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Severe Cholestasis Predicts Recurrent Primary Sclerosing Cholangitis Following Liver Transplantation

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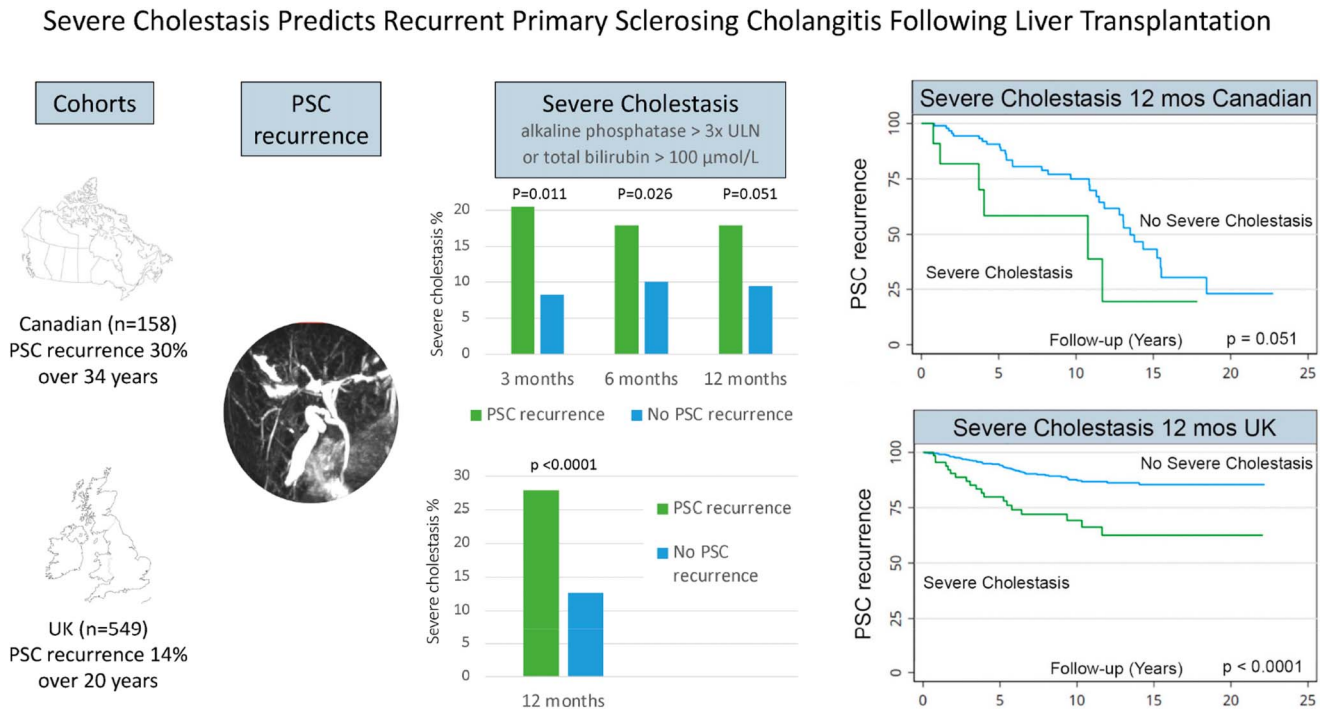
INTRODUCTION: **Primary sclerosing cholangitis (PSC) may reoccur following liver transplantation (LT), and the diagnosis established once imaging studies demonstrate the diagnostic cholangiographic appearance. To evaluate whether the development of recurrent PSC (rPSC) is associated with cholestasis soon after LT, we studied whether changes in hepatic biochemistry within the first 12 months were linked with the development of rPSC and graft loss.**



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METHODS: **We conducted a retrospective cohort analysis of 158 transplant recipients with PSC in Canada and 549 PSC transplant recipients from the United Kingdom. We evaluated serum liver tests within 12 months after LT and the subsequent development of a cholangiographic diagnosis of rPSC as a time-dependent covariate using Cox regression. Severe cholestasis was defined as either alkaline phosphatase > 3× upper limit of normal or total bilirubin > 100 μmol/L.**

RESULTS: **Patients who developed rPSC were more likely to have severe cholestasis vs those without at 3 months (20.5% vs 8.2%, $P = 0.011$), at 6 months (17.9% vs 10.0%, $P = 0.026$), and 12 months (15.4% vs 7.8%, $P = 0.051$) in the Canadian cohort and at 12 months in the UK cohort (27.9% vs 12.6%, $P < 0.0001$). By multivariable analysis, development of severe cholestasis in the Canadian cohort at 3 months (hazard ratio [HR] = 2.41, $P = 0.046$) and in the UK cohort at 12 months (HR = 3.141, $P < 0.0001$) was both associated with rPSC. Severe cholestasis at 3 months in the Canadian cohort was predictive of graft loss (HR = 3.88, $P = 0.0001$).**

DISCUSSION: **The development of cholestasis within 3–12 months following LT was predictive of rPSC and graft loss.**

KEYWORDS: cholestatic liver disease; hepatic transplantation; graft survival; semi-Markov model; illness-death model

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D369

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BILIARY

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease characterized by extrahepatic and intrahepatic biliary strictures (1,2). The etiology of PSC is complex, and disease is believed to occur as a combination of genetic predisposition, alterations in gut microbiome, biliary homeostasis, and potential environmental agent(s) (1,3,4). A role for autoimmunity has been proposed based on the genetic risk with other autoimmune diseases, the presence of autoantibodies, and that elevated IgG4 provides a worse prognosis (5–7). Up to 80% of patients have comorbid inflammatory bowel disease (IBD). There is no effective treatment apart liver transplantation (LT) for end-stage liver disease, and even then, patients may develop recurrent PSC (rPSC).

