

## Original Article



# Initial Report of the Korean Organ Transplant Registry (KOTRY): Heart Transplantation

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### Conflict of Interest

The authors have no financial conflicts of interest.

### Author Contributions

Conceptualization: Kim JJ; Data curation: Kim JJ, Lee HY, Kang SM, Jeon ES; Formal analysis: Lee HY; Funding acquisition: Kim JJ; Investigation: Kim JJ, Lee HY, Kang SM,

## ABSTRACT

**Background and Objectives:** The Korean Organ Transplant Registry (KOTRY), which was the first national transplant registry in Korea, was founded by the Korean Society for Transplantation and the Korean Center for Disease Control in 2014. Here, we present the initial report of the Korean Heart Transplant Registry.

**Methods:** A total of 183 heart transplantation (HTPL) patients performed at 4 nationally representative hospitals were collected from April 2014 to December 2015. We analyzed donor and recipient characteristics, treatment patterns, and immediate post-transplantation outcomes.

**Results:** One hundred and eighty-three patients were enrolled. The mean age of the patients was 50.5±13.5 years. The mean age of the male recipients was 4 years greater than that of the female recipients (51.7±13.3 years vs. 47.9±13.7 years,  $p<0.050$ ). The mean age of donors was more than 12 years younger than that of heart recipients (37.6±10.1 years). Dilated cardiomyopathy was the predominant cause (69%) of heart failure in recipients, followed by ischemic heart diseases (14%) and valvular heart disease (4%). Rejection episodes were most frequent in the 1–6-month period after transplantation (48%), and rarely required intensive treatment. Infection episodes were most frequent <1 month after transplantation (66%) and bacterial and viral infections were equally reported. The 1-year survival rate was 91.6% and most mortality cases occurred during the perioperative period within 1 month after transplantation.

**Conclusion:** With the establishment of the KOTRY in 2014, it is now possible to present nationwide epidemiological data for HTPL in Korea for the first time. The KOTRY is the first national HTPL registry in Korea, and will continue until 2023.

**Keywords:** Heart transplantation; Heart failure; Registries

## INTRODUCTION

Advanced heart failure (HF) is a grave disease with typically poor prognosis.<sup>1,2)</sup> Heart transplantation (HTPL) remains the treatment of choice for carefully selected candidates with HF, with 1-year survival reported to be 90% and a median survival of 14 years for patients surviving the first year.<sup>3)</sup> Although controlled trials have never been conducted to investigate the question, there is consensus that transplantation significantly increases survival, exercise

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capacity, quality of life, and return to work in properly selected patients when compared with conventional treatment.<sup>4)</sup> In global registry data annually published by the International Society for Heart and Lung Transplantation (ISHLT), marked reductions in perioperative mortality and the development of immunosuppressive therapy have led to excellent 1-year survival rates of over 80% after cardiac transplantation, with almost 70% of patients surviving more than 5 years.<sup>3)</sup> In Korea, the heart transplant era began in 1992<sup>5)</sup> and 1,319 cases were performed between then and 2016. The establishment of related legal processes soon followed, initiated by the Korean Network for Organ Sharing (KONOS), which was established in 2000. Along with 21 hospital-based organ procurement organization (HOPO) hospitals, KONOS was appointed to oversee regional procurement and management of organs. As the organ donation rate after brain death has increased over the years, the rate of heart donation has also increased.<sup>6)</sup>

A national organ transplant registry is an important medical requirement for standardization, research, and planning of patient care. Even though KONOS has established a database for the administration of an organ waiting list, organ allocation, and to track the incidence of organ transplantation since 2000, an integrated registry including transplantation results and post-transplantation data is needed for a better understanding of organ transplantation. The Korean Organ Transplant Registry (KOTRY)<sup>7)</sup> was founded by the Korean Society for Transplantation (KST) and the Korean Center for Disease Control (KCDC) in 2014 to serve as the first national organ transplant registry in Korea. Here, we present the initial report of the Korean Heart Transplant Registry.

