Recurrence of Primary Sclerosing Cholangitis After Liver Transplant in Children : An International Observational Study

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Recurrence of primary sclerosing cholangitis after liver transplant in the Pediatric PSC Consortium: Epidemiology and risk factors.

Short title: Recurrent Sclerosing Cholangitis in children

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PSC: primary sclerosing cholangitis
LT: Liver transplant
rPSC: recurrent primary sclerosing cholangitis
ACR: acute cellular rejection
AIH: autoimmune hepatitis
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
GGT: gamma-glutamyltransferase
IBD: inflammatory bowel disease
PSC: primary sclerosing cholangitis
UDCA: ursodeoxycholic acid
CI: confidence interval
MRI: magnetic resonance imaging
MRCP: magnetic resonance cholangiopancreatography
ERCP: endoscopic retrograde cholangiopancreatography

Keywords: end-stage liver disease, biliary complications, primary sclerosing cholangitis in children, recurrent primary sclerosing cholangitis, pediatric liver transplantation.

Abstract:

Background: Recurrent primary sclerosing cholangitis (rPSC) following liver transplant (LT) has a negative impact on graft and patient survival; little is known about risk factors for rPSC or disease course in children.

Approach & Results: We retrospectively evaluated risk factors for rPSC in 140 children from the Pediatric PSC Consortium, a multicenter international registry, who underwent LT for PSC and had >90 days of follow-up. The primary outcome, rPSC, was defined using Graziadei criteria. rPSC occurred in 36 children representing 10% and 27% of the subjects at 2- and 5 years post-LT, respectively. A median follow-up after LT was 3.3-years [IQR 1.7-6.0]. Subjects with rPSC were younger at LT (12.9 vs. 16.2 years), had faster progression from PSC diagnosis to LT (2.5 vs. 4.1 years), and had higher ALT (112 vs. 66 IU/L) at LT; (all $p < 0.01$). IBD was more prevalent in the rPSC group (86% vs. 66%, p=0.025). After LT, rPSC subjects had more episodes of acute rejection (mean 3 vs 1, $p<0.001$), and higher prevalence of steroid-refractory rejection (41% vs. 20%, $p=0.04$). After rPSC: 43% of 36 subjects developed complications of portal hypertension, were re-listed for LT, or died within two years of the diagnosis. Mortality was higher in the rPSC group (11.1% vs. 2.9%, p=0.05).

Conclusion: rPSC was diagnosed in 27% of children at five-years post-LT, higher than previously reported. Patients with rPSC appear to have a more aggressive, immune-reactive phenotype, characterized by younger age at LT, faster progression to end-stage liver disease, higher prevalence of IBD, and more frequent, refractory acute rejection post-LT. rPSC was associated with increased morbidity and mortality.

Introduction:

Primary sclerosing cholangitis (PSC) is an autoimmune liver disease thought to involve the innate and adaptive arms of the immune system. Its exact triggers and driving mechanisms remain poorly understood(1-4). The association of PSC with inflammatory bowel disease (IBD) suggests that antigens associated with gut inflammation cause immune activation and liver inflammation, (4) influencing overall clinical outcomes. Recently, environmental factors, the microbiome, and imbalanced bile acid composition have been implicated as potential contributing factors(5, 6).

PSC accounts for <3 % of liver transplants (LT) in children (7, 8). Among children with PSC, 30% will require a LT within ten years of diagnosis(9). Most children with PSC undergo LT for life-threatening complications of cirrhosis and portal hypertension, while intractable pruritus, recurrent cholangitis(7, 10), and cholangiocarcinoma are less frequent indications(9). Although LT is the only treatment option for PSC-associated end-stage liver disease, it can recur in the allograft. The diagnosis of recurrent PSC (rPSC) is based on radiologic or histological findings of cholestatic hepatitis in the absence of acute or chronic allograft rejection(11). In adults, rPSC occurs in approximately 20% of LT recipients (8, 12, 13) and up to 12.4% with rPSC will require re-transplantation (14). However, despite decades of LT experience and the recognition that disease recurrence negatively impacts graft and patient survival, the real incidence of rPSC in children remains unknown. Furthermore, the effects of recipient and allograft factors in disease recurrence are not well elucidated. Standard diagnostic criteria are lacking and features of disease recurrence frequently overlap with other clinical presentations such as ischemia, infections, drug-induced liver injury, rejection, or biliary complications.

