Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Long-term outcome of living donor liver transplantation for primary biliary cirrhosis

Junichi Kaneko,[1] Yasuhiko Sugawara,[1] Sumihito Tamura,[1] Taku Aoki,[1] Kiyoshi Hasegawa,[1] Noriyo Yamashiki[2] and Norihiro Kokudo[1]

1 Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan
2 Organ Transplantation Service, University of Tokyo, Tokyo, Japan

Keywords
liver transplantation, living donor, pre-emptive therapy, primary biliary cirrhosis.

Correspondence
Yasuhiko Suagwara, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Tel.: 81 3 3815 5411; fax: 81 3 5684 3989; e-mail: yasusuga-tky@umin.ac.jp

Conflicts of Interest
The authors have declared no conflicts of interest.

Received: 10 May 2011
Revision requested: 20 June 2011
Accepted: 21 August 2011
Published online: 16 September 2011

doi:10.1111/j.1432-2277.2011.01336.x

Summary

In living donor liver transplantation (LDLT) for primary biliary cirrhosis (PBC), the majority of donors are genetically related to their recipients, leading to concerns of an earlier recurrence of PBC and a poorer prognosis due to genetic susceptibility. Totally 81 patients who underwent LDLT for PBC were the subjects of the present study. Immunosuppressive agents consisted of tacrolimus and methylprednisolone. In the outpatient clinic, when the aspartate and alanine aminotransferase level exceeded the upper limit of the normal range, the dose of methylprednisolone was increased from 4 to 6 mg/day for several months. Blood was examined every 2 weeks for 3 months and a liver biopsy was performed when aminotransferase levels did not decrease to the upper limit of the normal range after more than 3 months. Five-year survival and recurrence rates were estimated and the prognostic factors were analyzed. The mean observation period was 6.2 years. Five years after LDLT for PBC, the biopsy-proven PBC recurrence rate was 1%. The 5-year patient survival rate was 80%. The nonrelated or blood-related donor factor and number of human leukocyte antigen matches did not correlate with prognosis. PBC recurrence rate after LDLT in our series was lower than that in previous studies.

Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic autoimmune liver disease characterized by the destruction of interlobular and septal bile ducts, resulting in fibrosis and cirrhosis [1]. Genetic susceptibility is related with PBC. Selmi *et al.* [2] reported that of 16 pairs of twins within a 1400-family cohort, eight pairs were monozygotic. In five of the eight pairs, both individuals had PBC. Familial PBC accounted for 1% to 5% of all PBC cases. Recurrence occurs frequently in individuals with a family history of PBC, 4–6% [3].

Liver transplantation remains a definitive treatment for end-stage liver disease because of PBC [4,5]. Although living donor liver transplantation (LDLT) is an effective treatment option for PBC, the majority of donors are genetically related to their recipients. Thus, earlier recurrence of PBC and poorer prognosis are concerns. This manuscript reports the long-term outcome of PBC patients following LDLT.

Patients and methods

Patients

From January 1996 to December 2010 at University of Tokyo Hospital, 389 patients underwent adult-to-adult LDLT (Table 1). Among these, 81 (21%) underwent LDLT for PBC. The diagnosis of PBC was based on clinical, serologic and histologic findings. The mean age was 51 ± 8 years and 71 patients (88%) were female. The mean updated Mayo risk score [6] was 9.4 ± 2.0 and the preoperative total serum bilirubin level was 13.3 ± 9.4 mg/dl. The mean model for end-stage liver disease score [7] was 15.7 ± 6.8. Two patients had hepatocellular carcinoma. Two other patients had autoimmune hepatitis as part of an overlap syndrome and one had viral hepatitis C.

Table 1. Background of primary biliary cirrhosis (PBC) patients.

Patient characteristics (n = 81)	
Recipient age (year)	51 ± 8
Recipient gender (female)	88%
Updated Mayo risk score	9.4 ± 2.0
MELD score	15.7 ± 6.8
Preoperative total serum bilirubin level (mg/dl)	13.3 ± 9.4
Number of HLA-A, -B, -DR mismatches (≥3)	51%
Preoperative diabetes mellitus	19%
Preoperative osteoporosis	18%

MELD, model for end-stage liver disease; HLA, human leukocyte antigen.

