Table 1: Patient demographics

Variables	Total (n = 210)	Early graft loss		p-Value
		Yes (n = 13)	No (n = 197)	
Recipient age (years)	53.9 ± 10.5 (55, 18–73)	50.4 ± 10.9 (52, 21–64)	54.1 ± 10.5 (55, 18–73)	0.230
Recipient gender, male	102 (48.6)	5 (38.4)	97 (49.2)	0.451
Diseases				
Acute liver failure	16 (7.6)	1 (7.7)	15 (7.6)	0.748
Cholestatic cirrhosis	35 (16.7)	2 (15.4)	33 (16.8)	
Postnecrotic cirrhosis	154 (73.3)	9 (69.2)	145 (73.6)	
Others	4 (1.9)	0 (0.0)	4 (2.0)	
Hepatocellular carcinoma	112 (53.3)	3 (23.1)	109 (55.3)	0.024
Child-Pugh class				
A	10 (5.2)	0 (0.0)	10 (5.5)	0.380
B	56 (29.0)	2 (16.7)	54 (29.8)	
C	127 (65.8)	10 (83.3)	117 (64.7)	
MELD score	16.4 ± 6.4 15 (6–40)	20.7 ± 4.6 (20, 13–29)	16.2 ± 6.4 (15, 6–40)	0.019
Hospitalized status	82 (39.0)	10 (76.9)	72 (36.5)	0.004
Major shunt vessels	82 (39.0)	6 (46.1)	76 (38.6)	0.587
Donor gender, male	132 (62.9)	10 (76.9)	122 (61.9)	0.278
Donor age (years)	35.0 ± 10.6 (34, 19–62)	33.8 ± 12.9 (28, 21–62)	35.1 ± 12.9 (34, 19–62)	0.649
Incompatible blood type	10 (4.7)	0 (0.0)	10 (5.1)	0.461
Left lobe graft	122 (58.1)	8 (61.5)	114 (57.8)	0.795
GV (g)	476 ± 106 (464, 250–734)	486 ± 113 (480, 280–734)	475 ± 106 (460, 250–720)	0.725
GV/SLV ratio (%)	41.2 ± 8.4 (40.6, 23.7–72.5)	42.4 ± 8.1 (42.8, 29.7–58.7)	41.3 ± 8.4 (40.5, 23.7–72.5)	0.646
GRWR (%)	0.80 ± 0.18 (0.77, 0.45–1.78)	0.81 ± 0.14 (0.81, 0.61–1.06)	0.79 ± 0.18 (0.77, 0.45–1.78)	0.767
PVP at laparotomy (mmHg)	24.1 ± 6.1 (24, 7–40)	23.0 ± 5.1 (24.5, 15–30)	24.2 ± 6.2 (24, 7–40)	0.512
Splenectomy	136 (64.7)	7 (53.8)	129 (65.4)	0.380
Cold ischemic time (min)	98 ± 89 (72, 25–377)	100 ± 42 (96, 40–179)	98 ± 91 (71, 25–377)	0.951
Warm ischemic time (min)	39 ± 11 (37, 22–102)	42 ± 12 (40.5, 26–62)	39 ± 11 (36, 22–102)	0.352
Hepatic arterial flow (mL/min)	101 ± 64 (89, 15–580)	108 ± 53 (114, 30–192)	101 ± 65 (88.5, 15–580)	0.701
Portal venous flow (L/min)	1.76 ± 0.67 (1.64, 0.27–3.85)	1.73 ± 0.56 (1.53, 1.00–2.65)	1.77 ± 0.67 (1.65, 0.27–3.85)	0.855
PVP at the closure (mmHg)	16.3 ± 4.1 (16, 6–37)	17.9 ± 7.4 (16, 11–37)	16.2 ± 3.8 (16, 6–26)	0.165
Duct-to-duct biliary reconstruction	181 (86.2)	12 (96.2)	168 (85.7)	0.454
Operation time (min)	805 ± 180 (777, 437–1519)	861 ± 246 (818, 579–1315)	802 ± 176 (773, 437–1519)	0.293
Operative blood loss (L)	5.2 ± 6.4 (3.4, 0.2–50.4)	10.7 ± 12.3 (4.0, 0.75–35.4)	4.9 ± 5.8 (3.3, 0.2–50.4)	0.003
LDLT before 2008	112 (53.3)	9 (69.2)	103 (52.3)	0.223
Maximum values within POD 28				
Total bilirubin (mg/dL)	10.5 ± 8.2 (7.6, 1.4–46.7)	29.5 ± 6.3 (29.4, 9.2–46.7)	9.1 ± 6.3 (7.0, 1.4–32.1)	<0.001
Daily ascites output (L)	1.2 ± 1.4 (0.8, 0.2–11.3)	2.1 ± 1.4 (1.5, 0.7–1.8)	1.1 ± 1.4 (0.7, 0.2–11.3)	0.017
PT-INR	1.8 ± 0.4 (1.8, 1.2–3.8)	2.2 ± 0.6 (2.2, 1.8–3.8)	1.8 ± 0.3 (1.8, 1.2–3.6)	<0.001
Ammonia (μg/dL)	77 ± 40 (71, 14–353)	121 ± 77 (87, 48–353)	74 ± 34 (70, 14–286)	<0.001

Continued

Table 1: Continued.

Variables	Total (n = 210)	Early graft loss		p-Value
		Yes (n = 13)	No (n = 197)	
Values on POD 14				
Total bilirubin (mg/dL)	6.0 ± 7.1 (2.8, 0.4–41.3)	19.7 ± 5.6 (18.6, 2.9–41.3)	5.1 ± 5.6 (2.6, 0.4–29.3)	<0.001
Daily ascites output (L)	0.4 ± 0.9 (0, 0–8.9)	1.3 ± 1.6 (0, 0.7–5.7)	0.3 ± 0.8 (0, 0–8.9)	<0.001
PT-INR	1.3 ± 0.6 (1.1, 0.9–3.3)	1.5 ± 0.5 (1.3, 1.1–3.3)	1.2 ± 0.6 (1.1, 0.9–2.6)	0.032

MELD = model for end-stage liver disease; GV = graft volume; SLV = standard liver volume; GRWR = graft recipient weight ratio; PVP = portal venous pressure; LDLT = living donor liver transplantation; POD = postoperative day; PT-INR = prothrombin time international normalized ratio.

defined as hyperbilirubinemia (e.g. T.Bil > 20 mg/dL for >seven consecutive days occurring after postoperative day [POD] 7). Early graft loss was defined as graft loss occurring within 6 months after LDLT.

