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Impact of Human T Cell Leukemia Virus Type 1 in Living Donor Liver Transplantation

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Human T cell leukemia virus type 1 (HTLV-1) is an endemic retrovirus in southwestern Japan, which causes adult T cell leukemia (ATL) or HTLV-1 associated myelopathy in a minority of carriers. Here, we investigated the impact of HTLV-1 status in living donor liver transplantation (LDLT). Twenty-six of 329 (7.9%) HTLV-1 carriers underwent primary LDLT. One recipient negative for HTLV-1 before LDLT received a graft from an HTLV-1 positive donor. Eight donors were HTLV-1 positive. Twenty-seven recipients (13 male and 14 female; mean age 52.5 years) were reviewed retrospectively. ATL developed in four recipients who ultimately died. The intervals between LDLT and ATL development ranged from 181 to 1315 days. Of the four ATL recipients, two received grafts from HTLV-1 positive donors and two from negative donors. The 1-, 3- and 5-year HTLV-1 carrier survival rates were 91.3%, 78.3% and 66.3%, respectively. Fulminant hepatic failure as a pretransplant diagnosis and a pretransplant MELD score ≥ 15 was identified as risk factors for ATL development in this study ($p = 0.001$ and $p = 0.041$, respectively). In conclusion, LDLT can be performed for HTLV-1 positive recipients. However, when fulminant hepatic failure is diagnosed, LDLT should not be performed until further studies have revealed the mechanisms of ATL development.

Key words: ATL, living donor liver transplantation, HTLV-1

Abbreviations: ATL, adult T cell leukemia; DM, diabetes mellitus; GW, graft weight; HAM, human T cell leukemia virus type-1 associated myelopathy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HGF, hepatocyte growth factor, HIV, human immunodeficiency virus; HTLV-1, human T cell leukemia virus type-1; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, model for end-stage liver disease; SLW, standard liver weight.

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Introduction

Human T cell leukemia virus type 1 (HTLV-1) is a retrovirus endemic in southwestern Japan, West Africa, the Caribbean, South America and the Middle East (1,2). HTLV-1 is vertically transmitted from mothers to infants and the virus is maintained within the infant's family (3). The virus is vertically transmitted from generation to generation in this way. Other routes of transmission include contact with blood, blood products and sexual contact. Although most carriers remain asymptomatic, a minority develop adult T cell leukemia (ATL) or HTLV-1 associated myelopathy (HAM). It is unknown why ATL or HAM is a late-onset disease and only develops in a very small minority of HTLV-1 infected people. Only 5% of HTLV-1 carriers in Japan develop ATL (2). Recipients or donors of organ transplantation may be HTLV-1 carriers in endemic areas, such as Japan. HTLV-1 infected recipients who are concurrently treated with immunosuppressive drugs following organ or bone marrow transplantations, might exhibit an accelerated or altered developmental course of HTLV-1 associated diseases (2,4). Some case reports have described donor-derived transmission of HTLV-1 after organ transplantation (5), but in renal transplant recipients with positive pretransplant HTLV-1 serology, no definitive development of more rapid HTLV-1-related disease has been reported (6). We previously reported three cases of ATL that developed in HTLV-1 carrier recipients after living donor liver transplantation (LDLT) (7). Since this report, more LDLT for HTLV-1 carriers have been performed, thus generating a larger cohort. Therefore, the aim of this study was to clarify the impact of HTLV-1 status in LDLT.

Patients and Methods

Recipients

Between May 1997 and March 2011, 329 adult patients (167 females and 162 males) underwent primary LDLT at Kyushu University Hospital. Twenty-six patients (7.9%) were HTLV-I positive (+). Furthermore, one recipient who was HTLV-1 negative (–) before LDLT received a graft from an HTLV-1 (+)

donor after fully informed consent. In total, 27 recipients were reviewed retrospectively. The primary diagnosis for transplantation was as follows: hepatitis C virus (HCV) in 12 recipients (11 had hepatocellular carcinoma, HCC), fulminant hepatic failure (FHF) in six recipients, hepatitis B virus (HBV) in two recipients (both had HCC), autoimmune hepatitis in two recipients, cryptogenic in two recipients (one had HCC), primary biliary cirrhosis in one recipient, alcohol abuse in one recipient and biliary atresia in one recipient (Table 1). Our selection criteria for performing LDLT were as follows: (1) no modality except LDLT was available to cure the recipients, and (2) no other organ dysfunction was present. There was no restriction on the HTLV-1 status of the recipient.

Donor and graft selection

Donors were selected from candidates who volunteered to be living donors (8,9). They were required to be within a third degree of consanguinity with recipients or spouses, and were aged between 20 and 65 years old. For a donor outside of the third degree of consanguinity with the recipient, individual approval was obtained from the Ethics Committee of Kyushu University Hospital. Good Samaritan donation was not used. HBV or human immunodeficiency virus (HIV) carriers were prohibited from being living donors; however, there was no restriction on the status of HTLV-1 carriers. Three-dimensional CT was introduced for volumetric analysis and delineation of vascular anatomy. The standard liver weight (SLW) of recipients was calculated according to the formula of Urata (10). Graft weight (GW) was predicted by CT volumetric analysis. Decisions about the graft types for the recipients were based upon the preoperatively predicted GW to SLW (GW-SLW) ratio. A left lobe graft was used when the preoperatively predicted GW-SLW ratio was more than 35%.

Postoperative management

The graft retrieval technique, recipient surgery and perioperative management of the recipients, including immunosuppression regimens have been described elsewhere (8–10). Immunosuppression was initiated using a protocol based on either tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) or cyclosporine A (Neoral; Novartis Pharma K.K., Tokyo, Japan) with steroid and/or mycophenolate mofetil (MMF; Chugai Pharmaceutical Co. Ltd., Tokyo, Japan). Tacrolimus was used in 17 recipients, and cyclosporine in 10 recipients. A target trough of tacrolimus was set at 10 ng/mL for 3 months after LDLT, followed by 5–10 ng/mL thereafter. A target trough level of cyclosporine A was set at 250 ng/ml for 3 months after LDLT, followed by 150–200 ng/mL thereafter. Methylprednisolone was initiated on the day of LDLT, tapered and converted to prednisolone 7 days after LDLT. Prednisolone treatment was tapered and discontinued 6 months after LDLT. MMF was used in 17 recipients and was started at 1000 mg/day on the day after LDLT, tapered and discontinued until 6 months after LDLT. A trough level was not measured for MMF. Fifteen grafts were ABO identical, 12 were compatible and 1 was incompatible. Rituximab was not used in the recipient who received an ABO incompatible graft.

All recipients had monthly follow-ups. The mean follow-up period was 1534 days, with 441 days and 2447 days as the 25th and 75th percentiles, respectively. Recipient survival was defined as the time period between LDLT and recipient death.

Factors associated with ATL development after LDLT

A univariate analysis using the Fisher's exact test was performed to identify risk factors associated with ATL development after LDLT for 27 recipients. Variables that were used for the analysis included recipient age, recipient sex, primary diagnosis, presence of pretransplant diabetes mellitus (DM), pretransplant model for end-stage liver disease (MELD) score, GW-SLW ratio, donor age and sex, HTLV-1 status of the donor, ABO blood type, the presence of consanguinity between donor and recipient and immunosuppressive drugs.

Statistical analysis

Recipient survival rates or ATL development rates were calculated by the Kaplan–Meier product-limited method. Recipients were censored on the day of death when a recipient died from disease other than ATL, in order to calculate the ATL development rate. Data are expressed as mean values. All statistical analyses were performed using Stat View 5.0 software (SAS Institute, Inc., Cary, NC, USA). A p value of < 0.05 was considered significant.

Results

There were 13 male and 14 female recipients with a mean age of 52.5 years (range, 25–69). The mean MELD score was 14.6 (range, 4–26). The grafts used were as follows: fifteen of left lobe with caudate lobe graft; 2 of left lobe graft; 9 of right lobe without middle hepatic vein graft and 1 with dual grafts from the recipient's wife and son (11). The mean GW-SLW ratio was 42.3 (range, 23.6–57.1). Eighteen donors were male and nine were female with a mean age of 35.0 years (range, 20–56). Eight of 28 donors were HTLV-1 (+). The clinical courses of these eight donors were not eventful after hepatectomy. The mean hospital stay after donor surgery was 11 days (data not shown). No donors developed ATL after the surgery. The characteristics of the present recipients and donors at LDLT are shown in Table 1.

ATL developed in four recipients (recipients #1, 2, 10 and 12 in Table 1). The interval between LDLT and ATL development was 181, 823, 291 and 1315 days, respectively. Two of the ATL recipients received grafts from HTLV-1 carriers and two from noncarriers (Table 1). Fluorescent *in situ* hybridization revealed that the development of ATL in two of the recipients was due to recipient HTLV-1 (7).

The 1-, 3- and 5-year ATL development rates were 9.3%, 14.4% and 20.1%, respectively (Figure 1). Three recipients died because of ATL despite chemotherapy (recipient #1, 10, 12). One ATL recipient died of chronic rejection because of the withdrawal of calcineurin inhibitor (#2). The interval between ATL development and recipient death was 15 days (recipient #1), 15 months (#2), 5 months (#10) and 27 months (#12), respectively. The 1-, 3- and 5-year HTLV-1 (+) recipient survival rates were 91.3%, 78.3% and 66.3%, respectively (Figure 1). Other causes of death were HCC recurrence in three recipients, posttransplant lymphoproliferative disorder in the brain (PTLD) in one recipient and suicide in one recipient (Table 1). The survival rates of the HTLV-1 (+) recipients were not significantly different from those of HTLV-1 (–) recipients (Figure 1).

