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Review Article

Liver transplantation for HIV/hepatitis C virus co-infected patients

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Since the introduction of antiretroviral therapy (ART) in the mid-1990s, AIDS-related death has been dramatically reduced, and hepatitis-C-virus (HCV)-related liver failure or hepatocellular carcinoma has currently become the leading cause of death in HIV/HCV co-infected patients. Liver transplantation may be one of the treatments of choices in such cases, but the indications for transplantation, perioperative management including both HIV and HCV treatments, immunosuppression and the prevention/treatment of infectious complications are all still topics of debate. With the improved understanding of the viral behaviors of both HIV and HCV and the development of novel strategies, especially to avoid drug interactions between ART and immunosuppression, liver transplantation has become a realistic treatment for HIV/HCV co-infected patients.

Key words: hepatitis C virus, HIV, liver transplantation

INTRODUCTION

IN JAPAN, IN the late 1980s, contaminated blood production of coagulation factor for hemophilia caused co-infection of HIV and hepatitis C virus (HCV). Actually, greater than 90% of HIV-infected patients have HCV as well.[1]

After antiretroviral therapy (ART) was introduced in the late 1990s, successful control of HIV was achieved in most cases and death due to AIDS was dramatically reduced, but HCV-related death due to liver failure or hepatocellular carcinoma became a serious problem, not only in Japan, but all over the world.[2–6] In such cases, liver transplantation (LT) is the only treatment option to achieve long-term survival, but several modifications of perioperative management are required. In this review, the outcome and the points of management of LT for HIV/HCV co-infected patients were reviewed.

REPORTED OUTCOME OF LT FOR HIV/HCV PATIENTS

THE REPORTED OUTCOMES of LT for HIV and HIV/HCV co-infected patients from Western countries after the introduction of ART are summarized in Table 1.[7–11] In general, most reports concluded that the results were worse than in the cases with HCV mono-infection, with a 3-year survival of approximately 60–70%. In Japan, the Tokyo group reported six cases of living donor liver transplantation (LDLT) between 2001 and 2004, of whom four died.[12] These unfavorable outcomes are likely related to the difficulties of determining the indications for LT and of perioperative management, including HIV/HCV treatment and the prevention and treatment of infectious complications. Terrault *et al.* reported that older donor age, combined kidney–liver transplantation, an anti-HCV positive donor and a body mass index of less than 21 kg/m^2 were independent predictors of graft loss.[10] After transplantation, several studies showed that acute cellular rejection was more frequent and severer in HIV/HCV co-infected patients than that in HCV mono-infected patients, possibly due to the difficulties in achieving optimal immunosuppression because of interactions between antiretroviral agents and immunosuppression.[10,11]

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Table 1 Outcome of liver transplantation for HIV/hepatitis C virus co-infection

Authors	Publication year	Country	*n*	Patient survival (%)		
				1 year	3 years	5 years
de Vera *et al.*[7]	2006	USA	27	67	56	33
Schreibman *et al.*[8]	2007	USA	15	73	73	–
Duclos-Vallee *et al.*[9]	2008	France	35	–	73	51
Terrault *et al.*[10]	2012	USA	89	76	60	–
Miro *et al.*[11]	2012	Spain	84	88	62	54

SPECIAL ISSUES REGARDING LT INDICATIONS FOR HIV/HCV CO-INFECTION

ART-related non-cirrhotic portal hypertension

IN HCV MONO-INFECTED patients, LT should be considered when the patients develop deteriorated liver function as indicated by a Child–Pugh classification of B or C. In HIV/HCV co-infected patients, liver failure due to HCV hepatitis was generally enhanced by ART-related hepatotoxicity, especially non-cirrhotic portal hypertension.[13–15] Accordingly, not only in cases with deteriorated liver function but also in class A cases, the patients can easily develop severe liver dysfunction suddenly,[16,17] so that all HIV/HCV co-infected patients should be carefully followed up so as not to miss the chance for LT. Also, Murillas *et al.* reported that Model for End-Stage Liver Disease (MELD) score is the best prognostic factor in HIV-infected patients,[18] so that HIV/HCV co-infected patients may be considered for LT before MELD score increase to achieve comparable results with HCV mono-infected patients. Several studies showed the aggressive fibrosis in HIV/HCV co-infected patients compared with HCV mono-infected patients,[19,20] but the mechanism of this aggressive fibrosis remains unclear. Recently, transient elastography or acoustic radiation force impulse imaging to check for liver stiffness has been introduced as an effective and non-invasive modality to determine patients' candidacy for LT.[21–23]

Count of CD4$^+$ T lymphocytes

Generally, the count of CD4$^+$ T lymphocytes has been required to be more than 200/μL to perform general elective surgeries in HIV-infected patients,[24] but in HIV/HCV co-infected patients, current studies show that a count of more than 100/μL is acceptable,[25,26] because patients generally have portal hypertension which can cause pancytopenia. In such patients, the ratio of CD4/CD8 is reported to be a feasible marker to predict postoperative complications including opportunistic infections. When the ratio is less than 0.15, the incidence of infectious complications is significantly higher.[27]

Preoperative infections

In regard to latent opportunistic infections that occur before LT, they are not absolute contraindications when they can be expected to be controlled.[28] Infections regarded as contraindications for LT included uncontrollable multidrug resistance HIV infection, chronic *Cryptosporidium enteritis*, progressive multifocal leukoencephalopathy and lymphoma.[29]

MANAGEMENT OF HIV/HCV IN LT

Management of HIV

THE NUMBER OF HIV RNA copies before LT is suggested as an independent risk factor of postoperative mortality, so that HIV should be controlled sufficiently before LT.[30] Accordingly, in the patients who are under consideration to receive LT, ART can be safely stopped before LT because HIV is generally well-controlled for a long period by ART. After LT, ART should be restarted as soon as possible because HIV RNA appears at 3–30 days after ART is stopped,[31] but the timing of restart of ART depends on the patient's condition, including liver function.[32] As long as the liver function has not fully recovered, or partial liver graft such as in LDLT has not sufficiently regenerated yet, ART cannot be started. Castells *et al.* reported in their case–control study that ART was started at a median of 8 days after LT (range, 4–28 days).[33] In principle, the ART administrated after LT should be the same as the pretransplant regimen, but the majority of ART drugs including protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) have interactions with calcineurin inhibitors

(CNI) or mammalian target of rapamycin (mTOR),[34] so that the monitoring of blood levels of immunosuppression is extremely important to avoid infectious complications or rejection. Currently, a novel HIV-1 integrase inhibitor, raltegravir (RAL), is expected to be a feasible drug because it has no interactions with CNI, unlike other drugs.[35,36]

Management of HCV

The treatment strategy for HCV in HIV/HCV co-infected patients is the same as in HCV mono-infected patients. Combination therapy of pegylated interferon (PEG IFN) and ribavirin is the standard treatment both before and after LT. The timing of the induction therapy after LT is controversial. A Tokyo group proposed early induction as a preemptive therapy before patients develop hepatitis,[37] while several other reports showed favorable results when the treatment was administrated only after the development of hepatitis was confirmed by liver biopsy.[38,39] Theoretically, the treatment should be started as soon as possible, because in HIV/HCV co-infected patients, HCV recurrence may be accelerated in an immunocompromised state.[30,40] The novel protease inhibitor, telaprevir, is currently introduced as an effective drug to achieve sustained viral response of 70%, even in genotype 1b, with PEG IFN/ribavirin in a non-transplant setting,[41] but this drug is metabolized via cytochrome P450 as a substrate, as are CNI and various protease inhibitors of ART for HIV. Close monitoring of the CNI trough level should be performed, and although triple therapy with telaprevir/PEG IFN/ribavirin is currently reported to be effective to prevent HCV recurrence after LT in HCV mono-infected cases, special attention should be paid when this regimen is adapted in HIV/HCV co-infected patients.