The prevalence of rPSC has been reported to range from 6% to 60% following LT with a median recurrence rate of 20%–25% within 10 years (1,8–15). The need to study risk factors linked with recurrence is underscored by reports that the development of rPSC contributes to a four-fold increased risk of early graft loss (8,9). These risk factors also provide some insight into disease pathogenesis, such as the presence of active IBD or cholangitis either before or after transplantation, which has fueled the debate whether an infectious agent in the colon or other inflamed tissues may subsequently infect the allograft (14–17). The influence of other factors on rPSC, such as use of specific immunosuppression, has been inconsistent. Repeated episodes of acute allograft rejection and the augmented use of immunosuppression both appear to be linked with rPSC (15,16), but as observed with other inflammatory liver disorders, recurrent disease in the allograft is accompanied by alloimmunity and therefore difficult to distinguish from recurrent disease (18,19).

Evaluation of rPSC provides an opportunity to study early events in the disease process. By convention, it is challenging to identify rPSC within the first 3 months following LT because of its close resemblance to reperfusion or preservation-induced ischemic cholangitis (12). Because cholestasis at 3 months following LT has been linked with increased risk of rPSC and decreased graft survival (20), we hypothesized that the development of early cholestasis may be associated with rPSC and the degree of cholestasis may be associated with the development of graft loss in patients transplanted for PSC.

In this study, we evaluated the cumulative probability of rPSC and its association with abnormal serum liver tests within the first 12 months following LT, in patients undergoing LT in Western Canada and used a large UK validation cohort, to establish the impact of early cholestasis on graft loss and mortality.

METHODS

Ethics approval

We followed the principles as outlined in the Declaration of Helsinki. Locally, we obtained approval through the University of Alberta Health Research & Ethics Board. For the international UK cohort comparison, the National Health Service Blood and Transplant and National Information Governance Board provided approval.

Study population, definitions, and design

We conducted a retrospective cohort study of patients who underwent primary LT at the University of Alberta Hospital between 1985 and 2019 for PSC.

We excluded the following patients with (i) graft loss during the first 90 days after receiving liver transplant (12,18), (ii) concomitant nonliver solid organ transplant, (iii) established biliary anastomotic strictures, (iv) confounding diagnoses such as hepatic artery thrombosis or stenosis, ABO-incompatibility, or ductopenic rejection, and (v) unknown dates or reasons for major events and unavailable blood work.

The pretransplant diagnosis of PSC was determined by typical features on cholangiography and compatible liver biochemistry according to the international guidelines (21). Graft loss is defined as either repeat LT or death due to graft failure. We collected baseline characteristics from individual medical records, including age at the time of liver transplant, sex, comorbidities (including IBD and prior colectomy), Model for End-Stage Liver Disease at

the time of LT calculated without exception points and pre-LT laboratory tests. Furthermore, we also collected data on LT-related factors including donor age, donor sex, type of organ received (cadaveric, living donor), cold and warm ischemic times, and type of biliary anastomosis. Post-LT liver tests collected included bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) at 1 month, 3 months, 6 months, 9 months, and 12 months. We also assessed the development of T-cell-mediated rejection and graft survival.

Using the Mayo Clinic criteria, rPSC was defined based on cholangiography indicating nonanastomotic biliary strictures in patients with cholestatic liver enzyme elevation after 3 months following LT (12). We analyzed liver tests as multiples of upper or lower limit of normal based on the center-specific values. Patients were categorized as having either mild or severe cholestasis using previously accepted definitions: mild cholestasis was defined as ALP $>$ 2$\times$ upper limit of normal (ULN) or the combination of both abnormally elevated ALP and total bilirubin, while severe cholestasis was defined as ALP $>$ 3$\times$ ULN or total bilirubin $>$ 100 μmol/L (20,22).

A cohort of PSC transplant recipients from 1990 to 2010 was used to validate our ability to predict recurrence using retrospective data obtained from 6 national liver transplant units in the United Kingdom (10). The UK cohort included age at transplant, graft survival time, graft loss etiology, and liver tests at 12-month post-LT. Given that the UK cohort did not include other clinical data other than the 12-month liver tests, we did not expand the validation to the graft loss analysis to make the models comparable.

Statistical analysis

For descriptive analyses, categorical variables were described as percentages. Continuous nonnormal variables were described with median values and interquartile range, with normal variables being described using mean ± SD. Time-to-event analysis was completed to assess predictors of rPSC development. Univariate Cox regression analyses were performed for all the variables described above. Variables with P-value $<$ 0.1 were then entered in the multivariate regression analyses. Several models were then built based on the time point of each laboratory parameter. At each time point, 2 models were tested: one with ALP and/or total bilirubin as continuous variables, and the other with severe and/or mild cholestasis as categorical variables replacing ALP and/or total bilirubin.

To assess the effect of rPSC on graft survival, we performed a semi-Markov illness-death model (23). In this model, the endpoint is graft-loss due to death or retransplant. Patients who did not reach state 3 were censored at the time of their last clinical encounter. Patients can experience an intermediate state which is rPSC (see Figure S1, Supplementary Digital Content 1, http://links.lww.com/AJG/D369). rPSC is included as a time-dependent variable. Univariate Cox regression was performed to evaluate variables (P-value $<$ 0.1) that predicted graft loss. Each variable linked with graft survival was included in constructing several multivariable multistate models. Each biochemical variable was analyzed at different time points using multivariable semi-Markov models to determine whether a significant relationship existed with graft survival (23). STATA/IC version 16.1 was used for data descriptive analyses and to perform time-to-event analyses for the development of rPSC. R version 4.0.4 was used to perform a multistate model analysis for graft survival.

