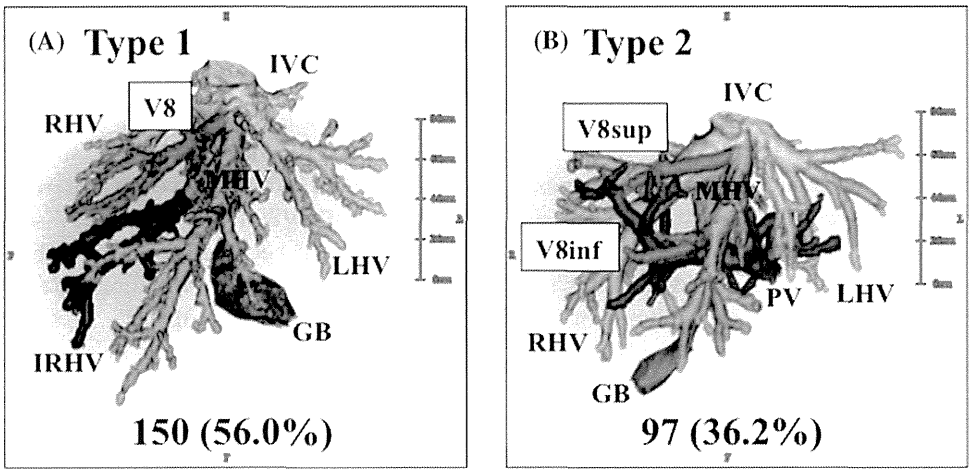

Fig. 3 3D-CT images of V8 variations. **a** Type 1 anatomy. A single large V8 enters the root of the MHV. **b** Type 2 anatomy. The V8sup/V8inf enters the MHV separately. The LHV, RHV and IVC are colored aqua. The MHV, IRHV and PV are colored *yellow*, *red* and *dark blue*, respectively. The V8, including the V8sup/V8inf, is colored *purple*. *3D-CT* three-dimensional computed tomography, *GB* gallbladder, *IRHV* inferior right hepatic vein, *IVC* inferior vena cava, *LHV* left hepatic vein, *MHV* middle hepatic vein, *PV* portal vein, *RHV* right hepatic vein, *V8* the MHV tributaries draining segment VIII, *V8sup/V8inf* the superior/inferior veins draining segment VIII

hepatectomy was performed with intermittent inflow occlusion under the hanging maneuver. To prevent biliary complications, donor hilar dissection was performed only at the corresponding first Glissonean branch, and donor parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA^{TM}, Valleylab Inc., Boulder, CO, USA). For right lobe grafts, the graft was procured by transecting along the right side of the MHV. The significant inferior right hepatic veins and MHV tributaries were clipped and procured with the liver graft for reconstruction on the back table. The size and number of MHV tributaries were measured. Recipient total hepatectomy was usually performed while preserving the IVC. In right lobe grafts, a hilar PV from the top of the umbilical portion to both the anterior and posterior right branches was procured for the interposition graft on the back table. Then, the interposition graft was anastomosed to the MHV tributaries of the liver graft.

Postoperative evaluation of the reconstructed MHV tributaries

The patency of the reconstructed MHV tributaries was checked by CT on postoperative day (POD) 7. The serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were measured every day until POD 14. In the 46 right lobe LDLT cases, the recipients were divided into the four groups: both V5 and V8 were patent, only V5 was patent, only V8 was patent and both V5 and V8 were occluded. The patent groups included the recipients in which the MHV tributaries had been reconstructed and that were patent on POD 7. The occluded group included the recipients in which the MHV tributaries had been reconstructed and that were not patent on POD 7, and those in which the MHV tributaries had not been reconstructed and were not patent.

Statistical analysis

The data were expressed as the mean ± standard deviation. Statistical evaluations of numerical variables between different groups were performed using Student's *t* test. Differences in liver functions were analyzed using a one-way analysis of variance. The significance of differences was determined by a post hoc test and Fisher's exact probability test. The differences were considered significant when the *P* value was <0.05. All analyses were performed using the Stat View^{TM} software program (Version 5.0, Abacus Concepts, Berkeley, CA, USA).

Results

Analysis of the V5 variations

In terms of the V5 variations, types 1, 2 and 3 were found in 30 (11.2 %), 120 (44.8 %) and 114 (42.5 %) cases, respectively (Fig. 2a–c). In the 46 right lobe grafts, five cases were type 1, 23 cases were type 2 and 18 cases were type 3. The calculated total VCRs of each branch were as follows: 6.7 % (range 3.2–9.9) in total for type 1; 21.5 % (range 8.3–36.1) for type 2; and 17.2 % (range 7.2–29.5) in total, 5.6 % (range 1.5–12.6) in the V5sup and 11.6 % (range 3.5–25.8) in the V5inf in type 3.

Reconstruction of V5 was performed in 0 (0.0 %) case with type 1, 19 (82.6 %) cases with type 2 and eight

Table 1 The venous congestion rate (VCR), reconstruction rate and patency rate according to the variations in V5 and V8 in 46 right lobe grafts

Type	VCR (%) (mean values)			Reconstruction rate (%)	Patency rate (%)
	Total	Reconstructed	Not reconstructed		
V5					
Type 1	6.7 ± 2.4 (n = 5)	–	6.7 ± 2.4 (n = 5)	0.0	–
Type 2	21.5 ± 9.0 (n = 23)	23.7 ± 8.3 (n = 19)	11.2 ± 2.1 (n = 4)	82.6	73.7
Type 3					
Total	17.2 ± 6.5 (n = 18)	20.3 ± 6.1 (n = 8)[a]	14.6 ± 5.8 (n = 10)	44.4	25.0
V5sup	5.6 ± 3.0 (n = 18)	4.5 ± 2.1 (n = 2)	5.7 ± 3.1 (n = 16)	11.1	0.0
V5inf	11.6 ± 5.8 (n = 18)	14.6 ± 7.5 (n = 7)	9.7 ± 3.7 (n = 11)	38.9	28.6
V8					
Type 1	10.7 ± 5.6 (n = 27)	14.2 ± 6.1 (n = 12)	7.9 ± 3.3 (n = 15)	44.4	75.0
Type 2					
Total	9.8 ± 3.8 (n = 17)	9.5 ± 2.5 (n = 3)	9.9 ± 4.1 (n = 14)	17.6	33.3
V8sup	2.5 ± 3.2 (n = 17)	–	2.5 ± 3.2 (n = 17)	0.0	–
V8inf	7.3 ± 3.7 (n = 17)	9.5 ± 2.5 (n = 3)	6.8 ± 3.8 (n = 14)	17.6	33.3

VCR (%), the hepatic venous congestion volume of each hepatic venous branch/the right lobe volume

[a] In one case, V5 sup and V5inf were both reconstructed; in one case, only V5sup only was reconstructed and in six cases, only V5inf was reconstructed

(44.4 %) cases with type 3 variations. In the type 3 cases, one case was reconstructed in both the V5sup and V5inf, one case was reconstructed only in the V5sup and six cases were reconstructed only in the V5inf. In other words, reconstruction was performed in two (11.1 %) cases in the V5sup and seven (38.9 %) cases in the V5inf.

The VCR in type 1 cases was significantly lower than that in cases of types 2 and 3 ($P < 0.05$). Although there were no significant differences, the VCR in the type 2 cases tended to be higher than that in the type 3 cases ($P = 0.09$), and the reconstruction rate was significantly higher for the V5 in type 2 cases than for the type 3 case ($P < 0.05$). The VCR in the cases with type 2 variation was higher in the reconstruction group than in the non-reconstruction group (23.7 and 11.2 %, respectively; $P < 0.05$), and tended to be higher in total in the type 3 cases (20.3 and 14.6 %, respectively; $P = 0.06$). However, in the type 3 cases, there were no significant differences between the reconstruction and non-reconstruction groups in terms of the VCR in the V5sup (4.5 and 5.7 %, respectively) or the V5inf (14.6 and 9.7 %) (Table 1).

Among the 46 right lobe LDLT cases, 14 (73.7 %) type 2 and two (25.0 %) type 3 cases were patent on POD 7. In type 3 cases, 0 (0.0 %) V5sup and two (28.6 %) V5inf were patent on POD 7. The patency rate in the type 2 cases was therefore significantly higher than that in the type 3 cases ($P < 0.05$) (Table 1). Regarding the 23 recipients with the type 2 V5 variations, the number of patients who had both V5 and V8 patency was seven (30.4 %), another seven had only V5 patency (30.4 %), one patient had only V8 patency (4.3 %) and eight patients had no patency in either vein (34.8 %).

We compared the aminotransferase levels between the group with both V5 and V8 patency and the group with only V8 patency, and between the only V5 patent group and the both V5 and V8 occluded group. There were no significant differences found between the both V5 and V8 patent group and the only V8 patent group (Fig. 4a). However, the ALT level on POD 5 was significantly lower in the only V5 patent group than in the both V5 and V8 occluded group (123 vs. 191 IU/dL; $P < 0.05$) (Fig. 4b), although the congestion area from V8 occlusion was not significantly different between these two groups (10.0 vs. 11.7 %). Therefore, we think that this phenomenon might be influenced more by the patency of type 2 V5 rather than by other congestion due to V8 occlusion.

Analysis of V8 variations

Regarding V8, the variations in type 1 and 2 were found in 150 (56.0 %) and 97 (36.2 %) cases, respectively (Figs. 3a, b). In the 46 right lobe grafts, 27 cases were type 1 and 17 cases were type 2. The calculated VCRs of each branch were as follows: 10.7 % (range 2.5–27.8) in type 1 and 9.8 % (range 3.5–18.3) in total, with 2.5 % (range 0.0–10.7) in the V8sup and 7.3 % (range 0.0–13.0) in the V8inf in type 2. Reconstruction of V8 was performed in 12 (44.4 %) cases with type 1 and three (17.6 %) cases with type 2 variations. In the type 2 group, all three cases were reconstructed only in V8inf. In other words, reconstruction was performed in 0 (0.0 %) case in the V8sup and three (17.6 %) cases in the V8inf. There were no significant differences in the VCR between types 1 and 2. However, the reconstruction rate of V8 in the type 1 cases was

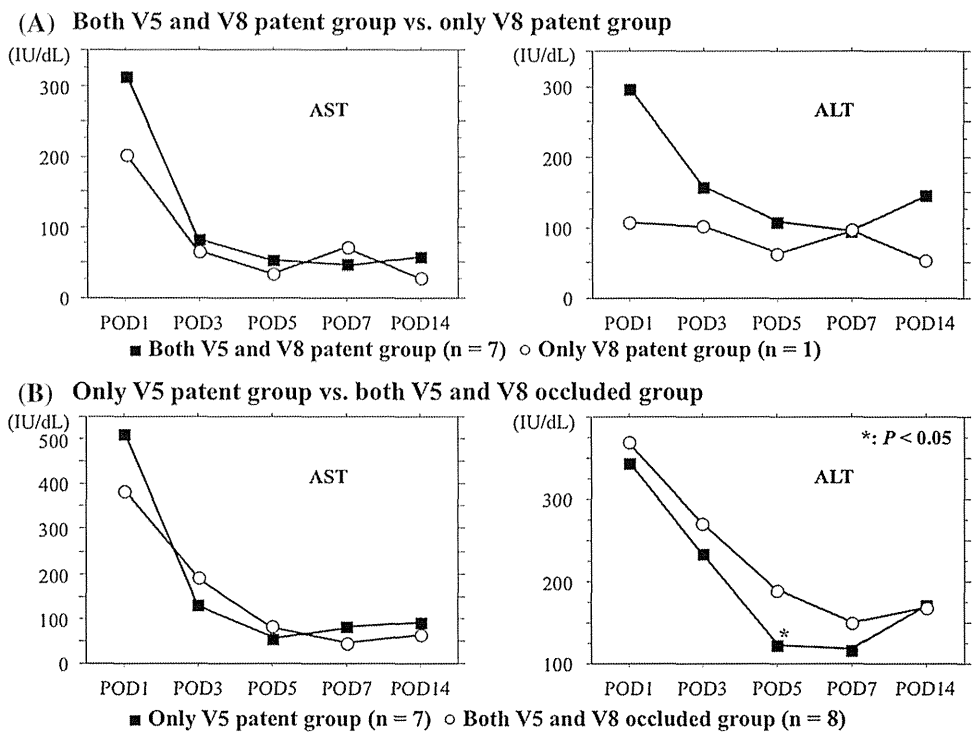

Fig. 4 The postoperative serial changes in the serum liver enzyme levels in the cases with type 2 V5 tributaries. **a** The both V5 and V8 patent group vs. the only V8 patent group. There were no significant differences between these two groups. **b** The only V5 patent group vs. the both V5 and V8 occluded group. The ALT level on POD 5 in the only V5 patent group was significantly lower than that in the both V5 and V8 occluded group (123 vs. 191 IU/dL; $P < 0.05$). *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *POD* postoperative day

significantly higher than that in the type 2 cases ($P < 0.05$). The VCR in the reconstruction group was higher than that in the non-reconstruction group in the type 1 cases (14.2 and 7.9 %, respectively; $P < 0.01$). However, there were no significant differences between the reconstruction and non-reconstruction groups in terms of the total VCR (9.5 and 9.9 %, respectively) and the VCR in the V8inf (9.5 and 6.8 %, respectively) in the type 2 cases (Table 1).

