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Prognostic Value of Ambulatory Status at Transplant in Older Heart Transplant Recipients: Implications for Organ Allocation Policy

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ABSTRACT

Background: Shortage of organ donors in the Republic of Korea has become a major problem. To address this, it has been questioned whether heart transplant (HTx) allocation should be modified to reduce priority of older patients. We aimed to evaluate post-HTx outcomes according to recipient age and specific pre-HTx conditions using a nationwide prospective cohort.

Methods: We analyzed clinical characteristics of 628 patients from the Korean Organ Transplant Registry who received HTx from January 2015 to December 2020. Enrolled recipients were divided into three groups according to age. We also included comorbidities including ambulatory status. Non-ambulatory status was defined as pre-HTx support with either extracorporeal membrane oxygenation, continuous renal replacement therapy, or mechanical ventilation.

Results: Of the 628 patients, 195 were < 50 years, 322 were 50–64 years and 111 were ≥ 65 years at transplant. Four hundred nine (65.1%) were ambulatory and 219 (34.9%) were non-ambulatory. Older recipients tended to have more comorbidities, ischemic cardiomyopathy, and received older donors. Post-HTx survival was significantly lower in older recipients

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

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($P = 0.025$) and recipients with non-ambulatory status ($P < 0.001$). However, in contrast to non-ambulatory recipients who showed significant survival differences according to the recipient's age ($P = 0.004$), ambulatory recipients showed comparable outcomes ($P = 0.465$).

Conclusion: Our results do not support use of age alone as an allocation criterion. Transplant candidate age in combination with some comorbidities such as non-ambulatory status may identify patients at a sufficiently elevated risk at which suitability of HTx should be reconsidered.

Keywords: Heart Transplantation; Age; Ambulatory Status; Survival; Outcome

INTRODUCTION

Heart transplantation (HTx) has become the standard treatment for selected patients with advanced heart failure (HF). Increased prevalence of HF leads to more patients with advanced HF necessitating HTx.^{1,2} HTx was initially performed primarily in younger recipients, due to higher risk of worse clinical outcomes in older recipients.³ However, improvements in immunosuppressant therapy, donor procurement, surgical techniques, and standardized post-HTx care have resulted in expanding the recipient age range to 65–70+ years.^{4–8} Donor shortages have become a major problem in most countries, and thus the issue of whether age should be used to deprioritize HTx allocation is being considered by some. In fact, some regions have policies that include HTx candidate age in allocation algorithms.⁹ Inclusion of candidate age as an organ allocation criterion has also been used in the Republic of Korea.

Although higher chronologic age may reflect poor physical or comorbid conditions, it may not be uniformly applied to the entire elderly population. Given limited data, the heterogeneity of allocation systems according to the recipient's age implies an unmet clinical need to better evaluate older recipients. Furthermore, non-ambulatory status with the use of extracorporeal membrane oxygenation (ECMO), continuous renal replacement therapy (CRRT), or mechanical ventilation (MV) before HTx negatively affects post-HTx outcomes.^{10–12} The differential contemporary outcomes of HTx recipients according to age and specific pre-HTx conditions need to be better studied. Therefore, we aimed to evaluate the impact of age and comorbidities including ambulatory status on post-HTx outcomes in a nationwide prospective cohort.

METHODS

Study design and population

The Korean Organ Transplant Registry (KOTRY) is a prospective, multi-center cohort that consecutively enrolled patients who received HTx at four major hospitals in the Republic of Korea since March 2014.¹³ We analyzed clinical data from the KOTRY of patients who received HTx including heart-kidney multiorgan transplant between January 2015 and December 2020. Follow-up data after transplantation were assessed and recorded at 1, 6 months, and annually for the first 5 years. The overall study population was divided into three groups according to age: under 50, between 50 and 64, and over 65 years. Non-ambulatory recipients were defined as those who received either ECMO, CRRT, or MV before HTx, as these patients were in a bed-bound status. Information including baseline demographics and clinical data of recipients and donors was collected. The patients in this contemporary prospective nationwide cohort received care under a standardized protocol.¹⁴

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Korean heart allocation policy

Cardiac allocation policy in Republic of Korea is categorized into five statuses, ranging from 0 (highest urgency) to 4. Status 0 is assigned to patients requiring ECMO, an extracorporeal ventricular assist device (VAD), MV, or refractory ventricular tachyarrhythmia requiring mechanical circulatory support. Status 1 is for patients with a durable VAD or those needing intravenous inotropes for over four weeks. Upon the availability of a donor, priority is given to patients with higher urgency, followed by those with matching blood types. The country is divided into three regional zones, and within the same urgency status and blood type, patients in the same zone with the donor site are prioritized. Followed by these factors, allocation also considers waiting time, age, and previous organ donation history. Regarding age, additional points are awarded as follows: no extra points for individuals over 70, one point for those aged 19 to 69, and two points for patients under 19. The comprehensive cardiac allocation policy is detailed in the **Supplementary Fig. 1**.