Prior studies reported that patients who received an extended-criteria donor (ECD) graft (13), use steroid-free Thymoglobulin induction(8) or primary immunosuppression with tacrolimus(15), develop allograft rejection (16), have poorly controlled IBD, or develop *de novo* IBD(7, 17), were all at a higher risk of disease recurrence. At the same time, colectomy was protective (13, 15). The

negative impact of rPSC in patient and graft survival is well established for adults(14, 15, 18, 19). These risk factors are not well established in children and most pediatric reports are small, single-center cohorts (8, 20, 21). The only pediatric multicenter registry study did not demonstrate that rPSC has a negative impact on patients or allografts outcome (7).

We aimed to assess the epidemiology, risk factors, and long-term outcomes for rPSC in children from a large, multicenter cohort: the Pediatric PSC Consortium. We aim to improve our understanding of this condition and provide insights into the diagnosis and risk factors of rPSC.

Methods:

Study population and data source

The international Pediatric PSC Consortium is an active research registry involving 54 sites throughout Europe, the Middle East, Asia, North and South America (9). Thirty-four centers collected retrospective data from cases undergoing LT for a primary indication of PSC before 18 years of age, between 1986 to 2019. Data were abstracted after a detailed review of medical records, deidentified by the collaborating investigators at the local study sites, and submitted through the secure Research Electronic Data Capture (REDcap) platform(22). A detailed description of the whole cohort has been previously reported (9). The indication for and timing of LT were based on local clinical practices and established guidelines. Analyzed variables included demographics, laboratory data, donor and graft type, perioperative data, type of immunosuppression, histopathology reports, cholangiography, and endoscopy on each patient. Recipients of LT with less than 90 days of follow-up were excluded from this analysis.

Outcomes

The study primary outcome was diagnosis of rPSC as defined by Graziadei (11). Criteria for rPSC include: (a) confirmed diagnosis of PSC before LT (b) cholestatic biochemistry with cholangiography showing multifocal non-anastomotic biliary strictures with beading of bile

ducts or fibro-obliterative lesions, (c) in the absence of chronic ductopenic rejection, hepatic artery thrombosis/stenosis, or donor-recipient blood type incompatibility at least 90 days after LT. Any questions or discrepancies regarding the data points needed to define disease recurrence were resolved between the local co-investigator and study authors.

To evaluate the impact of rPSC and the overall patient and graft outcomes, secondary clinical endpoints were established: (a) the development of portal hypertensive complications (ascites, hepatic encephalopathy, or esophageal varices with or without bleeding), (b) re-LT or listing for LT, or (c) death from liver disease progression or during re-LT. Event-free survival was defined as the absence of all of (a-c) the above.

Statistical analysis

Descriptive statistics were calculated: continuous variables were reported as median and interquartile range (IQR), and categorical variables as count and proportions. Continuous variables were compared using the rank-sum test, and categorical variables were compared with chi-square analysis. We created a retrospective cohort of all children with LT who met inclusion criteria, starting at the LT date. Observations were censored at the date of the last known follow-up. We used the Kaplan-Meier method to calculate outcome probabilities and Cox regression to compare the association between demographic, phenotypic, biochemical, donor, graft, and post-transplant medication factors and rPSC. The proportional hazards assumption was assessed graphically. Stata version 16.0 (StataCorp, College Station, TX) was used for statistical analysis.

Ethical considerations

The institutional review board of each participating center approved all research work. This research was conducted following the Declaration of Helsinki guidelines of good practice.

Results:

Study Population:

In our cohort of 1325 children with PSC, 172 underwent LT. We excluded 32 patients with less than 90 days of follow-up after LT, leaving 140 for analysis. Median age at LT was 15.3 years [IQR 12.3-17.7], 55% were male. The median time from original PSC diagnosis to LT was 3.7 years [IQR: 1.6-5.9]. Patients were followed after LT for a median of 3-years [IQR 1.1-6.1], representing 592 total person-years of follow-up. The 1, 5 and 10-year graft survival was 97% [95%CI 92-99%], 91% [95%CI 83-95%], and 71% [95%CI 52-84%], respectively.