Among the 46 right lobe LDLT cases, nine type 1 (75.0 %) and one type 2 (33.3 %) cases were patent on POD 7. The patency rate was significantly higher in type 1 cases than in type 2 cases ($P < 0.05$) (Table 1). Regarding the 27 recipients with the type 1 V8 variations, there were six (22.2 %) cases with patency for both V8 and V5, three (11.1 %) cases with only V8 patency, three (11.1 %) cases with only V5 patency and there were 15 (55.6 %) cases without patency of either V8 or V5. We compared the aminotransferase levels between the both V8 and V5 patent group and the only V5 patent group, and between the only V8 patient group and the both V8 and V5 occluded group. There were no significant differences between the both patent group and the only V5 patent group (Fig. 5a). However, the AST level on POD 3 was significantly lower in the only V8 patent group than in the both V8 and V5 occluded group (50 vs. 121 IU/dL; $P < 0.05$) (Fig. 5b), although the congestion area due to V5 occlusion was not significantly different between these two groups (12.4 vs. 14.2 %). Therefore, we think that this phenomenon might have been influenced more by the patency of the type 1 V8 than by other congestion due to V5 occlusion.

Discussion

In LDLT, the left lobe graft is considered to be the most ideal graft in terms of the donor safety. It was reported that the incidence of donor complications based on 1841 donors in Japan was significantly higher in donors of the right lobe than in donors of the left lobe and the left lateral segment [13]. The surgical mortality for right lobe donors was estimated to be as high as 0.5–1.0 % [14]. We previously reported that left lobe LDLT was a feasible treatment modality to maintain minimal mortality and morbidity in donors [11], and that the number of biliary complications was significantly lower in left lobe LDLT than in right lobe LDLT [12]. However, with a left lobe graft, major problems with small-for-size (SFS) grafts often occur [15–17]. The initial experience related to left lobe grafts demonstrated a higher incidence of SFS, graft failure and recipient complications [18]. SFS is characterized by synthetic dysfunction and prolonged cholestasis [13]. Small-for-size grafts should be considered highly vulnerable to insult, with an increased risk of significant sequelae from complications or additional metabolic stress in the immediate postoperative period. Consequently, right lobe grafts have been used routinely at many centers [15, 19, 20].

In right lobe grafts without MHV, the anterior sector is usually hemodynamically altered due to ligation of the MHV tributaries, and HVC could subsequently occur in the anterior sector. HVC not only affects the regenerative capacity of the liver graft, but also induces parenchymal

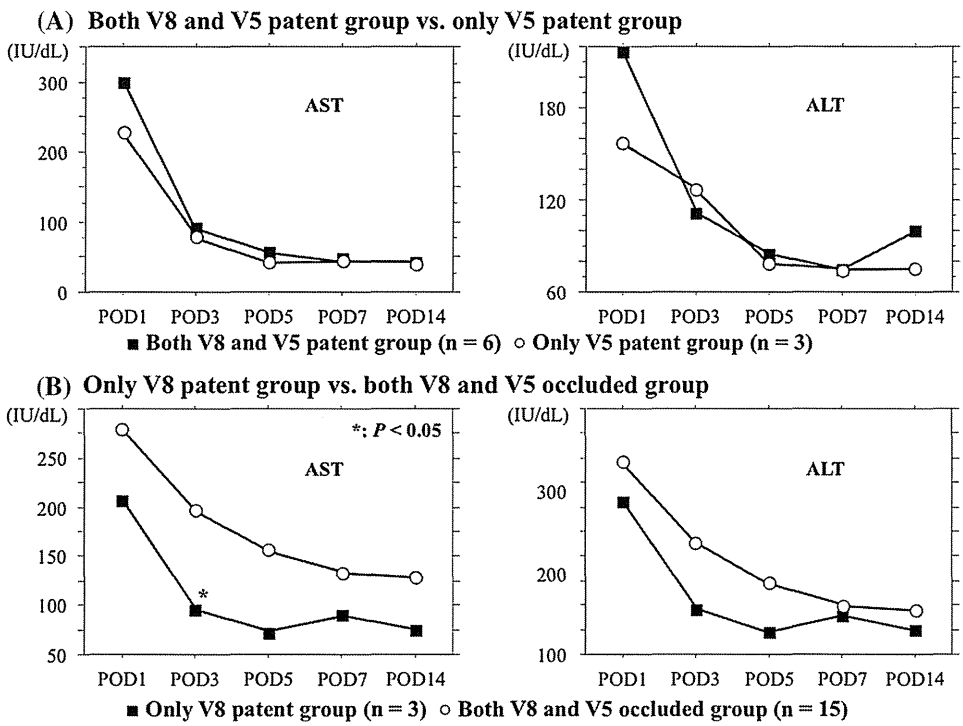

Fig. 5 The postoperative serial changes in the serum liver enzyme levels in cases with type 1 V8 tributaries. **a** The both V8 and V5 patent group vs. the only V8 patent group. There were no significant differences between these two groups. **b** The only V8 patent group vs. the both V8 and V5 occluded group. The AST level on POD 3 in the only V8 patent group was significantly lower than that in the both V8 and V5 occluded group (50 vs. 121 IU/dL; $P < 0.05$). *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *POD* postoperative day

cell injury, and even severe metabolic dysfunction [2, 21, 22]. In recipients receiving right lobe grafts without MHV, several reports have demonstrated that the regeneration of the congested area was significantly poorer in comparison to that of the non-congested area, especially during the early postoperative period [23, 24]. It is possible that the impaired regeneration caused by congestion may be attributed to the abnormal hemodynamics of the congestion area, where the outflow from the congested area cannot be entirely compensated for by the function of the pre-existing collaterals, and where the portal branches substitute as venous pathways due to regurgitation [9, 21]. Several reports have demonstrated that the collateral between the ligated MHV tributaries and the right hepatic vein (RHV) is formed over several days [25–27]. Therefore, to prevent liver dysfunction during the early postoperative period and eventual graft failure, the concept of the reconstruction of the MHV tributaries is an accepted modality [10, 28], and the evaluation of anatomical variations of the MHV tributaries is essential.

The 3D-CT visualization has been extremely helpful in facilitating understanding of the anatomy of a donor's hepatic vessels [6, 7], such that when there is an anomaly with regard to the hepatic or portal veins, it is relatively easy to develop a surgical strategy. Surgical simulations using these anatomical images contribute to a reduction in the risk, not only to donors, but also to recipients, because it is a very useful tool for understanding the anatomical variations in the MHV tributaries. Using computed 3D venous mapping, Radtke et al. [29] have advocated the concept of the "territorial belonging of the MHV" based on territorial vein dominance. According to their concept for types A and B with normal remnants, the right graft should preferably include the MHV, whereas donors with small left remnants should retain the MHV. In contrast, donors with type D findings should retain the MHV in the remnant, irrespective of remnant size, because they are at high risk of small-for-size graft syndrome [29]. Their graft selection algorithm, using three parameters based on 3D-CT, namely, the hepatic vein dominance classification, graft and remnant graft volume/body weight ratios and congestion volumes [30], is reasonable and applicable. However, for donor safety in our institution, the right lobe graft with MHV has not been used in principle. Therefore, the preoperative evaluation of the MHV tributaries is of great importance for the reconstruction of the MHV in recipients.

At many centers, the criteria used for the reconstruction of the MHV tributaries include the size of the MHV branches. Traditionally, tributaries that are >5 mm are uniformly considered to require reconstruction, and those that are <5 mm are occasionally ligated. In the present study, all reconstructed MHV tributaries were ≥5 mm. The mean sizes of the reconstructed V5 (type 2), V5sup (type 3), V5inf (type 3), V8 (type 1) and V8inf (type 2) were 11.4 mm (range 7.0–17.0), 5.0 mm (range 5.0–5.0), 11.8 mm (range 7.0–15.0), 7.8 mm (range 5.0–10.0) and 6.5 mm (range 6.0–7.0), respectively. We have previously

reported that a branch <5 mm was not thought to be a significant branch, but our current study revealed that some branches <5 mm had a high VCR (>10 %) [7]. Therefore, our criteria for reconstruction of the MHV tributaries did not include the size of the MHV tributaries.

In the present study, the variations in V5 were mostly classified into three types, and V8 variations were mainly classified into two types. There was no correlation among the PV variations, V5 variations and V8 variations (data not shown). In V5 variations, almost all cases ($n = 234$; 87.3 %) were classified as type 2 or type 3. The patency rate was significantly higher in type 2 than in type 3 cases ($P < 0.05$) (Table 1), and the ALT level on POD 5 in the only V5 patent group was significantly lower than that in the both occluded group ($P < 0.05$) (Fig. 4b). In terms of V8 variations, the rate in type 1 cases ($n = 150$; 56.0 %) was higher than that in type 2 cases ($n = 97$; 36.2 %). The patency rate was significantly higher in type 1 than in type 2 cases ($P < 0.05$) (Table 1), and the AST level on POD 3 was significantly lower in the only V8 patent group than in the both occluded group ($P < 0.05$) (Fig. 5b). As a result, reconstruction of the MHV tributaries would be necessary for a right lobe graft with a single large V5 (type 2) or a single large V8 (type 1). In fact, the VCR in the reconstruction group was larger than that in the non-reconstruction group in terms of the type 2 V5 variation (23.7 and 11.2 %, respectively, $P < 0.05$) (Table 1), and in type 1 in terms of the V8 variation (14.2 and 7.9 %, respectively, $P < 0.01$) (Table 1). In other words, the MHV tributaries draining a large volume required reconstruction.

We can select donor candidates partially based on our classification, because we can decide if their liver is suitable as a right lobe graft using our classification. In such a sense, our new classification of the MHV tributaries is very useful. However, an evaluation of the congestion volume in each donor caused by deprivation of the drainage from the MHV tributaries using 3D-CT volumetry is necessary to determine the best reconstruction strategy for right lobe LDLT. In the setting of the high degree of variability in the MHV, individualized planning using 3D-CT is mandatory for determining the optimal outcome for both the donors and recipients, especially in right lobe LDLT.

In conclusion, right lobe LDLT can be performed safely, but there is a potential risk due to various anatomical variations. To minimize complications, anatomical variations should be rigorously simulated preoperatively using 3D-CT.

Conflict of interest Dr. Kayashima and the co-authors have no conflicts of interest to declare in association with this study.

