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LETTER TO THE EDITORS

False Positivity for the Human Immunodeficiency Virus Antibody After Influenza Vaccination in a Living Donor for Liver Transplantation

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TO THE EDITORS:

Because of increased productivity and availability, more people have had the chance to undergo prophylactic influenza vaccination. It has been reported that influenza vaccination has cross-reactivity with human immunodeficiency virus (HIV) antibody assays, but this information is not well known in the field of transplantation.[1] Recently, we experienced a case of living donor liver transplantation in which a healthy donor candidate was frightened and was further screened for the HIV antibody.

The patient was a 43-year-old female who was a candidate for partial liver donation for her husband, who was suffering from hepatocellular carcinoma associated with hepatitis B liver cirrhosis. She had never undergone a blood transfusion or abused drugs before her screening for living partial liver donation. According to her laboratory results, she was positive for the HIV antibody (1.7 cut off index). Otherwise, all data, including hepatitis B antibody results, were within normal limits. It was found that she had undergone vaccination for influenza 1 week before the screening. She was referred to a specialist in HIV infection, and western blotting for all antibodies (GP160, GP110/120, P68/66, P55, P52/51, GP41, P40, P34/31, P24/25, and P18/17) was negative. HIV RNA was undetectable in her blood (<40 copies/mL). Thus, she was considered to be HIV-negative with a high level of confidence and subsequently donated the left lobe of her liver. The recipient remained negative for the HIV antibody even after living donor liver transplantation.

With the prevalence of influenza vaccination and organ donation, physicians should keep in mind that recent inoculation with any brand of influenza vaccine is associated with a false-positive screening assay for HIV antibodies.[2]

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The protocol for our living donor liver transplantation received a priori approval by the institutional review committee.

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Original Article

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

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Aim: To clarify the role of disease recurrence as a cause of graft loss after living-donor liver transplantation (LDLT) for primary biliary cirrhosis (PBC), we investigated explant grafts, as well as the native liver and liver biopsy specimens, of patients who underwent retransplantation.

Methods: Of 516 patients who underwent LDLT for PBC and were registered in the Japanese Liver Transplant Registry, nine patients (1.7%) underwent retransplantation.

Results: Seven patients undergoing retransplantation later than 6 months after primary liver transplantation (LT) were enrolled. All seven patients were female, with ages ranging from 34–57 years, and Model for End-Stage Liver Disease scores ranging 10–28. The right lobe was used as graft in one and the left lobe in six. The initial immunosuppression regimen was tacrolimus in six and cyclosporin in one. The period between the primary LT and retransplantation ranged 11–120 months, with a median of 36 months. Three patients survived and four patients died due to poor graft functions or complications after retransplantation. The primary causes of primary graft loss revealed by histological examination of the explant livers were chronic rejection in three, portal thrombus and/or steatohepatitis in three and outflow block in one. PBC recurrence was observed in 3 and the stage was mild in all.

Conclusion: PBC recurrence has a small impact as a cause of graft loss after LDLT.

Key words: histology, living-donor liver transplantation, primary biliary cirrhosis, recurrence, retransplantation

INTRODUCTION

PRIMARY BILIARY CIRRHOSIS (PBC) is a major indication for liver transplantation (LT). Because autoimmune mechanisms possibly contribute to the etiology of PBC, the possibility of recurrence after transplantation and the impact on the clinical course have been reason for considerable concern. Rates of recurrence have been reported to range 9–35% in deceased-donor LT in Western countries.[1] In living-donor liver transplantation (LDLT) in Japan, the rates have been reported to range 1–40% on the basis of histological evidence.[2–6] However, this range is not reliable because routine liver biopsy is not standard. Furthermore, the impact of recurrence on the clinical course is unclear. The proportion of grafts lost due to disease recurrence was reported to be 2% 10 years after transplantation by Rowe *et al.*[7] On the other hand, Charatcharoenwitthaya *et al.* reported that recurrent PBC was not associated

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with death or retransplantation.[8] There have been no reports of graft failure secondary to recurrent PBC in Japan, either.[2–6]

The difficulty of performing histological diagnosis of recurrent PBC using needle biopsy specimens is a barrier for studying the impact of recurrent PBC, although histological examination is the gold standard.[6,9,10] Heterogeneity of histological changes is a major hurdle for diagnosis on the basis of needle biopsy specimens. To overcome this problem, we conducted a multicenter study using whole hepatic grafts explanted during retransplantation for PBC.