IMMUNOSUPPRESSION

AS PREVIOUSLY MENTIONED, many factors including ART, anti-HCV treatment and an HIV-related immunocompromised state make post-LT immunosuppressive treatment difficult. Many ART drugs, both PI and NNRTI, cause instability in the blood concentration of CNI through the cytochrome P3A4 (CYP3A4)-related metabolism. Most PI cause the overconcentration of CNI by inhibiting CYP3A4, while most NNRTI cause decreased levels of CNI by stimulating CYP3A4.[29,42] As mentioned earlier, RAL is introduced as a key drug in LT in HIV positive patients, because the metabolism of this drug is not related to CYP450, so it does not affect the blood concentration of CNI. Several reports have demonstrated both the *in vitro* and *in vivo* effectiveness of rapamycin in reducing HIV replication,[43–45] and Di Benedetto *et al.* found that rapamycin monotherapy was significantly beneficial in long-term immunosuppression maintenance and HIV control after LT.[46] Mycophenolate mofetil is expected to be an effective immunosuppressive drug because of its efficacy in reducing HIV infection by both virological and immunological mechanisms.[47–49] Using these drugs, a more effective regimen of immunosuppression with ART may be established.

In regard to the steroid, several studies proposed that a steroid-free regimen can be safely applied and effective in LT for HCV cirrhosis. Also, in HIV/HCV co-infected patients, steroid-free protocol may be beneficial to prevent both HIV and HCV recurrence after LT.[50,51]

CONCLUSIONS

LIVER TRANSPLANTATION FOR HIV/HCV co-infected patients remains challenging, but with recent developments in perioperative management and novel drugs for both HIV and HCV, the results are likely to be improved.

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Laparoscopy-Assisted Hybrid Left-Side Donor Hepatectomy: Rationale for Performing LADH

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We are pleased to have the opportunity to respond to the letter to the editor and would like to thank Dr. Ishizawa and his colleagues for their interest in our study and very important comments. We agree with their concerns about donor safety. As we have stated in our article [1], the most important issue in donor hepatectomy is 'donor safety'. If donor safety is threatened for any reason in a new procedure as compared with the traditional procedure, it would not be acceptable.

On the other hand, most liver donors experience postoperative difficulties arising from the mental and physical changes caused by a big skin incision [2]. As surgeons, we cannot help but consider alleviation of such stress in donors by making efforts to minimize the skin incision, while ensuring donor safety.

Fortunately, owing to the development of surgical devices and the accumulating experience of surgeons, laparoscopic hepatectomy has become established and is now widely practiced routinely all over the world. Among the techniques for laparoscopic hepatectomy, the hybrid technique is a combination of laparoscopic mobilization of the liver and open hepatectomy under direct vision through the skin incision, and that carries the benefits of both safety and minimal invasiveness. One can easily realize after sufficient experience in using the hybrid technique that a large skin incision is not necessary for performing hepatectomy after the liver is adequately mobilized from the retroperitoneum, which is the point of this procedure.

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Although we experienced two incidental injury episodes, it was not difficult to manage them promptly under direct vision through a skin incision. Besides, we were always prepared to extend the incision to perform traditional open donor hepatectomy in the event of any unexpected trouble with the laparoscopy-assisted hybrid donor hepatectomy (LADH) procedure.

In view of the live liver donor mortalities and potentially life-threatening events reported in the literature [3], we cannot be too careful when securing donor safety during surgery.

We again emphasize our approach to establishing the new technique. First, we already had adequate experience of both open donor hepatectomy and laparoscopic hepatectomy when we started this study [4, 5]. We analyzed the incidence of morbidities in our open donor surgery [4], and found that the operative time was shortened and the blood loss decreased according to the surgeons' experience; furthermore, we have not encountered any case of bile leak in donor hepatectomy since 2007. We have performed a sufficient number of laparoscopic hepatectomies, including hybrid hepatectomy [5], so that our center was approved as one of the leading centers for highly advanced medical treatment (laparoscopy-assisted hepatectomy) by the Ministry of Health, Labour and Welfare, Japan, in April 2008. We think that mastery of both donor hepatectomy and laparoscopic hepatectomy is a minimal requirement for safe performance of LADH. Second, we have taken a step-by-step approach to introducing LADH from left lateral sectionectomy to left lobectomy. Left lateral sectionectomy in LADH was simpler than left lobectomy in terms of mobilization of the liver and parenchymal dissection. In fact, our experience in left lateral sectionectomy was quite useful in performing left lobectomy. This step-by-step approach is quite important

when introducing any new technique. Third, this study was conducted with the approval of the institutional review board after discussing the ethics of performing LADH. Furthermore, the risks of LADH as well as of donor surgery were explained to the donor and his/her family in detail, and informed consent was obtained from each donor.

Thus, we carefully planned the application of LADH using these three approaches in our study, as described in the article.

We do not propose that all donor surgeries should be changed to LADH based on the results of our study. Careful approaches and the best practice of each surgical team, needless to say, are necessary in live-donor hepatectomy to minimize morbidity. Another important message from our study is our belief that only experienced surgical teams can be allowed to perform LADH safely and effectively.

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ELSEVIER

Clinical Outcome of Pancreas Transplantation From Marginal Donors in Japan

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ABSTRACT

In Japan, absolute shortage of donors still continues even after the law allowing organ transplantation from deceased donors came into force in 1997. With the passage of the waiting period after registration for pancreas transplantation (PTx), both deaths and serious cases of diabetic complications necessitating withdrawal of the registration have undoubtedly increased. Therefore, so-called "marginal donor" (MD) has been considered as a potential solution for shortage of donors in Japan. The aim of the present study is to evaluate feasibility of MD in terms of post-PTx outcomes using data from Japan Organ Transplantation Network. A total of 148 PTx were performed from deceased donors in Japan from 2000 to 2012. MD was defined as follows: (1) >45 years old; (2) hemodynamically unstable at harvest using a high-dose dopamine or more than 2 vasopressors; or (3) non–heart-beating status. Postoperative outcomes after PTx were compared between the MD group and the non-MD group. Among the 148 PTx donors, 108 donors (73.0%) satisfied the criteria of MD. Early graft loss of pancreas graft during 3 months post-transplant was observed in 15 patients (10.1%), and the marginality (MD vs non-MD) was not significantly correlated with the early loss of pancreas graft. The overall patient survival of the MD group (1, 3, 5 years: 94.7%, 94.7%, 94.7%) was not significantly different from that of the non-MD group (1, 3, 5 years: 95.0%, 95.0%, 95.0%). Pancreas graft survival in the MD group (1, 3, 5 years: 80.9%, 73.2%, 66.0%) seemed to be slightly lower than that in the non-MD group (1, 3, 5 years: 92.5%, 85.2%, 77.4%), but no statistically significant differences were found between the 2 groups. These results suggest the feasibility of the use of MD for PTx.

