Table 3. Education Program for 3-Consecutive-Day Course for Second Semester

	Contents
Day 1	① History of organ donation and transplantation in Japan
	② Organ Transplant Act and Network network System system in Japan
	③ Outcome of organ transplantation in Japan
	④ Post-transplant nursing care
Day 2	④ Flow of organ donation, site visit to JOT office
	⑥ Brain death (pathology and legal determination)
	⑦ Roles of procurement transplant coordinator (PTC)
	⑤ Family approach by JOT-PTC
	⑥ Roles of In-Hp PTC
	⑩ How to organize simulation seminars in each hospital
	⑪ Family care (national survey of DCD donor family) (role play)
	⑫ Grieving process of families (role play)
Day 3	⑬ Pediatric organ donation, How to deny child abuse
	⑭ How to present an option for organ donation
	⑮ Donor assessment and management, and management in operating room
	⑯ Summary and written exam

RESULTS

A survey of participants after the program revealed that most were satisfied with the program, topics and duration. As most participants were not full-time In-Hp PTCs, they preferred to attend the 3-day program. Although not many organ donations have been performed in the hospitals in which the participants are working, many participants are now working as main In-Hp PTCs and establishing their own organ donation systems in their hospitals. Three In-Hp PTCs experienced BD organ donation after this education program.

DISCUSSION

Although the Transplantation Act was revised in 2010 and BD organ donation increased from 13 to 47 cases in a year, the number was still much smaller than in other developed countries. In these circumstances, In-Hp PTC may play a significant role in increasing organ donation and making procurement procedure smoother.

Our nationwide survey of In-Hp PTCs [5] revealed that respondents' occupations were nurse (66%), physician (18%), or other (16%). Although 52% of respondents belonged to a hospital that was designated for brain-death organ donation by the government, only 46% had any experience with a cadaveric donor. Only 2% were full-time In-Hp PTCs. They mainly played a role in preparing their own manual for organ procurement (57%), providing in-hospital lectures (44%) or their own simulation exercise (29%), as well as coordinating donation cases. Although 77% had attended seminar about organ donation provided by JOT or the prefecture PTC, 93% wanted more professional education. However, it was difficult for them to attend these activities, to manage a rare and sudden donation case, and to find time to learn about organ donation because they had other jobs.

Although it might be effective to establish a full-time In-Hp PTC in every donor hospital, it would be very hard to do so, because the number of organ donation has been so much smaller in Japan than in other developed countries. Therefore, we need to establish special educational program for these part-time In-Hp PTCs in Japan.

Based on the results from this national survey, our department held a special educational seminar for In-Hp PTCs to establish an educational program for In-Hp PTC in Japan from May to October 2012.

The topics that responders of the nationwide survey wanted to learn about were donor family care (72%), overall organ/tissue donation procedures (65%), the role of In-Hp PTC (67%), simulations of donation (65%), legislation and social systems of organ donation (61%), medical indications for donation (61%), current status of donation and transplantation in Japan (57%), donor management (56%), and case studies (49%). There were significant variations in the topics of interest, depending on the other occupations of the In-HP PTCs. Therefore, the education program topics were history of transplantation, current status of organ transplantation and donation in Japan, legislation and network system of organ transplantation in Japan, outcomes of organ transplantation in Japan, nursing care of transplant recipients, pathophysiology and diagnosis of BD, the role of PTC, process of organ donation, sight visit of JOT office, family care and informed consent for organ donation, survey of donor family, donor evaluation and management, role of In-Hp PTCs, case studies and simulation of organ donation, pediatric organ donation, determination of child abuse, informing organ donation, and care of family of end-life patients. In other words, all participants could learn about all topics that responders of the nationwide survey wanted to learn in this program.

The survey of participants revealed that although they were all satisfied with the program, they still wanted on-the-job training. But because they had another post, they could find only a few days for professional education, such as lectures. Therefore, it was difficult for them to attend practical on-the-job training.

In conclusion, to establish an organ procurement system and increase organ donation, a nationwide education program of In-Hp PTCs should be established in Japan. However, most In-Hp PTCs do not work full time in this position and therefore require more professional education. Our education program may help to establish a systematic national program in Japan. Although we may be able to establish an education curriculum for In-Hp PTCs in the near future, national support is essential to provide these programs to all In-Hp PTCs in Japan.

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The Registry Report of Heart Transplantation in Japan (1999–2013)

Takeshi Nakatani, MD, PhD; Norihide Fukushima, MD, PhD; Minoru Ono, MD, PhD; Yoshikatsu Saiki, MD, PhD; Hikaru Matsuda, MD, PhD; Ryohei Yozu, MD, PhD; Mitsuaki Isobe, MD, PhD

Heart transplantation is accepted as the gold standard therapy for patients with end-stage heart failure.[1] In Japan, the *Organ Transplant Law* was enacted in October 1997, and the first heart transplantation procedure was performed in accordance with this law in 1999.[2] The number of annual transplantations has gradually increased until amendments to the Law were made in July 2010.