Recipient #27, who was HTLV-1 (–) before LDLT had positive HTLV-1 proviral loads 7 days after LDLT, following the receipt of a graft from an HTLV-1 (+) donor. He received tacrolimus and steroid immunosuppressive medication. Figure 2 demonstrates his clinical course after LDLT. The virus titer did not disappear following its appearance after

Table 1: Characteristics of recipients and donors at LDLT, and outcome after LDLT

#	R-age	R-sex	R-HTLV1	Dx	MELD	CNI	D-age	D-sex	D-HTLV1	Graft	GW-SLW (%)	ABO	Relation to R	ATL	ST(yr)	Alive	COD
1	39	F	Y	FHF-unknown	23	TAC	46	M	Y	LL	35.1	I	Sibling	Y	0.53	N	ATL
2	45	M	Y	FHF-unknown	22	TAC	56	F	Y	LL	42.6	C	Sibling	Y	3.49	N	CR
3	38	F	Y	FHF-drug	17	TAC	38	F	Y	RL	56.8	I	Sibling	N	4.86	N	PTLD
4	42	F	Y	LC-C	4	CYA	22	M	Y	LL+C	34.6	I	Child	N	5.46	N	Sx
5	68	M	Y	LC-C	14	CYA	33	F	N	LL+C	31.9	I	Child	N	0.70	N	HCC
6	63	F	Y	LC-C	10	CYA	34	M	N	LL+C	40.1	I	Child	N	8.34	Y	
7	53	M	Y	LC-B	10	CYA	22	M	N	LL+C	35.8	I	Child	N	1.88	N	HCC
8	25	M	Y	BA	5	TAC	54	M	N	LL+C	47.1	C	Parent	N	7.65	Y	
9	50	F	Y	LC-B	16	TAC	47	M	N	RL	57.1	IC	Spouse	N	7.60	Y	
10	67	M	Y	FHF-B	22	TAC	34	M	N	RL	54.9	C	Child	Y	1.18	N	ATL
11	40	F	Y	PBC	19	TAC	49	M	Y	LL+C	34.5	I	Sibling	N	6.75	Y	
12	48	M	Y	FHF-B	25	CYA	20	M	N	RL	50.2	I	Child	Y	5.77	N	ATL
13	64	M	Y	LC-C	8	CYA	32	M	N	LL+C	51.6	C	Child	N	5.89	Y	
14	50	F	Y	LC-C	17	CYA	48	M	Y	LL+C	36.5	C	Sibling	N	4.98	Y	
15	47	F	Y	LC-C	19	TAC	20	F	N	LL+C	23.6	I	Child	N	2.53	N	HCC
16	52	M	Y	LC-C	15	CYA	25	F	N	RL	39.6	I	Child	N	4.79	Y	
17	51	M	Y	LC-C	11	TAC	42	F	N	Dual	31.0	C	Spouse	N	4.78	Y	
							21	M	N		23.0	C	Child				
18	50	F	Y	FHF-B	26	TAC	20	M	N	LL+C	39.9	C	Child	N	4.38	Y	
19	65	F	Y	AIH	12	TAC	35	F	N	LL+C	39.9	I	Child	N	4.30	Y	
20	58	M	Y	LC-C	4	TAC	26	M	N	LL+C	43.3	C	Child	N	4.07	Y	
21	65	F	Y	LC-C	14	TAC	36	M	N	LL+C	43.0	I	Child	N	3.72	Y	
22	49	F	Y	LC	18	TAC	27	F	N	RL	48.6	I	Child	N	2.80	Y	
23	58	M	Y	LC-C	14	CYA	20	M	N	RL	50.9	I	Child	N	0.40	Y	
24	62	F	Y	LC-C	10	CYA	30	M	Y	LL+C	36.9	I	Child	N	0.22	Y	
25	59	F	Y	AIH	16	TAC	42	F	N	RL	56.4	C	Niece	N	0.19	Y	
26	69	M	Y	LC	12	TAC	40	M	N	LL+C	34.9	C	Child	N	0.17	Y	
27	41	M	N	Alcohol	11	TAC	43	F	Y	RL	44.8	C	Sibling	N	6.32	Y	

Dx, diagnosis; FHF = fulminant hepatic failure; FHF-B = FHF due to HBV; LC-C = liver cirrhosis type C; LC-B = liver cirrhosis type B; AIH = autoimmune hepatitis; BA = biliary atresia; IS = immunosuppression; TAC = tacrolimus; CYA = cyclosporine A; MMF = mycophenolate mofetilLL; left lobe graft, LL+C; extended left lobe with caudate lobe graft, RL; right lobe graft, GW = graft weight, SLW = standard liver weight; ATL = ATL development; ST = survival time; ABO I = identical; ABO C = compatible; ABO IC = incompatible; COD = cause of death; Sx = suicide; CR = chronic rejection; PTLD = posttransplant lymphoproliferative disorder.
Patient 17 got dual grafts from two donors.

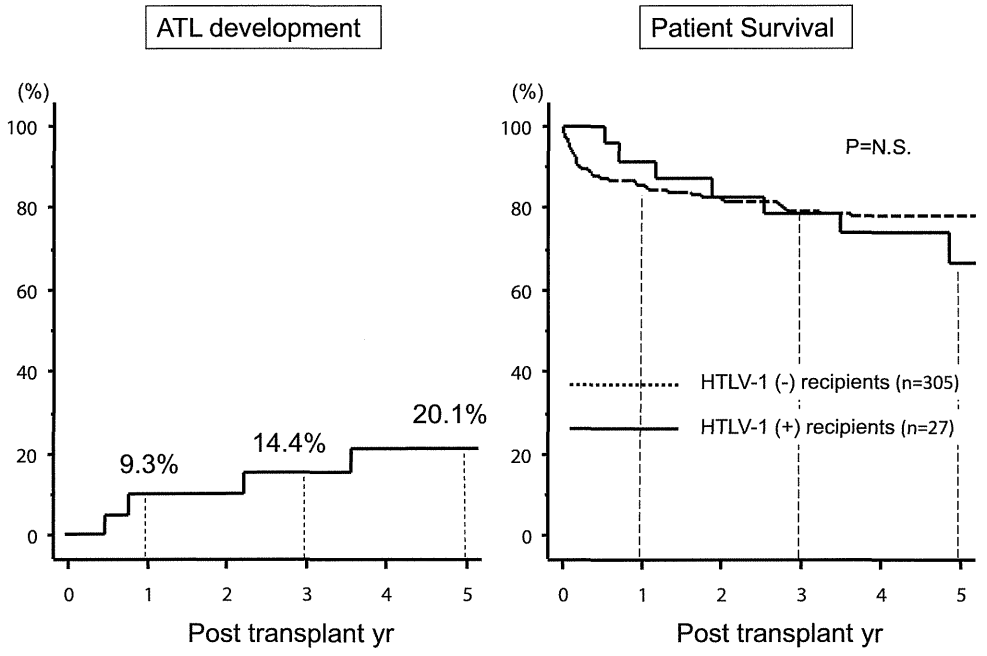

Figure 1: ATL development rate and recipient survival after LDLT. The 1-, 3- and 5-year ATL development rates were 9.3%, 14.4% and 20.1%, respectively. The 1-, 3-, and 5-year survival rates of the HTLV-1 (+) recipients were 91.3%, 78.3% and 66.3%, respectively. The survival rates of the HTLV-1 (+) recipients were not significantly different from those of HTLV-1 (−) recipients.

transplantation. Interestingly, no antibodies against HTLV-1 were detected, probably due to the immunosuppressive medication. ATL cells were not detected in the peripheral blood, and the recipient has since returned to work (Figure 2).

Univariate analysis revealed that fulminant hepatic failure as a pretransplant diagnosis and a pretransplant MELD score $\geq$ 15 were risk factors for ATL development in this study ($p = 0.001$ and $p = 0.041$, respectively) (Table 2). Other factors, including donor HTLV-1 status, were not risks for ATL development.

Discussion

Previously we have published three cases of ATL that developed in HTLV-1 carrier recipients after LDLT (7), and the current study represents an extension of this using a larger cohort. We observed that a primary diagnosis of fulminant hepatic failure was a risk factor for ATL development after LDLT. A pretransplant MELD score $\geq$ 15 was also a risk factor, but this was mediated by the fulminant hepatic failure diagnosis as all these recipients had a MELD score $\geq$ 15. In our previous report, we speculated that hepatocyte growth factor (HGF)-c-Met, the receptor of HGF, was present on ATL cells, and that signaling through this pathway might augment the proliferation of HTLV-1 infected cells (7). However, the duration from LDLT to ATL development was variable in our four cases. The longest case (recipient #12) took 1315 days after LDLT until ATL development, suggesting a mechanism other than HGF-c-Met signaling might be involved. Of eight HTLV-1 (+) donors, two underwent right hepatectomy and six left hepatectomy. It has been shown that HGF levels are elevated after hepatectomy or partial liver transplantation (12), yet no HTLV-1 (+) donor developed ATL after hepatectomy despite increased HGF levels, again suggesting that other mechanisms might be responsible for ATL development.

Zou et al. recently reported that in a mouse model of FHF, the number of natural killer (NK) cells in the liver was markedly increased, whereas the number of NK cells decreased significantly in peripheral blood, spleen, and bone marrow (13). NK cells directly mediate the cytolysis of cells harboring active HTLV-1 gene expression (14). The disruption of the localization of NK cells in FHF recipients might play a pivotal role in the pathogenesis of ATL development.

Activated Kupffer cells produce inflammatory cytokines, which can activate hepatic T cells, which in turn can induce phagocytosis and cytokine production in Kuppfer cells (15). These immunological events are crucial to protect the host from bacterial and viral infections. Patients with severe liver diseases often have an impaired immune system. Therefore, a defect in the host defense might lead to ATL development in the patients with a pretransplant MELD score $\geq$ 15.

