







ORIGINAL ARTICLE

Recurrence of primary sclerosing cholangitis after liver transplantation – analysing the European Liver Transplant Registry and beyond

Thijmen Visseren^{1,2} , Nicole Stephanie Erler^{3,4}, Wojciech Grzegorz Polak² , René Adam⁵, Vincent Karam⁵ , Florian Wolfgang Rudolf Vondran⁶, Bo-Goran Ericzon⁷, Douglas Thorburn⁸, Jan Nicolaas Maria IJzermans², Andreas Paul⁹, Frans van der Heide¹⁰, Pavel Taimr¹¹, Petr Nemeč¹², Jacques Pirenne¹³, Renato Romagnoli¹⁴ , Herold Johnny Metselaar¹ , Sarwa Darwish Murad¹ 
for the European Liver and Intestine Transplantation Association (ELITA)

1 Department of Gastroenterology and Hepatology, Erasmus MC Transplant Institute, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands

2 Department of Surgery, Division of Hepatopancreaticobiliary and Transplant Surgery, Erasmus MC Transplant Institute, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands

3 Department of Biostatistics, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands

4 Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands

5 Centre Hépatobiliaire, AP-HP Hôpital Paul Brousse, Université Paris-Saclay, Villejuif, France

6 Department of General, Visceral and Transplant Surgery, Hannover Medical School, Hannover, Germany

7 Division of Transplantation Surgery, Karolinska University Hospital, Stockholm, Sweden

8 Sheila Sherlock Liver Centre and UCL Institute of Liver and Digestive Health, Royal Free Hospital, London, UK

9 Department of General and Transplant Surgery, University Hospital Essen, Essen, Germany

10 Department of Gastroenterology and Hepatology, University of Groningen and University Medical Centre Groningen, Groningen, The Netherlands

SUMMARY

Liver transplantation for primary sclerosing cholangitis (PSC) can be complicated by recurrence of PSC (rPSC). This may compromise graft survival but the effect on patient survival is less clear. We investigated the effect of post-transplant rPSC on graft and patient survival in a large European cohort. Registry data from the European Liver Transplant Registry regarding all first transplants for PSC between 1980 and 2015 were supplemented with detailed data on rPSC from 48 out of 138 contributing transplant centres, involving 1,549 patients. Bayesian proportional hazards models were used to investigate the impact of rPSC and other covariates on patient and graft survival. Recurrence of PSC was diagnosed in 259 patients (16.7%) after a median follow-up of 5.0 years (quantile 2.5%–97.5%: 0.4–18.5), with a significant negative impact on both graft (HR 6.7; 95% CI 4.9–9.1) and patient survival (HR 2.3; 95% CI 1.5–3.3). Patients with rPSC underwent significantly more re-transplants than those without rPSC (OR 3.6, 95% CI 2.7–4.8). PSC recurrence has a negative impact on both graft and patient survival, independent of transplant-related covariates. Recurrence of PSC leads to higher number of re-transplantations and a 33% decrease in 10-year graft survival.

Transplant International 2021; 34: 1455–1467

Key words

bayesian statistics, disease recurrence, liver transplantation, patient and graft survival, primary sclerosing cholangitis

Received: 28 March 2021; Revision requested: 15 May 2021; Accepted: 18 May 2021; Published online: 28 June 2021

11 Department of Hepatogastroenterology, Institut Klinické Experimentální Medicíny, Prague, Czech Republic

12 Centre of Cardiovascular Surgery and Transplantations, Brno, Czech Republic

13 Abdominal Transplantation Surgery, University Hospitals Leuven, Leuven, Belgium

14 Liver Transplantation Center, Azienda Ospedaliero-Universitaria, Città della Salute e della Scienza di Torino, Turin, Italy

Correspondence

Sarwa Darwish Murad MD, PhD, Erasmus MC University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Office NA605, post office NA 606, PO BOX 2040, 3000 CA Rotterdam, the Netherlands.

