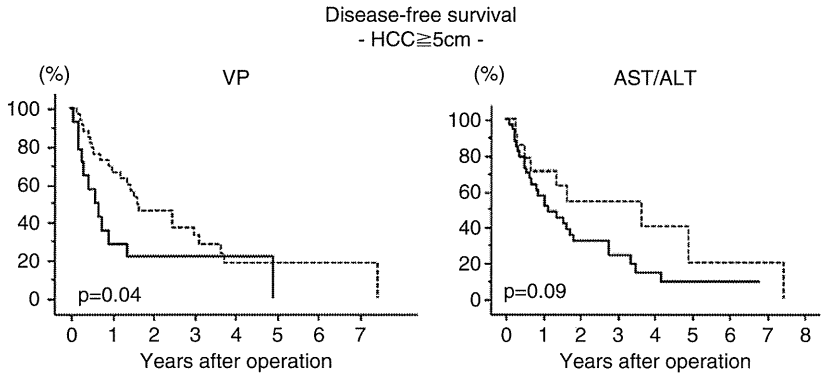

Figure 3 In patients with hepatocellular carcinoma (HCC) ≥5 cm, the disease-free survival (DFS) curves of the two groups divided by portal vein tumor thrombus (VP; – or +) or aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (≥80 or <80 IU/L) are illustrated. The DFS was significantly worse in patients with VP+ ($P = 0.04$). ----, VP– ($n = 34$); ——, VP+ ($n = 14$); ----, AST/ALT <80 IU/L ($n = 14$); ——, AST/ALT ≥80 IU/L ($n = 34$).

patients (16.5%) had early recurrence and 41 patients (51.9%) had late recurrence. In patients with HCC of 5 cm or more, 23 patients (47.9%) had early recurrence, a significantly higher rate ($P = 0.01$). In addition, all 13 patients (27.1%) with late recurrence had the risk factor of AST/ALT of 80 IU/L or more.

DISCUSSION

TWO FACTORS WERE thought to be the causes of HC-HCC recurrence in patients after curative hepatic resection: 'metastasis of cancer cells and multicentric occurrence'. Early recurrence of HC-HCC would relate mainly to metastasis of cancer cells, whereas recurrence of HC-HCC would relate mainly to multicentric occurrence.[23] A review of the published work suggests that the risk factors for recurrence of HC-HCC can be divided roughly into two groups, tumor-related factors, such as tumor size[11] and portal vein invasion,[12] and remnant liver-related factors, such as hepatitis activity and liver fibrosis.[5–8] Generally speaking, patients with tumor-related risk factors for the recurrence of HC-HCC would face early recurrence, and patients with remnant liver-related risk factors for recurrence of HC-HCC would face late recurrence. Also in our series, early recurrence (<1 year) was common (47.9%) in patients with HCC of 5 cm or more, and late recurrence (≥1 year) was predominant in both patients with HCC of 2 cm or less (57.0%) and patients with HCC of more than 2 cm to less than 5 cm (51.9%).

Previous reports have shown that hepatitis activity is an important factor for the recurrence of HC-HCC. We have shown that the histological hepatitis activity and postoperative levels of transaminase are significant risk factors for HC-HCC recurrence in small HCC.[5–8] To assess hepatitis activity, periodical biopsies of residual liver after hepatic resection would provide accurate information, but this would not be acceptable on ethical grounds. Serum AST/ALT level was thought to relate to remnant liver inflammatory necrosis,[9,10] and in our series, AST/ALT (either AST or ALT) of 80 IU/L or more

Table 8 Recurrence patterns according to the primary HC-HCC size

Tumor diameter	Liver, solitary	Liver, multiple	Distant
HCC ≤2 cm	35*	3	1
(39/56; 69.6%)	(62.5%)	(5.4%)	(1.8%)
>2 cm to <5 cm	42	9	3
(54/79; 68.4%)	(53.2%)	(11.4%)	(3.8%)
HCC ≥5 cm	8	18**	10**
(36/48; 75.0%)	(16.7%)	(37.5%)	(20.8%)

*$P < 0.01$, **$P = 0.02$, ***$P = 0.04$.
HC, hepatitis C; HCC, hepatocellular carcinoma.

Table 9 Durations of recurrence according to the primary HC-HCC size

Tumor diameter	<1 year	≥1 year
HCC ≤2 cm	7	32*
(39/56; 69.6%)	(12.5%)	(57.0%)
>2 cm to <5 cm	13	41
(54/79; 68.4%)	(16.5%)	(51.9%)
HCC ≥5 cm	23**	13
(36/48; 75.0%)	(47.9%)	(27.1%)

*$P < 0.01$, **$P = 0.01$.
HC, hepatitis C; HCC, hepatocellular carcinoma.

was an independent risk factor for HC-HCC recurrence after curative hepatic resection, irrespective of the primary HC-HCC size. We picked not preoperative but postoperative serum AST/ALT level to assess the effects of postoperative hepatitis activity in our series.

We have reported the improvement of long-term outcomes in HC-HCC in the modern era.[24] The effectiveness of postoperative interferon therapy for HC-HCC was confirmed by several randomized controlled trial studies,[13,14] but the target of this therapy is thought to be multicentric occurrence rather than metastasis of cancer cells. In our series, patients with HCC of 5 cm or more had significantly high rates of multiple liver recurrence (37.5%) and distant recurrence (20.8%) within 1 year postoperatively.

We reported that a combination of two factors such as HCC of 5 cm or more and DCP of 300 mAU/mL or more was useful in the selection of candidates for living donor liver transplantation for HCC.[25] These would be the most important tumor-related factors in the recurrence of HCC because the remnant liver disappeared in living donor liver transplantation. In our series, DCP of 100 mAU/mL or more is an independent risk factor for the recurrence of HC-HCC in patients with HCC of more than 2 cm to less than 5 cm, and VP+ is an independent risk factor for the recurrence of HC-HCC in patients with HCC of 5 cm or more.

Another possible factor in the high recurrence rate of active hepatitis is the enhancement of metastasis by upregulated adhesion molecules on the sinusoidal lining cells of the liver.[26,27] Our own results suggest, however, that remnant liver inflammation represented by AST/ALT of 80 IU/L or more should be a risk factor for multicentric recurrence in the late period. According to our own series in long-term follow up, even in patients with HCC of 5 cm or more, AST/ALT of 80 IU/L or more was a risk factor for HC-HCC recurrence in the late period. However, in patients with AST/ALT of 80 IU/L or more, Figure 1 (HCC, ≤2 cm) demonstrates the high rate of recurrence of HC-HCC within 2 years and the same low rate of recurrence of HC-HCC after 5 years. Of the nine patients with HCC of 2 cm or less who had a recurrence of HC-HCC within 2 years, seven (78%) had pathological cancer spreads or poor differentiation.[28] The low rate of recurrence of HC-HCC after 5 years in patients with HCC of 2 cm or less might have been due to the relatively short follow-up period (median, 7.6 years).

In conclusion, AST/ALT of 80 IU/L or more is an independent risk factor for recurrence of primary solitary HC-HCC after curative resection, irrespective of the primary HC-HCC size. AST/ALT of 80 IU/L or more is considered a risk factor for multicentric occurrence in the late period. A good target of postoperative interferon therapy would be patients with primary HC-HCC of less than 5 cm or patients with HCC of 5 cm or more 1 year or more after hepatic resection.

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Impact of Conversion From Pegylated Interferon-α2b to Interferon-α2a for Treating Recurrent Hepatitis C After Liver Transplantation

The clinical outcomes of conversion from pegylated (peg) interferon (IFN)-α2b to peg-IFN-α2a therapy in combination with ribavirin for recurrent hepatitis C after liver transplantation (LT) have not been reported (*1–3*).

Living-donor liver transplantation (LDLT) was performed in 156 patients for hepatitis C at Kyushu University. Of these, 103 received peg-IFN-α2b and ribavirin and 22 patients underwent conversion from peg-IFN-α2b to peg-IFN-α2b. Indications for conversion included (a) no response (NR; n=14) to peg-IFN-α2b, (b) relapse after viral response (VR; n=5) following completing peg-IFN-α2b therapy, and (c) to prevent relapse (n=3) for VR during peg-IFN-α2b and ribavirin therapy. Splenectomy was performed in 47 (95.9%) recipients to prevent pancytopenia associated with antiviral therapy (*4*). The immunosuppression was induced with triple therapy of tacrolimus or cyclosporine with mycophenolate mofetil and steroids (*5*).

Peg-IFN-α2b with ribavirin (Pegintron with Rebetol; Merck & Co., Whitehouse Station, NJ) was used as the primary treatment for recurrent hepatitis C after LDLT. Peg-IFN-α2b was started at the dose of 0.5–1.0 μg/kg per week with 200–400 mg per day of ribavirin. The doses were escalated in a stepwise manner up to 1.5 μg/kg per week and 800 mg per day. Peg-IFN-α2a with ribavirin (Pegasys with Copegus; Chugai Pharmaceutical, Chuo-ku, Tokyo, Japan) was primarily used for patients with NR or relapse during treatment with peg-IFN-α2b with ribavirin. Peg-IFN-α2a was started at the dose of 90–120 μg per week with 200–400 mg per day of ribavirin. The doses were escalated in a stepwise manner up to 180 μg per week and 800 mg per day. The serum hepatitis C virus (HCV)-RNA level was determined by a real-time HCV assay (Accu-Gene HCV; Abbott Molecular, Des Plaines, IL) and IL28B genotyping was performed using TaqMan GTXpress Master Mix (Life Technologies, Tokyo, Japan). Peg-IFN-induced immune-mediated graft dysfunction (peg-IGD) was defined as the Levitsky et al. (*6*) did. Values are expressed as mean±standard deviation. Variables were analyzed using χ^2 tests for categorical values or the Mann–Whitney test for continuous variables. Values of $P<0.05$ were considered statistically significant.