RESULTS

Recipient characteristics and rPSC recurrence

Of the 158 patients who met the inclusion criteria in the Canadian PSC transplant cohort, 3 were excluded from the semi-Markov

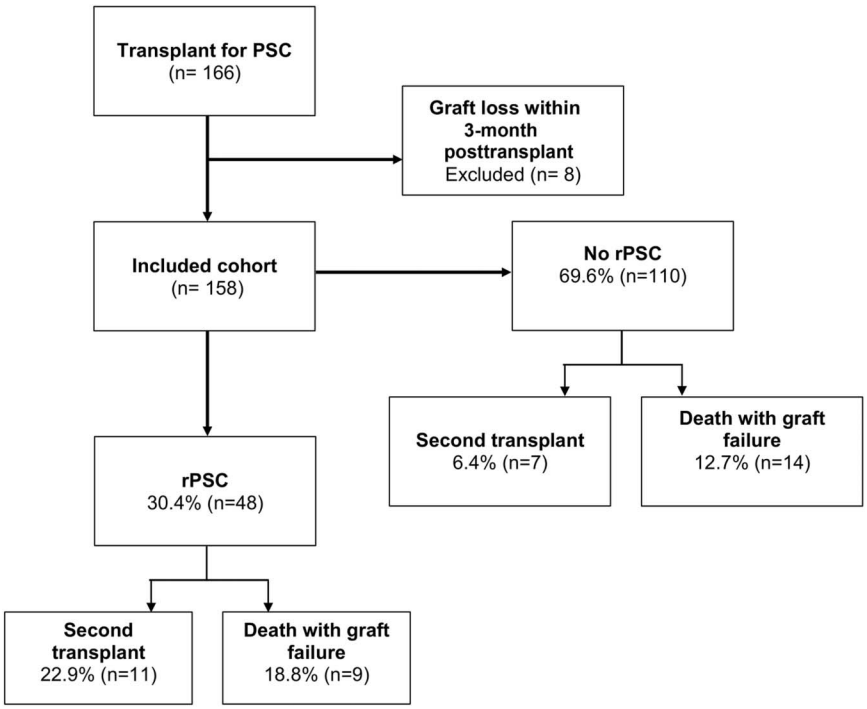

Figure 1. Outcomes for patients undergoing liver transplantation for PSC in the Canadian cohort. PSC, primary sclerosing cholangitis; rPSC, recurrent primary sclerosing cholangitis.

analysis because of an unknown cause of graft loss. A total of 26.5% (41/155) patients experienced graft loss over the follow-up period due to death (23/41) or because of a second transplant procedure (18/41) (Figure 1).

The rate of total rPSC in the Canadian cohort was 30.4% (48/158) over a period of 34 years. By comparison, the UK cohort experienced a 13.8% rate of rPSC (76/549) over the 20-year observation period. The overall 1-, 5-, 10-, and 15-year cumulative probability of recurrence was 1%, 12%, 25%, and 58%, respectively, for the Canadian cohort and 1%, 8%, 15%, and 18%, respectively, for the UK cohort (Figure 2a,b). However, the graft survival characteristics at 5, 10, and 15 were comparable in both cohorts at 89%, 78%, and 62%, respectively, in the Canadian cohort and 88%, 76%, and 63% in the UK cohort (Figure 2c,d).

Risk factors for rPSC

The univariate analysis revealed that patient race may affect the development of rPSC because White patients were relatively protected (hazard ratio [HR] = 0.27, 95% confidence interval [CI] 0.08–0.90). Owing to the limited number of non-White patients (n = 6); however, this observation was not factored into subsequent models (Table 1). Indicators of an advanced state of disease before transplantation were also predictive of PSC recurrence that included transplantation from the intensive care unit (HR = 2.66, 95% CI 1.02–6.98) and an elevated pretransplant bilirubin (HR = 1.03, 95% CI 1.01–1.06) (Table 2).

We then assessed the relationship of liver tests in the first 12 months following LT and the subsequent development of rPSC. From 3 months onward, the median serum AST, ALT, ALP, and total bilirubin levels were elevated in patients developing rPSC (see Figure S2, Supplementary Digital Content 1, http://links.lww.com/AJG/D369). The median ALP became increasingly predictive of disease recurrence at 3 months (HR = 1.22, 95% CI 1.07–1.40), 6 months (HR = 1.32, 95% CI 1.13–1.54), and then at 12 months post-LT (HR = 1.45, 95% CI 1.15–1.84) (Table 2). Serum AST elevation was associated with increased risk of rPSC at 3 months only (HR = 1.31, 95% CI 1.02–1.68) (Table 2; see Figure S2, Supplementary Digital Content 1, http://links.lww.com/AJG/D369) and bilirubin at 6 months (HR = 1.79, 95% CI 1.09–2.93) (Table 2; see Figure S2,

