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Twenty-Year Experience of Heart Transplantation: Early and Long-Term Results

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Background: We evaluated early and long-term results after heart transplantation (HTPL). **Methods:** One hundred five consecutive patients (male:female=80:25) who underwent HTPL between 1994 and 2013 were enrolled. Based on the changes in immunosuppressive regimen, the study patients were divided into two groups. Early and long-term clinical outcomes were evaluated and compared between the patients who underwent HTPL before (group E, n=41) and after July 2009 (group L, n=64). The group L patients were older ($p<0.001$), had higher incidence of hypertension (p=0.001) and chronic kidney disease ($p<0.001$), and more frequently needed preoperative mechanical ventilation (p=0.027) and mechanical circulatory support (p=0.014) than the group E patients. **Results:** Overall operative mortality was 3.8%, and postoperative morbidities included acute kidney injury (n=31), respiratory complications (n=16), reoperation for bleeding (n=15) and wound complications (n=10). There were no significant differences in early results except acute kidney injury between group E and group L patients. Overall survival rates at 1, 5, and 10 years were 83.8%, 67.7%, and 54.9%, respectively, with no significant difference between the two patient groups. Rejection-free rates at 1 and 5 years were 63.0% and 59.7%, respectively; rates were significantly higher in group L than in group E ($p<0.001$). **Conclusion:** Despite increased preoperative comorbidities, group L patients showed similar early and long-term outcomes and significantly higher rejection-free rates when compared with group E patients.

Key words: 1. Transplantation
2. Heart
3. Outcome assessment

Introduction

Since the first report in 1967, more than 100,000 patients have undergone heart transplantation (HTPL) worldwide, and it has become a gold standard treatment for patients with end-stage heart disease [1,2]. The current report from the International Society for Heart and Lung Transplantation (ISHLT) demonstrated that 1- and 5-year survival rates were 81% and 69%, respectively [3,4]. The aims of this study were to evaluate early and long-term results of HTPL and to analyze changes in patient characteristics and clinical

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Table 1. Preoperative characteristics of the study patients

Variable	Total (n=105)	Group E (n=41)	Group L (n=64)	p-value
Age (yr)	50.8±14.3	43.6±11.5	55.4±14.1	<0.001
Sex (female)	25 (23.8)	6 (14.6)	19 (29.7)	0.077
Diagnosis				0.214
Dilated cardiomyopathy	57 (54.3)	27 (65.9)	30 (46.9)	
Ischemic cardiomyopathy	27 (25.7)	7 (17.1)	20 (31.3)	
Others	21 (20.0)	7 (17.1)	14 (21.9)	
Comorbidities				
Diabetes mellitus	25 (23.8)	6 (14.6)	19 (29.7)	0.077
Hypertension	38 (36.2)	7 (17.1)	31 (48.4)	0.001
Dyslipidemia	17 (16.2)	2 (4.9)	15 (23.4)	0.012
Coronary artery disease	27 (25.7)	6 (14.6)	21 (32.8)	0.038
Chronic kidney disease	24 (22.9)	1 (2.4)	23 (35.9)	<0.001
History of cerebrovascular accident	12 (11.4)	4 (9.8)	8 (12.5)	0.666
Preoperative mechanical ventilation	15 (14.3)	2 (4.9)	13 (20.3)	0.027
Preoperative mechanical circulatory support	20 (19.0)	3 (7.3)	17 (26.6)	0.014
Follow-up duration (mo)	57.4±62.3	101.9±79.3	28.9±17.5	<0.001

Values are presented as mean±standard deviation or number (%).
Group E, patients who underwent HTPL before July 2009; group L, patients who underwent HTPL after July 2009.
HTPL, heart transplantation.

Table 2. Operative data of the study patients

Variable	Total (n=105)	Group E (n=41)	Group L (n=64)	p-value
History of cardiac surgery	22 (21.0)	8 (19.5)	14 (21.9)	0.772
Donor ischemic time (min)	155±52	145±43	162±57	0.083
Recipient aortic cross clamp time (min)	93±27	77±27	102±23	<0.001
Recipient cardiopulmonary bypass time (min)	247±74	194±49	281±68	<0.001
Kidney co-transplantation	4 (3.8)	0	4 (6.3)	0.154
Donor				
Age (yr)	33.1±12.0	30.3±11.6	35.0±11.9	0.050
Sex (female)	25 (23.8)	7 (17.1)	18 (28.1)	0.195

Values are presented as number (%) or mean±standard deviation.
Group E, patients who underwent HTPL before July 2009; group L, patients who underwent HTPL after July 2009.
HTPL, heart transplantation.

outcomes of HTPL in the early and late periods.