Tel./fax: +31 10 703 5942;

e-mail: s.darwishmurad@erasmusmc.nl

Introduction

Primary sclerosing cholangitis (PSC) is an immune-mediated disorder in which there is progressive damage and narrowing of the intra- and extrahepatic bile ducts. The pathophysiology is only partially elucidated and so far, disease-specific therapy has been lacking [1]. PSC occurs more commonly in men than in women, occurs at any age with a peak incidence around 40 years and is strongly associated with inflammatory bowel disease [2]. PSC is generally progressive and culminates in life threatening complications such as decompensated liver cirrhosis, recurrent cholangitis, hepatocellular carcinoma and cholangiocarcinoma. Liver transplantation (LT), reserved for selected patients with advanced or complicated disease, is the only potential curative treatment [3]. PSC is most prevalent in the northern parts of the European and American continents with 6–16 cases per 100.000 inhabitants [4–6] and hence an important indication for LT in these countries [7]. A Dutch population-based epidemiological study estimated that the median survival from diagnosis until LT or PSC-related death was 21.3 years [4]. The outcome after LT for PSC in terms of patient survival is excellent with reported 1-, 5- and 10-year survival of 87%, 79% and 70%, respectively [8].

A major consideration, however, is recurrence of PSC (rPSC) in the new graft, which is reported to occur in 8–27% of patients after a median of 4.7 years [8–13]. Over the past few decades, the impact of rPSC on both graft and patient survival has been the subject of investigation in several studies, which have reported conflicting outcomes [14]. Two multicentre studies, each based on national registries, showed that rPSC has a negative impact on graft survival and is, therefore, associated with higher re-transplant rates [8,13]. The negative effect on patient survival, however, was not consistent in the multivariable models used, possibly explained by the different statistical methods applied. In contrast, a

recent study of two European centres showed no negative effect of rPSC on patient survival [15], rendering the impact of rPSC on patient survival still uncertain.

This study was initiated to investigate the impact of rPSC after LT for PSC on graft and patient survival and the need for re-transplantation in a large dataset, derived from the standard registry data of the European Liver Transplant Registry (ELTR), supplemented with individual centre data on the development and outcome of rPSC. The outcomes of interest were graft and patient survival and the need for re-transplantation.

Patients and methods

Study design and patient population

Registry data were requested from the ELTR and included all first LTs for PSC, performed between 1980 and 2015. Follow-up was until 31 October 2017. Nearly all European LT centres (138 centres in 23 countries) are contributing to the ELTR, collecting prospective donor, recipient and transplant data. All 138 centres were individually contacted with a request to report data on rPSC, any subsequent transplants and updated outcomes. Ethical approval is embedded in participation in the ELTR and is arranged locally in each centre.

Data collection and rPSC definition

The following data were extracted from the ELTR registry: recipient data (age, gender and blood type), donor data of the first graft (age, gender, blood type, graft type, date of transplant and total ischaemic time (warm and cold combined)), outcome (alive, death and re-transplant), cause of graft failure and patient death. Type of graft and type of donor were combined into one categorical variable, with categories donation after brain death (DBD) full graft, DBD split graft, donation after circulatory death (DCD) (all full grafts) and living

donor liver transplantation (LDLT). Cause of graft failure and cause of patient death were categorized into 1) liver related; 2) nonliver related; and 3) unknown.

Participating centres were instructed to define rPSC according to the established Mayo criteria, which were specified in the personal inquiry [10]. These criteria include a confirmed diagnosis of PSC before LT; a cholangiogram showing nonanastomotic biliary strictures of the intrahepatic and/or extrahepatic biliary tree with beading and irregularity occurring > 90 days after LT or a liver biopsy showing fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis or cirrhosis. All these should be in the absence of hepatic artery thrombosis/stenosis, ductopenic rejection, donor-recipient ABO blood type incompatibility, anastomotic stricturing alone and nonanastomotic strictures before day 90 post-LT.

Exclusion criteria

Patients were excluded from analysis in case of 1) ABO blood type incompatibility; 2) recipient age below 18 years at time of first transplant; 3) obvious errors in dates of follow-up or transplantation (e.g. LT date was after death or last follow-up); or 4) lack of information on rPSC.