Liver biopsy

Graft biopsies early after LDLT were obtained percutaneously or under laparotomy. For left lobe grafts, percutaneous biopsy was performed because manual compression of the punctured liver is possible. For right lobe grafts, open biopsy for suturing the punctured site was performed if indicated. If PGD was highly suspected because of hyperbilirubinemia with stable transaminase levels, biopsy was postponed.

Statistical analysis

Values are expressed as the mean ± standard deviation (median, minimum–maximum). Variables were analyzed using the χ^2 tests for categorical values or the Mann–Whitney's test for continuous variables. Cumulative survival analyses were determined using the Kaplan–Meier method with the log-rank test. Sensitivity (%) was calculated as true positive (n)/[true positive (n) + false negative (n)]. Specificity was calculated as true negative (n)/[true negative (n) + false positive (n)]. Values of p value <0.05 were considered statistically significant. Receiver operating characteristic curve analysis was also performed.

Results

Characteristics of the recipients, donors and grafts

The mean age of the recipients was 53.9 ± 10.5 years (Table 1). Indications for LDLT included acute liver failure (n = 16, 7.6%), cholestatic cirrhosis (n = 35, 16.7%), post-necrotic viral or nonviral cirrhosis (n = 154, 73.3%) and others (n = 4, 1.9%). Approximately half of the patients had hepatocellular carcinomas (n = 112, 53.3%). The majority of the patients were Child-Pugh class C (n = 127, 65.8%). The mean MELD score was 16.4 ± 6.4. Overall, 39% of the patients (n = 82) had been hospitalized before LDLT and had major (>1.0 cm) shunt vessels (n = 82, 39.0%).

The mean age of the donors was 35.0 ± 10.6 years. Graft types included left lobe grafts (n = 122, 58.1%) and right lobe grafts (n = 88, 41.9%). Ten donors (4.7%) provided blood type incompatible donors. The mean GV was 476 ± 106 g, the mean GV/SLV was 41.2 ± 8.4 and the mean GRWR was 0.80 ± 0.18. Splenectomy was performed in 136 cases (64.7%) and duct-to-duct biliary reconstruction was performed in 181 cases (86.2%). The mean operative

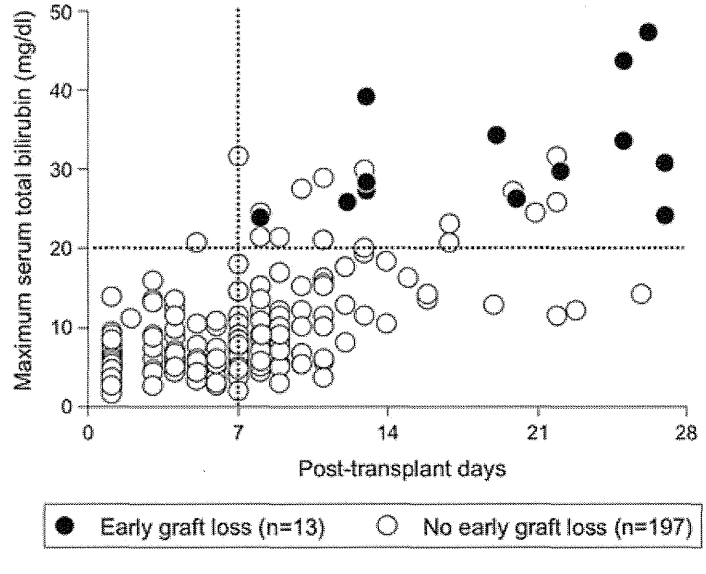

Figure 2: Maximum total bilirubin values within 28 days after transplantation plotted against the post-operative date (n = 210). All of the patients with early graft loss (black dots; n = 13) had maximum total bilirubin >20 mg/dL later than 1 week after transplantation (p < 0.001).

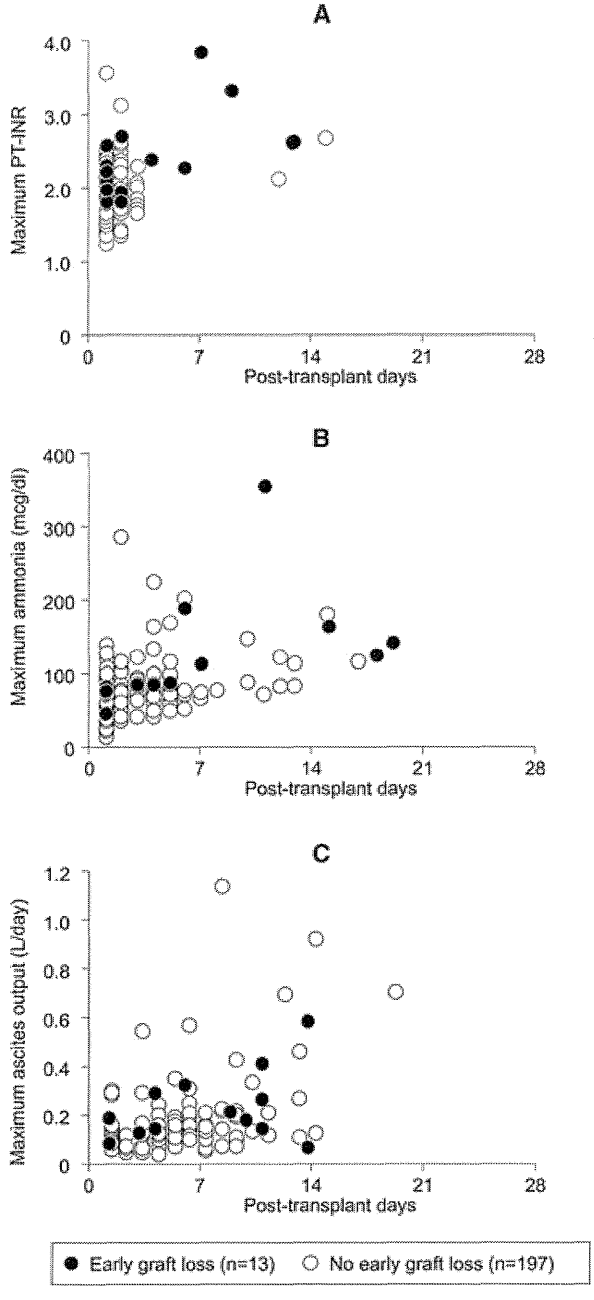

Figure 3: Maximum prothrombin international normalized ratio (PT-INR, A), ammonia levels (B) and ascites output (C) plotted against the postoperative date (n = 210). The black dots (n = 13) represent patients with early graft losses.

time was 805 ± 180 min and the mean blood loss was 5.2 ± 6.4 L.