Since the revised law came into effect, the number of transplantations has increased dramatically.[3–6] Because few heart transplantations have been performed in Japan, waiting times are long, and many transplant recipients are on a left ventricular assist device (LVAD) as bridge to transplantation (BTT) therapy. Although extracorporeal pulsatile LVADs were previously common, since April 2011 nonpulsatile implantable-type LVADs have been covered by Japanese national health insurance as BTT therapy, and their use is increasing. The Japanese Society for Heart Transplantation collects data concerning heart transplant cases in Japan, and here we present the latest results current to December 2013.

Changes in the Number of Brain-Dead Organ Donations and Heart Transplantations

In Japan, the first organ transplantation from a brain-dead donor in accordance with the *Organ Transplant Law 1997* was performed in February 1999. There were 4 brain-dead donations in 1999, with roughly 5 brain-dead donation per year at first, slowly increasing to approximately 10 per year from 2005. Following the 2010 amendments to the *Organ Transplant Act*, the number of brain-dead organ donors has increased markedly, exceeding 40 annually since 2011.

Heart transplantations have been performed under the transplant law, increasing from approximately 5 per year at first to 10 per year by 2006, further increasing to approximately 30 per year following enactment of the revised *Organ Transplant Act*. In 2013, 37 heart transplant operations were performed (**Figure 1**). The first Japanese heart transplant recipient under the organ transplant law was on BTT therapy, and as described below, most of the patients undergoing heart transplantation are on some form of LVAD as BTT. At first, extracorporeal devices were the norm. Implantable devices were initially only used as part of clinical trials, but BTT therapy using an implantable LVAD, allowing treatment at home, is increasingly coming into use since medical insurance coverage became available for nonpulsatile implantable LVADs in April 2011.

Results

We examined the following parameters for heart transplantation procedures performed in Japan: number of heart transplantations performed, recipient demographics, waiting status, transplant procedures, immunosuppressive therapy, and recipients' return to society and survival rates. Survival rates were calculated using the Kaplan-Meier method.

Number of Heart Transplantations Performed

A total of 759 heart transplant candidates were registered with the Japan Organ Transplant Network between October 1997 and June 2014. Of these, 185 underwent heart transplantation, and 2 had heart-lung transplantations. A further 20 candidates cancelled their registration, and 217 died while on the waiting list. As of 6 January 2014, there were 288 registered candidates (including 4 requiring heart-lung transplantation). From the standpoint of medical priority, 186 (65%) are in Status 1 and supported by VAD or continuous infusion of intravenous inotropes in intensive care rooms such as ICU or CCU, while 90 (31%) are in Status 2, and 12 (4%) are considered temporarily unsuitable for transplantation in Status 3.

In Japan, the first heart transplantation in accordance with the *Organ Transplant Law* was performed in February 1999, with a total of 185 procedures (excluding 1 heart-lung transplant) performed until 31 December 2013. **Figure 1** shows the numbers by year. Before enactment of the revised *Organ Transplant Act*, the highest number of heart transplantations performed in 1 year was 11 in 2008, whereas post-enactment the number of procedures increased approximately 3-fold,

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Department of Transplantation, National Cerebral and Cardiovascular Center, Suita (T.N.); Department of Transplant Medicine, Osaka University Graduate School of Medicine, Suita (N.F.); Department of Cardiothoracic Surgery, the University of Tokyo, Tokyo (M.O.); Department of Cardiovascular Surgery, Tohoku University School of Medicine, Sendai (Y.S.); Department of Cardiovascular Surgery, Higashi Takarazuka Satoh Hospital, Takarazuka (H.M.); Keio University School of Medicine, Cardiovascular Surgery, Tokyo (R.Y.); Department of Cardiovascular Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo (M.I.); Japanese Society for Heart Transplantation, Osaka (T.N., N.F., M.O., Y.S., H.M.); and Cardiac Transplantation Committee of the Japanese Circulation Society, Tokyo (R.Y., M.I.), Japan
Mailing address: Takeshi Nakatani, MD, PhD, Director, Department of Transplantation, Department of Clinical Nutrition, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: tnakatan@ncvc.go.jp
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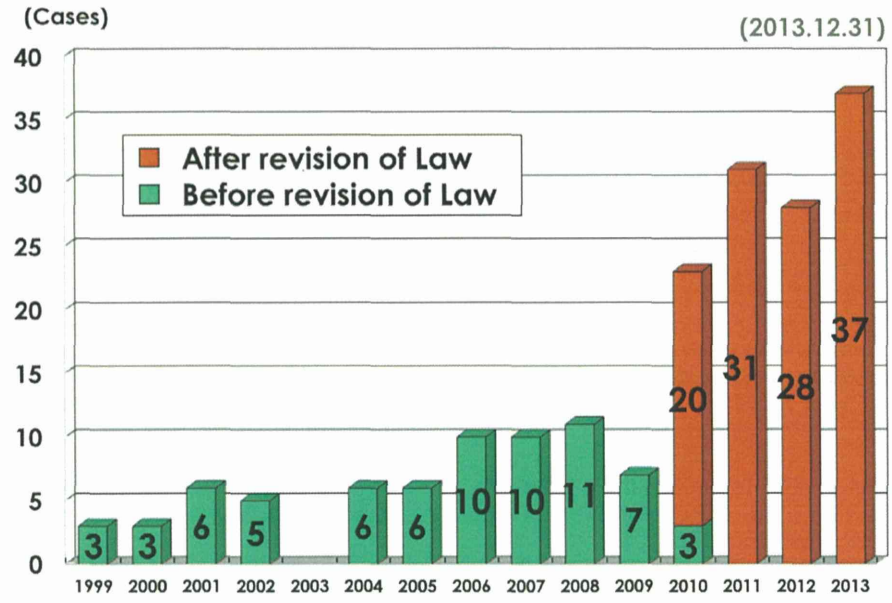