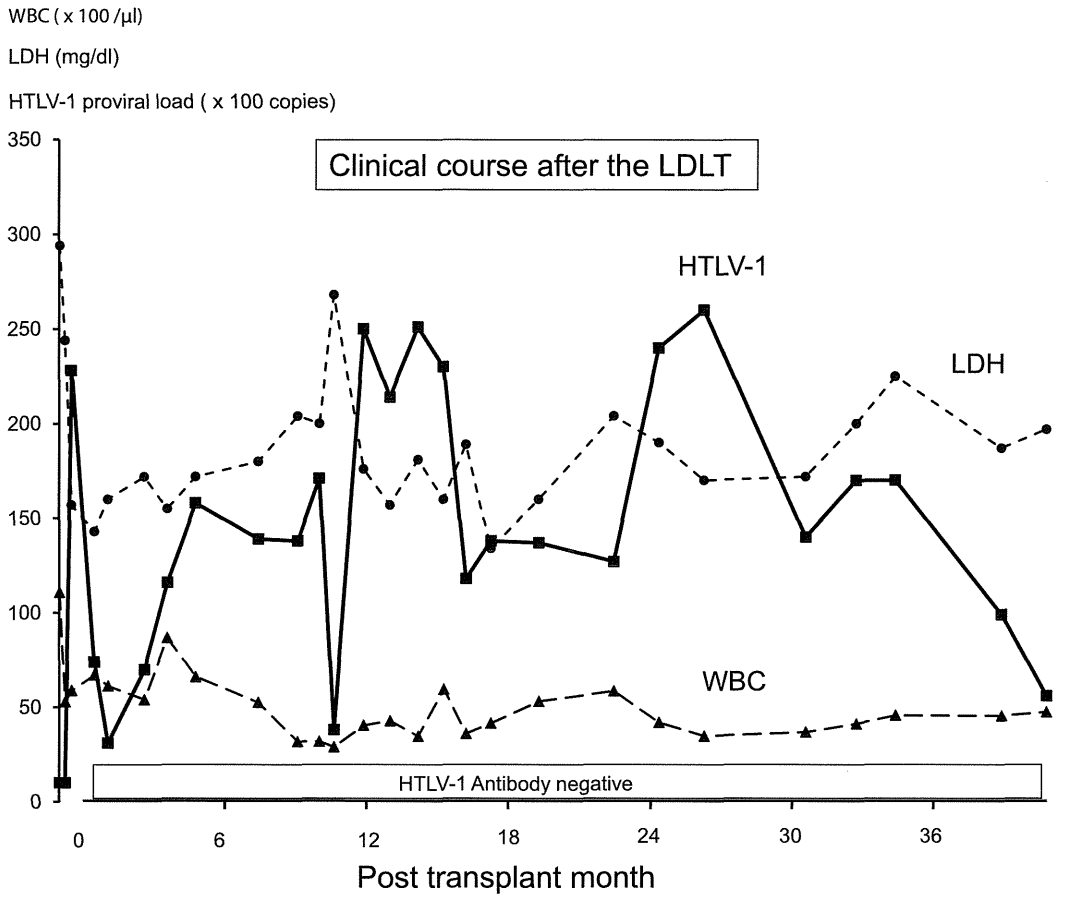

Figure 2: Postoperative course of a pretransplant HTLV-1 (−) recipient who received a graft from an HTLV-1 (+) donor. HTLV-1 proviral loads turned positive 7 days after LDLT and remained detectable. Interestingly, antibody titers against HTLV-1 remained negative. Checking the proviral load is necessary to diagnose the transmission of the virus. White blood cell (WBC) count and serum lactate dehydrogenase (LDH) levels returned to a normal range soon after LDLT and remained constant during the postoperative course.

One HTLV-1 (+) recipient died due to PTLD in the brain (#3). We initially suspected ATL in this case, due to a primary diagnosis of fulminant hepatic failure; however, no ATL cells were detected in the peripheral blood. It is notable that five of six HTLV-1 (+) LDLT recipients who had fulminant hepatic failure died.

Conventional chemotherapy is not established for acute-type ATL. Of three recipients (#2, 10, 12) that received chemotherapy, one recipient (#2) achieved complete remission. However, chronic rejection occurred due to withdrawal of calcineurin inhibitor treatment. A second recipient (#12) achieved partial remission after chemotherapy, but later died due to ATL recurrence 27 months after ATL onset.

However, the use of HTLV-1 positive donors is increasing due to the growing disparity between organ availability and demand. Recipients with an urgent need might be willing to accept an increased risk in HTLV-1-related disease transmission in order to undergo liver transplantation (LT). LT should be performed in selected recipients who agree to accept these risks in order to rapidly obtain a life-saving organ (2,16). Fully informed consent was given for the recipient and the donor where this occurred in our study (recipient #27). Fortunately, ATL or HAM has not developed in the recipient, although careful follow-up checks are still performed to identify the development of any HTLV-1 associated disease. It is of great interest that the presence of antibodies against HTLV-1 has not been detected in this recipient, who was HTLV-1 negative before the LDLT. Checking the proviral load is necessary to diagnose the transmission of the virus and to follow-up the recipient's condition (18), otherwise, it might have been assumed that the recipient was not infected with HTLV-1.

To reduce the risk of unintentional transmission of blood-borne pathogens including HTLV-1, HBV, HCV or HIV through organ transplantation, sensitive tests for both chronic and acute infections, namely, serology and

Table 2: Risk factors for ATL development: Univariate analysis

Variables		Rate of ATL development	p-Value
Recipient variables			
Age	≥ 60 years (n = 8)	12.5%	0.66
	< 60 years (n = 19)	15.8%	
Sex	Male (n = 13)	23.1%	0.33
	Female (n = 14)	7.1%	
Etiology	FHF (n = 6)	66.7%	0.001
	Others (n = 21)	0%	
MELD	≥ 15 (n = 13)	30.8%	0.041
	< 15 (n = 14)	0%	
Diabetes mellitus	Yes (n = 3)	0%	1.00
	No (n = 24)	16.7%	
Calcineurin inhibitor	TAC (n = 15)	20.0%	0.61
	CYA (n = 12)	8.3%	
Bile duct stenosis	Yes (n = 5)	40.0%	0.14
	No (n = 22)	9.1%	
Donor/graft variables			
Age	≥ 40 years (n = 11)	18.2%	1.00
	< 40 years (n = 16)	12.5%	
Graft	Left lobe (n = 17)	11.7%	0.61
	Right lobe (n = 10)	20.0%	
GW–SLW ratio (%)	< 40 (n = 13)	7.7%	0.60
	≥ 40 (n = 14)	21.4%	
Donor HTLV-1	Positive (n = 8)	25.0%	0.56
	Negative (n = 19)	10.5%	
Donor-recipient matching			
ABO identical	Yes (n = 15)	13.3%	1.00
	No (n = 12)	16.7%	
Consanguinity	No (n = 2)	0%	1.00
	Yes (n = 25)	16.0%	
Donor–recipient gender	Mismatch (n = 15)	13.3%	1.00
	Match (n = 12)	16.7%	

nucleic acid testing (NAT) should be performed. In the living donor organ transplantation setting, transplant centers should screen living donors for such pathogens as close to the time of organ recovery and transplantation as possible, using serology and NAT (19). Furthermore, clinicians should advise living donors during their evaluation, of their obligation to avoid behavior that would put them at risk for acquiring blood-borne pathogens before organ donation.

Recently, Haynes et al. reported an *in vivo* study where it was confirmed that cyclosporine A treatment before HTLV-1 infection enhanced early viral expression compared with untreated HTLV-1 infected rabbits, yet treatment 1 week after infection diminished HTLV-1 expression (20). They suggested that cyclosporine A treatment 1 week after infection disrupted viral spread, possibly by inhibiting viral-induced activation of target cells. This model mimics conditions observed in human transplant recipients. An HTLV-1 (+) recipient is exposed to the virus before immunosuppression. In contrast, an HTLV-1 (−) recipient who receives an HTLV-1 (+) donation is exposed to the virus and immunosuppressive drugs simultaneously. In this case, the acquired immune response to HTLV-1 is limited, allowing the elevation of proviral loads and development of HTLV-1-related disease. Blocking lymphocyte activation in target cells during the early phase of HTLV-1 spread by cyclosporine A may provide the opportunity for blocking the infection after exposure and may offer hope for therapeutic intervention (20).

It is known that specific HLA alleles, such as HLA-A26, -B40, -B48 and -DR09, determine susceptibility to ATL among HTLV-1 carriers. Carriers with such HLA alleles are permissive to HTLV-1 without any positive immune response and are predisposed to leukemogenesis (3, 21). Although eight recipients had HLA-A26 or -DR09 in this study, only two recipients developed ATL among them (data not shown). Thus, HLA alleles were not associated with ATL development after LDLT.

Twelve of 27 recipients had HCV in this study. Type-1 interferon can suppress viral expression in HTLV-1 infected T cells *in vitro* (22). The impact of interferon therapy, which was applied to 10 of 12 recipients, on ATL development is not apparent *in vivo*. Four of 10 recipients achieved sustained virological responses, four recipients were nonresponders, and two recipients are still receiving the therapy. No HTLV-1 related disease has occurred among them, which might be due to the interferon therapy.

In conclusion, HTLV-1 (+) recipients can undergo LDLT. However, when the primary diagnosis of HTLV-1 (+) recipients is fulminant hepatic failure, LDLT should not be performed until further study reveals the mechanism of ATL development.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Left Lobe Living Donor Liver Transplantation in Adults

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Adult left lobe (LL) living donor liver transplantation (LDLT) has not generally been recognized as a feasible procedure because of the problem of graft size. The objectives of this study were to assess the feasibility and short- and long-term results of adult LL LDLT in comparison with right lobe (RL) LDLT. Data on 200 consecutive LL LDLTs, including five retransplants, were retrospectively compared with those of 112 RL LDLTs, in terms of survival, complications and donor morbidity. The mean graft weight to standard volume ratio of LL grafts was 38.7% whereas that of RL grafts was 47.6% ($p < 0.0001$). The 1-, 5- and 10-year patient survival rates of LL LDLT were 85.6%, 77.9% and 69.5%, respectively, which were comparable to those of RL LDLT (89.8%, 71.3% and 70.7%, respectively). The incidence of small-for-size syndrome was higher in LL LDLT (19.5%) than in RL LDLT (7.1%) ($p < 0.01$). The overall donor morbidity rates were comparable between LL (36.0%) and RL (34.8%), whereas postoperative liver function tests and hospital stay were significantly better ($p < 0.0001$) in LL donors. In conclusion, adult LL LDLT has comparable outcomes to that of RL LDLT. LL LDLT is viable and is the first choice in adult LDLT.

Key words: Adult, left lobe graft, living donor transplantation, long-term graft survival, small-for-size graft

Abbreviations: GRWR, graft-to-recipient weight ratio; GV/SLV, graft volume-to-recipient standard liver volume; HPCS, hemiportocaval shunt; LDLT, living donor liver transplantation; LL, left lobe; MHV, middle hepatic vein; PCS, portocaval shunt; RL, right lobe; RPS, right posterior segment; SFSS, small-for-size syndrome.

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Introduction

Living donor liver transplantation (LDLT) in adults has been a legitimate and established procedure for the treatment of patients with end-stage liver disease especially in countries such as Japan and other Asian countries, where deceased donors are not often available. Makuuchi et al. (1) performed the first successful adult-to-adult LDLT using a left lobe (LL) graft in 1993. Since then, LL grafts had been exclusively used for adult patients. However, Tanaka et al. (2) reported in their early series of 39 LL LDLTs that survival was 82.1% in patients with a graft-to-recipient weight ratio (GRWR) $\geq$0.8 (n = 28), but only 54.5% in those with a GRWR <0.8 (n = 11). Furthermore, Kiuchi et al. (3) revealed inferior graft survival rates for smaller grafts, which prompted the use of larger grafts, namely, right lobe (RL) grafts. Because the introduction of the RL graft, the use of LL grafts has been almost abandoned in the adult population and the number of RL LDLTs has dramatically increased worldwide, with risks for the RL donors.

The risks for RL donation are far from negligible; in fact, a review on LD mortality revealed that a total of 33 living LD deaths have been identified worldwide, including three donors who died after an attempted rescue with a liver transplant (4). At least 21 of the 33 deaths seem to be related to the procedure. Among these, at least 14 cases (67%) were related to the RL donation. Based on an estimate of 14 000 LDLT performed worldwide, the donor death rate was estimated to be 0.1–0.3%, possibly reaching 0.5% when using the RL. Furthermore, in 2010, two more RL donor deaths in the leading LDLT programs were reported in the United States (5). These facts challenge the legitimate continuation of RL LDLT programs for adult patients.