We have performed 346 adult-to-adult LDLTs between May 1997, adult-to-adult LDLT program started, and July 2011. The cumulative 2-year graft survival rate since 2004 (87.0%, n = 228) was significantly better than before 2004 (70.8%, n = 118, p < 0.001). Therefore, to exclude possible technical or learning bias and to focus on PGD, only cases treated since 2004 were included in the current analysis.

PGD

Overall, 13 cases experienced early graft loss within 6 months after adult-to-adult LDLT; none of these cases were associated with technical, immunological or hepatitis-related issues (Table 1). The mean graft survival of these 13 cases was 1.7 ± 1.0 months. Early graft loss in all of the cases was caused by PGD. Prior hospitalization of the recipient (46.1% vs. 38.6%; p = 0.004), higher MELD score (20.7 ± 4.6 vs. 16.2 ± 6.4; p = 0.019), absence of hepatocellular carcinoma (23.1% vs. 55.3%; p = 0.024) and massive intraoperative blood loss (10.7 ± 12.3 L vs. 4.9 ± 5.8; p = 0.003) were significantly associated with early graft loss. Graft GV/SLV ratio and GRWR were not associated with early graft loss.

The maximum T.Bil values (29.5 ± 6.3 mg/dL vs. 9.1 ± 6.3 mg/dL; p < 0.001), daily ascites output (2.1 ± 1.4 L vs. 1.1 ± 1.4 L; p < 0.001), PT-INR (2.2 ± 0.6 vs. 1.8 ± 0.3, p < 0.001) and ammonia levels (121 ± 77 μg/dL vs. 74 ± 34 μg/dL; p < 0.001) measured by POD 28 were significantly greater in cases with early graft loss. The mean values of T.Bil (19.7 ± 5.6 mg/dL vs. 5.1 ± 5.6 mg/dL; p < 0.001), daily ascites output (1.3 L ± 1.6 vs. 0.3 ± 0.8 L; p < 0.001) and PT-INR (1.5 ± 0.5 vs. 1.2 ± 0.6; p = 0.032) on POD 14 were also significantly greater in cases with early graft loss. Grafts with early mortality had significantly worse hepatic parameters at both a fixed date (i.e. on POD 14) and within a fixed time (i.e. within POD 28). However, grafts may show worse hepatic parameters in the early postoperative period because of the deteriorated recipient's condition or may show delayed worsening as a result of PGD.

Therefore, maximum T.Bil (Figure 2) and other hepatic parameters (Figure 3), including maximal PT-INR, ammonia and ascites output, were plotted against their corresponding POD. All 13 cases with early functional graft loss (n = 13) had maximum T.Bil >20 mg/dL after POD 7 (p < 0.001; Figure 2). No definite relationship with early graft loss was observed between the other hepatic parameters including PT-INR, ammonia and ascites output (Figure 3).

The maximum T.Bil values within POD 28 after LDLT were also plotted against GV/SLV or GRWR (Figure 4). Grafts with maximum T.Bil >20 mg/dL were evenly distributed with GV/SLV and GRWR.

DFH

Because the maximum T.Bil >20 mg/dL detected after POD 7 was associated with PGD, which persisted for a number of consecutive days, we defined DFH as described in the methods. We calculated the sensitivity and specificity for early graft loss caused by functional graft failure