Figure 1. Number of heart transplants performed in Japan by year.

reaching 37 in 2013. Only 69 heart transplants were performed in the 12 years before the revised *Organ Transplant Act*, 116 were performed in the ensuing 3 years and 6 months. And the first pediatric heart transplantation using a pediatric donor heart was performed in 2011.[7]

Selection of heart transplant candidates in Japan is a 2-stage process, with an assessment of suitability by both the treating institution and the Heart Transplant Candidate Registry Committee of the Japanese Circulation Society.[4] Commencing in 1997 with enactment of the *Organ Transplant Law*, the Heart Transplant Candidate Registry Committee initially assessed 40–60 applicants per year. Accompanying the increased number of heart transplantations performed since enactment of the revised *Organ Transplant Act* and coverage of national medical insurance for nonpulsatile implantable LVADs as BTT therapy at home, the number of applications for assessment of heart transplant candidacy has now reached 120–130 per year (**Figure 2**).

Heart transplantation in Japan commenced at 3 institutions: the National Cerebral and Cardiovascular Center, Osaka University, and Tokyo Women's Medical University. A further 6 institutions were then certified (Tokyo University, Kyushu University, Saitama Medical University (now Saitama International Medical Center, Saitama Medical University), Tohoku University, Hokkaido University, Okayama University), giving the present total of 9 heart transplant hospitals. In addition, following enactment of the revised *Organ Transplant Act*, 3 institutions were certified for heart transplants in children aged <10 years old: the National Cerebral and Cardiovascular Center, Osaka University, and Tokyo University, followed by Tokyo Women's Medical University in 2013. One heart transplantation has been performed in a child aged <10 years old, at Osaka University.[7] The number of heart transplantations performed at each institution is as follows: 58 (27 pre-revision/31 post-revision) at the National Cerebral and Cardiovascular Center, 50 (21/29) at Osaka University, 44 (9/35) at Tokyo University, 12 (4/8) at Tokyo Women's Medical University, 8 (3/5) at Kyushu University, 7 (2/5) at Tohoku University, 5 (2/3) at Saitama Medical University (International Medical Center), and 1 (0/1) at Okayama University.

Transplant Recipients

Of the 185 heart transplant recipients to date, 134 (72%) have been male and 51 (28%) female, with ages ranging from under 10 to 62 years old (average, 37.6 years). The age distribution is as follows: <10 years 1%, 10–19 years 8%, 20–29 years 22%, 30–39 years 24%, 40–49 years 22%, 50–59 years 18%, and ≥60 years 5%; the 3rd to 6th decades of life each accounting for approximately 20% of the total.

Underlying conditions in these patients are shown in **Figure 3**, with dilated cardiomyopathy the most common cause in 119 recipients (64%), followed by the dilated phase of hypertrophic cardiomyopathy in 22 (12%), and ischemic cardiomyopathy in only 14 (8%).

Waiting Status

Of the 185 Japanese heart transplant recipients to date, only one child <10 years old was in Status 2, and the others have been Status 1 while awaiting transplantation. Of the Status 1 recipients, only 17 (9%) were in intensive care with continuous intravenous infusion of inotropes, with the remaining 167 (90%) on BTT therapy with some form of VAD. **Figure 4** shows the waiting periods of heart transplant candidate before and after revision of the *Organ Transplant Act*. Of 167 candidates on BTT therapy, 100 (54%) were given the NIPRO-Toyobo extracorporeal pulsatile VAD, whereas use of implantable nonpulsatile type VADs, covered by medical insurance as BTT in April 2011, has increased after revision of the Act.