Study outcome

The primary endpoint of the study was the survival rate after transplantation. Secondary endpoints comprised rates of infection, cardiac allograft vasculopathy (CAV, defined as any stenosis $\geq 30\%$), and acute rejection. CAV was adjudicated following the criteria of the International Society for Heart and Lung Transplantation (ISHLT).¹⁵ Rejection was defined as acute cellular rejection of grade 2R or higher and/or antibody-mediated rejection (AMR) of pathologic grade pAMR2 or higher.¹⁶ Infection was considered as any episode of clinically significant infection defined by requirement of intravenous antimicrobial agents at least 2 weeks or necessitating hospital admission or extension of hospital stay.

Statistical analysis

Continuous variables are presented as mean \pm standard deviation and the difference was evaluated using analysis of variance. Categorical variables are presented as percentages and were compared using Pearson χ^2 or Fisher's exact test as appropriate. The study endpoint was estimated using the Kaplan-Meier method, and the differences were compared using the log-rank test. The hazard of clinical variables was analyzed with a Cox proportional hazard model, and multivariable analyses were performed adjusting the variables with clinical relevance. Statistical significance was defined as $P < 0.05$ on univariable Cox regression analyses. The proportional hazards assumption was tested by examining the log (-log survival) curves and Schoenfeld residuals. The interaction between recipient age and ambulatory status was estimated from the Wald's test of Cox model. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM, Armonk, NY, USA). All comparisons were two-sided, and P values < 0.05 were regarded as statistically significant.

Ethics statement

The registry was approved by the Institutional Review Board at each center involved (Asan Medical Center, Seoul, Korea, #2014-0746). The study was conducted in compliance with the Declaration of Helsinki, and informed consent was obtained from all study participants.

RESULTS

Baseline characteristics of the study population

A total of 628 patients who underwent HTx between January 2015 and December 2020 were included. The mean age at transplant was 53.1 ± 12.8 years, and 70.4% were male. A total

of 140 (22.3%) had ischemic cardiomyopathy (CM) and 488 (77.7%) had non-ischemic CM. A total of 219 (34.9%) were non-ambulatory recipients at the time of HTx, of whom 192 (30.6%) received ECMO, in 97 (15.4%) received CRRT, and 144 (22.9%) were on MV. Some of these treatments were used in combination (Fig. 1). Older recipients had more comorbidities, were more likely to have ischemic or valvular CM and a higher proportion of pre-transplant support with left ventricular assist device (LVAD) (Table 1). Induction and maintenance immunosuppressive therapies were generally comparable between the groups (Supplementary Table 1). The total operation and cardiopulmonary bypass time were significantly longer in the older recipient group, possibly driven by a differential proportion of pre-transplant LVAD (Supplementary Table 2). Donor age was also higher in recipients aged over 50 years. Duration on the waitlist, pre-transplant ECMO or CRRT support, and ischemic time did not show inter-group differences.

Post-transplant survival by recipient's age and ambulatory status

Among the 93 HTx recipients who died within the 5-year follow-up period, infection was the leading cause of death (Supplementary Table 3). Survival after HTx was significantly lower among older recipients ($P = 0.025$, Fig. 2A). Specifically, recipients aged over 65 years exhibited significantly lower survival rates than recipients under 50 years of age (73.3% vs. 85.3% at 5 years after transplant, $P = 0.006$). In a multivariable analysis, age over 65 years was associated with an increased risk of post-HTx mortality (hazard ratio [HR], 2.22; 95% confidential interval [CI], 1.18–4.15; $P = 0.013$) (Table 2).

The survival rate of the non-ambulatory recipients was significantly lower than that of ambulatory recipients ($P < 0.001$, Fig. 2B). Non-ambulatory status remained predictive of post-HTx mortality after multivariable adjustment (HR, 3.13; 95% CI, 2.05–4.78; $P < 0.001$) independent of other clinical variables (Table 2).

We next explored the differences in survival according to age and ambulatory status. Recipients with non-ambulatory status showed a significant survival difference according to age ($P = 0.004$), with the lowest survival observed in older (age ≥ 65) recipients (Fig. 3B).