Nonetheless, balancing the safety of the donor with a satisfactory outcome for the recipient is an integral part of the process of living donation. From the standpoint of donor safety, LL LDLT may be the best option available provided that LL grafts sustain the metabolic demands of the adult recipients. On the basis of this belief, we have continuously performed and advocated the feasibility and usefulness of LL LDLT for adult patients (6,7). However, there have been no large-scale, reliable study comparing the outcomes of adult LL and RL LDLT.

The goal of this study was to present the outcomes of the largest-to-date single center experience of adult LL LDLT and discuss whether LL grafts can be used for adult patients on a routine basis.

Patients and Methods

Patient characteristics

Between October 1996 and March 2010, 357 consecutive LDLTs, including seven retransplants (2.0%), were performed at Kyushu University Hospital, Fukuoka, Japan, with approval from the Ethics and Indications Committee of Kyushu University. This comprised 313 adults (aged ≥18 years) and 44 children (aged <18 years). Of the 313 adults, a total of 200 patients (63.9%) underwent LDLTs using LL grafts with (n = 184) or without (n = 16) the caudate lobe, whereas 109 (34.8%) patients received RL grafts with (n = 3) or without (n = 106) the middle hepatic vein (MHV). Three patients (1.0%) received right posterior segment (RPS) grafts with the right hepatic vein. One patient received both RL and LL dual grafts. In this study, pediatric patients and the patient with a dual graft were excluded from the analysis. The three cases with RPS grafts were included in the analysis as RL LDLT. The indications for retransplant included hepatic artery thrombosis (n = 1), small-for-size syndrome (SFSS, n = 1), chronic rejection (n = 1), recurrent primary biliary cirrhosis (n = 1), anterior segment congestion (n = 1) and portal vein thrombosis arising from an intrahepatic arterioportal (AP) shunt in LL LDLT (n = 1) and chronic rejection in RL LDLT (n = 1). The patient characteristics of LL and RL recipients are summarized in Table 1.

Graft selection criteria

Our current selection criteria for grafts in adult LDLT is shown in Figure 1. In the early phase of the adult LDLT program, we exclusively used LL grafts for all cases. A predicted graft volume-to-recipient standard liver volume (GV/SLV) ratio >30% was the basic criteria for acceptance. However, grafts of predicted GV/SLV <30% were accepted and used in four cases. By October 2000, we had had 10 cases of SFSS out of 50 cases (20%) and lost one graft (retransplantation) because of the complication. To decrease the incidence of SFSS and to maximize the success rate, we decided to use RL grafts more often since December 2000, especially for patients whose GV/SLV ratio was going to be <35% or for patients with a high Model for

Table 1: Patient characteristics

Factors	Left lobe (n = 200)	Right lobe (n = 112)	p-Value
Recipient			
Age (years)	51.5 ± 12.2*	49.8 ± 11.8	NS
Sex (M/F)	87/113	71/41	0.0007
Body weight (kg)	57.2 ± 9.5	65.0 ± 11.4	<0.0001
Etiology (n)			NS
Cirrhosis	25	25	
HCC	85	50	
Cholestatic	42	19	
FHF	36	13	
Others	6	4	
Retransplant	6	1	
Child-Pugh A/B/C/NA (n)	21/57/83/29	6/17/75/14	NS
MELD score	14.4 ± 8.0	15.8 ± 0.8	NS
<10 (n)	55	22	
≥11, <20	100	62	
≥21, <30	37	22	
≥30	8	6	
Graft			
GV (g)	432 ± 83	566 ± 83	<0.0001
GV/SLV ratio (%)	38.7 ± 7.3	47.6 ± 7.8	<0.0001
≥20, <25% (n)	2	0	
≥25, <30%	19	0	
≥30, <35%	43	3	
≥35, <40%	51	15	
≥40%	85	94	
GRWR (%)	0.82 ± 0.71	0.9 ± 0.20	NS
<0.6% (n)	26	2	
≥0.6, <0.8%	93	30	
≥0.8, <1.0%	62	55	
≥1.0%	19	25	
Donor			
Age (years)	34.9 ± 11.1	38.5 ± 11.5	0.0057
Sex (M/F)	155/45	49/63	<0.0001
Blood type compatibility (n)			NS
Identical	154	80	
Compatible	38	26	
Incompatible	8	6	

*mean ±SD.; HCC = hepatocellular carcinoma; FHF = fulminant hepatic failure; NA = not applicable; MELD = model for end-stage liver disease; GV = graft volume; SLV = standard liver volume; GRWR = graft-to-recipient weight ratio.

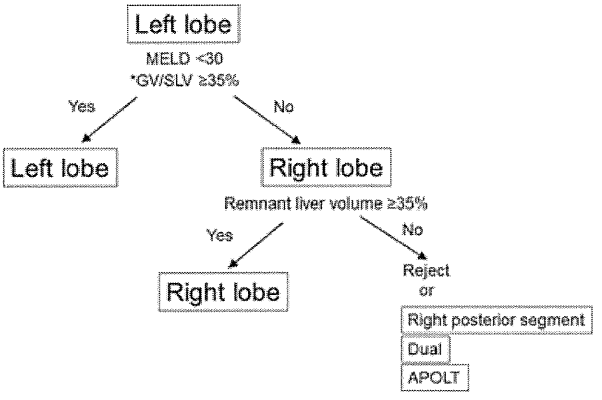

Figure 1: Graft selection algorithm in Kyushu University. *A left lobe graft of GV/SLV <35% was considered to be used when the donor was younger than 40 years old or recipient's liver function was good or low MELD score without severe portal hypertension. APOLT = auxiliary partial orthotopic liver transplantation

end-stage liver disease (MELD) score. The decision for RL grafts was partly influenced on the report from Kyoto group in 1999 (2,3), which revealed inferior graft survival rates for smaller grafts. Currently, our selection criteria for LL grafts include a predicted GV/SLV ≥35%, whereas those for RL grafts include an estimated remnant liver volume ≥35% in the donor. However, graft selection is still carried out on a case-by-case basis, with consideration of various factors including anatomical variations and recipient condition surrogated by MELD score. To be precise, even when a LL graft has sufficient liver volume, unfavorable arterial anatomy such as triple arteries mandates us to consider other type of grafts. Furthermore, recipient condition such as MELD >30 also makes us to use a bigger graft than a marginal LL graft (such as graft with GV/SLV 35%), provided the remnant liver volume of the donor is sufficient.

The donors' relationship with the LL recipients were father (n = 12), mother (n = 13), son (n = 127), daughter (n = 44), husband (n = 22), wife (n = 23), siblings (n = 53), aunt (n = 1) and others (n = 18). Our donor follow-up principle after the initial hospital discharge is as follows: weekly or biweekly outpatient clinic for the first month, monthly until 1 year and yearly afterward. After 1 year, donors of failed recipients tend to drop off whereas more than 90% of our donors visit our outpatient clinic regularly.

Technical details of donor and recipient procedures

The transplant procedures for LL donors and recipients were, briefly, as follows. In the early phase of the adult LDLT program (the first 16 LL cases), we exclusively used LL grafts without the caudate lobe. Since September 1999, we decided to include the left side of the caudate lobe (Spiegel lobe) for all LL grafts for two reasons. First, we found the GV was going to increase by 2% with the addition of the left side of the caudate lobe (8). Second, hanging maneuver during parenchymal transection is technically easier with the caudate lobe attached to the LL. However, the short hepatic veins draining the caudate lobe have never been reconstructed. The parenchymal transection was performed on the right side of the MHV and on the demarcation line, using a Cavitron Ultrasonic Surgical Aspirator (CUSA™, Tyco Healthcare, Mansfield, MA, USA) and the electrocautery or the dissecting sealer (TissueLink Monopolar Dissecting Sealer 3.0™; Valleylab, Boulder, CO, USA) performed under the hanging maneuver (9). Pringle's maneuver was liberally used as indicated (10). The bile duct was cut after completing parenchymal transection, with surrounding tissue attached. This was done after cholangiography with two metal clips on the designated cutting line. Hepatic venoplasty was performed if necessary (11).

In the recipient, the LL graft was transplanted usually without bypass. There are two reasons to use a veno-venous (V-V) bypass in our program. First, we used a V-V bypass for patients with severe portal hypertension in both LL and RL LDLT. Second, it is used when long anhepatic time to reconstruct the multiple venous tributaries in the back table with a total clamping of the inferior vena cava (IVC) is necessary. Therefore, RL grafts were more often required V-V bypass than LL grafts in our series. A temporary portocaval shunt (PCS) during the anhepatic period was created in some cases for SFS grafts with GV/SLV <35% (n = 7), fulminant hepatic failure (n = 9) and an absence of liver cirrhosis (n = 2) and severe portal hypertension (n = 12). There were two cases for whom permanent hemi-PCS (HPCS) was created to alleviate the excessive portal flow in an extremely small graft (GV/SLV 23.7% and 27.2%), for one of which delayed closure of the HPCS on POD4 was performed because of portal steal phenomenon (12). The MHV and LHV conduit was extended longitudinally to the right for wider hepatic vein anastomosis (13). Hepatic arteries were always reconstructed under the microscope (14). Duct-to-duct biliary reconstruction has been the routine procedure since June 2001(15). Concomitant splenectomy (n = 72, 36.0%) or ligation of the proximal splenic artery (SAL, n = 16, 8.0%) were performed in some patients with a LL graft for two reasons: first, to decrease the portal flow, thereby expecting decreased relative hyperperfusion of SFS grafts; second, to obtain a rapid increase in platelet count after LDLT, thereby facilitating postoperative management leading to early induction of interferon therapy for hepatitis C. There has been a chronological evolution regarding the concept of the portal flow modulation. Until October 2000, we did not modulate portal flow at all. Between October 2000 and May 2004, we preferred SAL as a mean to decrease the portal flow. Splenectomy was rather an exception until 2004 because splenectomy was a very hazardous procedure with a significant blood loss. However, we found that the effect of SAL was unpredictable and unsatisfactory in terms of portal flow reduction and increase in platelet count.

With the increase in HCV patients and with the advent of tieless splenectomy in 2005, we have exclusively used splenectomy instead of SAL resulting in a uniform portal flow reduction and rapid increase in platelet count soon after LDLT, which facilitate posttransplant interferon (IFN) therapy for HCV patients. Currently, our tieless splenectomy technique is highly standardized using the vessel sealing system (LigaSure Atlas™; Valleylab) and stapling devices (Endo GIA™ universal; Ethicon Inc., Tokyo, Japan), which allows for bloodless and easy splenectomy in liver transplant patients (16). We usually finish splenectomy during the 15–30 min waiting time for the donor graft. Immediately after reperfusion of the reconstructed hepatic artery, the blood flow of the portal vein and hepatic artery as well as hepatic veins were routinely checked by color Doppler ultrasound and an electromagnetic flowmeter. The portal pressure was continuously monitored by a catheter inserted in one of the jejunal veins.