References

1. Raia S, Nery JR, Mies S. Liver transplantation from liver donors. Lancet. 1989;2:497.
2. Fan ST, De Villa VH, Kiuchi T, Lee SG, Makuuchi M. Right anterior sector drainage in right-lobe live-donor liver transplantation. Transplantation. 2003;75:S25.
3. Lee SG, Park KM, Hwang S, Lee YJ, Choi DN, Kim KH, et al. Congestion of right liver graft in living donor liver transplantation. Transplantation. 2001;71:812.
4. Ito T, Kiuchi T, Yamamoto H, Maetani Y, Oike F, Kaihara S, et al. Efficacy of anterior segment drainage reconstruction in right-lobe liver grafts from living donors. Transplantation. 2004; 77:865.
5. Yu PF, Wu J, Zheng SS. Management of the middle hepatic vein and its tributaries in right lobe living donor liver transplantation. Hepatobiliary Pancreat Dis Int. 2007;6:358.
6. Kayashima H, Taketomi A, Yonemura Y, Ijichi H, Harada N, Yoshizumi T, et al. Accuracy of an age-adjusted formula to assess the graft volume in living donor liver transplantation. Liver Transpl. 2008;14:1366.
7. Yonemura Y, Taketomi A, Soejima Y, Yoshizumi T, Uchiyama H, Gion T, et al. Validity of preoperative volumetric analysis of congestion volume in living donor liver transplantation using three-dimensional computed tomography. Liver Transpl. 2005;11: 1556.
8. Taketomi A, Takeishi K, Mano Y, Toshima T, Motomura T, Aishima S, et al. Total resection of the right hepatic vein drainage area with the aid of three-dimensional computed tomography. Surg Today. 2012;42:46.
9. Fukuhara T, Umeda K, Toshima T, Takeishi K, Morita K, Nagata S, et al. Congestion of the donor remnant right liver after extended left lobe donation. Transpl Int. 2009;22:837.
10. Ikegami T, Soejima Y, Taketomi A, Yoshizumi T, Harada N, Uchiyama H, et al. Explanted portal vein grafts for middle hepatic vein tributaries in living-donor liver transplantation. Transplantation. 2007;84:836.
11. Soejima Y, Taketomi A, Yoshizumi T, Uchiyama H, Harada N, Ijichi H, et al. Feasibility of left lobe living donor liver transplantation between adults: an 8-year, single-center experience of 107 cases. Am J Transplant. 1004;2006:6.
12. Taketomi A, Kayashima H, Soejima Y, Yoshizumi T, Uchiyama H, Ikegami T, et al. Donor risk in adult-to-adult living donor liver transplantation: impact of left lobe graft. Transplantation. 2009; 87:445.
13. Umeshita K, Fujiwara K, Kiyosawa K, Makuuchi M, Satomi S, Sugimachi K, et al. Japanese Liver Transplantation Society. Operative morbidity of living liver donors in Japan. Lancet. 2003;362:687.
14. Brown RS Jr, Russo MW, Lai M, Shiffman ML, Richardson MC, Everhart JE, et al. A survey of liver transplantation from living adult donors in the United States. N Engl J Med. 2003;348:818.
15. Miller CM, Gondolesi GE, Florman S, Matsumoto C, Munoz L, Yoshizumi T, et al. One hundred nine living donor liver transplantations in adults and children: a single-center experience. Ann Surg. 2001;234:301.
16. Kawasaki S, Makuuchi M, Matsunami H, Hashikura Y, Ikegami T, Nakazawa Y, et al. Living related liver transplantation in adults. Ann Surg. 1998;227:269.
17. Grewal HP, Thistlewaite JR Jr, Loss GE, Fisher JS, Cronin DC, Siegel CT, et al. Complications in 100 living-liver donors. Ann Surg. 1998;228:214.
18. Ben-Haim M, Emre S, Fishbein TM, Sheiner PA, Bodlan CA, Kim-Schluger L, et al. Critical graft size in adult-to-adult living

donor liver transplantation: impact of the recipient's disease. Liver Transpl. 2001;7:948.
19. Lo CM, Fan ST, Liu CL, Yong BH, Wong Y, Lau GK, et al. Lessons learned from one hundred right lobe living donor liver transplants. Ann Surg. 2004;240:151.
20. Ito T, Kiuchi T, Egawa H, Kaihara S, Oike F, Ogura Y, et al. Surgery-related morbidity in living donors of right-lobe liver graft: lessons from the first 200 cases. Transplantation. 2003;76: 158.
21. Maema A, Imamura H, Takayama T, Sano K, Hui AM, Sugawara Y, et al. Impaired volume regeneration of split livers with partial venous disruption: a latent problem in partial liver transplantation. Transplantation. 2002;73:765.
22. Kiuchi T, Kasahara M, Uryuhara K, Inomata Y, Uemoto S, Asonuma K, et al. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation. 1999;67:321.
23. Akamatsu N, Sugawara Y, Kaneko J, Sano K, Imamura H, Kokudo N, et al. Effects of middle hepatic vein reconstruction on right liver graft regeneration. Transplantation. 2003;76:832.
24. Mizuno S, Iida T, Yagi S, Usui M, Sakurai H, Isaji S, et al. Impact of venous drainage on regeneration of the anterior segment of right living-related liver grafts. Clin Transplant. 2006;20: 509.
25. Kaneko T, Kaneko K, Sugimoto H, Inoue S, Hatsuno T, Sawada K, et al. Intrahepatic anastomosis formation between the hepatic veins in the graft liver of the living related liver transplantation: observation by Doppler ultrasonography. Transplantation. 2000; 70:982.
26. Yan L, Wu H, Chen Z, Luo Y, Lu Q, Zhang Z, et al. Intrahepatic venous collaterals formation following outflow block in adult-to-adult living donor liver transplantation. J Surg Res. 2008;146: 172.
27. Kayashima H, Shirabe K, Taketomi A, Soejima Y, Uchiyama H, Ninomiya M, et al. Three-dimensional computed tomography analysis of venous collaterals between the middle hepatic vein tributaries and the right hepatic vein in the donor remnant right lobe: report of a case. Surg Today. 2011;41:1266.
28. Soejima Y, Shimada M, Suehiro T, Yoshizumi T, Kishikawa K, Maehara Y. Reconstruction of the middle hepatic vein tributaries using the recipient's recanalized umbilical vein in right-lobe living-donor liver transplantation. Surgery. 2006;139:442.
29. Radtke A, Sgourakis G, Sotiropoulos GC, Molmenti EP, Saner FH, Timm S, et al. Territorial belonging of the middle hepatic vein in living liver donor candidates evaluated by three-dimensional computed tomographic reconstruction and virtual liver resection. Br J Surg. 2009;96:206.
30. Radtke A, Sgourakis G, Sotiropoulos GC, Beckebaum S, Molmenti EP, Saner FH, et al. Donor/recipient algorithm for management of the middle hepatic vein in right graft live donor liver transplantation. Am J Surg. 2010;199:708.

Asian Journal of Endoscopic Surgery
Official Journal of JSES, ELSA, and AETF

Asian J Endosc Surg ISSN 1758-5902

ORIGINAL ARTICLE

Pure laparoscopic right-sided hepatectomy in the semi-prone position for synchronous colorectal cancer with liver metastases

Satoshi Ida,[1,2] Eiji Oki,[1] Koji Ando,[1] Yasue Kimura,[1] Yo-ichi Yamashita,[1] Hiroshi Saeki,[1] Toru Ikegami,[1] Tomoharu Yoshizumi,[1] Masayuki Watanabe,[2] Masaru Morita,[1] Ken Shirabe,[1] Tetsuya Kusumoto,[1] Tetsuo Ikeda,[1] Hideo Baba[2] & Yoshihiko Maehara[1]

1 Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
2 Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Keywords
Colorectal cancer; laparoscopy; liver metastasis

Correspondence
Eiji Oki, Department of Surgery and Science, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan.
Tel: +81 92 642 5466
Fax: +81 92 642 5482
Email: okieiji@surg2.med.kyushu-u.ac.jp

Received: 17 August 2013; revised 22 December 2013; accepted 13 January 2014

DOI:10.1111/ases.12098

Abstract

Introduction: Simultaneous resection for colorectal cancer and synchronous colorectal liver metastases (SCRLM) has been found to be safe and effective. However, pure laparoscopic simultaneous resection (PULSAR) for primary colorectal cancer and SCRLM is usually difficult, especially in the right lobe of the liver. The purpose of this study was to assess the feasibility of PULSAR for patients with primary colorectal cancer and SCRLM.
Methods: From January 2008 to December 2012, a total of 10 patients (9 men and 1woman; mean age, 64 years) underwent PULSAR for a primary tumor and SCRLM.
Results: Seven patients (70%) with lesions in the right lobe (segments 6, 7, and 8) successfully underwent resection with a pure laparoscopic procedure while in the left semi-prone position. No patient was converted to conventional open surgery. The mean operative duration, volume of bleeding, and postoperative hospital stay were 606 ± 46 min, 585 ± 145 mL, and 18 ± 3.5 days, respectively. Although a liver abscess developed in one patient, no colonic complications or perioperative death occurred.
Conclusion: PULSAR for primary colorectal cancer and SCRLM is a feasible multidisciplinary treatment. Moreover, PULSAR can be safely and effectively performed with the patient in the semi-prone position, even when SCRLM exists in the right lobe of the liver.

Introduction

Among patients newly diagnosed with colorectal cancer (CRC), approximately 25% are found to have synchronous liver metastases (1). Surgery remains the only treatment that can achieve a potential cure, and the 5-year survival rate of patients who undergo curative liver resection is now approximately 40%–50% (2,3).

The optimal timing for surgical resection of synchronous metastasis has been debated and continues to evolve. The recommended surgical management for synchronous colorectal metastasis is a staged approach, with initial resection of the primary lesion followed by hepatic resection (4,5). Several recent reports have demonstrated that simultaneous resection does not increase mortality or morbidity rates and reduces hospital stays. Thus, it is an acceptable option in patients with resectable synchronous colorectal liver metastasis (SCRLM) (6,7). However, the safety of simultaneous resection of primary CRC and SCRLM, especially in the right lobe, has not been established.

A laparoscopic approach for CRC surgery was recently developed, and this approach is being increasingly applied following demonstrations of its oncological safety in randomized prospective trials (8,9). It has been reported that laparoscopic surgery can be performed safely, even for liver resection. Laparoscopic liver surgery has seen a remarkable surge in popularity worldwide (10).

Furthermore, successful major laparoscopic resections have been recently reported (10–12). We recently reported pure laparoscopic right hepatectomy, which involves complete intracorporeal laparoscopic hepatectomy without hand assistance. In addition, it can be performed with the patient in the semi-prone position (13,14). However, the application of pure laparoscopic surgery has not yet been fully accepted for right lobe hepatectomy.

In this report, we review the clinical results of pure laparoscopic simultaneous resection (PULSAR) for primary CRC and SCRLM.

Materials and Methods

From January 2008 to December 2012, 22 patients with a primary CRC tumor and SCRLM underwent simultaneous resection by laparoscopy or conventional laparotomy at the Department of Surgery and Science (Department of Surgery II) of Kyushu University Hospital in Fukuoka, Japan. Among them, 10 patients underwent PULSAR for the primary tumor and SCRLM; this group included nine men and one woman and had a mean age of 64 years (range, 42–83 years).

The staging of the tumor was based on the UICC-TNM classification (15). The diagnostic assessments included endoscopy, barium enema, CT, ^{18}F-fluorodeoxyglucose PET-CT, and MRI. SCRLM were identified at the time of diagnosis of the primary CRC.

In this study, we reviewed 10 patients with SCRLM treated by PULSAR and analyzed their surgical data to evaluate the feasibility, safety, and effectiveness of this procedure. Postoperative complications were defined as grade II or higher according to the Clavien-Dindo classification (16) Data were available for all patients and are expressed as mean ± standard error. The study and patients' informed consent statements were approved by the Institutional Review Board of the Kyushu University Hospital.

Treatment strategy

Our criteria for laparoscopic simultaneous resection of SCRLM were as follows: (i) the primary lesion and liver tumors were resectable with curative intent; (ii) there was no extrahepatic metastatic disease; (iii) the patient had normal liver function and no high-risk background; and (iv) the procedure did not exceed segmentectomy of the liver. When the patients met these criteria, hepatic resection and primary resection were performed simultaneously. Initially, patients with SCRLM who did not receive induction chemotherapy were selected to undergo the operation; otherwise, induction chemotherapy was administered to patients for initially unresectable liver metastasis. Oxaliplatin-based chemotherapy was administered using either cetuximab combined with S-1 plus oxaliplatin or bevacizumab combined with oxaliplatin plus 5-fluorouracil and leucovorin. If an initially unresectable liver metastasis responded to chemotherapy and became resectable with curative intent at any time during the imaging evaluation, surgical resection was performed as soon as possible after prompt completion of the induction chemotherapy. All patients who underwent simultaneous resection received adjuvant chemotherapy as induction chemotherapy.

