Recurrent Primary Sclerosing Cholangitis in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study: Comparison of Risk Factors Between Living and Deceased Donor Recipients

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Primary sclerosing cholangitis (PSC) recurs in 15%-25% of patients transplanted for PSC. In the United States, PSC transplant patients are more likely to receive an organ from a living donor (LD) than patients without PSC. Our aims were to (1) compare risk of PSC recurrence in LD versus deceased donor recipients and (2) identify risk factors for PSC recurrence. There were 241 living donor liver transplantations (LDLTs) and 65 deceased donor liver transplantation (DDLT) patients transplanted between 1998 and 2013 enrolled in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study who were evaluated. PSC recurrence risk for LDLT and DDLT recipients was compared using Kaplan-Meier survival curves and log-rank tests. Cox models were used to evaluate PSC risk factors. Overall PSC recurrence probabilities were 8.7% and 22.4% at 5 and 10 years after liver transplantation (LT), respectively. The risk of PSC recurrence was not significantly different for DDLT versus LDLT recipients ($P = 0.36$). For DDLT versus LDLT recipients, unadjusted 5- and 10-year PSC recurrence was 9.4% versus 9.5% and 36.9% versus 21.1%. Higher laboratory Model for End-Stage Liver Disease (MELD) score at LT, onset of a biliary complication, cholangiocarcinoma, and higher donor age were associated with increased risks of PSC recurrence: for MELD (hazard ratio [HR] = 1.06; 95% confidence interval [CI] 1.02-1.10 per MELD point, $P = 0.002$); for biliary complication (HR, 2.82; 95% CI, 1.28-6.25; $P = 0.01$); for cholangiocarcinoma (HR, 3.98; 95% CI, 1.43-11.09; $P = 0.008$); for donor age (per 5-years donor age; HR, 1.17; 95% CI, 1.02-1.35; $P = 0.02$). Factors not significantly associated with PSC recurrence included the following: first-degree relative donor ($P = 0.11$), post-LT cytomegalovirus infection ($P = 0.38$), and acute rejection ($P = 0.22$). Risk of recurrent PSC was not significantly different for DDLT and LDLT recipients. Biliary complications, cholangiocarcinoma, MELD, and donor age were significantly associated with risk of PSC recurrence.

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Since the initiation of Model for End-Stage Liver Disease (MELD) score–based allocation of liver organs in 2002, patients with primary sclerosing cholangitis (PSC) have been significantly more likely to receive a living donor liver transplantation (LDLT) when compared with patients without PSC.[1] In fact, since 2002, nearly 15% of transplant recipients with PSC in the United States received an LDLT, compared with 4% of non-PSC patients, despite PSC patients

comprising only 6% of the population receiving a deceased donor liver transplantation (DDLT).[1]

Recent data from Japan demonstrated a 25% risk of recurrent PSC in LDLT recipients, with a significantly increased risk when the living donor (LD) was a first-degree relative of the recipient.[2] Additional risk factors for recurrence included higher MELD scores at transplant, postoperative cytomegalovirus (CMV) infections, and early biliary anastomotic complications. Importantly, in this cohort, recurrent PSC was associated with a higher risk of graft loss. Despite the potential risk of recurrent PSC, a recent analysis of all transplant recipients in the United States showed that, among transplant recipients with cholestatic liver disease (PSC or primary biliary cirrhosis), recipients of an LDLT had significantly higher posttransplant graft and patient survival compared with those who received DDLT.[3] Analysis using data from the national Organ Procurement and Transplantation Network, which does not collect data on recurrent PSC, showed superior graft and patient survival among LDLT recipients with PSC, in contrast to the Japanese report that revealed high PSC recurrence rates and graft loss in LDLT recipients.

