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Long-term Prognosis and Recurrence of Primary Sclerosing Cholangitis After Liver Transplantation: A Single-Center Experience

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Background. Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease, with liver transplantation being the sole life-saving treatment for end-stage PSC-related liver disease. However, recurrence of PSC after liver transplantation is a common complication, with the risk factors for recurrence being controversial. **Methods.** We conducted a retrospective chart review of 45 patients who had undergone liver transplantation for PSC at our institute. The risk factors for PSC recurrence and graft failure after liver transplantation were analyzed. **Results.** The graft survival rates were 55.4% at 5 years and 32.8% at 10 years after liver transplantation for PSC. PSC recurrence was diagnosed in 16 (40%) of 40 patients, at a median 30 months (range, 9-70 months) after liver transplantation. The cumulative incidence rate of PSC recurrence was 24.5% at 3 years, 39.3% at 5 years, and 45.8% at 6 years. Among the 16 patients diagnosed with PSC recurrence, the graft survival rate was 56.3% at 5 years, and 21.9% at 10 years after the recurrence. Active inflammatory bowel disease after liver transplantation was identified as an independent risk factor for PSC recurrence. Age younger than 30 years at the time of PSC diagnosis and bacteremia were factors significantly associated with graft failure after liver transplantation on multivariate analysis. **Conclusions.** PSC frequently recurred and progressed to graft failure after liver transplantation for PSC. Maintaining an inactive status of inflammatory bowel disease might offer protection against PSC recurrence.

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Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease, with the cause and pathogenesis of PSC remaining to be clarified.[1-3] No effective medical therapy for PSC has been defined, with liver transplantation providing the only life-saving treatment for patients with PSC-related end-stage liver disease. However, the recurrence of PSC after living transplantation can lead to graft failure.[4-9]

In 2009, we reported our 10-year experience with living donor liver transplantation (LDLT) among 30 patients with PSC at our center.[5] At that time, we reported frequent recurrence of PSC after LDLT, with rapid progression of the disease after recurrence that resulted in a high rate of graft failure. Two significant risk factors were associated with PSC recurrence in that study: cytomegalovirus (CMV) disease within 3 months posttransplantation and blood-related donor-recipient relationship. In particular, a blood-related donor-recipient relationship was associated with a high frequency of PSC recurrence after LDLT. Therefore, after our initial,

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small, single-center study, we conducted a large, multicenter retrospective study of 114 patients from a Japanese registry of LDLT[6] to determine the rate of PSC recurrence and the risk factors for recurrence. In that study, we reported a recurrence rate of PSC after LDLT of 32% at 5 years and 52% at 10 years. PSC recurrence was significantly associated with graft failure after LDLT. The following risk factors for PSC recurrence were identified: a high Model for End-Stage Liver Disease (MELD) score, first-degree-relative donor-recipient relationship, postoperative CMV infection, and early biliary anastomotic complications. From these results, we concluded that LDLT using a graft from a first-degree-relative donor was one of the contributing factors to the high frequency of PSC recurrence after LDLT in Japan.

Contrasting results were reported by Gordon et al[8] in their large, multicenter, prospective cohort study comparing the risk for PSC recurrence, and the associated risk factor for recurrence, between LDLT and deceased donor liver transplantation (DDLT) in the United States. Based on the data of 241 LDLT and 65 DDLT cases, no difference in the risk of PSC recurrence between LDLT and DDLT recipients was identified. Gordon et al identified the following risk factors for PSC recurrence: a high MELD score, biliary complication, cholangiocarcinoma, and high donor age. First-degree relative donor and CMV infection after liver transplantation were not significantly associated with PSC recurrence in their study.

Therefore, our aim in this study was to reevaluate the long-term survival and PSC recurrence after liver transplantation in our institution, 10 years after our previous study. The risk factors for PSC recurrence and graft failure after liver transplantation were determined as a single center study from our 20-year experience with LDLT.

MATERIALS AND METHODS

Patients

Between July 1996 and June 2015, 45 patients with a diagnosis of PSC underwent liver transplantation at Kyoto University. We retrospectively extracted the data from the medical records of these 45 patients, up to October 2016, to determine long-term patient and graft survival, PSC recurrence rate and risk factors for PSC recurrence and graft failure. The study protocol was approved by the Ethics Committee at Kyoto University and performed in compliance with the Helsinki Declaration.

