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Outcome of Liver Retransplantation in Patients With Primary Sclerosing Cholangitis

Antonio Molinaro[1,2,3] | Lise Katrine Engesæter[2,3,4,5] | Carl Jorns[6] | Arno Nordin[7] | Allan Rasmussen[8] | Pål-Dag Line[4,9] | Virge Pall[10] | Bo-Göran Ericzon[6] | William Bennet[11] | Johannes R. Hov[2,3,4,5] | Espen Melum[2,3,4,5,12]

[1]Department of Molecular and Clinical Medicine, Wallenberg Laboratory, University of Gothenburg, Gothenburg, Sweden | [2]Norwegian PSC Research Center, Division of Surgery and Specialized Medicine, Oslo University Hospital, Oslo, Norway | [3]Research Institute of Internal Medicine, Division of Surgery and Specialized Medicine, Oslo University Hospital, Oslo, Norway | [4]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway | [5]Section of Gastroenterology, Department of Transplantation Medicine, Division of Surgery and Specialized Medicine, Oslo University Hospital, Oslo, Norway | [6]Division of Transplantation Surgery, Department of Clinical Science, Intervention, and Technology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden | [7]Department of Transplantation and Liver Surgery, University Hospital, Helsinki, Finland | [8]Department of Surgical Gastroenterology and Liver Transplantation, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark | [9]Section of Transplantation Surgery, Department of Transplantation Medicine, Division of Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital, Oslo, Norway | [10]Transplantation Centre, Tartu University Hospital, Tartu, Estonia | [11]Transplant Institute, Sahlgrenska University Hospital, The Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden | [12]Hybrid Technology Hub-Centre of Excellence, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway

Correspondence: Espen Melum (espen.melum@medisin.uio.no)

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Keywords: liver transplantation | primary sclerosing cholangitis | retransplantation

ABSTRACT

Background and Aims: Primary sclerosing cholangitis (PSC) is among the most common indications for liver transplantation in the Nordic countries and with an increasing trend in Europe and North America. Due to post-transplant complications and high prevalence of disease recurrence this group is at risk of requiring retransplantation (re-LTX). Results from re-LTX for PSC are not extensively studied and there is a lack of knowledge regarding prognosis after re-LTX in this population.

Methods: Graft and patient survival after re-LTX for patients with PSC and a comparable comparison group from the Nordic liver transplant registry were analysed. One-hundred and eighty-five patients with PSC and 208 patients in the comparison group were included.

Results: The graft and patient survival were better for patients with PSC compared to the comparison group ($p < 0.001$). Re-LTX for recurrence of PSC (rPSC) compared to other aetiologies had similar and better outcomes for graft and patient survival ($p = 0.093$ and $p = 0.023$, respectively). Moreover, re-LTX for rPSC compared to the comparison group had a lower 30-day and 5-year mortality ($p < 0.001$ and $p = 0.041$, respectively).

Abbreviations: ALF, acute liver failure; BMI, body mass index; HBc, hepatitis B virus core; HBs, hepatitis B virus surface antigen; HCV, hepatitis C virus; LTX, liver transplantation; NLTR, Nordic Liver Transplant Registry; PSC, primary sclerosing cholangitis; re-LTX, liver retransplantation; rPSC, recurrent primary sclerosing cholangitis.

Conclusion: Outcomes after retransplantation for PSC were similar or better compared to the comparison group. Retransplantation represents a treatment option with the potential for excellent outcomes in patients with PSC and should be considered in transplanted PSC patients with graft failure.

1 | Introduction

Primary sclerosing cholangitis (PSC) is a cholestatic liver disease characterised by chronic inflammation and fibrosis of large bile ducts, leading to progressive destruction of the biliary tree and cirrhosis [1, 2]. The pathogenesis of PSC is not well-defined and no pharmacological treatment is available to slow the disease process [1]. Liver transplantation is the only definitive therapeutic option and PSC is a leading indication for liver transplantation in Nordic countries [3] and has now increasing trends also in North America [4] and in Europe [5, 6]. Liver transplantation for PSC compared to other aetiologies has in general a good outcome [5]. Unfortunately, recurrent PSC (rPSC) occurs in a substantial proportion of the PSC transplants (20%–30%), with a median time to recurrence of around 5 years [7, 8]. No clinical interventions have been found to treat or prevent rPSC in the transplanted graft and rPSC is therefore also a common indication for retransplantation (re-LTX) [9, 10].

Re-LTX has worse outcome than the first transplant, independently of the aetiology [11], but compete with first liver transplant candidates for the same pool of donors. A liver re-LTX can be technically demanding and raises questions related to both health economics and ethical aspects in organ allocation policies [12]. Given the challenges with rPSC it is important to establish whether the outcomes following re-LTX in patients originally transplanted for PSC are acceptable, and comparable to re-LTX for other aetiologies. Outcomes of re-LTX in patients with PSC have not been well documented, and recent findings are not consistent between cohorts and may be affected by study size and selection of the appropriate comparison groups [10, 13–15].