Changes in the number of Status 1 candidates on the waiting list and their waiting periods are shown in **Figure 5**. Wait-

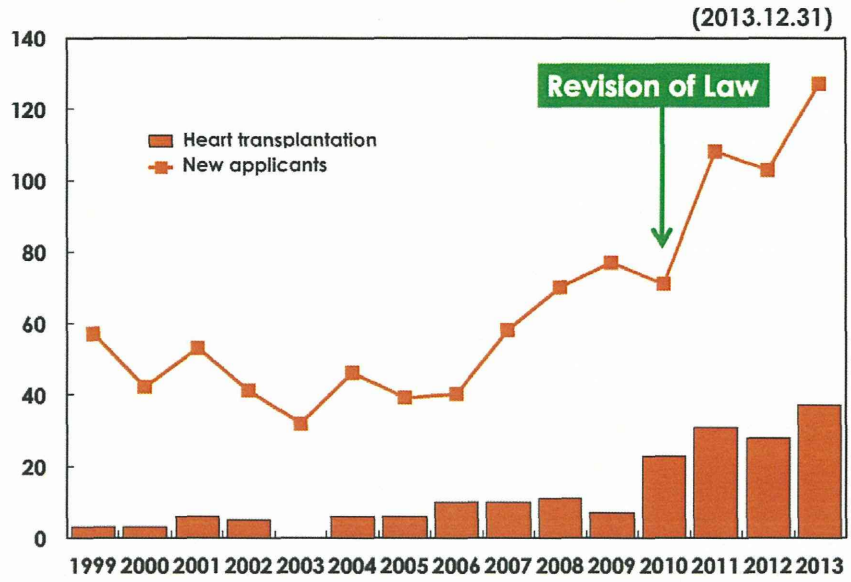

Figure 2. Numbers of new applicants for heart transplantation vs. number of heart transplants performed in Japan.

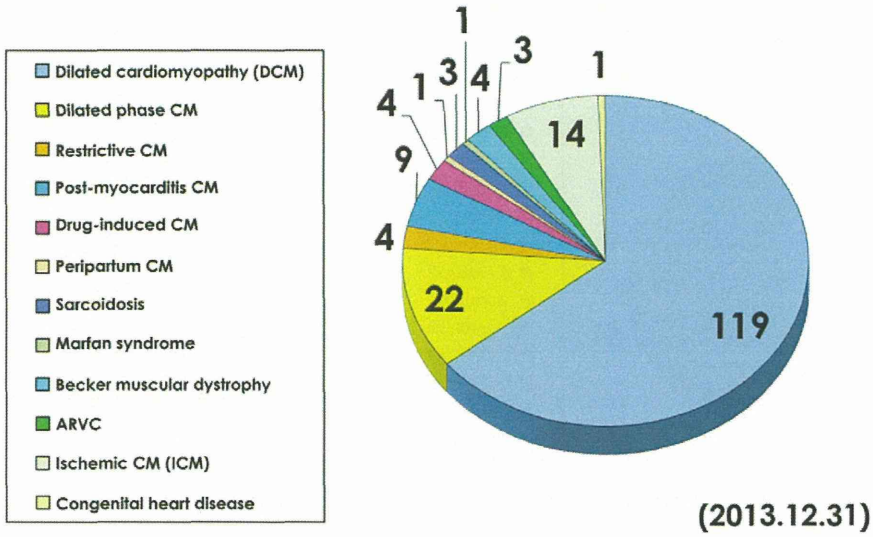

Figure 3. Underlying conditions necessitating heart transplantation in Japan. ARVC, arrhythmogenic right ventricular cardiomyopathy.

ing periods for Status 1 candidates ranged from 29 to 1,707 days (average, 855 days), at first remaining within 1 year, but subsequently becoming more prolonged until reaching 850–900 days after 2005. No reduction in waiting periods has been seen after revision of the *Organ Transplant Act*. Candidates on BTT therapy were on their devices for 21–1,738 days (average, 896 days), with almost all post-revision transplant recipients who are on BTT therapy using extracorporeal type and implantable type VADs.

Heart Preservation Solutions and Transplant Techniques

The heart preservation solutions used were modified Collins solution in 9 cases, St. Thomas solution in 7, Bredshnieder solution in 3, University of Wisconsin solution in 7, and Celsior