METHODS

OF 516 PATIENTS who underwent LDLT for PBC and who were registered in the Japanese Liver Transplant Registry, nine patients (1.7%) underwent retransplantation. The demographic data of the recipients and primary donors and information on the clinical courses were obtained.

A current author (Y. N.) performed histological investigation of the native liver, the liver biopsy specimens if present, and the explant grafts. The diagnosis of acute cellular rejection (ACR) and chronic rejection was made according to the Banff criteria.[11,12] Staging of PBC was based on the Nakanuma staging system.[13]

This study was approved by the Ethical Committee of Tokyo Women's Medical University as the central office of the multicenter study, or at each institution if necessary, and it conforms to the provisions of the Declaration of Helsinki (as revised in Seoul, Korea, October 2008).

RESULTS

OF THE NINE patients who underwent retransplantation, two died within 6 months after retransplantation. One died due to graft failure secondary to severe acute rejection and another due to small-for-size syndrome. In both cases, we examined the clinical courses and explanted livers, and confirmed the diagnoses. We enrolled the remaining seven patients in this study.

The demographic and operative data of the recipients and primary donors and the clinical courses are shown in Table 1. All patients were female and had histories of pregnancies. Human leukocyte antigen DR8 was detected in all recipients except no. 5 and in the donors of recipients no. 3, 6 and 7. The donor was the patient's husband in two cases, son in three, sister in one and mother in one.

Primary immunosuppression was performed with a triple regimen consisting of calcineurin inhibitor, steroids and antimetabolites (azathioprine, mizoribine) in three patients, and calcineurin inhibitor and steroids in four patients. The calcineurin inhibitor was tacrolimus in all patients except no. 6 in which cyclosporin was converted to tacrolimus 1 year after transplantation.

All patients were treated with ursodeoxycholic acid (UDCA) and no. 1 and 7 with bezafibrate prior to primary transplantation. All patients were given UDCA after transplantation and only no. 3 was given bezafibrate transiently.

Patients 1, 4, 6 and 7 continued to complain of fatigue even after transplantation. Postoperative complications are shown in Table 1. The period between the primary transplantation and retransplantation ranged 11–120 months, with a median of 36 months. Three patients survived and four patients died due to poor graft functions or complications after retransplantation.

Histological findings of the native liver, the liver biopsy specimens and the explant grafts are summarized in Table 2. The stage of PBC of the native liver was 4 in all patients except no. 7. The primary causes of primary graft loss were chronic rejection in three (no. 2, 3 and 6), portal thrombus in one (no. 7), nonalcoholic steatohepatitis (NASH) in one (no. 4), portal thrombus and NASH in one (no. 5), and outflow block in one (no. 1). Briefly, submassive necrosis from ischemic etiology and liver cirrhosis of chronic congestive etiology were observed in no. 1. Foamy cell arteriopathy, duct loss with degenerative epithelial damage with severe cholestasis, and centrilobular and C-C and P-C bridging fibrosis were observed in no. 2. In both patients 4 and 5 with NASH, the stage had progressed from stage 2 in the biopsy specimens to stage 3 in the explanted livers.[14] Portal vein thromboembolism and altered intrahepatic circulation was also observed in no. 5. Marked centrilobular necrosis and hemorrhage with mild inflammation and fibrosis and portal venopathy with repeated thromboemboli were observed in no. 7.