## METHODS

KOTRY is a prospective, multicenter cohort study that includes information for kidney, liver, lung, pancreas, and HTPLs in Korea. Patients are consecutively enrolled upon transplantation and then followed-up accordingly. HTPL patients from 4 nationally representative hospitals are enrolled in KOTRY. The registry accumulates data on individual patients, not individual hospitalizations. KOTRY data include demographics, causes of HF, comorbidities (hypertension, diabetes, and dyslipidemia), and immunosuppressive medications.

Chronic kidney disease (CKD) was defined as a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m<sup>2</sup> for more than 3 months. Immunologic elements, such as human leukocyte antigen (HLA) mismatches and panel-reactive antibody (PRA) levels were also selected as variables. Regular follow-up data for transplantations, including rejection episodes, infections, and outcomes, were included. The study was reviewed and approved by the institutional review board of each transplantation center.

KOTRY collected human samples using the Pharmacoepidemiology and Clinical Trial Application X (PhactaX) System, which is hosted by the Medical Research Collaborating Center (MRCC) of Seoul National University Hospital. The MRCC played a main role as the coordinating center, harmonizing the data-collecting activity of all participating centers. The collected data were coded and stored, and direct access to raw data was strictly controlled. Each transplantation hospital input data through a web-based case report form according to a standardized protocol.

Written informed consent was obtained from each recipient prior to transplantation. If patients were unable to provide consent due to disease severity, informed consent was obtained from

a relative or legal representative. The attending physician completed a web-based case report form using the Clinical Data Management System (iCReaT) from the Korea National Institute of Health (NIH) with the assistance of a clinical research coordinator. After discharge, events including all-cause death and re-hospitalization were recorded. The most recent information regarding each patient's clinical manifestations, biochemistry, endomyocardial biopsy results, and medication were collected at the first re-visit 30 days after surgery, and at 3, 6, 12, 24, 36, 48, and 60 months thereafter. The follow-up data were collected from patients by the attending physician and stored using the web-based case report form. Graft vascular disease was defined as abnormal coronary angiography findings diagnosed either by coronary angiography with or without intravascular ultrasound (IVUS), or by computed tomography (CT) coronary angiography, and graded using the ISHLT nomenclature, as previously described.<sup>8)</sup>

For the analysis of KOTRY data, a file was generated for each year and descriptive analysis was performed for each category of variables. Continuous variables are expressed as the mean  $\pm$  standard deviation (SD). Categorical data are summarized as the frequency and proportion. Patient survival was measured using the Cox proportional hazards regression model, taking into account gender, age, causes of HF, immunosuppressive regimen, and comorbidities as covariates. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Clinical features of HTPL recipients

A total of 183 HTPLs from 4 national representative hospitals were collected from April 2014 to December 2015. One hundred and eighty-three patients (male:female=123:60) were enrolled. During this period, the total number of HTPL cases in Korea was 235, and therefore KOTRY covered 78% of the total cases. The mean age of the patients was  $50.5 \pm 13.5$  years. The mean age of male recipients was 4 years greater than that of female recipients ( $51.7 \pm 13.3$  years vs.  $47.9 \pm 13.7$  years,  $p < 0.050$ ) (Figure 1). The predominant cause of transplantation was dilated cardiomyopathy (DCMP, 69%) followed by ischemic cardiomyopathy (ICMP, 14%), and valvular heart disease (4%). Re-HTPL cases made up 3% of cases (Figure 2). Twenty-eight percent (52 patients) of the recipients were older than 60 years of age, and ranged from 19 to 74 years old. ABO types and mismatch cases (permitted mismatch, for example heart from type O donor transplanted to type A recipient) were as follows: 71 patients ABO type A (6 mismatches), 46 patients type B (5 mismatches), 42 patients type O, and 24 patients type AB (11 mismatches).