The characteristics of the patients who underwent conversion from peg-IFN-α2b to peg-IFN-α2a antiviral treatment are described in Table 1. The outcomes of conversion from peg-IFN-α2b to peg-IFN-α2a antiviral treatment are summarized in Figure 1. Among the 14 patients with NR following peg-IFN-α2b with ribavirin therapy, 6 patients achieved VR and 3 had sustained VR (SVR) after conversion. Among the five patients with viral relapse following peg-IFN-α2b–based therapy, four patients achieved VR after conversion. Among the three patients with conversion during

TABLE 1. Patient characteristics

Variables	Values
Recipient age, yr	51.4±8.6 (54.5)
Recipient gender, male	15 (68.2)
Donor age, yr	35.7±11.3 (34.5)
Donor gender, male	16 (72.7)
Left lobe graft	13 (59.7)
GV/SLV (%)	41.4±6.4 (40.4)
Splenectomy	17 (77.3)
Tacrolimus	12 (54.5)
Mycophenolate mofetil	20 (54.5)
Steroid free	5 (22.7)
HCV-RNA titer at LDLT, log IU/mL	5.5±0.6 (5.7)
IFN before LDLT	9 (40.9)
HCV genotype 1b, 2a, and 2b	16 (72.7), 5 (22.7), and 1 (4.6)
Donor rs8099917 genotype, T/T	7 (31.8)
Recipient rs8099917 genotype, T/T	8 (36.4)
Time from LDLT to peg-IFN-a2b, mo	14.3±18.2 (8.1)
Peg-IFN-a2b dose, mg/kg/wk	1.1±0.3 (1.0)
Ribavirin dose peg-IFN-a2b, mg/kg/d	6.1±2.9 (6.2)
Duration of peg-IFN-a2b treatment, mo	12.1±14.2 (10.7)
HCV-RNA titer at conversion, log IU/mL	4.1±2.6 (4.9)
Peg-IFN-a2a dose, mg/kg/wk	2.1±0.8 (1.9)
Ribavirin dose with peg-IFN-a2a, mg/kg/d	3.5±4.3 (2.1)
Duration of peg-IFN-a2a treatment, mo	14.2±10.1 (9.8)
VR with peg-IFN-a2b	8 (36.4)

GV, graft volume; HCV, hepatitis C virus; IFN, interferon; LDLT, living-donor liver transplantation; peg, pegylated; SLV, standard liver volume; VR, viral response.

VR by peg-IFN-α2b–based therapy, two patients achieved SVR. However, all three patients with conversion during VR by peg-IFN-α2b–based therapy had peg-IGD, including de novo autoimmune hepatitis (n=2) and chronic rejection (n=1), resulting in graft loss in two patients.

The viral status after peg-IFN conversion is summarized in Table 2. Among patients with NR, relapse after VR, HCV-RNA seropositivity, and VR following peg-IFN-α2b, the rates of VR after converting to peg-IFN-α2a were 42.8%, 100.0%, 57.9%, and 100.0%, respectively. The rates of SVR were 21.4%, 80.0%, 36.8%, and 40.9%, respectively.

Univariate analysis was performed to identify factors associated with VR after conversion from peg-IFN-α2a to peg-IFN-α2b. In this analysis, only history of VR during peg-IFN-α2a with ribavirin treatment (57.1% vs. 0.0%; P=0.02) was significantly associated with VR after conversion (Table 3). By contrast, low HCV-RNA titer at conversion (1.8±1.9 vs. 5.3±2.0 log IU/mL; P<0.01) and history of VR during peg-IFN-α2a with ribavirin treatment (66.7% vs. 14.3%; P=0.03) were significantly associated with SVR after conversion (Table 4).

The major structural difference between peg-IFN-α2b and peg-IFN-α2a is the conjugated polyethylene glycol (*7–10*). Peg-IFN-α2b (12 kDa) has a single-branched polyethylene glycol, whereas peg-IFN-α2a (40 kDa) has bulky multiple branched conjugates. Consequently, peg-IFN-α2a has a smaller distribution volume (10 vs. 40 L), longer absorption half-life (50 vs. 4.6 hr), and longer elimination half-life (80 vs. 40 hr). Moreover, it was reported that the serum concentration of peg-IFN-α2a was 20 mg/mL at 7 days after injection compared with almost zero for peg-IFN-α2b (*8*).

As a posttransplantation primary antiviral agent for recurrent hepatitis C, peg-IFN-α2a was used in very limited series, and peg-IFN-α2b has become the most widely used and studied regimen for use after LT (*11–13*). Among them, Dinges et al. (*14*) only reported the actual rate of SVR (47%) following peg-IFN-α2a with ribavirin for 19 patients after LT, whereas dose

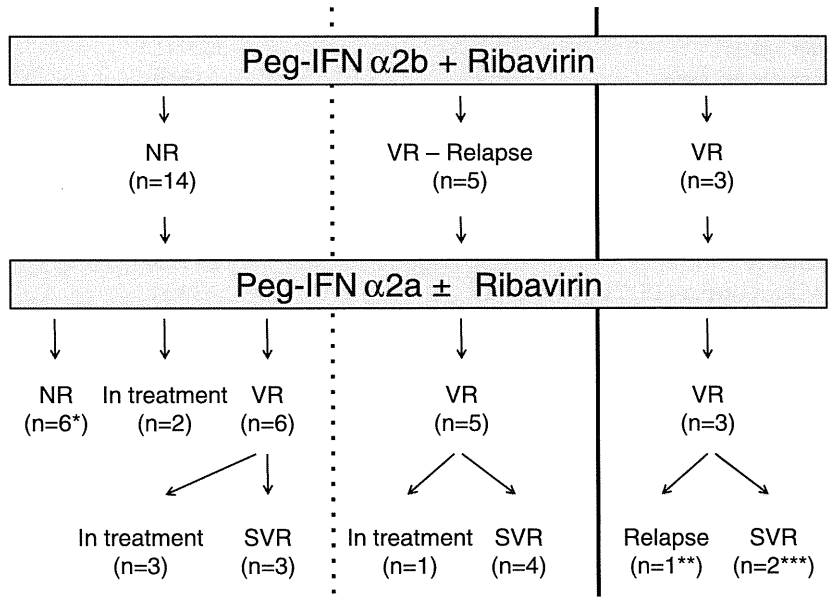

FIGURE 1. Twenty-two patients who received peg-IFN-α2b with ribavirin were converted to peg-IFN-α2a with or without ribavirin. *AIH (n=1); **AIH (n=1); ***AIH (n=1) and CR (n=1). AIH, autoimmune hepatitis; CR, chronic rejection; IFN, interferon; NR, no response; peg, pegylated; SVR, sustained viral response; VR, viral response.

TABLE 2. Viral status after conversion from peg-IFN-α2b to peg-IFN-α2a antiviral therapy

Response to peg-IFN-α2b	VR for peg-IFN-α2a (%)	SVR for peg-IFN-α2a (%)
NR	6/14 (42.8)	3/14 (21.4)
Relapse after VR	5/5 (100.0)	4/5 (80.0)
Positive HCV-RNA	11/19 (57.9)	7/19 (36.8)
VR	3/3 (100.0)	2/3 (67.7)
Total	14/22 (63.6)	9/22 (40.9)

HCV, hepatitis C virus; IFN, interferon; NR, no response: peg, pegylated; SVR, sustained viral response; VR, viral response.

modification was necessary in 26% of patients. Although their study was small and nonrandomized, the rate of SVR was superior to that achieved by peg-IFN-α2b with ribavirin (~30%) (*15*).

Restarting peg-IFN-α2a with ribavirin in nontransplantation settings after a poor response to previous IFN therapy has been reported in a few studies (*16–18*). Jensen et al. (*16*) conducted a randomized trial in which treatment was restarted in 950 patients who did not respond to prior peg-IFN-α2b with ribavirin therapy. In that study, the rate of SVR after 72 weeks of peg-IFN-α2a with ribavirin treatment was 16%. Herrine et al. (*17*) randomized 124 patients with poor response to peg-IFN-α2b with ribavirin therapy. In that study, 37% of patients had SVR after conversion to peg-IFN-α2a with ribavirin. Therefore, we think that the 21.4% of SVR rate after conversion from peg-IFN-α2b to IFN-α2a is fairly acceptable.

However, the main adverse outcome of conversion to peg-IFN-α2a is peg-IGD, a concept recently proposed by Levitsky et al. (*6*). It was reported that IFN could lead to IGD, which may include acute rejection, chronic rejection, and autoimmune hepatitis as well as graft loss (*15, 19, 20*). They reported that

TABLE 3. Predictors for VR after conversion from peg-IFN-α2b to peg-IFN-α2a

	VR		
Variables	No (n=6)	Yes (n=14)	*P*
Recipient age, yr	58.8±5.1	51.4±8.6	0.85
Recipient gender, male	3 (50.0)	11 (78.6)	0.20
Donor age, yr	32.5±11.1	34.5±9.5	0.68
Donor gender, male	3 (50.0)	11 (78.6)	0.20
Left lobe graft	3 (50.0)	8 (57.1)	0.77
GV/SLV, %	41.7±4.7	41.1±7.6	0.84
Splenectomy	4 (66.7)	11 (78.6)	0.57
Tacrolimus	4 (66.7)	6 (42.6)	0.33
Mycophenolate mofetil	6 (100.0)	12 (85.7)	0.33
Steroid free	2 (33.3)	3 (21.4)	0.57
HCV-RNA titer at LDLT, log IU/mL	5.7±0.2	5.6±0.6	0.67
IFN before LDLT	2 (33.3)	6 (42.9)	0.69
HCV genotype 1b, 2a, and 2b	6 (100.0)	9 (64.3)	0.09
Donor rs8099917 genotype, T/T	3 (50.0)	11 (78.6)	0.20
Recipient rs8099917 genotype, T/T	3 (50.0)	9 (64.3)	0.55
Time from LDLT to peg-IFN-a2b, mo	12.1±18.5	16.0±19.6	0.67
Peg-IFN-a2b dose, mg/kg/wk	1.1±0.3	1.0±0.3	0.35
Ribavirin dose, with peg-IFN-a2b, mg/kg/d	6.6±3.8	5.6±2.8	0.77
Duration of peg-IFN-a2b treatment, mo	20.8±24.8	8.9±5.6	0.52
HCV-RNA titer at conversion, log IU/mL	4.7±2.8	3.5±2.6	0.34
Peg-IFN-a2a dose, mg/kg/wk	2.2±0.8	1.9±0.8	0.51
Ribavirin dose, with peg-IFN-a2a, mg/kg/d	3.3±5.4	2.8±3.3	0.81
Duration of peg-IFN-a2a treatment, mo	26.7±16.2	12.9±10.5	0.06
VR with peg-IFN-a2b	0 (0.0)	8 (57.1)	0.02

GV, graft volume; HCV, hepatitis C virus; IFN, interferon; LDLT, living-donor liver transplantation; peg, pegylated; SLV, standard liver volume; VR, viral response.