Thirty-six subjects met criteria for rPSC, at a median of 3.3 years [IQR 1.7-6.0] after LT. The probability of rPSC at two years after LT was 10% (95% confidence interval [CI] 6-17%), at five years was 27% (95%CI 19-37%), and at ten years was 47% (95%CI 35-62%), **Figure 1**.

A combination of biochemical (100%), histological (47%), and radiological findings (100%) fulfilled the diagnostic criteria of rPSC.

Risk factors for disease recurrence in allograft:

The demographics and laboratory values at diagnosis of PSC and LT are shown in **Table 1**. Patients with rPSC (n=36) were younger at the time of LT, and the time from initial PSC diagnosis to LT was significantly shorter for those with rPSC. IBD was more prevalent in the rPSC group, particularly in the ulcerative colitis phenotype. Two patients underwent colectomy before LT, and neither developed rPSC. Five patients underwent colectomy after LT, and two developed rPSC.

At PSC diagnosis, liver transaminases, bilirubin, hemoglobin, and platelet count were similar in both groups (**Table 1**). At LT, those with rPSC had higher ALT, AST and bilirubin. MELD scores were similar in both groups at listing and LT. (**Table 2**). At 6 months post-LT, transaminases and bilirubin did not differ between the two groups. But at 12-months, patients with rPSC had significantly higher GGT, AST and ALT than those without rPSC. Type of graft and biliary anastomosis were not associated with rPSC. (**Table 2**). Biliary leaks occurred in only

7 (6.8%), with no reported anastomotic strictures. Portal vein thrombosis and hepatic artery thrombosis occurred in only 5 patients each in the whole cohort.

Complete data on post-LT immunosuppression was available in 103 subjects. Neither induction nor maintenance immunosuppression was associated with rPSC (**Table 3**). The rPSC patients had a higher number of allograft acute rejection episodes (median 3 vs.1, $p<0.001$), and those rejection episodes were more likely to be steroid-resistant (41% vs. 20%, $p=0.04$). The majority of rejection episodes occurred before the diagnosis of rPSC, (**Table 4**)**.** Those with rPSC were more likely to have EBV viremia during follow-up.

Impact of disease recurrence on patient and graft survival:

After the diagnosis of rPSC, survival with allograft was 90% (95%CI 72-97%) at one year, 81% (95%CI 59-92%) at two years, and only 63% (95%CI 37-80%) at five years, as shown in **Figure 2**. Seven patients (4.3% of 140) died during post-LT follow-up; mortality was higher in the rPSC cohort (11.1% vs. 2.9%, $p=0.05$). The causes of death in those with rPSC were liver failure while awaiting re-LT (1), perioperative during re-transplant for rPSC (1), sepsis and multiorgan failure (1), and PTLD (1). In those without rPSC, one patient died from metastatic cholangiocarcinoma and 2 of sepsis with multiorgan failure. Overall, event-free survival after diagnosis of rPSC was 71% (95%CI 52-84%) at 1 year, 57% (95%CI 36-74%) at 2 years, as shown in **Figure 3.** Seven patients developed portal hypertensive complications at a median of 1.7 years, six patients were re-listed for transplantation at median of 1.2 years, and five patients died at median 2 years after rPSC diagnosis, respectively.

Discussion:

We analyzed a multicenter cohort of children who underwent LT for PSC. There were three main findings from this study. First, we showed a 27% probability of rPSC by five years after LT, and that rPSC was associated with substantial morbidity and mortality. Second, we established that rPSC was associated with a more aggressive, immunoreactive phenotype of PSC pre-LT and more frequent and difficult to treat allograft rejections. Third, we identified no modifiable peri-transplant risk factors associated with rPSC.

Data regarding rPSC incidence in children are sparse and heterogeneous (7, 8). In this multicenter, multi-national series of children transplanted for PSC, 27% developed rPSC by 5 years post-LT. The 27% recurrence rate at 5 years reported here is a higher prevalence than the 17.5% reported by Gordon et al., 12% reported by Campsen et al. (19), but lower than the 37% reported by Vera et al. (23), all these in studies reporting adults experience with similar follow-up time. Miloh et al. identified rPSC in 6 of 61 (10%) of the children followed for 18.7+13.8 months post-LT, which is similar to our observed 2 years disease recurrence rate. Our cohort has a longer duration of follow-up with 33.5% having a 5-year follow-up compared to only 20% in the group reported by Miloh (7), which could explain the higher detection rate of rPSC in our study. The high variability in reporter rPSC incidence could be due to differences in diagnostic criteria, length of follow up, and varying disease phenotype (24).