Recurrence of PBC was observed in no. 2, 6 and 7 in the specimens of on-demand needle or wedge biopsies and confirmed in the explanted livers (Figs 1–3). Histological progression of PBC was very mild or mild and the recurrence was not the main cause of graft failure. We evaluated: (i) mononuclear inflammatory infiltrates; (ii) formation of lymphoid aggregates; (iii)

Table 1 Demographic data, operative data and clinical courses

Patient no.	1	2	3	4	5	6	7
Age (years)	52	40	34	37	47	47	57
Time from diagnosis to LT (months)	22	3	60	55	65	132	99
AMA	>320	80	40	80	NA	Negative	160
Anti-M2 (mg/dL)	1859	1550	NA	NA	NA	NA	152
IgM (mg/dL)	1037.8	172.8	426	115	340	NA	524
IgG (mg/dl)	1945.7	884.2	1774	1373	2921	NA	180
ANA	640	±	Negative	±	Negative	320	NA
Child–Pugh score	7	8	11	12	12	14	10
MELD score	10	11	17	24	22	28	11
Primary donor							
Relation	Husband	Mother	Husband	Sister	Son	Son	Son
Age (years)	50	60	34	47	19	20	23
Sex	Male	Female	Male	Female	Male	Male	Male
Operative variables							
Blood type combination	Compatible	Identical	Identical	Compatible	Compatible	Compatible	Identical
GRWR	1.00	0.95	0.88	0.77	1.07	0.58	0.90
Graft type	Left	Right	Left	Left	Left	Left	Left
Operation time (min)	751	550	665	615	730	680	870
Cold ischemic time (min)	82	38	56	53	111	95	131
Warm ischemic time (min)	53	44	33	40	38	45	41
Blood loss (g)	2400	2470	850	10 320	6190	8005	4500
Postoperative complications	Hemoperitoneum, biliary stenosis, ACR, hepatic vein stenosis	Biliary stenosis, ACR, EBV infection	Chronic rejection	ACR	ACR Artery-portal shunt	Biliary leakage and stenosis	Portal vein thrombosis
Time of retransplantation (months)	39	24	36	88	120	20	11
Outcome of retransplantation	Dead (49 days)	Alive	Dead (59 days)	Alive	Alive	Dead (15 days)	Dead (284 days)
Causes of death	Lung bleeding		Graft failure			Graft failure	Graft failure

ACR, acute cellular rejection; AMA, antimitochondrial antibody; ANA, antinuclear antibody; EBV, Epstein–Barr virus; GRWR, graft recipient weight ratio; Ig, immunoglobulin; LT, liver transplantation; MELD, Model of End-stage Liver Disease; NA, not applicable.

Table 2 Histological findings of the native liver, biopsy specimens and explanted liver

Patient no.	1	2	3	4	5	6	7
PBC staging of native livers							
Stage	4	4	4	4	4	4	2
Bile duct loss	3	3	3	3	3	2	1
Fibrosis	3	2	3	3	3	3	1
Orcein deposition	3	2	3	3	3	2	1
Hepatitis activities	1	1	1	0	0	1	1
Cholangitis activities	0	0	0	0	0	0	0
Needle biopsies	Congestion at 6 months	Suspected rPBC (duct loss and hepatitis) at 20 months	No biopsy	rPBC (cholangitis) and NASH at 71 months	rPBC (cholangitis and granuloma) and NASH at 90 months	No biopsy	ACR at 9 months
Main diagnosis	Outflow block	Chronic rejection	Chronic rejection	NASH	PVT and NASH	Chronic rejection	PVT
PBC recurrence	No	Mild (mild chronic cholangitis)	No	Mild (focal duct damage and portal fibrosis)	Mild (focal duct loss and portal inflammation)	No	No

ACR, acute cellular rejection; NASH, non-alcoholic steatohepatitis; PVT, portal vein thrombosis; rPBC, recurrence of PBC.

epithelioid granuloma; and (iv) bile duct damage according to Neuberger's criteria for the diagnosis of recurrent PBC based on liver histology.[15] In patient no. 2, biopsy showed (i) and (iv) (probable recurrence) and the explanted liver showed (i), (ii) and (iv) (definite recurrence); in no. 6, biopsy showed (i), (ii) and (iv) (definite recurrence), and the explanted liver showed (i), (ii) and (iv) (definite recurrence); and in no. 7, biopsy showed (i), (iii) and (iv) (definite recurrence), and the explanted liver showed (i), (ii) and (iv) (definite recurrence).