For standard LDLT, donors were selected among a recipient's parents, grandparents, siblings, offspring, and spouses. In domino transplantation, the donors were recipients of LDLT for familial amyloid polyneuropathy. Tacrolimus and low-dose steroid or mycophenolate mofetil (MMF) were administered as immunosuppression therapy in most patients. MMF and steroid administration was terminated at 3 to 6 months after liver transplantation. One patient received cyclosporine instead of tacrolimus. MMF and/or prednisolone were readministered to patients who experienced refractory rejection or required a reduction in the dose of tacrolimus or cyclosporine due to adverse events. Azathioprine was added, at the physician's discretion, for patients with inflammatory bowel disease (IBD). If acute cellular rejection was confirmed by liver histology, patients received a 3-day course of intravenous corticosteroid pulse therapy, with 10 mg/kg per day of methylprednisolone. Active IBD was defined when the patient had melena and/or diarrhea, and active colitis was confirmed by colonoscopy.

Diagnosis of PSC Recurrence

PSC recurrence was strictly defined using both the inclusion and exclusion criteria described by Graziadei et al.[10] Criteria included a confirmed diagnosis of PSC before transplantation, intrahepatic biliary multiple strictures, confirmed by cholangiography, occurring more than 90 days after transplantation, and biopsy findings showing fibrous cholangitis and/or fibro-obliterative lesions, with or without ductopenia, biliary fibrosis or biliary cirrhosis. All patients with hepatic artery thrombosis/stenosis, established chronic (ductopenic) rejection, nonanastomotic strictures occurring before posttransplantation day 90, and donor-recipient ABO blood group incompatibility were excluded from the analysis of PSC recurrence. Patients who had a biliary anastomotic complication were included when it was successfully treated and nonanastomotic stricture did not develop just after successful initial treatment.

Liver biopsies were performed if alanine aminotransferase, alkaline phosphatase and/or bilirubin levels became elevated to levels $\geq 1.5\times$ the normal upper limit, as well as being performed at regular intervals of 2 to 3 years over the follow-up period. Informed consent for biopsy was obtained in all cases. Biopsy specimens were evaluated by a pathologist with extensive experience in liver transplantation pathology. Cholangiography was performed by magnetic resonance cholangiography, endoscopic retrograde cholangiography, or percutaneous transhepatic cholangiography.

Statistical Analysis

Patient and graft survival curves were calculated using the Kaplan-Meier method. Graft failure was defined as patient death or retransplantation. The cumulative incidence of PSC recurrence was estimated where the graft loss without PSC recurrence was considered as the competing risk. The univariate log-rank test was used to evaluate the effects of patient and graft characteristics on PSC recurrence and graft failure after LDLT. Multivariate Cox regression analysis was used to evaluate the association between PSC recurrence or graft failure and patient characteristics, and to estimate the associated hazard ratio (HR) and associated 95% confidence interval (CI) for significant risk factors. The following factors were included in our analyses of PSC recurrence and graft failure: age at the time of PSC diagnosis and liver transplantation; sex; MELD score; New Mayo score; donor age; donor sex; donor-recipient sex mismatch; donor-recipient familial relationship; HLA-A, -B, and -DR-matched number; donor and recipient HLA-DR15 status; graft type; biliary construction; number of biliary anastomoses; IBD status, before and after liver transplantation; immunosuppressant therapy used during the initiation phase and at 1 year posttransplantation; acute rejection, corticosteroid pulse for acute cellular rejection, CMV antigenemia, and CMV disease within 3 months of transplantation; biliary anastomotic complication, and bacteremia within 1 year after transplantation. All statistical analyses were performed using IBM SPSS Statistics (version 22, IBM Corporation, Armonk, NY).

Characteristics of patients who underwent primary liver transplantation for PSC

|	n = 45
Age at the time of PSC diagnosis, y	23 (1-60)
Age at LT, y	30 (5-67)
Male/female	18/27
IBD	26 (58%)
IBD diagnosed pre-LT	21 (47%)
IBD diagnosed post-LT	5 (11%)
Cholangiocarcinoma at LT	2 (4%)
LDLT/DDLT/Domino LT	39/2/4
Donor age at LT, y	48 (16-62)
Donor male/female	28/17
Donor relationship to recipient	
First-degree/other blood relative/no blood relation	25/9/11
Graft type left/right/posterior/whole	14/25/2/4
ABO incompatible	4 (9%)
Type of biliary anastomosis duct-to-duct/Roux-en-Y	6/39
Immunosuppression	
Calcineurin inhibitor tacrolimus/cyclosporine	44/1
Prednisolone	38 (84%)
Antimetabolites	20 (44%)
Follow-up after LT, mo	62.7 (0.5 - 243.9)

Qualitative variables are shown as a count, and quantitative variables expressed as the median (range).
LT, liver transplantation.