The observation period ranged from 0.1 to 13.4 (median, 6.2) years. The living donors were sons (n = 23), daughters (n = 21), spouses (n = 13), sisters (n = 11), brothers (n = 8), fathers (n = 1), aunts (n = 1), and nieces (n = 1). The average donor age was 36 years. Forty-three donors were male and 38 were female.

The selection criteria for recipients and donors were as previously reported [8,9]. The volume ratio (estimated volume of the liver graft compared with the standard liver volume [10]) of the recipient was required to be >40%. In a low-risk case (updated Mayo risk score, <15), we allowed a liver graft with a ratio of more than 35% of the recipient standard liver volume. The volume of the entire liver and its vascular territory in the donor were estimated using enhanced computed tomography and precise volume was estimated using region-growing software (Hitachi Medical Co, Ltd, Tokyo, Japan).

Human leukocyte antigen typing

Complete donor–recipient human leukocyte antigen (HLA) typing was performed prospectively. HLA-A and HLA-B typing was performed using a standard complement-dependent microcytotoxicity assay with the Terasaki HLA tray (One Lambda Inc, Los Angeles, CA, USA). HLA-DR typing was performed using two-color fluorescence.

Immunosuppressive agents

Basic immunosuppressive agents, tacrolimus and methylprednisolone, were used. The target trough serum level of tacrolimus was 15–20 ng/ml in the first week after transplantation. Six months after surgery, the target trough level was gradually decreased from 8 to 5 ng/ml. Simultaneously, methylprednisolone (20 mg/kg) was used prior to the anhepatic phase of surgery and the dose was subsequently reduced to the maintenance level. We replaced tacrolimus with cyclosporine therapy in patients who developed side effects from tacrolimus [11]. Acute and chronic rejection was diagnosed using the Banff schema classification [12]. Diagnosis of cytomegalovirus infection was established by a positive pp65 antigenemia assay, defined by the presence of more than five antigen-positive cells/50 000 white blood cells [13]. The patients were treated with ganciclovir.

Patient management in the outpatient clinic

Antimitochondrial M2 antibody was checked every 6–12 months after LDLT. Aspartate aminotransferase (normal range, 9–38 U/l), alanine aminotransferase (4–36 U/l), and alkaline phosphatase (115–359 IU/l) were used as biochemical markers of cholestasis [14]. Gamma-glutamyl transpeptidase (4–68 U/l) and total bilirubin (0.3–1.3 mg/dl) levels were measured every month.

Protocol for low-dose administration of methylprednisolone and UDCA

All PBC patients were maintained on low-dose methylprednisolone (2–6 mg/day) and ursodeoxycholic acid (UDCA, 5–15 mg/kg/day). In the outpatient clinic, aspartate (normal range, 9–38 U/l) and alanine aminotransferase level (normal range, 4–36 U/l) were measured every month and when they exceeded the upper limit of the normal range in two consecutive measurements, 2–4 mg/day of methylprednisolone was added for several months. A liver biopsy was performed for patients whose aspartate and alanine aminotransferase levels did not decrease to normal levels after more than 3 months despite the increased dose of methylprednisolone. When aspartate and alanine aminotransferase levels decreased to the normal range, the dose was reduced to its maintenance level.

Histology study

The diagnosis of acute or chronic rejection was based on the Banff schema [12]. Recurrence of PBC was assessed in accordance with the following histologic features; mononuclear portal infiltration, portal lymphoid aggregate, portal granulomas, and bile duct damage [15]. Ludwig's classification was used to morphologically stage PBC [16].

Diagnosis of diabetes mellitus

Fasting blood glucose, hemoglobin A1c (HbA1c), and glycoalbumin levels were measured every month together with a glucose tolerance test [17]. Diabetes mellitus and impaired glucose were defined as follows: patients treated with an oral antidiabetic drug or insulin and fasting blood glucose level higher than 126 mg/dl, HbA1c level higher than 6.5%, and/or glycoalbumin higher than 20%,

according to the criteria of the Japan Diabetes Society [18].

Screening for osteoporosis and treatment

In the pretransplant phase, plain radiographs or magnetic resonance images were obtained in patients with lumbago. For patients diagnosed with lumbar vertebral fractures or severe osteoporosis, treatment with calcium L-aspartate hydrate (Aspara-CA; Mitsubishi Tanabe Pharma Co, Tokyo, Japan) and vitamin D or bisphosphonate therapy was begun after transplantation. More than 1 year after liver transplantation, patients complaining of lumbago underwent dual-energy X-ray absorptiometry for evaluation of their bone mineral density.