Case report of three patients with histological diagnoses of recurrent PBC

Patient no. 2 had refractory ACR requiring steroid pulse therapy on postoperative day (POD) 12, 36, 43, 97, 103, 420 and OKT3 monoclonal antibody on POD 434. Liver dysfunction associated with biliary dilatation developed 20 months after LDLT and we performed hepaticojejunostomy and wedge liver biopsy, which revealed suspected recurrence of PBC. Immunosuppression consisted of tacrolimus (3.0 mg/day), steroid (5 mg) and mizoribine (50 mg). Immunoglobulin M was 136, antimitochondrial antibody (AMA) 80 and anti-M2 152 mg/dL. Aggressive liver failure developed despite increased immunosuppression thereafter. She underwent retransplantation 24 months after LDLT.

In patient no. 4, alkaline phosphatase (ALP) began to increase 65 months after LDLT and liver dysfunction developed thereafter. Liver biopsy was performed 71 months after LDLT. Immunosuppression consisted of tacrolimus (2.0 mg/day) and steroid (5 mg). Aspartate aminotransferase (AST) was 44, ALP 432, γ-glutamyltransferase (γ-GT) 17, total bilirubin 1.7 mg/dL, AMA 80 and AMA-M2 155 mg/dL. Tacrolimus was changed to Neoral (Cyclosporine; Novartis, Basel, Switzerland), and mycophenolate mofetil (MMF) (2000 mg/day) was added. Ascites developed 1 year after and liver failure developed. She underwent retransplantation 88 months after LDLT.

In patient no. 5, liver dysfunction developed (AST, 82 IU/L; ALP, 685 IU/L) 50 months after LDLT and was successfully treated with steroid pulse therapy. Liver dysfunction developed and liver biopsy was performed 90 months after LDLT. Total bilirubin was 1.2 mg/dL, AST 57 IU/L, ALP 585 IU/L and γ-GT 48 IU/L. AMA and M2 were not measured. Immunosuppression consisted of tacrolimus only (4.0 mg/day), and MMF (2000 mg) was added thereafter. Portal hypertension started to develop. Radiological examinations yielded a diagnosis of artery-portal shunt of segment 3 of the graft. Shunt

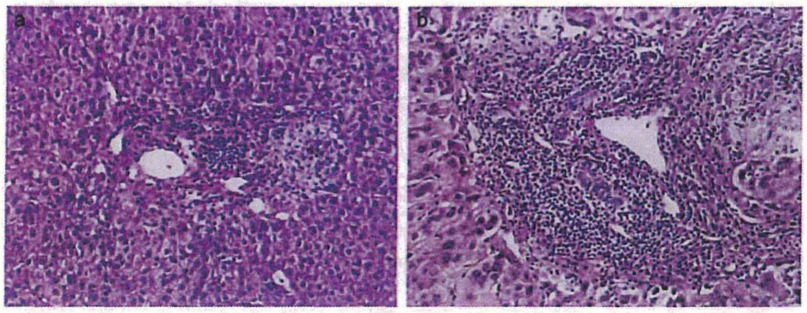

Figure 1 Histological findings of patient no. 2. (a) Wedge liver biopsy at postoperative month 20. Suspected recurrence of primary biliary cirrhosis (PBC) with bile duct loss and mild lobular and portal hepatitis. (b) Second explant liver (allograft). Suspected recurrence of PBC with moderate portal hepatitis and minimal bile duct damage (hematoxylin–eosin, original magnification ×200).

occlusion using metallic coils failed and led to liver failure. She underwent retransplantation 120 months after LDLT.