RESULTS

Patients' Characteristics

Relevant characteristics of the 45 patients included in our retrospective analysis are presented in Table 1. The median age of the study population at the time of PSC diagnosis and liver transplantation was 23 years (range, 1-60 years) and 30 years (range, 5-67 years), respectively. Among the 45 patients, 27 (60%) were female. Twenty-one patients (47%) had a diagnosis of IBD before liver transplantation, with an additional 5 patients diagnosed with IBD after liver transplantation. Cholangiocarcinoma was identified in the extracted liver of 2 patients at the time of transplantation. Thirty-nine (87%) patients received a living donor liver graft from a parent (n = 21), siblings (n = 9), offspring (n = 4), or spouse (n = 5). With regard to graft type, 14 patients received a left lobe, 25 a right lobe, 2 a right posterior segment, with the remaining 4 receiving whole liver grafts. The donor-recipient blood type was incompatible for 4 patients. A Roux-en-Y choledocho-jejunal anastomosis was performed in 39 (87%) patients. The median follow-up period was 62.7 months (range, 0.5-243.9 months), up to October 2016.

All 45 patients were included in our analysis of patient and graft survival, and identification of risk factors for graft failure. Among our 45 patients, an ABO-incompatible graft was used in 4 patients, and 1 patient developed hepatic artery thrombosis after liver transplantation. These cases were excluded from our analysis of PSC recurrence. Therefore, recurrence rates and risk factors were evaluated from the data of the remaining 40 patients.
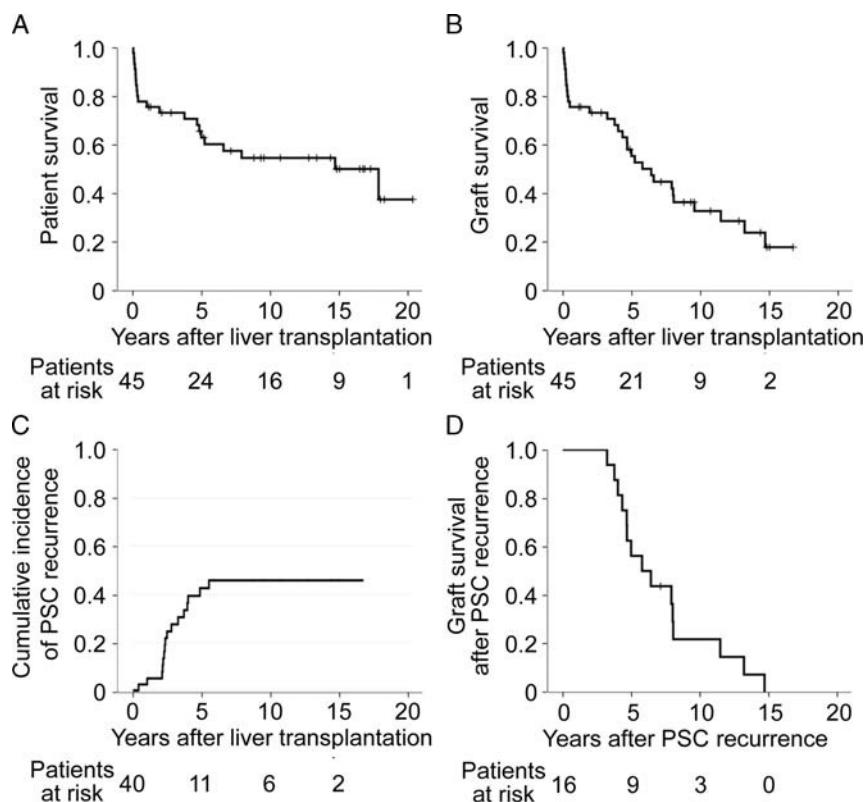
FIGURE 1. Rates of patient survival (A), graft survival (B), and recurrence of PSC (C) after liver transplantation, and the graft survival rate after PSC recurrence (D). Patient and graft survival was estimated using the Kaplan Meier analysis (A, B, D). The cumulative incidence of PSC recurrence was estimated where the graft loss without PSC recurrence was considered as a competing risk (C).