TABLE 4. Predictors for SVR after conversion from peg-IFN-α2b to peg-IFN-α2a

Variables	SVR		P
	No (n=7)	Yes (n=9)	
Recipient age, yr	55.9±6.1	51.7±9.1	0.21
Recipient gender, male	4 (57.1)	7 (77.8)	0.38
Donor age, yr	33.7±12.1	39.0±9.5	0.30
Donor gender, male	3 (42.8)	8 (88.9)	0.06
Left lobe graft	4 (57.1)	5 (55.6)	0.95
GV/SLV (%)	42.6±5.5	39.2±7.7	0.24
Splenectomy	5 (71.4)	6 (66.7)	0.84
Tacrolimus	5 (71.4)	4 (44.4)	0.28
Mycophenolate mofetil	7 (100.0)	6 (66.7)	0.69
Steroid free	3 (42.8)	2 (22.2)	0.38
HCV-RNA titer at LDLT, log IU/mL	5.6±0.5	5.4±0.7	0.57
IFN before LDLT	2 (28.5)	4 (44.4)	0.51
HCV genotype 1b, 2a, 2b	7 (100.0)	6 (66.7)	0.09
Donor rs8099917 genotype, T/T	4 (57.1)	8 (88.9)	0.14
Recipient rs8099917 genotype, T/T	4 (57.1)	6 (66.7)	0.69
Time from LDLT to peg-IFN-a2b, mo	10.3±12.5	21.6±24.8	0.17
Peg-IFN-a2b dose, mg/kg/wk	1.1±0.3	1.0±0.3	0.35
Ribavirin dose, with peg-IFN-a2b, mg/kg/d	6.0±3.7	5.7±3.1	0.84
Duration of peg-IFN-a2b treatment, mo	12.7±17.6	11.1±5.4	0.78
HCV-RNA titer at conversion, log IU/mL	5.3±2.0	1.8±1.9	<0.01
Peg-IFN-a2a dose, mg/kg/wk	2.0±0.8	1.5±0.5	0.13
Ribavirin dose, with peg-IFN-a2a, mg/kg/d	3.2±5.0	2.6±3.2	0.79
Duration of peg-IFN-a2a treatment, mo	26.7±16.2	16.3±12.1	0.23
VR with peg-IFN-a2b	1 (14.3)	6 (66.7)	0.03

GV, graft volume; HCV, hepatitis C virus; IFN, interferon; LDLT, living-donor liver transplantation; peg, pegylated; SLV, standard liver volume; SVR, sustained viral response; VR, viral response.

7.2% of patients treated with peg-IFN develop peg-IGD over 10 years, with a significantly higher mortality rate. Additionally, the use of peg-IFN-α2a (odds ratio=4.7) was a significant risk factor for this event (*6*). In the current series, peg-IGD occurred in all three patients who converted from peg-IFN-α2b to peg-IFN-α2a, with graft loss in two patients.

In conclusion, conversion to peg-IFN-α2a–based antiviral therapy for recurrent hepatitis C after LT is a safe option, with increased VR and SVR rate, only for patients with NR or relapse on previous peg-IFN-α2b therapy.

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ERRATUM

Anonymity and Live-Donor Transplantation: An ELPAT View: Erratum

In the February 27, 2013 issue of *Transplantation* in the article by Mamode et al, "Anonymity and Live-Donor Transplantation: An ELPAT View" the author Frank Dor should have been listed as Frank J.M.F. Dor.

REFERENCE

Mamode N, Lennerling A, Citterio F, et al. Anonymity and live-donor transplantation: an ELPAT view. *Transplantation.* 2013; 95: 536.

Rendezvous Ductoplasty for Biliary Anastomotic Stricture After Living-Donor Liver Transplantation

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Background. Biliary anastomotic stricture (BAS) after living-donor liver transplantation (LDLT) is difficult to manage. We used rendezvous ductoplasty (RD) to treat BAS after LDLT.

Methods. We retrospectively analyzed 53 patients with BAS after adult-to-adult LDLT with duct-to-duct biliary reconstruction.

Results. BAS was classified according to endoscopic retrograde cholangiography findings after normal-pressure contrast injection: type I (n=32) in which the stricture was visualized; type II (n=13) in which the common hepatic duct and graft intrahepatic ducts were visualized, but the stricture was not visualized; or type III (n=8) in which the stricture and graft intrahepatic ducts were not visualized. In right lobe grafts, types II and III occurred more frequently than type I (P=0.0023). Type I had significantly shorter cold ischemic time (76±11 vs. 118±12 min; P=0.0155) and warm ischemic time (38±2 vs. 49±3 min; P=0.0069) than types II and III. The number of attempts to pass the guidewire through the stricture was significantly lower in type I (1.2±0.2 attempts) than type II (2.2±0.2 attempts; P=0.0018) or type III (2.8±0.3 attempts; P<0.0001). The treatment success rate was 78.1% for type I, 38.5% for type II, and 50.0% for type III (P=0.0282). RD was the first successful treatment in a higher proportion of types II and III patients than type I patients (66.7% vs. 6.3%; P<0.0001). Cumulative treatment success rates were not significantly different between the RD and the non-RD groups (P=0.0920).

Conclusions. RD was a useful treatment for difficult cases of BAS after LDLT and achieved successful outcomes.

Keywords: Living-donor liver transplantation, Biliary anastomotic stricture, ERC, PTC.

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Living-donor liver transplantation (LDLT) is one of the treatment options for end-stage liver disease, especially in countries with a shortage of deceased donors. Duct-to-duct biliary reconstruction, which preserves biliary function, is now preferred over hepaticojejunostomy (*1–4*). Biliary complications, including biliary anastomotic stricture (BAS), are the most common complications after LDLT and have been reported to occur in 19% of LDLT patients (*5, 6*). BAS treatment is difficult and requires frequent and prolonged hospitalizations, resulting in loss of quality of life (*2*).

Currently, many institutes manage BAS via the endoscopic transpapillary approach, but this approach has a failure rate of more than 40% (*7*). The percutaneous transhepatic approach may be used as second-line treatment (*4, 8, 9*). Surgery may be considered when other modalities have failed and may include conversion from duct-to-duct anastomosis to hepaticojejunostomy. However, surgical treatment carries a risk of related complications (*10*), and a nonsurgical approach is therefore preferable when reasonable results can be expected.

We performed rendezvous ductoplasty (RD; Fig. 1) in patients with BAS who were difficult to manage. The aims of this study were to classify BAS, to evaluate the difficulty of treatment according to BAS type, and to evaluate the usefulness of RD for treating BAS.

RESULTS

BAS Classification

To evaluate the difficulty of passing a guidewire through the stricture, we classified BAS into three types according to cholangiography findings after normal-pressure contrast injection. In type I, the common hepatic duct, stricture, and graft intrahepatic ducts were visualized (Fig. 2A). In type II, the common hepatic duct and graft intrahepatic ducts were visualized, but the area of the stricture was not visualized (Fig. 2B). In type III, the common hepatic duct was visualized,

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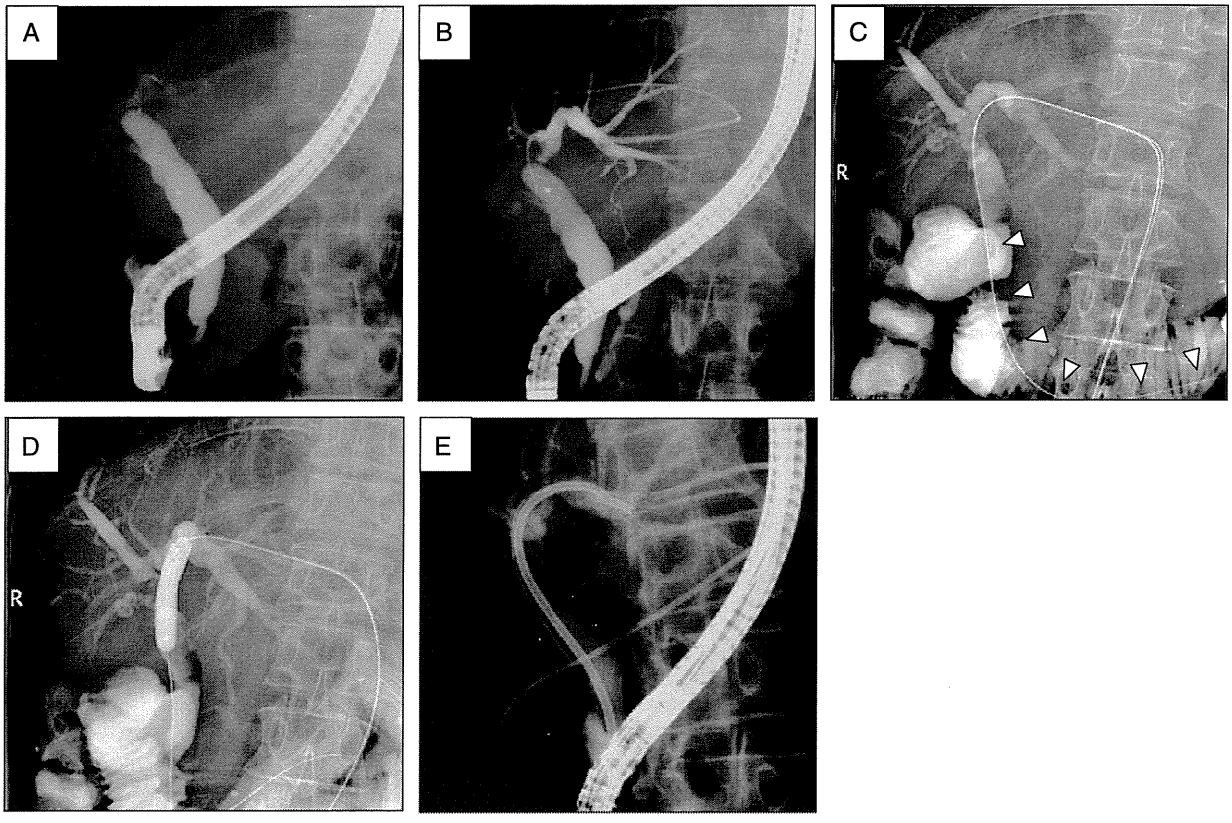