Surgical techniques

We performed the hepatectomy first followed by the colorectal resection. Details of our pure laparoscopic hepatectomy procedures were previously described (13,14). In brief, metastatic tumors in the right side lobe (S6, S7, and S8) were resected with the patient in the left semi-prone position (Figure 1). Four 12-mm trocars were placed in the right upper abdomen and in the navel. One 5-mm trocar was placed between the navel and rib. The locations of the metastases were identified with ultrasonography. The Glisson sheath was taped, and a Pringle maneuver using a Nelaton tube was performed. Resection of the metastatic tumor was then performed laparoscopically using an EnSeal (Ethicon Endo-Surgery, Cincinnati, USA). After completion of the hepatectomy, laparoscopic colorectal resection was performed. The patient was then changed to the lithotomy position. Colorectal resection with radical lymph node dissection

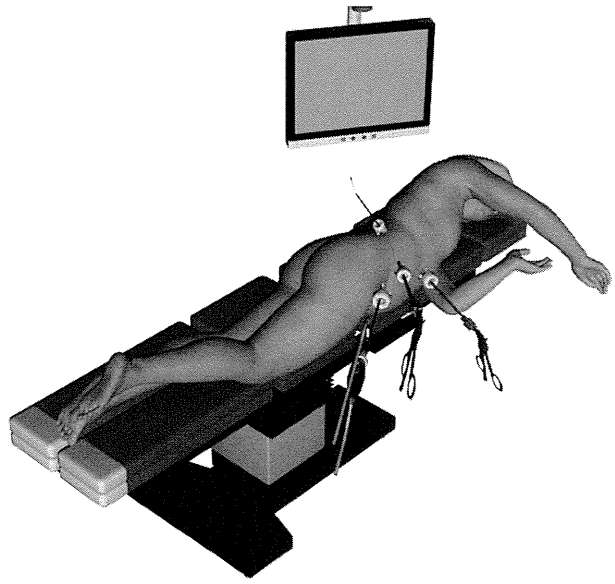

Figure 1 Illustration of patient position and trocar placement.

Asian J Endosc Surg **7** (2014) 133–137

Table 1 Patient characteristics and perioperative data

Case	Age (years)/Sex	Location of CRC	Location of CRCLM	Induction chemotherapy	Operative method		Complication
					Liver	Colon	
1	76/M	Cecum	S4, S8	–	Partial resection	Ileo-cecal resection	Liver abscess
2	61/M	Rectum	S2	–	Subsegmentectomy	Miles'	–
3	79/M	Sigmoid	S7	–	Partial resection	HAR	–
4	52/M	Ascending	S3	–	Subsegmentectomy	Right hemicolectomy	–
5	83/F	Rectum	S6	–	Partial resection	LAR	–
6	55/M	Sigmoid	S6	Cet+SOX	Subsegmentectomy	Sigmoidectomy	–
7	81/M	Sigmoid	S8	–	Subsegmentectomy	Sigmoidectomy	–
8	58/M	Rectum	S6	Bev+ mFOLFOX6	Partial resection	LAR	–
9	42/M	Sigmoid	S4	–	Partial resection	Sigmoidectomy	–
10	48/M	Rectum	S6, S8	–	Partial resection	LAR	–

Bev+mFOLFOX6, bevacizumab combined with oxaliplatin plus 5-fluorouracil and leucovorin; Cet+SOX, cetuximab combined with S-1 plus oxaliplatin; CRC, colorectal cancer; CRCLM, colorectal cancer liver metastases; F, female; HAR, high anterior resection; LAR, low anterior resection; M, male.

(D3) based on a no-touch isolation technique was performed. The incision on the navel was extended to 4 cm, and the liver and colorectal specimens were extracted from the peritoneal cavity. We designated this procedure as pure laparoscopic surgery because the large incision was only created to remove the specimen and not to perform the operation.

Results

Table 1 shows the clinical characteristics and treatment for the SCRLM. Primary CRC was located within the right colon ($n = 2$), left colon ($n = 4$), or rectum ($n = 4$). According to the TNM classification, these primary CRC were staged as T3 and T4a lesions in six and four patients, respectively. Lymph node metastasis in N0, N1, N2, and N3 disease were detected in one, four, three, and two patients, respectively. All patients underwent a radical resection for the primary cancer (colectomy, $n = 5$; anterior resection, $n = 4$; Miles' operation, $n = 1$) followed by anastomosis using a linear or circular stapler. CRC and liver metastases were located in the following places: S2 ($n = 1$), S3 ($n = 1$), S4 ($n = 2$), S6 ($n = 4$), S7 ($n = 1$), and S8 ($n = 3$); two patients had two metastatic lesions (patients 1 and 10). Two patients (patients 6 and 8) were initially treated with chemotherapy. Hepatectomy included partial resection ($n = 6$) and subsegmentectomy ($n = 4$). No patient was converted to conventional open surgery.

The mean operative duration and bleeding volume were 606 ± 46 min (median, 550 min; range, 416–804 min) and 585 ± 145 mL (median, 400 mL; range, 16–1179 mL), respectively. A liver abscess developed in one patient. However, no colonic complications (pelvic abscesses or anastomotic leakage) occurred. The mean postoperative hospital stay was 18 ± 3.5 days (median, 13.5 days; range, 10–45 days). In addition, the 30-day mortality rate was 0% (Table 2).

Table 2 Operative results

Variables	PULSAR ($n = 10$)
Median operative time, min (range)	550 (416–804)
Median blood loss, mL (range)	400 (16–1179)
Postoperative complications (n)	
Any	1
Liver abscess	1
Surgical-site infection	0
Ileus	0
Liver failure	0
Anastomotic leakage	0
Mortality (n)	0
Median postoperative hospital stay, days (range)	13.5 (10–45)

PULSAR, pure laparoscopic simultaneous resection.

Comparison of the intraoperative and postoperative outcomes of patients who underwent right lobe (S6–S8) or left lobe (S2–S4) hepatectomy showed no significant differences in the median operative time (554 vs 540 min, respectively), blood loss (400 vs 665 mL, respectively), or hospital stay (15 vs 12 days, respectively). Overall, the operative outcomes were good (Figure 2).

Discussion

In this study, we showed that PULSAR is safe and feasible for patients with SCRLM. Furthermore, in patients who underwent resection for SCRLM located in the right lobe, changing to a lithotomy position from the semi-prone position allowed for successful completion of PULSAR.

Compared with conventional laparotomy, the laparoscopic approach has several advantages. Many previous series have demonstrated the safety and feasibility of

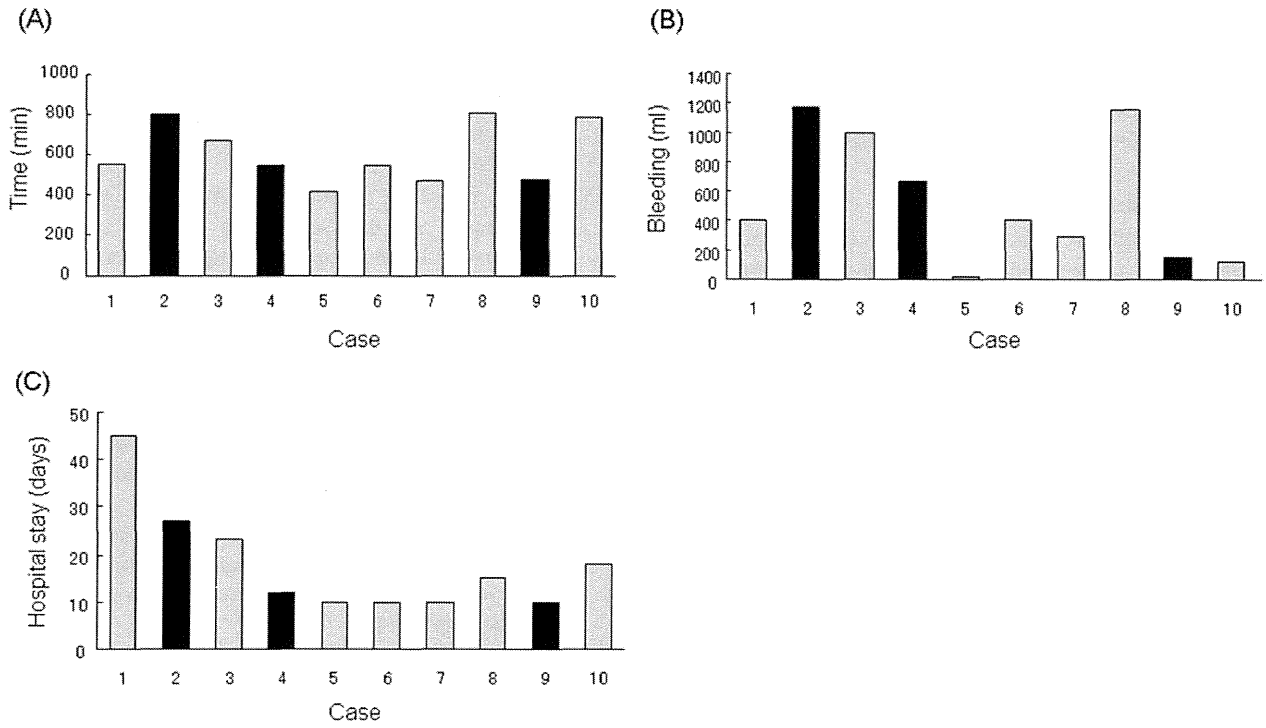

Figure 2 Intraoperative and postoperative outcomes. (a) Operative time, (b) intraoperative blood loss, and (c) postoperative hospital stay. Gray bar indicates a left-lobe (S2–4) hepatectomy; black bar indicates a right-lobe (S5–8) hepatectomy.

laparoscopy for minor resections of the liver edge and lateral segmentectomy (17,18). In addition, Nguyen *et al.* reported that laparoscopic right hepatectomy was performed in about 10% of international cases and was safe even when major hepatectomy was performed (10). However, hepatectomy of the right lobe, especially in S6–S8, is difficult with a pure laparoscopic method because of the technical difficulty associated with parenchymal transection, hemostasis at the transaction plane, risk of CO_2 embolism, and limitations in exploring the deeper regions of the liver (19–22). Therefore, we proposed the method of left semi-prone positional hepatectomy combined with laparoscopic colorectal surgery (13,14). The semi-prone position allows for a maximal amount of space within the subphrenic region, thus providing an expanded field of view of the back side of the liver produced by the weight of the liver's right lobe.

Recent studies comparing simultaneous and staged resections have confirmed that the simultaneous approach has significantly shorter operative times, reduced blood loss, reduced hospital stays, and reduced morbidity (6,23). Some reports have described simultaneous resection of colon cancer and liver metastases under laparoscopic surgery. Liver resection is often carried out using hybrid techniques such as hand-assisted or laparoscopically assisted methods (11,24). Some groups have described the safety and efficacy of pure laparoscopic procedures for simultaneous resection (24,25). In these studies, laparoscopic hepatic resection was performed in 20 cases, nine of which were right lobe resection in the lithotomy or left semi-decubitus position. The median operative time of these cases was 449 min (range, 230–540 min). In the current study, as in previous studies, seven patients (70%) with lesions in the right lobe successfully underwent simultaneous resection with a pure laparoscopic procedure. The median operative time was longer than in previous studies, but this increase likely occurred because of the time necessary to shift patients from the semi-prone position to the lithotomy position and to complete the colorectal procedures involved (i.e. anterior resection, Miles' operation). Spampinato *et al.* concluded that a laparoscopic approach involving simultaneous resection of primary CRC and liver metastasis is reasonable for selected patients (25). Obviously, patient selection is mandatory to achieve a good outcome. Reddy *et al.* indicatedfound that particular attention should be paid to elderly patients who undergo synchronous major hepatectomy (5). Furthermore, in a systematic review, Lupinacci *et al.* demonstrated that simultaneous resection is a very good option for non-rectal primaries and peripheral lesions requiring limited hepatectomy or left lateral sectionectomy (26). We share

Asian J Endosc Surg **7** (2014) 133–137

this belief, and at present, major hepatectomy is an exception to the indications for PULSAR. However, we safely performed laparoscopic major hepatectomy with patients in the semi-prone position (13,14). Therefore, major hepatectomy can also be performed for PULSAR cases in the near future.

In conclusion, PULSAR for primary CRC and SCRLM is a feasible multidisciplinary treatment. Our procedures for laparoscopic right-sided hepatectomy in the semi-prone position will allow patients to undergo cancer treatment more efficiently but without increased risks.

Acknowledgment

The authors have no conflicts of interest to disclose and received no financial support for this study.