Methods

The study protocol was reviewed by the institutional review board of the Seoul National University Hospital and approved as a minimal risk retrospective study (approval number: H-1512-068-727) that did not require individual consent based on the institutional guidelines for waiving consent.

1) Patient characteristics

One hundred five patients (male:female=80:25) underwent HTPL between March 1994 and December 2013. There were 4 patients who underwent combined heart-kidney transplantation. Mean recipient age at time of operation was 50.8±14.3 years, and mean donor age was 33.1±12.0 years. Dilated cardiomyopathy (n=57, 54.3%) and ischemic cardiomyopathy (n=27, 25.7%) were the two most common causes of end-stage heart disease. Twenty-two patients (21.0%) had a history of previous cardiac surgery. Based on the changes in immunosuppressive regimen in our institute, the study patients were divided into group E (patients who underwent HTPL before July 2009; n=41), and group L (patients who underwent

HTPL after July 2009; n=64) (Table 1). Group L patients were significantly older, and had more comorbidities such as hypertension, dyslipidemia, coronary artery disease (CAD), and chronic kidney disease (CKD) than group E patients. Patients from group L more often needed mechanical ventilation or mechanical circulatory support preoperatively. Recipient aortic cross-clamp and cardiopulmonary bypass times were significantly longer in group L than in group E. Donor age was also older in group L than in group E (Table 2).

2) Surgical techniques and operative data

The bicaval and single left atrial anastomosis technique was used in most patients (n=102, 97.1%). The biatrial anastomosis technique was used in 3 patients who underwent HTPL in the early period. Before implantation of the donor heart, an additional dose of cold cardioplegic solution was infused through the aortic root or retrograde coronary sinus cannula in most of the patients. The mean donor ischemic, recipient aortic cross-clamp, and cardiopulmonary bypass times were 155±52, 93±27, and 247±74 minutes, respectively (Table 2).

3) Immunosuppressive therapy

Our immunosuppressive regimens for HTPL were: (1) a calcineurin inhibitor such as cyclosporine or tacrolimus, (2) an antiproliferative agent such as azathioprine (AZA, Imuran) or mycophenolate mofetil (MMF), and (3) corticosteroids such as prednisone or prednisolone, as previously reported [5]. Cyclosporine, AZA, and prednisolone were used in the early period until June 1999, when MMF replaced AZA as the antiproliferative agent. Cyclosporine was changed to tacrolimus with an addition of interleukin-2 receptor antagonists after July 2009. Intravenous methylprednisolone (500 mg) was administered intraoperatively, followed by 3 doses (150 mg every 8 hours) postoperatively. Then, prednisone medication was given at a daily dose (1 mg/kg) and tapered over six months to 0.1 mg/kg per day.

4) Evaluation of clinical outcomes

All patients underwent surveillance endomyocardial biopsy after HTPL for the monitoring of rejection. In group E, endomyocardial biopsy was performed weekly for the first 4 weeks, once every 4 weeks until the third month, and then every 3 months until the second year. In group L, endomyocardial biopsy was less frequently performed at the discretion of the cardiologists: monthly for the first 3 months, and every 3 months during the first year. Rejection severity was graded from 0 to 3R based on the ISHLT grading system, and significant rejection was defined as rejection grade 2R or higher [6]. Chronic kidney disease was defined as decreased kidney function (decreased glomerular filtration rate) for 3 or more months. Postoperative acute kidney injury was defined as an increase of more than 50% in serum creatinine level from the preoperative value or a need for renal replacement therapy irrespective of serum creatinine level.

All patients underwent regular postoperative follow-up through the outpatient clinic at 3- or 4-month intervals. The patients were also contacted by telephone for confirmation of their condition if they were not present on their last scheduled visit. Clinical follow-up was completed on August 31, 2014. Follow-up was completed in all patients with a median follow-up duration of 36.9 months. Operative mortality was defined as any death within 30 days after surgery.