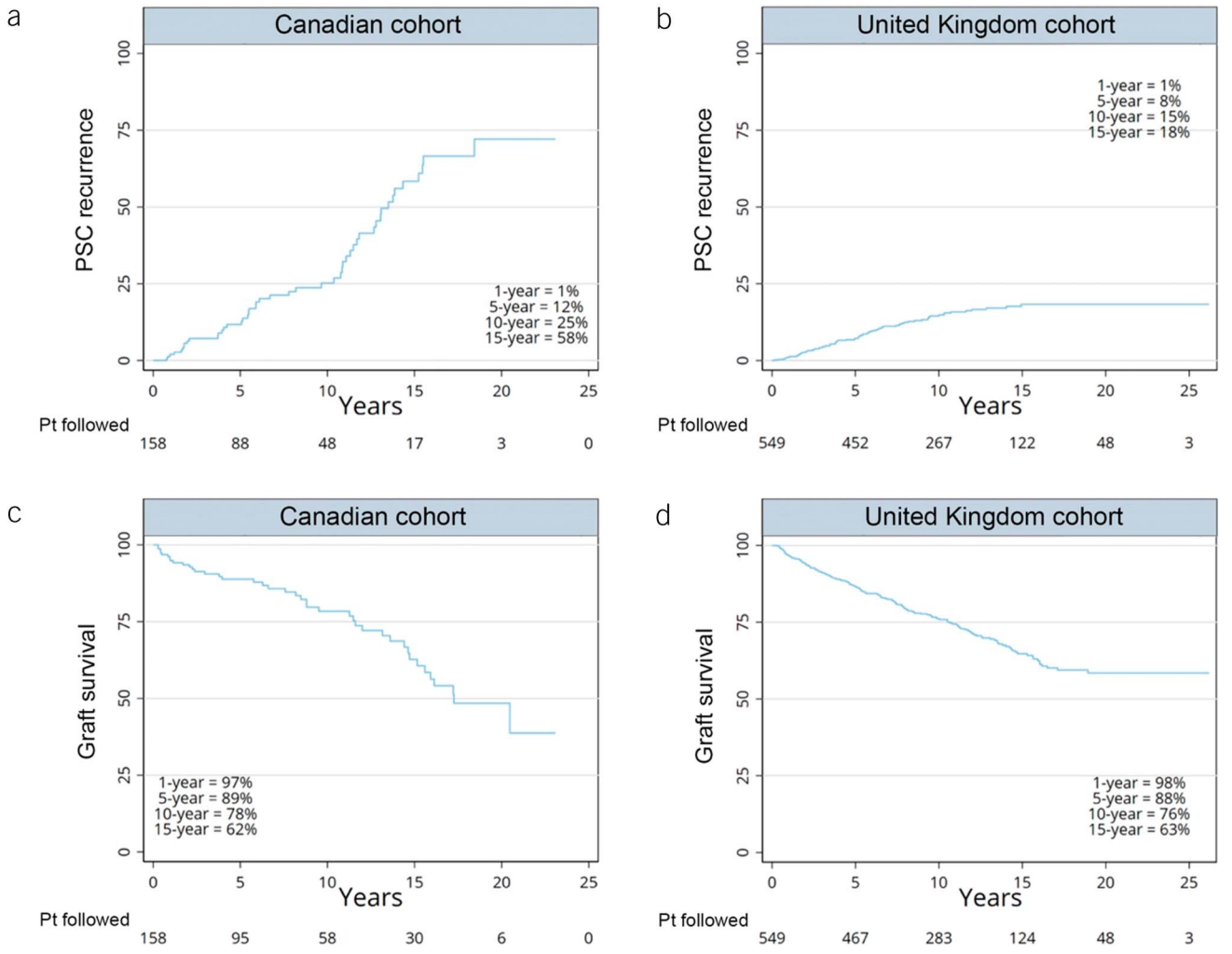

Figure 2. Kaplan-Meier curves showing (**a**) cumulative probability of PSC recurrence in the Canadian cohort and (**b**) in the UK cohort for patients receiving liver transplantation for PSC; as well as cumulative probability of graft survival in (**c**) the Canadian cohort and (**d**) the UK cohort. PSC, primary sclerosing cholangitis.

Table 1. Characteristics of Canadian cohort undergoing liver transplantation for PSC[a]

		Nonrecurrent PSC (n = 110)		rPSC (n = 48)				
	Total (n = 158)	Median/% (n)	Range	Median/% (n)	Range	HR	95% CI	*P* value
Recipient sex (male)	74.1% (117/158)	74.5% (82/110)		72.9% (35/48)		0.92	0.49–1.75	0.805
Age at transplant	41.8 (158)	40.9 (110)	6.02–71.99	43.1 (48)	14.84–64.34	1.01	0.99–1.03	0.599
Non-White ethnicity[b]	4.3% (6/140)	3.2% (3/93)		6.4% (3/47)		0.27	0.08–0.90	0.033
IBD	82.3% (130/158)	78.2% (86/110)		91.7% (44/48)		1.84	0.66–5.14	0.243
Colectomy	17.6% (23/131)	18.4% (16/87)		15.9% (7/44)		0.90	0.40–2.03	0.808
Transplant year	1985–2019					1.05	1.00–1.11	0.055
Transplant from ICU	18.6% (26/140)	21.3% (20/94)		13.0% (6/46)		2.66	1.02–6.98	0.046
Living donor	26.5% (41/155)	31.8% (34/107)		14.9% (7/47)		0.95	0.41–2.20	0.912
Donor age	35.4 (142)	34 (98)	3.6–67	40 (44)	8–73	1.02	1.00–1.-04	0.108
Donor sex (male)	63.5% (94/148)	61.2% (63/103)		68.9% (31/45)		1.36	0.72–2.58	0.348
Sex match	66.9% (99/148)	64.1% (66/103)		73.3% (33/45)		1.24	0.64–2.40	0.523
Cold ischemia time (min)	232 (138)	180 (99)	14–843	287 (39)	20–835	1.00	1.00–1.00	0.454
Warm ischemia time (min)	54 (142)	56 (87)	23–322	51.5 (36)	36–153	1.01	1.00–1.02	0.185
Roux-en-Y anastomosis	92.6% (138/149)	93.2% (96/103)		91.3% (42/46)		1.10	0.39–3.08	0.854
T-cell mediated rejection	42.3% (66/156)	38.0% (41/108)		52.1% (25/48)		1.13	0.64–2.00	0.669
Immunosuppression[c]								
Tacrolimus	85.1% (126/148)	89.3% (92/103)		75.6% (34/45)		0.88	0.44–1.76	0.717
Sirolimus	22.3% (33/148)	22.3% (23/103)		22.2% (10/45)		0.68	0.34–1.38	0.286
Cyclosporine	15.5% (23/148)	11.7% (12/103)		24.4% (11/45)		0.90	0.45–2.18	0.77
MMF	54.1% (80/148)	62.1% (64/103)		35.6% (16/45)		1.15	0.60–1.81	0.679

CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; ICU, intensive care unit; MMF, mycophenolate mofetil; PSC, primary sclerosing cholangitis; rPSC, recurrent primary sclerosing cholangitis.
[a]Cox regression was used to calculate the HR of variables on PSC recurrence (data are presented as median and range, or percentage).
[b]Non-White patients include Aboriginal Canadian, African, Asian, Filipino, and Middle Eastern descent.
[c]Immunosuppression used within the first year following liver transplantation.

Supplementary Digital Content 1, http://links.lww.com/AJG/D369). In the UK cohort, liver tests data were only available at 12 months following LT. At that time, patients who later developed rPSC had significantly elevated median AST, ALT, ALP, and total bilirubin compared with those without disease recurrence (Table 2).