Immunosuppressive drugs

The immunosuppressive regimen consisted of a combination of calcineurin inhibitor (tacrolimus: Prograf®; Astellas, Tokyo, Japan or cyclosporine: Neoral®; Novartis Pharma, Basel, Switzerland) and steroids with or without mycophenolate mofetil (MMF; CellCept®, Roche Pharmaceuticals, Basel, Switzerland). Currently, the triple regimen including calcineurin inhibitor, steroids and MMF has been the standard protocol. Steroids were basically tapered off by 6 months after LDLT. MMF 1000–2000 mg/day was started from postoperative day 1 and maintained for 3–6 months. For ABO incompatible LDLT, the protocol consisted of a single dose (375 mg/m^2) of rituximab (Rituxan®; Roche Pharmaceuticals, Basel, Switzerland) 2–4 weeks before LDLT given in an outpatient clinic, several sessions of pretransplant plasma exchange to decrease antidonor blood-type antibody titer to

less than 32 and a triple immunosuppressive regimen including tacrolimus, steroids and MMF after LDLT (17). MMF was started 7 days before LDLT. In the LL cohort, only eight patients (4%) had ABO incompatible grafts, whereas 154 had identical and 38 had compatible grafts (Table 1).

Definition of grade of donor postoperative complications

The postoperative complications of the donor were graded according to the modified Clavien classification (18). A postoperative peak total bilirubin level >5mg/mL was defined as Clavien grade 2.

Definition of small-for-size syndrome

The definition of SFSS was as reported previously (5,6). Briefly, SFSS is defined as having prolonged functional cholestasis (total bilirubin >10 mg/dL at postoperative day 14) and intractable ascites (daily production of ascites of >1 L at postoperative day 14 or >500 mL at postoperative day 28).

Statistical analysis

Continuous variables were compared using a two-tailed, unpaired Student t-test for independent samples. All values are expressed as mean ±standard deviation. Categorical data were compared using the chi-square test. Analysis of patient survival was performed using the Kaplan–Meier method and compared between groups using the log-rank test. p-Values <0.05 were considered significant. All statistical analyses were done using SPSS 17.0 (SPSS Inc., Chicago, IL).

Results

Patient characteristics

There were no significant differences in patient age and MELD score between RL and LL groups (Table 1). The mean GV of LL grafts was 432 g (range 220–750 g), which was significantly smaller than that of RL grafts (566 g, range 395–760g, $p < 0.0001$). The mean GV/SLV ratio and GRWR were 38.7% (range, 21.0–66.1%) and 0.82% (range, 0.41–1.51%), respectively in LL grafts, which were, again, significantly smaller than those of RL grafts (47.4% and 0.9%, respectively). Twenty-one LL grafts were extremely small, namely, GV/SLV <30%, although the preoperative predicted GV/SLV was >35% in 17 grafts. The smallest LL graft GV/SLV was 21.0%, for which auxiliary partial orthotopic liver transplantation was performed in patients with primary sclerosing cholangitis (8). Hepatocellular carcinoma was the main indication both in LL (42.5%) and RL (44.6%) LDLT.

Overall patient and graft survival rates

As shown in Figure 2A, the cumulative overall 1-, 5- and 10-year patient survival rates were 85.6%, 77.9% and 69.5%, respectively, in patients with LL grafts, which were comparable to those of patients with RL grafts. The cumulative 1-, 5- and 10-year graft survival rates were similar, 84.0%, 76.5% and 59.6%, respectively, in LL grafts, which again were comparable to those of RL grafts (Figure 2B). Figure 3 shows patient survival in LL grafts according to the GV/SLV ratio. To investigate the impact of the graft size, the GV/SLV ratio was classified into four subgroups as follows: <30% (n = 21); ≥30%, <35% (n = 43); ≥35%, <40% (n = 51) and ≥40% (n = 85). There were no significant differences in patient and graft survival rates between these subgroups (Figure 3). Furthermore, 119 (59.5%) out of 200 LL grafts in our series were GRWR <0.8. The 1- and 5-year graft survival rates of this group of patients were 84.1% and 75.6%, respectively, which were comparable to those of patients with LL grafts of GRWR ≥0.8 (83.7% and 76.3%).

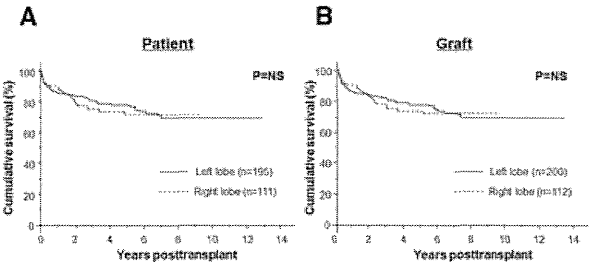

Figure 2: Comparison of cumulative patient (A) and graft (B) survival rates between left lobe (LL) and right lobe (RL) living donor liver transplant (LDLT).

Donor operative outcomes

Table 2 shows the comparison of operative outcomes between LL and RL donors. The mean operative time was comparable whereas blood loss was significantly less in RL donors (493 mL vs. 649 mL). However, we did not give homologous blood transfusion to any of the LL and RL donors. Postoperative liver function tests including peak total bilirubin, peak aspartate aminotransferase and alanine aminotransferase were significantly better in LL donors. Furthermore, lengths of hospital stay were significantly shorter in LL donors (12.2 days vs. 17.3 days), whereas overall morbidity rates were comparable. These data suggest that LL donation is potentially safer than RL donation, although there was no procedure-related mortality in either group. Ten LL donors with gastric stasis (n = 5), biloma/bile

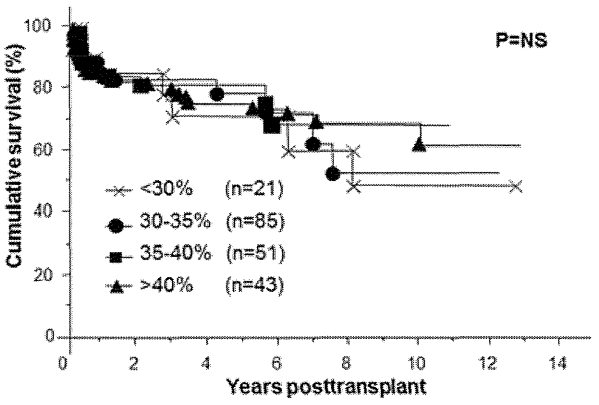

Figure 3: Comparison of cumulative graft survival according to GV/SLV ratio in LL LDLT. The log-rank test found no statistically significant differences.

Table 2: Donor outcomes

Factors	Left lobe (n = 200)	Right lobe (n = 112)	p-Value
Donor			
Operative time (min)	448 ± 78*	449 ± 71	NS
Blood loss (mL)	659 ±5 01	493 ± 327	0.0025
Blood transfusion (%)	0	0	NS
Postoperative LFTs			
Peak T.Bil (mg/dL)	2.4 ± 1.4	3.1 ± 1.5	<0.0001
Peak AST (IU/L)	482±254	562±279	0.013
Peak ALT (IU/L)	529 ± 265	604 ± 351	0.038
Morbidity (%)	36.0	34.8	NS
Clavien I	14.5	13.4	
Clavien II	14.0	11.6	
Clavien IIIa	5.0	7.1	
Clavien IIIb	2.5	2.7	
Clavien IV	0	0	
Clavien V	0	0	
Hospital stay (days)	12.2 ± 5.2	17.3 ± 10.0	<0.0001

*Mean ±SD. T.Bil = total bilirubin; AST = aspartate amino transferase; ALT = alanine amino transferase.

leakage (n = 3) and wound sequelae (n = 2) and eight RL donors with biloma/bile leakage (n = 2), bile duct strictures (n = 2) and pneumothorax/pleural effusion (n = 4) had non-surgical intervention (Clavien's IIIa). Furthermore, five LL donors (2.5%) with incisional hernia (n = 2), bile leakage from the closed stump of the left hepatic duct (n = 1), bile duct strictures (n = 1) and postoperative bleeding (n = 1) and three RL donors (2.7%) with bile duct stricture (n = 1), an incisional hernia (n = 1) and a cosmetic wound defect (n = 1) underwent reoperation (Clavien's IIIb). Two donors (19-year-old male LL and 56-year-old male RL donors) with normal liver function tests died from suicide and an unknown sudden cardiovascular cause 5 years and 1 year, respectively after donation. A 47-year-old male donor developed chronic myeloid leukemia 4 years after donation for whom imatinib was given to achieve complete remission. In terms of procedure-related complications, we have not experienced any Clavien's grade IV and V complications so far.

Recipient operative outcomes

Table 3 shows a comparison of operative data between LL and RL recipients. The mean operative time was approximately 2 h longer in RL recipients and RL recipients more often required V-V bypass. Concomitant splenectomy was performed in 36% of LL and 47.3% of RL recipients. A temporary PCS was created during the anhepatic phase in 16.5% of LL recipients because of SFS grafts with GV/SLV <35% (n = 7), fulminant hepatic failure (n = 9) and an absence of liver cirrhosis (n = 2) and other reasons (n = 12), compared with 9.0% of RL recipients. The mean GV/SLV of patients who had a temporary PCS was 36.9%.

Figure 4 compares the 1-year graft survival rates between LL and RL LDLT according to the MELD scores. In all categories, the LL group revealed comparable results with the RL group. However, in patients with a MELD score >30, the LL group (n = 8) tended to show the worst outcome compared with the RL group (n = 7) (1-year graft survival 50% vs. 66.7%). Four LL patients with a MELD score >30 were lost because of hepatic artery thrombosis (n = 1), graft dysfunction and PVT (n = 1), hepatic infarction because of portal infusion therapy (n = 1) and graft dysfunction and subarachnoid hemorrhage (n = 1), whereas only one patient with a RL graft was lost because of hepatocellular carcinoma recurrence. Even though there was no statistical significance, the decrement in outcomes for LL grafts in high MELD patients is obvious. Therefore, RL grafts should be considered first over LL grafts for very sick patients with MELD score >30.

Incidence of small-for-size syndrome

The incidence of SFSS was higher in LL LDLT (19.5%) than in RL LDLT (7.1%) ($p < 0.01$). The mean GRWR in the patients with who developed SFSS was 0.74, which was comparable to those without SFSS (0.78, p = NS). Therefore, graft size is not the sole determinant to develop SFSS in our series.