Miloh et al. reported that the prevalence of complications after LT for PSC did not differ significantly from the complication rate in children transplanted for other indications and that disease recurrent did not have a negative impact in patient and graft survivals. However, in our cohort, at 2.5 years after rPSC diagnosis, almost half of our patients had a complication related to disease recurrence. The negative impact of rPSC in patients and grafts survival is well established for adults(14, 15, 18, 19), but this is the first sizeable pediatric cohort reporting this finding. Careful monitoring, prompt diagnosis, and new therapeutic strategies are needed to improve graft and patient survival.

Our data suggest that rPSC represents a more aggressive form of the disease in the allograft—which may be in conjunction with, triggering, or following other immune activation (acute cellular rejection). Patients with rPSC showed a more severe, immune-reactive phenotype of PSC pre-LT. Our observations concur with previous reports demonstrating that patients with rPSC were younger at LT(8), had a faster progression from diagnosis to LT(15, 17), and higher ALT at LT(25). In addition to more immune reactive disease, patients with rPSC also had a significantly higher frequency of IBD, as has been reported in other pediatric (7, 8) and adult studies(13, 15, 17, 18, 23). One explanation for the well-known association between disease recurrence and IBD activity(23) is that intestinal microbiota modulates liver disease(5). In agreement with other reports (16, 26), rPSC subjects in this cohort had more frequent and more steroid-refractory allograft rejection occurring before the diagnosis of PSC. Increased risk of rejection and recurrence of the primary disorder makes post-LT management—of immunosuppression and other interventions—very challenging. It is possible, though, that some patients were misdiagnosed with rejection rather than receiving the appropriate diagnosis of rPSC. This finding highlights the need for new diagnostic algorithms—and high clinical suspicion— to facilitate accurate differentiation of rejection from rPSC.

The rPSC cohort had higher liver enzymes levels (ALT, AST, GGT) at 1-year post-LT , which aligns with Miloh et al. that report significantly higher levels of aminotransferases at 5 years post-LT in patients with PSC when compare with patients undergoing LT for non-PSC indication. Despite the lack of specificity of liver enzymes elevations, there is an overall tendency to default to the diagnosis of rejection in transplant recipients, thought our finding might point towards early disease recurrence. The allografts of LT recipients for PSC should undergo detail histological and radiological evaluation to exclude other possible etiologies of graft dysfunction before increasing immunosuppression. This strategy could prevent over-

immunosuppression, limiting the side effects associated with it. Interestingly, the higher frequency of EBV viremia in the rPSC group may indirectly indicate a higher exposure to immunosuppression (27). Also, it seems likely that they received more immunosuppression, given that they had more rejection episodes. Alternatively, augmented immunosuppression during graft dysfunction due to misdiagnosing rPSC as rejection could have also contributed. Translational investigations have demonstrated that T and B-cells activated and expanded pre-LT remain in the body; they can trigger allo- or autoimmune responses post-LT due to cross-reactive antigen recognition(28, 29). A more substantial lymphocyte expansion pre-LT could induce stronger alloimmune and autoimmune responses post-LT. Post-LT graft dysfunction might represent a combination outcome. Increased risk of rejection and recurrence of the primary disorder makes post-LT management—of immunosuppression and other interventions—very challenging. It is possible, though, that some patients were misdiagnosed with rejection rather than receiving the appropriate diagnosis of rPSC. This observation highlights the need for new diagnostic algorithms—and high clinical suspicion— to facilitate accurate differentiation of rejection from rPSC and facilitate a more precise therapy when graft dysfunction arises.