The development of severe cholestasis (defined as ALP > 3× ULN or total bilirubin > 100 μmol/L (20,22)) was associated with an even higher risk of developing rPSC (Figure 3a). In the Canadian cohort, this was especially the case for the presence of severe cholestasis at 3 months (HR = 2.81, 95% CI 1.27–6.23) and at 6 months following transplantation (HR = 2.55, 95% CI 1.12–5.81), whereas only a trend was observed by 12 months in the Canadian cohort (Table 2, Figure 3a). In the UK cohort, the presence of severe cholestasis at 12 months was doubled in patients with rPSC vs those without (27.9% vs 12.6%, HR = 3.141, 95% CI 1.85–5.34), providing a three-fold increased risk of rPSC (Figure 3a). The presence of mild cholestasis was also associated with an increased risk of rPSC as well (HR = 1.79, 95% CI 1.04–3.07) (Table 2).

We checked other risk factors of rPSC in univariate analysis including recipient's and donor's age and sex, IBD diagnosis, colectomy, type of colectomy, transplant year, donor type (living vs deceased), cold and warm ischemia times, T-cell mediated rejection, and immunosuppression used within the first year posttransplant. None of these were significantly correlated with rPSC.

In the multivariate analysis (Figure 3b, see Table S1, Supplementary Digital Content 1, http://links.lww.com/AJG/D369), we found that patients subsequently diagnosed with rPSC had an elevated serum bilirubin before transplantation (HR = 1.03, 95% CI 1.01–1.06) (model 1), and severe cholestasis at 3 (HR = 2.41, 95% CI 1.02–5.70) (model 2) and at 12 months post-LT both (HR = 2.34, 95% CI 0.97–5.64) (model 3) (Figure 3b). Also, patients with a higher ALP at 3 months posttransplant were more likely to be diagnosed with rPSC (HR = 1.176, 95% CI 1.01–1.36) and similarly at 12 months following LT (HR = 1.429, 95% CI 1.13–1.81) (see Table S1, Supplementary Digital Content 1, http://links.lww.com/AJG/D369).

Graft survival outcome

To determine which variables were required to build the multivariable, multistate models for survival (see Table S2, Supplementary Digital Content 1, http://links.lww.com/AJG/D369), we performed univariable Cox regression. We observed that patients with IBD had improved graft survival (HR = 0.36, 95% CI 0.18–0.73) in the Canadian cohort, which was mostly attributable to ulcerative colitis (HR = 0.50, 95% CI 0.27–0.95) rather than Crohn's disease (HR = 1.00, 95% CI 0.44–2.28). The need for colectomy whether prior or posttransplant was not associated