Patient and Graft Survival Rate and PSC Recurrence

The rate of patient survival, estimated by Kaplan Meier analysis, was 77.8% at 1 year, 73.2% at 3 years, 63.0% at 5 years, 57.5% at 7 years, and 54.6% at 10 years (Figure 1A). Over the same period, graft survival rates were as follows: 75.6% at 1 year, 73.2% at 3 years, 55.4% at 5 years, 44.9% at 7 years, and 32.8% at 10 years (Figure 1B). PSC recurrence was diagnosed in 16 (40%) of 40 patients, and the median duration from liver transplantation to the diagnosis of PSC recurrence was 30 months (range, 9-70 months; Figure 2). The cumulative incidence rate of PSC recurrence among these 40 patients was: 2.5% (95% CI, 0.2-11.3%) at 1 year, 24.5% (95% CI, 12.2-39.1%) at 3 years, 39.3% (95% CI, 23.6-54.7%) at 5 years, and 45.8% (95% CI, 29.0-61.1%) at 6 years and thereafter (Figure 1C). The rate of graft survival among the 16 patients diagnosed with PSC recurrence was 100% at 3 years, 56.3% at 5 years, 43.8% at 7 years, 21.9% at 10 years, and 0% at 15 years after the recurrence (Figure 1D).

The clinical course of the 16 patients with PSC recurrence after the first liver transplantation is shown in Figure 2. After PSC recurrence, graft failure occurred within a median of 33 months (range, 9-131 months) in 15 of the 16 patients, case 16 being the exception. Among patients who experienced graft failure, 10 (no. 1-10) underwent retransplantation using a graft from a blood-related living-donor (n = 7), unrelated living-donor (n = 1) or deceased-donor (n = 2). Among these 10 cases, 6 patients developed re-recurrence of PSC at a median of 10 months (range, 7-16 months) after retransplantation, with 1 patient passing away 2 months after the retransplantation (no. 10). Liver failure developed in 3 (no. 1-3) of the 6 patients with PSC rerecurrence. Among these 3 patients, 1 (no. 1) underwent a third transplantation using a deceased-donor graft, but experienced a third recurrence of PSC at 53 months after the third transplantation. The other 2 patients were on a waiting list for DDLT at the end-point of analysis for our study. Therefore, 6 of the 7 patients (no. 1-7) who underwent retransplantation for PSC developed a PSC rerecurrence over the 2-year follow-up. Among the 6 patients (no. 11-16) who did not undergo retransplantation, 5 patients died, 12 to 106 months after PSC recurrence.

Risk Factors for PSC Recurrence

Factors that could predict PSC recurrence were analyzed by comparing patients with (n = 16) and without (n = 24) PSC recurrence, after excluding the 5 patients who had ABO-incompatible LDLTs (n = 4) or hepatic artery thrombosis (n = 1). The results of all factors analyzed are summarized in **Table S1, SDC** (http://links.lww.com/TXD/A56) with representative results presented in Table 2. Recipient and donor HLA-DR15 status was analyzed in detail, as HLA-DR 15 is more frequently reported in recipients (18/39; 46%) than the incidence of HLA-DR 15 (14.8%) in Japan. On univariate log-rank analysis, the following factors were significantly associated with PSC recurrence: younger than 30 years at the time of PSC diagnosis (P = 0.031), positive donor HLA-DR15 status (P = 0.014), positive donor and recipient HLA-DR15 status (P = 0.028), active IBD after liver transplantation (P = 0.006), and positive CMV antigenemia within 3 months after liver transplantation (P = 0.019). No other significant associations were identified, including donor-recipient blood-relationship; HLA-A-, -B-, and -DR-matched number; and IBD before liver transplantation. On multivariate analysis, active IBD after liver transplantation was retained as a significant predictor of PSC recurrence (HR, 4.86; 95% CI, 1.61-14.7; P = 0.005).