It is of great importance to validate these findings in a North American cohort, as donor-relatedness is a potentially modifiable risk factor in 2 ways. First, if the relationship applies to North American patients, LDLT recipients with more than 1 potential LD could be counseled to preferentially accept a nonrelated donor in order to reduce the risk of posttransplant PSC recurrence. Second, for those whose only potential donor is a first-degree relative, consideration of deferring LDLT and waiting for a DDLT and/or a potential donor swap might be options. In contrast, if the risk of recurrent PSC in those who receive a liver from a first-degree related donor in North America is much lower, then this issue should not affect donor selection. Thus, we used data from the only large multicenter prospective cohort of LDLT in North America, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL), to estimate the risk of recurrent PSC in North American LDLT recipients and to identify risk factors for recurrence.

Patients and Methods

STUDY POPULATION

Patients in this study underwent transplantation for PSC between January 1, 1998, and July 31, 2013, at all centers participating in A2ALL. A2ALL is an observational cohort study designed to investigate outcomes in both donors and recipients of adult-to-adult LDLT, with comparison to DDLT recipients who had an LD evaluated. A2ALL was carried out in 2 phases: A2ALL-1 (January 1, 1998 to August 31, 2009, which included both LDLT and DDLT recipients) and A2ALL-2 (September 1, 2009 to January 31, 2014, which continued follow-up of A2ALL-1 LDLT and DDLT recipients and included new LDLT recipients). Nine North American centers were involved in each phase, with 6 centers spanning both phases. This analysis includes patients transplanted for PSC at 1 of the 9 A2ALL-2 centers (8 US centers, 1 Canadian center). At the 3 new A2ALL-2 centers, non-A2ALL recipients (both LDLT and DDLT) transplanted for PSC during the A2ALL-1 time period were included in the PSC study by waiver of consent if they met the A2ALL-1 entry criteria of having had at least 1 potential LD evaluated. Patients in the 3 A2ALL-1 centers that were not part of A2ALL-2 were not included.

Both retrospective and prospective data were collected as part of A2ALL. The current study required data in addition to that collected as part of A2ALL. These data, as well as imaging reports documenting PSC recurrence and biliary complications, were

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obtained through detailed chart review under a waiver of consent. Data fields specific to the PSC substudy included the following: PSC type, inflammatory bowel disease, colectomy, cholangiocarcinoma, CMV status, immunosuppression, rejection, surgical technique, and PSC recurrence. Immunosuppression was at the discretion of each center. Each center and the data coordinating center had study protocols and consents approved by the institutional review board prior to collection and analysis of data.

Recurrent PSC, the primary outcome of interest, was defined using the Graziadei criteria, which require the following: confirmed diagnosis of PSC prior to transplantation and either cholangiography demonstrating multiple biliary strictures >90 days after transplantation or biopsy findings of fibrous cholangitis and/or fibro-obliterative lesions, in the absence of hepatic artery thrombosis/stenosis, chronic ductopenic rejection, isolated anastomotic strictures, nonanastomotic strictures prior to posttransplant day 90, and donor-recipient blood-type incompatibility.[4] "Biliary complication" was defined as anastomotic stricture, bile leak, or biliary cast after transplantation. All data needed to define recurrent PSC were captured from each center using a standardized data form, with the case definition being adjudicated by each site's primary investigator. Secondary outcomes were graft failure and death. Graft failure was defined as retransplantation or death.

STATISTICAL METHODS

Study patients were followed from the time of transplant to the time of either death or chart review, whichever was earliest. Descriptive statistics are given as means and standard deviations (SDs) for continuous variables or as frequencies and percentages for categorical variables. Differences between DDLT and LDLT were compared using t tests for continuous characteristics and chi-square tests for categorical characteristics. Probabilities of PSC recurrence, retransplant, or death as the first event were displayed with a cumulative incidence graph using competing risks methods. To specifically examine PSC recurrence and risk factors associated with recurrence, we estimated cause-specific outcomes, censoring at retransplant and death.