FIGURE 1. RD procedure. A, endoscopic access in the prone position. B, percutaneous transhepatic access under fluoroscopic guidance with endoscopic contrast agent injection. C, guidewire is passed from the percutaneous transhepatic side through the stricture and the ampulla of Vater. D, E, balloon dilatation followed by stent placement using the endoscope. RD, rendezvous ductoplasty.

but the area of the stricture and the graft intrahepatic ducts were not visualized (Fig. 2C).

Clinical Characteristics in the Three Types of BAS

Analysis of variance showed a significant association between graft type and BAS type. Among patients with type I BAS, 24 had left lobe (LL) grafts, 8 had right lobe (RL) grafts, and none had posterior segment (PS) grafts; among patients with type II BAS, 4 had LL grafts, 8 had RL grafts, and 1 had a PS graft; and among patients with type III BAS, 3 had LL grafts, 3 had RL grafts, and 2 had PS grafts (P=0.0079). There were significant differences among types I to III in cold ischemic time (76±11 vs. 131±16 vs. 98±20 min; P=0.0240) and warm ischemic time (38±2 vs. 54±3 vs. 40±4 min; P=0.0015). In addition, Tukey–Kramer's tests revealed significant differences between types I and II in cold ischemic time (P=0.0011) and warm ischemic time (P=0.0431). Multivariate analyses comparing types I and II showed that warm ischemic time was an independent risk factor for type II (odds ratio, 1.17; 95% confidence interval, 0.70–0.96; P=0.0030). Multivariate analyses comparing types I and III showed that an RL graft was an independent risk factor for type III compared with an LL graft (odds ratio, 5.00; 95% confidence interval, 1.01–29.24; P=0.0491). There were no significant differences among BAS types in the rates of hepatitis C virus infection (P=0.5933) or other recipient factors, donor factors, operative factors, or postoperative factors (Table 1).

Evaluation of Difficulty of Treatment in the Three Types of BAS

We evaluated the difficulty of treatment in the three types of BAS using two factors: the number of attempts to pass the guidewire through the stricture and the rate of successful completion of treatment. The number of attempts to pass the guidewire was significantly lower in type I than type II (1.2±0.2 vs. 2.2±0.2 attempts; P=0.0018) or type III (1.2±0.2 vs. 2.8±0.3 attempts; P<0.0001), but there was no significant difference in the number of attempts between types II and III (Table 1). The rate of successful treatment was 78.1% in type I, 38.5% in type II, and 50.0% in type III (P=0.0282).

First Successful Treatment Modality in Each Type of BAS

We analyzed the first successful treatment modality in each type of BAS. Overall, we performed endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), and RD in 66.0% (n=35), 3.8% (n=2), and 30.2% (n=16) of cases, respectively (Fig. 3A). In type I, we performed ERC, PTC, and RD in 87.4% (n=28), 6.3% (n=2), and 6.3% (n=2) of cases, respectively (Fig. 3B). In type II, we

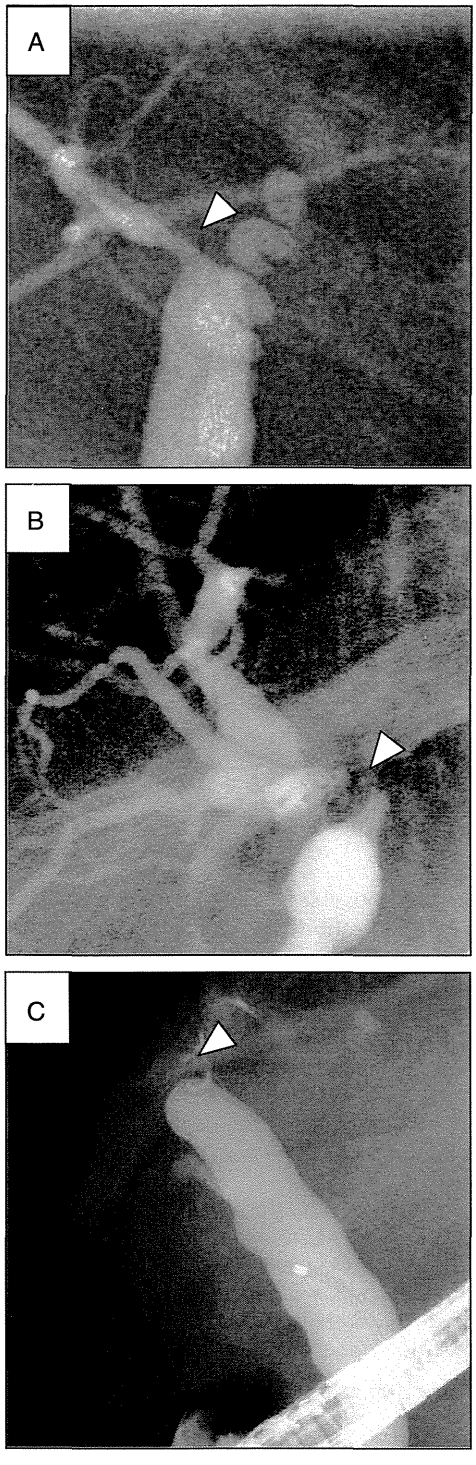

FIGURE 2. Three types of BAS according to cholangiography findings. A, type I, with the narrow stricture visualized. B, type II, with the common hepatic duct and graft intrahepatic ducts visualized, but the stricture not visualized. C, type III, with the stricture and the donor intrahepatic ducts not visualized. Arrowheads indicate the stricture site. BAS, biliary anastomotic stricture.

performed ERC, PTC, and RD in 46.2% (n=6), 0% (n=0), and 53.8% (n=7) of cases, respectively (Fig. 3C). In type III, we performed ERC, PTC, and RD in 12.5% (n=1), 0% (n=0), and 87.5% (n=7) of cases, respectively (Fig. 3D). The rate of RD was significantly higher in types II and III than type I (66.7% vs. 6.3%; $P<0.0001$).

Comparison of Cumulative Treatment Success Rates between the RD and the Non-RD Groups

To evaluate the usefulness of RD, we divided patients into two groups: an RD group (n=16) and a non-RD group (n=37). The 1- and 4-year cumulative treatment success rates were 26.7% and 87.6%, respectively, in the RD group and 51.3% and 89.0%, respectively, in the non-RD group (Fig. 4). The cumulative success rates were not significantly different between the two groups ($P=0.0920$). None of the 53 patients with BAS underwent surgical treatment.

DISCUSSION

Although efforts to prevent BAS have decreased the frequency of this complication, from 14.5% to 32.5% of patients who receive LDLT still develop BAS (*1, 3, 11–13*). Development of BAS is related to various factors, such as the fragile vascular networks in the biliary tree, ischemia-reperfusion injury, age-related changes, fibrous scar formation as part of the normal healing process, tiny or multiple bile duct orifices, and immunologic reactions (*1, 12, 14, 15*). We focused on careful dissection of the peribiliary tissues to preserve maximal vascular integrity of the recipient's bile duct and achieved a BAS rate of 14.5%, which is lower than the rate of 32.5% reported in the literature (*1, 16*). However, other factors causing BAS have not been overcome, and BAS is still thought to be an inevitable complication after LDLT.

In this study, BAS was classified into three types according to cholangiography findings, and the difficulty of treating each type was evaluated. Lee et al. (*13*) reported that stricture morphology was a significant factor ($P<0.0001$) in the success rate of primary endoscopic management. Kato et al. (*2*) reported that cholangiography findings were related to the risk of failure of stent deployment. However, no studies have reported on the difficulty of treatment according to BAS type.

The current study found that graft type, cold ischemic time, and warm ischemic time were associated with BAS type after LDLT. Previous studies reported that the incidence of BAS was higher in RL grafts than LL grafts because of the anatomy of the right bile duct (*3, 15, 17–19*). Graft stumps tend to be more horizontal in PS grafts than RL grafts. Interestingly, there were no cases of type I BAS in patients with PS grafts in this study, which suggests that both bile duct size and the biliary anastomotic angle have an effect on BAS type. Although cold ischemic time was not significantly associated with BAS in our series, it is thought to induce postreperfusion endothelial damage, resulting in impaired perfusion (*1*). Warm ischemic time has also been reported to be a risk factor for BAS after LDLT because of its impact on graft microcirculation (*12, 20*). We therefore assumed an association between the microcirculation around the biliary tree and BAS type. Other reported risk factors for BAS, such as hepatic artery flow (*21*) and biliary leakage (*1, 15, 22*), were not significantly associated with BAS type in this series.