Risk Factors for Graft Failure

The same variables were analyzed to identify predictive factors of graft failure, comparing the group of patients with (n = 30) and without (n = 15) graft failure (Table 2 and **Table S1, SDC,** http://links.lww.com/TXD/A56). The following predictive factors of graft failure were identified on univariate log-rank analysis: younger than 30 years at the time of PSC diagnosis (P = 0.005), female donor (P = 0.029), HLA-DR15 positive donor and recipient status (P = 0.032), and bacteremia within 1 year after liver transplantation (P = 0.014). On multivariate analysis, younger than 30 years at the time of PSC diagnosis (HR, 3.77; 95% CI, 1.28-11.1; P = 0.016) and bacteremia within 1 year after liver transplantation (HR, 2.38; 95% CI, 1.07-5.30; P = 0.034) were retained as independent predictors.
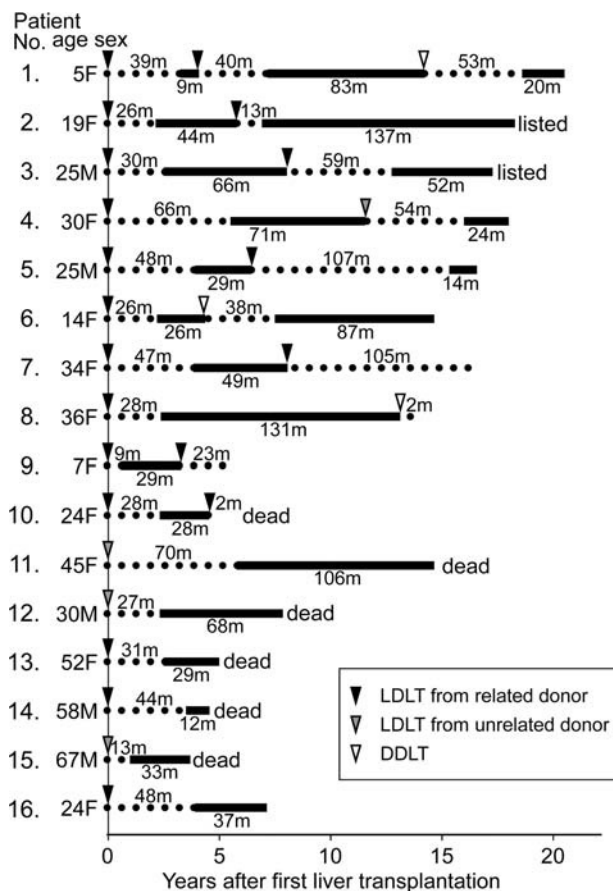
FIGURE 2. The clinical course of the 16 patients diagnosed with PSC recurrence after the first liver transplantation. Dotted and solid lines indicate the recurrence-free period and the recurrence period, respectively. Black, gray, and white arrowheads indicate LDLT from a blood-related donor, LDLT from an unrelated donor, and DDLT, respectively. Age (years) of recipients and sex (F, female; M, male) are shown. Duration of the recurrence-free period and the recurrence period are reported in months (m). Patients on the waiting list for DDLT are shown as listed.

Risk factors for PSC recurrence and graft failure on univariate analysis

Characteristics	Recurrence (16/40)		Graft failure (30/45)	
	rec/total (%)	*P*-value	failure/total (%)	*P*-value
Age at diagnosis of PSC				
< 30 y	12/25 (48%)	0.031	24/29 (83%)	0.005
≥ 30 y	4/15 (27%)		6/16 (38%)	
MELD score				
< 21	8/21 (38%)	0.560	14/25 (56%)	0.099
≥ 22	7/18 (39%)		15/19 (79%)	
Unknown	1			
Donor sex				
Female	5/13 (38%)	0.290	14/17 (82%)	0.029
Male	11/27 (41%)		16/28 (57%)	
Donor				
Unrelated	4/10 (40%)	0.828	6/11 (55%)	0.345
Related	12/30 (40%)		24/34 (71%)	
Donor				
Unrelated/related (sibling/uncle)	6/18 (33%)	0.329	11/20 (55%)	0.089
Related (parent/son)	10/22 (45%)		19/25 (76%)	
HLA-DR matched number				
0	2/6 (33%)	0.072	3/6 (50%)	0.659
1	9/28 (32%)		22/33 (67%)	
2	4/5 (80%)		4/5 (80%)	
Unknown	1		1	
HLA-DR15 (donor)				
Positive	6/22 (27%)	0.014	14/25 (56%)	0.154
Negative	9/17 (53%)		15/19 (79%)	
Unknown	1		1	
HLA-DR15 (donor and recipient)				
Positive	10/28 (36%)	0.028	18/32 (56%)	0.032
Negative	5/11 (45%)		11/12 (92%)	
Unknown	1		1	
IBD before LT				
Without	8/22 (36%)	0.391	15/24 (63%)	0.578
With	8/18 (44%)		15/21 (71%)	
Active IBD after LT				
Without	6/29 (21%)	0.006	19/32 (59%)	0.911
With	10/11 (91%)		11/13 (85%)	
CMV antigenemia within 3 mo				
Negative	8/25 (32%)	0.019	17/27 (63%)	0.188
Positive	8/15 (53%)		13/18 (72%)	
Biliary anastomotic complications within 1 y				
Without	10/33 (30%)	0.145	24/37 (65%)	0.577
With	6/7 (86%)		6/8 (75%)	
Bacteremia within 1 y				
Without	11/24 (46%)	0.605	13/25 (52%)	0.014
With	3/13 (23%)		14/17 (82%)	
Unknown	3		3	