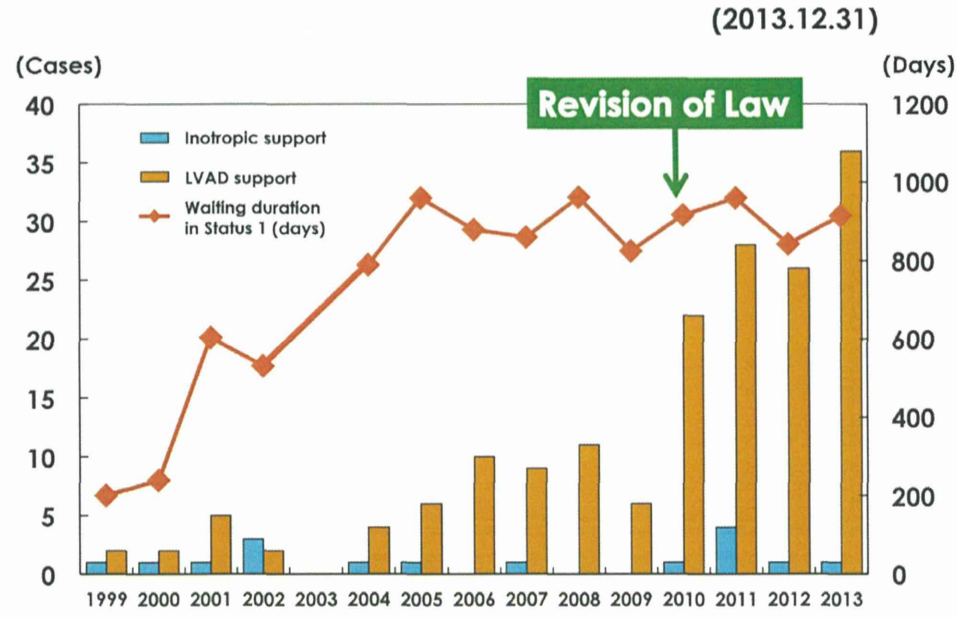

Figure 4. Number of heart transplants performed and mean waiting duration for Status 1 candidates by year in Japan. LVAD, left ventricular assist device.

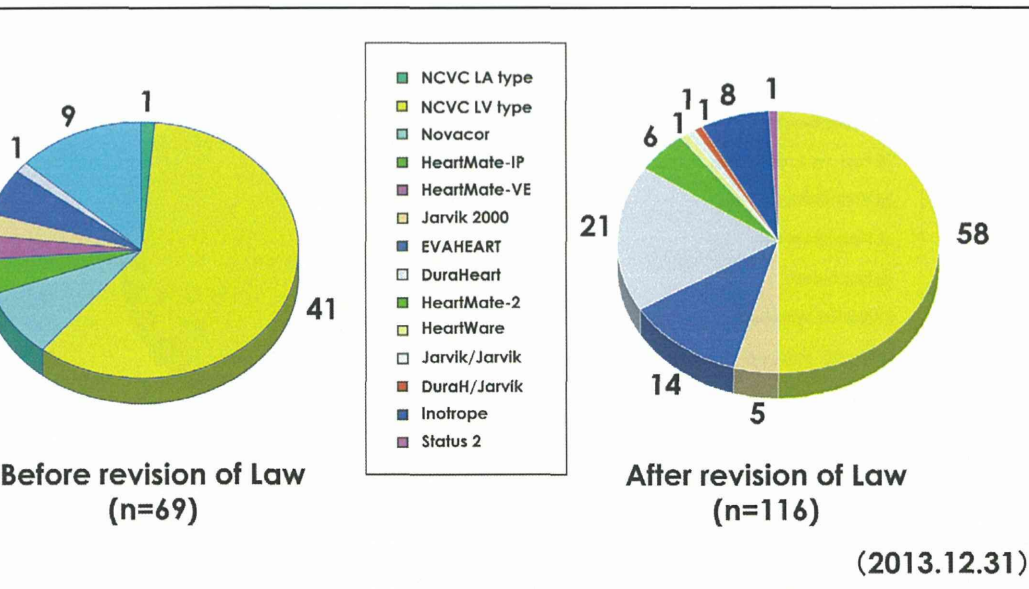

Figure 5. Types of ventricular assist devices used as bridge to transplantation therapy.

solution in 159. Presently, almost all Japanese heart transplant hospitals use Celsior solution.

The operative techniques used were the Lower-Shamway method in 26 cases, the bicaval method in 2, the modified bicaval method in 155, the total heart transplant method in 1, and the other for the patient with dextrocardia. In most cases, the modified bicaval method, developed in Japan, is now used.[8]