Here, we analyse data from the Nordic Liver Transplant Registry (NLTR) evaluating the results of re-LTX performed in a large number of patients originally transplanted for PSC and a similarly sized comparison group originally transplanted for non-PSC liver disease. We also evaluate the impact of rPSC on re-LTX graft and patient survival.

2 | Patients and Methods

2.1 | Patients

NLTR was used as the data source in this project. NLTR includes all patients undergoing LTX in Denmark, Estonia, Finland, Iceland, Norway and Sweden from the first transplant in 1982. LTX and re-LTX are performed in all these countries except for Icelandic patients who have been transplanted in Denmark or Sweden. We included adult recipients (above 18 years of age at the time of the first transplant) listed with PSC as the primary transplant indication. As comparison group, we selected recipients transplanted due to a non-viral, non-malignant and non-acute liver disease (i.e. patients with alcohol related, autoimmune, metabolic and cryptogenic liver diseases). Patients listed with acute liver failure (ALF) or with hepatocellular carcinoma or cholangiocarcinoma as the primary diagnosis were excluded from the analysis. Patients with positive serology for hepatitis C virus (HCV), hepatitis B virus surface (HBs) antigen or hepatitis B virus core (HBc) antibodies or a first transplant outside of the Scandiatransplant area were also excluded. Complete follow-up data were available until 31 December 2022 for all patients.

We considered re-LTX performed > 5 years after liver transplantation for PSC as likely due to rPSC. To evaluate this cut-off, we retrospectively reviewed a cohort of patients that were retransplanted at two of the transplant centres included in NLTR (Oslo and Gothenburg). For the patients retransplanted in Oslo ($n = 22$), the diagnosis of rPSC was based on medical chart review, including re-evaluation of all MRIs and liver biopsies done on both routine follow-ups and on clinical indication in transplanted PSC patients. For these patients the diagnosis of rPSC was made according to criteria described in Graziadei et al. [16]. For the patients retransplanted in Gothenburg ($n = 17$), we evaluated those listed for retransplant and whether they were listed with a diagnosis of rPSC based on the clinician's assessment.

2.2 | Statistical Analysis

All statistical analyses were performed using R and IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). Clinical and biochemical variables were compared between groups using the Mann–Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. Graft survival was calculated from the date of the first/second transplant to the follow-up/death or eventual second/third liver transplant where appropriate. Patient survival was calculated from the second transplant to death or last available follow-up (31 December 2022). Survival was visualised with Kaplan–Meier plots and the log-rank test was used to compare survival distributions. Variables predicting graft or patient survival were evaluated using univariate and multivariate Cox regression. $p < 0.05$ were considered statistically significant.

3 | Results

3.1 | PSC Patients and Comparison Group

During the period 1982–2022, 8486 patients recorded in NLTR received a first liver transplant and 866 of them also underwent a re-LTX (10.2%). Patients under 18 years of age at first transplant, those undergoing LTX due to urgent call or acute liver failure, previous/ongoing HCV or HBV infection and those with liver cancers were excluded. Patients with PSC

Summary

- Retransplantation is necessary in selected cases when the transplanted organ fails.
- By using a high-quality Nordic liver transplant registry, we show that retransplantation in patients originally transplanted due to primary sclerosing cholangitis (PSC) compared to those transplanted for other liver diseases has acceptable outcomes, with good graft and patient survival.
- Our findings strongly support the practice of offering retransplantation to PSC patients, even for those with recurrent disease after transplantation.

undergoing a re-LTX ($n = 185$) were compared to a group of patients with non-viral, non-cancer, non-urgent, non-ALF liver transplant indication undergoing a re-LTX (comparison group, $n = 208$, Figure 1). The comparison group was chosen based on representing a relevant competitor population for organ allocation in re-LTX for PSC. They consisted of patients with alcoholic (22%), autoimmune (17%), metabolic-cryptogenic (23%), other aetiology (e.g. Budd–Chiari and polycystic liver disease) (14%) and other cholestatic liver diseases (25% of which 92% were due to primary biliary cholangitis) (Table 1). At re-LTX, the PSC group was younger than the comparison group ($p < 0.001$), had a lower BMI ($p < 0.001$) and a male predominance ($p < 0.001$). The MELD scores at re-LTX were similar in the PSC and comparison groups. Fewer patients in the PSC group were in dialysis (13% vs. 16.8%, $p = 0.023$) or received respiratory support (11% vs. 19%, $p = 0.004$) at time of re-LTX. Donor characteristics did not differ between groups. There was an increased rate of re-LTX in the PSC group compared to the comparison group (18.9% and 10.1% respectively, $p = 0.011$). The PSC group had longer graft survival following the first liver transplant than the comparison group (logrank $p < 0.001$, Figure S1), with a median survival of 4.1 years versus 0.4 years. Urgent retransplantation after the primary transplant (within 30 days) was also less frequent in the PSC group, 10% versus 34% in the comparison group ($p < 0.001$) (Table 1).