Statistical analysis

Categorical variables were expressed as counts and percentages (n, %) and continuous variables as median (2.5% quantile and 97.5% quantile). Follow-up was calculated from date of first transplant to event (death in case of patient survival, and re-transplant or death in case of graft survival). Patients without an event were censored at the end of follow-up. Both patient and graft survival were analysed using the Kaplan–Meier method.

We used Bayesian proportional hazards models to investigate the association between the determinant of interest, rPSC, and graft and patient survival. The same was done for the transplant-related covariates. The Bayesian methodology allowed us to include cases with missing values in some covariates rather than excluding them altogether when performing multivariable analyses [16]. The proportional hazards assumption of the model implies constant hazard ratios throughout follow-up. By definition, rPSC cannot be diagnosed in the first 90 days after transplantation, and hence, other causes such as infections, technical failures and primary dysfunction are the most likely causes for graft failures in the first 90 days after transplant. Since these types of events are not of primary interest, but would impact

the estimated hazard ratio, we excluded all patients who died within 90 days after LT from the patient survival analyses. Additionally, we excluded all grafts with an event (graft failure) within 90 days after LT from the graft survival analyses. All results from the Bayesian analyses are presented as posterior mean and 95% credible intervals (95% CI).

For continuous covariates, we used natural cubic splines to investigate whether these variables had nonlinear effects in a preliminary analysis using only complete cases. The decision whether or not to include the nonlinear spline specification versus a standard linear effect was based on visual inspection of the resulting effect plots and likelihood ratio tests. Since rPSC can occur years after LT, the variable rPSC was included as a time-varying covariate, where patients, once recurrence was diagnosed, maintained this status during the rest of their follow-up, even when they had subsequent transplants. To take into account that survival may be associated with the number of previous transplants, both models (for patient and graft survival) also included a time-varying variable enumerating the grafts (categorized into first, second and third or more). Additionally, differences in the re-transplantation rate between patients with and without rPSC were investigated using a Bayesian proportional odds cumulative logit model for the number of received transplants (1, 2 and 3 or more). This model included rPSC (never vs ever) as only covariate.

To facilitate the visual interpretation of the independent effect of one covariate on the investigated outcome, we plotted the expected patient and graft survival with corresponding 95% CI for different scenarios with regards to the covariate of interest while assuming reference values for all other covariates. Reference values were defined as the reference category for categorical variables (male recipient, donor graft type DBD, no rPSC), and the median of the observed data for continuous variables (recipient age of 41.9 years, total ischaemic time of 8.8 hours, donor age of 44 years, year of first transplant 2004).

All statistical analyses were performed in R version 4.0.3 (R Core Team 2020), and the Bayesian models were fitted using the R package JointAI version 1.0.0 [17].

Results

Baseline data

Forty-eight transplant centres responded to the inquiry and provided supplementary data on rPSC and

outcomes in 1,573 patients. Of these, 24 were excluded as follows: 4 had an incompatible ABO blood type; 5 were less than 18 years of age at the first LT; 5 had inconsistent outcome data; and for 10 patients the date of rPSC was unknown, leaving 1,549 patients for KM analysis, 1,428 for multivariable patient survival and 1,336 for graft survival analysis (Fig. 1).

The patient characteristics for this dataset are shown in Table 1. The majority of recipients were male ($n = 1,045$; 67.5%), and the median recipient age at first LT was 42.5 years (23.0–62.6). Median donor age was 43.0 years (16.0–68.0), 831 were male (56.9%) and the vast majority of donors were brain dead (DBD, $n = 1,398$; 90.3%). The median total ischaemic time was 8.7 hours (3–14.6).

Rate of rPSC

Considering all transplants (including re-transplants), rPSC was diagnosed 259 times (16.7%) after a median of 5.1 years (0.4–18.5). In the majority of patients ($n = 126$; 48%) rPSC occurred within 5 years after LT, in 82 patients (32%) between 5 years and 10 years after LT, and in 51 patients (20%) more than 10 years after LT.