Furthermore, We did not identify any modifiable peri-or post-transplant risk factors for rPSC—highlighting the need for developing new therapies to prevent and treat rPSC to improve long-term outcomes. Others have reported that Colectomy in the peri-transplant period seems protective for rPSC(13, 15). Given our limited sample size—particularly those with colectomy—we could not explore its potential protective effects. As reported by others, graft and donor type were not associated with rPSC in our cohort. Interestingly, the type of biliary reconstruction was also not associated with rPSC, and a Roux-hepaticojejunostomy was not found to be protective against rPSC. Contrary to previous findings (13, 16), we did not observe any differences in immunosuppression management between the 2 groups, and immunosuppression medications—

although variable—did not appear to impact rPSC incidence . However, this finding could be due to our modest sample size and incomplete data (e.g., no doses or tacrolimus troughs available) due to the study's retrospective nature. Non-adherence can trigger rejection and possibly increase the recurrence of autoimmune liver disease. Adherence to prescribed medications likely represents one of the few modifiable risk factors to prevent graft loss in these patients. Autoimmune liver disorders have been reported among the highest causes of graft loss and mortality in young adults during the transition of care(30) and most children with end-stage liver disease from PSC are teenagers who transition to adult care programs soon after LT. Unfortunately, out of the scope of this retrospective study is the impact of patient non-adherence to immunosuppression on rPSC and graft dysfunction, but it is a formidable topic for future study. Over the three decades from which our registry includes data, no new therapies have been developed to improve these patients' outcomes

Strengths and Limitations:

This study includes the largest reported number of pediatric patients transplanted for PSC, a rare disease for analysis, and was only possible due to collaboration between many centers participating in the Pediatric PSC Consortium database. This is the first pediatric study describing the negative the impact of rPSC on patient and allograft survival, emphasizing the importance of conducting prospective well-designed multicenter collaborations to elucidate the risk factors for rPSC and to subsequently modify disease behavior. Limitations include the retrospective nature of data collection, creating the potential for missing cases of rPSC, supporting the notion that the incidence of rPSC could be higher. Furthermore, our report lacks detail in areas of interest such as liver histology, IBD activity, HLA phenotyping and immunosuppression. The gaps reported in this cohort reflect the lack of standard diagnostic or management practices in our multicenter clinical cohort, particularly in the surveillance and

workup for rPSC and IBD activity. The actual rate of rPSC may have been higher had all patients undergone protocol liver biopsy and/or cholangiography at set time points. A more rigorous endoscopic assessment could also have led to better IBD control. We should also acknowledge that a limitation in the field is the lack of a standard clinical assessment that provides accurate differentiation between allograft rejection and rPSC. Additional longitudinal studies that include histology review—to identify biopsies or other early markers of rPSC and differentiate it from acute rejection—would also help earlier, more accurate diagnoses of recurrence, and potentially allow treatment optimization or even prepare the field for clinical trials for new drugs. Further studies of these remaining gaps could facilitate the development of specific immunosuppression management protocols to tamper immunoreactivity and avoid rejection and reactivation of donor-reactive lymphocytes.

Conclusions:

In summary, while LT is a successful therapy for patients with complications related to PSC, disease recurrence affects around one-quarter of children with follow-up available through 5 years after transplantation with increasing incidence overtime. A more aggressive, immune-reactive phenotype of the condition characterized by faster progression to end-stage liver disease, higher frequency of IBD, and more severe hepatobiliary inflammation at LT is associated with rPSC. Graft rejections were diagnosed more frequently, occurred earlier after transplantation, and were refractory to conventional management in subjects who developed rPSC. Liver transaminases were higher at 1-year post-LT in patients with rPSC and should prompt histological and radiological evaluation for rPSC. Disease recurrence is associated with substantial morbidity and mortality early after diagnosis. Our data identify the issues, but are not sufficiently detailed to identify variables amenable to modifying disease behavior or improving outcomes. More zealous radiological and histological monitoring of the allograft might provide

an accurate assessment of alloreactivity and disease recurrence timing. Societal guidance should reflect this need in order to change current clinical practices. There is an urgent need to unravel the pathogenesis of PSC and rPSC, to support the development of novel diagnostic and therapeutic approaches to control the immune reactivity that fuels a resurgent immune attack on the allograft.

Table 1: Demographics and laboratory values at diagnosis and time of liver transplantation (LT) in the recurrent PSC (rPSC) and no PSC recurrence cohorts.