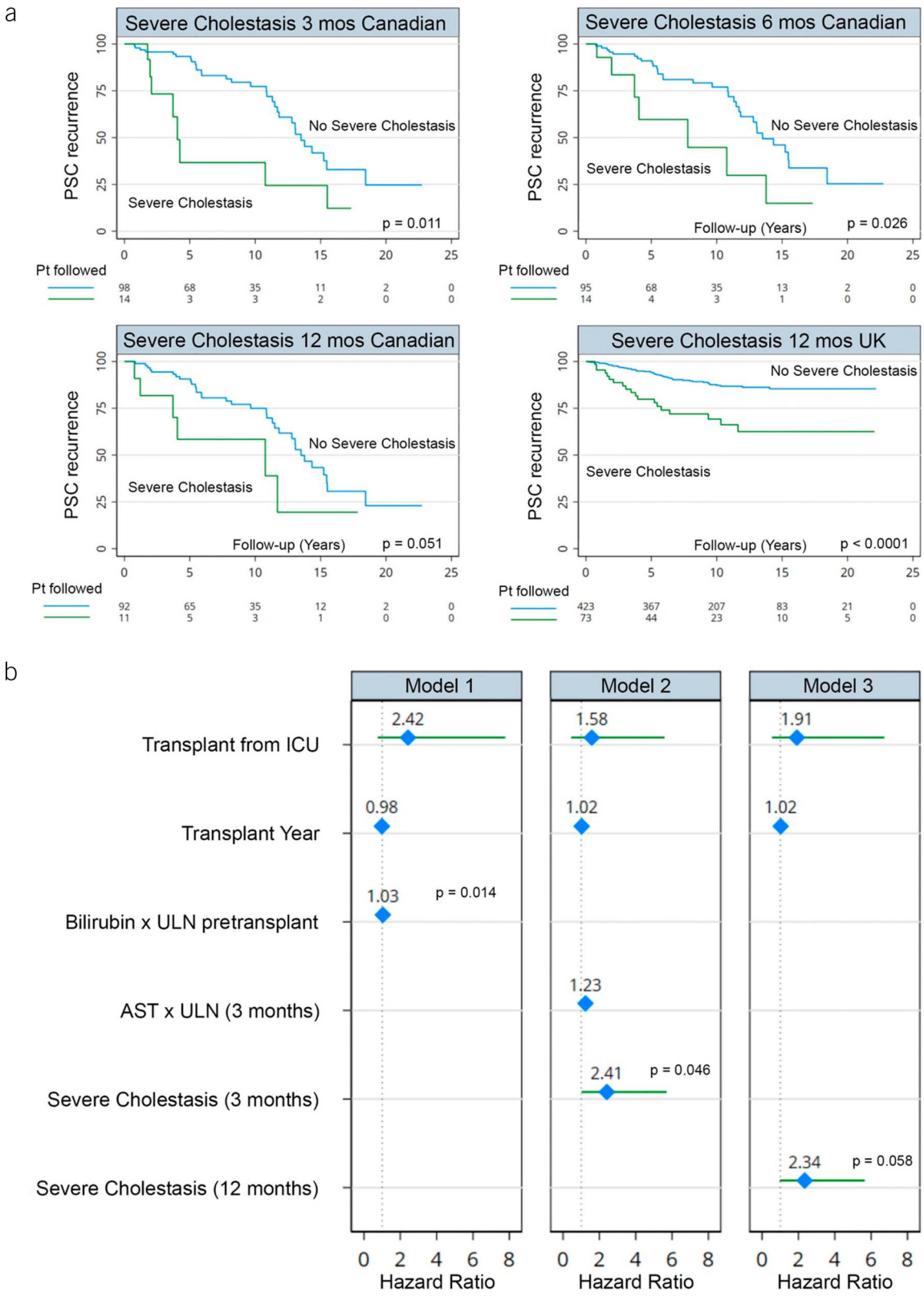

Figure 3. Factors linked with recurrent PSC following liver transplantation. (**a**) Kaplan-Meier analyses showing the relationship between severe cholestasis at different time points following liver transplantation and rPSC-free survival probability. (**b**) Multivariate Cox regression models of factors predicting rPSC in the Canadian cohort. Model 1: serum hepatic biochemistry pretransplantation, model 2: serum hepatic biochemistry at 3-month posttransplantation, model 3: serum hepatic biochemistry at 12-month posttransplantation. AST, aspartate aminotransferase; ICU, intensive care unit; PSC, primary sclerosing cholangitis; rPSC, recurrent primary sclerosing cholangitis; ULN, upper limit of normal.

Table 2. Liver biochemistries related to rPSC[a]

	Nonrecurrent PSC (n = 110) Median/%(n)	rPSC (n = 48) Median/%(n)	HR	95% CI	*P* value
Canada pretransplant					
Albumin ×ULN	0.91 (79)	0.93 (40)	0.37	0.06–2.07	0.256
Creatinine ×ULN	0.68 (99)	0.71 (40)	0.99	0.40–2.43	0.977
INR	1.3 (81)	1.2 (35)	1.02	0.43–1.40	0.963
MELD	22 (46)	16 (29)	1.02	0.98–1.07	0.295
AST ×ULN	2.95 (77)	3.2 (38)	0.97	0.87–1.07	0.509
ALT ×ULN	1.44 (63)	1.98 (33)	0.97	0.78–1.21	0.798
ALP ×ULN	2.5 (78)	2.4 (39)	1.01	0.90–1.12	0.932
Total bilirubin ×ULN	5.15 (99)	6.2 (41)	1.03	1.01–1.06	0.013
Mild cholestasis	15.1% (13/86)	17.5% (7/40)	0.94	0.42–2.13	0.883
Severe cholestasis	77.9% (67/86)	75.0% (30/40)	1.010	0.49–2.07	0.978
Canada 3-month posttransplant					
AST ×ULN	0.68 (71)	0.78 (39)	1.31	1.02–1.68	0.036
ALT ×ULN	0.64 (62)	0.9 (23)	1.15	0.96–1.37	0.14
ALP ×ULN	0.96 (73)	1.15 (39)	1.23	1.07–1.40	0.002
Total bilirubin ×ULN	0.5 (73)	0.6 (39)	1.18	0.96–1.44	0.117
Mild cholestasis	11.0% (8/73)	10.3% (4/39)	1.46	0.51–4.17	0.481
Severe cholestasis	8.2% (6/73)	20.5% (8/39)	2.81	1.27–6.23	0.011
Canada 6-month posttransplant					
AST ×ULN	0.73 (69)	0.88 (39)	1.32	0.91–1.91	0.143
ALT ×ULN	0.68 (60)	0.90 (24)	1.04	0.76–1.42	0.795
ALP ×ULN	0.992 (70)	1.19 (39)	1.32	1.13–1.54	<0.0001
Total bilirubin ×ULN	0.50 (68)	0.55 (39)	1.79	1.09–2.93	0.020
Mild cholestasis	12.9% (9/70)	17.9% (7/39)	1.31	0.57–2.98	0.522
Severe cholestasis	10.0% (7/70)	17.9% (7/39)	2.55	1.12–5.81	0.026
Canada 12-month posttransplant					
AST ×ULN	0.63 (63)	0.90 (39)	1.13	0.80–1.59	0.496
ALT ×ULN	0.57 (58)	0.90 (27)	1.28	0.87–1.88	0.206
ALP ×ULN	0.97 (64)	1.15 (39)	1.45	1.15–1.84	0.002
Total bilirubin ×ULN	0.55 (62)	0.55 (39)	0.976	0.83–1.14	0.765
Mild cholestasis	9.4% (6/64)	17.9% (7/39)	1.46	0.64–3.31	0.368
Severe cholestasis	7.8% (5/64)	15.4% (6/39)	2.39	1.00–5.74	0.051
UK 12-month posttransplant[b]					
AST ×ULN	0.60 (270)	0.70 (51)	1.26	1.05–1.50	0.013
ALT ×ULN	0.58 (223)	0.65 (28)	1.67	1.22–2.25	0.001
ALP ×ULN	1.14 (428)	1.85 (68)	1.14	1.06–1.23	<0.0001
Total bilirubin ×ULN	0.55 (427)	0.75 (68)	1.10	1.05–1.16	<0.0001
Mild cholestasis	15.9 (68/428)	26.5 (18/68)	1.79	1.04–3.07	0.034
Severe cholestasis	12.6% (54/428)	27.9% (19/68)	3.14	1.85–5.34	<0.0001

Mild cholestasis was reported as a binary variable and defined as ALP > 2× ULN or the combination of both abnormally elevated ALP and total bilirubin.
Severe cholestasis was reported as a binary variable and defined as ALP > 3× ULN or total bilirubin > 100 μmol/L.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PSC, primary sclerosing cholangitis; rPSC, recurrent primary sclerosing cholangitis; ULN, upper limit of normal.
[a]Univariate Cox regression analysis.
[b]Biochemical data only available at 12 months following liver transplantation for UK cohort.