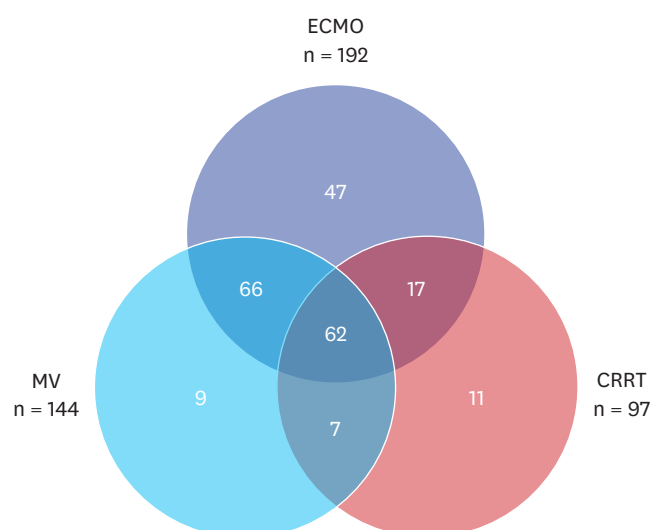


Fig. 1. Non-ambulatory heart transplant recipients classified by supporting therapy. CRRT = continuous renal replacement therapy, ECMO = extracorporeal membrane oxygenation, MV = mechanical ventilation.

Table 1. Baseline characteristics

Variables	Age < 50 yr (n = 195)	Age 50–64 yr (n = 322)	Age ≥ 65 yr (n = 111)	P value
Recipient demographics				
Age, yr	37.1 ± 9.2	57.7 ± 4.2	67.9 ± 2.4	< 0.001
Male, gender	141 (72.3)	222 (68.9)	79 (71.2)	0.705
Height, cm	169.3 ± 8.3	164.6 ± 8.5	163.9 ± 7.6	< 0.001
Body weight, kg	64.7 ± 13.6	62.0 ± 11.4	60.9 ± 10.2	0.010
Body mass index, kg/m ²	22.5 ± 4.0	22.8 ± 3.4	22.6 ± 3.0	0.556
Hypertension	39 (20.0)	106 (32.9)	48 (43.2)	< 0.001
Diabetes	33 (16.9)	120 (37.3)	41 (36.9)	< 0.001
Chronic kidney disease	16 (8.2)	70 (21.7)	28 (25.2)	< 0.001
Duration on waitlist, days	70 (21–176)	81 (24–194)	79 (21–297)	0.705
Indication for heart transplantation				
Ischemic	21 (10.8)	88 (27.3)	31 (27.9)	< 0.001
Dilated	107 (54.9)	152 (47.2)	54 (48.6)	0.231
Hypertrophic	18 (9.2)	13 (4.0)	3 (2.7)	0.016
Valvular	1 (0.5)	16 (5.0)	11 (9.9)	< 0.001
Congenital	14 (7.2)	9 (2.8)	1 (0.9)	0.010
Re-transplantation	11 (5.6)	10 (3.1)	3 (2.7)	0.294
Others	23 (11.8)	34 (10.6)	8 (7.2)	0.441
Pre-transplant support				
ECMO	68 (34.9)	94 (29.2)	30 (27.0)	0.267
LVAD	7 (3.6)	26 (8.1)	18 (16.2)	0.001
With ECMO	1 (0.5)	4 (1.2)	0 (0.0)	
CRRT	30 (15.4)	50 (15.5)	17 (15.3)	0.998
Mechanical ventilation	49 (25.1)	68 (21.1)	27 (24.3)	0.534
Donor characteristics				
Age, yr	36.2 ± 11.3	42.6 ± 10.7	42.1 ± 11.7	< 0.001
Male, gender	145 (74.4)	231 (71.7)	74 (66.7)	0.356
Height, cm	170.5 ± 7.1	168.9 ± 7.4	168.3 ± 7.4	0.018
Body weight, kg	68.7 ± 11.2	67.5 ± 12.0	66.1 ± 12.9	0.184
LVEF, %	62.2 ± 7.9	62.4 ± 6.9	61.6 ± 7.3	0.601
Surgical characteristics				
Warm ischemic time, min	56.7 ± 30.4	59.4 ± 30.6	63.9 ± 33.2	0.160
Cold ischemic time, min	119.3 ± 64.3	110.5 ± 58.7	118.3 ± 64.5	0.233
Total operation time, min	354.4 ± 101.8	348.1 ± 89.6	378.9 ± 106.8	0.015
Time on cardiopulmonary bypass, min	156.4 ± 58.1	156.1 ± 50.3	178.3 ± 99.3	0.004

Values are mean ± standard deviation, number (%) or median (interquartile range).

ECMO = extracorporeal membrane oxygenation, LVAD = left ventricular assist device, CRRT = continuous renal replacement therapy, LVEF = left ventricular ejection fraction.

