 year after HTx, 3.6 (3.2-4.3) liter/min/m² vs 3.6 (3.3-4.2) liter/min/m², $p = 0.99$]. Serum creatinine and brain natriuretic peptide (BNP) levels 1 year after HTx were higher in the SAD group than in the YD group [serum

Table 1 Characteristics of Recipients

Characteristics	65 years ≥ (SAD) ($n = 12$)	65 years < (YD) ($n = 140$)	p-value
Clinical backgrounds			
Recipient age, years	60 (46-63)	42 (31-52)	< 0.001
18 ≤ Recipient age < 55, *n* (%)	5 (42)	114 (81)	
55 ≤ Recipient age < 65, *n* (%)	6 (50)	26 (19)	< 0.001
65 ≤ Recipient age < 70, *n* (%)	1 (8)	0 (0)	
70 ≤ Recipient age, *n* (%)	0 (0)	0 (0)	
Recipient male sex, *n* (%)	5 (42)	107 (76)	0.009
Recipient weight, kg	51 (44-62)	58 (51-66)	0.11
Recipient body surface area, m²	1.50 (1.36-1.78)	1.66 (1.52-1.78)	0.064
Ischemic cardiomyopathy, *n* (%)	1 (8)	13 (9)	0.91
Status 1 waiting period, *n* (days)	1,190 (781-1602)	1,080 (886-1381)	0.65
LVAD before HTx, *n* (%)	11 (92)	129 (92)	0.95
Complication before HTx			
Cerebral vascular events, *n* (%)	4 (33)	61 (44)	0.49
LVAD specific infection, *n* (%)	3 (25)	35 (25)	1.0
Implantable LVAD pump exchange, *n* (%)	1 (8)	6 (4)	0.52
Laboratory data before HTx (baseline)			
Creatinine (mg/dl)	0.96 (0.68-1.18)	0.89 (0.71-1.08)	0.80
Total bilirubin (mg/dl)	0.7 (0.6-1.4)	0.8 (0.5-1.0)	0.66
Hemoglobin (g/dl)	10.1 (9.5-12.2)	12.0 (10.2-13.4)	0.068
BNP (pg/ml)	232 (111-410)	153 (63-338)	0.26

Abbreviations: BNP, brain natriuretic peptide; HTx, heart transplantation; LVAD, left ventricular assist device; SAD, super-aged donor; YD, younger donor.

Table 2 Characteristics of Donors

Characteristics	65 years ≥ (SAD) ($n = 12$)	65 years < (YD) ($n = 140$)	p-value
Clinical backgrounds			
Donor age, years	68 (67-69)	44 (34-54)	< 0.001
15 ≤ Donor age < 55, *n* (%)	0 (0)	110 (79)	
55 ≤ Donor age < 65, *n* (%)	0 (0)	30 (21)	< 0.001
65 ≤ Donor age < 70, *n* (%)	10 (83)	0 (0)	
70 ≤ Donor age, *n* (%)	2 (17)	0 (0)	
Donor male sex, *n* (%)	5 (42)	79 (56)	0.32
Donor weight, kg	57 (45-70)	60 (52-70)	0.34
Donor body surface area, m²	1.55 (1.39-1.77)	1.66 (1.54-1.81)	0.11
Hypertension, *n* (%)	6 (50)	28 (20)	0.017
Diabetes mellitus, *n* (%)	2 (17)	8 (6)	0.14
Dyslipidemia, *n* (%)	0 (0)	4 (3)	0.55
Smoking, *n* (%)	5 (42)	80 (57)	0.30
Donor cause of death			
Cerebrovascular attack, *n* (%)	7 (58)	72 (51)	
Hypoxic encephalopathy, *n* (%)	2 (17)	46 (33)	0.59
Head trauma, *n* (%)	3 (25)	17 (12)	
Carbon monoxide intoxication, *n* (%)	0 (0)	3 (2)	
Others, *n* (%)	0 (0)	2 (1)	
Cardiac arrest, *n* (%)	5 (42)	74 (53)	0.46
High-dose inotropic agent, *n* (%)	0 (0)	15 (11)	0.23
Transthoracic echocardiography before HTx			
LVEF, % ($n = 148$)	63 ± 8	61 ± 9	0.47
LVEDD, mm ($n = 150$)	42 (41-47)	44 (41-48)	0.59
LVESD, mm ($n = 150$)	28 (27-29)	30 (26-33)	0.30
IVST, mm ($n = 146$)	10 (7-11)	10 (9-11)	0.58
PWT, mm ($n = 147$)	10 (9-11)	10 (9-11)	0.41
Trans mitral flow E wave, cm/s ($n = 114$)	71 (43-80)	65 (53-74)	1.00
LV hypertrophy (LV IVST/PWT > 13 mm), *n* (%)	0 (0)	19 (14)	0.17
LVEF < 55%, *n* (%)	2 (17)	28 (20)	0.78
LVEDD < 36 mm, *n* (%)	0 (0)	12 (9)	0.29