Table 3. Liver biochemistries related to graft loss in the Canadian cohort[a]

	HR	95% CI	*P* Value
Liver biochemistry pretransplantation			
Albumin × LLN	0.37	0.06–2.07	0.256
Creatinine × ULN	0.99	0.40–2.43	0.977
INR	1.02	0.43–2.40	0.963
MELD	1.02	0.98–1.07	0.295
AST × ULN	1.01	0.92–1.12	0.765
ALT × ULN	0.95	0.72–1.27	0.748
ALP × ULN	0.94	0.82–1.08	0.402
Total bilirubin × ULN	1.02	0.99–1.05	0.236
Mild cholestasis	0.50	0.15–1.65	0.254
Severe cholestasis	1.69	0.64–4.45	0.286
Liver biochemistry 3 months posttransplantation			
AST × ULN	1.26	0.99–1.61	0.059
ALT × ULN	1.12	0.90–1.38	0.319
ALP × ULN	1.22	1.07–1.40	0.003
Total bilirubin × ULN	1.24	1.03–1.49	0.023
Mild cholestasis	1.53	0.53–4.39	0.434
Severe cholestasis	3.88	1.72–8.76	0.001
Liver biochemistry 12-month posttransplantation			
AST × ULN	1.08	0.67–1.74	0.747
ALT × ULN	1.20	0.72–1.98	0.486
ALP × ULN	1.45	1.12–1.88	0.004
Total bilirubin × ULN	0.98	0.81–1.20	0.876
Mild cholestasis	1.21	0.46–3.20	0.699
Severe cholestasis	2.77	1.05–7.30	0.040

Liver biochemistries were analyzed as continuous variables and recorded in relation to ULN or LLN, whereas mild and severe cholestasis were recorded as binary variables.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; LLN, lower limit of normal; MELD, Model for End-Stage Liver Disease; ULN, upper limit of normal.
[a]Univariate Cox regression analyses.

with graft survival in the Canadian cohort (HR = 1.51, 95% CI 0.72–3.17). The use of Tacrolimus was protective against graft loss, whereas cyclosporine was associated with diminished graft survival (see Table 1S, Supplementary Digital Content 1, http://links.lww.com/AJG/D369).

None of the serum liver test parameters before transplant were predictive of graft survival. Three months following LT, most indicators of cholestasis were associated with graft loss (Table 3) and these included ALP (HR = 1.22, 95% CI 1.07–1.40), total bilirubin (HR = 1.24, 95% CI 1.03–1.49), and severe cholestasis (HR = 3.88, 95% CI 1.72–8.76). Elevated ALP levels and to a greater extent severe cholestasis were also associated with a higher risk of graft loss at 12 months (HR = 1.45, 95% CI 1.12–1.88) and (HR = 2.77, 95% CI 1.05–7.30), respectively (Table 3).

We then constructed multivariate, multistate models to assess the effect of transition between rPSC (state 2) and graft loss (state 3) (see Figure S1, Supplementary Digital Content 1, http://links.lww.com/AJG/D369). Patients with rPSC were more likely to experience graft loss in both the 3-month and 12-month models (Table 4). Also, an elevated serum ALP was found to be an independent predictor of graft loss at both 3-month (HR = 1.28, 95% CI 1.09–1.51) and 12-month post-LT (HR = 1.43, 95% CI 1.06–1.95) following transplantation. However, severe cholestasis had a greater impact on the probability of graft loss at 3 months (HR = 5.70, 95% CI 2.01–16.17) and 12 months after LT (HR = 3.21, 95% CI 1.03–10.03) (Table 4).

DISCUSSION

In this study, we addressed the question of whether the development of abnormal hepatocellular or cholestatic biochemistry tests within the first 12 months of LT can predict PSC recurrence and possibly indicate the development of rPSC before cholangiographic confirmation. In comparison with those without rPSC, we found that patients with rPSC demonstrated elevated median levels of bilirubin, AST, ALT, and ALP from 3 to 12 months following LT. Recipients with severe cholestasis at 3 or 6 months in the Canadian cohort and at 12 months in the UK cohort demonstrated a 2.5–3.2-fold increased risk of recurrent disease. We confirmed prior studies that patients with rPSC

Table 4. Prediction of graft failure in the Canadian cohort[a]

Model at 3-month posttransplant (n = 144)			
	HR	95% CI	*P* value
Donor age	1.02	0.99–1.04	0.171
Ulcerative colitis	0.48	0.22–1.05	0.067
Tacrolimus	0.56	0.04–9.00	0.686
Cyclosporine	1.82	0.10–31.57	0.681
Transplant year	1.04	0.94–1.14	0.436
AST × ULN	0.85	0.63–1.16	0.306
Severe cholestasis	5.70	2.01–16.17	0.001
PSC recurrence	8.19	3.12–21.51	<0.0001
Model at 12-month posttransplant (n = 137)			
	HR	95% CI	*P* value
Donor age	1.00	0.976–1.02	0.955
Ulcerative colitis	0.76	0.331–1.72	0.506
Tacrolimus	0.22	0.016–2.95	0.251
Cyclosporine	1.01	0.065–15.78	0.992
Transplant year	1.07	0.969–1.18	0.182
Severe cholestasis	3.21	1.027–10.03	0.045
PSC recurrence	7.05	2.861–17.37	<0.0001

AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; PSC, primary sclerosing cholangitis; ULN, upper limit of normal.
[a]Multivariable, multistate models using cholestasis as a categorical variable, where PSC recurrence was included as a time-dependent covariate and the event studied was graft loss through retransplant or dying with a failing graft.

experience diminished graft and overall survival (10,14). Using the semi-Markov model, subjects developing severe cholestasis at 3 months experienced a 5.7-fold increased risk of losing their allograft, and then those developing rPSC experienced an 8.2-fold risk of decreased survival (Table 4). These outcomes are somewhat comparable with our recent report of patients undergoing LT for primary biliary cholangitis (PBC), where severe cholestasis at 6 and 12 months following LT was linked with an 1.8- and 1.5-fold increased risk of recurrent PBC, respectively, and PBC recurrence was associated with decreased overall survival (18).