Potential factors associated with PSC recurrence were examined with multivariate Cox regression models stratified by donor type (DDLT, LDLT). The best subsets selection method was used to find parsimonious models. The following covariates were included in the model selection process: degree of relatedness between donor and LDLT recipient (first-degree relative versus all others); time-dependent biliary complication; immunosuppression; time-dependent rejection and rejection treatment; recipient age, sex, race, ethnicity, and blood type; MELD score at transplant; PSC type; pretransplant colectomy; ulcerative colitis; cholangiocarcinoma; cold ischemia time; warm ischemia time; presence of Roux-en-Y anastomosis; number of biliary anastomoses; and donor age, sex, race, ethnicity, and blood type. A history of a biliary complication was a time-dependent covariate, as the complication itself may have led to an inflammatory cascade, and/or discovery of recurrent PSC. Because donation by a first-degree relative has been previously shown to be associated with PSC recurrence, we forced inclusion of that covariate in 1 model. To examine the association of PSC recurrence with the outcomes of graft failure and death, Cox regression models with time-dependent covariates for PSC recurrence were used.

Statistical analyses were carried out using SAS, version 9.4 (SAS Institute, Cary, NC). The cumulative incidence function was calculated using the comprisk macro available from the Mayo Clinic.[5] Results with a 2-sided P value of ≤0.05 were considered statistically significant.

Results

PATIENT CHARACTERISTICS

The characteristics of the PSC study sample are shown in Table 1 separately for recipients of DDLTs (n = 65) and LDLTs (LD; n = 242). The distributions of donor and recipient race and ethnicity were significantly different between DDLT and LDLT, with higher percentages of African Americans (9.2% versus 4.1%) and Hispanics/Latinos (12.3% versus 2.5%) for DDLT compared with LDLT. DDLT recipients had a higher mean laboratory MELD score at transplant than LDLT recipients 20.2 versus 14.7, respectively ($P < 0.001$). Mean cold and warm ischemia times were significantly longer for DDLT than LDLT grafts. The use of Roux-en-Y type biliary anastomoses were more common in LDLT procedures than DDLT (90.5% versus 75.4%, $P = 0.001$).

There were 121 patients treated for 181 episodes of acute cellular rejection (ACR): 87 LDLT recipients were treated for 127 episodes, and 34 DDLT recipients were treated for 54 episodes of ACR. The proportions of patients with ACR was similar between LDLT and DDLT recipients. Chronic rejection was