Abbreviations: HTx, heart transplantation; IVST, interventricular septum thickness; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PWT, posterior wall thickness; SAD, super-aged donor; YD, younger donor.

Table 3 Relationship Between Recipients' and Donors' Perioperative Characteristics

Characteristics	65 years ≥ (SAD) ($n = 12$)	65 years < (YD) ($n = 140$)	p-value
Relationship between recipient and donor			
Donor-offered rank, *n*	24 (11-32)	2 (1-7)	< 0.001
Sex mismatch, *n* (%)	2 (17)	43 (31)	0.31
Donor/recipient weight ratio	0.97 (0.86-1.42)	1.03 (0.90-1.20)	0.93
Donor/recipient weight mismatch (< 0.8), *n* (%)	0 (0)	5 (4)	0.51
Perioperative characteristics			
Cold ischemic time (minutes)	177 (171-202)	188 (162-212)	0.60
Cold ischemic time < 240 minutes, *n* (%)	12 (100)	136 (97)	0.55
Induction therapy, *n* (%)	12 (100)	65 (46)	< 0.001
Duration of mechanical ventilation (days)	1 (0-2)	1 (0-1)	0.20
IABP, *n* (%)	1 (8)	9 (6)	0.80
Duration of IABP (days) ($n = 10$)	7 (7-7)	3 (2-5)	0.16
ECMO, *n* (%)	1 (8)	5 (4)	0.42
Duration of ECMO (days) ($n = 6$)	8 (8-8)	2 (2-3)	0.21
Inotropic agent, *n* (%)	12 (100)	140 (100)	-
Duration of inotropic agent (days)	7 (4-11)	5 (3-9)	0.33
Duration of ICU stay (days)	3 (3-4)	4 (3-6)	0.15

Abbreviations: ECMO, venoarterial extracorporeal membrane oxygenation; IABP, Intra-aortic balloon pump; ICU, intensive care unit; SAD, super-aged donor; YD, younger donor.