3.2 | Re-LTX for PSC has a Superior Outcome

Patients undergoing a re-LTX in the PSC group had a better graft survival than in the comparison group. The graft survival at 1, 5, 10, 15 and 20 years post re-LTX in the PSC group were 85%, 73%, 61%, 41% and 36%, respectively, while the respective numbers in the comparison group were 66%, 54%, 44%, 33% and 17% (logrank $p < 0.001$, Figure 2). Next, we evaluated potential predictors of graft survival in both groups jointly (Table 2). In addition to PSC as first transplant indication, transplant year, transplant centre and time from LTX to re-LTX were associated with improved graft survival in univariate Cox-regression analyses. Recipient age, dialysis, respiratory support, donor age and the use of a split graft were associated with reduced graft survival. Significant variables in the univariate analysis were then included in a multivariate Cox regression analysis (Table 2).

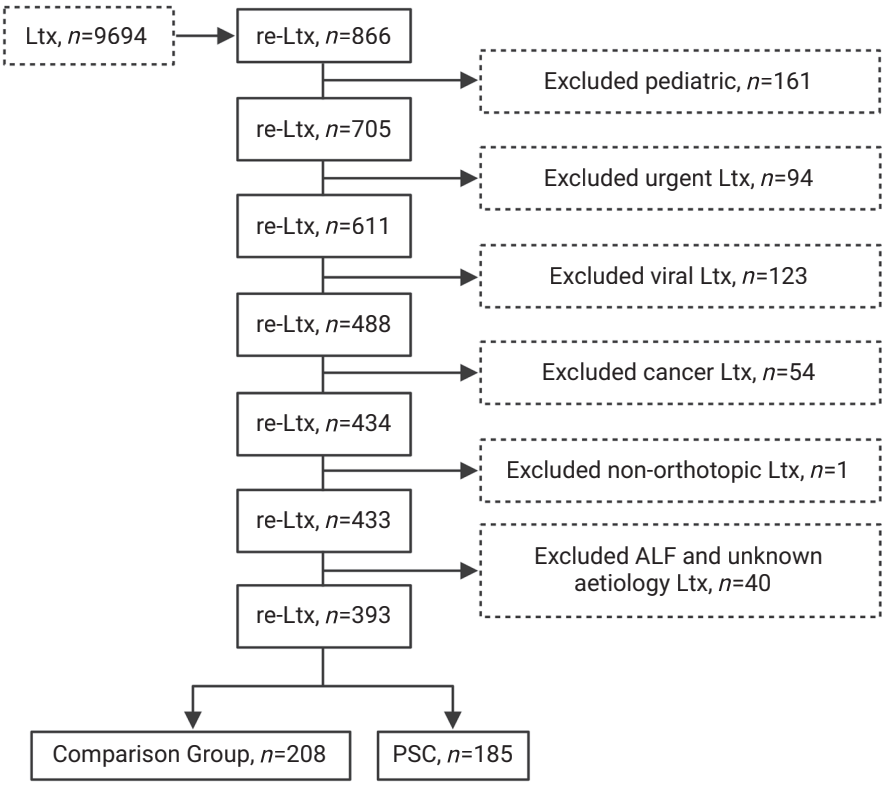

FIGURE 1 | Selection criteria for study population for patients with primary sclerosing cholangitis (PSC) and the comparison group undergoing retransplantation (re-LTX). Patients under 18 years of age, patients with positive serology for hepatitis B virus (HBV) or hepatitis C virus (HCV), patients with urgent liver transplantation (LTX) or with liver transplant due to acute liver failure (ALF) were excluded from the analysis. Figure was made with Bio-Render.

TABLE 1 | Clinical characteristics of patients with primary sclerosing cholangitis (PSC) and patients in the comparison group.