In contrast, survival in ambulatory recipients was similar among the three patient age groups ($P = 0.465$) (**Fig. 3A**). For ambulatory recipients, the cumulative 5-year survival rate was 89.9% for those under 50 years of age, 81.7% for those between 50 and 64 years, and 89.1% for those over 65 years. No significant interaction was found between recipient age and ambulatory status (P for interaction = 0.308). Sensitivity analyses were conducted restricted to recipients who underwent an isolated first HTx. The findings from these analyses were consistent with the results from the entire study population (**Supplementary Fig. 2**).

Pre-HTx ECMO support (HR, 2.02; 95% CI, 1.23–3.30; $P = 0.005$) and use of CRRT (HR, 2.44; 95% CI, 1.47–4.05; $P = 0.001$) were independently associated with post-HTx mortality, and there was a non-significant trend for higher mortality with MV use (**Supplementary Table 4**). Predictive value according to various combination of supporting devices was presented in the **Supplementary Table 5**. Recipients who had ECMO support and were aged between 50–64 years ($P < 0.001$) or over 65 years ($P < 0.001$) exhibited decreased survival rates (**Supplementary Fig. 3**). The impact of pre-transplant ECMO support on survival was different

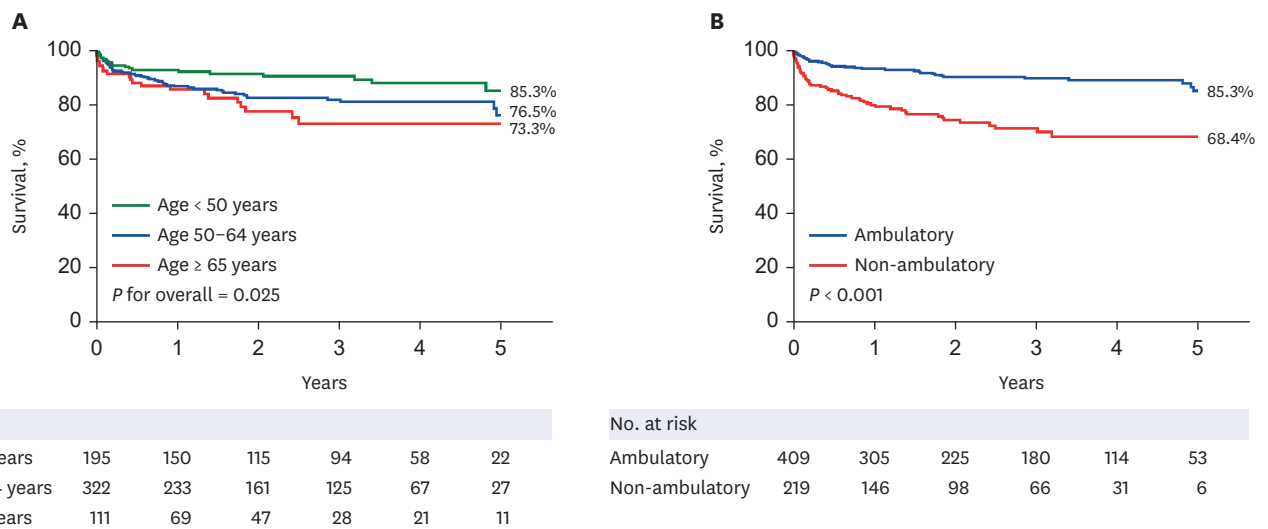


Fig. 2. Survival curves according to (A) recipient age and (B) pre-transplant ambulatory status.

Table 2. Regression analysis for post-transplant mortality risk

Outcomes	Univariable		Multivariable	
	HR (95% CI)	P value	HR (95% CI)	P value
Recipient age, yr				
< 50	Ref.	Ref.	Ref.	Ref.
50–64	1.69 (1.01–2.84)	0.046	1.66 (0.98–2.82)	0.060
≥ 65	2.29 (1.24–4.24)	0.008	2.22 (1.18–4.15)	0.013
Male, gender	1.02 (0.65–1.60)	0.925		
Predicted heart mass, % difference	0.997 (0.99–1.01)	0.997		
Hypertension	1.34 (0.88–2.05)	0.173		
Diabetes	2.02 (1.34–3.05)	0.001	1.65 (1.08–2.51)	0.021
Chronic kidney disease	1.89 (1.18–3.01)	0.008	N/S	N/S
Ischemic etiology	1.81 (1.18–2.79)	0.007	N/S	N/S
Cold ischemic time	0.999 (0.99–1.004)	0.640		
Donor age	1.00 (0.98–1.02)	0.990		
Donor LVEF	1.01 (0.98–1.04)	0.510		
Non-ambulatory status	3.11 (2.05–4.73)	< 0.001	3.13 (2.05–4.78)	< 0.001

HR = hazard ratio, CI = confidential interval, LVEF = left ventricular ejection fraction, N/S = not significant.

depending on recipient age, showing a more diverging trend with older age ($P < 0.001$).