PANCREAS TRANSPLANTATION (PTx) is an established treatment for type 1 diabetes [1–3]. It is the only effective therapeutic option to restore normal glucose metabolism, to improve quality of life of the patients, and to even reduce chronic complications of the diabetes. Although its outcome was not satisfactory previously, graft survival has much improved during the last 30 years because of development in immunosuppressants, surgical techniques, and postoperative management.

In Japan, the Organ Transplant Law was enforced on October 1997, and it was revised on July 2010. Since the revision, the number of donation is increasing. However, absolute shortage of donors still continues even after the revision. With the passage of the waiting period after registration for PTx, both deaths and serious cases of diabetic complications necessitating withdrawal of the registration have undoubtedly increased. Accordingly, we have had to depend on the so-called "marginal donor" (MD). To date, however, the feasibility of PTx from MD has not yet investigated well. In this regard, the present study was performed to evaluate its feasibility in terms of postoperative outcomes using data from Japan Organ Transplantation Network.

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PATIENTS AND METHODS

Patients

Between April 2000 and December 2012, a total of 148 PTx were performed for type 1 diabetes from deceased donors in Japan. Among the 148 cases of PTx, 146 cases were from brain-dead donors and the remaining 2 were non–heart-beating donors. In Japan, PTx is performed in 17 approved institutions. Characteristics of the 148 patients are shown in Table 1.

Criteria of Marginal Donor

The criteria of MD for PTx of Kapur et al were used in this study; donors of 45 years of age and more, hemodynamically unstable donors at the time of harvest (with dopamine dose > 10 μg/k/min, or 2 or more vasopressors), or non–heart-beating donors [4]. Based on these criteria, the donors were divided into 2 groups: the MD group and the non-MD group.

Graft Failure

Pancreas graft failure was defined as return to insulin-dependence or serum C-peptide level < 0.3 ng/mL. Kidney graft failure was defined as return to dialysis. Death with a functioning graft was also considered be a graft failure. Early graft loss was defined as that within 3 months post-PTx in this study.

Statistical Analysis

Survival was calculated according to the Kaplan–Meier method and compared using the log-rank test. Statistical analysis was performed using StatView (version 5.0; SAS Institute Inc., Cary, NC, United States). A P value <.05 was considered statistically significant.

Table 1. Characteristics of 148 PTx Patients (n = 148)

Factors	
Donor-related factors	
Age (≤45 y/>45 y)	74/74
Gender (male/female)	80/68
Body mass index (kg/m^2) (<25/≥25)	115/33
Cause of death (CVA/trauma/others)	87/28/33
Type of death (brain-dead/non-heart-beating)	146/2
Hemodynamics (stable/unstable)	87/61
Cardiopulmonary resuscitation (−/+)	86/62
Marginality (MD/non-MD)	108/40
Recipient-related factors	
Age (≤50 y/>50 y)	123/25
Gender (male/female)	56/92
Duration of diabetes (<30 y/≥30 y)	90/58
Duration of dialysis (<10 y/≥10 y)	72/47
PTx-related factors	
TCIT (<12 h/≥12 h)	86/62
Type of PTx (SPK/PAK/PTA)	119/20/9
Duct management (bladder drainage/enteric drainage)	30/118
GDA reconstruction (−/+)	35/87
Immunosuppressive regimen	
CNI (TAC/CyA)	144/4
Antibody (−/+)	7/141

Abbreviations: PTx, pancreas transplantation; CVA, cerebrovascular accident; MD, marginal donor; TCIT, total cold ischemic time; SPK, simultaneous pancreas and kidney transplantation; PAK, pancreas transplantation after kidney transplantation; PTA, pancreas transplantation alone; GDA, gastroduodenal artery; CNI, calcineurin inhibitor; TAC, tacrolimus; CyA, cyclosporine.

RESULTS

Ratio of Marginal Donors

Among the 148 donors at the PTx, 74 were 45 or more years old. Sixty-one donors were hemodynamically unstable at the time of harvest. Two donors were non–heart-beating donors. In total, 108 donors (73.0%) of the 148 donors satisfied the criteria of MD and categorized into the MD group, and the remaining 40 donors (27.0%) were categorized into the non-MD group. Characteristics of the 148 patients are shown in Table 1.

Risk Factors for Early Loss of Pancreas Graft

Among the 148 PTx cases, early graft loss of pancreas graft was observed in 15 patients (10.1%). Thrombosis was the most frequent cause of the graft loss (8/15, 53%). The other causes were as follows: sepsis in 3, rejection in 2, duodenal perforation in 1, and cardiogenic shock in 1.

To investigate whether the marginality (MD vs non-MD) is a risk factor for the early loss of pancreas graft, as well as to identify factors that significantly correlate with the early graft loss, donor-related factors were compared between cases with the early graft loss and without the early graft loss (Table 2). The incidence of the early graft loss was significantly higher in donors with total cold ischemic time (TCIT) ≥12 hours (P = .05), and the marginality (MD vs non-MD) was not significantly correlated with the graft loss.

Long-Term Outcome After Pancreas Transplantation

We examined long-term outcomes of PTx in terms of overall patient survival, pancreas graft survival, and kidney graft survival (SPK cases). As shown in Table 3, in all the 148 cases, postoperative mortality was found in 5 patients in the MD group (4.6%) and in 3 patients in the non-MD group (7.5%). The incidence was not significantly different between the 2 groups (P = .45). Overall patient survival in the 148 cases was 94.8%, 94.8%, and 94.8% at 1, 3, and 5 years, respectively. The overall patient survival of the MD group (1, 3, 5 years: 94.7%, 94.7%, 94.7%) was not significantly different from those of the non-MD group (1, 3, 5 years: 95.0%, 95.0%, 95.0%; P = .42, Fig 1A). Twenty-four pancreas grafts were lost during the observation period

Table 2. Correlation of Donor-Related Factors With Early Loss of Pancreas Graft in the 148 PTx Cases

Factor	Early Graft Loss (−) (n = 133)	Early Graft Loss (+) (n = 15)	P Value
Age (≤45 y/<45 y)	66/67	8/7	.79
Gender (male/female)	70/63	10/5	.41
Body mass index (kg/m^2) (<25/≥25)	103/30	12/3	.56
Cause of death (CVA/others)	78/55	10/5	.59
Hemodynamics (stable/unstable)	80/53	7/8	.41
Cardiopulmonary resuscitation (−/+)	78/55	8/7	.78
TCIT (<12 h/≥12 h)	81/52	5/10	.05
Marginality (MD/non-MD)	96/37	12/3	.76

Abbreviations: PTx, pancreas transplantation; CVA, cerebrovascular accident; MD, marginal donor; TCIT, total cold ischemic time.