TABLE 1. Characteristics of Study Population

	DDLT (n = 65)	LDLT (n = 242)	P Value
Recipient characteristics			
Recipient age, years	45.7 (13.8)	44.4 (13.1)	0.45
Female recipient	15 (23.1)	77 (31.8)	0.17
Recipient race			0.01
Asian	1 (1.5)	5 (2.1)	
African American	6 (9.2)	10 (4.1)	
Native American	0 (0.0)	1 (0.4)	
White	47 (72.3)	195 (80.6)	
Multiracial	3 (4.6)	0 (0.0)	
Unknown	8 (12.3)	31 (12.8)	
Recipient ethnicity			0.002
Hispanic/Latino	8 (12.3)	6 (2.5)	
Non-Hispanic/non-Latino	43 (66.2)	194 (80.2)	
Unknown	14 (21.5)	42 (17.4)	
PSC type			0.11
Intrahepatic	25 (38.5)	127 (52.5)	
Extrahepatic	1 (1.5)	12 (5.0)	
Intrahepatic and extrahepatic	36 (55.4)	96 (39.7)	
Small duct	2 (3.1)	3 (1.2)	
Unknown	1 (1.5)	4 (1.7)	
Laboratory MELD at transplant	20.2 (9.0)	14.7 (7.2)	<0.001
Inflammatory bowel disease			0.32
Ulcerative colitis	33 (50.8)	134 (55.4)	
Crohn's disease	8 (12.3)	37 (15.3)	
Indeterminate	0 (0.0)	5 (2.1)	
None	24 (36.9)	66 (27.3)	
Cholangiocarcinoma found at or before transplant	4 (6.2)	22 (9.1)	0.45
Transplant and donor characteristics			
Donor age, years	42.5 (19.7)	38.0 (10.2)	0.12
Female donor	26 (40.0)	113 (46.7)	0.34
Donor race			<0.001
Asian	1 (1.5)	4 (1.7)	
Black	4 (6.1)	9 (3.7)	
White	43 (66.2)	214 (88.4)	
Unknown	17 (26.2)	15 (6.2)	
Donor ethnicity			<0.001
Hispanic/Latino	3 (4.6)	5 (2.1)	
Non-Hispanic/non-Latino	19 (29.2)	215 (88.8)	
Unknown	43 (66.1)	22 (9.1)	
LDLT graft type			
Right lobe	NA	227 (93.8)	
Left lobe		12 (4.9)	
Left lateral segment		2 (0.8)	
Unknown		1 (0.4)	
DDLT donor type			
Missing	3 (4.6)	NA	
DBD	60 (92.3)		
DCD	2 (3.0)		
Donor relationship to recipient			
First-degree LDLT	NA	120 (49.6)	
Other blood relative LDLT		23 (9.5)	
Other LDLT		99 (40.9)	
Cold ischemia time, minutes	489.3 (170.9)	80.8 (81.2)	<0.001
Warm ischemia time, minutes	45.8 (32.8)	36.2 (13.6)	0.03
Type of biliary anastomosis			0.001
All duct-to-duct	16 (24.6)	23 (9.5)	
At least 1 Roux-en-Y	49 (75.4)	219 (90.5)	

NOTE: Data are given as mean (SD) or n (%).
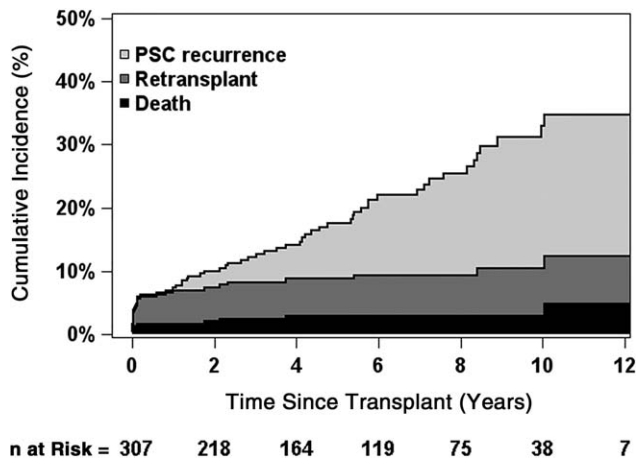
FIG. 1. Overall risk of PSC recurrence, death, and retransplant for LT recipients with PSC, based on the cumulative incidence function (n = 307).

also similar between LDLT and DDLT recipients (4.5%, respectively).

There were 26 patients diagnosed with cholangiocarcinoma at (n = 6) or before (n = 20) transplant. Of these, 5 (19.2%) had recurrence of cholangiocarcinoma. Among these 5, 1 had PSC recurrence 2.25 years after transplant, and all 5 died at a median of 2.4 years.

OVERALL OUTCOMES

Median follow-up time was 5 years, and maximum follow-up time was 15 years. The cumulative incidence of death, retransplant, and PSC recurrence is shown in Fig. 1. Fifty-four percent of retransplants were performed within 3 months of the primary transplant. PSC recurrence tended to occur later after transplant; only 1 recurrence was observed within 1 year after transplant. The respective cumulative incidences at 1, 3, 5, and 10 years were 1.6%, 2.5%, 3.0%, and 3.0% for death; 5.4%, 5.8%, 5.8%, and 7.5% for retransplant; and 0.3%, 4.0%, 8.7%, and 22.4% for PSC recurrence. Recurrence-free survival probabilities (alive with original graft and no PSC recurrence) at 1, 3, 5, and 10 years were 92.7%, 87.7%, 82.5%, and 67.0%, respectively.