	PSC	Comparison group	*p*	% missing values
n	185	208	—	—
Age (years)	48 (40–61)	53 (44–61)	**< 0.001**	0
Male sex, *n* (%)	129 (69.7)	101 (48.6)	**< 0.001**	0
BMI (m^2/kg)	22.5 (20.6–25.2)	24.5 (21.6–27.8)	**< 0.001**	15.8
Aetiology, *n* (%)				
Alcohol	0	46 (22.1)	—	0
Autoimmune	0	35 (16.8)		
Metabolic-cryptogenic	0	48 (23.1)		
Other	0	28 (13.5)		
PSC	185 (100)	—		
Other cholestatic	0	51 (24.5)		
MELD	17.4 (9.4–25.3)	20.4 (10.7–28.5)	0.11	40
Dialysis, *n* (%)	24 (13)	35 (16.8)	**0.023**	26.2
Respiratory support, *n* (%)	20 (10.8)	40 (19.2)	**0.004**	26.2
Donor age (years)	50 (34.3–62)	50 (36–60)	0.90	1.2
Donor male sex, *n* (%)	85 (45.9)	103 (49.5)	0.07	1.2
DCD donor, *n* (%)	1 (0.5)	1 (0.5)	—	0
Blood group miss-match, *n* (%)	5 (2.7)	8 (3.9)	0.35	1
Split transplant, *n* (%)	8 (4.3)	8 (3.8)	0.50	0
Liver retransplant year, *n* (%)				
< 2000	16 (8.6)	42 (20.2)	**0.011**	0
2000–2004	16 (8.6)	25 (12.0)		
2005–2009	31 (16.8)	34 (16.3)		
2010–2014	35 (18.9)	38 (18.3)		
2015–2019	56 (30.3)	46 (22.1)		
2020–2022	31 (16.8)	23 (11.1)		
Transplant centre, *n* (%)				
Gothenburg	53 (28.6)	53 (25.5)	0.70	0
Oslo	48 (25.9)	47 (22.6)		
Stockholm	31 (16.8)	34 (16.3)		
Helsinki	22 (11.9)	31 (14.9)		
Copenhagen	28 (1.1)	38 (18.3)		
Uppsala	3 (1.6)	3 (1.4)		
Tartu	0 (0)	2 (1)		
Time from first transplant (years)	4.11 (0.4–8.7)	0.4 (0.1–3.5)	**< 0.001**	0
Retransplant within 30 days, *n* (%)	18 (9.7)	68 (33.7)	**< 0.001**	0

Note: Data are expressed as median and interquartile range or as proportions. *p*-values were calculated using Mann–Whitney *U*-test. Categorical variables' distribution was compared by Fisher exact test.
Abbreviations: BMI, body mass index; DCD, donation after circulatory death; MELD, model for end-stage liver diseases.

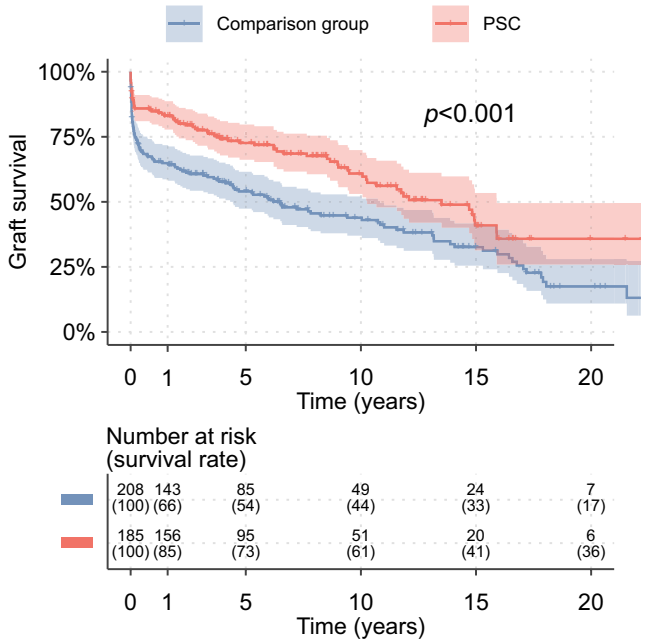

FIGURE 2 | Kaplan–Meier plot for graft survival in years after retransplantation for patients in the PSC and comparison group. *p* value was calculated with log-rank test. The numbers shown below the survival graphs indicate the number of patients contributing to the analyses at that specific time point and in parenthesis the survival rate for patients with PSC and the comparison groups 1, 5, 10, 15 and 20 years after retransplantation. PSC, primary sclerosing cholangitis.

Recipient age, dialysis at time of transplant, donor age, use of split graft and PSC as first transplant indication remained significant predictors of graft survival in the multivariate analysis (hazard ratio [HR] for PSC: 0.59, 95% confidence interval [CI]: 0.41–0.87, $p = 0.007$).

When evaluating patient survival, a significant difference between PSC and the comparison group was observed (log-rank $p < 0.001$, Figure S2). In multivariate Cox regressions, dialysis, use of split graft and PSC as transplant indication were significant predictors of patient survival (HR for PSC: 0.57 [95% CI: 0.35–0.98], $p = 0.041$ [Table S1]). However, the PSC group had a higher rate of multiple retransplantations (defined as more than one re-LTX: 19% vs. 10%, $p = 0.013$).