5) Statistical analysis

Statistical analysis was performed using the IBM SPSS software ver. 19.0 (IBM Co., Armonk, NY, USA). Data were expressed as mean±standard deviation, median with ranges, or proportions. Comparisons between the two groups were performed using the chi-square or Fisher exact test for categorical variables and Student t-test for continuous variables. Survival rates were estimated using the Kaplan-Meier method and comparisons between 2 groups were performed using the log-rank test. The Cox proportional hazard model was adopted for multivariable analysis of risk factors for time related events. To identify significant predictors of overall survival and freedom from rejection, variables with $p < 0.1$ on univariate analysis and clinically important factors were included in the multivariate model. A p-value < 0.05 was considered as statistically significant.

Results

1) Early results

Operative mortality (any death within 30 days)

Table 3. Early clinical results

Variable	Total (n=105)	Group E (n=41)	Group L (n=64)	p-value
Operative mortality (≤30 day)	4 (3.8)	1 (2.4)	3 (4.7)	0.557
Early morbidities				
Acute kidney injury	31 (29.5)	7 (17.1)	24 (37.5)	0.025
Arrhythmia	4 (3.8)	1 (2.4)	3 (4.7)	0.557
Wound complication	10 (9.5)	3 (7.5)	7 (10.9)	0.563
Respiratory complication	16 (15.4)	6 (15.0)	10 (15.6)	0.932
Cerebrovascular accident	6 (5.8)	1 (2.5)	5 (7.8)	0.258
Reoperation for bleeding	15 (14.4)	3 (7.5)	12 (18.8)	0.112
Postoperative mechanical circulatory support	22 (21.0)	8 (19.5)	14 (21.9)	0.772
Intensive care unit stay (day)	16±13	14±15	18±12	0.162
Discharge (day)	42±32	35±19	46±38	0.063

Values are presented as number (%) or mean±standard deviation.
Group E, patients who underwent HTPL before July 2009; group L, patients who underwent HTPL after July 2009.
HTPL, heart transplantation.

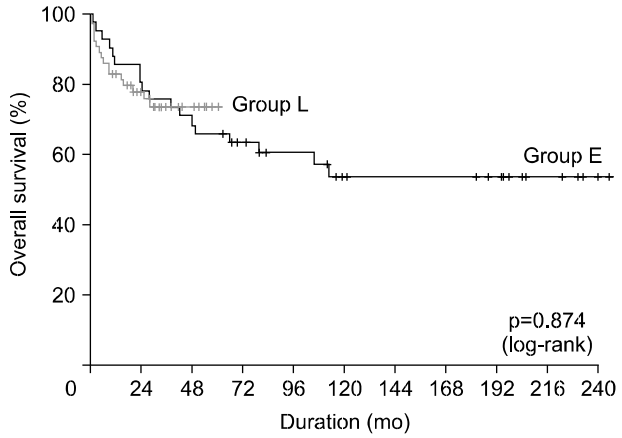

Fig. 1. Kaplan-Meier curve of overall survival.

was 3.8% (4/105; 1 in group E and 3 in group L). There were no patients who showed the suggested diagnostic criteria of primary graft failure. In-hospital mortality (any death before hospital discharge, including operative mortality) was 9.5% (10/105); this included 3 patients in group E and 7 patients in group L. Postoperative complications included acute kidney injury (n=31, 29.5%), respiratory complications (n=16, 15.4%), reoperation for bleeding (n=15, 14.4%), wound complication (n=10, 9.5%), cerebrovascular accident (n=6, 5.8%), and arrhythmia (n=4, 3.8%). Use of postoperative mechanical circulatory support such as an intra-aortic balloon pump and extracorporeal membrane oxygenation was considered if patients showed difficulties in weaning from cardiopulmonary bypass for >30 minutes after completion of all anastomoses. Postoperative mechanical circulatory support was needed in 22 patients (21.0%); intra-aortic balloon pump in 12 patients and extracorporeal membrane oxygenation in 14 patients. Four patients were supported by both intra-aortic balloon pump and extracorporeal membrane oxygenation. There were no significant differences in operative mortality (p=0.557) and in postoperative complications between the two patient groups, except for a higher incidence of acute kidney injury in group L compared to group E (p=0.025) (Table 3).