References

1. Garden OJ, Rees M, Poston GJ *et al.* Guidelines for resection of colorectal cancer liver metastases. *Gut* 2006; **55**: Suppl 3: iii1–iii8.
2. Fong Y, Fortner J, Sun RL *et al.* Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: Analysis of 1001 consecutive cases. *Ann Surg* 1999; **230**: 309–318. discussion 18-21.
3. Kokudo N, Imamura H, Sugawara Y *et al.* Surgery for multiple hepatic colorectal metastases. *J Hepatobiliary Pancreat Surg* 2004; **11**: 84–91.
4. Capussotti L, Ferrero A, Vigano L *et al.* Major liver resections synchronous with colorectal surgery. *Ann Surg Oncol* 2007; **14**: 195–201.
5. Reddy SK, Pawlik TM, Zorzi D *et al.* Simultaneous resections of colorectal cancer and synchronous liver metastases: A multi-institutional analysis. *Ann Surg Oncol* 2007; **14**: 3481–3491.
6. Martin RC, 2nd, Augenstein V, Reuter NP *et al.* Simultaneous versus staged resection for synchronous colorectal cancer liver metastases. *J Am Coll Surg* 2009; **208**: 842–850.discussion 50-2.
7. Vigano L. Treatment strategy for colorectal cancer with resectable synchronous liver metastases: Is any evidence-based strategy possible? *World J Hepatol* 2012; **4**: 237–241.
8. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. *N Engl J Med* 2004; **350**: 2050–2059.
9. Bai HL, Chen B, Zhou Y *et al.* Five-year long-term outcomes of laparoscopic surgery for colon cancer. *World J Gastroenterol* 2010; **16**: 4992–4997.
10. Nguyen KT, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. *Ann Surg* 2009; **250**: 831–841.
11. Kim SH, Lim SB, Ha YH *et al.* Laparoscopic-assisted combined colon and liver resection for primary colorectal cancer with synchronous liver metastases: Initial experience. *World J Surg* 2008; **32**: 2701–2706.
12. Tranchart H, Diop PS, Lainas P *et al.* Laparoscopic major hepatectomy can be safely performed with colorectal surgery for synchronous colorectal liver metastasis. *HPB (Oxford)* 2011; **13**: 46–50.
13. Ikeda T, Yonemura Y, Ueda N *et al.* Pure laparoscopic right hepatectomy in the semi-prone position using the intrahepatic Glissonian approach and a modified hanging maneuver to minimize intraoperative bleeding. *Surg Today* 2011; **41**: 1592–1598.
14. Ikeda T, Mano Y, Morita K *et al.* Pure laparoscopic hepatectomy in semiprone position for right hepatic major resection. *J Hepatobiliary Pancreat Sci* 2013; **20**: 145–150.
15. UICC International Union Against Cancer. *TNM classification of malignant tumors*, 7th edn. Hoboken, NJ: Wiley-Blackwell, 2009.
16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; **240**: 205–213.
17. Chang S, Laurent A, Tayar C *et al.* Laparoscopy as a routine approach for left lateral sectionectomy. *Br J Surg* 2007; **94**: 58–63.
18. Vigano L, Tayar C, Laurent A *et al.* Laparoscopic liver resection: A systematic review. *J Hepatobiliary Pancreat Surg* 2009; **16**: 410–421.
19. Cho JY, Han HS, Yoon YS *et al.* Outcomes of laparoscopic liver resection for lesions located in the right side of the liver. *Arch Surg* 2009; **144**: 25–29.
20. Dagher I, Di Giuro G, Dubrez J *et al.* Laparoscopic versus open right hepatectomy: A comparative study. *Am J Surg* 2009; **198**: 173–177.
21. Han HS, Yoon YS, Cho JY *et al.* Laparoscopic right hemihepatectomy for hepatocellular carcinoma. *Ann Surg Oncol* 2010; **17**: 2090–2091.
22. Jayaraman S, Khakhar A, Yang H *et al.* The association between central venous pressure, pneumoperitoneum, and venous carbon dioxide embolism in laparoscopic hepatectomy. *Surg Endosc* 2009; **23**: 2369–2373.
23. Chen J, Li Q, Wang C *et al.* Simultaneous vs. staged resection for synchronous colorectal liver metastases: A metaanalysis. *Int J Colorectal Dis* 2011; **26**: 191–199.
24. Hayashi M, Komeda K, Inoue Y *et al.* Simultaneous laparoscopic resection of colorectal cancer and synchronous metastatic liver tumor. *Int Surg* 2011; **96**: 74–81.
25. Spampinato MG, Mandala L, Quarta G *et al.* One-stage, totally laparoscopic major hepatectomy and colectomy for colorectal neoplasm with synchronous liver metastasis: Safety, feasibility and short-term outcome. *Surgery* 2013; **153**: 861–865.
26. Lupinacci RM, Andraus W, De Paiva Haddad LB *et al.* Simultaneous laparoscopic resection of primary colorectal cancer and associated liver metastases: A systematic review. *Tech Coloproctol* 2014; **18**: 129–135.

ELSEVIER

Chronic Immune-Mediated Reaction Syndrome as the Cause of Late Graft Mortality in Living-Donor Liver Transplantation for Primary Biliary Cirrhosis

N. Harimoto[a,*], T. Ikegami[a], H. Nakagawara[a], Y.-I. Yamashita[a], T. Yoshizumi[a], H. Uchiyama[a], Y. Soejima[a], T. Ikeda[a], K. Shirabe[a], S. Aishima[b], Y. Oda[b], and Y. Maehara[a]

From the Departments of [a]Surgery and Science and [b]Anatomic Pathology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

ABSTRACT

Introduction. Few studies to date have investigated the causes of late graft mortality after living-donor liver transplantation (LDLT) for primary biliary cirrhosis (PBC).

Patients and Methods. Fifty-five LDLTs for PBC were retrospectively reviewed. Factors prognostic of graft survival after LDLT were investigated, and histologic findings in patients with late graft loss were assessed.

Results. The 1-, 5-, and 10-year cumulative graft survival rates were 85.1%, 82.5%, and 66.9%, respectively. Multivariate Cox regression analysis found that male donor and ≥4 HLA mismatches were independently associated with poor graft survival. Among the 13 grafts lost, 5 were lost >1 year after LDLT, including 1 each due to chronic rejection, veno-occlusive disease, and obliterative portal venopathy, and 2 to other causes. Pathologic reviews of the serial biopsy specimens and explanted grafts from these 5 patients, with graft rejections from "chronic immune-mediated reaction syndrome," showed reciprocal changes over time. No patient died of recurrent PBC.

Conclusions. Male donor and ≥4 HLA mismatches were independent factors associated with poor graft survival. Late graft mortality after LDLT for PBC in some patients was due to chronic immune-mediated reaction syndrome, including chronic rejection, veno-occlusive disease, and obliterative portal venopathy, but not to recurrent PBC.

PRIMARY biliary cirrhosis (PBC) is a cholestatic disease characterized by granulomatous destruction of the bile ducts and the appearance in serum of antimitochondrial antibodies. The disease is progressive and leads to liver failure in many patients. Liver transplantation (LT) has shown efficacy in patients with PBC, with good survival outcomes and improvements in quality of life [1-3]. Improvements in surgical techniques and organ preservation in Japan has enhanced long-term survival after living-donor LT (LDLT) in patients with PBC. PBC recurrence rates after LT have been reported in 0.6% to 32% of grafts [4-10], although PBC recurrence has little influence on graft and patient survival [11]. One study reported that the proportion of grafts lost due to PBC recurrence 10 years after LT was 2% [12], whereas another study reported that recurrent PBC was not associated with graft loss in patients followed up for 20 years [13].

Although needle biopsy is necessary for the differential diagnosis of recurrent PBC, its histologic diagnosis is much more difficult in transplanted livers because of the occurrence of many graft abnormalities, including rejections and

This study was supported in part by a grant from the Scientific Research Fund of the Ministry of Education of Japan (H23-Nanchi-Ippan-025).

*Address correspondence to Norifumi Harimoto, MD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: nharimotoh1@fukuoka.email.ne.jp

0041-1345/14/$-see front matter
http://dx.doi.org/10.1016/j.transproceed.2014.02.021

adverse drug reactions, as well as biliary strictures. There is little information regarding long-term clinical outcome of LDLT for PBC. We therefore retrospectively reviewed investigated factors associated with graft survival in patients who underwent LDLT for PBC and examined entire explanted livers for the cause of graft loss.

PATIENTS AND METHODS

Patient Characteristics

Of the 401 LDLT operations performed at Kyushu University Hospital (Fukuoka, Japan) from October 1996 to December 2012, a total of 55 were adult-to-adult LDLTs for PBC. Mean ± SD follow-up time was 5.06 ± 4.17 years. The study protocol was approved by the Ethics and Indications Committee of Kyushu University.

Graft Selection

Grafts were selected as described previously [14]. Left lobe grafts were the primary graft if the graft volume/standard live volume (GV/SLV) ratio was ≥35%. Right lobe grafts were used if the simulated GV/SLV ratio of the left lobe graft was <35% and the donor's remnant liver volume was ≥35%. Posterior segment grafts were used if their GV/SLV ratio was ≥35% with isolated branching of the posterior pulmonary vein (PV).

Transplant Procedures

The transplant procedures for both the donors and recipients have been described previously [15]. Donor parenchymal transection was performed by using the Cavitron Ultrasonic Surgical Aspirator (Valleylab Inc, Boulder, Colo, United States) with the hanging maneuver. After donor hepatectomy, the graft was perfused, weighed, and stored in University of Wisconsin solution (Viaspan, DuPont Pharmaceuticals, Wilmington, Del, United States). After recipient hepatectomy, the grafts were transplanted in a piggyback fashion. The orifice of the recipient's hepatic vein was enlarged by making an incision on the vena cava to allow the venous anastomosis to provide sufficient outflow. The PV was reconstructed and reperfused, followed by arterial reconstruction under a microscope. Whenever possible, biliary reconstruction involved duct-to-duct biliary anastomosis.

Splenectomy

The indications for splenectomy during LDLT included hypersplenism and PV pressure of ≥20 mm Hg. Tieless splenectomy was performed by using a vessel-sealing system (LigaSure Atlas, Valleylab Inc) and endostapling devices (Echelon Staplers 60 2.5 mm, Ethicon Endo-Surgery Inc, Blue Ash, Ohio, United States) [16].

Immunosuppression

The basic immunosuppression protocol consisted of tacrolimus or cyclosporine with mycophenolate mofetil and steroids. Mycophenolate mofetil was used from patient #42 onward. The target tacrolimus and cyclosporine concentrations 1 month after LDLT were 10 to 14 ng/mL and 150 to 250 ng/mL, respectively, decreasing to 7 to 10 ng/mL and 100 to 150 ng/mL over the next few months. The initial dose of mycophenolate mofetil was 2 g/d, tapered to 1 g/d over 1 to 3 months and to 0 at 6 months. Each patient received 1 g of methylprednisolone immediately after reperfusion, which was decreased from 200 to 20 mg/d over the following week and was then switched to oral prednisolone, which was tapered off at 3 months.

Posttransplant Medical Care

Perioperative prophylaxis consisted of intravenous cefotaxime (4 g/d) and ampicillin sulbactam (6 g/d) 4 times per day for 3 days, starting 30 minutes before surgery. The central venous catheters that had been placed in the internal jugular vein before surgery were usually removed within 5 days after LDLT and replaced with peripheral catheters. Most patients required prolonged ascites drainage over 14 days after left lobe LDLT. The amount of ascites drained via the indwelling abdominal drains was recorded. Fluid loss due to ascites drainage was corrected by administration of intravenous saline containing 5% albumin to maintain a serum albumin level >3.5 mg/dL. All recipients were maintained on ursodeoxycholic acid (5–15 mg/kg per day) and methylprednisolone during the follow-up period. A liver biopsy was performed when patients showed clinical or biochemical signs of graft dysfunction. Protocol biopsies were not performed.

Histologic Assessments

All resected specimens were cut into serial 5- to 10-mm-thick slices and fixed in 10% formalin. After macroscopic examination, the slice with the greatest dimensions was trimmed, embedded in paraffin, and cut into 4-μm microscopic sections. The sections were stained with hematoxylin and eosin or Masson's trichrome. A diagnosis of acute or chronic rejection (CR) was based on the 1995 Banff criteria [17,18]. A diagnosis of recurrent PBC was confirmed by detection of florid duct lesions with mixed portal inflammatory infiltrates.