Next, we evaluated potential predictors of survival within the PSC group for graft and patient survival. In the multivariate analysis, donor age was a significant predictor of graft survival (Table S2), while blood group mismatch and transplant year were significant predictors of patient survival (Table S3).

Moreover, when comparing retransplant outcomes for patients with a primary indication of PSC with patients with other important primary indications for transplant in the comparison group such as alcohol-related liver disease (ALD) or primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH), patients with PSC had a better graft and patient survival (graft: PSC vs. PBC/AIH $p = 0.005$ and PSC vs. ALD $p = 0.013$; patient: PSC vs. PBC/AIH $p < 0.001$ and PSC vs. ALD $p < 0.001$, respectively, log-rank, data not shown).

When we analysed re-LTX outcomes for the entire NLTR registry including patients originally transplanted with a viral or cancer indication, we could observe that for both graft and patient survival patients undergoing a re-LTX in the PSC group had a better graft survival than in the comparison group ($p < 0.001$ and $p < 0.001$, respectively, log-rank, data not shown).

When we analysed the cohort of patients listed for retransplantation in an intention-to-treat analysis with the same inclusion/exclusion criteria as in the main analysis, patients in the PSC group had a better graft survival than in the comparison group (logrank $p < 0.001$, data not shown).

3.3 | Re-LTX for rPSC has Similar Outcome as the Comparison Group

To evaluate a potential impact of PSC recurrence (rPSC) in the first graft on re-LTX outcomes, we selected patients with PSC undergoing re-LTX at least 5 years after LTX with the assumption that the most likely indication for re-LTX after this time point would be rPSC. We then compared the rPSC group with an appropriate subgroup of the comparison group comprising patients undergoing re-LTX due to long-term or late post-LTX complications (> 5 years from LTX). To systematically evaluate this 5 years post-LTX cut-off for rPSC, we assessed two cohorts of patients undergoing re-LTX for PSC in Oslo and Gothenburg. In these two centres, 86% and 88% of re-LTX performed after at least 5-years from the LTX were due to rPSC, indicating that our cut-off was reliable to discriminate rPSC.

The rPSC subgroup had a lower BMI and a higher frequency of males than the comparison group ($p < 0.001$, Table S4). Patients undergoing re-LTX in the rPSC group had a trend towards better graft survival than the comparison group, with survival rates at 1, 5, 10 and 15 years post re-LTX of 87%, 79%, 59% and 43%, respectively, in the rPSC group and 69%, 60%, 56% and 47%, respectively in the comparison group (log-rank $p = 0.09$, Figure 3). In univariate Cox regression analysis, predictors of graft survival were BMI, dialysis and donor age (Table 3), while only use of dialysis before transplant was a significant predictor of graft survival in the multivariate analysis.

The rPSC patients, had a significantly improved patient survival compared to the comparison group (log-rank $p = 0.023$, Figure S3). In multivariate Cox regression analysis for patient survival, MELD score and donor age were significant predictors of patient survival, but not rPSC (Table S5). The re-retransplantation rate was not significantly different between the groups (13% vs. 14%, $p = 0.85$).

Next, we evaluated potential predictors of survival within the rPSC group for graft and patient survival. In the univariate analysis, dialysis was a significant predictor of graft survival (Table S6), while MELD-score, dialysis and transplant with split grafts were significant predictors of patient survival (Table S7). No variables were significant in the multivariate analysis of patient survival.

TABLE 2 | Uni- and multivariate Cox regression for graft survival after liver retransplantation in the study cohort.

	Univariate				Multivariate			
	B	**HR**	**95% CI**	***p***	***B***	**HR**	**95% CI**	***p***
Age (years)	0.82	2.27	1.29–3.98	**0.004**	0.74	2.10	1.05–4.19	**0.036**
Male sex	−0.09	0.91	0.69–1.29	0.53				
BMI (m^2/kg)	0.23	1.26	0.52–3.06	0.61				
MELD	0.33	1.39	0.97–1.99	0.08				
Dialysis	0.89	2.43	1.69–3.49	**< 0.001**	0.80	2.22	1.31–3.75	**0.003**
Respiratory support	0.54	1.72	1.18–2.51	**0.005**	0.32	1.38	0.78–2.46	0.27
PSC versus comparison group	−0.53	0.59	0.44–0.79	**< 0.001**	−0.52	0.60	0.41–0.87	**0.007**
Donor age (years)	0.01	1.01	1.00–1.02	**0.010**	0.70	2.03	1.29–3.19	**0.002**
Donor male sex	−0.05	0.96	0.72–1.27	0.96				
Blood group miss-match	0.48	1.62	0.76–3.45	0.21				
Split transplant	0.65	1.92	1.01–3.63	**0.046**	1.19	3.27	1.54–6.91	**0.002**
Liver retransplant year, (years)	−0.21	0.81	0.74–0.89	**< 0.001**	−0.46	0.96	0.93–0.98	**< 0.001**
Transplant centre								
Gothenburg	Ref	Ref	Ref	—	Ref	Ref	Ref	—
Oslo	−0.21	0.81	0.54–1.22	0.31	−0.43	0.65	0.41–1.02	0.06
Stockholm	−0.06	0.95	0.66–1.36	0.77	−0.24	0.79	0.48–1.29	0.34
Helsinki	−0.23	0.74	0.48–1.15	0.18	0.11	1.11	0.42–2.94	0.83
Copenhagen	0.69	0.50	0.33–0.76	**0.001**	−0.26	0.77	0.41–1.45	0.42
Uppsala	−0.23	0.80	0.53–1.20	0.28	−1.16	0.31	0.04–2.50	0.27
Tartu	2.40	11.04	3.19–38.19	**< 0.001**	—	—	—	—
Time from first transplant (years)	−0.04	0.96	0.93–0.99	**0.015**	0.04	1.04	0.94–1.15	0.42
Retransplant within 30 days	0.31	1.36	0.98–1.87	0.06				