Variables	**rPSC (n=36)**	**No rPSC (n=104)**	**p**
Demographics and phenotype			
Male sex	61%	52%	0.340
Age at PSC diagnosis	9.5 [7.8-12.3]	12.3 [7.8-14.2]	0.082
Age at LT	12.9 [10.7-14.7]	16.2 [13.6-18.0]	**<0.001**
Time between diagnosis and LT	2.5 [0.7-4.6]	4.1 [2.3-6.6]	**0.003**
Features of overlap with AIH (%)	42	29	0.091
Presence of IBD (%)	86%	66%	**0.025**
IBD phenotype (% of the total IBD)			
UC	75%	53%	0.050
CD	11%	13%	
IBD active	33%	27%	0.64
IBD in remission	67%	73%	
Laboratory values at PSC diagnosis			
Hemoglobin	12.2 [10.3-14.2]	12.3 [11.1-13.3]	0.852
Platelet count	279 [93-463]	216 [113-352]	0.401
INR	1.2 [1-1.3]	1.1 [1-1.3]	0.942
Albumin	3.7 [3.2-3.9]	3.7 [3.3-4.0]	0.901
Gamma-glutamyltransferase	234 [153-440]	307 [170-448]	0.968
AST (IU/L)	144 [72-308]	143 [69-239]	0.841
ALT (IU/L)	168 [105-298]	118 [82-196]	**0.049**
Total bilirubin	2.7 [0.7-8.8]	1.3 [0.6-3.8]	0.217
Laboratory values at liver transplantation			
Hemoglobin	10.9 [9.4-12.6]	11.7 [9.6-13.4]	0.232
Platelet count	97 [60-250]	89 [50-150]	0.463
INR	1.4 [1.2-1.7]	1.3 [1.1-1.5]	0.338
Albumin	3.3 [2.9-3.6]	3.4 [2.9-4.1]	0.331
Gamma-glutamyltransferase	157 [66-358]	167 [90-280]	0.966
AST (IU/L)	112 [52-290]	108 [75-164]	0.315
ALT (IU/L)	112 [46-319]	66 [51-114]	**<0.001**
Total bilirubin	8.2 [3.3-21.3]	4.4 [2.1-10.3]	0.124
Laboratory values 6 months after liver transplantation			
Hemoglobin	12.6 [11.3-14.1]	12.2 [10.5-14]	0.542
Platelet count	161 [130-218]	171 [112-227]	0.916
INR	1.1 [1-1.3]	1.1 [1-1.2]	0.399
Albumin	4.2 [4-4.4]	4.2 [3.9-4.5]	0.799
Gamma-glutamyltransferase	41 [19-82]	31 [19-91]	0.701
AST (IU/L)	33 [21-69]	26 [20-48]	0.388
ALT (IU/L)	28 [21-71]	33 [19-61]	0.958
Total bilirubin	0.7 [0.4-1.9]	0.7 [0.5-1.4]	0.768
Laboratory values 12 months after liver transplantation			
Hemoglobin	12.7 [10.7-14.4]	13.1 [11.7-14.7]	0.332
Platelet count	196 [138-292]	162 [129-234]	0.215
INR	1.1 [1-1.3]	1.1 [1-1.2]	0.863
Albumin	4 [3.9-4.3]	4.2 [3.9-4.3]	0.376
Gamma-glutamyltransferase	61 [35-312]	36 [19-74]	**0.020**
AST (IU/L)	58 [31-77]	28 [20-46]	**<0.001**
ALT (IU/L)	55 [27-93]	30 [19-57]	**0.018**
Total bilirubin	0.9 [0.5-1.9]	0.7 [0.5-1.4]	0.597

Table 2. Graft type and perioperative variables

Variables	rPSC (n=25)	No rPSC (n=79)	p
Donor type			
Living-related	18%	20%	0.601
Living-unrelated	0%	6%	
Deceased (braindead)	64%	62%	
Deceased (after cardiac death)	18%	12%	
Donor age (Median [IQR])	27 [16-42]	24 [15-39]	0.951
Graft type			
Whole	73%	68%	0.594
Technical variant graft	27%	32%	
Biliary anastomosis			
Duct-to-duct	13%	25%	0.210
Duct-to-roux	87%	75%	
Ischemia time in minutes			
Warm (Median [IQR])	23 [0-45]	43 [31-45]	0.265
Cold (Median [IQR])	204 [65-342]	170 [33-257]	0.860
MELD			
At listing (Median [IQR])	15 [11-23]	15 [10-21]	0.845
At LT (Median [IQR])	19[15-29]	22 [17-30]	0.941
Increase, from listing to LT (Median [IQR])	+4[2-7]	+2 [0-14]	0.377