PSC RECURRENCE BY DONOR TYPE

Overall, there were 34 recorded patients of recurrent PSC in the study group, 24 in LDLT recipients, and
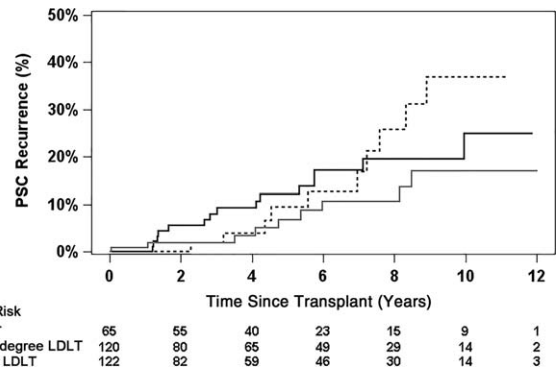
FIG. 2. Probability of PSC recurrence by DDLT, first-degree relative donors, and nonfirst-degree relative donors (censored at graft failure).

10 in DDLT recipients. The diagnosis of recurrence was made by contrast cholangiography in 8, by computed tomography or magnetic resonance imaging in 14, and by histology in 15 (3 patients were diagnosed with 2 methods). Time to PSC recurrence, censored at retransplant or death, is shown by group in Fig. 2 for DDLT, first-degree relative LDLT, and other LDLT. There was no significant difference in recurrence rate among the 3 groups (log-rank $P = 0.36$), between all LDLT recipients compared with DDLT recipients ($P = 0.36$), or between first-degree relative and other LDLT ($P = 0.25$).

RISK FACTORS FOR PSC RECURRENCE (UNIVARIATE MODELS)

In univariate models, PSC recurrence was significantly associated with the time-dependent onset of a biliary complication, including stricture, leak, or biliary cast (hazard ratio [HR], 2.69; 95% confidence interval [CI], 1.23-5.85; $P = 0.01$), the presence of cholangiocarcinoma (HR, 3.27; 95% CI, 1.24-8.62; $P = 0.02$), higher MELD at transplantation (HR, 1.04 per point; 95% CI, 1.00-1.08; $P = 0.04$), and donor age (HR, 1.16 per 5 years; 95% CI, 1.02-1.32; $P = 0.02$; Table 2).

RISK FACTORS FOR PSC RECURRENCE (MULTIVARIATE MODELS)

Multivariate Cox regression using best subset selection was performed to identify risk factors for

TABLE 2. Cox Models of Time to PSC Recurrence, Stratified by Donor Type (Living Versus Deceased)

Factor	Single-Factor Models			Multivariate Model*		
	HR	95% CI	P Value	HR	95% CI	P Value
Time-dependent biliary complication	2.69	1.23-5.85	0.01	2.82	1.28-6.25	0.01
Cholangiocarcinoma diagnosed at or before transplant	3.27	1.24-8.62	0.02	3.98	1.43-11.09	0.008
Laboratory MELD at transplant (per point higher)	1.04	1.00-1.08	0.04	1.06	1.02-1.10	0.002
Donor age (per 5 years older)	1.16	1.02-1.32	0.02	1.17	1.02-1.35	0.02
First-degree related donor	1.62	0.71-3.71	0.25			
Recipient age (per 5 years older)	0.95	0.82-1.10	0.49			
Female donor	0.82	0.41-1.65	0.58			
Female recipient	0.49	0.20-1.20	0.12			
Donor race nonwhite	1.72	0.41-7.27	0.46			
Recipient race nonwhite	1.02	0.24-4.29	0.98			
Recipient Hispanic/Latino	0.49	0.07-3.60	0.48			
Time-dependent rejection	1.54	0.78-3.05	0.22			
Posttransplant CMV	0.39	0.05-2.88	0.38			
>1 biliary anastomosis	1.56	0.70-3.46	0.28			
Roux-en-Y anastomosis	1.42	0.48-4.21	0.53			
Cold ischemia time (per hour)	0.92	0.76-1.11	0.39			
Ulcerative colitis or Crohn's disease	1.00	0.49-2.07	>0.99			
Pretransplant colectomy performed	1.02	0.40-2.66	0.96			
Steroid	0.60	0.29-1.24	0.17			
Sirolimus or everolimus	0.70	0.17-2.93	0.63			
Azathioprine or mycophenolate mofetil or mycophenolic acid	1.51	0.77-2.96	0.23			