2) Long-term survival and event-free rates

Late mortality (any death >30 days after surgery) was 29.7% (30/101). The common causes of late mortality were infection (n=14), rejection (n=7), and malignancy (n=3). The 1-, 5-, and 10-year survival rates were 83.8%, 67.7%, and 54.9%, respectively; there were no significant differences in overall survival between the two patient groups (p=0.874) (Fig. 1). Multivariable analysis demonstrated that preoperative mechanical ventilation (p=0.034), CKD (p=0.007), recipient aortic cross-clamp (p=0.037), and cardiopulmonary bypass times (p=0.001) were significant risk factors for overall survival. Change in immunosuppressive regimen (p=0.020) was the significant protective factor for overall survival (Table 4). Freedom from infection rates at 1, 5, and 10 years were 64.7%, 47.0%, and 47.0%, respectively; there were no significant differences between the two patient groups

Table 4. Analysis of risk factors for overall survival using a Cox proportional hazard model

Variable	Univariate		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Categorical variables				
Sex (male)	0.58 (0.27–1.21)	0.145		
Donor sex (male)	0.83 (0.39–1.78)	0.632		
Diagnosis				
Non-CMP (ref=CMP)	1.29 (0.53–3.13)	0.570		
Preoperative mechanical ventilation	2.42 (1.04–5.62)	0.040	2.89 (1.08–7.71)	0.034
Preoperative mechanical circulatory support	1.50 (0.65–3.48)	0.341		
Diabetes mellitus	0.69 (0.29–1.67)	0.412		
Hypertension	1.04 (0.51–2.15)	0.910		
History of cerebrovascular accident	1.04 (0.37–2.95)	0.944		
Dyslipidemia	0.37 (0.09–1.55)	0.174		
Chronic kidney disease	2.82 (1.28–6.21)	0.010	4.39 (1.49–12.95)	0.007
Coronary artery disease	0.87 (0.38–2.03)	0.755		
History of cardiac surgery	1.16 (0.53–2.57)	0.707		
Immunosuppressive regimen		0.990		0.020
Cyclosporine+MMF+Pd (ref: cyclosporine+AZA+Pd)	1.07 (0.41–2.81)	0.891	0.62 (0.21–1.84)	0.385
Tacrolimus+MMF+Pd (ref: cyclosporine+AZA+Pd)	1.02 (0.44–2.36)	0.969	0.16 (0.05–0.58)	0.005
BMI (kg/m^2)		0.294		
<18.5 (ref: $18.5 \leq$ BMI < 23)	0.48 (0.11–2.09)	0.328		
≥ 23 (ref: $18.5 \leq$ BMI < 23)	1.41 (0.71–2.83)	0.329		
Continuous variables				
Age (yr)	1.02 (0.99–1.04)	0.194		
Donor age (yr)	1.02 (0.99–1.05)	0.143		
Donor ischemic time (min)	1.00 (1.00–1.01)	0.512		
Recipient aortic cross-clamp time (min)	1.02 (1.00–1.03)	0.017	1.02 (1.00–1.03)	0.037
Recipient cardiopulmonary bypass time (min)	1.01 (1.00–1.01)	0.024	1.01 (1.00–1.01)	0.007

HR, hazard ratio; CI, confidence interval; CMP, cardiomyopathy; ref, reference; MMF, mycophenolate mofetil; Pd, prednisone; AZA, azathioprine; BMI, body mass index.

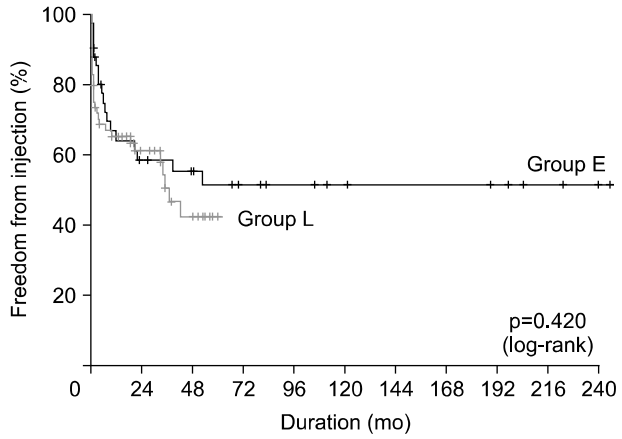

Fig. 2. Kaplan-Meier curve of freedom from infection.