rec., recurrence.

To evaluate the possible association between specific bacteria in blood and graft failure, a detailed analysis of blood culture to graft failure was performed, including the data from 42 patients for whom blood culture data were available (Table 3). The presence of *Enterococcus* sp ($P = 0.014$) and coagulase-negative *Staphylococcus* ($P = 0.023$) in blood culture was significantly associated with graft failure, with a tendency for graft failure for most other bacteria as well.

Association of Bacteria in Bile Culture With PSC Recurrence and Graft Failure

We next analyzed the association between bacteria in bile culture to PSC recurrence (Table 4). Among our patients who underwent liver transplantation for PSC, a bile culture was not obtained within 1-year posttransplantation in 4 patients, and the results for 3 other patients were not available. Therefore, these 7 patients were excluded from this analysis. Three

TABLE 3.

Risk factors for PSC recurrence and graft failure: Bacteria in blood culture within 1 year

Characteristics	Recurrence (14/37)		Graft failure (27/42)	
	rec./total (%)	P	Failure/total (%)	P
Gram-positive cocci				
Without	13/29 (45%)	0.399	19/32 (59%)	0.089
With	1/8 (13%)		8/10 (80%)	
Gram-negative rods				
Without	13/27 (48%)	0.225	17/29 (59%)	0.062
With	1/10 (10%)		10/13 (77%)	
Enterobacteriaceae				
Without	14/29 (48%)	0.078	20/32 (63%)	0.304
With	0/8 (0%)		7/10 (70%)	
Enterococcus sp				
Without	13/33 (39%)	0.458	23/38 (61%)	0.014
With	1/4 (25%)		4/4 (100%)	
Staphylococcus sp				
Without	14/30 (47%)	0.166	20/33 (61%)	0.071
With	0/7 (0%)		7/9 (78%)	
Coagulase-negative *Staphylococcus*				
Without	14/32 (44%)	0.345	21/35 (60%)	0.023
With	0/5 (0%)		6/7 (86%)	

(18%) of 17 patients in whom more than 2 bacterial strains were detected in bile culture within 1 year after liver transplantation had PSC recurrence, whereas 8 (50%) of 16 patients with 0 to 2 bacterial strains detected in bile culture experienced PSC recurrence after liver transplantation, suggesting that the number of bacterial strains in bile culture tended to be inversely correlated to PSC recurrence ($P = 0.068$). The detailed analysis of bacterial strains in bile culture revealed the following inverse association between the presence of bacteria/fungi in bile culture and PSC recurrence (Table 4): gram-negative rods ($P = 0.041$), *Enterobacteriaceae* ($P = 0.023$), and *Candida* sp ($P = 0.048$).

With regard to the association of bacterial strains in bile culture with graft failure (Table 4), the presence of *Klebsiella* sp in bile culture was significantly associated with graft failure ($P = 0.010$).

DISCUSSION

Based on the 20-year experience with LDLTs in our center, we report a high rate of PSC recurrence after liver transplantation and high graft mortality after PSC recurrence. The rate of graft failure at 10 years after liver transplantation, estimated by Kaplan-Meier analysis, was 67.2%. The cumulative incidence rate of PSC recurrence at 10 years after liver transplantation, analyzed by a competing risk method in our cohort, was 45.8%. Sixteen (40%) of 40 patients experienced a recurrence of PSC at a median of 30 months after liver transplantation, with 15 (94%) of these patients progressing to graft failure, even in cases of retransplantation.