Cause of graft loss

Of the 200 LL grafts, 54 grafts were lost because of hepatic artery thrombosis (n = 2), chronic rejection (n = 4), hepatic infarction (n = 5), graft dysfunction/sepsis (n = 8), including SFSS (n = 3), graft-versus-host disease (n = 1), recurrent hepatitis C (n = 5), recurrent hepatocellular carcinoma (n = 10), *de novo* malignancy (n = 1) and other causes (n = 18) including hepatic abscess (n = 1), suicide (n = 1), drowning (n = 1), cardiac failure (n = 1), pancreatic fistula leading to rapture of pseudoaneurysm (n = 1), subarachnoid hemorrhage (n = 1), respiratory failure (n = 1), adult T-cell leukemia (n = 1), cholangitis (n = 1), sepsis after biliary stenting (n = 1), procedure-related iatrogenic bleeding (n = 2) and arterio-portal fistula (n = 1), uncontrollable bleeding during transplant (n = 2), late portal vein thrombosis (n = 1), recurrent PBC (n = 1), colonic perforation (n = 1), late-onset acute rejection (n = 1). Among these, 23

Table 3: Recipient outcomes

Factors	Left lobe (n = 200)	Right lobe (n = 112)	p-Value
Operative time (min)	766 ± 151*	893 ± 201	<0.0001
Blood loss (mL)	6929 ± 17 073	7485 ± 7815	NS
Blood transfusion			
PRBC (U)	17.9 ± 29.4	21.9 ± 19.2	NS
FFP (U)	18.5 ± 21.4	26.6 ± 20.1	0.001
PLT (U)	16.8 ± 24.2	23.1 ± 20.4	0.02
Portal pressure (mmHg)			
At laparotomy	21.7 ± 6.2	20.9 ± 6.4	NS
Before closure	16.3 ± 3.5	16.2 ± 4.0	NS
Portal flow (mL/min)	1423 ± 584	1870 ± 693	<0.0001
Portal flow (mL/min/g liver)	3.35 ± 1.40	3.35 ± 1.25	NS
V-V bypass (%)	5.5	36.7	<0.0001
Splenectomy (%)	36.0	47.3	NS
SA ligation (%)	8.0	6.3	NS
Temporal portocaval shunt (%)	16.5	8.9	NS
Permanent hemiportocaval shunt (%)	1.0	0	NS
Complications (%)			
SFSS	19.5	7.1	0.0063
HAT	2.0	1.7	NS
PVT	2.0	0.9	NS
ACR	16.0	17.0	NS
Bile leak	6.5	5.4	NS
Bile duct strictures	20.0	17.0	NS
Relaparotomy	15.0	8.9	NS
In-hospital mortality (%)	12.0	8.0	NS

*Mean ±SD. PRBc = packed red blood cells; FFP = fresh frozen plasma; PLT = platelet; V-V = veno-venous; SA = splenic artery; SFSS = small-for-size graft syndrome; HAT = hepatic artery thrombosis; PVT = portal vein thrombosis; ACR = acute cellular rejection.

(42.6%) were lost within 3 months after LDLT. In particular, hepatic infarction was probably associated with catheterization for portal infusion therapy, which had been used for some time periods. On the other hand, 27 RL grafts were lost because of chronic rejection (n = 4), recurrent hepatitis C (n = 2), recurrent hepatocellular carcinoma (n = 4), multiple liver abscess (n = 1), graft dysfunction/sepsis (n = 7), anterior segment congestion (n = 1) and other causes (n = 8) including adult T-cell leukemia (n = 1), biopsy-related liver hematoma (n = 1), *de novo* autoimmune hepatitis (n = 1), recurrent colon cancer (n = 1), esophageal cancer (n = 1), recurrent epithelioid hemangioendothelioma

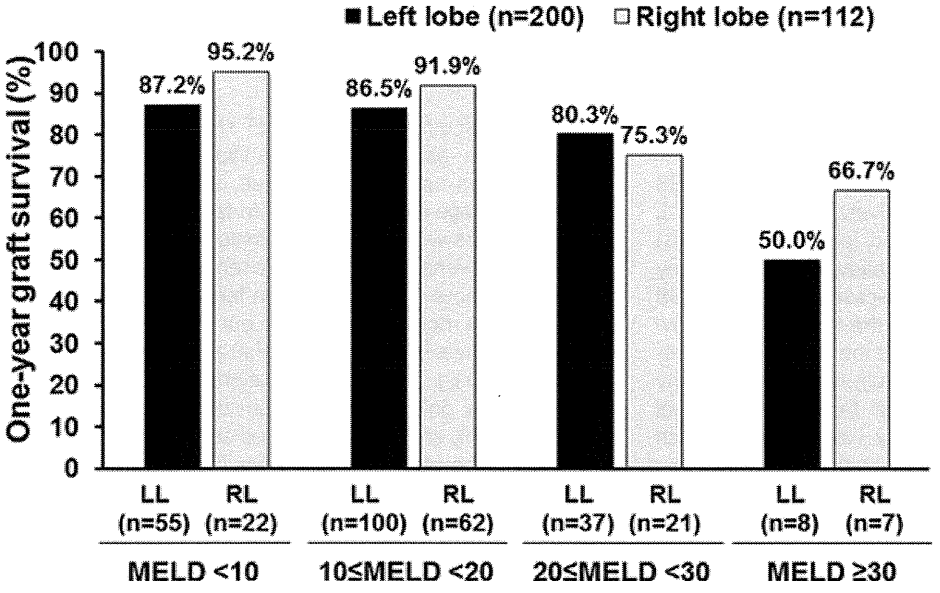

Figure 4: Comparison of LL and RL graft survival rates according to the MELD score. There was no significant difference between the two types of graft at any level of the MELD score.

(n = 1), acute renal failure (n = 1) and nonocclusive mesenteric ischemia (n = 1). Among these, eight cases (29.6%) were lost within 3 months after LDLT.

Discussion

This study clearly showed that the outcomes of LL LDLT were comparable with those of RL LDLT, although SFSS occurred more often in LL LDLT. However, this does not necessarily lead to graft loss. In our cohort, only three patients lost their grafts directly as a result of SFSS.

SFSS is characterized clinically by a combination of prolonged functional cholestasis, intractable ascites and a delayed recovery of both prothrombin time and encephalopathy (19). The mechanism of SFSS remains unknown but is probably multifactorial. Excessive portal perfusion and pressure to the small graft is suggested to be one of the most important factors (20). Therefore, some groups have advocated the use of temporary PCS to reduce or minimize the influence of detrimental substances accumulating during portal clamping (21,22). Troisi et al. reported that an intentional decrease in portal flow by HPCS improved the survival of patients who received LL grafts with a GW/RW <0.8 (23). Yamada et al. selectively used HPCS for LL grafts with GW/RW between 0.6 and 0.8 and showed 100% patient survival (24). Botha et al. also reported excellent results in patients with small LL grafts (the median GW/RW was 0.67) with HPCS: the 1-year patient and graft survival were 87% and 81%, respectively (25). They all concluded that a small LL graft with modulation of portal flow by HPCS may prevent SFSS while at the same time providing adequate liver volume. Furthermore, the Kyoto group showed that portal venous pressure <15 mmHg was the major factor for a better outcome (26). However, we used HPCS in only two patients, one with a very small-for-size graft (GV/SLV of 24%) whose HPCS was closed 4 days after LDLT because of the portal steal phenomenon and one with a small graft (GV/SLV of 27%) with excessive portal flow. Therefore, we do not think HPCS is always necessary to prevent SFSS.

Our current approach in managing the problem of SFSS is to perform splenectomy aggressively. In the last 50 LL cases, splenectomy was performed for 35 cases (70%) whereas seven cases (14%) had already had splenectomy before LDLT. We have had only three cases (6%) with SFSS out of the last 50 cases and two of the three cases recovered from the complication whereas the other required retransplantation. In terms of the usefulness of splenectomy for low GRWR (<0.8) patients, the 1-year graft survival rates in patients with splenectomy were 93.4%, which was significantly better than those without splenectomy (79.2%) (data not shown). Therefore, we believe concomitant splenectomy is very useful especially for patients with a small graft to control the portal flow and platelet count, thereby improving the overall results.

We did not set strict definition of the "excessive" portal flow or portal pressure. However, we think that portal flow more than 2500 mL/min or 500 mL/min per 100 g liver and portal pressure more than 20 mmHg are both detrimental to the graft. Therefore, Portal flow modulation should aggressively be tried for these patients. In a successful case with extremely small graft (GV/SLV 23%), the portal flow to the LL graft was reduced to 270 mL/min with the combination of a permanent hemi PCS and splenectomy. In another case with an extremely small graft (GV/SLV 27.2%), the portal flow before hemi PCS was 2500 mL/min, which was decreased to 1000 mL/min with a hemi PCS and splenectomy. Both of the cases were successful without small-for-size syndrome.

Technically speaking, LL LDLT is simpler than RL LDLT as indicated by the shorter length of the operative time. LL grafts usually have a single hepatic vein, a single portal vein and a single bile duct although hepatic artery reconstructions are sometimes multiple. On the other hand, RL LDLT requires additional reconstructions of MHV tributaries and multiple bile duct reconstructions, which prolongs the total operative time.

In terms of donor safety, our data confirmed the results of published series (27,28), which revealed the superiority of LL donation over RL donation. Gastric stasis, which is a specific complication after LL donation, occurred in 12 cases in LL donors (6%). Among these, five required endoscopic correction. This complication probably results from rotation of the distal stomach and the duodenum adhering to the raw surface of the remnant liver, therefore this could be prevented by using an antiadhesive film such as hyaluronic acid-carboxymethylcellulose membrane (Seprafilm®; Genzyme Corp., Cambridge, MA, USA) before closing the abdomen or by early resumption of feeding after donation. The film should be attached to the surface of the antropyloric region of the stomach (not to the cut surface of the liver) just before closing the abdomen.

There is a discussion that LL LDLT should not be used in large patients, especially those in Western countries. We believe this is not necessarily true provided that the LL donor is as large as the recipient. In fact, our data showed that LL donors were more often male and LL LDLTs were more often given to smaller female recipients. On the other hand, RL donors were more often female whereas RL recipients were more often male. In our 200 LL cohort, 5 patients were heavier than 80 kg whereas 22 patients were more than 70 kg. There was no patient heavier than 90 kg. Among them, only a female patient of 81 kg body weight (GV/SLV 39.7% and GRWR 0.6) died early (<3 months after LDLT) because of SFSS and sepsis. The other 20 patients (95%) survived LDLT. Therefore, we insist that as far as the donor LL grafts have sufficient GV (GV/SLV > 35% or GRWR > 0.8), LL LDLT should be feasible even for heavier Western patients.