Table 3. Incidence of Mortality and Graft Failures in MD Group and Non-MD Group

	MD Group	Non-MD Group	*P* Value
Mortality	5/108 (4.6%)	3/40 (7.5%)	.45
Cardiogenic	1	2	
Cerebral bleeding	1	0	
Sepsis	2	1	
GVHD	1	0	
Pancreas graft failure	24/108 (22.2%)	4/40 (10.0%)	.08
Thrombosis	7	1	
Duodenal perforation/ bleeding	2	0	
Pancreatitis	1	0	
Recurrent diabetes	2	0	
Rejection	12	3	
Kidney graft failure	8/88 (9.1%)	1/31 (3.2%)	.44
Thrombosis	0	0	
Primary nonfunction	1	0	
Rejection	7	1	

Abbreviations: MD, marginal donor; GVHD, graft-versus-host disease.

among the 108 cases in the MD group, and 4 pancreas grafts were lost in the 40 cases in the non-MD group (Table 3). The incidence of the pancreas graft failure in the MD group tended to be higher than the non-MD group ($P = .08$, Table 3). Especially, thrombosis and rejection were frequently observed as a cause of the graft failure in the MD group. Pancreas graft survival in all the 148 cases was 84.8%, 76.4%, and 68.9% at 1, 3, and 5 years, respectively. Pancreas graft survival in the MD group and the non-MD group was 80.9% and 92.5%, 73.2% and 85.2%, and 66.0% and 77.4% at 1, 3, and 5 years post-PTx, respectively, and there was no significant difference between the 2 groups ($P = .35$, Fig 1B). Incidence of kidney graft failure in 119 SPK cases was also compared. The incidence was not significantly different between the 2 groups ($P = .44$, Table 3). Kidney graft survival in the SPK cases was 84.8%, 76.4%, and 68.9% at 1, 3, and 5 years, respectively. Kidney graft survival of the MD group (1, 3, 5 years: 89.1%, 89.1%, 86.0%) was not significantly different from that of the non-MD group (1, 3, 5 years: 93.5%, 93.5%, 84.2%; $P = .77$, Fig 1C).

DISCUSSION

The present study first showed that MD has been mostly utilized for PTx in Japan, compared with the condition of PTx donors in the United States [2,3]. However, the patient survival and graft survival were not significantly different from that in the United States. In case of simultaneous liver harvest in Japan, the reconstruction of gastroduodenal artery in pancreas graft has been done as much as possible (71.3%) to increase the blood flow in pancreas head region [5]. It remains unknown whether this procedure will have an effect on the early graft outcome.

The present study also demonstrated that there are no statistically significant differences in long-term outcomes after PTx between the MD group and the non-MD group. Furthermore, we investigated risk factors for the early loss of pancreatic graft and found that the marginality (MD vs non-MD) is not statistically significantly correlated with the early loss. These findings suggested the possibility that PTx from MDs is feasible in terms of postoperative outcomes. We also showed that the incidence of the early pancreatic graft loss within 3 months posttransplant is significantly increased when TCIT is over 12 hours. On the other hand, in the United States, it has been reported that preservation time of pancreatic graft >20 hours is significantly associated with post-PTx complications [6,7]. In this regard, a permissive range of the preservation time is likely to be narrow in Japan as compared to the United States where non-MDs are mostly available.

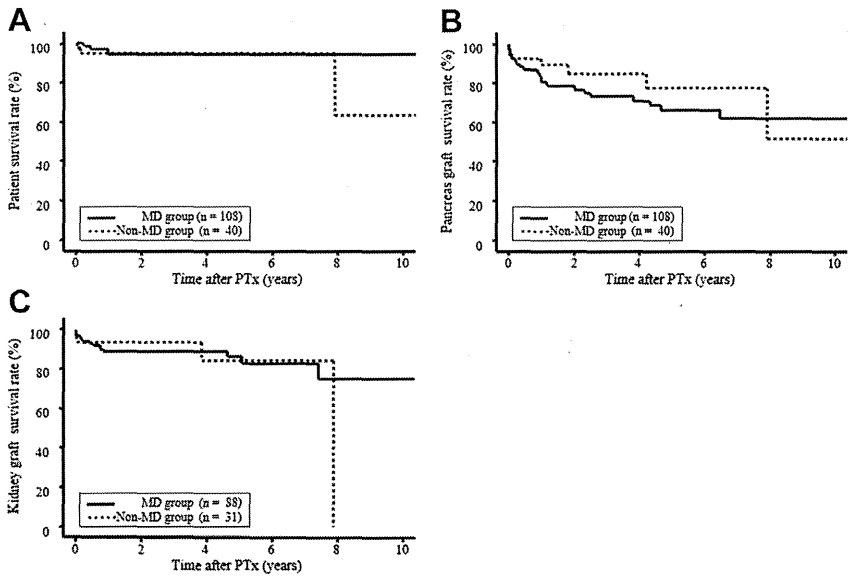

Fig 1. Long-term outcome after pancreas transplantation. Overall patient survival (**A**), pancreas graft survival (**B**), and kidney graft survival (**C**) were compared between the MD group (solid lines) and the non-MD group (dotted lines). Overall patient survival and pancreas graft survival were calculated in all the 148 PTx cases, and kidney graft survival was calculated in 119 simultaneous pancreas and kidney transplantation cases. Survival was not significantly different between the 2 groups. MD, marginal donor; PTx, pancreas transplantation.

In addition to the preservation time of the graft, to date, many donor-related risk factors have been considered as key determinants of outcomes after PTx such as donor age, obesity, donation after cardiac death, and cause of death. Especially, donor age is one of the most common risk factors. In general, aging affects nearly all the kinds of cells that play roles in outcomes of PTx including insulin-producing islet cells and endothelial cells of blood vessels, potentially affecting formation of thrombus. Salvalaggio et al reported from the United States data that old donors (>45 years) result in poorer long-term outcome in comparison to younger donors [8]. European data suggest equivalent outcomes [9]. Furthermore, donor age has been recognized as one of the factors composing scoring index for assessment of donor risk [10,11].

Indeed, the results of the present study may help expand the donor pool and resolve the donor shortage by using pancreas from MD. However, based on these previous reports, there seems to be another possibility that the current study enrolled too few cases to find statistically significant differences in post-PTx outcomes between the MD group and the non-MD group. Actually, the incidence of the pancreas graft failure in the MD group tended to be higher than the non-MD group, though the difference of the incidence was not statistically significant. To allow any conclusion on whether usage of grafts from MD is an acceptable option at PTx, studies with larger PTx numbers will be needed. If the outcome of PTx from MDs is judged to be worse than those from non-MDs, further investigations may be also necessary to clarify factors that contribute to better outcomes in MDs.