Similar to the ECMO outcome, the pre-transplant use of CRRT was significantly associated with decreased survival in all age groups, and a diverging trend of post-HTx survival with age was also observed (Supplementary Fig. 4).

Post-transplant morbidity by recipient's age and ambulatory status

Freedom from rejection, CAV, infection according to age and ambulatory status are shown in Fig. 4. Although the rates of rejection ($P = 0.466$) and CAV ($P = 0.136$) were not different, the rate of infection after HTx was significantly higher in older recipients ($P < 0.001$, Fig. 4A-C). Similar to age, non-ambulatory recipients had more episodes of infection after HTx ($P < 0.001$) but similar outcomes in terms of rejection ($P = 0.869$) and CAV ($P = 0.464$) (Fig. 4D-F). Furthermore, infection after HTx was a significant comorbid condition in elderly recipients with both pre-transplant ambulatory ($P < 0.001$) and non-ambulatory status ($P = 0.002$) (Fig. 5). Although the risk of infection was higher in both ambulatory (HR, 2.84; 95% CI, 1.79–4.49; $P < 0.001$) and non-ambulatory (HR, 2.55; 95% CI, 1.52–4.27; $P < 0.001$) recipients

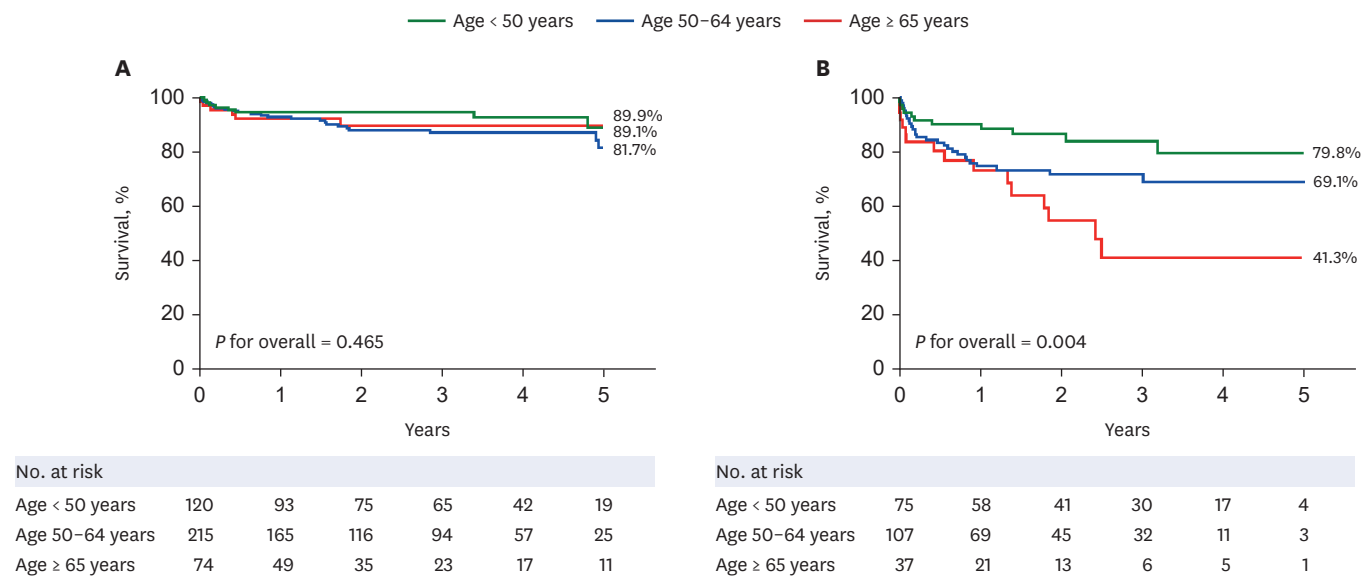


Fig. 3. Survival curve and hazard of mortality according to pre-transplant ambulatory status and age of recipient. Post-transplant survival according to the recipient's age in (A) pre-transplant ambulatory and (B) non-ambulatory status.