Table 4 Characteristics of Patients After HTx

Characteristics	65 years ≥ (SAD) ($n = 12$)	65 years < (YD) ($n = 140$)	p-value
Transthoracic echocardiography 1 month after HTx (baseline)			
LVEF, % ($n = 150$)	58 ± 9	60 ± 5	0.76
LVEDD, mm ($n = 151$)	40 (38-40)	42 (39-45)	0.032
LVESD, mm ($n = 151$)	25 (23-27)	26 (24-29)	0.19
IVST, mm ($n = 151$)	9 (8-10)	9 (8-11)	0.85
PWT, mm ($n = 151$)	9 (8-10)	9 (8-11)	0.38
Trans mitral flow E wave, cm/s ($n = 148$)	73 (62-97)	73 (62-87)	0.75
E/e' (average) ($n = 101$)	12.5 (9.0-16.8)	9.5 (7.5-11.9)	0.026
Transthoracic echocardiography 1 year after HTx			
LVEF, % ($n = 145$)	61 ± 2	59 ± 4	0.10
LVEDD, mm ($n = 146$)	40 (38-44)	41 (38-45)	0.23
LVESD, mm ($n = 146$)	25 (20-26)	26 (23-29)	0.11
IVST, mm ($n = 146$)	9 (9-11)	8 (8-10)	0.046
PWT, mm ($n = 146$)	9 (8-10)	9 (8-10)	0.51
Trans mitral flow E wave, cm/s ($n = 143$)	87 (73-110)	78 (66-93)	0.19
E/e' (average) ($n = 111$)	12.0 (8.6-13.3)	7.9 (6.6-10.6)	0.007
Right heart catheterization 1 month after HTx (baseline)			
Mean blood pressure, mm Hg ($n = 123$)	81 (74-88)	82 (75-92)	0.77
Mean PAWP, mm Hg ($n = 149$)	7 (5-10)	8 (6-11)	0.54
Mean PAP, mm Hg ($n = 149$)	13 (13-16)	15 (12-18)	0.69
Mean RAP, mm Hg ($n = 149$)	5 (3-6)	4 (3-6)	0.99
CI (Fick), liter/min/m² ($n = 131$)	2.9 (2.6-3.2)	3.3 (3.0-3.8)	0.006
CI (Thermo), liter/min/m² ($n = 148$)	2.8 (2.4-3.2)	3.3 (2.9-3.9)	0.014
Right heart catheterization 1 year after HTx			
Mean blood pressure, mm Hg ($n = 139$)	91 (83-97)	85 (80-92)	0.16
Mean PAWP, mm Hg ($n = 147$)	8 (5-11)	7 (6-9)	0.31
Mean PAP, mm Hg ($n = 147$)	14 (13-18)	14 (12-16)	0.49
Mean RAP, mm Hg ($n = 147$)	3 (3-4)	3 (2-4)	0.53
CI (Fick), liter/min/m² ($n = 133$)	3.3 (2.6-3.6)	3.4 (3.0-3.8)	0.30
CI (Thermo), liter/min/m² ($n = 145$)	3.6 (3.2-4.3)	3.6 (3.3-4.2)	0.99
Laboratory data 1 year after HTx			
Creatinine (mg/dl) ($n = 147$)	1.15 (0.94-1.21)	0.91 (0.77-1.09)	< 0.001
Total bilirubin (mg/dl) ($n = 147$)	0.4 (0.3-0.7)	0.5 (0.4-0.7)	0.29
Hemoglobin (g/dl) ($n = 147$)	11.4 (9.9-12.0)	12.5 (10.9-13.5)	0.041
BNP (pg/ml) ($n = 141$)	105 (80-131)	50 (31-88)	0.003

Abbreviations: BNP, brain natriuretic peptide; CI, cardiac index; HTx, heart transplantation; IVST, interventricular septum thickness; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PWT, posterior wall thickness; RAP, right atrial pressure; SAD, super-aged donor; YD, younger donor.

creatinine, 1.15 (0.98-1.21) mg/dl vs 0.91 (0.77-1.09) mg/dl, $p < 0.001$; BNP, 105 (80-131) pg/ml vs 50 (31-88) pg/ml, $p = 0.003$, respectively].

Clinical outcomes

The clinical events that occurred 3 years after HTx are shown in Table 5. There were no significant differences in hospitalization due to heart failure, ACR greater than ISHLT grade 2R, donor-transmitted atherosclerosis, CAV greater than ISHLT grade 1 for up to 1 and 3 years, PCI, CABG, and electrical device implantation between the groups, except for all-cause death (17% vs 2%, $p = 0.007$). Kaplan-Meier curve analysis showed inferior 3-year survival in SAD group compared to that in YD group (81.5% vs 97.8%, log-rank $p = 0.006$) (Figure 3A). Among 2 deceased patients in the SAD group, one patient died from sudden death, and the other died from mediastinitis. In YD group, sudden death ($n = 1$), bowel obstruction ($n = 1$), and cerebral hemorrhage ($n = 1$) were observed within 3 years after transplantation. Regarding the composite endpoint, the groups had no significant differences (62.5% vs 83.8%, $p = 0.11$) (Figure 3B).