Recurrence of PSC did not only affect the first graft. While rPSC was present in 232 (15.0%) cases in the 1549 first grafts, rPSC was diagnosed in 25 (8.6%) of the 288 second grafts. The third ($n = 34$) and fourth ($n = 8$) grafts were affected by rPSC in 1 (2.9%) and 1 (12.5%) case, respectively. All 1,879 transplants, rPSC diagnoses, and outcomes are displayed in Fig. 2.

Patient survival after LT for PSC

In total, $n = 474$ (30.6%) patients died after a median time of 2.1 years (range 0.0–27.7). One hundred twenty-one patients died (7.8% of total and 25.6% of all deaths) within the first 90 days. Causes of death were stratified in liver related ($n = 94$, 19.8%), nonliver related ($n = 255$, 53.8%) and unknown ($n = 125$, 26.4%). Patient survival after first LT for PSC at 1, 5, 10 and 20 years was 89%, 80%, 73% and 57%, respectively (Fig. 3).

Multivariable analysis, accounting for all available transplant-related covariates, showed that rPSC had a significant negative impact on patient survival after LT (HR 2.31; 95% CI: 1.54–3.33; Table 2 a). Furthermore, the timing of rPSC diagnosis appeared to be of

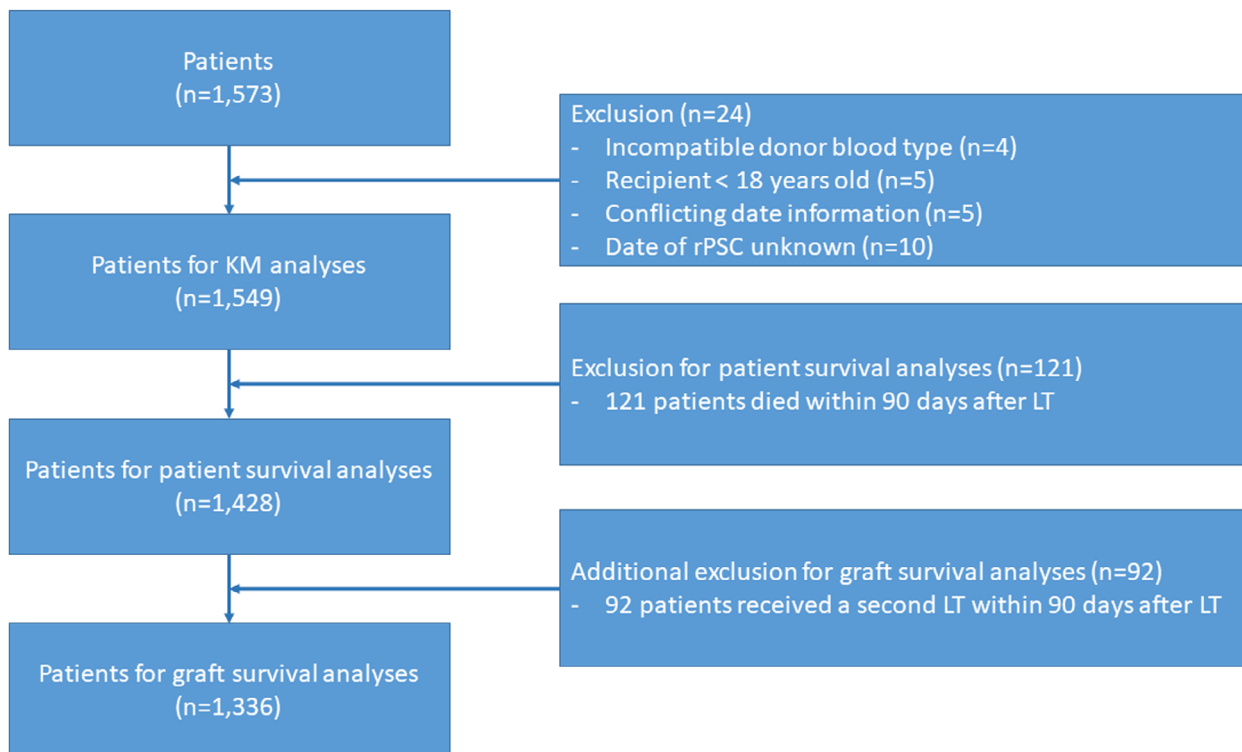


Figure 1 Flow chart of the 1,573 patients transplanted for PSC. The flow chart shows the number of patients ($n = 1,573$) for which additional data were provided by 48 transplant centres, patients who were excluded ($n = 24$), and the number of patients used for patient ($n = 1,428$) and graft ($n = 1,336$) survival analyses.