*Covariates for multivariate model were selected based on best subset selection method.

posttransplant PSC recurrence in liver transplantation (LT) recipients. A parsimonious 4-variable model demonstrated that time-dependent onset of a biliary complication, higher MELD scores at transplant, higher donor age, and the presence of pretransplant cholangiocarcinoma had statistically significant associations with higher risk of PSC recurrence (Table 2). To test whether the degree of donor-relatedness was associated with PSC recurrence, we added a covariate for first-degree related donor to the model specified above. The estimated HR for first-degree relative was 1.99 (95% CI, 0.86-4.64) compared with other LDLT recipients, but this result was not statistically significant ($P = 0.11$). Adding the first-degree related donor term to the model resulted in only very small changes to the parameter estimates for the other factors in the model.

RISK FACTORS FOR GRAFT FAILURE AND MORTALITY (MULTIVARIATE MODELS)

There were 59 graft failures (26 retransplants and 33 deaths) and 43 deaths (10 following retransplant) recorded during posttransplant follow-up. Multivariate models using time-dependent PSC recurrence as a predictor of graft failure and death with covariate selection informed by the best subset method

demonstrated the following risk factors for graft failure: time-dependent PSC recurrence (HR, 4.16; 95% CI, 1.75-9.86; $P = 0.001$), time-dependent biliary complication (HR, 4.00; 95% CI, 2.17-7.36; $P < 0.001$), cholangiocarcinoma diagnosed at or before transplantation (HR, 4.01; 95% CI, 2.12-7.57; $P < 0.001$), laboratory MELD at transplant (HR, 1.03 per point increase; 95% CI, 1.00-1.054; $P = 0.05$), and donor age (1.15 per 5 years older; 95% CI, 1.03-1.27; $P = 0.01$). Risk factors for death included time-dependent PSC recurrence (HR, 2.70; 95% CI, 1.01-7.25; $P = 0.049$), time-dependent biliary complications (HR, 3.21; 95% CI, 1.59-6.50; $P < 0.001$), cholangiocarcinoma diagnosed at or before transplantation (HR, 6.85; 95% CI, 3.44-13.62; $P < 0.001$), laboratory MELD at transplant (HR, 1.03 per point increase; 95% CI, 1.00-1.06; $P = 0.08$), and donor age (1.10 per 5 years older; 95% CI, 0.97-1.24; $P = 0.15$).