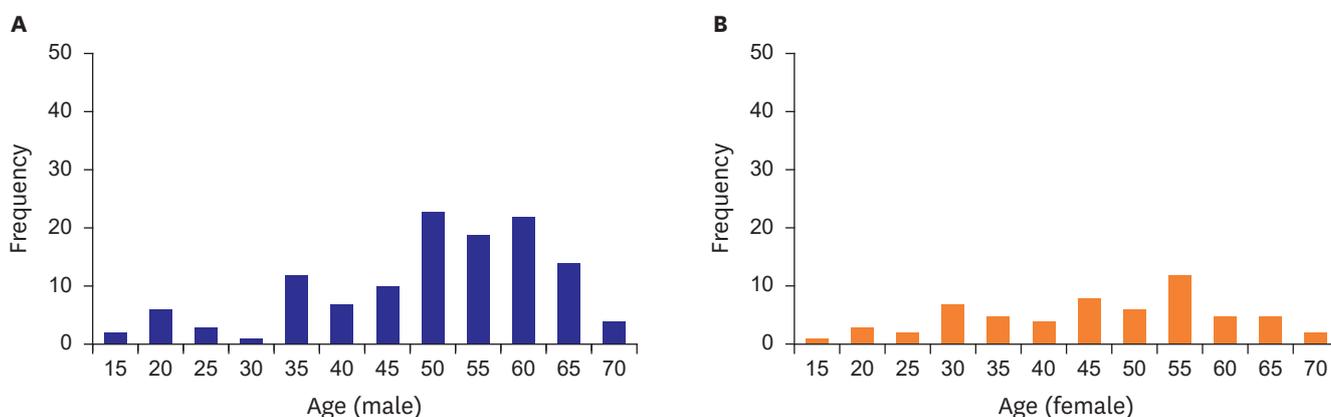
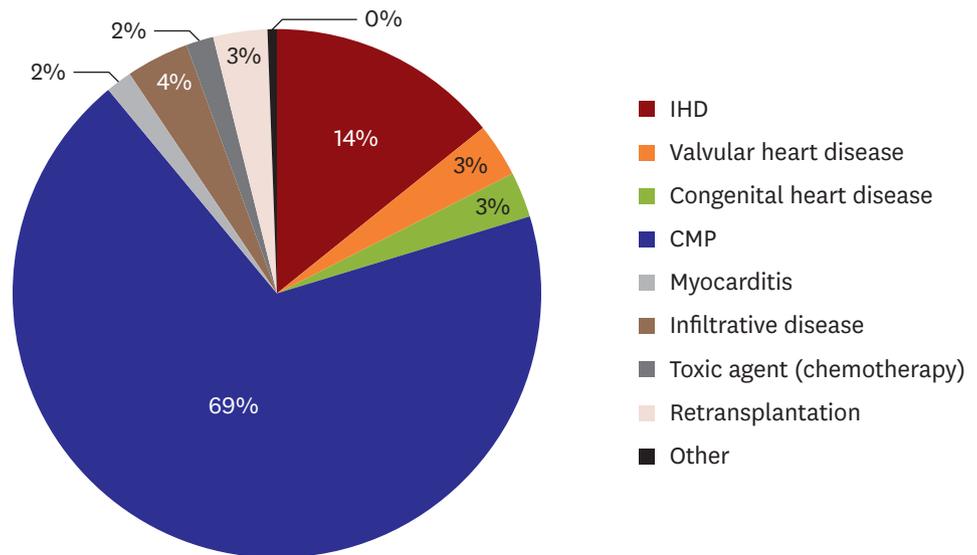


Figure 1. Age distribution of heart recipients. (A) Male, (B) Female.



**Figure 2.** Causes of HF.  
 CMP = cardiomyopathy; HF = heart failure; IHD = ischemic heart disease.

Regarding co-morbidity, 22% of recipients had diabetes mellitus. Among them, 60% required insulin for hypoglycemic control. A total of 28% of the recipients had hypertension and 8% had previous histories of malignancy. Twenty-two percent of patients had CKD and 9% were on dialysis. Of all patients, 71% had at least one co-morbidity with HF.

The majority of the recipients (93%) received HTPL with inotropic support. Nineteen percent of the recipients were on circulatory assisting devices and 16% were on mechanical ventilation. Twenty-three percent (23 patients) of the recipients required renal replacement therapy, of which 87% (20 patients) were receiving continuous renal replacement therapy.