Table 4: Left lobe living donor liver transplantation in adults: world experience

Ref. #	Author	Year	Patients (n)	GV/SLV* (%)	GRWR* (%)	Portal flow modulation (%)				SFSS** (%)	Survival (%)	
						NO	HPCS	SPL	SAL		1-Year	5-Year
29	Kawasaki	1998	13	40.2	NA	100	0	0	0	NA	NA	NA
30	Miller	2001	9	NA	0.69	100	0	0	0	44.0	78.0	NA
7	Soejima	2006	107	40.5	0.81	78.5	0.0	7.5	15.0	25.2	81.4	74.7
24	Yamada	2008	7	NA	0.65	14.3	85.7	0	0	0	NA	NA
31	Ikegami	2009	120	39.9	NA	100	0	0	0	0.8	87.5	80.1
25	Botha	2010	21	NA	0.67	23.8	76.2	0	0	4.8	87.0	NA
32	Ishizaki	2011	42	39.8	NA	100	0	0	0	0	100.0	91
Present series	Soejima	2011	200	38.7	0.82	43.5	1.0	36.0	8.0	19.5	85.6	77.9

*Mean, **definition of SFSS differ between the studies. NA = not available; GV/SLV = graft-to-standard volume ratio; GRWR = graft-to-recipient weight ratio; HPCS = hemiportocaval shunt; SPL = splenectomy; SAL = splenic artery ligation; SFSS = small-for-size syndrome.

With refinement of surgical procedures, postoperative management as well as better graft and patient selection, we have achieved significant progress in cases and outcomes. I summarized the world experience of LL LDLT in Table 4 (29–32). The 1-year patient and graft survival rates in the last 50 LL LDLT in our series is now >95% (data not shown). We therefore currently think that adult LDLT can be successful with either a LL or a RL graft provided that an appropriate graft is selected.

Finally, we summarize our current criteria and recommendation for adult LDLT. The LL grafts is not only a viable option for adults patients but the procedure that should be considered first except for a sick patient with MELD ≥30. The estimated GV/SLV is ideally more than 35% for patients with a MELD score <30 whereas a graft with estimated GV/SLV <35% is still an option for patients with low MELD score without severe portal hypertension. Splenectomy is a viable option to reduce portal flow and pressure especially for patients with a SFS graft. Moreover, the combination of splenectomy and HPCS can be an effective modality for an extra-small graft.

In conclusion, further utilization of LL grafts should be recommended to minimize donor morbidity and mortality while maintaining the outcome for recipients equivalent to that of RL LDLT.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Risk Factors That Increase Mortality After Living Donor Liver Transplantation

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Background. Female liver to male recipient is a well-accepted risk factor for graft loss in cadaveric liver transplantation. However, gender matching is infeasible because of an insufficient number of available donors. No studies have been performed on the role of gender in the field of living donor liver transplantation. This report investigates the effect of gender mismatch on the outcome of living donor liver transplantation.

Methods. A total of 335 patients and donors were classified into four groups according to the following gender combinations: male donor to male recipient group (n=104), male donor to female recipient group (n=120), female donor to male recipient (FM) group (n=59), and female donor to female recipient group (n=52). Patient and graft survival were compared among the groups. We performed a multivariable analysis to identify the factors associated with patient mortality.

Results. The 1-, 3-, 5-, and 10-year patient survival rates in the FM group were 80.6%, 66.8%, 61.8%, and 47.7%, respectively. The FM group showed significantly shorter patient survival compared with the other three groups. Independent risk factors for patient mortality were: FM group (P=0.006), pretransplant diabetes mellitus (P=0.001), and a model for end-stage liver disease score more than or equal to 20 (P=0.004).

Conclusions. Male recipients of transplants from female donors, pretransplant diabetes mellitus, and a model for end-stage liver disease score more than or equal to 20 have poor survival rates.

Keywords: Donor, Gender, Transplantation, Mismatch.

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The role of gender in the transplantation of body parts such as the kidney, lung, bone marrow, and heart has been extensively studied (*1–4*). In general, today's solid organ donors cannot be matched by gender because of a disparity between supply and demand (*5*). Some reports indicate that gender mismatch has an impact on graft failure, specifically in male recipients of female livers in cadaveric liver transplantation (LT) (*6–8*). Marsman et al. reported that female recipients had a higher incidence of early rejection within 6 months of LT compared with male recipients. They also found decreased graft survival rate in male recipients of female livers (*9*). In contrast, Lehner et al. (*10*) recently reported no significant differences in patient survival in gender-mismatched LT in a single-center database of 1355 recipients.

Donor age, high model for end-stage liver disease (MELD) score, graft size, and portal hypertension are risk factors for graft failure after living donor liver transplantation (LDLT) for patients with chronic liver failure (*11*). Standard liver volume is proportional to body surface area (*12*). Therefore, the difference in body size between males and females sometimes results in a small-for-size graft (SFSG) in males who receive livers from female donors. Data show poor LDLT outcomes with a graft-weight to recipient-weight ratio of less than 0.8 (*13*). Despite this difference between cadaveric LT and LDLT, there are no studies on gender and LDLT. Therefore, the aim of this study was to clarify the effect of gender mismatch on LDLT outcomes.

RESULTS

Table 1 shows a comparison of variables among the four groups classified by gender combination. The distribution of the primary diagnosis was markedly skewed because of the presence of diseases such as hepatitis C (HCV), primary biliary cirrhosis, and primary sclerosing cholangitis (PSC). Operation time and blood loss were greater in the female donor to male recipient (FM) group than in the other three groups. More left lobe was used in the male donor to male

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TABLE 1. Comparison of variables between the groups classified by gender combination

Variables	MM group (n=104)	FF group (n=52)	MF group (n=120)	FM group (n=59)	*P*
Recipient variables					
Age, yr (range)	52.5 (19–69)	49.4 (18–71)	52.7 (18–73)	49.9 (23–68)	NS
Primary diagnosis					<0.001
Liver cirrhosis					
Hepatitis C (HCC)	61 (49)	18 (15)	41 (33)	27 (17)	
Hepatitis B (HCC)	12 (10)	1 (1)	9 (7)	6 (5)	
Non-B non-C (HCC)	5 (2)	3 (1)	3 (2)	6 (2)	
Alcohol (HCC)	6 (4)	2 (0)	1 (0)	3 (2)	
Fulminant hepatic failure (FHF)	11	7	25	7	
Primary biliary cirrhosis	3	10	31	1	
Primary sclerosing cholangitis	4	1	1	5	
Biliary atresia	1	3	1	1	
Others	1	7	8	3	
Body mass index (kg/m^2)	23.6±3.0	22.4±3.7	23.0±3.6	23.9±3.7	0.08
MELD score	14.0±7.0	15.4±8.5	15.5±8.4	15.6±8.2	NS
Pretransplant DM (yes/no)	24/80	0/52	15/105	12/47	0.001
Operation time (min)	834±174	765±136	751±139	866±209	<0.001
Blood loss (mL)	6498±6940	4936±5296	4617±5006	8676±7884	0.001
Donor/graft variables					
Graft (left/right/posterior)	72/31/1	28/24/0	95/22/3	15/43/1	<0.001
GW-SLW ratio (%)	40.9±8.2	40.9±9.7	44.2±9.0	40.7±7.1	0.01
GW-BW ratio (%)	0.77±0.16	0.82±0.03	0.88±0.02	0.76±0.02	<0.001
ABO (identical/compatible/incompatible)	84/16/3	39/11/2	82/27/10	39/18/2	NS
Consanguinity (yes/no)	100/4	50/2	97/23	33/26	<0.001
Age, yr (range)	31.7 (20–62)	35.9 (20–58)	36.9 (20–65)	40.2 (22–60)	<0.001
Body mass index (kg/m^2)	22.6±3.1	21.4±2.8	22.9±2.6	21.3±2.3	0.001
Operation time (min)	458±80	426±58	443±67	437±76	0.07
Cold ischemic time (min)	86±59	87±61	66±35	122±69	<0.001
Warm ischemic time (min)	41±12	39±13	37±9	45±11	0.001
Blood loss (mL)	582±340	470±288	630±505	531±442	NS

DM, diabetes mellitus; GW, graft weight; SLW, standard liver weight calculated by 706.2×body surface area+2.4; MM, male donor to male recipient; FF, female donor to female recipient; MF, male donor to female recipient; FM, female donor to male recipient; NS, not significant; HCC, hepatocellular carcinoma; FHF, fulminant hepatic failure; MELD, model for end-stage liver disease; BW, body weight.

recipient (MM) and male donor to female recipient (MF) groups compared with the other two groups. Nevertheless, the ratio of graft weight (GW) to standard liver weight (SLW) and the ratio of GW to body weight were higher in the MF group than in the other three groups. LDLT between spouses was included in the FM and MF groups, reducing consanguinity between donors and recipients. Donors in the MM group were younger than those in the other three groups. Cold and warm ischemic times were longest in the FM LDLT group. Most such cases involve the use of a right lobe graft, which requires hepatic vein reconstruction.

In our series, 80 patients died after LDLT. Hepatocellular carcinoma (HCC) recurrence occurred in 14 patients, sepsis in 13 patients, HCV recurrence in 9 patients, graft failure in 9 patients, bleeding in 8 patients, de novo malignancy in 7 patients, chronic rejection in 4 patients, multiple organ failure in 4 patients, fungal infection in 3 patients, and other conditions in 9 patients. There was no difference in cause of death among the groups. Furthermore, 23 patients died in the FM group. Nine patients died of surgery-related causes (sepsis in five, graft failure in one, multiple organ failure in one, abdominal bleeding in one, and fungal infection in one). The other 14 patients died of medical reasons (HCC recurrence in 4, chronic rejection in 3, HCV recurrence in 2, PSC recurrence in 1, hemangioendothelioma recurrence in 1, fungal infection in 1, adult T-cell leukemia in 1, and subcapsular hemorrhage of the hepatic graft secondary to liver biopsy in 1).

Figure 1 shows the overall patient and graft survival rates among the four groups. The 1-, 3-, 5-, and 10-year patient survival rates in the MM group were 87.0%, 77.7%, 76.2%, and 70.2%, respectively. Those in the female donor to female recipient (FF) group were 94.0%, 84.6%, 81.6%, and 81.6%, respectively. Those in the MF group were 83.3%, 83.3%, 81.7%, and 75.4%, respectively. Those in the FM group were 80.6%, 66.8%, 61.8%, and 47.7%, respectively. The FM group had significantly worse patient survival rates compared with the FF ($P<0.01$), MF ($P<0.01$), and MM ($P<0.05$) groups.