Statistical analysis

Kaplan–Meier life table analysis with a log-rank test was used to assess whether each variable significantly affected post-transplantation patient survival. A statistical software package (SPSS 16.0J; SPSS Japan Inc., Tokyo, Japan) was used for univariate or multivariate analysis. Data are expressed as mean ± standard deviation. A *P*-value of 0.05 was considered to be statistically significant.

Results

Twelve recipients (15%) died during the follow-up period. Among them, five (6%) died within 6 months of LDLT. The causes of these early deaths were as follows: pneumonia followed by sepsis in two patients (at 1.7 and 1.9 months, respectively), simultaneous thrombosis of the portal vein and hepatic artery (at 0.2 months), brain hemorrhage (at 0.9 months), thrombotic microangiopathy (at 1.0 month), and cryptococcosis (at 3.6 months) in one patient each. The remaining seven patients died more than 1 year after transplantation. The causes of these later deaths included virus associated hemophagocytic syndrome (at 1.0 year), hepatitis C liver cirrhosis, uncontrollable chronic rejection (at 3.7 years), pneumonia (at 3.9 years), Langerhans cell sarcoma (at 5.1 years), rupture of a thoracic aneurysm (at 6.1 years), and oral cavity carcinoma (at 6.5 years).

Six recipients (7%) discontinued UDCA more than 6 months after transplantation due to diarrhea. All of the recipients continued methylprednisolone during the follow-up period.

A total of 96 liver biopsy specimens were obtained during the observation period. Among them, 71 biopsies from 40 recipients were performed within 6 months after transplantation, eight from four recipients between 6 and 12 months, and five from three recipients between 1 and 3 years after surgery, and 12 from five recipients between 3 and 9 years after LDLT. A total of 50 (52%) biopsies led to a diagnosis of acute rejection and 42 (44%) led to a diagnosis of indeterminate acute rejection. Two biopsies obtained from the same patient showed PBC recurrence (stage I) at 5.1 and 6.4 years after transplantation, respectively. Chronic rejection was observed in one patient and another had hepatitis C-related cirrhosis.

At end of this study, 19 recipients (28%) had exceeded the upper limit of the normal range of alkaline phosphatase and/or gamma-glutamyl transpeptidase. Among them, nine recipients had biliary stricture and underwent stent placement successfully. Two recipients (3%) had high aspartate and alanine aminotransferase level (56/72 and 40/45 U/l, respectively). These recipients were diagnosed as a chronic rejection and a recurrent PBC. High total bilirubin level (2.1 mg/dl) was showed in the chronic rejection patient (1%).

The cumulative incidence of diabetes mellitus at 1, 3, and 5 years after transplantation was 7%, 10%, and 13%, respectively. Dual-energy X-ray absorptiometry was performed in 13 patients with lumbago at an average of 6 years after transplantation. All but one patient with a spinal compression factor had normal bone mineral density.

Grafts weight of <460 g was a poor prognostic factor (Table 2). The 1-, 3-, and 5-year survival rates were 90%, 88%, and 80%, respectively (Fig. 1). No retransplantation was performed. The biopsy-proven PBC recurrence rate was 1% at 5 years after transplantation.

Table 2. Five-year patient survival estimates according to various variables.

Variable		*n*	5-year patient survival	*P*
MELD scores	<20	63	88	0.95
	≥20	18	87	
Updated Mayo score	<10	53	92	0.26
	≥10	28	79	
Recipient sex	Female	71	89	0.15
	Male	10	80	
Recipient age (years)	<50	38	90	0.51
	>51	43	85	
Donor age (years)	<30	36	85	0.86
	>31	45	89	
HLA-A, -B, and -DR locus mismatches	0–2	41	94	0.21
	≥3	40	83	
Blood relative donor	Yes	68	86	0.59
	No	13	90	
Graft weight (g)	<460	33	74	0.04
	≥460	48	97	
Immunosuppressant	Tacrolimus	67	87	0.54
	Cyclosporine	14	91	

MELD, model for end-stage liver disease; HLA, human leukocyte antigen.