Table 3: Immunosuppression management

Variables	rPSC (n=25)	No rPSC (n=79)	p
Immunosuppression induction			
Steroid induction	91%	90%	0.809
Basiliximab	8%	19%	0.234
Thymoglobulin	8%	10%	0.809
Initial steroid taper duration (months)	4 [2-6]	4 [2-8]	0.831
Immunosuppression Maintenance			
Tacrolimus monotherapy	44%	42%	0.510
Tacrolimus + mycophenolate	36%	43%	
Tacrolimus + thiopurines	4%	5%	
Tacrolimus + mTOR inhibitor	16%	6%	
Cyclosporine monotherapy	0%	3%	
Ursodeoxycholic Acid post-LT	65%	54%	0.326

Table 4: Post-transplant Complications

Variables	**rPSC (n=25)**	**No rPSC (n=79)**	**p**
Allograft Rejection			
Number of episodes	3 [1-5]	1 [0-2]	**<0.001**
Episodes of rejection per year after LT	0.8	0.3	**<0.001**
Time to first episode	3.8mo [1mo-1yr]	6.3mo [1.5mo-1.9yr]	0.345
Steroid resistant	41%	20%	**0.046**
Viral replication and serologies			
EVB viral replication	41%	26%	**0.103**
EBV recipient positive	37%	47%	0.434
EBV donor positive	83%	63%	0.173
EBV recipient negative/donor positive	73%	43%	0.425
CMV replication	11%	9%	0.731
CMV patient positive	42%	37%	0.661
CMV donor positive	65%	53%	0.411
CMV recipient negative/donor positive	27%	29%	0.852

Figure 1. Recurrence of primary sclerosing cholangitis after liver transplantation in children