These data are consistent with the model that recurrent cholangitis can occur as an early event after LT before the development of the diagnostic cholangiography appearance of rPSC. Biochemical cholestasis usually precedes radiographic features of rPSC that occur within a range from 0.7 to 5.7 years depending on the period of follow-up (12,24,25). By convention, the diagnosis of rPSC is established 90 days after LT because of 85% of postoperative complications involving the hepatic artery or biliary tree that mimic PSC occurs within this period (12).

It is difficult to conclude whether severe cholestasis during the first year is due to rPSC in the graft or because of another pathological process that leads to it. However, evidence for recurrence of PSC within 3 months following LT may shed light on the pathophysiology of the idiopathic disease process. It has been debated that PSC is an autoimmune disease because much of the genetic susceptibility is immune-mediated and observed in patients with IBD and other autoimmune diseases (26). Others have suggested that PSC is atypical because not all patients develop autoantibodies, immunosuppression is of little clinical utility pretransplantation and following transplantation intensified corticosteroid treatment leads to increased rates of rPSC (1,2,14,27,28). We can make an argument that the development early cholestasis in patients with rPSC is more consistent with an infectious than an autoimmune etiology because the maximal use of immunosuppression following transplantation would favor an infectious process (18). Similar events are reported in chronic infectious diseases, such as hepatitis C virus infection, where early biochemical elevation of liver enzymes following LT is associated with recurrence (14).

Others have proposed the protective effect of colectomy before or at the time of LT may be associated with removing an infectious source of disease (14,29). Disease activity with IBD in general is an independent risk factor for developing rPSC (10,30) and the presence of remnant colon affects outcomes because total colectomy with end-ileostomy provides additional protection as compared with colectomy with an ileoanal pouch (31). Also, patients with rPSC requiring a second liver transplant for rPSC are at risk of developing a rapid onset and more aggressive rPSC in their second allograft (10,30,31). The process of accelerated allograft failure following a second transplantation for recurrent disease is well-documented for patients with chronic viral hepatitis (32). Taken together, these observations are suggestive of a different underlying process of rPSC within the first few months of transplantation rather than an autoimmune disease process because of the high levels of immunosuppression employed in the first year following transplantation. Infection may be one of the significant factors playing an important role in a complex process together with the genetic and immune reactions of the patient.

The limitations of our study include the single-center and limited sample size in the Canadian cohort, missing information about the deceased graft type (donation after brain vs cardiac death), and the inability to validate the early liver test changes in the UK database. Accordingly, the presence of early biochemical abnormalities and presence of cholestasis in the Canadian cohort warrant further investigation with larger, multicenter studies. Moreover, the absence of clinical data, other than laboratory results, from the UK database deemed it difficult to validate the multivariable model calculated using the Canadian cohort using the UK patients' data. We were able to only validate the crude effect of severe cholestasis using the UK cohort. In an ideal prospective study, all patients would need to have MRCP at predefined time points, regardless of liver biochemistries, to be able to capture morphologic evidence of rPSC at its earliest presentation. Also, the discrepancies in the rates of rPSC between our and the UK database appear disparate but are likely related to the much longer follow-up period in the Canadian database. Collective data from other case series approaching 3 decades in follow-up have reported higher rates of rPSC (24,25). Nevertheless, other differences in posttransplant surveillance protocols, immunosuppressive regimens, or even environmental factors may have led to population-level differences. For example, the Canadian center has adopted a "steroid-free" immunosuppressive regimen that may allow for differences in rPSC activity. This study also lacked a more granular analysis of the influence of IBD and the effects of donation after cardiac death in the development of rPSC.

In summary, rPSC occurs commonly post-LT and is associated with graft loss. Abnormal hepatic biochemistry as early as 3 months, persisting up to 12 months following LT may help to stratify patients at risk of rPSC and indicate the potential development of rPSC before cholangiographic diagnosis. Our data add to the growing understanding of rPSC and support a hypothesis that an infectious agent(s) that may persist and resurface in patients with PSC as soon as 3 months after LT. Larger, multicenter studies and characterization of potential environmental agents are needed to characterize this relationship more definitively.

CONFLICTS OF INTEREST

Guarantor of the article: Andrew L. Mason, MBBS.

Specific author contributions: Conceptualization of the study was performed by A.L.M., B.H., S. Wasilenko, and A.J.M.-L.; Data curation and formal analyses: E.L., C.M.-V., M.A., B.G., D. Manas, A.M., D. Mirza, G.F., N.O., D.T., K.R., P.S., S. Wigmore, B.A., A.A., F.C., B.F., V.I., M.M., and G.S.; Investigation and methodology, B.A., B.K., S. Wasilenko, A.J.M.-L., B.H., and A.L.M.; Project Administration B.A., E.L., and A.L.M.; Original draft B.A., B.K., M.C., and S. Wasilenko; Review and editing A.L.M., M.C., E.L., M.A., C.M.-V., B.G., D.M., A.M., D.M., G.F., N.O., D.T., K.R., P.S., S. Wigmore, B.A., A.A., F.C., B.F., V.I., M.M., and G.S.; Validation R.R., S.J., B.A., E.L., B.H., and A.L.M.; Funding and supervision A.L.M.

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Study Highlights

WHAT IS KNOWN

- ✓ Median primary sclerosing cholangitis recurrence (rPSC) posttransplant is 20%–25% over 10 years.
- ✓ Active inflammatory bowel disease pretransplant or posttransplant is a risk factor for rPSC.
- ✓ Patients with rPSC posttransplant have 4 times risk of early graft loss.

WHAT IS NEW HERE

- ✓ Severe cholestasis as early as 3-month posttransplant predicts rPSC.
- ✓ Advanced disease state pretransplant, indicated by transplant from intensive care unit and/or markedly elevated bilirubin, is associated with increased risk of rPSC.
- ✓ Severe cholestasis as early as 3-month posttransplant is an independent predictor, from rPSC, for early graft loss. Patients with severe cholestasis 3-month posttransplant have 5.7 times the risk of losing their graft earlier.

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