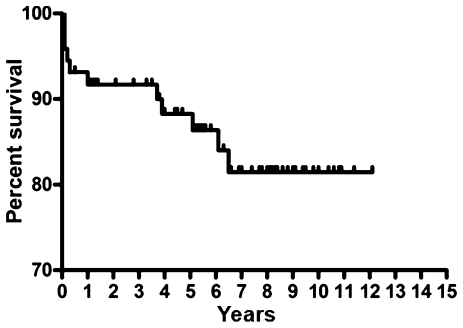

Figure 1 Overall survival.

Discussion

Primary biliary cirrhosis recurs in liver transplant recipients. Based on the experience with deceased donor liver transplantation (DDLT), PBC recurrence was first reported in 1982 [19]. Neuberger *et al.* [20,21] reported that PBC recurred in 23% ($n = 485$) at 6.6 years after transplantation (Table 3). Charatcharoenwitthaya *et al.* [22] reported that the incidence was 22%, 37%, and 43% at 5, 10, and 15 years, respectively. Several transplant centers reported that they performed protocol biopsy every 1–5 years after transplantation [20–26]. There has been no consensus, however, regarding the appropriate interval for protocol biopsy after transplantation.

Many transplant programs [27–33] do not perform protocol biopsy. When a biopsy is performed only when clinical features appear, the recurrence rate is likely underestimated [34]. Montano *et al.* [27] reported a recurrence rate of 13% and 26% at 5 and 10 years, respectively, after transplantation based on no protocol biopsy (i.e., biopsy performed when liver dysfunction was detected). Although PBC recurrence may be common, its effect on patient or graft survival is insignificant in DDLT [21], which makes it difficult justify protocol biopsy in PBC patients.

Another problem is that there is no pathologic definition diagnosis of PBC recurrence. The histologic features of PBC are not specific to PBC. For example, lymphoid aggregates with bile duct damage are observed in transplanted liver with chronic hepatitis [35]. PBC-like inflammatory bile duct damage and/or vanishing bile duct are associated with chronic rejection [12]. Hubscher *et al.* [15] reported the pathologic features of PBC recurrence; mononuclear portal infiltration, portal lymphoid aggregate, portal granulomas, and bile duct damage. Several investigators have subsequently adopted their diagnostic criteria [21,25,28,29]. The pathologic definition on PBC recurrence continues to be discussed.

Human leukocyte antigen mismatching on PBC recurrence remains controversial. Morioka *et al.* [28] emphasized that a high number of HLA mismatches were also related to poor survival (40%) at 5 years after LDLT. Balan *et al.* [36] reported that higher HLA mismatch tended to decrease long-term survival in DDLT patients without a significant difference. Other reports showed

Table 3. Recurrent primary biliary cirrhosis (PBC) after liver transplantation.

Author	*N*	Protocol biopsy (Y/N)	Pre-emptive therapy	Median follow-up period (years)	Recurrence rate (%)	Median duration (years) to recurrence	Year
DDLT							
Sebagh [26]	69	Y	ND	–	9	8	1998
Polson [38]	23	N	ND	3.1	39	2.5	1989
Khettry [39]	43	N	ND	–	19	3.5	2003
Levitsky [40]	46	N	ND	–	15	6.5	2003
Sanchez [24]	169	Y	ND	6	11	4.1	2003
Neuberger [19]	485	Y	ND	6.6	23	5.2	2004
Guy [29]	48	N	ND	4.2	35	ND	2005
Jacob [23]	100	Y	UDCA	9.8	14	5	2006
Charatcharoenwitthaya [22]	154	Y	ND	10.8*	34	3.5	2007
Montano-Loza [27]	108	N	ND	6.9	26	5.8	2010
Manousou [25]	103	Y	ND	9	35	3.6	2010
LDLT							
Takeishi [41]	5	Y	ND	1.8*	25	1	2003
Hashimoto [42]	8	Y	UDCA	8.5	75	2	2007
Morioka [28]	50	N	ND	2.4	18	3	2007
The present study	81	N	UDCA/MP	6.2	1	5.1	–

DDLT, deceased donor liver transplantation; LDLT, living donor liver transplantation; MP, methylprednisolone; ND, no description; UDCA, ursodeoxycholic acid.