TABLE 1. Patient characteristics by type of BAS after LDLT

	Type I (n=32)	Type II (n=13)	Type III (n=8)	*P*
Recipient factors				
Age, yr	57.1 ± 1.5	56.3 ± 2.3	57.9 ± 2.9	0.9109
Gender, male (%)	19 (59.4)	9 (69.2)	3 (37.5)	0.3544
MELD score, points	14.9 ± 0.0	18.2 ± 1.4	16.3 ± 1.8	0.1409
Hepatitis C virus infection (%)	21 (65.6)	7 (53.9)	6 (75.0)	0.5933
Donor factors				
ABO-incompatible graft (%)	1 (3.1)	1 (7.7)	1 (12.5)	0.5477
Graft type (LL/RL/PS)	24/8/0	4/8/1	3/3/2	0.0079[a]
GV/SLV (%)	40.1 ± 1.2	45.5 ± 1.9	39.7 ± 2.4	0.0740
Operative factors				
Operation time, min	750 ± 31	848 ± 49	785 ± 62	0.2458
Cold ischemic time, min	76 ± 11	131 ± 16	98 ± 20	0.0240[a]
Warm ischemic time, min	38 ± 2	54 ± 3	40 ± 4	0.0015[a]
Operative blood loss, L	6.12 ± 1.21	5.76 ± 1.89	4.19 ± 2.41	0.7680
HAF at closure, mL/min	90 ± 9	91 ± 15	96 ± 19	0.9586
No. donor bile ducts (1/2/3)	25/6/1	11/2/0	7/1/0	0.8640
Bile ductoplasty (%)	9 (28.1)	4 (30.8)	2 (25.0)	0.9594
Postoperative factors				
Bile leakage (%)	4 (12.5)	3 (23.1)	2 (25.0)	0.5666
Time to biliary stricture, yr	0.95 ± 0.16	0.68 ± 0.26	0.87 ± 0.33	0.6700
Difficulty of treatment				
No. attempts	1.2 ± 0.2	2.2 ± 0.2	2.8 ± 0.3	<0.0001[a]
Treatment success rate (%)	25 (78.1)	5 (38.5)	4 (50.0)	0.0282[a]

[a] $P<0.05$.

BAS, biliary anastomotic stricture; GV, graft volume; HAF, hepatic artery flow; LDLT, living-donor liver transplantation; LL, left lobe graft; MELD, model for end-stage liver disease; PS, posterior segment; RL, right lobe; SLV, standard liver volume.

Because the current first-line therapy for BAS is endoscopic balloon dilatation and stent placement, passage of a guidewire through the stricture is critical (*2, 8, 13*). The success rate of primary endoscopic treatment is 40% to 90% (*6*), and percutaneous treatment may be performed as second-line therapy if endoscopic treatment has failed (*4, 8, 9*). However, it is difficult to access the intrahepatic duct using ultrasonography if it is not dilated. Giampalma et al. (*23*) reported a percutaneous treatment failure rate of 10% (5 of 48). When both endoscopic and percutaneous treatments have failed, surgical therapy is usually unavoidable (*10*).

When performing RD, we were easily able to access nondilated intrahepatic ducts after visualizing them with endoscopic contrast agent injection. We therefore assume that it is easier to treat BAS using RD than PTC. We were able to apply sufficient force to both ends of guidewire, via the patient's mouth and the transhepatic route, to enable us to align the stricture and place stents. Use of RD therefore avoided the need for external stents, which would have reduced quality of life. The duration of treatment tended to be shorter in the non-RD group than the RD group, but cumulative treatment success rates were not significantly different between the RD and the non-RD groups (P=0.0920). None of our patients required hepaticojejunostomy or repeat transplantation. These results indicate the importance of successful initial treatment of BAS after LDLT.

The main limitations of this study are its retrospective nature, possible biases due to the learning curves for surgical techniques, and possible biases in patient selection for RD. However, the indications for LDLT and our graft selection criteria were consistent. Another limitation is the relatively small number of cases. Although our findings support the use of RD for BAS after LDLT with duct-to-duct biliary reconstruction, they do not provide definitive evidence of the usefulness of BAS, because it was not possible to make direct comparisons between RD and control treatments. Further analysis of a larger number of patients in a multicenter study, such as a randomized controlled trial, is necessary to confirm our findings.

In conclusion, ERC findings predicted the difficulty of treatment of BAS after LDLT with duct-to-duct reconstruction. Most cases of BAS were successfully treated with endoscopic therapy, and RD was a useful treatment modality for more difficult cases. We therefore advocate using RD as second-line therapy instead of percutaneous transhepatic approach.

MATERIALS AND METHODS

Patients

Between June 2001 and July 2012, 289 LDLTs with duct-to-duct biliary reconstruction were performed at Kyushu University Hospital (Fukuoka, Japan). Fifty-three (18.3%) of these patients developed BAS and were included in this study.

Donor Surgery

The surgical techniques for graft harvesting have previously been described (*24*). From 2005, we performed minimal dissection around the bile duct to preserve the blood supply. Before 2005, we performed more extensive

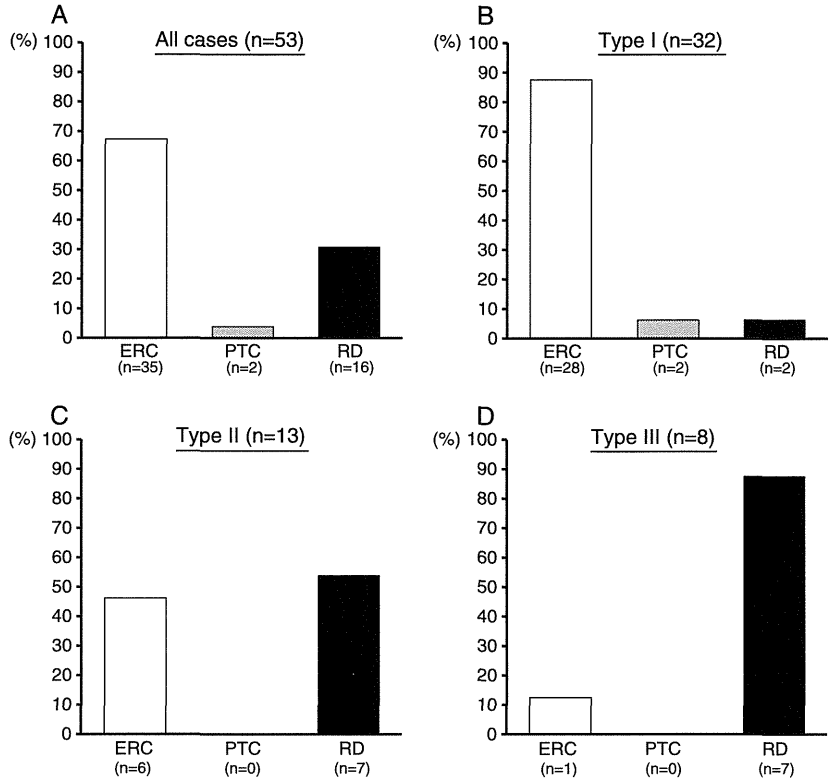

FIGURE 3. First successful treatment modalities in each type of BAS: (A) all cases, (B) type I cases, (C) type II cases, and (D) type III cases. BAS, biliary anastomotic stricture; ERC, endoscopic retrograde cholangiography; PTC, percutaneous transhepatic cholangiography; RD, rendezvous ductoplasty.

dissection of the tissues surrounding the bile duct. After complete parenchymal transection, we performed intraoperative fluorocholangiography to examine the anatomical details of the biliary ducts and determine the location and angle for hepatic duct transection. Intraoperative fluorocholangiography was performed with a portable C-arm unit (Arcadis Avantic; Siemens, Berlin, Germany) from 2005 and with a static X-ray film unit before 2005. Ductoplasty was sometimes performed during the cold phase if multiple bile ducts were located close together in the graft.

Recipient Surgery

We introduced duct-to-duct biliary reconstruction in 2001 (*25*). From April 2006, we used the minimal hilar dissection technique (*1, 16*) to preserve maximal vascular integrity of the recipient biliary tree. Before April 2005, we dissected the peribiliary connective tissues to isolate the common bile duct. After portal and arterial reconstruction, biliary reconstruction was performed as follows. Interrupted 6-0 absorbable monofilament sutures were placed over a straight silicone external stent tube (2.0–3.0 mm retrograde transhepatic biliary drainage tube; Sumitomo Bakelite, Tokyo, Japan) with the knots outside the lumen. The silicone stent tube was anchored at the biliary anastomosis and passed through the anterior wall of the recipient's common bile duct. Intraoperative fluorocholangiography was performed to confirm that there were no biliary strictures or leakages. The stent tube was removed in a two-step process under fluoroscopic guidance at least 3 months after surgery, as previously described (*26*). We have not changed our procedure since 2006.

Diagnosis and Treatment of BAS

Biliary stricture was suspected when a patient developed elevated liver enzyme levels or symptoms such as jaundice, itching, or fever. BAS was confirmed by direct imaging techniques such as ERC. The time of onset of BAS was defined as the day of diagnosis on imaging findings, and the completion of treatment was defined as the day a stent-free state was achieved (free passage of injected contrast agent and good drainage from the intrahepatic duct on cholangiography). When BAS was diagnosed, endoscopic treatment was attempted first. If several attempts to pass the guidewire through the stricture failed, RD was performed. Biliary stents were changed endoscopically every

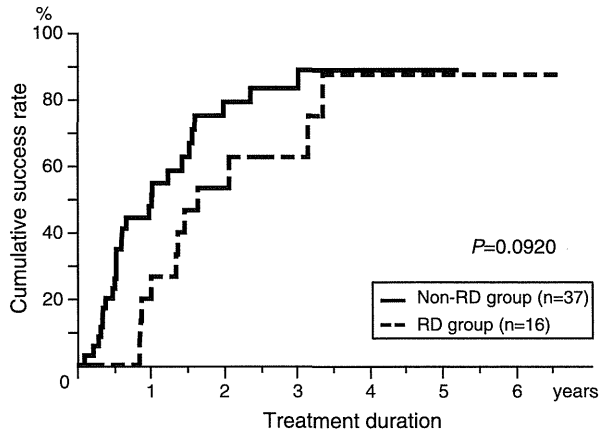

FIGURE 4. Cumulative 1- and 4-year treatment success rates were 26.7% and 87.6%, respectively, in the RD group (n=16) and 51.3% and 89.0%, respectively, in the non-RD group (n=37; P=0.0920). RD, rendezvous ductoplasty.