In summary, the current study suggested that PTx from MDs is feasible in terms of postoperative outcomes based on data obtained so far from a nationwide database in Japan. At the same time, considering the small number of PTx in Japan compared to other countries, the finding should be validated in studies with a larger number of PTx cases.

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ORIGINAL ARTICLE

Outcomes of living donor liver transplantation for hepatitis C virus-positive recipients in Japan: results of a nationwide survey

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Keywords
hepatitis C virus, living donor liver transplantation, nationwide survey.

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Summary

A nationwide survey of living donor liver transplantation (LDLT) for hepatitis C virus (HCV)-positive recipients was performed in Japan. A total of 514 recipients are reported and included in the study. The cumulative patient survival rate at 5 and 10 years was 72% and 63%, respectively. Of the 514 recipients, 142 patients (28%) died until the end of the observation, among which the leading cause was recurrent hepatitis C (42 cases). According to Cox regression multivariate analysis, donor age (>40), non-right liver graft, acute rejection episode, and absence of a sustained virologic response were independent prognostic factors. Of the 514 recipients, 361 underwent antiviral treatment mainly with pegylated-interferon and ribavirin (preemptive treatment in 150 patients and treatment for confirmed recurrent hepatitis in 211). The dose reduction rate and discontinuation rate were 40% and 42%, respectively, with a sustained virologic response rate of 43%. In conclusion, patient survival of HCV-positive recipients after LDLT was good, with a 10-year survival of 63%. Right liver graft might be preferable for HCV-positive recipients in an LDLT setting.

Introduction

End-stage liver disease caused by chronic hepatitis C virus (HCV) infection is the leading cause of liver transplantation in Western countries [1,2] and Japan [3]. Liver transplantation, including deceased donor liver transplantation (DDLT) and living donor liver transplantation (LDLT), is an established treatment for these patients, although it unfortunately does not cure HCV-infected recipients. Reinfection by HCV occurs universally and the progression of recurrent hepatitis C in the graft is accelerated compared with chronic hepatitis C infection in the nontransplant population, resulting in the impaired outcome of HCV-positive recipients compared with those with other indications [4–6]. Recently, effective antiviral therapies with new protease inhibitors have been aggressively investigated [7]; however, post-transplant antiviral treatment with pegylated-interferon (PEG-INF) and ribavirin (RBV) has been the main strategy to improve the outcome in both DDLT and LDLT [8] in our study period. While patient survival is significantly improved by achieving a sustained virologic response (SVR) with antiviral treatment among patients with chronic hepatitis C [9], the efficacy of antiviral treatment varies among HCV-positive liver transplant recipients [10].

Here, we conducted a nationwide survey of LDLT for HCV-positive patients and investigated the outcome and prognostic factors for patient survival to further improve the LDLT outcome. We also provide an overview of the antiviral treatment for LDLT recipients in Japan.

Patients and methods

Liver transplantations performed between 1998 and 2012 were collected and reviewed, and the initial LDLT was the subject of this study. The survey was conducted by the Research Group on Hepatitis under the aegis of the Japanese Ministry of Health, Welfare, and Labor. The indication of LDLT for HCV-positive recipients in Japan is similar to that for deceased donor liver transplantation (DDLT) in Western countries [11]. As for cases with hepatocellular carcinoma (HCC), Milan criteria are basically used; however, all institutions apply center-specific extended criteria for those beyond Milan provided that they are without extrahepatic lesions and macroscopic vascular invasions [12]. Data of all consecutive HCV-positive cases were enrolled in the study during this period, completing questionnaire items on computerized database by each institution. A total of 514 HCV-positive recipients from 12 institutions were enrolled in the present retrospective analysis. We first analyzed patient outcome and investigated the factors associated with poor survival among the collected variables. Next, we administered a survey regarding antiviral treatment after LDLT in Japan.

Evaluated variables

The following variables were obtained from the nationwide survey. As for recipient factors, patient age, sex, the existence of pretransplant antiviral treatment, HCV genotype, model for end-stage liver disease (MELD) score, the coexistence of hepatocellular carcinoma, the type of calcineurin inhibitor, use of mycophenolate mofetil (MMF), existence of steroid withdrawal, existence of steroid bolus treatment, splenectomized or not, episodes of acute rejection, existence of the post-transplant antiviral treatment, and achievement of SVR were collected. The diagnosis of acute rejection was based on internationally accepted histologic criteria (Banff guidelines) based on liver biopsies, which was treated with steroid bolus injection initially in the majority of center. The second-line treatments were center dependent, such as 1500–3000 mg of MMF or basiliximab, an interleukin-2 receptor antagonist. Additionally, donor age and the type of partial liver graft were added as variables. The number of LDLT cases per year at each center was also incorporated as a variable, with a cutoff value of 20 cases per year. All these factors were completely fulfilled by each center and assessed for their association with patient outcome. Other incomplete variables which may have a possible association with patient survival, such as IL-28 gene polymorphisms, histological findings, biliary complications, and cytomegalovirus infection, were not incorporated into the analysis.

We then surveyed post-LDLT antiviral treatment. The timing of the antiviral treatment (preemptive or after confirmation of recurrent disease), the antiviral treatment regimen used, time from LDLT to starting antiviral therapy, duration of antiviral therapy, adherence to the treatment, dose reduction rate, and finally the SVR rate were summarized.

Statistical analysis

Continuous variables are reported as medians and ranges, and categorical variables are reported as numbers (proportions). Cumulative survival is presented with Kaplan–Meier curves, and differences in survival between the groups were analyzed with a log-rank test. Factors associated with survival in the log-rank test were then analyzed using a Cox regression analysis. Five patients were lost to follow up during the observation period, and they were censored in the survival analysis. The cutoff value for the continuous variables was basically set according to each mean value, except for the recipient age for which it was set at 60 (mean value of 57) based on literatures. All statistical tests were two-sided, and a P-value of <0.05 was considered significant. The statistical analyses were performed with SPSS statistical software (Chicago, IL, USA) 18.0 for Windows.

Table 1. Characteristics of living donor liver transplantations for HCV-positive recipients in Japan.

	Total n = 514 (%)
Age (years)	57 (19–73)
Gender: male/female	320 (62)/194 (38)
Body mass index	25 (16–41)
Pretransplant antiviral treatment: yes/no	230 (45)/284 (55)
HCV genotype: 1b/other types	404 (79)/110 (21)
Co-existence of HCC: yes/no	330 (64)/184 (36)
MELD score	15 (4–47)
Transplant at the center with LDLT cases over 20 per year: yes/no	259 (50)/255 (50)
Calcineurin inhibitor: Tac/CsA	324 (63)/198 (37)
Mycophenolate mofetil yes/no	251 (49)/ 263 (51)
Steroid withdrawal: yes/no	144 (28)/370 (72)
Splenectomy: yes/no	284 (55)/230 (45)
Episode of acute rejection: yes/no	127 (25)/387 (75)
Steroid bolus injection: yes/no	414 (81)/100 (19)
Post-transplant antiviral treatment: yes/no	361 (71)/153 (29)
Achievement of SVR: yes/no	154 (30)/360 (70)
Donor age (years)	35 (17–66)
Type of graft: right/non-right	259 (50)/255 (50)

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

Results

Patient characteristics

The characteristics of 514 HCV-positive recipients are summarized in Table 1. There were 320 men and 194 women, with a median age of 57 years (range = 19–73). The median follow-up period was 3.5 years (range = 0.4–13), with a wide spectrum of follow-up duration due to death or shorter observation period from LDLT. The median MELD score was 14.7 (range = 4–47). HCV genotype was 1b in 405 patients (79%). The median age of the living donors was 35 years (range = 17–66), and the graft type was right liver in 259 cases (50%), left liver in 239 cases (46%), and the right lateral sector in 16 cases (4%).