DISCUSSION

HISTOLOGICAL EXAMINATION IS the gold standard for recurrent PBC. Hubscher *et al.* reported the histological features to be mononuclear portal inflammation, portal lymphoid aggregate, portal granulomas and bile duct damage.[9] These findings are observed also in complications other than recurrent PBC. Lymphoid aggregate can be observed in chronic hepatitis, and bile duct damage and/or vanishing bile duct can be observed in chronic rejection or in the end stage of chronic cholangitis. Foamy cell arteriopathy, which is another specific feature of chronic rejection, is seldom observed on needle biopsy. Duct loss without portal granuloma suggests chronic rejection. The current study focusing on explanted allografts was conducted to avoid these uncertain factors.

Recently, late cellular rejection, chronic hepatitis, and de novo autoimmune hepatitis were discussed as causes of late liver allograft dysfunction.[16] Haga *et al.* reported perivenular lymphoplasmacytic infiltration in a case of their series, which simulated autoimmune hepatitis rather than typical PBC. In our series, ANA was strongly positive prior to primary transplantation in two patients but there were no such findings.

The incidence of recurrent PBC increased along with long-term follow up. Montano-Loza *et al.* studied the cumulative probability of PBC recurrence after LT.[17] Their histological study was not based on protocol biopsy. The overall 5- and 10-year probability of recurrence was 13% and 29%, respectively, in their series. They analyzed risk factors for recurrence and the clinical impacts. Although PBC transplant recipients receiving cyclosporin have a lower risk of disease recurrence, the development of recurrent PBC had no impact on long-term patient survival during 10 years of follow up. The incidence in LDLT based on protocol biopsy was 40% during 10 years of follow up.[3] Besides the increasing incidence, progression of recurrent PBC is still a concern, although progression of recurrent PBC was slow within 10 years of follow up in our series. In Japanese registries of LT, some cases of mortality after 10 years have been reported but information about their causes is not available.[18] A precise study of these cases is required to reveal the risks including recurrence in long-term follow-up.

Protocol biopsies for early diagnosis of recurrent PBC may not be essential to improve clinical courses of

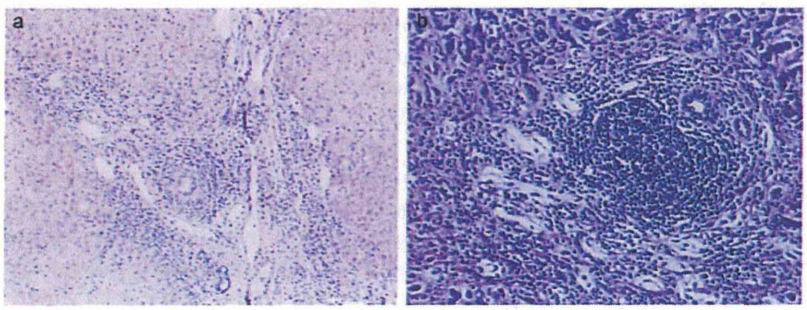

Figure 2 Histological findings of patient no. 4. (a) Needle liver biopsy at postoperative month 71. Recurrence of primary biliary cirrhosis (PBC) with non-suppurative cholangitis and moderate portal hepatitis and fibrosis. (b) Second explant liver (allograft). Suspected recurrence of PBC with focal duct damage and portal inflammation (hematoxylin–eosin, original magnifications: [a] ×150; [b] ×200).

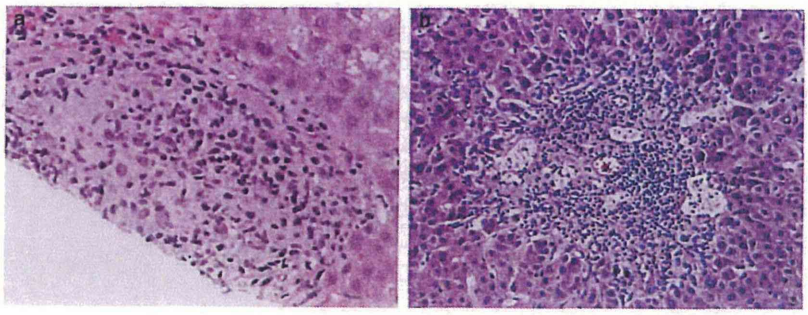

Figure 3 Histological findings of patient no. 5. (a) Needle liver biopsy at postoperative month 90. Recurrence of primary biliary cirrhosis (PBC) with focal cholangitis and epithelioid granuloma. (b) Second explant liver (allograft). Suspected recurrence of PBC with bile duct loss and portal inflammation (hematoxylin–eosin, original magnifications: [a] ×250; [b] ×200).

patients after LT for PBC. Timely biopsies and suitable radiological examinations, when hepatic chemistries deteriorate, are important to improve the clinical course within 10 years after transplantation.