Discussion

Due to persistent and severe donor shortage in our country, the donor usage rate of HTx has exceeded 70%. Our program has endeavored to accept likely high-risk marginal donors, including 12 SADs aged ≥65 years, for selected recipients.[22] However, this study showed no significant differences in preoperative and perioperative donor and recipient characteristics, including preoperative donor heart function, between the groups, except for recipient age, prevalence of donor hypertension, male recipients, use of induction therapy after transplantation, and donor-offered

Table 5 Outcomes of Patients

Events within up to 3 years post HTx	65 years ≥ (SAD) ($n = 12$)	65 years < (YD) ($n = 140$)	p-value
All-cause death, n (%)	2 (17)	3 (2)	0.007
Heart failure hospitalization, n (%)	0 (0)	3 (2)	0.61
Acute cellular rejection > grade 2R, n (%)	0 (0)	12 (9)	0.29
Donor-transmitted atherosclerosis, n (%) ($n = 148$)	9 (75)	81 (60)	0.29
CAV > ISHLT grade 1 up to 1 year, n (%) ($n = 141$)	6 (55)	90 (69)	0.32
CAV > ISHLT grade 1 up to 3 years, n (%) ($n = 120$)	3 (43)	85 (75)	0.06
PCI, n (%)	0 (0)	3 (2)	0.61
CABG, n (%)	1 (8)	2 (1)	0.099
Electronic device implantation, n (%)	1 (8)	4 (3)	0.31
Composite endpoint, n (%)	4 (26)	22 (16)	0.12

Abbreviations: CABG, coronary artery bypass grafting; CAV, cardiac allograft vasculopathy; HTx, heart transplantation; ISHLT, International Society for Heart and Lung Transplantation; PCI, percutaneous coronary intervention; SAD, super-aged donor; YD, younger donor.