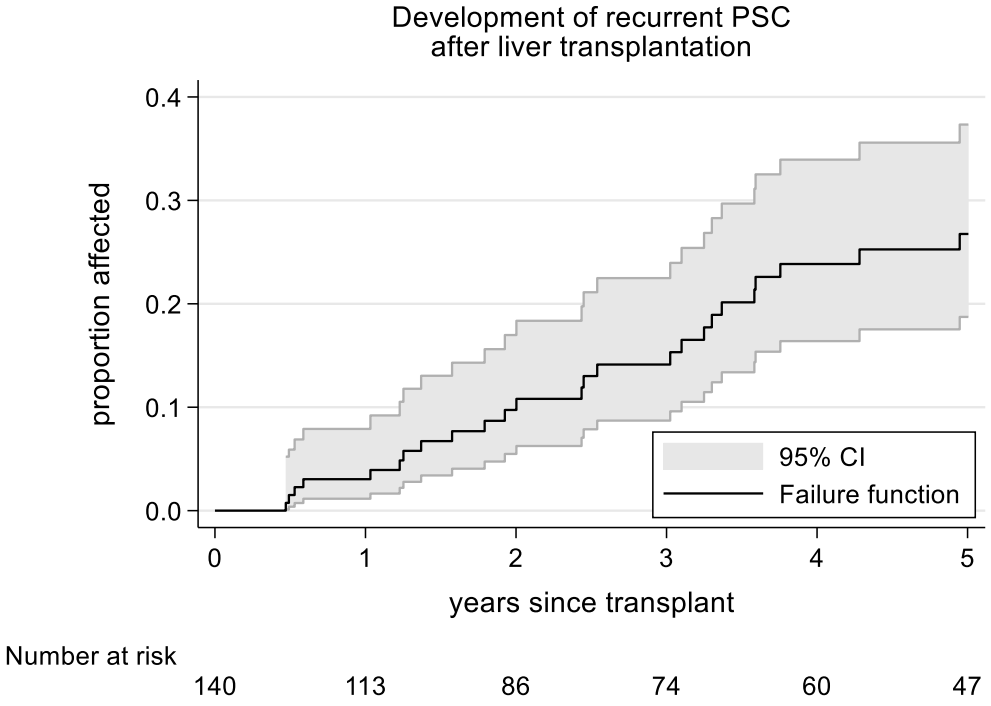


Figure 2. Survival with transplanted liver after diagnosis of recurrence of PSC

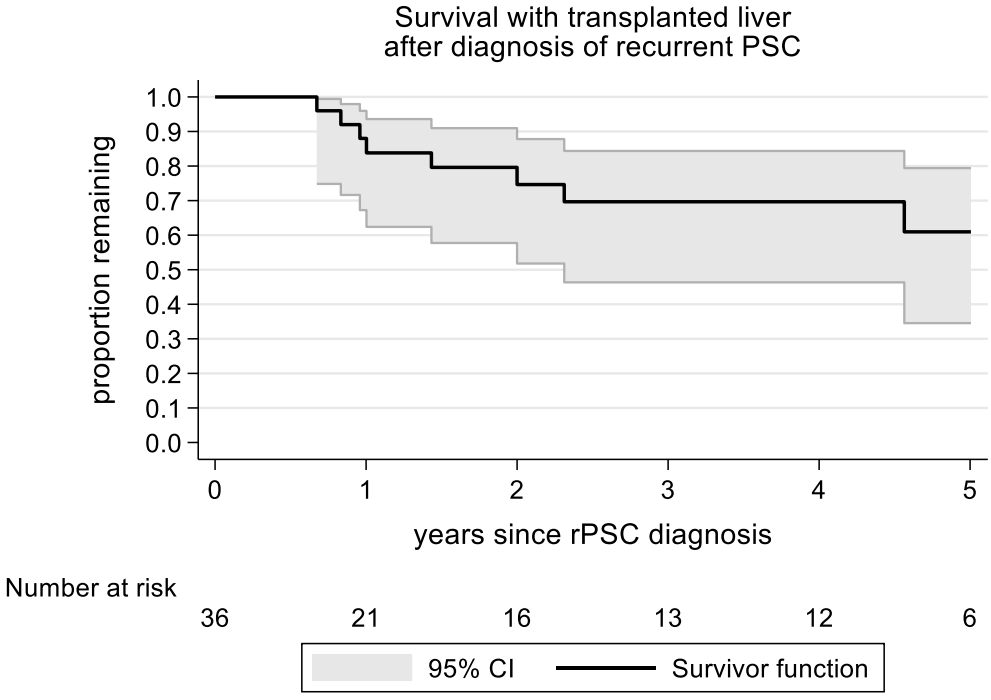
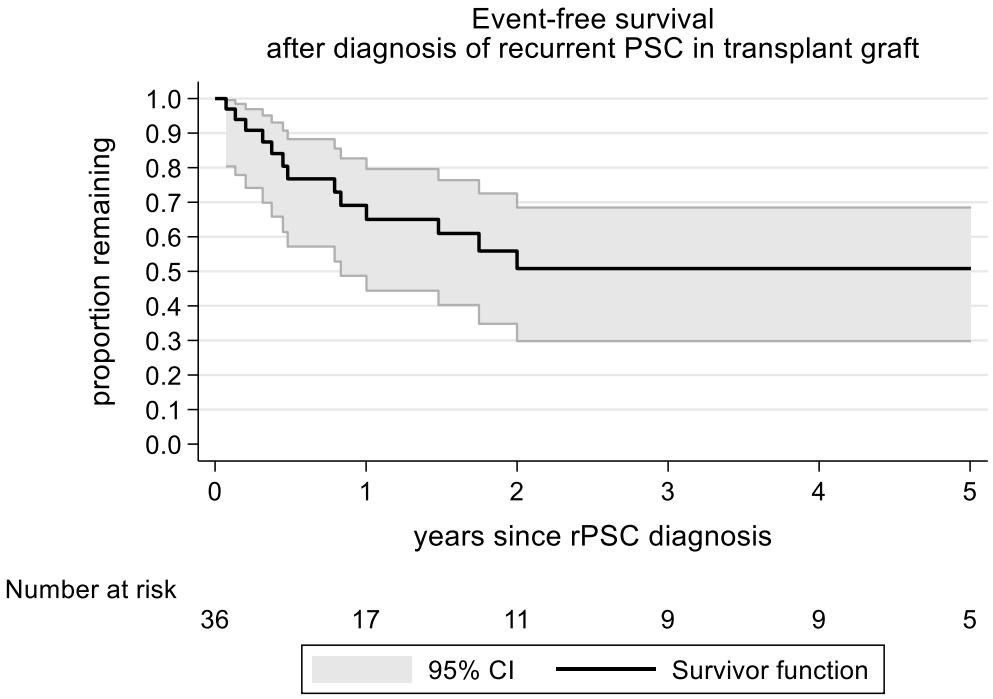


Figure 3. Event-free survival after diagnosis of rPSC



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