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MELD, model for end-stage liver diseases.

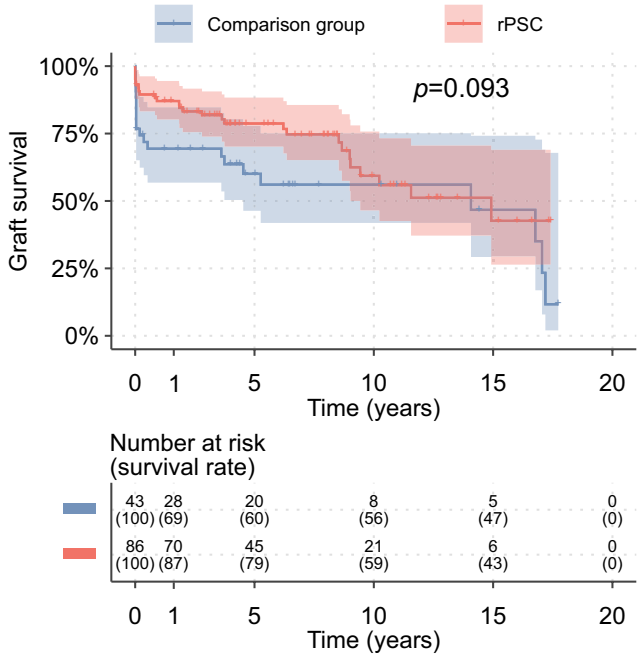

FIGURE 3 | Kaplan–Meier plot for graft survival in years after re-transplantation in a subset of patients with recurrence of PSC after transplantation (rPSC) and in an appropriate comparison group. rPSC defined as retransplantation performed > 5 years after first liver transplant in PSC. *p*-value was calculated with log-rank test. The numbers shown below the survival graphs indicate the number of patients contributing to the analyses at that specific time point and in parenthesis the survival rate for patients with PSC and the comparison groups 1, 5, 10, 15 and 20 years after retransplantation. PSC, primary sclerosing cholangitis.

3.4 | Re-LTX for PSC has Acceptable Outcomes When Evaluated by Futility Criteria

Finally, we evaluated if re-LTX is futile in PSC by assessing 90-day and 5-year mortality rates after transplantation, which have been proposed as indicators of futility in liver transplantation. Indicative of futility are a high 90-day mortality and 5-year mortality exceeding 50% [17, 18]. The mortality rates following re-LTX in the PSC group were 5% at 90 days and 33% at 5 years while the corresponding rates in the comparison group were 10% and 52%, respectively ($p = 0.06$ and $p < 0.001$, Figure 4A). The 90-day mortality was similar in the rPSC and the comparison group ($p = 0.35$), while the 5-year mortality in rPSC was significantly lower ($p = 0.041$, Figure 4B).

4 | Discussion

In this study, the outcome of primary and retransplant for PSC was better or comparable to a relevant comparison group both in terms of graft and patient survival. Specifically, patients deemed to undergo re-LTX for presumed rPSC had outcomes similar to non-PSC undergoing re-LTX for late/long-term post-LTX complications. Moreover, re-LTX for PSC had lower 90-day and 5-year mortality than the comparison group and, importantly, below commonly accepted thresholds for futility in liver transplantation.