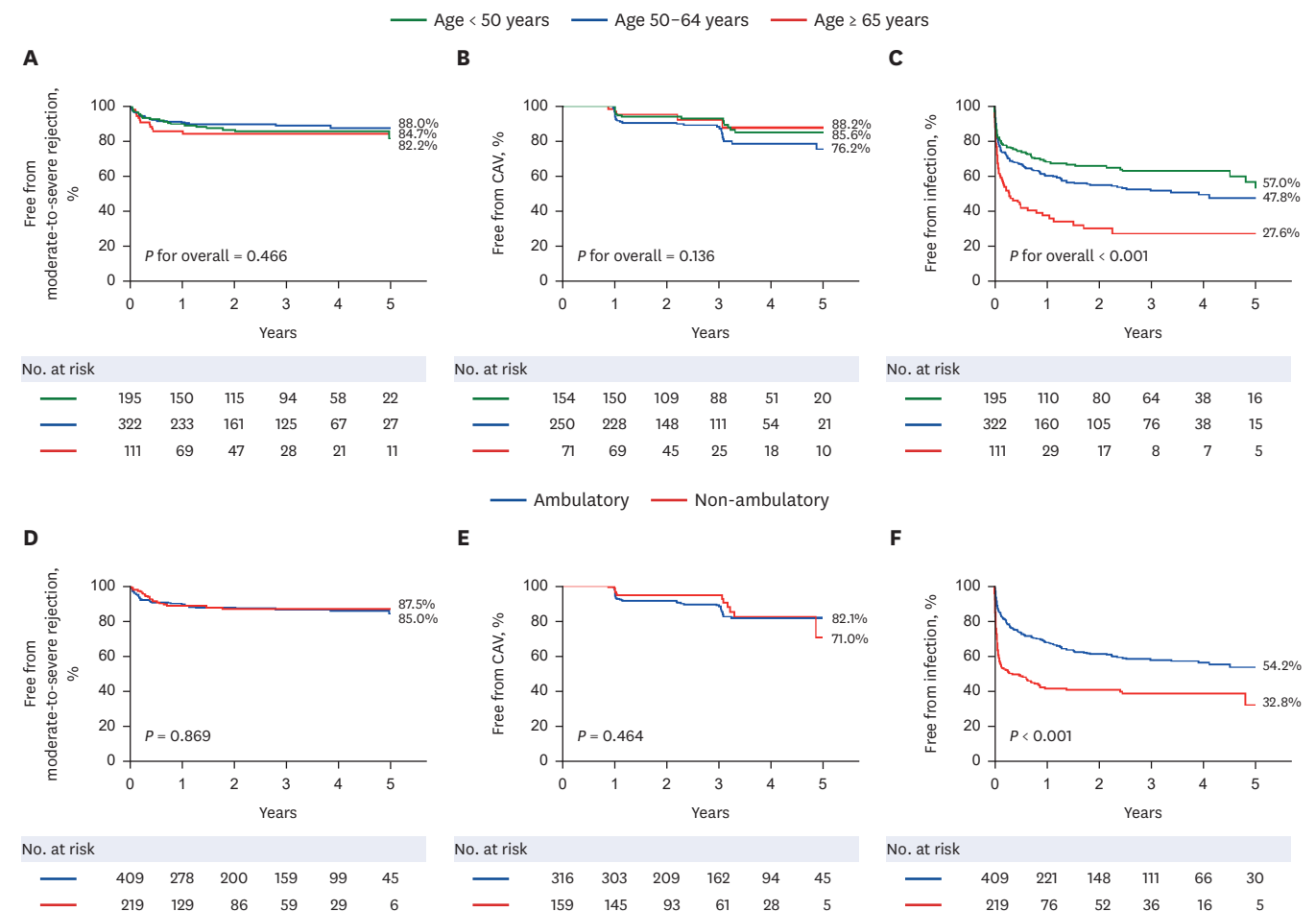


Fig. 4. Freedom from rejection, CAV, and infection according to age and ambulatory status. Freedom from (A) moderate-to-severe rejection, (B) CAV, and (C) infection according to recipient age. Freedom from (D) moderate-to-severe rejection, (E) CAV, and (F) infection according to ambulatory status. CAV = cardiac allograft vasculopathy.