(p=0.420) (Fig. 2). Freedom from rejection rates at 1, 5, and 10 years were 69.9%, 61.6%, and 61.6%, respectively; freedom from rejection rates were significantly higher in group L than in group E ($p < 0.001$) (Fig. 3). Multivariable analysis demonstrated that change in immunosuppressive regimen was the significant protective factor for freedom from rejection rates ($p < 0.001$) (Table 5).

Discussion

The present study demonstrated two main findings. First, HTPL patients of the late period had more comorbidities compared to the early HTPL patients; they were older, more of them had hypertension and chronic kidney disease, and needed preoperative mechanical ventilation and mechanical circulatory sup-

port more frequently than the earlier patients. Second, the late period HTPL group showed similar early and long-term outcomes and a lower rejection rate in spite of increased preoperative comorbidities when compared with early period HTPL patients.

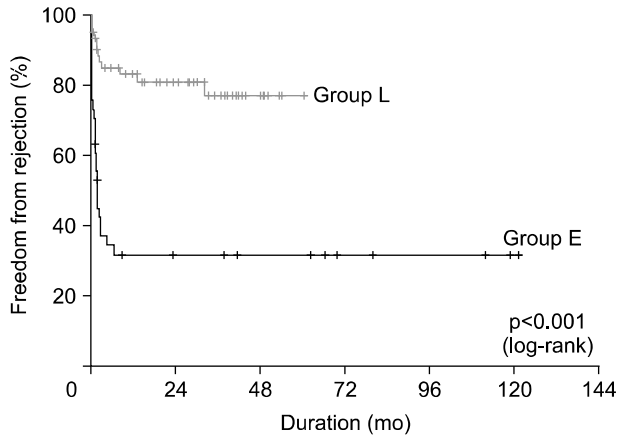

Fig. 3. Kaplan-Meier curve of freedom from rejection.

Since the first procedure in 1967, HTPL has become a gold standard treatment for patients with end-stage heart failure and more than 100,000 patients have undergone HTPL worldwide [1,2]. During the past half-century, there have been advances in donor and recipient selection, perioperative care, and immunosuppression strategies of HTPL [1]. The ISHLT reported that there have been changes in adult HTPL recipients' profiles over time. The changes included increased comorbidities and high-risk characteristics of recipients, which might result from a combination of changing demographics of the general population as well as the willingness of clinicians to transplant higher risk patients. The age and comorbidity of do-

Table 5. Analysis of risk factors for freedom from rejection using a Cox proportional hazard model

Variable	Univariate		Multivariable	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Categorical variables				
Sex (male)	1.16 (0.54–2.54)	0.701		
Donor sex (male)	0.88 (0.43–1.81)	0.735		
Diagnosis				
Non-CMP (ref: CMP)	0.51 (0.18–1.44)	0.204		
Preoperative mechanical ventilation	0.29 (0.07–1.21)	0.090		
Preoperative mechanical circulatory support	0.45 (0.16–1.27)	0.130		
Diabetes mellitus	1.05 (0.51–2.15)	0.905		
Hypertension	0.63 (0.31–1.27)	0.198		
History of cerebrovascular accident	1.22 (0.48–3.11)	0.682		
Dyslipidemia	0.87 (0.36–2.07)	0.751		
Chronic kidney disease	0.25 (0.08–0.81)	0.021		
Coronary artery disease	0.57 (0.25–1.29)	0.175		
History of cardiac surgery	0.89 (0.39–2.02)	0.784		
Immunosuppressive regimen		<0.001		<0.001
Cyclosporine+MMF+Pd (ref: cyclosporine+AZA+Pd)	0.17 (0.07–0.43)	<0.001	0.12 (0.97–1.00)	<0.001
Tacrolimus+MMF+Pd (ref: cyclosporine+AZA+Pd)	0.09 (0.05–0.20)	<0.001	0.12 (0.06–0.27)	<0.001
BMI (kg/m^2)		0.355		
<18.5 (ref: 18.5≤BMI<23)	0.43 (0.13–1.42)	0.165		
≥23 (ref: 18.5≤BMI<23)	1.02 (0.52–2.00)	0.948		
Continuous variables				
Age (yr)	0.97 (0.95–0.99)	0.009		
Donor age (yr)	0.97 (0.94–1.00)	0.034		
Donor ischemic time (min)	0.99 (0.99–1.00)	0.074		
Recipient aortic cross-clamp time (min)	0.98 (0.96–0.99)	0.002		
Recipient cardiopulmonary bypass time (min)	0.99 (0.98–0.99)	<0.001		