Patient survival

The cumulative patient survival rate at 1, 3, 5, and 10 years was 86%, 76%, 72%, and 63%, respectively (Fig. 1). The causes of patient loss are summarized in Table 2. A total of 142 patients died until the end of the observation. Patient loss due to recurrent hepatitis, which was the leading cause of recipient death in this cohort, occurred in 42 cases, corresponding to 3% of all cases and 30% of lost cases, respectively. Hepatocellular carcinoma recurrence and sepsis were second, with 22 cases each. Additionally, the number of patient death was presented among two groups stratified by the achievement of SVR.

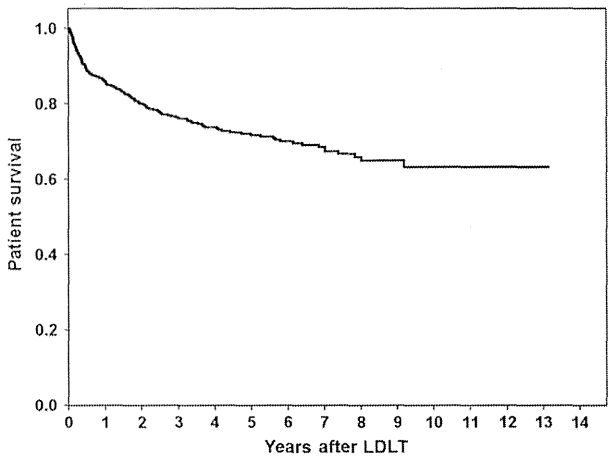

Figure 1 Kaplan–Meier survival curve of the cohort. LDLT, living donor liver transplantation.

Prognostic factors associated with patient survival after LDLT

Recipient and donor factors were analyzed for overall mortality. The results of univariate and multivariate analyses are shown in Table 3. Univariate analysis by the log-rank test revealed that donor age (>40 years; $P < 0.001$), non-right liver graft ($P = 0.036$), an episode of acute rejection ($P < 0.001$), steroid bolus injection ($P < 0.001$), and the absence of SVR ($P < 0.001$) were significant predictors of a poorer outcome of HCV-positive recipients. The Kaplan–Meier survival curves stratified by these factors are presented in Fig. 2. According to Cox regression multivariate analysis, donor age (>40), non-right liver graft, an acute rejection episode, and the absence of SVR were independent prognostic factors (Table 3).

Additionally, we did the same analysis among those achieved SVR after antiviral treatment (n = 154), in which no factor was revealed to be associated with the patient survival (Table 4).

Antiviral treatment after LDLT

Of the 514 recipients, while 153 patients have never undergone antiviral treatment including five patients achieving preoperative SVR, 361 underwent antiviral treatment. Of those, 211 patients (58%) received antiviral treatment after confirmation of recurrent hepatitis C, while the remaining 150 recipients received antiviral treatment preemptively. The summary of the antiviral treatment is shown in Table 5. Time from LDLT to beginning treatment was

Table 2. Causes of patient death.

Patient group	All patients (n = 514) n (%)	With SVR (n = 154) n (%)	Without SVR (n = 360) n (%)
Recurrent HCV	42 (30)	0	42 (37)
Recurrent HCC	22 (15)	8 (30)	14 (12)
Infection	22 (15)	4 (15)	18 (16)
Cerebrovascular diseases	12 (8)	4 (15)	8 (7)
Rejection	8 (6)	0	8 (7)
Graft thrombosis	7 (5)	0	7 (6)
Small for size syndrome	6 (4)	0	6 (5)
Other causes	23 (17)	11 (40)	12 (10)
Total	142	27	115

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

rather short (median: 3 months), whereas the treatment duration was long (median: 17 months), the rate of dose reduction (40%) and discontinuation (42%) were high, and the SVR rate was 43%.

Discussion

This is the largest series of LDLT for HCV-positive recipients reported to date. A total of 514 recipients from 12 Japanese institutions were enrolled and reviewed, with 5- and 10-year cumulative patient survival rates of 72% and 63%, respectively. A recent article from the United Network for Organ Sharing (UNOS) database in the United States of America (USA) reported patient survival rates of 76% and 71% at 5 and 10 years, respectively, among 15 147 HCV-positive DDLT recipients [1]. Similarly, the European Liver Transplant Registry reported 5- and 10-year patient survival rates of 65% and 53%, respectively, among 10 753 HCV-positive DDLT recipients [2]. Based on these reports, the present outcomes of the Japanese nationwide survey of LDLT for HCV-positive recipients are comparable with those of deceased donor whole liver transplantation (DDLT) in both the USA and Europe. However, caution should be paid in comparing the survival results of HCV-positive recipients between LDLT and DDLT. As shown in previous reports [13,14], laboratory MELD score of HCV-positive recipients was higher in DDLT recipients than that in LDLT recipients. Actually, our result, mean MELD score of 15 (median: 14.7, range: 4–47) was lower than that reported in DDLT recipients in Western countries (around 20), which might have a positive impact on patient survival in our study. Another point which should be noted is that the observation period of database of USA and Europe was longer than that of Japan, which might result in the bias of the improvement in techniques and managements in liver transplant.

Table 3. Factors associated with patient survival after living donor liver transplantation for HCV-positive recipients.