Immunosuppressive Therapy

Induction therapy was administered to 58 heart transplant re-

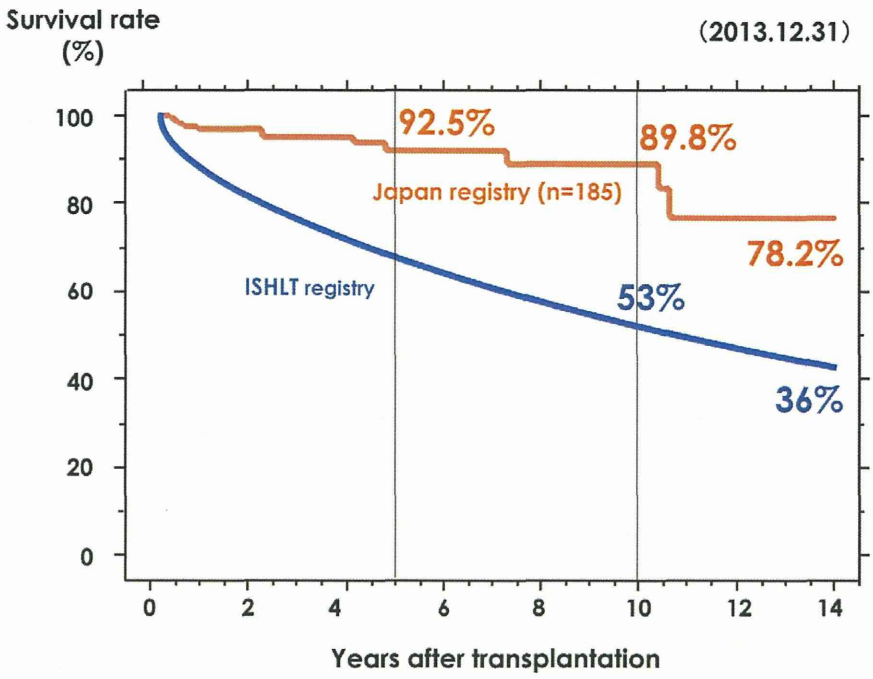

Figure 6. Cumulative survival rates following heart transplantation in Japan. ISHLT, International Society for Heart & Lung Transplantation.

cipients, at first comprising anti-CD3 antibody (monoclonal anti-CD3 antibody: OKT3, 7 cases) or anti-thymocyte globulin (ATG, 7 cases). More recently, basiliximab (Simulect®) has been used as induction therapy, in a total of 44 recipients.

Initial immunosuppressive therapy in Japan comprises triple therapy with a calcineurin inhibitor (CNI), an antimetabolite, and a corticosteroid. CNIs used include cyclosporine A (CyA) and tacrolimus (Tac), with the use of Tac increasing recently. The antimetabolite used in the first 3 heart transplantations was azathioprine (AZP), with mycophenolate mofetil (MMF) used in subsequent cases. CyA with AZP/MMF and steroid was administered in 64 recipients (34.6%) in the initial phase and Tac with MMF and steroid in 121 (65.4%). Although everolimus (Certican®) recently received medical insurance approval, it is not yet used in Japan as initial immunosuppressive therapy, but instead in patients with post-transplant coronary arterial disease, renal dysfunction, malignancies, or MMF intolerance (gastrointestinal symptoms, leukopenia).

Recipients' Survival Rates and Return to Society

Survival rates for the 185 Japanese heart transplant recipients are shown in **Figure 6**. There have been 12 deaths, the cause of death being multiple organ failure in 2 cases (17 days and 67 days, respectively, post-transplant), infection in 6 (2 months, 4 months, 8 months, 2 years, 4 years, and 4 years, respectively, post-transplant), post-transplant coronary arterial disease in 1 (7 years post-transplant), gastric cancer in 1 (10 years post-transplant), kidney failure in 1 (11 years post-transplant), and other in 1 (2 years post-transplant). Two recipients have survived more than 14 years post-transplant, the longest being 14 years 7 months. The survival rates 5 and 10 years post-transplant are 92.5% and 89.8%, respectively, better than that in the Registry of the International Society for Heart & Lung Transplantation.[9,10] Furthermore, more than 100 recipients have been able to return to society (including home duties and part-time work). However, the 2012 Report of the Ministry of Health, Labour and Welfare Transplant Verification Committee indicated that less than 40% of heart transplant recipients were able to return to full-time work, fewer than for lung, liver, pancreas or kidney transplant recipients.

This survey by the Japanese Society for Heart Transplantation found that of 148 recipients who achieved a return to society, 24 were housewives, house husbands or domestic helpers, 15 were students, 2 were working part-time, 31 were still in rehabilitation, 9 were seeking employment, and 7 were retired or unemployed.

Conclusions

In the 3 years and 7 months since the revised *Organ Transplant Law* was enacted, 116 heart transplantations have been performed in Japan, 37 of them in 2013. Before the original *Organ Transplant Law* was passed, Japanese candidates for heart transplantation travelled overseas for their heart transplant operations, and even after its enactment Japanese patients, in particular children, continued to travel overseas seeking heart transplantations. Following enactment of the revised law, the number of heart transplantations performed in Japan rose dramatically. In 2013, the number of Japanese candidates undergoing heart transplantation in Japan exceeded that undergoing heart transplantation overseas. Although brain-dead organ donation from a child became possible with the revised

law, only 2 heart transplant recipients have been aged <10 years. Even after enactment of the revised *Organ Transplant Law*, children, in particular those aged <10 years, continue to travel overseas for their heart transplantations, representing a challenge for the future. From February 2013, the age limit for heart transplant candidates in Japan was raised from <60 to <65 years. Under the revised law, hearts can be procured from donors aged ≥60 years, necessitating examination of transplantation into elderly recipients as well.