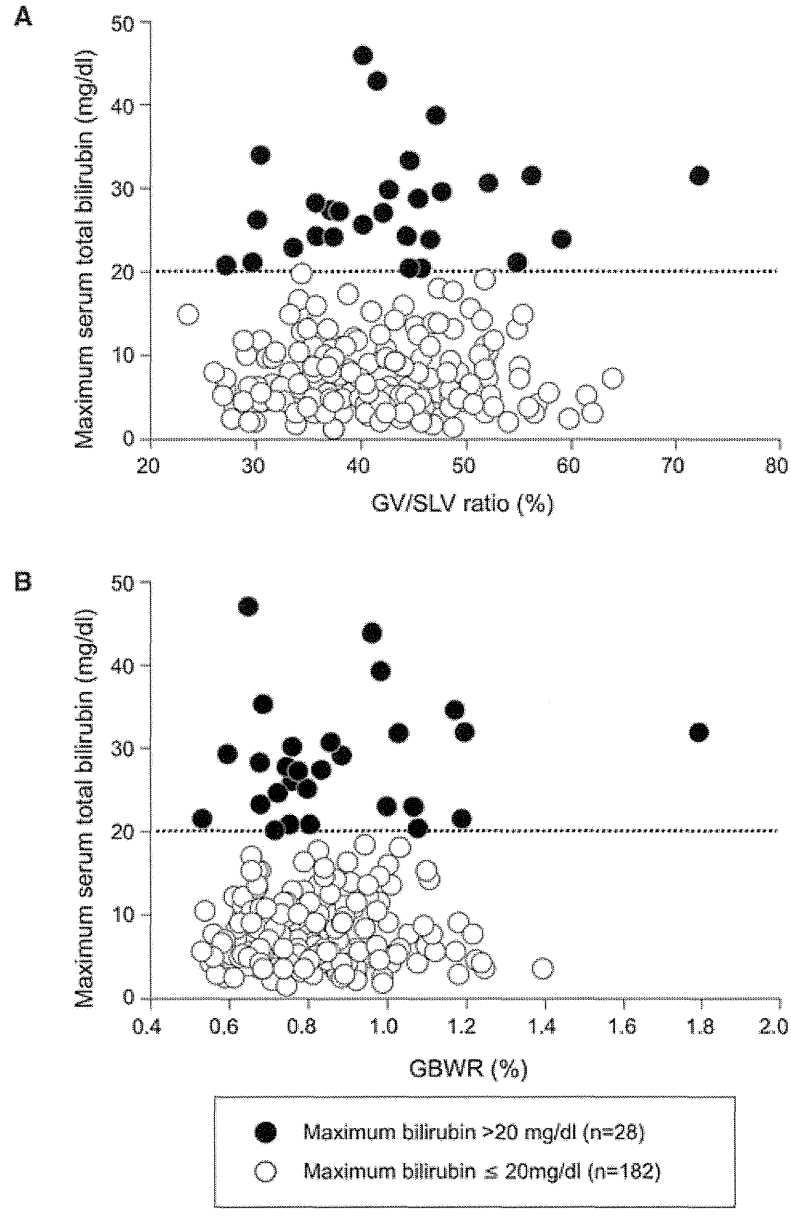

Figure 4: Maximum total bilirubin values within 28 days after transplantation plotted against GV/SLV (A) and GRWR (B) (n = 210). GRWR = graft recipient weight ratio; GV = graft volume; SLV = standard liver volume.

using several definitions (Table 2), including DFH with T.Bil >10, 15, 20 or 25 mg/dL for >seven consecutive days after POD 7 (DFH-10, DFH-15, DFH-20 and DFH-25, respectively), small-for-size graft dysfunction as defined by Dahm et al. (8), SFSS as defined at our institute in 2006 (15), and SFSS as defined by Hill, et al. (14). The sensitivities of the previous definitions of small-for-size graft dysfunction or syndrome for early loss caused by PGD were <50%. On the other hand, DFH-20 (i.e. T.Bil > 20 mg/dL for >seven consecutive days after POD 7) showed the highest sensitivity (100%) and the second highest (95.4%) specificity for detecting early graft loss caused by nontechnical, nonimmunological and nonhepatitis-related PGD.

Characteristics of grafts with DFH-20

The effects of DFH-20 on cumulative graft survival are shown in Figure 5. The 1- and 2-year graft survival rates were 40.9% and 35.1% for grafts with DFH-20 (n = 22) versus 97.6% and 93.8% for grafts without DFH-20 (n = 188), respectively ($p < 0.001$).

Risk factors for DFH-20

Univariate analyses (Table 3) showed that recipient Child class C (yes; 14.1% vs. 5.1%; p = 0.047), MELD score >15 (yes; 15.5% vs. 4.3%; p = 0.008), hospitalized status (yes; 17.3% vs. 6.3%; vs. p = 0.012), the presence of major shunt vessels >1 cm in diameter (yes; 15.9% vs. 7.0%;

Table 2: Sensitivity and specificity for detecting early graft loss caused by primary graft dysfunction after LDLT

	Early graft loss because of primary graft dysfunction		
Definitions	Sensitivity (%)	Specificity (%)	Area under ROC
Delayed functional hyperbilirubinemia (DFH)			
with T.Bil >10 mg/dL (DFH-10)	100.0	71.6	0.857
with T.Bil >15 mg/dL (DFH-15)	100.0	89.3	0.946
with T.Bil >20 mg/dL (DFH-20)	100.0	95.4	0.977
with T.Bil >25 mg/dL (DFH-25)	53.8	97.4	0.756
*For >seven consecutive days after POD 7, excluding technical, immunological and hepatitis factors.			
Small-for-size graft dysfunction, Dahm et al. (8)	23.1	95.9	0.595
*GRWR <0.8 and the presence of two of the followings for three consecutive days during the first postoperative week: T.Bil >100 μmol/L, PT-INR >2 and encephalopathy grade 3 or 4, excluding technical, immunological and infectious factors.			
Small-for-size graft syndrome, Soejima, et al. (16)	30.7	87.3	0.590
*Prolonged cholestatis (T.Bil >10 mg/dL on POD14) and intractable ascites (ascites > 1 L on POD 14 or >0.5 L on POD 28).			
Small-for-size graft syndrome, Hill et al. (14)	46.2	95.9	0.687
*T.Bil >10 mg/dL (and continuing to increase) after POD 7, PT-INR >1.5 and ascites >2 L, excluding mechanical/technical problems.			

LDLT = 8 living donor liver transplantation; ROC = receiver operating characteristic curve; T.Bil = total bilirubin; DFH = delayed functional hyperbilirubinemia; POD = postoperative day; GRWR = graft recipient weight ratio; PT-INR = prothrombin time-international normalized ratio.

p = 0.042), donor age >45 years (yes; 21.3% vs. 7.4%; p = 0.006), PVP >20 mmHg at the end of the surgery (yes; 20.6% vs. 8.5%; p = 0.004) and intraoperative blood loss >1 0 L (yes; 38.1% vs. 7.4%; p < 0.001) were risk factors for DFH with T.Bil >20 mg/dL. On the other hand, graft type, GV/SLV and GRWR were not significant risk factors. Multivariate analysis was not included in the current report because of the smaller number of the patients with DFH-20.

We performed additional univariate analyses (Table 4) to compare cases with (n = 13) or without (n = 9) early graft loss among those with DFH-20 (n = 22). The maximum PT-INR was 2.4 ± 0.6 and 1.8 ± 0.3 for grafts with and without

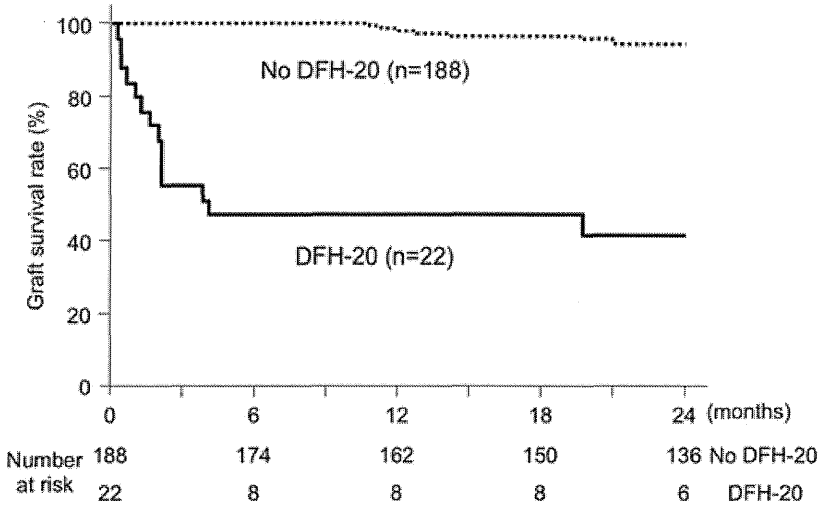

Figure 5: Cumulative graft survival of patients with (n = 22) or without (n = 188) DFH. The difference in survival was significantly different (p < 0.001). DFH = delayed functional hyperbilirubinemia: total bilirubin >20 mg/dL for >7 consecutive days after postoperative day 7, excluding technical, immunological and hepatitis factors.

early graft loss, respectively. Categorical analysis showed that early graft loss was more frequently associated with coagulopathy (PT-INR >2) compared with grafts without early graft loss (76.9% vs. 11.1%; p = 0.011).