Univariate analysis	Hazard ratio (95% confidence interval)	P-value
Recipient age: ≥60 years vs. <60 years	1.322 (0.915–1.876)	0.122
Recipient gender: male versus female	1.072 (0.765–1.432)	0.682
Body mass index: ≥25 vs. <25	0.999 (0.64–1.559)	0.995
Pretransplant antiviral treatment: yes versus no	0.921 (0.721–1.387)	0.912
HCV genotype: 1b versus other types	1.211 (0.781–1.901)	0.723
Co-existence of HCC: yes versus no	0.893 (0.612–1.223)	0.754
MELD score: ≥15 vs. <15	1.125 (0.878–1.389)	0.801
LDLT cases per year: ≥20 vs. <20	1.122 (0.669–1.881)	0.663
Calcineurin inhibitor: Tac versus CyA	0.887 (0.643–1.511)	0.789
Mycophenolate mofetil: yes versus no	0.963 (0.642–1.446)	0.857
Steroid withdrawal: yes versus no	1.003 (0.761–1.621)	0.932
Splenectomy: yes versus no	0.961 (0.623–1.367)	0.889
Episode of acute rejection: yes versus no	3.101 (2.013–5.871)	<0.001
Steroid bolus injection: yes versus no	2.512 (1.541–3.512)	0.003
Achievement of SVR: yes versus no	0.167 (0.121–0.254)	<0.001
Donor age: ≥40 years vs. <40 years	2.231 (1.401–3.331)	<0.001
Type of graft: right liver versus non-right liver	0.422 (0.311–0.711)	0.029
Multivariate analysis		
Episode of acute rejection: yes versus no	3.241 (1.789–5.329)	<0.001
Achievement of SVR: yes versus no	0.181 (0.124–0.301)	<0.001
Donor age: ≥40 years vs. <40 years	2.311 (1.498–3.311)	<0.001
Type of graft: right liver versus non-right liver	0.467 (0.331–0.621)	0.001

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

The present analysis of prognostic factors for impaired patient survival revealed four variables as independent predictors: donor age over 40 years, an acute rejection episode, absence of SVR, and a non-right liver graft. In contrast to the report from USA [13], the center experience did not affect the outcome of patient outcome.

The impact of donor age on outcome has gained increased attention in the DDLT setting due to the

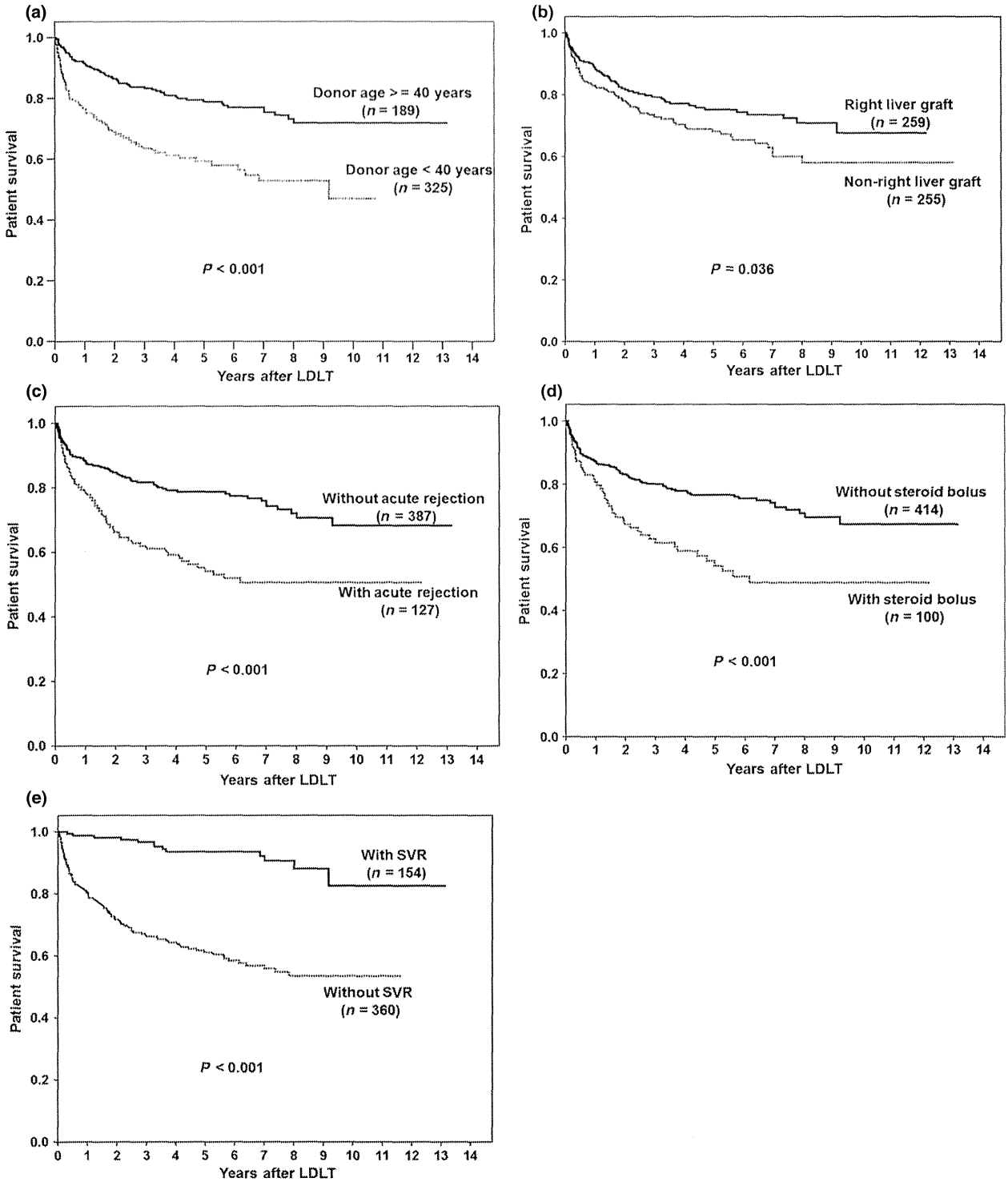

Figure 2 Kaplan–Meier curves stratified by each variable: (a) donor age, (b) graft type, (c) acute rejection, (d) steroid bolus, and (e) sustained virologic response. LDLT, living donor liver transplantation; SVR, sustained virologic response.

increased use of liver grafts from older donors. For HCV-positive recipients, two large retrospective reports from the Scientific Registry of Transplant Recipients and UNOS databases reported that donor age over 40 is an independent predictor of patient death [15,16]. Other accumulating reports [14,17,18] indicate that the grafts from older

Table 4. Factors associated with patient survival among those achieved SVR (n = 154).

Cox regression analysis	Hazard ratio (95% confidence interval)	*P*-value
Recipient age: ≥60 years (n = 43) vs. <60 years (n = 111)	1.424 (0.318–2.385)	0.644
Recipient gender: male (n = 100) versus female (n = 54)	4.709 (0.918–24.161)	0.063
Pretransplant antiviral treatment: yes (n = 66) versus no (n = 88)	1.666 (0.350–7.931)	0.522
HCV genotype: 1b (n = 112) versus other types (n = 42)	0.873 (0.203–3.747)	0.855
Co-existence of HCC: yes (n = 54) versus no (n = 100)	0.728 (0.179–2.694)	0.635
MELD score: ≥15 (n = 54) vs. <15 (n = 98)	1.354 (0.578–3.204)	0.785
LDLT cases per year: ≥20 (n = 82) vs. <20 (n = 72)	1.054 (0.458–1.254)	0.854
Calcineurin inhibitor: Tac (n = 94) versus CyA (n = 60)	3.580 (0.736–17.421)	0.114
Mycophenolate mofetil: yes (n = 78) versus no (n = 76)	0.932 (0.456–1.884)	0.781
Steroid withdrawal: yes (n = 40) versus no (n = 114)	0.449 (0.096–2.102)	0.31
Splenectomy: yes (n = 59) versus no (n = 95)	1.402 (0.335–5.873)	0.644
Episode of acute rejection: yes (n = 34) versus no (n = 120)	1.854 (0.216–15.914)	0.574
Steroid bolus injection: yes (n = 26) versus no (n = 128)	0.16 (0.019–1.386)	0.096
Donor age: ≥40 years (n = 43) vs. <40 years (n = 111)	1.18 (0.296–4.698)	0.815
Type of graft: right liver (n = 80) versus non-right liver (n = 74)	2.799 (0.818–9.573)	0.101

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; Tac, tacrolimus; CsA, cyclosporine; SVR, sustained virologic response.

donors are at greater risk for disease progression and impaired graft/patient survival compared with those from younger donors. Our results are definitely consistent with these reports.