PATIENT AND GRAFT SURVIVAL AFTER PSC RECURRENCE

For those patients with documented PSC recurrence, the 5-year unadjusted patient and graft survival probabilities were 66.5% and 56.8%, respectively. There were no statistically significant survival differences after PSC recurrence between living donor (LD) and
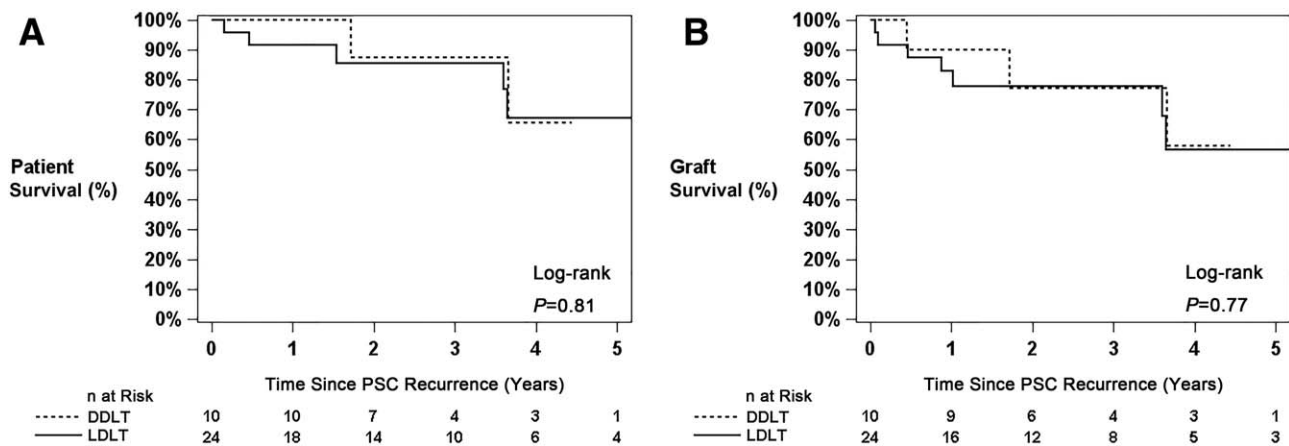
FIG. 3. (A) Patient and (B) graft survival following recurrence of PSC after LT.

deceased donor (DD) recipients (Fig. 3) for patient survival ($P = 0.81$) or graft survival ($P = 0.77$).

Discussion

As an immune-mediated liver disease, PSC may be affected by LT in several ways. The transplanted organ brings with it innumerable immune features such as cellular antigens, passenger lymphocytes, DNA, and infectious agents. The recipient immune system, including the presence of inflammatory bowel disease, prior surgery, prior infection exposure, and sex, may play a role in PSC recurrence.[6] Transplantation issues, including ischemia time, immunosuppression, type of biliary anastomosis, and hepatic artery thrombosis, may potentially affect the liver allograft.[7] Weismüller et al.[6] postulated that the etiopathogenesis of PSC was multifactorial and included genetics (human leukocyte antigen [HLA]), autoimmunity, and inflammation caused by infectious agents. Recipients of first-degree relative donor organs may have increased exposure to these factors. Differences in these characteristics may exist between LDLT and DDLT recipients. In this study, we were able to investigate these characteristics in a large North American cohort of LDLT and DDLT recipients transplanted for PSC.

In 2007, the first case series examining LDLT outcomes in 8 PSC patients, as part of a larger report on LDLT from Tokyo, was published. All received a related-donor allograft, and 4/8 (50%) had recurrent PSC after a mean of 3.3 years.[8] In a retrospective, single-center North American cohort, Kashyap et al.[9] compared outcomes in 14 LDLT and 44 DDLT

patients transplanted for PSC. The LDLT recurrence rate was 28% with a mean follow-up of time of 41.5 ± 24.8 months. The DDLT recurrence rate was 16% with a mean follow-up of 57.2 ± 35.9 months ($P = 0.29$). Among biologically related donors, the rate of recurrence was 37%. Retransplantation rates for LDLT and DDLT were similar (7% versus 20%; $P = 0.25$). One-, 3-, and 5-year patient and graft survivals were also similar in the 2 groups (96%, 90%, 88% and 89%, 83%, 81%, respectively). A 2010 analysis of the United Network for Organ Sharing database, including 972 recipients of DDLT and 185 recipients of LDLT for PSC, demonstrated similarly high 1- and 5-year patient and graft survivals but did not assess for PSC recurrence.[10]