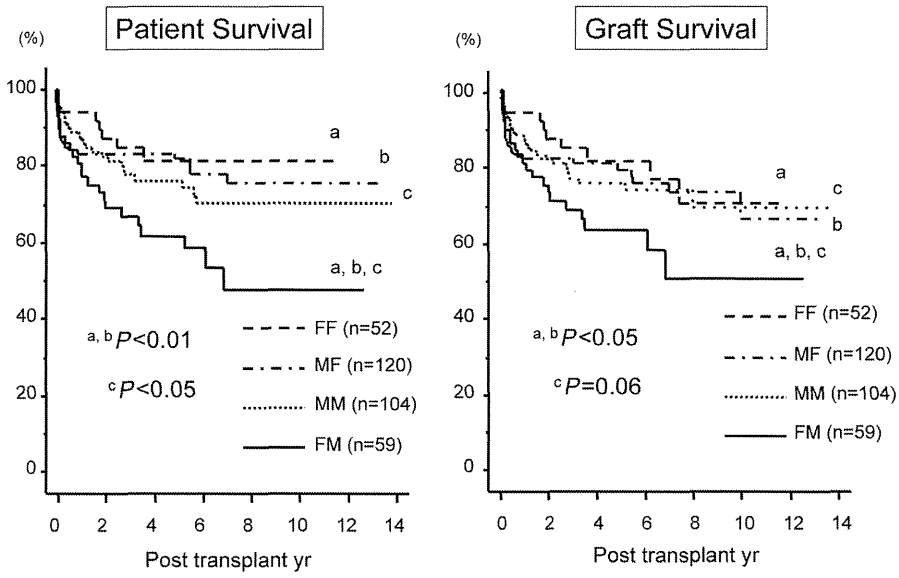

FIGURE 1. Patient and graft survival after LDLT among the four groups defined according to gender combination. The FM group had significantly worse patient survival rates compared with the FF (a, $P<0.01$), MF (b, $P<0.01$), and MM (c, $P<0.05$) groups. The FM group had significantly worse graft survival rates compared with the FF (a, $P<0.05$) and MF (b, $P<0.05$) groups. FM, female donor to male recipient; FF, female donor to female recipient; MF, male donor to female recipient; MM, male donor to male recipient; LDLT, living donor liver transplantation.

The 1-, 3-, 5-, and 10-year graft survival rates in the MM group were 86.2%, 76.9%, 75.5%, and 65.4%, respectively. Those in the FF group were 94.1%, 84.7%, 81.6%, and 70.4%, respectively. Those in the MF group were 81.2%, 81.2%, 78.4%, and 65.8%, respectively. Those in the FM group were 80.9%, 67.0%, 62.0%, and 47.1%, respectively. The FM group had significantly worse graft survival rates compared with the FF ($P<0.02$) and MF ($P<0.05$) groups.

Univariable analysis revealed the following risk factors for patient mortality after LDLT: MELD score more than or equal to 20; the presence of pretransplant diabetes mellitus (DM); absence of consanguinity between the donor and recipient; and inclusion in the FM group (Table 2). The following variables had P values of less than 0.10: donor age more than 60 years and liver failure without HCC. A multivariable analysis including these variables revealed that the FM group ($P=0.006$), the presence of DM ($P=0.001$), and a MELD score more than or equal to 20 ($P=0.004$) were independent risk factors for patient mortality after LDLT (Table 3). Figure 2 shows the overall patient survival rate according to each risk factor.

DISCUSSION

This is the first report on the impact of gender and LDLT outcomes. That a multivariable analysis identified organ donation from a female to a male recipient as an independent risk factor for patient mortality after LDLT is of interest. Because the male–female difference in body size is believed to be a factor in lower survival rates, we performed a subgroup analysis in the FM group according to the GW-SLW ratio. Patients were classified into two subgroups: those with a GW-SLW ratio of less than 40% (n=26) and those with a GW-SLW ratio of more than or equal to 40% (n=33). Findings showed no significant differences between the subgroups (data not shown). Recipient age and primary diagnosis, such as HCV or fulminant hepatic failure, also had no effect on outcomes (data not shown). Biliary issues (type of reconstruction and stricture), which are likely important and related to infection complications, were assessed in the univariable analysis. They did not affect outcomes either (Table 2).

When using a right lobe graft, complicated reconstruction of the middle hepatic vein (MHV) is necessary (*12*). Therefore, the FM group had the highest operation time, cold ischemic time, and recipient blood loss (Table 1). The prevalence of a complicated operation for right lobe graft might have affected outcomes in this study. The patency rate of these reconstructed veins confirmed by Doppler echo 7 days after LDLT was 80%. The frequency of SFSG syndrome in each group was assessed. A total of 30 of 120 cases using a right hepatic graft developed SFSG syndrome. Among them, 10 were in the MF group (47.6%), 12 were in the FM group (27.9%), 5 were in the FF group (20.8%), and 3 were in the MM group (9.7%). The difference was significant ($P=0.02$); however, the frequency rate of SFSG syndrome was more in the MF group than in the other three groups.

In this study, the prevalence of DM, which is a well-accepted risk factor for mortality in cadaveric LT (*14*), differed between males and females (Table 1). Furthermore, the presence of DM was an independent risk factor for mortality.

In the FM group, 44% of recipients received grafts from nonconsanguineous donors (spouses). Univariable analysis revealed that a lack of consanguinity between donor and recipient was a risk factor for mortality, although the frequency of acute cellular rejection did not differ among the four groups. Therefore, it is not clear how consanguinity affected outcomes in this study.

Although Marino et al. (*15*) reported that livers from female donors yielded poorer results even in female recipients, perhaps because of a gender-related immunologic factor or sex hormones, this study confirmed that the FF group had the best patient survival (Fig. 1). It also showed that having a female donor was not a risk factor for survival.

Outcomes from this study are somewhat consistent with those of prior reports on cadaveric LT (*6*, *8*). The increased risk of graft failure in male recipients of female livers may be related to the lack of estrogen and/or progesterone in male recipients (*16*). Furthermore, the human liver has gender-related differences, such as increased hepatic content of microsomal oxidative enzymes in males and different

TABLE 2. Risk factors for patient survival after LDLT: univariable analysis

Variables	Patient survival 1 yr	3 yr	5 yr	P
Recipient variables				
Age (%)				
≥60 yr (n=84)	85.4	75.4	73.4	NS
<60 yr (n=251)	85.7	79.5	77.0	
Etiology (%)				
HCV (n=147)	87.7	77.5	75.3	NS
Others (n=188)	84.0	79.4	76.9	
HCC (%)				
No (n=180)	80.5	74.7	73.0	0.077
Yes (n=155)	91.7	83.2	80.0	
MELD score (%)				
≥20 (n=72)	72.2	65.7	63.3	0.003
<20 (n=258)	89.1	82.4	80.0	
Diabetes mellitus (%)				
Yes (n=51)	70.9	63.9	61.0	0.005
No (n=284)	88.3	81.3	79.0	
Bile duct reconstruction (%)				
Roux-en-Y (n=81)	82.3	76.6	74.9	NS
Duct to duct (n=251)	87.0	79.6	76.9	
Bile duct stenosis (%)				
Yes (n=71)	94.3	83.6	80.3	NS
No (n=262)	83.8	78.0	75.9	
Donor/graft variables				
Age (%)				
≥60 yr (n=6)	66.7	66.7	66.7	0.089
<60 yr (n=329)	86.0	78.9	76.5	
Graft (%)				
Left lobe (n=210)	84.2	80.0	77.9	NS
Others (n=125)	88.2	76.4	73.4	
GW-SLW ratio (%)				
≤35 (n=68)	83.4	77.7	75.4	NS
>35 (n=264)	86.1	78.8	76.3	
Donor-recipient matching				
ABO incompatible (%)				
Yes (n=17)	86.2	86.2	86.2	NS
No (n=318)	85.5	78.3	75.9	
Consanguinity (%)				
No (n=55)	80.9	68.6	68.6	0.030
Yes (n=280)	86.6	80.6	77.8	
Donor-recipient gender (%)				
Mismatch (n=179)	82.4	77.6	74.9	NS
Match (n=156)	89.3	79.9	78.0	
FM group (%)				
Yes (n=59)	80.6	66.8	61.8	0.002
No (n=276)	86.7	81.3	79.5	

LDLT, living donor liver transplantation; GW, graft weight; SLW, standard liver weight calculated by 706.2×body surface area+2.4; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NS, not significant; MELD, model for end-stage liver disease; FM, female donor to male recipient.

TABLE 3. Risk factors for patient survival after LDLT: multivariable analysis

Variables	Odds ratio	95% CI	P
FM group			
Yes vs. No	2.10	1.24–3.57	0.006
Diabetes mellitus			
Yes vs. No	2.76	1.56–4.88	0.001
MELD score			
≥20 vs. <20	2.12	1.27–3.53	0.004
Donor age (yr)			
≥60 vs. <60	2.79	0.85–9.17	0.09
HCC			
No vs. yes	1.54	0.90–2.64	0.11
Consanguinity			
No vs. yes	1.37	0.77–2.43	0.28

LDLT, living donor liver transplantation; CI, confidence interval; FM, female donor to male recipient; MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma.

numbers of estrogen and androgen receptors on hepatocytes between males and females (*7*).

In a rodent hepatectomy model, serum estrogen levels and the number of estrogen hepatic receptors increased concomitantly with liver regeneration (*17*). Kahn et al. (*18*) also demonstrated a reduction in the number of estrogen receptors in the livers of gender-mismatched recipients 10 days after transplantation. Thus, it is possible that the poor outcome in the FM group was caused by reduced serum estrogen levels in the male recipients and a lower number of estrogen receptors in the female organ. Further long-term study is warranted to clarify how hormonal factors affect the outcome of LT.

Because of the shortage of donor organs, the gender of donors is not routinely used as a selection criterion for LDLT (*19*). Although LDLT allows for elective planning of the procedure, which may enable selection of the most suitable donor from among the candidates (*19*), it is important to be mindful of hormonal and/or immunological differences between the genders to improve LDLT outcomes. At the same time, we need to remember that a multiplicity of donor and recipient factors influence posttransplant outcomes (*20*). For these reasons, further study in this area is called for before any changes in clinical decision-making based on findings in this report.

In conclusion, male recipients who received transplants from female donors had the worst survival among the four donor-recipient groups. Being a male recipient receiving a transplant from a female donor was an independent risk factor for patient mortality after LDLT. Further study is warranted to clarify the mechanism of this outcome.

MATERIALS AND METHODS

Patients

A total of 335 adult patients (172 women and 163 men) who had undergone LDLT because of end-stage liver disease at Kyushu University Hospital between May 1997 and March 2011 were enrolled in the trial; seven retransplanted cases were included. The cause of liver disease (women/men) was hepatitis C (59/88), fulminant hepatic failure (32/18), primary biliary cirrho-