### Clinical features of HTPL donors and recipients

The mean age of donors was more than 12 years younger than that of heart recipients ( $37.6 \pm 10.1$  years). Eleven percent (21 patients) of the donors were older than 50 years, with the range of 15–58 years. The mean duration of cold ischemic time was  $115.34 \pm 57.95$  minutes and of warm ischemic time was  $614.13 \pm 23.04$  minutes. Similar to other countries, the waiting list for organs in Korea is stratified according to urgency status.<sup>6)</sup> Following urgency status, 24 cases received HTPL with status 0, 154 cases with status 1, and 5 cases with status 2.

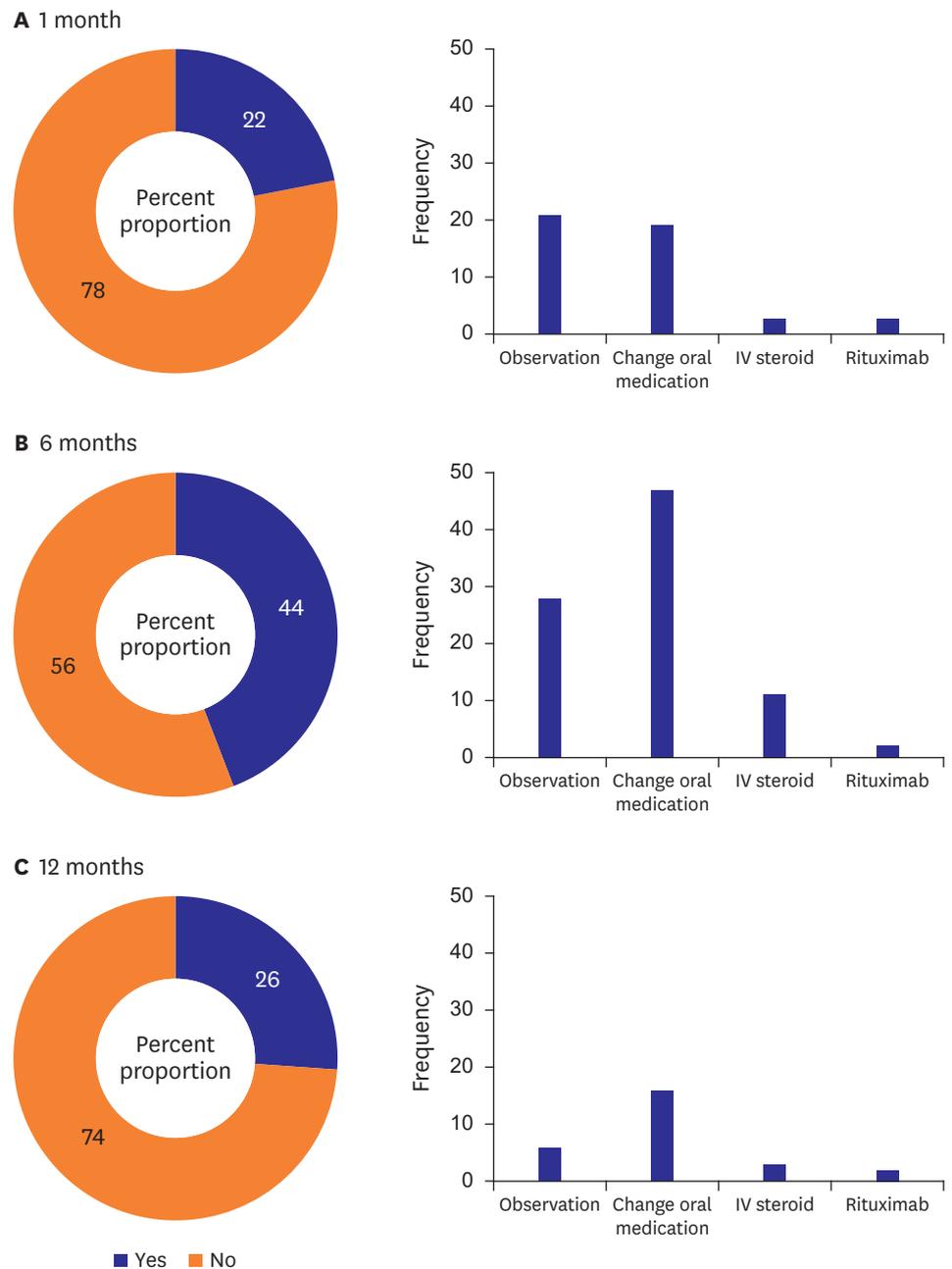
Regarding cytomegalovirus (CMV) IgG status, 94% of HTPL cases were donor (+)/recipient (+), 3.4% were recipient (+) only, and 2.8% were donor (+) only.