*Data shown as mean level.

that HLA-B [23] or HLA-DR [29,36] mismatch significantly increased the chance for PBC recurrence. In contrast, Manousou *et al.* [25] reported that there was no effect of HLA matching on PBC recurrence, consistent with our results.

Postoperative administration of UDCA and glucocorticoids might be related with a low PBC recurrence rate in our study. UDCA effectively improves alkaline phosphatase levels and may suppress PBC recurrence after liver transplantation. Charatcharoenwitthaya *et al.* [22] reported that 38 patients with recurrent PBC received UDCA over a 36-month period and that more than 50% of them showed normalization of serum ALP and alanine aminotransferase levels compared to 22% of patients who received no UDCA. Jacob *et al.* [23] reported that patients treated with UDCA from the time of their DDLT had a recurrence rate of 32% over a 13-year period. Rautiainen *et al.* [37] studied the concomitant use of budesonide (a nonhalogenated glucocorticoid; 6 mg/kg/day) and UDCA (15 mg/kg/day) in patients with PBC. Fibrosis was improved by 25% in patients administered both drugs. If UDCA was used alone, however, the degree of fibrosis increased, suggesting an important role of steroids in suppressing recurrence.

In summary, the PBC recurrence rate after LDLT was lower in the present series than in previous studies of the pathologic basis. Prophylactic UDCA and steroid therapy may reduce the frequency of liver biopsies needed after LDLT.

Authorship

JK and YS: designed research/study. ST, TA, KH, NY, and NK: performed study, collected and analyzed data and wrote the paper.

Funding

This work was supported by a Grant-in-aid for Scientific Research from the Ministry of Education, Culture, Sports, Science of Japan.

References

1. Lindor K. Ursodeoxycholic acid for the treatment of primary biliary cirrhosis. *N Engl J Med* 2007; **357**: 1524.
2. Selmi C, Mayo MJ, Bach N, *et al.* Primary biliary cirrhosis in monozygotic and dizygotic twins: genetics, epigenetics, and environment. *Gastroenterology* 2004; **127**: 485.
3. Brind AM, Bray GP, Portmann BC, Williams R. Prevalence and pattern of familial disease in primary biliary cirrhosis. *Gut* 1995; **36**: 615.
4. Kaplan MM, Gershwin ME. Primary biliary cirrhosis. *N Engl J Med* 2005; **353**: 1261.
5. Poupon R. Primary biliary cirrhosis: a 2010 update. *J Hepatol* 2010; **52**: 745.
6. Murtaugh PA, Dickson ER, Van Dam GM, *et al.* Primary biliary cirrhosis: prediction of short-term survival based on repeated patient visits. *Hepatology* 1994; **20**: 126.
7. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864.
8. Kokudo N, Sugawara Y, Imamura H, Sano K, Makuuchi M. Tailoring the type of donor hepatectomy for adult living donor liver transplantation. *Am J Transplant* 2005; **5**: 1694.
9. Yamashiki N, Sugawara Y, Tamura S, *et al.* Selection of liver-transplant candidates for adult-to-adult living donor liver transplantation as the only surgical option for end-stage liver disease. *Liver Transpl* 2006; **12**: 1077.
10. Urata K, Kawasaki S, Matsunami H, *et al.* Calculation of child and adult standard liver volume for liver transplantation. *Hepatology* 1995; **21**: 1317.
11. Tamura S, Sugawara Y, Kishi Y, *et al.* Conversion to cyclosporine provides valuable rescue therapy for living donor adult liver transplant patients intolerant to tacrolimus: a single-center experience at the University of Tokyo. *Transplant Proc* 2004; **36**: 3242.
12. 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.
13. Akamatsu N, Sugawara Y, Kaneko J, Kishi Y, Makuuchi M. Risk factors of cytomegalovirus infection after living donor liver transplantation. *Hepatogastroenterology* 2005; **52**: 197.
14. Hohenester S, Oude-Elferink RP, Beuers U. Primary biliary cirrhosis. *Semin Immunopathol* 2009; **31**: 283.
15. Hubscher SG, Elias E, Buckels JA, Mayer AD, McMaster P, Neuberger JM. Primary biliary cirrhosis. Histological evidence of disease recurrence after liver transplantation. *J Hepatol* 1993; **18**: 173.
16. Ludwig J, Dickson ER, McDonald GS. Staging of chronic nonsuppurative destructive cholangitis (syndrome of primary biliary cirrhosis). *Virchows Arch A Pathol Anat Histol* 1978; **379**: 103.
17. Kishi Y, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Makuuchi M. New-onset diabetes mellitus after living donor liver transplantation: possible association with hepatitis C. *Transplant Proc* 2006; **38**: 2989.
18. Neville SE, Boye KS, Montgomery WS, Iwamoto K, Okamura M, Hayes RP. Diabetes in Japan: a review of disease burden and approaches to treatment. *Diabetes Metab Res Rev* 2009; **25**: 705.