3 to 6 months, at which time the BAS was reevaluated. Stenting was continued until the stricture had resolved.

Endoscopic Transpapillary Approach Procedure

Our endoscopic transpapillary approach procedure was as follows. Under conscious sedation, the patient was placed prone and the ampulla of Vater was cannulated. Contrast agent was injected through the cannula to show the common hepatic duct and the graft intrahepatic ducts. If the graft intrahepatic ducts were not visible, we used balloon occlusion to increase the pressure of the contrast injection. We then tried to pass the guidewire through the stricture followed by balloon dilatation and stent placement.

RD Procedure

RD was performed as follows (Fig. 1). First, endoscopic access was obtained in the prone position. The patient was then placed supine, keeping the endoscope in position, and percutaneous transhepatic access was obtained under fluoroscopic guidance. If the intrahepatic ducts could not be visualized (type III), we used balloon occlusion to increase the pressure of the contrast agent injection. The guidewire from the percutaneous transhepatic side was passed through the stricture and through the ampulla of Vater. We then performed balloon dilatation before or after the guidewire was withdrawn through the mouth using the endoscope followed by stent placement as for the endoscopic transpapillary approach. If the guidewire could not be passed through the stricture during the RD procedure, we placed a temporary external drainage stent via the percutaneous transhepatic route to reduce duct edema. During subsequent RD sessions, we inserted the guidewire via the external drainage route and then attempted to pass it through the stricture. After RD, we usually removed the balloon via the percutaneous transhepatic route. We did not experience any cases of clinical bile leakage or biliary peritonitis.

Statistical Analysis

All statistical analyses were performed using SAS software (JMP 9.0.1; SAS Institute, Cary, NC). Multiple comparisons were performed using analysis of variance and Tukey–Kramer tests. Cumulative treatment success rates were analyzed using the Kaplan–Meier method and compared using the log-rank test. All variables are expressed as mean±standard deviation. $P<0.05$ was considered statistically significant.

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ORIGINAL ARTICLE

A high MELD score, combined with the presence of hepatitis C, is associated with a poor prognosis in living donor liver transplantation

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Abstract
Purpose The feasibility of performing living donor liver transplantation (LDLT) for patients with high end-stage liver disease (MELD) scores needs to be assessed.
Methods A total of 357 patients who underwent LDLT were included in this analysis.
Results Overall, 46 patients had high MELD scores ($\geq$25) and their graft survival was similar to that in patients with low MELD scores (<25; $n = 311$; $p = 0.395$). However, among patients with high MELD scores, a multivariate analysis showed that the presence of hepatitis C ($p = 0.013$) and LDLT in Era-I ($p = 0.036$) was significantly associated with a poorer prognosis. Among patients with hepatitis C ($n = 155$), the 5-year graft survival rate was significantly lower in patients with high MELD scores (33.7 %, $p < 0.001$) than in patients with low MELD scores. The 5-year graft survival rate was significantly lower in patients in Era-I ($n = 119$) compared with those in Era-II/III when stratified by low (73.0 vs. 82.5 %, $p = 0.040$) and high (55.0 vs. 86.1 %, $p = 0.023$) MELD scores. Among the patients with high MELD scores, those with hepatitis C and LDLT in Era-I had the worst 5-year graft survival rate (14.3, $p < 0.001$).
Conclusion The graft outcomes in patients with high MELD scores and the presence of hepatitis C were found to be particularly poor.

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Keywords Living donor liver transplantation · Hepatitis C · Model for end-stage liver disease · Learning curve

Abbreviations

GRWR	Graft recipient weight ratio
GV	Graft volume
GW	Graft weight
LDLT	Living donor liver transplantation
MELD	Model for end-stage liver disease
PVF	Portal venous flow
PVP	Portal venous pressure
SLV	Standard liver volume

Introduction

The model for end-stage liver disease (MELD) was originally developed as a scoring system to assess the severity of terminal liver diseases. Therefore, it is often used as part of the criteria for allocating deceased donor livers [1, 2]. Previous studies have shown that the MELD system might also predict graft outcomes after deceased donor liver transplantation (DDLT), although this possibility is still widely debated [3–5].

Partial grafts are always used in living donor liver transplantation (LDLT), but might be too small to fulfill the recipient's metabolic needs [6]. Therefore, the pre-transplant disease severity, as represented by a high MELD score, might be an important determinant of the graft outcome [7]. The technical advances in LDLT in the last decade have dramatically improved the overall graft outcomes after LDLT [8–10]. The Toronto group recently reported that LDLT could provide excellent graft outcomes, even in patients with high MELD scores [11].

However, the impact of high MELD scores on the outcome of LDLT has not been fully elucidated, and is hotly debated [7–11]. Moreover, there has so far been no subgroup analyses of patients with high MELD scores aimed at elucidating the factors associated with the graft outcomes after LDLT.

Therefore, the aims of this study were to evaluate the overall impact of the MELD score on the graft outcomes in LDLT, and to identify clinically relevant prognostic factors in patients with high MELD scores.

Materials and methods

Patients

We retrospectively analyzed our prospective database of all adult-to-adult LDLTs performed since May 1997 ($n = 357$). The recipients included 172 males (48.2 %), and the mean age of the recipients was 51.6 ± 11.6 years. Hepatitis C infection was present in 155 (43.4 %) patients, and hepatocellular carcinoma was present in 156 (43.8 %). The primary liver diseases included liver cirrhosis ($n = 216$; hepatitis C, $n = 153$; hepatitis B, $n = 40$), cholestatic liver diseases ($n = 78$), acute liver or graft failure ($n = 54$; including hepatitis B, $n = 17$; hepatitis C, $n = 2$; hepatic artery thrombosis, $n = 1$; graft congestion, $n = 1$; primary graft failure, $n = 1$) and others ($n = 8$). A major shunt vessel was defined as a portosystemic shunt with a caliber >10 mm.

The donors included 231 males (64.8 %), and the mean age of the donors was 35.9 ± 11.1 years. Seventeen (4.8 %) donors were blood-type incompatible donors. The graft types included left lobe ($n = 223$, 62.6 %), right lobe ($n = 128$, 35.8 %) and posterior segment ($n = 6$, 1.7 %) grafts. The mean graft volume (GV), graft volume/standard liver volume (GV/SLV) ratio and graft recipient weight ratio (GRWR) were 479 ± 106 g, 41.7 ± 8.5 % and 0.81 ± 0.19. All of the LDLTs were performed after obtaining full informed consents from all patients and approval from the Liver Transplantation Committee of Kyushu University. The mean follow-up time was 4.8 ± 3.2 years.

MELD score

The pretransplant total bilirubin levels, creatinine levels and prothrombin time international normalized ratio (PT-INR) were used to calculate the medical MELD score without the additional MELD points [1]. A high MELD score is not a contraindication for LDLT at our center.

Graft selection and surgical procedures

The grafts were selected as described previously [12]. Left lobe grafts were considered to be the primary graft type if the desired GV/SLV was >35 %. Right lobe grafts were considered if the simulated GV/SLV of the left lobe graft was <35 % and the donor's remnant liver volume was >35 %.

The surgical procedures used are described elsewhere [12]. Briefly, the procured graft was perfused ex situ using University of Wisconsin solution (Viaspan™, DuPont Inc., Wilmington, DE). Splenectomy was performed to control the portal venous pressure after reperfusion or to treat thrombocytopenia before introducing interferon treatment for recurrent hepatitis C, if indicated [13].

Immunosuppression and anti-viral treatment for hepatitis C

The immunosuppression protocol consisted of tacrolimus or cyclosporine with mycophenolate mofetil and steroids [12]. The antiviral treatment for hepatitis C consisted of pegylated interferon α2a or 2b plus ribavirin [14].

Assessment of outcomes after LDLT

The endpoint of this study was graft loss, including patient death or re-transplantation. Deaths caused by infection, cardiovascular diseases or recurrent hepatocellular carcinoma were included as graft loss. However, deaths caused by de novo malignancies or accidents were censored.

Transplant era

The total cohort of 357 patients was divided into three groups of equal numbers of consecutively treated patients, Era-I ($n = 119$) consisted of patients 1–119 who were treated between May 1997 and February 2004, Era-II ($n = 119$) consisted of patients 120–238 who were treated between March 2004 and January 2008 and Era-III ($n = 119$) consisted of patients 239–357 who were treated since February 2009.

Statistical analysis

The values are expressed as the mean ± standard deviation or as n (%). Variables were analyzed using the χ^2 tests for categorical variables and the Mann–Whitney U test for continuous variables. The univariate and multivariate survival analyses were performed using the Kaplan–Meier method with the log-rank test and Cox proportional hazards model, respectively. Values of $p < 0.05$ were considered to be statistically significant.

Results

Surgical and postoperative outcomes

The 1- and 5-year cumulative graft survival rates were 87.1 and 78.2 %, respectively. The recipient and donor graft variables, and post-transplant characteristics, are summarized in Table 1.