Pathological findings of the grafts with DFH-20

Liver biopsy specimen was obtained in 8 of the 22 patients (21.3 ± 9.1 days after LDLT). Centrilobular hepatocyte ballooning and cholestasis were the most prominent and characteristic findings (Figure 6). Although ductular reaction was observed in six cases, other findings including necrosis, steatosis, nonspecific portal infiltration were not the consistent findings (Table 5).

Discussion

The primary endpoint of this study was to characterize PGD after LDLT, in which a smaller but qualified graft is usually transplanted with a short cold ischemic time is usually transplanted. We found that DFH-20 essentially encompassed PGD after LDLT with a high mortality rate. Other factors such as ammonia levels, PT-INR and ascites volume were not associated with PGD. The superior sensitivity and specificity of DFH-20 for detecting PGD after LDLT, compared with other definitions, is clinically relevant because it is important to know whether the graft is likely to recover, or fail and require retransplantation. Worryingly, the rate of graft loss was particularly high in cases with DFH-20 and coagulopathy (i.e. PT-INR >2). Therefore, these cases should be considered as candidates for retransplantation.

The significance of hyperbilirubinemia has been reported in both transplant and nontransplant settings in the literature. In LDLT, Marubashi et al. (20) reported that T.Bil >27 mg/dL is a significant indicator for early graft loss, regardless of the cause. Even in pediatric LDLT, Emond et al. (21) reported that cholestasis was more prominent and was prolonged in recipients with smaller LDLT grafts. Although studies evaluating prolonged hyperbilirubinemia in DDLT are limited, Fusai et al. (22) reported that functional hyperbilirubinemia >100 μmol/L sustained for at least 1 week after DDLT was associated with poor prognosis. After hepatic resection for tumors, Balzan et al. (23) showed that PT <50% and T.Bil >50 μmol/L on POD 5 is associated with a mortality rate exceeding 50% after hepatectomy.

PGD after LDLT and PNF after DDLT are quite different in terms of their pathogeneses and clinical manifestations. PNF after DDLT usually becomes evident during the immediate postoperative period with rapidly rising transaminase levels, absence of bile production, severe coagulopathy, acidosis and hemodynamic instability (1–3). These clinical characteristics of PNF after DDLT are attributed to massive hepatic cytolysis following reperfusion of a graft

Table 3: Univariate analysis of risk factors for DFH-20

	DFH with T.Bil >20 mg/dL		
Variables	Yes (n = 22)	No (n = 188)	p-Value
Recipient gender, male	10 (45.5)	92 (48.9)	0.721
Recipient age >60 years	4 (18.2)	52 (27.7)	0.341
Child-Pugh class C	18 (81.8)	109 (57.9)	0.066
MELD score >15	18 (81.8)	98 (52.2)	0.008
Total bilirubin >8 mg/dL	7 (31.8)	38 (20.2)	0.209
PT-INR > 1.8	10 (45.5)	34 (18.1)	0.003
Creatinine >1.0 mg/dL	4 (18.1)	23 (12.2)	0.430
Hospitalized status	14 (63.6)	68 (36.2)	0.012
Acute liver failure	1 (4.5)	16 (8.5)	0.518
Major shunt vessels	13 (59.1)	69 (36.7)	0.042
Donor gender, male	15 (68.2)	117 (62.2)	0.584
Donor age >45 years	10 (45.5)	37 (19.7)	0.006
Left lobe graft	12 (54.5)	110 (58.5)	0.721
GV/SLV ratio <30%	1 (4.5)	14 (7.4)	0.617
GV/SLV ratio <40%	8 (36.4)	92 (48.9)	0.264
GRWR < 0.6%	1 (4.5)	19 (10.1)	0.401
GRWR < 0.8%	12 (54.5)	104 (55.3)	0.944
PVP > 30 mmHg at laparotomy	2 (7.1)	26 (14.2)	0.963
No splenectomy	8 (36.4)	66 (35.1)	0.907
Cold ischemic time >120 min	8 (36.4)	43 (22.9)	0.167
Warm ischemic time >50 min	6 (27.3)	26 (13.9)	0.095
PVP > 20 mmHg at closure	7 (31.8)	27 (14.4)	0.036
Blood loss > 10 L	8 (36.4)	13 (6.9)	< 0.001

DFH-20 = delayed functional hyperbilirubinemia: total bilirubin >20 mg/dL for >7 consecutive days after postoperative day 7, excluding technical, immunological and hepatitis factors; MELD = model for end-stage liver disease; PT-INR = prothrombin time international normalized ratio; GV = graft volume; SLV = standard liver volume; GRWR = graft recipient weight ratio; PVP = portal venous pressure.