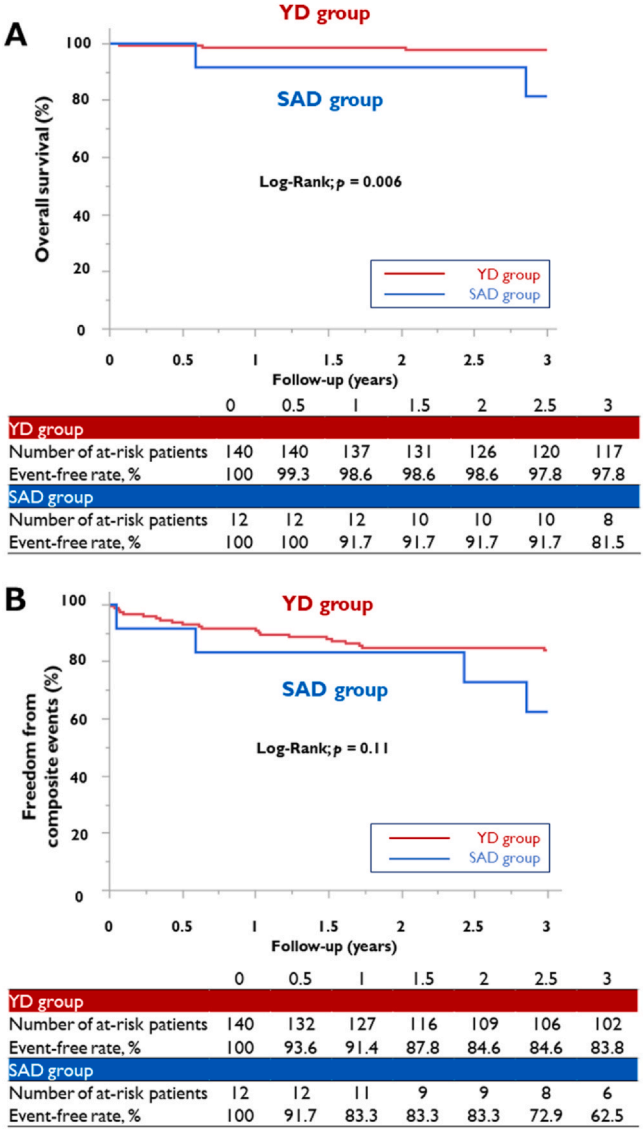

Figure 3 Kaplan-Meier curves for the freedom rate of end-points for 2 groups of patients: SAD and YD groups. (A) Primary end-point and (B) secondary end-point. SAD, super-aged donor; YD, younger donor.

rank. Furthermore, detailed assessments of the allograft revealed that SAD hearts demonstrated higher E/e' with normal range of left ventricular ejection fraction at both 1 month and 1 year after HTx, which may imply age-associated impaired diastolic function in super-aged allografts.[23-25] Hemodynamically, the CI of hearts from SAD was lower than that of hearts from YDs 1 month after HTx and was comparable at 1 year after HTx. Therefore, allograft function in SAD hearts demonstrates acceptable normal allograft function according to age.[26] Regarding outcomes, SAD group demonstrated inferior survival compared to YD group. However, no significant differences were found in secondary endpoints between the groups, including heart failure, ACR, PCI, CABG, and electronic device implantation.

Our study showed that SAD hearts from donors ≥ 65 years of age were viable options for older recipients in terms of allograft function since their allograft function, as assessed by both echocardiography and right heart catheterization, demonstrated normal values for older recipients. Furthermore, a 3-year overall survival of 81.5% in the SAD group is acceptable, as the 3-year overall survival in the SAD group was superior to that of transplant candidates on the waiting list for adult HTx in our country (74.9%).[27–29] Therefore, our study suggests that if potential older recipients cannot tolerate longer waiting times, SAD hearts may be a reasonable alternative.

Multiple reports have been published regarding the impact of older donor hearts.[30–34] However, to our knowledge, the current study evaluates the impact of HTx using hearts from SAD aged ≥ 65 years. The results of this study may expand the upper limit of donor age in modern HTx clinical practice. However, careful consideration is required when interpreting the results of this study to worldwide. First, this is a Japan-based study and enrolled recipients and donors were all Japanese, except for 1 Filipino recipient. Second, the HTx program in our country systematically introduces repeated evaluations of potential donor hearts before procurement. Since brain death is considerably associated with marked physiological instability, including cardiac dysfunction, a single evaluation can miss the true condition of

the potential donor heart. Serial evaluations enable identifying the true potential donor heart function before procurement, which leads to an increase in the acceptance rate of SAD hearts.[35] Furthermore, serial evaluation also enhances the reliability of echocardiographic evaluation of potential donor hearts since the interpretation of echocardiograms has been reported to vary among examiners.[36] Second, the MC system is pivotal in encouraging the proactive acceptance of SAD hearts. Optimizing donor conditions to align with donor management goals is associated with a higher likelihood of HTx.[37] Optimal hemodynamic and metabolic management, including euvolemia, maintenance of acid-base balance, and correction of hormonal perturbations, improves cardiac performance, raises blood pressure, and reduces inotrope requirements.[38] Carefully assessing and managing potential donor hearts may contribute greatly to improving and maintaining allograft function and favorable outcomes, even in SAD hearts; that could explain why preoperative characteristics, including cardiac function, in the SAD group were comparable to those in the YD group.