Statistical Analysis

Categorical variables were compared by using the χ^2 test or the Fisher exact test. Continuous variables were expressed as mean values ± SDs and compared by using the Student t tests. Graft survival was analyzed by using the Kaplan-Meier method and compared with the log-rank test. All statistical analyses were performed with Statview version 5.0 (Abacus Concepts, Inc, Berkeley, Calif, United States), with P values <.05 considered statistically significant.

RESULTS

The 1-, 5-, and 10-year cumulative graft survival rates were 85.1%, 82.5%, and 66.9%, respectively. Univariate analysis showed that male liver donor, ≥4 HLA mismatches, and absence of splenectomy were factors significantly associated with reduced graft survival after LDLT, whereas immunosuppressive regimens were not (Table 1). For example, the 5-year graft survival rates were 49% in patients with ≥4 HLA mismatches and 87.0% in patients with <4 HLA mismatches (Fig 1A) and 74.6% when donors were male and 100% when donors were female (Fig 1B). Multivariate Cox proportional hazards model of all clinical characteristics showed that male donor and ≥4 HLA mismatches were independent factors for poor graft survival, whereas lack of splenectomy was not (Table 2).

Of the 55 LDLT recipients, 13 (23.6%) died during the follow-up period. Eight of these patients (14.5%) died within 6 months after LDLT, including 3 from primary graft

Table 1. Univariate Analysis of Clinicopathologic Factors Associated With Graft Survival After LDLT

Factor	Patients	Survival at 3 Years (%)	*P* Value
Gender of recipient			
Male	7	100	.216
Female	48	80.2	
Age of recipient, y			
<50	21	88.0	.221
≥50	34	74.7	
Gender of donor			
Male	37	74.6	.039
Female	18	100.0	
Age of donor, y			
<40	22	66.6	.055
≥40	33	89.1	
Child-Pugh classification			
A + B	14	70.1	.299
C	41	86.3	
MELD			
≥25	8	87.5	.935
<25	47	81.8	
HLA mismatches			
≥4	14	49.0	.005
<4	32	87.0	
Splenectomy			
Yes	24	95.8	.0325
No	31	79.5	
GV/SLV, %			
>35	41	77.3	.246
≤35	14	100	
Mean portal pressure at closure, mm Hg			
≥25	36	80.9	.977
<25	10	78.7	
Graft			
Left	13	79.9	.564
Right	42	91.7	
CNI			
Cyclosporine	23	86.7	.425
Tacrolimus	32	76.4	
Antimetabolites (MMF, Aza)			
Yes	25	73.0	.080
No	30	87.1	
Postoperative biliary stricture			
Yes	9	100	.944
No	46	78.8	
Acute rejection			
Yes	21	85.7	.262
No	34	80.7	
CMV infection			
Yes	15	83.0	.780
No	40	78.3	

Abbreviations: AZA, azathioprine; CMV, cytomegalovirus; CNI, calcineurin inhibitor; GV/SLV, graft/standard liver volume; LDLT, living-donor liver transplantation; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil.

dysfunction (at 1, 1, and 2 months), 2 from intra-abdominal bleeding (at 1 and 3 months), 2 of liver infarction (at 2 and 4 months), and 1 of congestion of middle hepatic vein tributaries (at 4 months). Table 3 shows the cause of delayed graft loss after LDLT for PBC.

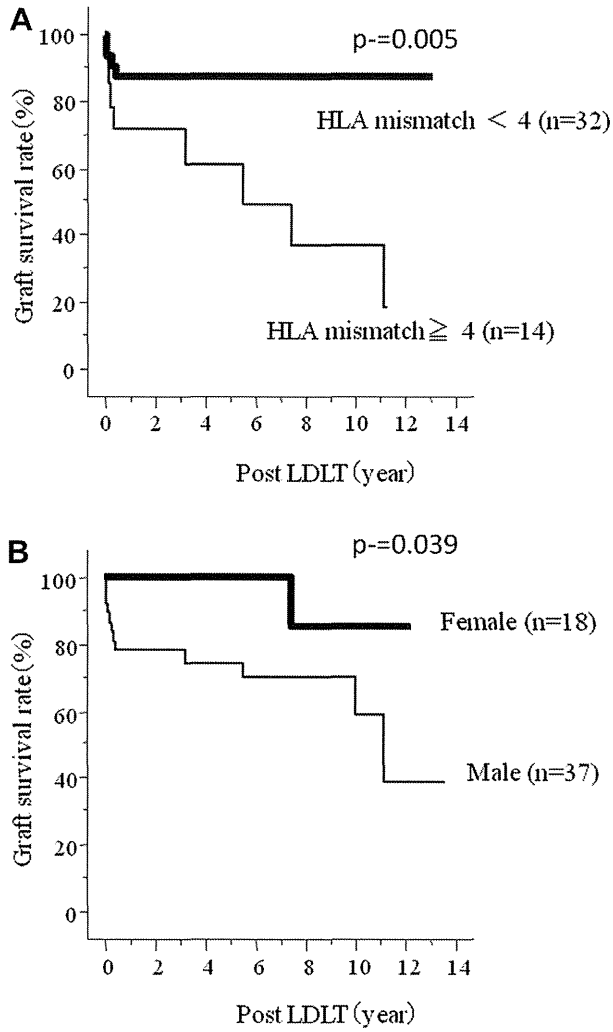

Fig 1. Graft survival after living-donor liver transplantation (LDLT) for primary biliary cirrhosis in patients receiving grafts from **(A)** donors with <4 and ≥4 HLA mismatches and **(B)** male and female donors. Graft survival was significantly poorer in patients with ≥4 HLA mismatches than <4 mismatches and in patients receiving grafts from male than female donors.

The remaining 5 patients died >1 year after LDLT. Examination of the explanted livers showed that the causes of graft failure included CR (patient #1), veno-occlusive disease (VOD; patient #3), and obliterative portal venopathy (OPV; patient #4). The other 2 patients died of spontaneous retroperitoneal hematoma (patient #2) and secondary biliary cirrhosis due to biliary stricture (patient #5). Patient #1 exhibited elevated liver enzyme levels 3 months after LDLT, with liver biopsy specimens revealing evidence of VOD. Increased immunosuppression was not effective, and a second liver biopsy was performed. This patient was diagnosed with CR and VOD. The graft was lost 3.4 years after LDLT due to CR. Patient #3 exhibited increased alkaline phosphatase levels, beginning 6 years after LDLT,

Table 2. Multivariate Analysis of Factors Independently Predictive of Graft Survival

Variable	Hazard Ratio	95% CI	*P* Value
Gender of donor: male	8.5	1.1–67.0	.010
HLA mismatch: ≥4	5.0	1.5–17.2	.042
Splenectomy: no	5.2	0.7–41.8	.119

Abbreviation: CI, confidence interval.

followed by the development of liver dysfunction. Results of a liver biopsy revealed recurrent PBC and VOD. Despite increased immunosuppression, the liver failed, and the patient was diagnosed with VOD at the time of graft loss. Patient #4 experienced acute cellular rejection 4.2 years after LDLT and required steroid pulse therapy. Results of a liver biopsy revealed VOD and ACR. Alkaline phosphatase levels began to increase 7.6 years after LDLT, followed by the development of liver dysfunction. Results of a liver biopsy revealed recurrent PBC and VOD. Liver failure developed despite increased immunosuppression, and the patient was finally diagnosed with OPV at graft loss. Increased immunosuppression in these patients included the addition of mycophenolate mofetil. None of these 3 patients was diagnosed with recurrent PBC at the time of graft loss.

Of the 5 patients who died >1 year after LDLT, 2 (patients #3 and #4) were histologically diagnosed with cholangitis of the interlobular bile duct (suggesting PBC) before LDLT. After LDLT, acute CR was histologically observed in patients #2, #4, and #5; CR in patient #1; VOD in patients #1, #3, and #4; and OPV in patient #4. None of these patients underwent splenectomy at the time of first LDLT.

Figure 2 displays the histologic findings in these patients. Patient #1, who was diagnosed with CR at graft death, exhibited histologic evidence of duct loss with degenerative epithelial damage and centrilobular fibrosis. Patient #3 had centrilobular congestion, central venulitis, and obliteration and was diagnosed with VOD. Patient #4 exhibited histologic evidence of obliterative changes in the portal veins without fibrosis and was diagnosed with OPV.

DISCUSSION

Multivariate analysis of 55 retrospectively evaluated patients who underwent LDLT for PBC indicated that male liver donor and ≥4 HLA mismatches were independently prognostic of poor graft survival. Similarly, a previous study reported that the number of HLA mismatches between recipients and donors significantly affects postoperative survival rates after LDLT for PBC [19]. In contrast, HLA incompatibility did not seem to have a significant impact on patient survival after LDLT for end-stage liver disease [20–22]. The pathophysiology of PBC is strongly associated with humoral autoimmunity, and HLA mismatches may induce and/or exacerbate humoral immunoreactions. Four of the 5 patients who experienced late graft loss received grafts from non–blood-related donors. Moreover, 4 of these donors were males (all 4 were the husbands of the recipients). Cumulative postoperative survival rates after LDLT for PBC were found to be significantly higher when donors were not blood relatives of the recipients [19].

Lack of splenectomy was significantly associated with poor prognosis in univariate (not multivariate) analysis. Splenectomy reportedly prolonged the effects of corticosteroids in mouse models of autoimmune hepatitis (AIH) and suppressed the development of AIH [23]. Patients with severe AIH have a high potential for recurrence after LT, increasing the likelihood of graft loss. Splenectomy may overcome this insufficiency, inducing prolonged remission of AIH. The same mechanism may occur in patients who undergo LT for PBC. In these patients, splenectomy may decrease humoral immunoreactions induced by HLA mismatches.

Pathologic reviews of the serial biopsy specimens and explanted grafts in patients with late mortality from CR, VOD, and OPV, collectively termed "chronic immune-mediated reaction syndrome," revealed reciprocal changes among them over time. None of these patients, however, died of recurrent PBC as the final diagnosis. Late cellular rejection may cause late liver allograft dysfunction [24]. CR in a biopsy specimen was defined as: (1) biliary epithelial senescence changes affecting a majority of the bile ducts with or without bile duct loss; (2) foam cell obliterative arteriopathy; or (3) bile duct loss affecting >50% of the portal tracts. Inadequate immunosuppression was usually accompanied by CR but not always. Immunologic pathogens

Table 3. Causes of Delayed Graft Loss After LDLT for PBC

Factor	Patient No. 1	2	3	4	5
Recipient (age [y]/sex)	34/F	57/F	37/F	47/F	47/F
Donor (age [y]/sex)	52/M	47/M	51/M	19/M	49/M
Relationship between donor and recipient	NBR	NBR	NBR	BR	NBR
Graft type	Left	Left	Left	Left	Left
GRWR	0.88	0.81	0.77	1.07	1.17
GV/SLV, %	42.6	35.7	31.6	49.3	48.6
HLA mismatch	4	6	5	NA	6
Splenectomy	No	No	No	No	No
Time to death, y	3.2	5.5	7.5	10.1	11.3
Complications after LDLT					
ACR	×	○	×	○	○
CR	○	×	×	×	×
VOD	○	×	○	○	×
OPV	×	×	×	○	×
Recurrent PBC	×	×	○	○	×
Cause of graft loss	CR	Retroperitoneal hematoma	VOD	OPV	Secondary biliary cirrhosis

Abbreviations: ACR, acute cellular rejection; BR, blood relative; CR, chronic rejection; F, female; GRWR, graft recipient weight ratio; GV/SLV, graft volume/standard liver volume; LDLT, living-donor liver transplantation; M, male; NA, not available; NBR, non–blood relative; OPV, obliterative portal venopathy; PBC, primary biliary cirrhosis; VOD, veno-occlusive disease.