The number of heart transplant candidate registrations continues to rise as the number of heart transplantations performed increases. Moreover, since April 2011 the application of small implantable nonpulsatile type LVADs have been covered by Japanese medical insurance, allowing BTT treatment at home, and these implantable LVADs can now be applied and managed by medical institutions that are not heart transplant hospitals. We can therefore anticipate that waiting periods will also continue to lengthen.

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Appendix

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SECTION 12. LIVING DONOR LIVER TRANSPLANTATION FOR PATIENTS WITH HIGH MODEL FOR END-STAGE LIVER DISEASE SCORES AND ACUTE LIVER FAILURE

Toshimi Kaido,[1,2] Koji Tomiyama,[1] Kohei Ogawa,[1] Yasuhiro Fujimoto,[1] Takashi Ito,[1] Akira Mori,[1] and Shinji Uemoto[1]

Abstract. Living donor liver transplantation (LDLT) for patients with high model for end-stage liver disease score and acute liver failure patients have little or not gained any substantial following among Western centers because of the "donor high risk-low recipient benefit scenario" that puts the donor at a significant risk against the survival odds for a recipient who is receiving a partial graft and considered marginal by Western standards. In most Asian countries, there is sometimes no other source of live graft but a willing live liver donor. There are individual Asian center reports that conclude that LDLT has comparable outcome to deceased donor liver transplant. However, the outcomes of a large number of patients after undergoing adult LDLT for high model for end-stage liver disease scores and acute liver failure at a single center have not been investigated. Here in, we present our experience with such subgroup of patients undergoing LDLT.

Keywords: Liver transplantation, Model for end-stage liver disease score, Acute liver failure.

Living donor liver transplantation (LDLT) for patients with high model for end-stage liver disease (MELD) scores remains debatable. Some reports describe decreased overall patient and graft survival rates for patients with high MELD scores after LDLT (*1, 2*). Others report that LDLT could provide excellent graft function and survival rates in such patients (*3, 4*). Liver transplantation is also an effective modality for treating acute liver failure (ALF) when patients are refractory to medical treatment. Acute liver failure has been predominantly treated using LDLT in Asian countries such as Japan and Korea (*5–7*). However, the outcomes of a large number of patients after undergoing adult LDLT for ALF at a single center have not been investigated.

We therefore assessed the impact of MELD scores on the outcomes of 223 patients who underwent adult-to-adult LDLT between January 2006 and April 2011 at Kyoto University. We also reviewed 72 adult patients who underwent LT for ALF at a single center over a period of 15 years.

LDLT FOR PATIENTS WITH HIGH MELD SCORES

This study enrolled 223 patients who underwent adult-to-adult LDLT between January 2006 and April 2011 at Kyoto University. Patients who underwent a repeated LT or LT for ALF were excluded. The ethics committee at Kyoto University approved the study, which proceeded in accordance with the Declaration of Helsinki of 1996.

The median MELD score was 17 (range, 6–47; Fig. 1). The graft-to-recipient weight ratio and incidence of ABO-incompatible LT did not differ among patients with MELD scores of <10, ≥10–15, ≥15–20, ≥20–25, ≥25–30, ≥30–35, and >35. Overall patient survival rates did not differ among the patients assigned to these groups. Overall patient survival rates also did not significantly differ between patients with low (<25) and high (≥25) MELD scores (Fig. 2). In conclusion, LDLT can facilitate acceptable outcomes for patients with high MELD scores.

LDLT FOR ACUTE LIVER FAILURE

We reviewed data from 72 adult ALF patients (male, n=33; median age, 42 years, range 19–68 years) with a median MELD score of 19 (range, 7–41) who underwent LDLT at a single center over a period of 15 years. Six patients were ABO incompatible, and 66 were identical or compatible. Total scores for predictive variables affecting the mortality of each patient with ALF were calculated based on the proposal of the Study Group of Intractable Hepatobiliary Diseases in Japan (*8*).

Among the 72 patients, 17 and 55 had acute and subacute ALF, respectively. The etiologies of ALF were hepatitis B virus (n=29), drug exposure (n=11), autoimmune hepatitis (n=2), and unknown (n=30). The total scores for predictive variables varied from 2 to 10 with a median of 7. The average score was significantly higher in patients with subacute than acute ALF (7.2 vs. 4.4; $P<0.001$).