### Immunosuppression for HTPL

Most recipients (76%) were not sensitized, with panel reactive antigen of 0%, and therefore only 6% of recipients underwent preoperative desensitization treatment. Only 1% (2 patients) were T cell HLA cross match positive. Induction immunosuppressant treatment was used in most recipients (98%). The maintenance immunosuppressant regimen was a triple combination of calcineurin inhibitors (tacrolimus 89%, cyclosporin 11%), antiproliferative agents (mycophenolate mofetil 100%), and steroids (98%). Proliferation signal or mammalian target-of-rapamycin inhibitors (everolimus) were used in 11% of patients.

**Clinical outcomes of HTPL**

Follow-up visits were recorded at 1 month, 6 months, and 12 months after surgery. A total of 48 patients completed the 1-month visit, 52 patients the 6-month visit, and the remaining 83 patients completed the 12-month visit. Rejection episodes were most frequent during the 1–6-month period (48%), and rarely required intensive treatment (**Figure 3**). At the first endomyocardial biopsy, 79% of samples did not show any signs of rejection while 20.1% of cases were rejection 1R, and only 1 case was rejection 2R. During the 6 months after HTPL, only 5 cases of acute antibody-mediated rejection were reported (2 cases within 1 month, 2 cases 1–6 months, 1 case after 6 months). Within 1 month after HTPL, only 22% of recipients (38 patients) experienced any type of rejection. Of these, 48% of rejections were resolved



**Figure 3.** Rejection after transplantation and treatment. (A) 1 month, (B) 6 months, (C) 12 months.

**Table 1.** Infections after transplantation requiring hospitalization

Characteristics	<1 month (n=172)	1–6 months (n=116)	7–12 months (n=69)
Any infection (%)	46	29	10
Organisms	-	-	-
Bacteria	78	21	2
Mycobacteria	0	0	0
Virus	85	30	5
Fungus	24	13	2
<i>Pneumocystis carinii</i>	0	0	1
Others	0	0	0

**Table 2.** Major events after transplantation

Characteristics	<1 month (n=172)	1–6 months (n=116)	7–12 months (n=69)
Death	10	2	0
Infection	7	2	-
Cardiovascular	1	-	-
Others	2 (1 postoperative, 1 suicide)	-	-
Re-transplantation	3	0	0
Rejection	38	51	18
Infection requiring hospitalization	80	34	7
Graft vascular disease	3	1	1
Hospitalization due to other causes	5	16	14
Gastrointestinal problems*	1	3	5
Diabetes mellitus control	1	2	2
Musculoskeletal problems†	1	3	2
Wound problems	1	1	2
Cardiovascular problems‡	-	5	2
Respiratory problems§	1	-	-
Ophthalmologic problems (cataracts)	-	2	1

\*Gastrointestinal problems included abdominal pain, diarrhea, poor oral intake, and bleeding. †Musculoskeletal problems included arthralgia and orthopedic surgery. ‡Cardiovascular problems included edema, arrhythmia, acute cerebral hemorrhage, and arteriovenous fistula operation. §Respiratory problems included cough, sputum, and pneumonia.

without specific treatment and only 6 patients required steroid pulse therapy (n=3) or rituximab treatment (n=3). During the 1–6-month period after HTPL, 44% of patients (n=51) experienced rejection. Most cases were resolved without medication (33%) or by increasing/changing immunosuppressive agents (56%).

Infection episodes were most frequent <1 month (66%) after HTPL, and bacterial and viral infections were equally reported as causative (**Table 1**). The 1-year survival rate among recipients was 91.6%, and most mortality cases occurred during the perioperative period, within 1 month after HTPL (**Table 2**).