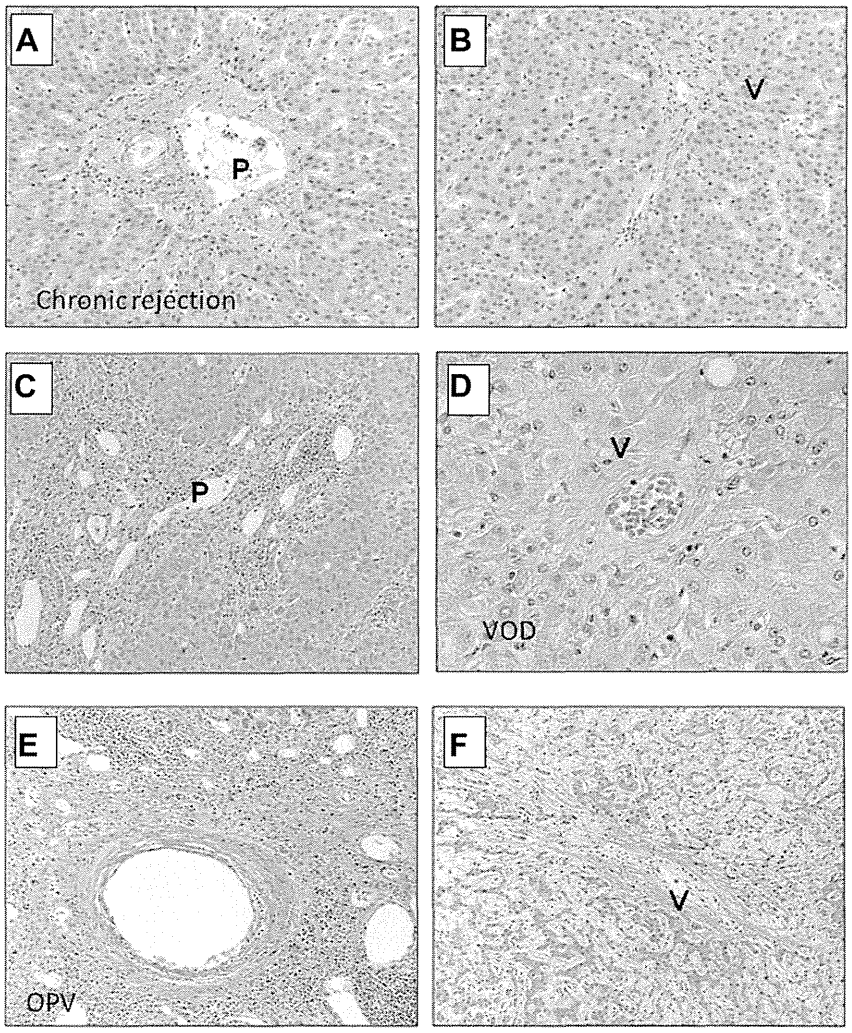

Fig 2. Histologic findings at the time of graft loss in (**A** and **B**) patient #1, (**C** and **D**) patient #3, and (**E** and **F**) patient #4. These 3 patients were diagnosed with chronic rejection, veno-occlusive disease (VOD), and obliterative portal venopathy (OPV), respectively. Hematoxylin and eosin staining; original magnification ×100 for **A**, **B**, **C**, **E**, and **F** and ×200 for **D**. Abbreviations: P, portal area; V, central vein area.

have not been identified to date. VOD has been defined as sinusoidal or perivenular fibrosis with inflammation, necrosis, hemorrhage, and/or endothelialitis in zone 3. Although VOD rarely causes liver graft loss, life-threatening VOD has been reported after LDLT [25]. Moreover, histologic features of VOD after LT have been observed in 2.3% of patients, with VOD possibly being immune mediated [26]. OPV has been defined as primary occlusion of the intrahepatic portal veins in the absence of cirrhosis, inflammation, and hepatic neoplasia [27]. Portal vasculopathy is prominent in medium-sized and preterminal veins, which are easily accessible on liver biopsy. OPV is considered a thrombotic- or immune-mediated disorder. Several studies have assessed the relationship between portal venopathy and PBC [28,29]. Our patient with OPV also experienced recurrence of PBC, suggesting that OPV may be a subtype of recurrent PBC. The pathophysiology of each of these conditions (CR, VOD, and OPV) is strongly associated with autoimmunity, although the mechanisms are not clear.

In conclusion, this retrospective analysis revealed causes of graft loss in patients who underwent LDLT for PBC. Male donor and ≥4 HLA mismatches were independent predictors of poor graft survival. CR, VOD, and OPV were found to be causes of graft loss, whereas recurrent PBC was not, suggesting that chronic immune-mediated reactions were among the pathologic conditions associated with graft loss. The mechanisms linking chronic immune reaction with long-term graft loss in patients with PBC require further investigation.

REFERENCES

[1] Liermann Garcia RF, Evangelista Garcia C, McMaster P, Neuberger J. Transplantation for primary biliary cirrhosis: retrospective analysis of 400 patients in a single center. Hepatology 2001;33:22–7.

[2] Khettry U, Anand N, Faul PN, et al. Liver transplantation for primary biliary cirrhosis: a long-term pathologic study. Liver Transpl 2003;9:87–96.

[3] Kashyap R, Safadjou S, Chen R, et al. Living donor and deceased donor liver transplantation for autoimmune and

cholestatic liver diseases—an analysis of the UNOS database. J Gastrointest Surg 2010;14:1362–9.

[4] Kaneko J, Sugawara Y, Tamura S, et al. Long-term outcome of living donor liver transplantation for primary biliary cirrhosis. Transpl Int 2012;25:7–12.

[5] Tamura S, Sugawara Y, Kaneko J, et al. Recurrence of cholestatic liver disease after living donor liver transplantation. World J Gastroenterol 2008;14:5105–9.

[6] Haga H, Miyagawa-Hayashino A, Taira K, et al. Histological recurrence of autoimmune liver diseases after living-donor liver transplantation. Hepatol Res 2007;37(Suppl 3):S463–9.

[7] Hashimoto E, Taniai M, Yatsuji S, et al. Long-term clinical outcome of living-donor liver transplantation for primary biliary cirrhosis. Hepatol Res 2007;37(Suppl 3):S455–61.

[8] Hashimoto E, Shimada M, Noguchi S, et al. Disease recurrence after living liver transplantation for primary biliary cirrhosis: a clinical and histological follow-up study. Liver Transpl 2011;7:588–95.

[9] Silveira MG, Talwalkar JA, Lindor KD, et al. Recurrent primary biliary cirrhosis after liver transplantation. Am J Transplant 2010;10:720–6.

[10] Jacob DA, Neumann UP, Bahra M, et al. Long-term follow-up after recurrence of primary biliary cirrhosis after liver transplantation in 100 patients. Clin Transplant 2006;20:211–20.

[11] Egawa H, Nakanuma Y, Maehara Y, et al. Disease recurrence plays a minor role as a cause for retransplantation after living-donor liver transplantation for primary biliary cirrhosis: a multicenter study in Japan. Hepatol Res 2013;43:502–7.

[12] Rowe IA, Webb K, Gunson BK, et al. The impact of disease recurrence on graft survival following liver transplantation: a single centre experience. Transpl Int 2008;21:459–65.

[13] Charatcharoenwitthaya P, Pimentel S, Talwalkar JA, et al. Long-term survival and impact of ursodeoxycholic acid treatment for recurrent primary biliary cirrhosis after liver transplantation. Liver Transpl 2007;13:1236–45.

[14] Yonemura Y, Taketomi A, Soejima Y, et al. Validity of preoperative volumetric analysis of congestion volume in living donor liver transplantation using three-dimensional computed tomography. Liver Transpl 2005;11:1556–62.

[15] Taketomi A, Morita K, Toshima T, et al. Living donor hepatectomies with procedures to prevent biliary complications. J Am Coll Surg 2010;211:456–64.

[16] Ikegami T, Toshima T, Takeishi K, et al. Bloodless splenectomy during liver transplantation for terminal liver diseases with portal hypertension. J Am Coll Surg 2009;208:e1–4.

[17] Demetris A, Adams D, Bellamy C, et al. Update of the International Banff Schema for Liver Allograft Rejection: working recommendations for the histopathologic staging and reporting of chronic rejection. An international panel. Hepatology 2000;31:792–9.

[18] Banff schema for grading liver allograft rejection: an international consensus document. Hepatology 1997;25:658–63.

[19] Morioka D, Egawa H, Kasahara M, et al. Impact of human leukocyte antigen mismatching on outcomes of living donor liver transplantation for primary biliary cirrhosis. Liver Transpl 2007;13:80–90.

[20] Jakab SS, Navarro VJ, Colombe BW, et al. Human leukocyte antigen and adult living-donor liver transplantation outcomes: an analysis of the organ procurement and transplantation network database. Liver Transpl 2007;13:1405–13.

[21] Balan V, Ruppert K, Demetris AJ, et al. Long-term outcome of human leukocyte antigen mismatching in liver transplantation: results of the National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Hepatology 2008;48:878–88.

[22] Manousou P, Arvaniti V, Tsochatzis E, et al. Primary biliary cirrhosis after liver transplantation: influence of immunosuppression and human leukocyte antigen locus disparity. Liver Transpl 2010;16:64–73.

[23] Maruoka R, Aoki N, Kido M, et al. Splenectomy prolongs the effects of corticosteroids in mouse models of autoimmune hepatitis. Gastroenterology 2013;145:209–20.

[24] Banff Working Group, Demetris AJ, Adeyi O, Bellamy CO, et al. Liver biopsy interpretation for causes of late liver allograft dysfunction. Hepatology 2006;44:489–501.

[25] Nakazawa Y, Chisuwa H, Mita A, et al. Life-threatening veno-occlusive disease after living-related liver transplantation. Transplantation 2003;75:727–30.

[26] Sebagh M, Azoulay D, Roche B, et al. Significance of isolated hepatic veno-occlusive disease/sinusoidal obstruction syndrome after liver transplantation. Liver Transpl 2011;17:798–808.

[27] Cazals-Hatem D, Hillaire S, Rudler M, et al. Obliterative portal venopathy: portal hypertension is not always present at diagnosis. J Hepatol 2011;54:455–61.

[28] Abraham SC, Kamath PS, Eghtesad B, et al. Liver transplantation in precirrhotic biliary tract disease: portal hypertension is frequently associated with nodular regenerative hyperplasia and obliterative portal venopathy. Am J Surg Pathol 2006;30:1454–61.

[29] Nakanuma Y, Ohta G, Kobayashi K, et al. Histological and histometric examination of the intrahepatic portal vein branches in primary biliary cirrhosis without regenerative nodules. Am J Gastroenterol 1982;77:405–13.

ELSEVIER

Application of Postoperative Model for End-Stage Liver Disease Scoring System for Evaluating Liver Graft Function After Living Donor Liver Transplantation

T. Toshima, T. Ikegami, K. Kimura, N. Harimoto, Y. Yamashita, T. Yoshizumi, Y. Soejima, T. Ikeda, K. Shirabe, and Y. Maehara

ABSTRACT

Background. The Model for End-Stage Liver Disease (MELD) score has been validated to predict the mortality rate of patients with various chronic liver diseases on the waiting list for liver transplantation (LT). The aim of this study was to assess the value of the postoperative MELD scoring system as an early postoperative predictor of outcome in patients undergoing living donor LT (LDLT).

Methods. A retrospective analysis of 217 adult-to-adult LDLT patients was performed. The values of the MELD score on various postoperative days (PODs) as predictors of graft loss within 6 months after LDLT were examined by calculating the areas under the receiver operating characteristic (AUROC) curves. The 6-months graft survival rates were compared between patients with (n = 22) and without (n = 195) graft loss. Univariate and multivariate analyses were performed to identify the factors associated with mortality.

Results. The MELD score on POD2 was a predictor of graft loss, with an AUROC c-statistic of 0.779, a specificity of 79.5%, and a sensitivity of 68.2% at optimal cutoff, whereas the preoperative MELD score c-statistic was 0.605 with 44.6% sensitivity. Multivariate analyses for postoperative mortality revealed MELD-POD2 $\geq$19 (odds ratio, 5.601; 95% confidence interval [CI], 1.395–4.508; P = .0009) as an independent predictor of short-term graft loss following LDLT, in addition to preoperative hospitalization status. Later MELD POD scores were also predictive of graft loss.

Conclusions. The early postoperative MELD scoring system is feasible as an index for prediction of postoperative mortality following LDLT.