Donor-transmitted atherosclerosis and the long-term prognosis are serious concerns when considering the acceptance of older donor hearts.[39–41] As shown in Table 3, the donor-offered rank in the SAD group was significantly lower than that in the YD group. This indicates SAD were previously declined by other higher-ranked candidates, probably due to the concern of coronary artery diseases and long-term prognosis. However, no catheter-based or CT-based coronary angiography has been performed on potential donors before procurement; therefore, a comprehensive approach, including the presence of coronary risk factors, serial ECG analysis, cardiac contractility with regional wall motion abnormality on echocardiography, coronary artery calcification on plain CT if available, and visual inspection together with palpation of the coronary artery at the time of procurement, is required. Furthermore, brain death, which affects "catecholamine storm" in potential donors, might be the most effective stress test to rule out significant coronary artery stenosis; therefore, favorable cardiac function with an acceptable ECG pattern may suggest no significant coronary artery stenosis in potential donor hearts. Nonetheless, coronary angiography should be considered in super-aged potential donors. Despite successful HTx, 1 patient in the SAD group received a donor heart from 69-year-old male found to have triple vessel coronary artery disease at scheduled CAG conducted 12 days after HTx and underwent CABG 17 days after HTx. Furthermore, another patient in the SAD group died from sudden death 2.8 years after HTx. These adverse events might have been avoided if CAG of potential donors were available before procurement. Therefore, we believe that the absence of significant coronary stenosis on CAG in potential donors strongly encourages donor acceptance, as previously reported.[42] This should be especially emphasized in super-aged potential donors.[43] We still lack sufficient data regarding long-term prognosis, as the median follow-up period in the SAD group was only 3.9 (1.6-5.7) years by the end of the study period. However, 1 female patient in the SAD group, who underwent transplantation in 2012 at 61 years, has been alive for more than 10 years. Therefore, we believe that long-term outcomes will be acceptable, even in the SAD group, if appropriate post-HTx care is provided.[44]

Considering the continuous improvement in the outcomes of implantable LVAD, the treatment choice between older donor HTx and destination therapy (DT) using HeartMate 3 is a topic worthy of debate. According to the MOMENTUM 3 trial result, the 3-year survival rate of DT-LVAD patients was 69%.[45] DT using HeartMate 3 has just launched in 2021 in Japan and a favorable prognosis equal to or greater than that of the MOMENTUM 3 trial is expected. DT using HeartMate 3 could be a promising alternative therapy for older individuals with advanced heart failure who are deemed eligible for HTx using SAD hearts.

Limitations

This study had several limitations. First, this retrospective observational study was conducted at a single center with a relatively small sample size over 22 years. The small sample size and various progress in transplant clinical practice during 22 years of study may affect the results. However, we believe this study significantly impacts HTx clinical practice, particularly regarding the usage of aged donor hearts (≥65 years), a topic not previously reported elsewhere. Second, this is a Japan-based study, and the Japanese population has reported a lower frequency of atherosclerotic disease than the Western population, careful consideration is necessary for extrapolating the findings of this study to a global population.[46] However, this study showed that even among older donors, some individuals possess sufficient potential for transplantation through careful and repeated quality assessment and donor management conducted by expert transplant physicians. Therefore, this study undoubtedly contributes to expanding the worldwide limited donor pool. Third, the follow-up period was relatively short, and long-term outcomes were not evaluated. However, the results of this study were comparable to or even better than those of previous reports in Japan, making them acceptable. Despite these limitations, our study offers novel insights into the feasibility of older donor hearts for HTx under donor shortage conditions and contributes to improving the survival of patients with advanced heart failure.

Conclusions

In conclusion, although the preliminary results are limited to Japanese population, this study revealed that carefully evaluated and properly managed donor hearts from donors aged ≥65 years can be used for HTx with acceptable outcomes and feasible allograft function for relatively older recipients. The proper management and assessment of potential donors by MC system may play an essential role for this result. As donor shortage has been a universal issue in

global transplant clinical practice, our study demonstrates the important clinical implications of expanding the potential donor pool, which may contribute to an increase in the donor heart-offer acceptance rate.

Author contributions

All authors contributed to the conception and design of the study. T.H. and N.K. contributed to the data collection. T.H. and O.S. performed data analysis. T.H., O.S., and N. F. drafted the manuscript, which all the authors critically revised. All authors have read and approved the final manuscript for submission.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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