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ORIGINAL ARTICLE

The Outcomes of Patients with Severe Hyperbilirubinemia Following Living Donor Liver Transplantation

Hajime Matsushima · Akihiko Soyama · Mitsuhisa Takatsuki · Masaaki Hidaka · Izumi Muraoka · Tamotsu Kuroki · Susumu Eguchi

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Abstract
Background Prolonged hyperbilirubinemia (HB) following living donor liver transplantation (LDLT) can be a risk factor for early graft loss and mortality. However, some recipients who present with postoperative hyperbilirubinemia do recover and maintain a good liver function.
Aim The purpose of this study was to investigate the risk factors for hyperbilirubinemia following LDLT and to identify predictors of the outcomes in patients with post-transplant hyperbilirubinemia.
Methods A total of 107 consecutive adults who underwent LDLT in Nagasaki University Hospital were investigated retrospectively. The patients were divided into two groups according to postoperative peak serum bilirubin level (HB group: ≥30 mg/dl; non-HB group: <30 mg/dl). These two groups of patients and the prognosis of patients in the HB group were analyzed using several parameters.
Results Seventeen patients (15.9 %) presented with hyperbilirubinemia, and their overall survival was significantly worse than patients in the non-HB group ($n = 90$). Donor age was significantly higher in the HB group ($P < 0.05$). Of the 17 patients in the HB group, nine survived. The postoperative serum prothrombin level at the time when the serum bilirubin level was >30 mg/dl was significantly higher in surviving patients ($P < 0.01$).
Conclusions The use of a partial liver graft from an aged donor is a significant risk factor for severe hyperbilirubinemia and a poorer outcome. However, those patients who maintain their liver synthetic function while suffering from hyperbilirubinemia may recover from hyperbilirubinemia and eventually achieve good liver function, thus resulting in a favorable survival.

Keywords Living donor liver transplantation · Hyperbilirubinemia · Partial graft · Small-for-size graft syndrome · Acute cellular rejection

Introduction

Hyperbilirubinemia following living donor liver transplantation (LDLT) can be caused by several mechanisms, such as initial poor function, acute cellular rejection, surgical complications, small-for-size syndrome, drug toxicity, among others. Hyperbilirubinemia has also been reported to be a risk factor for early graft loss and mortality [ ]. However, some recipients can overcome hyperbilirubinemia, and these patients subsequently achieve and maintain a good liver function after their eventual recovery from hyperbilirubinemia. The aim of this study was to retrospectively clarify the risk factors for the development of postoperative severe hyperbilirubinemia and to identify any predictors for the outcomes in patients who present with hyperbilirubinemia following LDLT.

Patients and Methods

We retrospectively analyzed the data of 107 consecutive adult patients (67 males, 40 females, median age 55 years, age range 16–68 years) who underwent LDLT in the Department of Surgery of Nagasaki University Hospital between November 1997 and January 2010. The etiologies

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of the liver disease were hepatitis C virus infection (35 patients), hepatitis B virus infection (25 patients), non-viral causes (40 patients), and fulminant liver failure (7 patients) (Table). During this period, we occasionally treated patients with a postoperative bilirubin level of >20 mg/dl. Marubashi et al. [ ] reported that a postoperative peak serum bilirubin level of >27 mg/dl could be a predictor of short-term graft outcome. Therefore, we defined those patients who had presented with a postoperative peak serum bilirubin level of >30 mg/dl as having hyperbilirubinemia (HB group); the remaining patients formed the non-HB group.