LIVING donor liver transplantation (LDLT) has become an effective treatment modality for end-stage liver disease since the first clinical report in 1989 [1]. Originally, the Model for End-Stage Liver Disease (MELD) scoring system was designed to assess short-term prognosis in patients undergoing transjugular intrahepatic portosystemic shunt [2]. The MELD score is based on 3 biochemical parameters: serum total bilirubin (T-Bil) level, International Normalized Ratio (INR) for prothrombin time, and serum creatinine (Cre) level. Since Wiesner et al [3] first demonstrated, in their pioneering study, that the c-statistic of MELD was 0.83 when it was used to predict the 3-month mortality of waiting list candidates, the MELD score has been developed to become an accurate predictor of waiting list mortality [4–6]. This risk model was validated to predict the mortality rate of different groups of patients with various types and stages of chronic liver disease, and especially of candidates on the waiting list for liver transplantation (LT) [4–6].

From the Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

This study was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare, Japan (H23-kannen-003). The funding source had no role in the collection, analysis, or interpretation of the data, or in the decision to submit the article for publication.

Address reprint requests to Takeo Toshima, MD, Department of Surgery and Science, Graduate School of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: toshima@surg2.med.kyushu-u.ac.jp

Published by Elsevier Inc.
360 Park Avenue South, New York, NY 10010-1710

0041-1345/13/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.09.034

Although its value for predicting pretransplantation survival has been established, the impact on post-transplantation outcome is still a matter of controversy. Regarding LDLT, we previously demonstrated that a high MELD score was a risk factor for graft failure following LDLT in patients with chronic liver failure [7–10]. However, some reports found that it was not predictive of the post-transplantation survival rate [11,12]. Until now, efforts to assess LDLT patients' postoperative course have almost exclusively been limited to preoperative evaluations, primarily biochemical blood tests (eg, serum T-Bil, INR, serum Cre, and serum albumin levels) and their combination within clinical risk scores such as the MELD score and Child-Pugh score [3,5]. Although preoperative parameters may be useful in screening patients for LT, early postoperative risk stratification might allow a more refined prediction of outcome as it incorporates the patient's preoperative status together with the indication for LDLT and postoperative course [13]. There is limited data on the use of the postoperative MELD scoring system as an early predictor of outcome following surgery [14]. Recently, postoperative clinical risk scores have been investigated, with the MELD score on postoperative day (POD) 5 found to be a major predictor of death after hepatic resection [14], and it provided a grading of severity to guide the patients' clinical management. The aim of this study was to assess the value of the postoperatively applied MELD scoring system as an early postoperative predictor of outcome in patients undergoing LDLT.

MATERIALS AND METHODS

Patient Characteristics

Between January 2004 and December 2010, a total of 224 adult patients who had undergone LDLT because of end-stage liver disease at Kyushu University Hospital (Fukuoka, Japan) were enrolled in the study. One patient who received dual living donor liver grafts was excluded from analysis, and the 6 patients who underwent graft loss within 6 months as a result of intraoperative bleeding (n = 1), bleeding after liver biopsy (n = 1), brain death (n = 1), chronic rejection (n = 1), cholangiocellular carcinoma (n = 1), or postoperative colon bleeding (n = 1) were also excluded. The indications for LDLT (n = 217) were liver cirrhosis resulting from hepatitis C (n = 104), cholestatic cirrhosis (n = 36), fulminant hepatic failure (n = 22), hepatitis B (21), cryptogenic (n = 12), alcohol abuse (n = 10), and others (n = 12).

All LDLT were performed after obtaining full informed consent from all patients and approval by the Liver Transplantation Committee of Kyushu University. The study protocol conformed to the ethical guidelines of the 1975 Helsinki Declaration and was approved by our institutional review board.

Graft Selection

The graft types included left lobe with caudate lobe graft (n = 118), right lobe graft without the mid-hepatic vein (n = 91), right lobe graft with the mid-hepatic vein (n = 3), and posterior segment graft (n = 5). Donors were required to be spouses or within the third degree of consanguinity with the recipients and to be between 20 and 65 years of age. For a donor who was not within the third degree of consanguinity, individual approval was obtained from the ethics committee of Kyushu University Hospital [7,15].

We used three-dimensional computed tomography for volumetric analysis and delineation of vascular anatomy. The standard liver volume of recipients was calculated according to the formula described by Urata et al [16]. Graft volume was predicted using computed tomographic volumetric analysis. The decision about graft type for the recipients was based on the preoperatively predicted graft volume to recipient's standard liver volume (GV/SLV) ratio [17,18]. A right lobe graft was procured if the estimated GV/SLV using the extended left lobe with caudate lobe was <35% when the preoperative predicted remnant liver volume was >35%.

Postoperative Management

The graft harvesting technique, recipient surgery, and perioperative management of the recipients, including immunosuppression regimens, have been previously described [19,20]. Bile ducts were reconstructed using the Roux-en-Y (n = 34) or duct-to-duct (n = 183) techniques. We initiated immunosuppression with a protocol based on tacrolimus (Prograf; Astellas Pharma Inc., Tokyo, Japan) or cyclosporine A (Neoral; Novartis Pharma K.K., Tokyo, Japan) [19]. All patients had monthly follow-ups, and the median follow-up period was 1219 days, with 540 days and 1935 days as the 25th and 75th percentiles, respectively.

Definition of Short-Term Graft Loss

Graft loss was defined as liver retransplantation (Re-LT) or patient death within 6 months following LDLT. The 6 patients with graft loss not related to deteriorated liver function or patient status, which may be related to intraoperative incidents, were excluded from the present analysis, as previously described. The 217 recipients were classified into 2 groups: patients with graft loss (n = 22) and without graft loss (n = 195). The 6-month graft survival rates were compared among the groups. Univariate and multivariate analyses were performed to identify the factors associated with the graft loss after LDLT.

Application of the MELD Scoring System With Postoperative Parameters

The MELD score was based on 3 biochemical parameters: serum T-Bil level, INR for prothrombin time, and serum Cre level, and was calculated as follows [3]:

$$\text{MELD} = 9.57 \times \ln(\text{Cre, mg/dL}) + 3.78 \times \ln(\text{T-Bil, mg/dL}) + 11.2 \times \ln(\text{INR}) + 6.43 \text{ (range, } 6 - 40).$$

The values of the applied MELD score on each POD, namely POD1, 2, 3, 5, 7, and 14, were examined as predictors of graft loss within 6 months after LDLT by calculating the AUROC curves.

Statistical Analysis

All statistical analyses were performed using JMP statistical software version 7.01 (SAS Institute Inc., Cary, NC, United States). The continuous variables were expressed as mean ± standard deviation. Multivariate analyses were performed using the Cox proportional hazards regression model. Survival was calculated using the Kaplan-Meier method, and differences in survival between the groups were compared using the log-rank test. The ROC curve is a plot of sensitivity versus 1-specificity for all possible cutoff values and the most commonly used index of accuracy is the area under the receiver operating characteristic (AUROC) curve, where values

Table 1. Characteristics of LDLT Patients (n = 217)

Variables	Total (n = 217)	Graft Loss		P
		Yes (n = 22)	No (n = 195)	
Recipient age, y	53.1 ± 10.2	51.1 ± 9.7	53.4 ± 10.3	.3326
Recipient gender, male	109 (50.2)	10 (45.5)	99 (50.8)	.6363
Disease				.0559
Liver cirrhosis				
Hepatitis C	104 (47.9)	8 (36.4)	96 (49.2)	
Hepatitis B	21 (9.7)	0	21 (10.8)	
Non-B non-C	12 (5.5)	4 (18.2)	8 (4.1)	
Alcohol	10 (4.6)	1 (4.6)	9 (4.6)	
Fulminant hepatic failure	22 (10.1)	1 (4.6)	21 (10.8)	
Cholestatic cirrhosis	36 (16.6)	6 (27.3)	30 (15.4)	
Others	12 (5.5)	2 (9.1)	10 (5.1)	
Body mass index, kg/m^2	23.6 ± 3.6	24.8 ± 6.0	23.4 ± 3.2	.0837
Hospitalized status	91 (41.9)	16 (72.7)	75 (38.5)	.0020
Donor age, y	35.2 ± 10.7	40.9 ± 11.4	34.6 ± 10.5	.0107
Donor gender, male	139 (64.1)	15 (68.2)	124 (63.6)	.6679
ABO incompatible	15 (6.9)	1 (4.6)	14 (7.2)	.6260
Left lobe graft	118 (54.4)	11 (50.0)	107 (54.9)	.6642
GV, g	482 ± 106	504 ± 109	480 ± 106	.3242
GV/SLV ratio, %	42.9 ± 8.7	43.8 ± 9.5	41.6 ± 8.3	.2677
GRWR, %	0.81 ± 0.19	0.83 ± 0.23	0.80 ± 0.18	.5109
PVP at laparotomy, mm Hg	23.8 ± 6.3	23.1 ± 5.8	23.9 ± 6.3	.5632
Splenectomy	135 (62.2)	11 (50.0)	124 (63.6)	.2189
Cold ischemic time, min	95.3 ± 87.0	91.9 ± 39.4	95.6 ± 91.0	.8477
Warm ischemic time, min	39.5 ± 11.3	40.2 ± 11.6	39.4 ± 11.3	.7695
Hepatic arterial flow, mL/min	99.4 ± 55.4	107.4 ± 60.3	98.4 ± 54.9	.4721
Portal venous flow, L/min	1.76 ± 0.68	1.54 ± 0.66	1.79 ± 0.68	.1037
PVP at closure, mm Hg	16.2 ± 4.1	17.5 ± 6.9	16.0 ± 3.6	.1333
Duct-to-duct biliary reconstruction	183 (83.9)	15 (68.2)	167 (85.6)	.0523
Operation time, min	806 ± 183	780 ± 196	809 ± 181	.5073
Operative blood loss, L	5.5 ± 8.7	8.5 ± 10.2	5.2 ± 8.6	.1129
MELD score-Pre	17.0 ± 7.3	18.9 ± 7.4	16.8 ± 7.3	.2056
MELD score-POD2	19.3 ± 3.8	22.7 ± 3.7	18.9 ± 3.7	<.0001

Abbreviations: GRWR, graft recipient weight ratio; GV, graft volume; SLV, standard liver volume; Pre, preoperative; PVP, portal vein pressure.
Note: Values are reported as mean ± SD or n (%).

close to 1.0 indicate high diagnostic accuracy, and 0.5 indicates a test of no diagnostic value [21–23]. P values <.05 were considered significant.

RESULTS

Characteristics of Recipients, Donors, and Grafts

Among the 217 patients who underwent LDLT, 22 (10.1%) had short-term graft loss and 195 (89.9%) had graft survival (Table 1). Compared with patients without graft loss, patients with graft loss had significantly higher rates of preoperative hospitalization (72.7% vs 38.5%; P = .0020) and the age of the donors with graft loss was significantly higher (40.9 ± 11.4 vs 34.6 ± 10.5 years; P = .0107). Notably, the preoperative MELD score (MELD-Pre) in patients with graft loss was not significantly different from that in patients without graft loss (18.9 ± 7.4 vs 16.8 ± 7.3; P = .2056), whereas the postoperative MELD score on POD2 (MELD-POD2) in patients with graft loss was significantly higher than that in patients without graft loss (22.7 ± 3.7 vs 18.9 ± 3.7; P < .0001).

Change of MELD-Pre and MELD-POD

The chronological change in the MELD-Pre and the MELD score on indicated PODs in patients with (n = 22) or without (n = 195) graft loss are shown in Figure 1. The MELD-Pre (18.9 ± 1.7 vs 16.8 ± 0.5; P = .2056) and MELD-POD1 (22.7 ± 0.7 vs 22.0 ± 0.2; P = .3855) scores in patients with graft loss were not significantly different from those in patients without graft loss, whereas MELD-POD2 scores in patients with graft loss were significantly higher than that in patients without graft loss (22.7 ± 0.8 vs 18.9 ± 0.3; P < .0001). In addition, the MELD scores later than POD2 in patients with graft loss were also significantly higher (P < .0001).

Causes of the mortality (n = 22) included primary graft dysfunction (n = 6), multiorgan failure (n = 6), sepsis (n = 5), intra-abdominal bleeding (n = 3), cerebrovascular accident (n = 1), and rejection (n = 1). Notably, MELD-POD2 in patients with graft loss by primary graft dysfunction (n = 6; 22.3 ± 1.5), multiorgan failure (n = 6; 24.5 ± 1.5), and sepsis (n = 5; 24.2 ± 1.6) were significantly higher