MELD score and graft survival

A number of patients with MELD scores of <5, 5–9, 10–14, 15–19, 20–24 and ≥25 were 0 (0.0 %), 41 (11.5 %), 108 (30.3 %), 94 (26.3 %), 68 (19.1 %) and 46 (12.8 %), respectively (Fig. 1a). The median and the mean MELD scores were 16 and 17.1 ± 6.9, respectively. The 5-year graft survival rates in the patients with MELD scores of <5 ($n = 148$), 5–25 ($n = 163$) and ≥25 ($n = 46$) were 79.9, 78.2 and 72.1 %, respectively ($p = 0.395$, Fig. 1b).

Characteristics of patients with high MELD scores

The patients were categorized into those with high (≥25, $n = 46$) or low (<25, $n = 311$) MELD scores. Patients with high MELD scores had significantly higher total bilirubin levels (20.8 ± 11.40 vs. 6.0 ± 7.0 mg/dl, $p < 0.001$), prolonged PT-INR (2.54 ± 1/17 vs. 1.48 ± 0.27, $p < 0.001$) and higher creatinine levels (0.8 ± 0.5 vs. 1.3 ± 1.4, $p < 0.001$). After LDLT, the incidence of cytomegalovirus infection (43.4 vs. 23.0 %, $p = 0.003$), bacterial sepsis (28.2 vs. 12.1 %, $p = 0.003$) and the peak total bilirubin levels

Table 1 Patient characteristics stratified by MELD score

Variables	MELD score		*p* value
	Low (<25, $n = 311$)	High (≥25, $n = 46$)	
MELD score	15.2 ± 4.6	30.1 ± 5.6	<0.001
Total bilirubin before LDLT	6.0 ± 7.0	20.8 ± 11.40	<0.001
PT-INR before LDLT	1.48 ± 0.27	2.54 ± 1.17	<0.001
Creatinine before LDLT (mg/dl)	0.8 ± 0.5	1.3 ± 1.4	<0.001
Donor age (years)	35.9 ± 11.4	35.6 ± 9.5	0.809
Donor gender, male	203 (65.5)	28 (60.9)	0.540
Incompatible blood type	17 (5.5)	0 (0.0)	0.104
Left lobe graft	198 (63.8)	25 (54.3)	0.795
GV (g)	478 ± 102	489 ± 127	0.481
GV/SLV ratio (%)	41.6 ± 8.4	42.3 ± 9.6	0.598
GRWR (%)	0.81 ± 0.19	0.83 ± 0.19	0.382
Recipient age (years)	52.2 ± 11.5	47.9 ± 12.2	0.230
Recipient gender, male	149 (48.1)	23 (50.0)	0.806
Hepatocellular carcinoma	153 (49.3)	3 (6.5)	<0.001
Hepatitis C	142 (45.5)	13 (28.3)	0.028
Cold ischemic time (min)	86.9 ± 54.9	95.2 ± 57.9	0.351
Warm ischemic time (min)	39.9 ± 11.9	39.0 ± 8.1	0.594
Hepatic arterial flow (ml/min)	106 ± 68	119 ± 56	0.231
Portal venous flow (l/min)	1.62 ± 0.65	1.54 ± 0.62	0.403
PVP at the closure (mmHg)	16.8 ± 4.4	17.2 ± 4.9	0.636
Major shunt vessels	62 (13.8)	6 (13.1)	0.266
Length of operation (min)	797 ± 174	796 ± 217	0.946
Intraoperative blood loss (l)	7.1 ± 15.4	7.2 ± 8.1	0.960
Acute cellular rejection	46 (14.9)	10 (21.7)	0.238
Hepatic artery thrombosis	6 (1.9)	1 (2.2)	0.918
Portal venous thrombosis	8 (2.6)	1 (2.2)	0.864
Cytomegalovirus infection	70 (23.0)	20 (43.4)	0.003
Pneumonia	36 (11.9)	10 (21.7)	0.067
Bacterial sepsis	37 (12.1)	13 (28.2)	0.003
Peak total bilirubin (mg/dl)	11.6 ± 9.7	17.3 ± 8.7	<0.001
Peak ascites output (l/day)	1.2 ± 1.4	1.3 ± 1.1	0.63

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

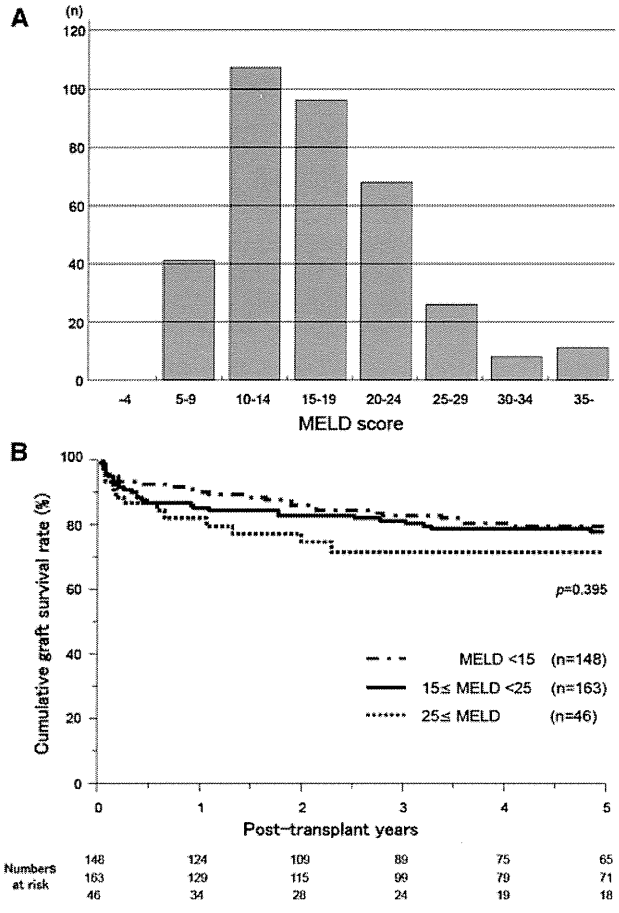

Fig. 1 Distribution of MELD scores (**a**), and the cumulative graft survival according to the MELD score (**b**)

(17.3 ± 8.7 vs. 11.6 ± 9.7, $p < 0.001$) were significantly higher in patients with high MELD scores.

We next evaluated the factors associated with graft loss among the patients with high MELD scores (≥25, $n = 46$). The univariate analysis showed that Era-I ($n = 119$, $p = 0.023$), recipient gender (male, $p = 0.045$), hepatitis C (positive, $p < 0.001$) and the presence of major shunt vessels (yes, $p = 0.010$) were significantly associated with early graft loss (Table 2). The multivariate analysis of these four factors showed that hepatitis C infection (yes, odds ratio 4.9, 95 % confidence interval 1.5–17.8, $p = 0.013$) and LDLT during Era-I (yes, odds ratio 4.0, 95 % confidence interval 1.2–15.8, $p = 0.036$) were independently associated with graft loss (Table 3).

Hepatitis C positive patients

The patients with hepatitis C were classified into four groups based on the MELD scores: <15 ($n = 82$), 15–19 ($n = 39$), 20–24 ($n = 21$) and ≥25 ($n = 13$). The 5-year graft survival rates in these four groups were 78.9, 80.0, 75.6 and 33.7 %, respectively. Patients with hepatitis C and MELD scores ≥25 had significantly worse graft outcomes compared with the other three groups ($p < 0.001$, Fig. 2a).

Among the patients without hepatitis C infection ($n = 202$), the 5-year survival rates in patients with low

Table 2 Results of the univariate analysis of graft mortality in patients with high (≥25) MELD scores

Variables	*n*	Graft survival rate (%)		
		1-year	5-year	*p* value
Era-I (first 1/3 cases)				
Yes	21	70.0	55.0	0.023
No	25	91.8	86.1	
Recipient gender, male				
Yes	23	77.3	54.1	0.045
No	23	86.5	86.5	
Emergency LDLT				
Yes	26	83.8	83.8	0.147
No	20	80.0	58.4	
Hepatitis C				
Yes	13	61.5	33.7	<0.001
No	33	90.4	86.6	
Donor age ≥40 years				
Yes	16	81.2	54.5	0.096
No	30	82.4	82.4	
Donor gender, male				
Yes	28	80.9	80.9	0.217
No	18	83.3	59.2	
Left lobe graft				
Yes	25	78.6	78.6	0.427
No	21	85.7	62.9	
GV/SLV <40 %				
Yes	21	88.0	84.1	0.623
No	25	91.7	72.4	
GRWR <0.8				
Yes	19	68.4	68.4	0.424
No	27	92.1	74.5	
Major shunt vessels				
Yes	6	50.0	33.3	0.010
No	40	84.1	77.9	
Splenectomy				
Yes	11	81.8	68.2	0.930
No	35	82.0	71.9	
Duct-to-duct				
Yes	16	75.0	66.8	0.686
No	43	90.1	80.8	

GRWR graft recipient weight ratio, *GV* graft volume, *LTLT* living donor liver transplantation, *MELD* model for end-stage liver disease, *SLV* standard liver volume

Table 3 Results of the multivariate analysis of graft mortality in patients with high (≥25) MELD scores

95 % confidence interval				
Variables	Odds ratio	Lower	Upper	*p* value
Hepatitis C	4.9	1.5	17.8	0.013
Era-I (first 1/3 cases)	4.0	1.2	15.8	0.036
Major shunt vessels	3.3	0.9	11.9	0.061
Recipient gender, male	3.1	0.8	12.2	0.106