In our study, we observed 5- and 10-year PSC recurrence rates of 9.5% and 21.1%, respectively, for LDLT recipients. This compares favorably to the Japanese cohort, which had recurrence rates of 32% at 5 years and 52% at 10 years.[2] This may be attributable to differing baseline population characteristics, surgical technique, or application of the definition of recurrent PSC to the data set. The risk of PSC recurrence was not significantly different in LDLT and DDLT recipients, and we observed excellent 1-, 3-, and 5-year recurrence-free survival rates (92.7%, 87.7%, and 82.5%, respectively). In patients with PSC recurrence, 1-, 3-, and 5-year patient and graft survivals were 94.1%, 85.9%, 66.5% and 85.0%, 77.3%, 56.8%, respectively. These rates also compare favorably to the Japanese cohort with recurrent PSC, who had graft survivals of 54% at 3 years and 39% at 5 years.[2]

Factors associated with increased risk of recurrent PSC after LDLT shared some similarities with the Japanese study[2]: MELD score at the time of transplantation and the occurrence of biliary complications. In addition, the present study demonstrated that donor age and cholangiocarcinoma were important recurrence risk factors. Pretransplant treatment of cholangiocarcinoma may result in chemotherapy-induced changes in the native hepatic artery, resulting in secondary sclerosing cholangitis in the transplanted liver, making it difficult to differentiate from recurrent PSC.[11,12]

Interestingly, Egawa et al.[2] found that a first-degree relationship between donor and recipient was statistically significant in predicting recurrence of PSC with an HR of 2.61. In the present study, although we noted a trend in the same direction, the HR of 1.99 for this association was not statistically significant. We investigated this further by excluding donor age from the model (LDLT donor age was 35 compared with DDLT donor age 42, $P < 0.001$) and still did not find a significant result (HR, 1.60; $P = 0.27$). Another possible explanation for the discrepant finding between the 2 studies may be a difference in definition of first-degree relative. The Japanese study limited first-degree relatives to the parent/child relationship, whereas the present study also included sibling donors. Application of the Japanese definition of first-degree relative to the present study data yielded an HR of 1.52 and $P = 0.39$ in our patient population. Similarly, applying the present study's definition of first-degree relative, but using the Japanese study's significant variables, the HR for first-degree relative was 1.68 and the P value was 0.22. This suggests that expansion or limitation of the definition of first-degree relative did not alter the findings of either study. The broader implication is that the North American and Japanese population may indeed differ with regard to risk of PSC recurrence.

Limitations of this study include the modest absolute number of PSC recurrences despite a large cohort. This may have resulted in underpowering of tests of the association of first-degree relative with PSC recurrence. Additionally, the recipients of DD livers may not be truly representative of all transplant candidates on the waiting list. This possibility was explored by Berg et al.,[13] who found there was no significant difference in portal hypertensive complications between those in whom LD was seriously contemplated and those who did not have a potential LD. Patients with pretransplant cholangiocarcinoma may have undergone more intensive posttransplant monitoring, which could result in a higher chance of discovering PSC recurrence. The diagnosis of recurrent PSC was made retrospectively by chart review using a standardized form, which created the potential for missing cases of recurrent PSC that were not identified in real-time. However, given that these LDLT recipients had frequent laboratory tests, an elevated alkaline phosphatase suggesting the potential for recurrent PSC would be easily identified, and it is likely that we captured most, if not all, cases of recurrent PSC. We were unable to collect adequate HLA data to assess its potential association with PSC recurrence.

In conclusion, our data do not support the notion that live donation from a first-degree relative increases the risk of recurrent PSC. When investigating the identified risk factors for recurrent PSC, no difference was seen between the LD and DD recipient groups. Attempts should be made by transplant centers to address modifiable pretransplant variables. These would include transplantation at lower MELD scores and younger donor age, both of which may be controllable with LDLT, and limitation of transplantation for cholangiocarcinoma to only optimized candidates. In addition, future studies investigating the observed differences between North American and Asian patients may yield further insight into the pathophysiology of PSC.

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