Acute rejection in conjunction with treatment with a steroid bolus is one of the most critical factors to address with respect to HCV recurrence. Historical studies [19,20] have demonstrated that steroid bolus for acute rejection in HCV-positive recipients accelerates the recurrence of hepatitis and decreases patient survival. A recent study reported that HCV-positive recipients who receive high-dose steroid treatment for acute rejection are at increased risk of severe recurrent hepatitis, in which older donor age and an episode of rejection are the two most important predictors of developing fibrosing cholestatic hepatitis [21]. Similarly, our study also revealed that both older donor age and acute rejection are independent predictors for impaired patient outcome among LDLT recipients.

Table 5. Summary of antiviral treatment.

	Total (n = 361)	Treatment for established recurrent hepatitis C (n = 211)	Preemptive treatment (n = 150)
Time since LDLT (months)	3 (0–102)	4 (0.5–102)	1 (0–68)
Treatment duration (months)	15 (0.3–99)	14 (0.3–99)	17 (0.3–55)
Regimen: PEG-INF alfa-2a/RBV	45 (12%)	33 (16%)	12 (8%)
PEG-INF alfa-2b/ RBV	223 (62%)	146 (69%)	77 (51%)
INF alfa-2b	93 (26%)	32 (15%)	61 (41%)
Dose reduction	143 (40%)	85 (40%)	58 (39%)
Discontinuation	150 (42%)	66 (31%)	84 (56%)
Sustained virologic response	154 (43%)	89 (42%)	65 (43%)

LDLT, living donor liver transplantation; PEG-INF, pegylated-interferon; RBV, ribavirin; INF, interferon.

The association between achieving SVR and graft/patient survival after liver transplantation for HCV-positive recipients is a matter of debate [10]. Many studies with standard dual treatment of PEG-INF/RBV for 12 months in a DDLT setting have implied a survival benefit of achieving SVR [8,22], but there has been no evidence to support the recommendation of antiviral treatment for recurrent graft hepatitis C due to the lack of clinical benefit with sufficient long-term observation and the existence of frequent severe adverse effects, as concluded by a recent Cochrane meta-analysis [10]. Recent retrospective cohort studies with a long follow-up duration reported improved patient/graft survival in patients who obtained an SVR after antiviral treatment [23–25]. In accordance with those reports, our retrospective analysis indicated a positive effect of achieving SVR on patient survival. Caution should be taken in interpreting our results; however, as SVR was assessed among the whole cohort, including patients who were not indicated for antiviral treatment, the follow-up period after achieving SVR was rather short, and most importantly, a large variety of antiviral treatment regimens were used in Japan, which will be described later.

A noteworthy finding in the present retrospective analysis is the impaired patient survival in recipients who received a non-right liver graft (left liver in 239 cases and right lateral sector in 16 cases). Recent studies comparing outcomes between LDLT and DDLT in HCV-positive recipients have reported equal or even improved outcomes both in patient/graft survival and in fibrosis progression in the LDLT setting, which could be attributed to the younger donor age and shorter ischemic time of LDLT grafts [13,14,26–29].

Based on these findings, LDLT for HCV-positive recipients is now widely accepted as an established alternative to DDLT, even in Western countries. On the contrary, however, the present finding may raise an alarm for reduced size grafts, as a left or posterior graft is clearly smaller than a right liver graft. Another point to be emphasized here is that all LDLTs investigated in the aforementioned studies comparing LDLT and DDLT were universally performed with right liver grafts. One possible explanation for the inferior outcome of the smaller graft is that the intense hepatocyte proliferation that occurs in smaller partial liver grafts may lead to increased viral translation and replication, as advocated by previous authors [30–32]. However, there are several limitations among these speculations. First, the data of the viral load, which is reported to reach a maximum level between the first and third post-transplant months [33], were not available in this study to demonstrate the higher viral replication in the smaller grafts during this period. Another is that the graft type selection is based on the ratio of the volume of the graft to recipient body weight or standard liver volume in our society, which will lead to the bias in the comparison of the right liver versus non-right liver graft. Despite these limitations, considering that comparable outcomes between left liver graft and right liver graft have been reported by us [34] and others [35] in LDLT recipients as a whole, caution should be taken in selecting the type of graft (left versus right) for HCV-positive recipients. Thus, future LDLT studies are required to investigate whether a smaller partial liver graft (left liver) is potentially inferior compared with a larger graft (right liver) in terms of graft/patient survival and recurrent hepatitis severity among HCV-positive recipients.

The antiviral treatment for recurrent hepatitis C after LDLT in Japan was also reviewed in the present study. As described elsewhere in detail [11], the antiviral treatment regimen in Japan differs widely from center to center; preemptive treatment versus treatment after confirmation of recurrent disease, starting dose and method of escalation, and the duration of treatment (usually longer than 12 months). Consequently, our data only present an overview of antiviral treatment in Japan, and no definite conclusion can be drawn regarding the actual efficacy of antiviral treatment after LDLT. Moreover, based on the recent prospective, multicenter, randomized study by Bzowej *et al.* [36], European and USA transplant societies do not support the routine use of preemptive antiviral therapy. A review of Western literature regarding the standard 12-month PEG-INF/RBV treatment for established recurrent hepatitis C after DDLT reveals that the median SVR rate is 33% (0–56%) with a dose reduction rate of 70% and a discontinuation rate of 30% [37]. The present result of an SVR rate of 43% with a dose reduction rate of 40% and a discontinuation rate of 42% seems not so different from those of previous literatures; however, as discussed above, the diversity in the methods, the doses, and the duration of treatment in Japan preclude the direct comparison with Western findings.

Conclusion

This retrospective analysis of the largest series of LDLT for HCV-positive recipients in Japan revealed 5- and 10-year survival rates of 72% and 63%, respectively, and that donor age (>40), non-right liver graft, an acute rejection episode, and the absence of SVR are independent predictors of patient survival. Based on the present result, caution should be made in the selection of the left liver graft for HCV-positive recipients; however, the development of more effective antiviral treatment in the near future may facilitate the application of the left liver graft.

Authorship

YM: designed the study. TI: collected data. NA, YS, NK, SE, TF, HO, HN, AT, YK, MS, YK, KY, KS, MM and MT: performed the study. NA and YS: analyzed and wrote the paper.

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