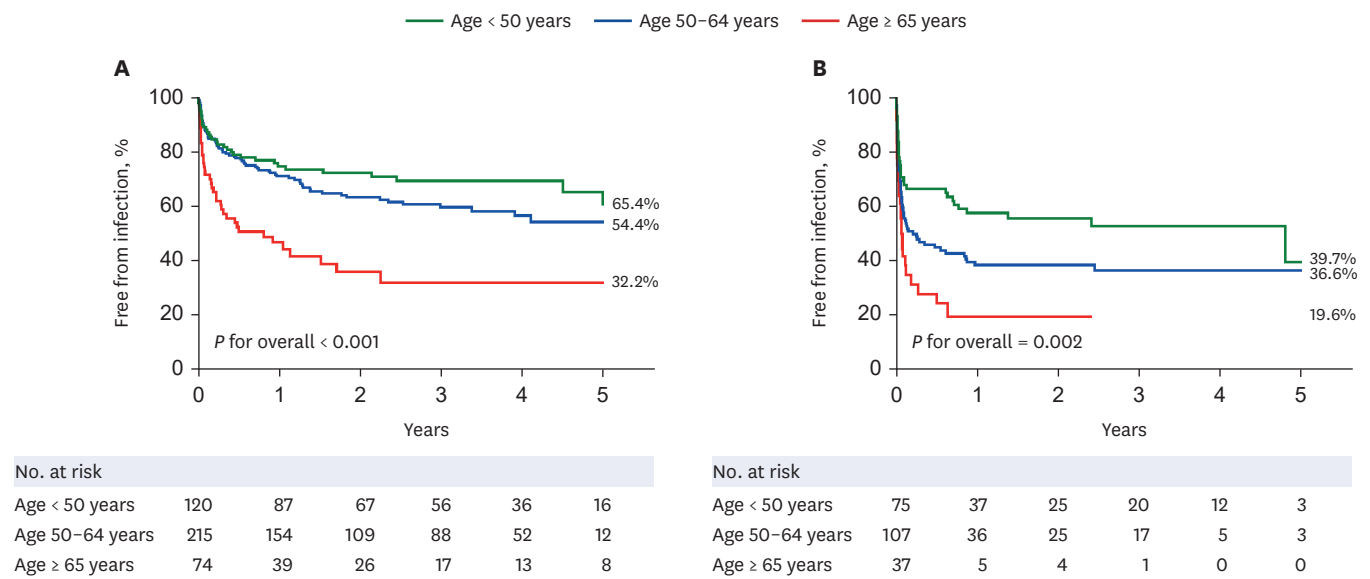


Fig. 5. Freedom from and hazard of infection according to pre-transplant ambulatory state and age of recipient. Freedom from post-transplant infection according to recipient's age in (A) pre-transplant ambulatory and (B) pre-transplant non-ambulatory status.

over 65 years of age compared to those aged under 50 years, the risk was significantly higher only in non-ambulatory patients aged between 50 and 64 years (HR, 1.58; 95% CI, 1.03–2.40; $P = 0.034$). In contrast, rates of rejection and CAV were not associated with recipient age in patients restricted to ambulatory (Supplementary Fig. 5) or non-ambulatory status (Supplementary Fig. 6).

DISCUSSION

In this study that analyzed a national cohort of HTx recipients, recipients age over 65 years was associated with decreased survival after HTx. However, we show that this excess risk was mostly limited to patients with additional comorbidities that resulted in a non-ambulatory status at transplant. Ambulatory elderly recipients had survival rates comparable to younger recipients.

The number of HTx performed in elderly patients has increased globally.¹⁴ In the United States, HTx performed on candidates aged 65 years and older increased from 11.9% in 2009 to 15.9% in 2020,⁴ and recipient age has also substantially increased in the Republic of Korea.⁶ Older recipient age can be a risk factor for adverse outcomes after HTx.¹⁷ Nevertheless, there are conflicting results, as some studies have reported that older recipients may have comparable survival rates after HTx.^{18,19} Interestingly, these studies reporting comparable survival rates between old and young recipients performed baseline adjustment for the use of mechanical circulatory support, MV, or RRT.

Because donor shortage is a major problem²⁰ and maximizing recipient outcomes is the main goal, some regions have a heart allocation system that incorporates recipient age.⁹ The current ISHLT guideline indicates HTx can be considered in carefully selected patients aged 70 years or older.²¹ However, specific selection criteria for HTx eligibility at an advanced age are not well-defined. Chronological age is a complex phenotype, as elderly patients tend to have more comorbidities that can affect post-HTx outcomes. It is therefore problematic to regard

recipient age as a single factor for determining HTx candidacy, and there is no agreement on whether recipient age should be incorporated into the allocation system.

In this context, our study suggests that even though chronological age can be a risk factor for adverse outcomes, it cannot be applied uniformly to the elderly population. Our data suggest that older recipients who require pre-transplant support with ECMO, CRRT, or MV that results in a bed-bound status have poor survival and, therefore, may be less appropriate candidates for HTx. In contrast, elderly recipients with ambulatory status who do not require ECMO, CRRT, or MV show comparable outcomes with younger recipients and can, therefore, be suitable candidates for HTx.

Recipient age is included in cardiac allocation policies in many countries, which can give a disadvantage to older recipients or those with a wide age gap between recipient and donor. Although recipient age is associated with a higher risk of mortality after HTx, the pre-transplant use of temporary circulatory support exerts the highest hazard of post-HTx mortality.²² Although chronological age may affect outcomes through comorbidities and frailty that limit physical performance,²³ the causes of death are usually graft failure, CAV, rejection, infection, and malignancy.²² In our study, elderly and non-ambulatory recipients showed a higher risk of infection, suggesting that infection may affect post-HTx mortality in these populations.