Table 4: Characteristics of cases with or without early graft loss under DFH-20

	Early graft loss		
Variables	Yes (n = 13)	No (n = 9)	p-Value
Recipient age (years)	50.9 ± 11.2 (52, 21–64)	48.2 ± 8.7 (46, 34–62)	0.552
MELD score	19.7 ± 4.0 (20, 13–27)	17.1 ± 3.8 (16, 12–26)	0.144
Donor age (years)	43.2±10.8 (46, 20–56)	36.4 ± 14.7 (36, 21–62)	0.249
GV (g)	483 ± 114 (480, 280–734)	524 ± 89 (540, 400–620)	0.385
GV/SLV ratio (%)	41.8 ± 8.3 (41.0, 29.7–58.7)	45.9 ± 11.8 (42.8, 33.7–72.5)	0.351
GRWR (%)	0.79 ± 0.16 0.79 (0.56–1.1)	0.91 ± 0.35 (0.74, 0.67–1.78)	0.289
PVP at laparotomy (mmHg)	23.5 ± 5.3 (25, 15–30)	25.4 ± 5.5 (27, 16–32)	0.459
Cold ischemic time (min)	141 ± 107 (90, 40–179)	100 ± 42 (162, 43–377)	0.951
Warm ischemic time (min)	41 ± 12 (40, 26–62)	43 ± 13 (40, 24–66)	0.799
Hepatic arterial flow (mL/min)	102 ± 55 (104, 29–192)	96 ± 66 (70.5, 21–224)	0.817
Portal venous flow (L/min)	1.67 ± 0.58 (1.46, 0.99–2.65)	1.61 ± 0.60 (1.40, 0.81–2.3)	0.842
PVP at the closure (mmHg)	18.4 ± 7.4 (17, 11–37)	17.0 ± 4.6 (17.5, 11–23)	0.640
Operation time (min)	854 ± 236 812 (579–1315)	942 ± 224 (978, 597–1360)	0.397
Operative blood loss (L)	13.1 ± 14.1 (5.9, 0.7–38.0)	111.5 ± 7.8 (10.0, 2.4–26.5)	0.774
Maximum values within POD 28			
Total bilirubin (mg/dL)	31.4 ± 8.1 (29.4, 21.8–46.7)	27.7 ± 3.1 (27.5, 23.1–32.1)	0.232
Daily ascites output (L)	1.8 ± 1.3 (1.5, 0.6–4.0)	1.6 ± 1.2 (1.6, 0.4–2.7)	0.820
PT-INR	2.4 ± 0.6 2.3 (1.9–3.8)	1.8 ± 0.3 1.8 (1.4–2.3)	0.011
PT-INR > 2	10 (76.9)	1 (11.1)	0.002
Ammonia (μg/dL)	125 ± 80 (90, 48–353)	115 ± 59 (89, 41–204)	0.767

DFH-20 = delayed functional hyperbilirubinemia: total bilirubin >20 mg/dL for >seven consecutive days after postoperative day 7, excluding technical, immunological and hepatitis factors; MELD = model for end-stage liver disease; GV = graft volume; SLV = standard liver volume; GRWR = graft recipient weight ratio; PVP = portal venous pressure; POD = postoperative day; PT-INR = prothrombin time international normalized ratio.

with steatosis, higher age or prolonged cold ischemic time (1,2,24). On the other hand, PGD after LDLT becomes evident in a gradual and delayed fashion, and is characterized by hyperbilirubinemia and sometimes massive ascites, without elevated of serum transaminase levels, representing functional intolerance during regeneration (13–16). Because these LDLT grafts show insufficient function rather than being nonfunctional, we termed than as PGD. Thus, PNF after DDLT corresponds to necrosis and PGD after LDLT represents functional intolerance.

The pathologic findings of DFH-20 were consistent with those of nonspecific preservation injuries as previously described, including prominent centrilobular hepatocyte ballooning, cholestasis, possibly accompanied by steatosis, necrosis, portal infiltration and ductular reaction (21,25,26). In electron-microscopic studies using postliver transplant specimens after DDLT, Ng et al. (27) showed that ballooned hepatocytes were characterized dilatation of the cisternae of the rough endoplasmic reticulum and mitochondria. In LDLT, Emond et al. (21) examined 25 patients and reported that the pathologic changes after LDLT are more prominent in smaller grafts. Thus, such centrilobular pathologic changes after LDLT might be attributed to overperfusion and ischemic stress.

In LDLT, the issue of graft size, namely SFSS, has been of significant concern since the first adult-to-adult LDLT

Table 5: Summary of the pathological findings in the grafts (n = 8/22) with DFH-20

	Case							
	#1	#2	#3	#4	#5	#6	#7	#8
Graft type	Left	Left	Left	Left	Left	Right	Left	Left
GV/SLV (%)	33.7	41.0	44.2	36.9	29.7	44.3	30.1	35.3
GRWR (%)	0.67	0.88	1.05	0.74	0.71	0.72	0.64	0.56
Maximum T.Bil (mg/dL)	24.1	43.3	33.3	24.9	25.9	24.5	34.2	28.1
Early graft loss	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Pathological findings								
Cholestasis	++	++	++	++	+++	++	++	++
Ballooning	++	++	+++	+++	++	++	++	++
Necrosis	++	+	+	−	−	−	+	+
Steatosis	+	+	−	−	−	+	+	++
Portal infiltration	+	−	+	−	−	−	−	−
Ductular reaction	−	+	+	+	+	−	+	+

DFH = delayed functional hyperbilirubinemia: total bilirubin >20 mg/dL for >seven consecutive days after postoperative day 7, excluding technical, immunological and hepatitis factors; GRWR = graft recipient weight ratio; GV = graft volume; SLV = standard liver volume.

was performed in 1998 (28). We consider that SFSS after LDLT is included in the concept of PGD after LDLT, because functional graft dysfunction after LDLT is now thought to be caused by graft size as well as several other factors (11–15). In this analysis, such additional factors included Child class C, MELD score >15, prolonged pretransplant hospitalized status, the presence of major shunt vessels, donor age >45 years, PVP >20 mmHg at the end of the surgery and intraoperative blood loss >10 L. Although small-for-size graft dysfunction was originally defined in 2005 (8) and has been used in many reports published since then, the descriptions better resemble PNF in DDLT, namely severe coagulopathy (PT-INR >2) and advanced encephalopathy (Grade 3 or 4) with T.Bil >100 μmol/L during the first postoperative week. It seems that PGD after LDLT characterized by DFH-20 encompasses SFSS and represents functional graft intolerance caused by multiple factors after LDLT (Figure 7).