The two groups of patients were compared for preoperative serum bilirubin level; donor age; the postoperative peak alanine aminotransferase (ALT); model for end-stage liver disease (MELD) score; graft weight (GW)/standard liver volume ratio [SLV; SLV (ml) = 706.2 × body surface area (m^2) + 2.4] [ ]; type of graft; development of acute cellular rejection [as proven by biopsy within postoperative day (POD) 60]; ABO compatibility; the development of biliary complications. We defined a biliary complication as anastomotic stenosis that needed interventions by means of balloon dilatation, stent placement, or re-operation. We divided the types of grafts into those for the right lobe and left lobe, respectively. The right lobe included the right lateral sector, and the left lobe included the left lateral segment.

In the HB group, we compared surviving and non-surviving patients for all of the above-mentioned parameters as well as for serum prothrombin [PT (%)] and creatinine levels at the time when the serum bilirubin level was >30 mg/dl. In the HB group, no patients received administration of fresh frozen plasma at the time of diagnosis. We used log-rank test for survival comparison. Group data were compared with the Mann–Whitney *U* test, and differences between proportions of categorical data were compared with the χ^2 test. Furthermore, several factors detected in the univariate analysis with *P* values of <0.15 were entered into a multivariate analysis. We used multivariate logistic regression analysis for the multivariate analysis. A *P* value <0.05 was considered to be statistically significant.

Table 1 Indication for liver transplantation

Cause of liver disease	Total ($n = 107$)	HB group ($n = 17$)	Non-HB group ($n = 90$)
Liver cirrhosis (hepatitis virus C)	35	6	29
Liver cirrhosis (hepatitis virus B)	25	4	21
Alcoholism	11	2	9
Primary biliary cirrhosis	8	3	5
Fulminant hepatitis	7	0	7
Liver cirrhosis (non-B non-C)	6	0	6
Primary sclerosing cholangitis	3	0	3
Budd–Chiari syndrome	1	0	1
Caroli's disease	1	0	1
Graft failure	4	2	2
Others	6	0	6

HB Hyperbilirubinemia

Results

Of the 107 consecutive adult patients who underwent LDLT at our hospital during the study period, 17 (15.9 %) met our criteria for HB and were included in the HB group; the remaining 90 patients (84.1 %) formed to the non-HB group. The overall survival rate was significantly different between the groups ($P < 0.01$) (Fig.). Time-zero biopsies showed no apparent differences between patients in the HB and non-HB group. Protocol biopsy was not performed postoperatively except in cases of cellular rejection or recurrence of hepatitis was suspected. The median donor age was significantly higher in the HB versus the non-HB group [50 (range 22–63) vs. 36 (19–67) years, respectively; $P < 0.05$], and ABO incompatibility was identified as a risk factor for posttransplant hyperbilirubinemia. The median preoperative serum bilirubin level tended to be higher in the HB group than in the non-HB group [5.4 (range 1.1–39.5) vs. 3.3 (0.6–42.7) mg/dl, respectively; $P = 0.06$]. The median postoperative peak ALT level was significantly higher in the HB group than in the non-HB group [569 (range 120–1,907) vs. 339 (79–3,359) IU/l,

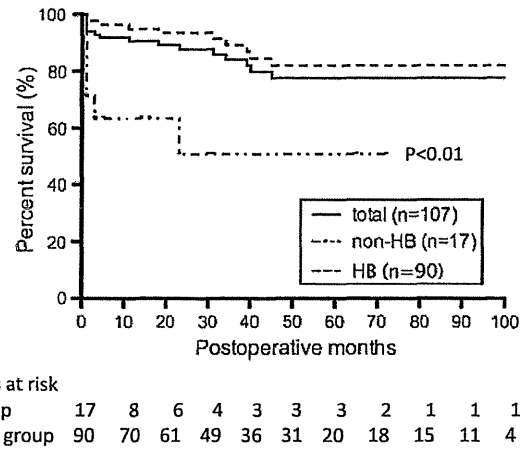

Fig. 1 Kaplan–Meier curves of the postoperative survival of patients with hyperbilirubinemia (*HB* group) and without hyperbilirubinemia (*non-HB* group)