A systematic review on PSC recurrence after liver transplantation reported a recurrence rate of PSC of 17% (161 of 949 patients) after liver transplantation for PSC, with a weighted recurrence rate based on the 14 studies included

in the analysis of 11%.[7] Moreover, 3 recent large multicenter studies in the United Kingdom, Germany, and the United States,[8,9,11] which included long-term clinical course outcomes after liver transplantation, reported rates of PSC recurrence and graft failures which were lower than those in our current study. Using the same methods to calculate recurrence and survival rates as in our study, Gordon et al[8] and Hildebrand et al[11] reported rates 22.4% and 36.0% for PSC recurrence, and 10.5% and 37.6% for graft failure at 10 years after liver transplantation, respectively. Ravikumar et al[9] reported that 81 (14.3%) of 679 patients who underwent a first liver transplantation for PSC developed a recurrence of PSC over a median follow-up of 9 years, with progression to graft failure identified in 37 (48.7%) patients. A Canadian single center experience by Moncrief et al[12] showed that 15 of 59 patients (25%) who underwent liver

TABLE 4.

Risk factors for PSC recurrence and graft failure: bacteria/fungi in bile culture within 1 year

Characteristics	Recurrence (11/33)		Graft failure (24/38)	
	rec./total (%)	P	Failure/total (%)	P
Gram-positive cocci				
Without	4/6 (67%)	0.065	6/7 (86%)	0.299
With	7/27 (26%)		18/31 (58%)	
Gram-negative rods				
Without	6/11 (55%)	0.041	8/13 (62%)	0.857
With	5/22 (23%)		16/25 (64%)	
Enterobacteriaceae				
Without	9/18 (50%)	0.023	13/21 (62%)	0.932
With	2/15 (13%)		11/17 (65%)	
Enterococcus sp				
Without	5/10 (50%)	0.214	8/12 (67%)	0.914
With	6/23 (26%)		16/26 (62%)	
Staphylococcus sp				
Without	8/19 (42%)	0.852	13/22 (59%)	0.146
With	3/14 (21%)		11/16 (69%)	
Klebsiella sp				
Without	10/29 (34%)	0.260	18/32 (56%)	0.010
With	1/4 (25%)		6/6 (100%)	
Enterococcus faecium				
Without	8/18 (44%)	0.183	14/21 (67%)	0.850
With	3/15 (20%)		10/17 (59%)	
Coagulase-negative *Staphylococcus*				
Without	9/22 (41%)	0.725	16/26 (62%)	0.250
With	2/11 (18%)		8/12 (67%)	
Alpha-streptococcus				
Without	9/26 (35%)	0.506	20/30 (67%)	0.284
With	2/7 (29%)		4/8 (50%)	
Enterobacter cloacae				
Without	9/22 (41%)	0.072	17/26 (65%)	0.370
With	2/11 (18%)		7/12 (58%)	
Pseudomonas aeruginosa				
Without	7/24 (29%)	0.923	17/27 (63%)	0.459
With	4/9 (44%)		7/11 (64%)	
Candida sp				
Without	11/27 (41%)	0.048	22/32 (69%)	0.192
With	0/6 (0%)		2/6 (33%)	

transplantation for PSC developed PSC recurrence in a median follow-up of 68 months, with a rate of graft failure at 10 years after liver transplantation of 32.4%. Compared with these studies, our results clearly demonstrated a higher rate of PSC recurrence and higher rate of graft failure.

The specific reasons for the higher rate of PSC recurrence in our institute are unknown. The clinical characteristics of our study participants and our study design, including follow-up periods, protocol of immunosuppression, procedure for liver transplantation, and diagnostic criteria for PSC recurrence, are not different from those of previous reports.[4-9] Our accuracy in diagnosis for PSC recurrence is also unquestionable, with all patients with PSC recurrence experiencing a rapid progression in disease status after diagnosis, these clinical findings providing evidence of PSC recurrence. Moreover, the diagnosis was confirmed by histopathological examination of the extracted liver graft at the time of retransplantation. The fact that PSC rerecurrence after retransplantation occurred in most of recipients is indicative of the likelihood of an important contribution of recipient-specific factors to recurrence of PSC. It is possible that ethnicity will be an important contributing factor to consider, with all of our patients being Japanese. Characteristics of PSC in Japan were revealed by a recent nationwide survey, identifying a second peak of PSC in the sixth decade of life and a low prevalence of IBD (37%).[13] These results suggest differences in Japanese patients with PSC from those in the United States and in European countries. Race-specific differences might, therefore, explain the higher recurrence rate of PSC in our study group than in other previously reported studies. A report from another Japanese institute confirms this possibility, with PSC recurrence identified in 4 of 9 patients after liver transplantation.[14]

HLA typing is one of the factors that varies among races. We confirmed the importance of donor HLA-DR15 for PSC recurrence in our current study, which was in agreement with our findings in a previous study.[5] This result suggests that HLA, or other genes located around HLA, in the liver (or bile duct) plays an important role in the pathogenesis of PSC. Since the donor HLA-DR15 contained both HLA-DR1501 and HLA-DR1502, as analyzed in our previous report,[5] the association between liver HLA and PSC recurrence would not be caused by HLA-DR15 itself, but by the other genes associated with HLA-DR15.