HR, hazard ratio; CI, confidence interval; CMP, cardiomyopathy; ref, reference; MMF, mycophenolate mofetil; Pd, prednisone; AZA, azathioprine; BMI, body mass index.

nors have also been increasing [3,4,7]. With increasing organ shortages, most centers are currently accepting higher risk donors, particularly older donors [3,4,7,8]. The present study also showed similar changes in HTPL recipients' profiles. Over the period of our study, recipients who underwent HTPL at our institution became older, and had more comorbidities such as hypertension, dyslipidemia, CAD, and CKD. In addition, the number of recipients requiring preoperative mechanical ventilation or mechanical circulatory support increased. Donor age also increased from 30.3±11.6 years in group E patients to 35.0± 11.9 years in group L patients.

The ISHLT reported that survival rates after HTPL were 81% and 69% at 1 and 5 years respectively, with a median survival of 11 years, and that risk factors such as preoperative mechanical circulatory support, preoperative mechanical ventilator, the cause of end-stage heart disease, recipient age, recipient height, donor age, donor heart ischemic time, retransplantation, transplant center volume, previous transfusion, recipient pre-transplant bilirubin level, and recipient pre-transplant creatinine level significantly influenced overall survival rates [3,4,7]. Additional factors such as previous sternotomy, body mass index, donor sex, race, smoking, and hypertension or diabetes mellitus of recipient were also known to significantly influence overall survival [9-13].

The present study demonstrated similar overall survival rates as those reported by the ISHLT. Despite higher risk factors of recipients and donors in the later period, early results and overall survival of HTPL patients were similar to those of the earlier period. In the multivariable analysis, preoperative mechanical ventilation, CKD, recipient aortic cross-clamp, and cardiopulmonary bypass times were significant risk factors affecting overall survival. In addition, change in immunosuppressive regimen was a significant protective factor affecting overall survival. However, previously reported factors, such as donor ischemic time, preoperative use of mechanical circulatory support, the cause of end-stage heart disease, and age of recipient or donor, were not risk factors for overall survival rates according to the present study. This might be due to the relatively small number of enrolled patients. Similar to the findings of this present study, one previous study demonstrated that increased warm ischemic time was related to a reduced survival in HTPL [14]. Warm ischemic time was defined as the time the donor organ arrived in the recipient operating room until reperfusion, which was approximately similar to recipient aortic cross clamp time. The previous study suggested that the finding of reduced survival in recipients with increased warm ischemic time warranted further investigation with analysis of a possible mechanism [14].

Risk factors for death from infection were demonstrated to include old recipient age, female sex, preoperative mechanical ventilator support, or mechanical circulatory support [15,16]. In the present study, the freedom-from-infection rate was similar between the two patient groups. One previous study developed and validated a novel 13-point risk score to predict acute rejection based on 4 variables (age, race, sex, human leukocyte antigen matching); younger age, race other than Asian, female sex, and increased degree of human leukocyte antigen mismatch were associated with increased rejection rate [17]. The tacrolimus/MMF combination therapy was also associated with greater freedom from rejection rates, compared with cyclosporine/MMF therapy [18]. The present study demonstrated a higher freedom from rejection rate in the later period, when tacrolimus replaced cyclosporine. In multivariable analysis, the change in immunosuppressive regimen was the only significant protective factor for freedom from rejection. Although older recipient age was a risk factor for freedom from rejection in univariate analysis, it became insignificant in the multivariable analysis. We assumed that the relatively small number of enrolled patients affected the results.

There are limitations to the present study that must be recognized. First, it is a non-randomized, retrospective study with observational data in a single institution. Second, the number of enrolled patients was relatively small to make a definite conclusion. Third, the follow-up duration for the group L patients was relatively short.

In conclusion, early and long-term results after HTPL showed a 30-day mortality rate of 3.8%, a 5-year survival rate of 71.2%, and a 10-year survival rate of 54.9%. Despite increased morbidities of HTPL recipients and donors, early and long-term clinical outcomes were similar between the earlier and later group patients. Rejection free survival rate increased significantly over a period of time, probably resulting

from the change in immunosuppressive regimen.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Acknowledgments

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