The limited availability of donor organs makes it crucial to identify the factors and patient groups associated with poor survival after re-LTX to avoid futile use of scarce liver grafts [19]. Re-LTX has a lower survival rate than primary liver transplantation [20] and specific attention is needed for this sub-group of patients. As recurrent PSC is common after liver transplantation, PSC is a patient population in which outcomes should be investigated in detail. We found that graft and patient survival at 1 year in rPSC were 79% and 86%, respectively. These results are in line with a previous reports from North America [13] and Europe [10] registries reporting a 1-year graft survival of 76% and 80% and patient survival of 82% and 89% after re-LTX in rPSC, respectively, consistent with good retransplant outcomes [13].

Futility in liver transplantation is a major concern for organ allocation policies and of particular relevance in re-LTX [20]. Our data clearly show, in accordance with previously published data [13], that re-LTX for PSC and for rPSC is not futile. These results are in line with the consensus statement from European Society of Organ Transplantation stating that retransplantation should be considered for patients with rPSC [21].

As patients listed for transplant 'compete' with each other with regards to available donor organs, it is important to assess how PSC performs compared with other groups undergoing re-LTX. We therefore selected a comparison group of patients with a chronic non-viral non-malignant liver disease for which there are no strong arguments in favour of prioritising one over the other if they require a retransplant. The analysis clearly demonstrates better graft and patient survival in PSC than in the comparison group. The definition of the comparison group is a critical point, and this group was characterised by patients with mostly alcohol and non-PSC cholestatic end-stage liver disease as primary transplant indication and are competing with PSC patients for organ allocation in case of re-LTX. The comparison group was constructed to exclude disease-related factors that could introduce bias by, for example, negatively impact their outcomes (e.g. different eras of HCV treatment or HCC indications for liver transplantation). Notably, our results were consistent in a sub analysis of patients undergoing re-LTX for rPSC. Previous reports on retransplantation [10, 13] have compared PSC patients with the entire pool of retransplants or compared the outcomes in retransplanted PSC patients without stratifying whether the indication was recurrent disease or not. The present analysis can provide more confidence on the impact of recurrent disease on the outcome of retransplantation in PSC.

In our analysis, the PSC population mainly represents a late re-transplant group while the comparison group represents mainly an early retransplant group. Despite these differences, we believe that the comparison between groups is still valid because they compete for the same pool of donors for retransplantation. Even when we perform a sub analysis in late retransplant (> 5 years from the first LTX) outcomes were very similar in both the rPSC and the selected comparison group.

One of the major strengths of the present study is that it includes the largest cohort of re-LTX in PSC performed in Europe, and that the participating centres are experienced in the clinical/surgical management of rPSC. On the other hand, a major limitation is the surrogate diagnosis of rPSC based on time trend from

TABLE 3 | Uni- and multivariate Cox regression for graft survival after liver transplantation in a subgroup of study cohort with primary sclerosing cholangitis after liver transplant (rPSC) and in an appropriate comparison group.

	Univariate				Multivariate			
	B	**HR**	**95% CI**	***p***	***B***	**HR**	**95% CI**	***p***
Age (years)	1.50	4.50	0.92–21.97	0.06				
Male sex	−0.26	0.77	0.44–1.36	0.37				
BMI (m^2/kg)	1.73	5.66	1.19–28.88	**0.029**	0.73	2.07	0.15–28.21	0.59
MELD	0.71	2.03	0.95–4.33	0.07				
Dialysis	2.28	9.79	3.62–26.51	**<0.001**	1.96	7.11	2.31–21.85	**<0.001**
Respiratory support	0.34	1.40	0.33–5.93	0.65				
PSC versus comparison group	−0.25	0.78	0.59–1.05	0.10	−0.57	0.57	0.25–1.30	0.18
Donor age (year)	0.94	2.56	1.19–5.50	**0.016**	0.91	2.49	0.95–6.49	0.06
Donor male sex	0.05	1.06	0.59–1.89	0.86				
Blood group miss-match	1.21	3.36	0.45–25.07	0.24				
Split transplant	−0.42	0.66	0.09–4.80	0.68				
Liver retransplant year (years)	−0.08	0.92	0.70–1.20	0.55				
Transplant centre								
Gothenburg	Ref	Ref	Ref	—				
Oslo	−0.89	0.41	0.17–0.99	0.05				
Stockholm	−0.02	0.98	0.42–2.30	0.97				
Helsinki	−0.49	0.61	0.26–1.43	0.26				
Copenhagen	−0.38	0.68	0.28–1.65	0.40				
Uppsala	−0.45	0.64	0.09–4.83	0.07				
Tartu	—	—	—	—				
Time from first transplant (years)	−0.45	0.64	0.084–4.828	0.67				

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MELD, model for end-stage liver diseases.