Patient survival rates were 65%, 65%, and 61% at 1, 3, and 5 years, respectively. The overall survival rates did not differ among patients according to the etiology of ALF ($P=0.693$), type of ALF ($P=0.745$), ABO compatibility ($P=0.912$), total scores for predictive variables ($P=0.975$), or having a graft-to-recipient weight ratio above or below 0.8% ($P=0.063$). Among the 72 patients, 27 died at a median of 1 (range, 0–60) month after LT. The most frequent cause of death after LT was infection (n=14) followed by multiple

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[1] Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan.
[2] Address correspondence to: Toshimi Kaido, M.D., Ph.D., Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Graduate School of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.
E-mail: kaido@kuhp.kyoto-u.ac.jp
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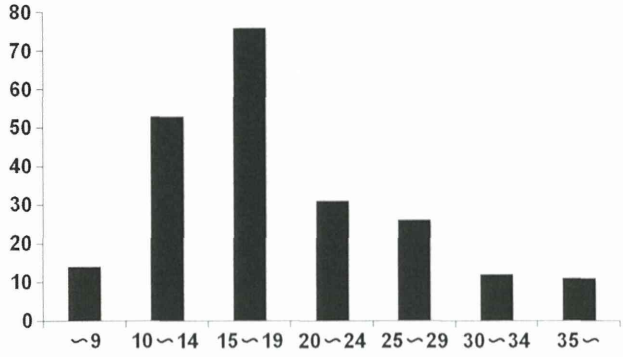

FIGURE 1. Distribution of MELD scores.

organ failure (n=3), cerebral bleeding (n=2) and graft failure (n=2). Moreover, overall patient survival rates did not significantly differ between patients with (n=20) and without (n=223) ALF among those who underwent LDLT between January 2006 and April 2011 (Fig. 3).

DISCUSSION

The overall survival rates in the present study were worse than those previously reported. One possible reason is that our tertiary care center might have included patients that had generally worse overall clinical status than those investigated in other studies. More than half of the patients in the present study died of infection, which is in line with our previous report that analyzed the mortality of all patients after LDLT (*9*). We recently reported that early posttransplant enteral nutrition with a new immune-modulating diet enriched with hydrolyzed whey peptide significantly prevented posttransplant bacteremia (*10*). This finding indicates that posttransplant intervention such as this type of nutritional therapy could effectively prevent lethal bacteremia arising even in patients with ALF who have little time to receive any preoperative intervention.

In conclusion, LDLT facilitates favorable outcomes in adult patients with ALF irrespective of the etiology, type of ALF, or pretransplant liver condition. The findings of these two short studies indicate that LDLT could afford acceptable

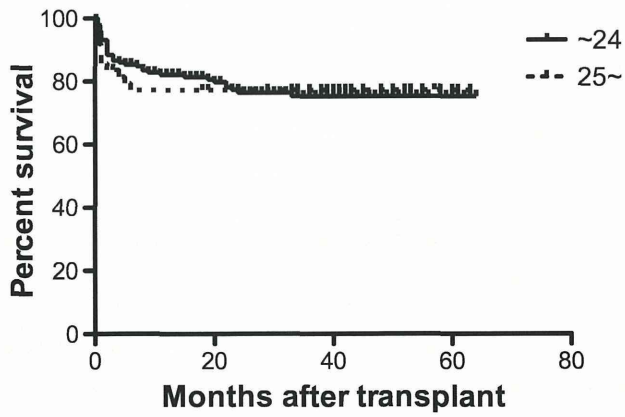

FIGURE 2. Overall survival rates in patients with low (<25) and high (≥25) MELD scores.

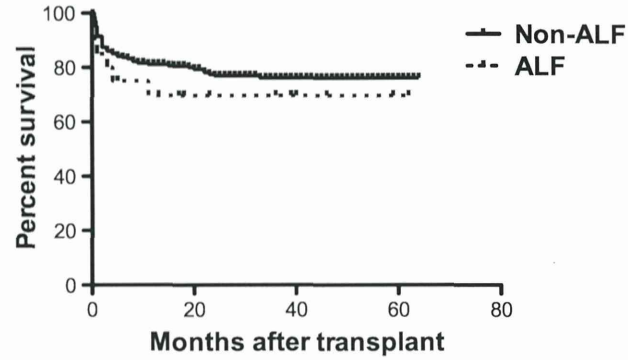

FIGURE 3. Overall survival rates in patients with ALF (n=20) and those with non-ALF (n=223) among those who underwent LDLT between January 2006 and April 2011.

outcomes for patients with high MELD scores or ALF in high volume centers.

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SECTION 13. SHORT-COURSE PRETRANSPLANT ANTIVIRAL THERAPY IS A FEASIBLE AND EFFECTIVE STRATEGY TO PREVENT HEPATITIS C RECURRENCE AFTER LIVER TRANSPLANTATION IN GENOTYPE 2 PATIENTS

Chih-Che Lin,[1] Catherine Kabiling,[1] Chao-Long Chen,[1,3] Yu-Hung Lin,[1] Yueh-Wei Liu,[1] Chih-Chi Wang,[1] Tsung-Hui Hu,[2] and King-Wah Chiu[2]