## DISCUSSION

The prevalence of HF is growing continuously due to social aging and better survival of initial cardiovascular events such as myocardial infarction.<sup>9)</sup> About 1% of acute HF patients require HTPL during hospitalization.<sup>1)</sup> Since the first orthotopic HTPL was successfully performed in 1992, more than 900 patients have received HTPL in Korea. Moreover, due to improvements of surgical techniques and transplantation outcomes, HTPL cases will undoubtedly continue to increase.<sup>10,11)</sup> Patient conditions that were previously considered to be relative contraindications of HTPL, such as hepatitis B infection<sup>12)</sup> or renal dysfunction,<sup>13)</sup> are no longer considered to be contraindications. The number of brain death donors in Korea,

around 300 people annually, is still almost times greater than the number of recipients, thus leaving further room for increase of HTPL frequency.<sup>6)</sup>

In the present study, we report the initial findings of the KOTRY HTPL registry. First, most recipients receiving HTPL had co-morbid conditions such as advanced age (over 60 years), diabetes mellitus, or circulatory assisting device applied. Second, DCM remained the predominant etiology in recipients, followed by ischemic heart diseases and valvular heart disease. Third, preoperative sensitization was not a major issue and most rejection episodes were successfully controlled by medication. Finally, the 1-year survival rate among HTPL recipients was 91.6%, which is better than that reported by the ISHLT registry.<sup>3)</sup>

The ISHLT provides annual reports of adult HTPL profiles over time. Recent worldwide changes in HTPL include increased co-morbidities and high-risk characteristics of recipients, which might be explained by a combination of changing demographics among the general population as well as improved operative results. The age and co-morbidity of donors have also increased.<sup>3)14)6)</sup> Our report shows similar trends in HTPL recipient profiles. Recipients who underwent HTPL were older and had more co-morbid conditions such as hypertension, dyslipidemia, coronary artery disease, and CKD. In addition, the number of recipients requiring preoperative mechanical ventilation or mechanical circulatory support increased. Donor age also increased.

A national organ transplantation database is warranted to cope with the rapidly expanding practice of organ transplantation in Korea, to examine the current situation, and to formulate adequate transplantation policies. KOTRY was established by transplantation physicians to improve outcomes for patients through clinical and translational research. KOTRY is officially supported by the Korean government through funding from the KCDC, so that the analysis of research results can lead to evidence-based changes in national organ transplantation policy.

The ISHLT reported that risk factors such as preoperative circulatory support, preoperative mechanical ventilator, recipient age, donor age, donor heart ischemic time, re-transplantation, transplant center volume, and recipient pre-transplant creatinine level significantly influenced overall survival rates.<sup>14)</sup> The results of the present study demonstrated better overall survival rates compared to those reported by the ISHLT. Although there have been arguments that conservative strategies, including younger donor/recipient age and fewer cases of pre-transplant coronary disease, may explain the better survival rates in Korea, the biological homogeneity of the Korean population and the lower incidence of graft vascular disease in Korea compared to other countries could also explain better survival.<sup>17)</sup>

One of the characteristic features of the KOTRY HTPL registry is the use of virtually identical immunosuppression protocols across 4 participating centers. In addition, all major hospitals in Korea share the same immunosuppressant protocols and yield comparable results, which enables the compilation of a nationwide KOTRY. The immunosuppression protocol used in Korea is more up-to-date than that of the ISHLT registry. For example, immunosuppressive induction was used in most recipients (98%), which was much higher than the ISHLT study in which 50% of recipients received immunosuppressive induction.<sup>3)</sup> There was also a near-complete transition from the older regimen of cyclosporin/azathioprine/steroid to a more current regimen of tacrolimus/mycophenolate mofetil/steroid during the depression period of HTPL in Korea, due to a transition of organ allocation authority from individual hospitals

to KONOS. Partly due to depression in the early 2000s, when the use of proliferation signals or mammalian target-of-rapamycin inhibitors was first introduced in addition to the older regimen,<sup>18)</sup> mammalian target of rapamycin (mTOR) inhibitors are still used in limited cases.

In conclusion, with the establishment of KOTRY in 2014, it is now possible to present the first nationwide epidemiological profile of Korean HTPL. The registry will continue until 2023.

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