MELD model for end-stage liver disease

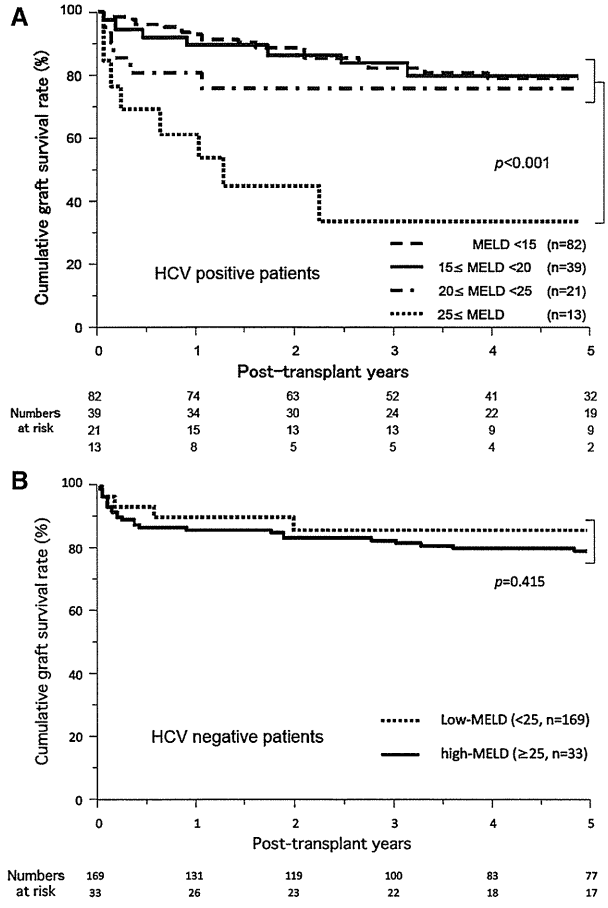

Fig. 2 Cumulative graft survival in patients with (**a**) or without (**b**) hepatitis C according to the MELD score

(<25, $n = 169$) and high (≥25, $n = 33$) MELD scores were 86.6 and 79.6 %, respectively ($p = 0.415$, Fig. 2b). Even when we excluded hepatitis C-negative patients with acute liver or graft failure from the analysis, the 5-year graft survival rates were comparable between those with low (<25, $n = 143$) and high (≥25, $n = 10$) MELD scores (81.5 and 80.0 %, respectively, $p = 0.926$). Therefore, hepatitis C was only associated with poor graft survival among the patients with high MELD scores.

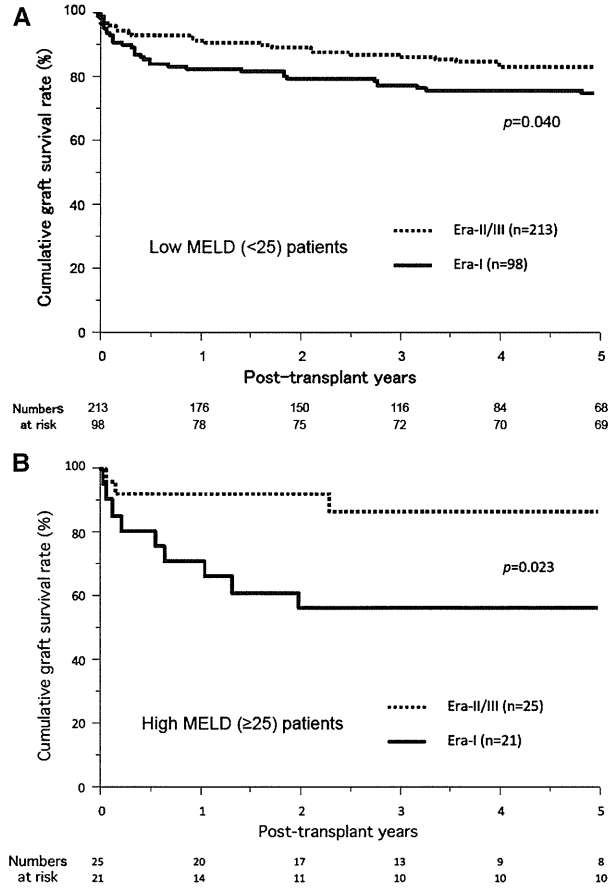

Fig. 3 Cumulative 5-year graft survival rate following LDLTs in Era-I (May 1997–February 2004) or Era-II/III (March 2004 onwards) in patients with low (**a**) or high (**b**) MELD scores

Transplant era and graft survival

The cumulative 5-year graft survival rate was compared between patients undergoing LDLT in Era-I or Era-II/III, and was stratified by high ($n = 46$) or low ($n = 311$) MELD scores. Among the patients with low MELD scores (Fig. 3a), the 5-year graft survival rate was significantly lower in patients who underwent LDLT in Era-I ($n = 98$), compared with Era-II/II ($n = 213$), with rates of 73.0 and 82.5 %, respectively ($p = 0.040$). The 5-year graft survival rate in patients with high MELD scores (Fig. 3b) was also significantly lower in the patients who underwent LDLT in Era-I ($n = 21$) than in Era-II/II ($n = 25$), with rates of 55.0 and 86.1 %, respectively ($p = 0.023$).

Effects of hepatitis C in combination with the transplant era

Patients with high MELD scores (≥25) were categorized into three groups according to the combination of time of

LDLT and hepatitis C status as follows: (1) LDLT in Era-II/III and absence of hepatitis C; (2) either LDLR in Era-I or the presence of hepatitis C; and (3) LDLT in Era-I and the presence of hepatitis C. The 5-year graft survival rates of these three groups of patients were 94.4, 72.6 and 14.3 %, respectively. Patients in group 3 (LDLT in Era-I and the presence of hepatitis C) had a significantly worse prognosis than those in the other two groups ($p < 0.001$). Among the patients with hepatitis C and high MELD scores who underwent LDLT in Era-I ($n = 7$), the causes of graft loss included graft dysfunction because of sepsis and multiple organ failure ($n = 3$), recurrent hepatitis C ($n = 2$) and recurrent hepatocellular carcinoma ($n = 1$). On the other hand, among patients with hepatitis C and high MELD scores who underwent LDLT in Era-II/III ($n = 6$), only one graft was lost because of recurrent hepatitis C. Although three out of the six (50 %) grafts in this group had aggressive recurrent hepatitis C, two patients underwent interferon treatment resulting in a viral response. Moreover, no grafts in patients with high MELD scores were lost as a result of septic complications in patients who underwent LDLT in Era-II/III (Fig. 4).

Discussion

The findings of the current study can be summarized as follows: first, the overall graft survival was not significantly different between patients with high or low MELD scores. Second, among patients with high MELD scores (≥25), the presence of hepatitis C and LDLT in Era-I (May 1997–February 2004) were significantly associated with a poor prognosis.

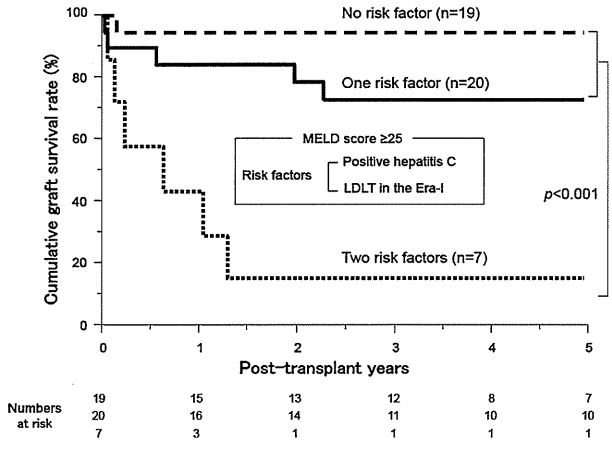

Fig. 4 Cumulative graft survival in three groups of patients with high MELD scores (≥25) stratified according to the time of LDLT and hepatitis C status: (1) LDLT in Era-II/II and the absence of hepatitis C ($n = 19$); (2) either LDLT in Era-I or the presence of hepatitis C ($n = 20$); and (3) LDLT in Era-I and the presence of hepatitis C ($n = 7$)

Regarding the overall general impact of high MELD scores, the current results appear to be convincing because it is generally accepted that surgical outcomes are largely influenced by the pre-surgical conditions [15]. However, the findings are reasonable considering the patient characteristics and transplant era, since the majority of patients had moderate MELD scores (median: 16, mean: 17) and most transplants were performed after 2000. On the other hand, the Kyoto group [10] analyzed 576 adult-to-adult cases since 1993, with a mean MELD score of 20, and found that patients with high MELD scores had an increased risk of graft loss (odds ratio 1.65). Their results are also reasonable, because their patients generally had higher MELD scores, and transplantation was done before 2000, before the introduction of major refinements in surgical techniques for adult-to-adult LDLT [16]. Marubashi et al. [7] reported similar results in their initial 39 cases with a higher mean MELD score of 22. In contrast, the Toronto group [11] recently reported a negative impact of the MELD score on graft outcomes. They analyzed more recent LDLTs since 2002 ($n = 271$); the mean MELD score of their patients was 17. Therefore, we would anticipate that our outcomes would be similar to those reported by the Toronto group. By taking into account these findings, it could be concluded that a high MELD score does not negatively affect the overall graft outcomes of patients undergoing LDLT in recent years, and with the application of the recent refinements in LDLT.

The negative effect of a high MELD score on graft outcomes in patients with hepatitis C patients is a particularly important finding. The difference in survival between patients with higher and lower MELD scores among those with hepatitis C became prominent within 3 months of LDLT, and the gap gradually increased with time, reaching 40 % 2 years after LDLT. The high risk of graft loss associated with a high MELD score and hepatitis C continues until 2 years after transplantation. This conflicts with the belief that the pre-transplant disease severity only affects graft outcomes in the very early post-transplant course, namely in the first 2–3 months after LDLT [10, 17]. In our patients, five out of 13 (38.5 %) with high MELD scores had aggressive recurrent hepatitis C, defined as cholestatic or fibrosing hepatitis C [14]. The incidence of aggressive hepatitis C was higher in patients with high MELD scores than in patients with low MELD scores (5/13 vs. 16/142, $p = 0.006$). Because there were no significant differences in the donor age, graft volume, immunosuppression protocol or viral load between patients with high or low MELD scores, the difference in the rate of aggressive hepatitis C might be attributed to the disease. However, there have so far been no reports describing an