As mentioned above, the nationwide survey of Japanese patients with PSC identified 2 age peaks for PSC occurrence, one at 35 to 40 years of age and the other at 65 to 70 years of age.[13] In our current study, the median age of the study population at the time of diagnosis of PSC was 23 years (range, 1-60 years). Therefore, the majority of patients who underwent liver transplantation for PSC were in the younger age peak. In fact, we identified age <30 years at the time of PSC diagnosis as a risk factor of PSC recurrence and graft failure after liver transplantation. Therefore, Japanese patients with PSC can be divided into several subpopulations, with young PSC patients being susceptible to PSC recurrence after transplantation and likely to form a typical PSC subpopulation.

Active IBD after liver transplantation was identified as a factor for PSC recurrence on multivariate analysis. Because the presence and activity of IBD before transplantation is not associated with PSC recurrence after transplantation, the development of IBD activity after liver transplantation

may have a causative relationship to PSC recurrence. Interestingly, Hildebrand et al[11] reported results compatible to ours, demonstrating that patients with IBD, ulcerative colitis, and, in particular, those with an active colitis after liver transplantation were at a significantly higher risk for PSC recurrence. Furthermore, Alabraba et al[4] reported that patients who underwent colectomy, before or during liver transplantation, were significantly less likely to develop PSC recurrence than patients who did not undergo colectomy at the time of transplantation or underwent colectomy postliver transplantation. From these results, we can consider that maintaining a remission state of IBD after liver transplantation may be a key protective factor against PSC recurrence after liver transplantation.

In our current study, we extensively analyzed the association between bacteria in bile and blood cultures with PSC recurrence and graft failure after liver transplantation. Surprisingly, positive findings of some bacteria/fungi in bile culture were negatively associated with PSC recurrence, indicating that these bacteria in bile after liver transplantation may exert a protective role against PSC recurrence. We suspect that stenosis of the biliary anastomosis would lower the bacteria in bile culture and could be involved in the pathogenesis of PSC recurrence. However, we did not identify a significant relationship between biliary anastomotic complication and the number of bacteria in bile culture. There might be a mechanism by which an early immune response to bacteria in bile duct would increase tolerance to an autoimmune reaction later. Overall, however, bacteremia within 1 year of liver transplantation was a significant risk factor for graft failure. Because most bacteria species in blood cultures were associated with an increased risk of graft failure, bacteremia itself, and not specific bacteria, would be a cause high mortality.

Initially, we expected that immunosuppressants used after liver transplantation might have been effective in offering protection from PSC recurrence, as well as in suppressing the progression of PSC after recurrence. Therefore, we analyzed the relationship between immunosuppressant therapy and PSC recurrence and graft failure in detail. However, we did not identify any effect of immunosuppressants on the rate of PSC recurrence or graft failure. It is possible that a more intensive immunosuppression therapy will be effective in preventing PSC recurrence and/or its progression. However, high dose of immunosuppressants would increase the risk of infection, with bacteremia itself being a risk factor for graft failure after liver transplantation, as we report in our study.

Limitations of this study were the retrospective study design and small sample size. Because the medical record did not include the detailed clinical information, such as the frequency of defecation and the erythrocyte sedimentation rate, the severity of IBD could not be analyzed. We have previously reported our 10-year experience with liver transplantation among 30 patients with PSC in 2009, and this report is an extension of the previous analysis.

In conclusion, PSC frequently recurred and progressed to graft failure after liver transplantation for PSC. Both genetic factors, including liver HLA type, and environmental factors, including IBD, CMV, and bacteria in bile duct, would contribute to the recurrence of PSC as well as to its progression. Maintaining an inactive status of IBD might offer protection against PSC recurrence. Further studies with a larger number

of patients are required to clarify the risk factors for PSC recurrence in Japan and other Asian countries.

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