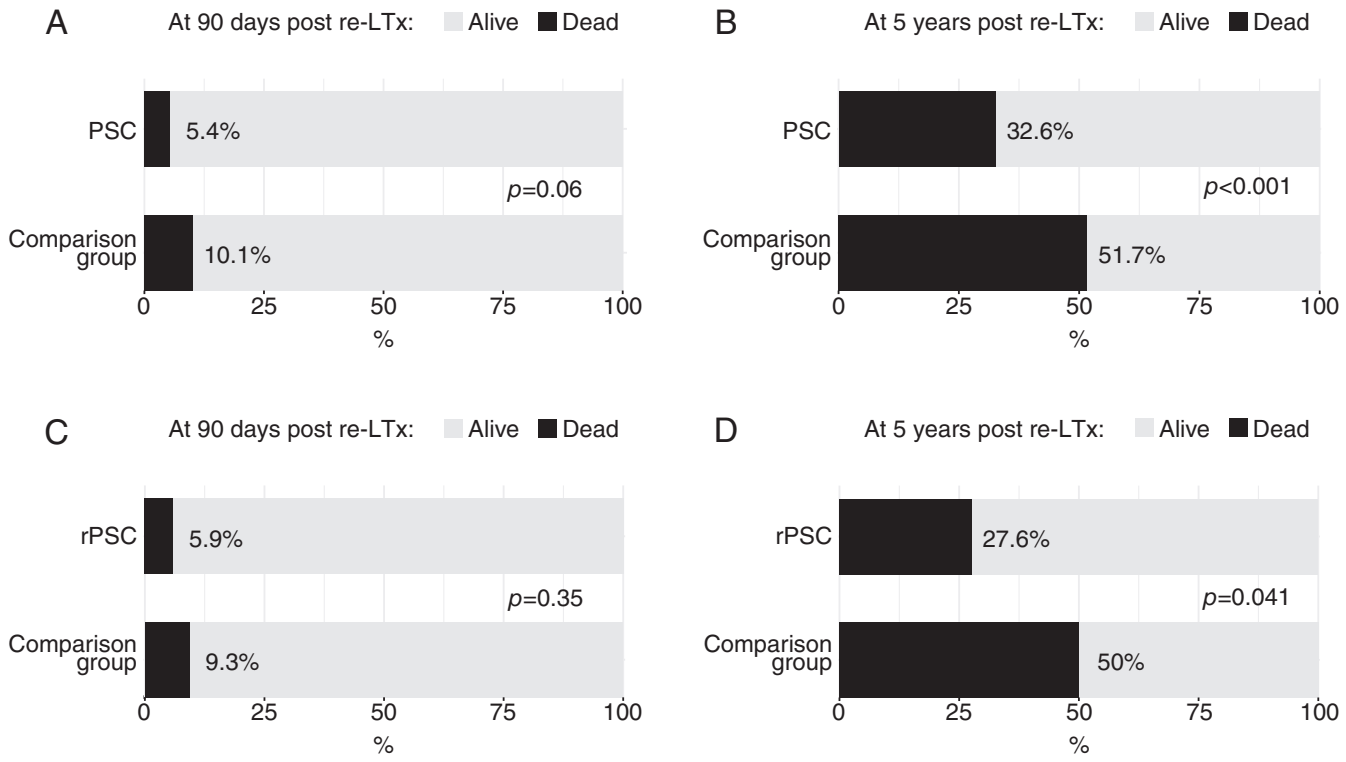

FIGURE 4 | Retransplant for PSC is not futile. Percentage of patients dead at 90 days (A) or after 5 years (B) from retransplantation in PSC and comparison group. Percentage of patients dead at 90 days (C) or after 5 years (D) from retransplantation in recurrence of PSC after transplantation (rPSC) and appropriate comparison group. *p* value were calculated using Fisher exact test. PSC, primary sclerosing cholangitis; rPSC, defined as re-transplantation performed > 5 years after first liver transplant in PSC.

liver transplant to re-LTX, which might not capture all the cases of rPSC due to changes in diagnostic criteria and in the quality of imaging. However, the applied cut-off provides a reasonable good certainty for the diagnosis as shown in the sub-cohorts from Oslo and Gothenburg.

In conclusion, our data suggest that re-LTX in PSC has a good performance in terms of graft and patient survival compared to other aetiologies and does not represent futile use of liver grafts. While we seek new and effective treatment strategies for PSC and rPSC, re-LTX in patients originally transplanted for PSC should be performed when needed and encouraged in the national and international liver transplant programmes.

Author Contributions

A.M. and L.K.E. performed data analysis. E.M. supervised data analysis and coordinated project contributions. A.M., L.K.E., J.R.H. and E.M. drafted the manuscript. E.M., C.J., A.N., A.R., A.R., P.-D.L., V.P., B.-G.E. and W.B. were responsible for and oversaw data collection. All authors revised and approved the final version of the manuscript.

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Ethics Statement

Collection of data has been approved by the individual centres and countries.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are owned by the Nordic Liver Transplant Group and can be made available for collaborative projects that can be coordinated by the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.