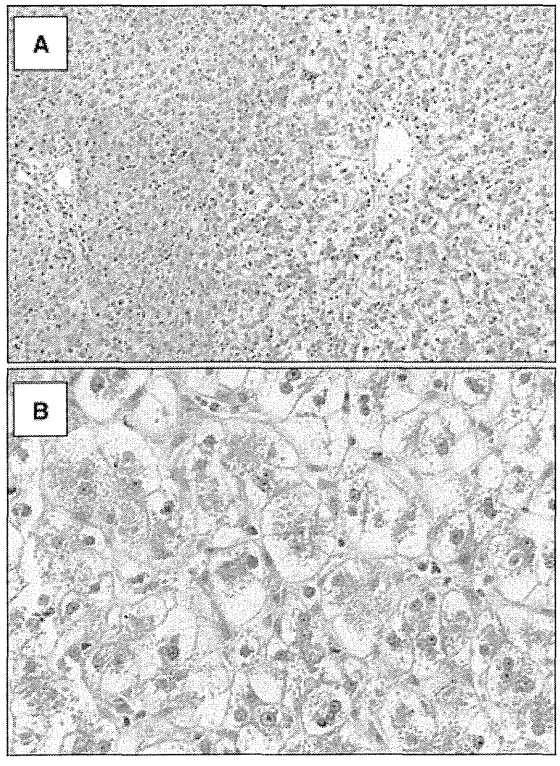

Figure 6: The representative microscopic findings of the graft with DFH-20 (Case #4). Centrilobular hepatocyte ballooning with cholestasis was prominent and the ballooned cells were well demarcated from the uninvolved cells (A, H.E. ×100). The ballooned hepatocytes showed intracellular cholestasis (B, H.E. ×400). DFH-20, delayed functional hyperbilirubinemia: total bilirubin >20 mg/dL for >seven consecutive days after postoperative day 7.

Nevertheless, it is also true that graft size is one of the main contributors to the clinical outcome (8,9). We started our adult-to-adult LDLT program in 1997 and exclusively used left lobe grafts with GV/SLV >30% (29) with an inferior 2-year graft survival rate (70.8%) before 2004. Since 2004, we have revised the graft selection criteria and now use left or right lobe grafts with GV/SLV >35% to provide an adequate safety margin (17). Therefore, all of the data in the current series were under obtained from our intent to maintain, keeping GV/SLV >35%. Besides intension of achieving a GV being an adequate safety margin, our transplant center has always considered the severity of recipient illness and potential surgical difficulties. We use a formula to score the overall risk of the procedure to maintain appropriate safety limits (30). Moreover, our surgical techniques to modulate portal and venous flows have been refined as previously reported (19,31–33). Based on these approaches, the 2-year graft survival rate at our center has reached 87.0% since 2004.

The main limitation of this study is that selection bias may confound our interpretations because GV was not correlated with mortality. Reports from other centers are also necessary to help generalize our current findings. Our results do not necessarily imply that small grafts without intentional selection or surgical refinements could yield satisfactory outcomes. The other limitation of this study is

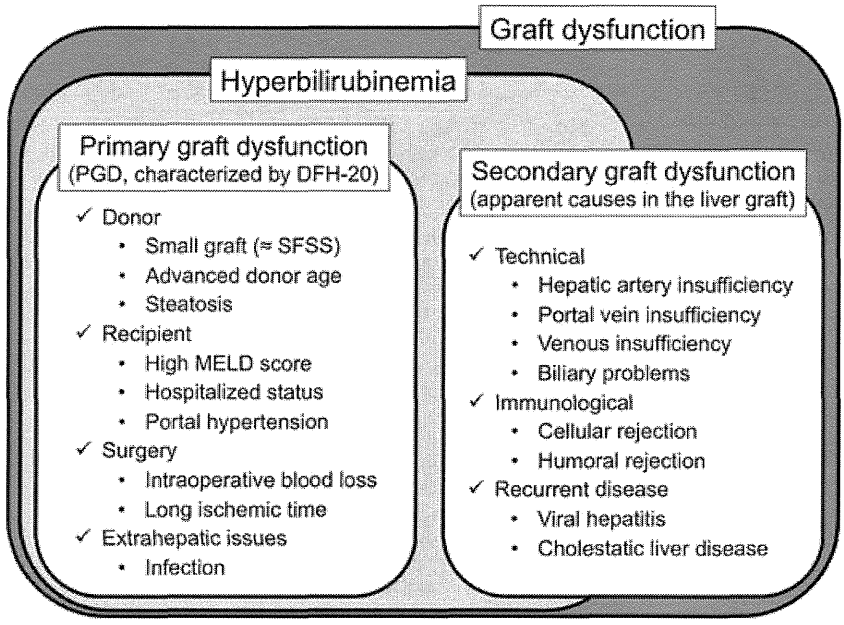

Figure 7: Associations between PGD, SFSS and secondary graft dysfunction. PGD, characterized by DFH-20, encompasses SFSS and other causes of functional and primary graft dysfunction. DFH-20: delayed functional hyperbilirubinemia (total bilirubin >20 mg/dL for >7 consecutive days after postoperative day 7, excluding technical, immunological and hepatitis factors); MELD, model for end-stage liver disease; PGD, primary graft dysfunction; SFSS, small-for-size syndrome.

that the immunological factors have not been completely ruled out because of insufficient histological evidence in the study population, no assessment of antibody and no thorough analysis of transfusion related immune events. Further prospective analysis is necessary to address such issues.

In conclusion, we have proposed a new concept for PGD after LDLT with a higher early graft mortality rate and characterized by DFH-20, which is caused by multiple factors.

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Disclosure

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1: The details of the cases excluded from the analysis

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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.