19. Neuberger J, Portmann B, Macdougall BR, Calne RY, Williams R. Recurrence of primary biliary cirrhosis after liver transplantation. *N Engl J Med* 1982; **306**: 1.
20. Liermann 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.
21. Neuberger J, Gunson B, Hubscher S, Nightingale P. Immunosuppression affects the rate of recurrent primary biliary cirrhosis after liver transplantation. *Liver Transpl* 2004; **10**: 488.
22. 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; **3**: 1236.
23. 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.
24. Sanchez EQ, Levy MF, Goldstein RM, *et al.* The changing clinical presentation of recurrent primary biliary cirrhosis after liver transplantation. *Transplantation* 2003; **76**: 1583.
25. 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.
26. Sebagh M, Farges O, Dubel L, Samuel D, Bismuth H, Reynes M. Histological features predictive of recurrence of primary biliary cirrhosis after liver transplantation. *Transplantation* 1998; **65**: 1328.
27. Montano-Loza AJ, Wasilenko S, Bintner J, Mason AL. Cyclosporine A protects against primary biliary cirrhosis recurrence after liver transplantation. *Am J Transplant* 2010; **10**: 852.
28. 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.
29. Guy JE, Qian P, Lowell JA, Peters MG. Recurrent primary biliary cirrhosis: peritransplant factors and ursodeoxycholic acid treatment post-liver transplant. *Liver Transpl* 2005; **11**: 1252.
30. Silveira MG, Talwalkar JA, Lindor KD, Wiesner RH. Recurrent primary biliary cirrhosis after liver transplantation. *Am J Transplant* 2010; **10**: 720.
31. Guichelaar MM, Kendall R, Malinchoc M, Hay JE. Bone mineral density before and after OLT: long-term follow-up and predictive factors. *Liver Transpl* 2006; **12**: 1390.
32. Saab S, Shpaner A, Zhao Y, *et al.* Prevalence and risk factors for diabetes mellitus in moderate term survivors of liver transplantation. *Am J Transplant* 2006; **6**: 1890.
33. Kim WR, Wiesner RH, Therneau TM, *et al.* Optimal timing of liver transplantation for primary biliary cirrhosis. *Hepatology* 1998; **28**: 33.
34. Williams R, Gershwin ME. How, why, and when does primary biliary cirrhosis recur after liver transplantation? *Liver Transpl* 2007; **13**: 1214.
35. Nakhleh RE, Schwarzenberg SJ, Bloomer J, Payne W, Snover DC. The pathology of liver allografts surviving longer than one year. *Hepatology* 1990; **11**: 465.
36. 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.
37. Rautiainen H, Karkkainen P, Karvonen AL, *et al.* Budesonide combined with UDCA to improve liver histology in primary biliary cirrhosis: a three-year randomized trial. *Hepatology* 2005; **41**: 747.
38. Polson RJ, Portmann B, Neuberger J, Calne RY, Williams R. Evidence for disease recurrence after liver transplantation for primary biliary cirrhosis. Clinical and histologic follow-up studies. *Gastroenterology* 1989; **97**: 715.
39. Khettry U, Anand N, Faul PN, *et al.* Liver transplantation for primary biliary cirrhosis: a long-term pathologic study. *Liver Transpl* 2003; **9**: 87.
40. Levitsky J, Hart J, Cohen SM, Te HS. The effect of immunosuppressive regimens on the recurrence of primary biliary cirrhosis after liver transplantation. *Liver Transpl* 2003; **9**: 733.
41. Takeishi T, Sato Y, Ichida T, Yamamoto S, Kobayashi T, Hatakeyama K. Short-term outcomes of living-related liver transplantation for primary biliary cirrhosis and its recurrence: report of five cases. *Transplant Proc* 2003; **35**: 372.
42. 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**: S455.