Our results provide valuable information regarding the criteria for HTx eligibility as stated in the current guideline.²¹ Although recipient age is an important factor that encompasses the general risk of adverse events, combined medical conditions, especially a non-ambulatory status, should be considered when deciding on eligibility for HTx. Our data serve as a recommendation for modification to the cardiac allocation policy in the Republic of Korea, to require a review process every 8 days to assess the maintenance of status after HTx registration for elderly recipients in status O, which mainly consists of non-ambulatory patients on ECMO and MV, thus limiting HTx in the high-risk elderly population.

Our study has several limitations. First, as the results were derived from the Korean national data, their applicability to other regions may be limited due to variations in donor availability. However, given the increased use of ECMO as a bridge therapy following changes in the heart allocation policy in the United States,²⁴ defining the role of chronological age in predicting transplant outcomes among patients with various supporting devices remains a relevant and meaningful endeavor. Furthermore, this study utilized data from a registry that includes four major heart transplant centers in Republic of Korea. Therefore, it may not fully represent the overall trends in transplantation across the entire country. Second, HTx outcomes are affected by other factors including sensitization level and heart size matching.^{25,26} Therefore, age and pre-transplant non-ambulatory status cannot be the sole factors determining candidacy. Nevertheless, in clinical practice, various complex clinical factors cannot be entirely considered in the allocation policy. The use of pre-HTx ECMO, CRRT, and MV and age are simple, representative markers that carry important prognostic value and, therefore, can be included in the allocation policy. Third, frailty is an important factor that reflects various conditions, including cardiac function, nutrition, and sarcopenia, and significantly affects HTx outcomes.²⁷ Although we did not include frailty data owing to source limitations, there is limited data to determine HTx eligibility based on frailty. Fourth, the non-ambulatory state, which was defined by the use of ECMO, CRRT, or MV, may not represent all non-ambulatory patients. Some ambulatory patients in the current study may be in a minimally ambulatory or bed-bound state. Nevertheless, although non-ambulatory status cannot be

solely defined by the use of pre-HTx ECMO, CRRT, or MV, these conditions are among the most representative of non-ambulatory status. Another limiting point was that the duration on supporting devices and ECMO configuration were not accounted for, which could represent a significant factor. Finally, in multivariable analysis, age remained an independent risk factor even after adjustment for ambulatory status. Our univariate analyses stratified by age and ambulatory status were used to explore the interaction between age and ambulatory status, and demonstrate the large differences in impact of age among the patients in the two ambulatory groups.

In conclusion, our results do not support use of age alone as an organ allocation criterion. Transplant candidate age in combination with some comorbidities such as non-ambulatory status may identify patients at a sufficiently elevated risk at which suitability of HTx should be reconsidered.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Surgical procedure and induction and maintenance immunosuppressant therapies according to recipient age

Supplementary Table 2

Total operation time of heart transplantation according to pre-transplant LVAD

Supplementary Table 3

Specific cause of death in heart transplant recipients

Supplementary Table 4

Regression analysis of post-transplant mortality risk according to pre-transplant ECMO, CRRT, and MV

Supplementary Table 5

Regression analysis of post-transplant mortality risk according to various combination of pre-transplant supporting devices

Supplementary Fig. 1

Heart allocation system in the Republic of Korea.

Supplementary Fig. 2

Sensitivity analyses of survival curve according to recipient age and pre-transplant ambulatory status for recipients restricted to isolated first heart transplantation. Graphs depict post-transplant survival according to (A) age, (B) pre-transplant ambulatory status of recipients who underwent an isolated first heart transplantation; age for recipient in pre-transplant (C) ambulatory status, (D) non-ambulatory status.

Supplementary Fig. 3

Survival curve according to recipient age and pre-transplant ECMO support. Graphs show post-transplant survival of recipients with (A) age and of overall recipients (B) under 50 years old, (C) between 50 and 64 years old, and (D) over 65 years old.

Supplementary Fig. 4

Survival curve according to recipient age and pre-transplant CRRT. Graphs show post-transplant survival of recipients with (A) age and of overall recipients (B) under 50 years old, (C) between 50 and 64 years old, and (D) over 65 years old.

Supplementary Fig. 5

Freedom from and hazard of rejection and CAV according to age in pre-transplant ambulatory recipients. Overall analyses were conducted in ambulatory recipients. Freedom from (A) moderate-to-severe rejection and (B) CAV according to recipient age.

Supplementary Fig. 6

Freedom from and hazard of rejection and CAV according to age in pre-transplant non-ambulatory recipients. Overall analyses were conducted in non-ambulatory recipients. Freedom from (A) moderate-to-severe rejection and (B) CAV according to recipient age.

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