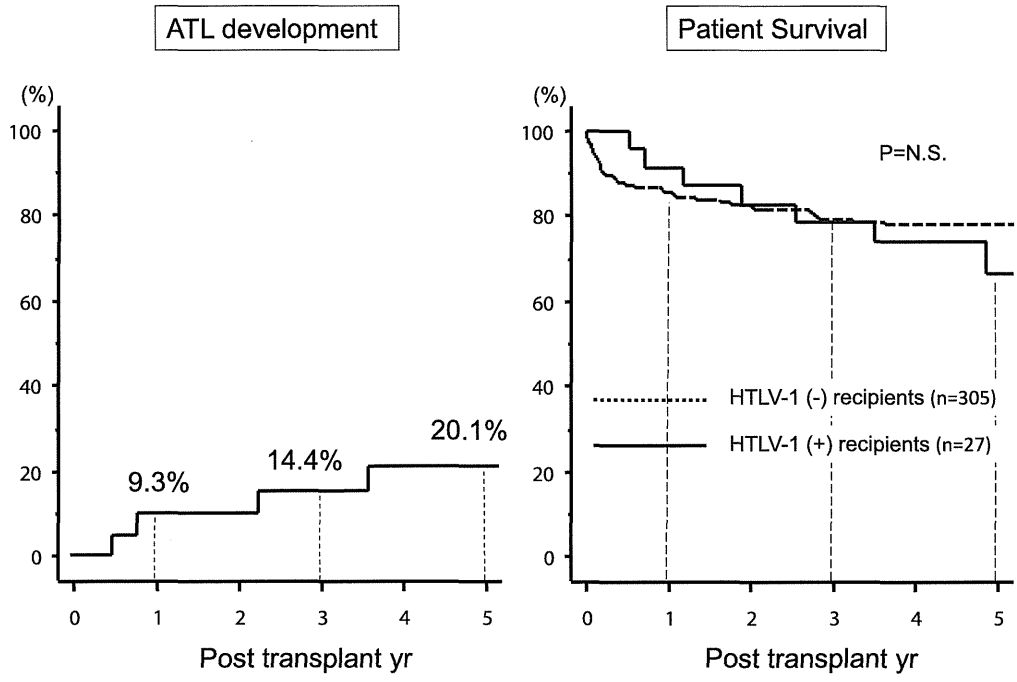

Figure 1: ATL development rate and recipient survival after LDLT. The 1-, 3- and 5-year ATL development rates were 9.3%, 14.4% and 20.1%, respectively. The 1-, 3-, and 5-year survival rates of the HTLV-1 (+) recipients were 91.3%, 78.3% and 66.3%, respectively. The survival rates of the HTLV-1 (+) recipients 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.

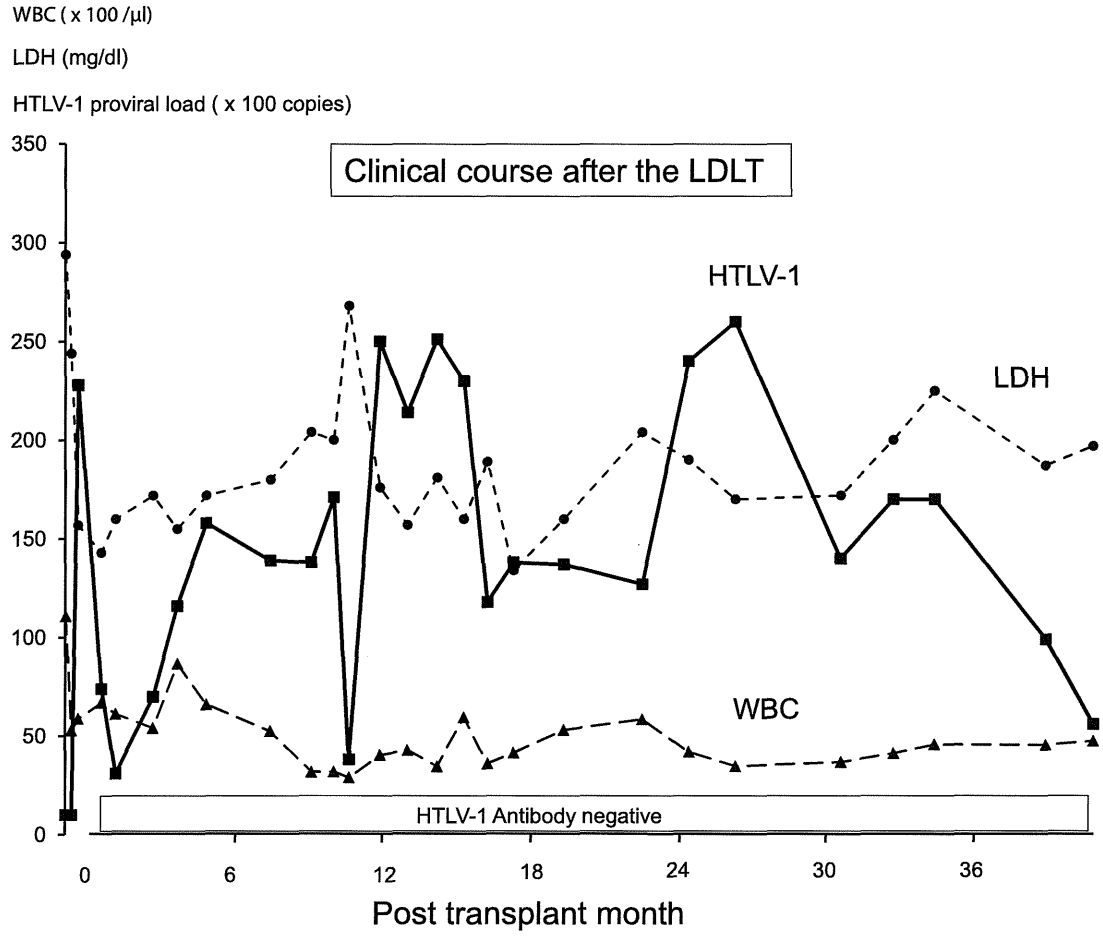

Figure 2: Postoperative course of a pretransplant HTLV-1 (−) recipient who received a graft from an HTLV-1 (+) donor. HTLV-1 proviral loads turned positive 7 days after LDLT and remained detectable. Interestingly, antibody titers against HTLV-1 remained negative. Checking the proviral load is necessary 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) ≥ 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.

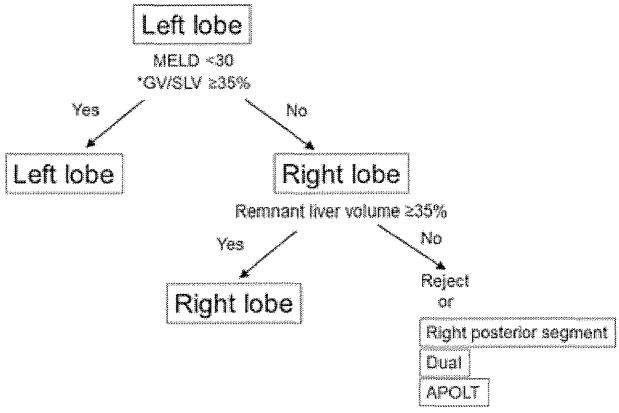

Figure 1: Graft selection algorithm in Kyushu University. *A left lobe graft of GV/SLV <35% was considered to be used when the donor was younger than 40 years old or recipient's liver function was good or low MELD score without severe portal hypertension. APOLT = auxiliary partial orthotopic liver transplantation

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