Table 1. Patient and donor characteristics at time of first transplantation.

	Total <i>n</i> = 1,549	Free of rPSC <i>n</i> = 1,290	rPSC <i>n</i> = 259
Male recipient	1,045 (67.5%)	855 (66.3%)	190 (73.4%)
Recipient age (years)	42.5 [23.0, 62.6]	43.4 [23.1, 63.0]	38.7 [22.9, 58.6]
Donor age (years)	43.0 [16.0, 68.0]	43.0 [17.0, 69.0]	46 [16.0, 66.0]
Missing	89 (5.7%)	75 (5.8%)	14 (5.4%)
Donor gender			
Male	831 (56.9%)	696 (57.3%)	135 (4.9%)
Female	630 (43.1%)	519 (42.7%)	111 (5.1%)
Missing	88 (5.7%)	75 (5.8%)	13 (5.0%)
Graft type			
DBD full graft	1,318 (88.6%)	1088 (87.9%)	230 (2.0%)
Living donor	78 (5.2%)	74 (6.0%)	4 (1.6%)
DBD split graft	80 (5.4%)	65 (5.3%)	15 (6.0%)
DCD full graft	12 (0.8%)	11 (0.9%)	1 (0.4%)
Missing	61 (3.9%)	52 (4.0%)	9 (3.5%)
Total ischaemic time (hours)	8.7 [3, 14.6]	8.6 [2.7, 14.9]	9.0 [4.2, 14.1]
Missing	170 (11.0%)	145 (11.2%)	25 (9.7%)
Calendar year of LT	2004 [1991, 2013]	2005 [1991, 2013]	2002 [1992, 2011]

DBD, donation after brain death; DCD, donation after circulatory death; rPSC, recurrence of primary sclerosing cholangitis; LT, liver transplantation.

Characteristics of 1,549 patients who underwent a liver transplantation for PSC, as a total and divided in two groups: free of rPSC and ever diagnosed with rPSC. Shown are numbers (%) or median (2.5% and 97.5% quantile).

influence (Fig. 4). When rPSC occurred relatively early (within 5 years) in the post-transplant course (panel a), the estimated 15-year survival probability dropped from 82% (95% CI: 78%–86%) to 64% (95% CI: 53%–74%). When rPSC was diagnosed after five (panel b) or ten years (panel c) after the initial transplant, the effect was less profound with an estimated 15-year survival of 72% (95% CI: 64%–78%) and 76% (95% CI: 71%–81%), respectively.

Moreover, survival worsened when patients received subsequent transplants (Table 2 a); for patients who did not experience rPSC, the HR for patient death following a second graft was 2.39 (95% CI 1.73–3.33), and following a third or fourth graft 2.73 (95% CI 0.93–6.42). The interaction between rPSC and the number of grafts can best be presented visually. Figure 5 shows the estimated survival probabilities over time under different scenarios with regards to rPSC and the number of transplants. The green curves represent scenarios in which a patient experienced recurrence 5 years after the first transplant, the purple curves represent scenarios without recurrence. Panel a shows that survival declines considerably faster after rPSC. Panel b depicts the impact of a re-transplantation after ten years. While the estimated survival for patients without recurrence declined faster after a re-transplant (i.e. for indications other than

rPSC), this was not the case for patients who received a re-transplant for the indication of rPSC.

Furthermore, there was a trend towards more favourable patient survival for female recipients (HR=0.82; 95% CI 0.65–1.03) and worse recipient survival for higher donor age (HR=1.01; 95% CI 1.00–1.02, Table 2). The nonlinear effect of recipient age and calendar year of first LT is best illustrated graphically in Fig. S1. While the estimated survival probability was relatively constant up to the recipient age of 45, thereafter every incremental increase in recipient age was associated with decreased patient survival (panel a). Patient survival improved every year from 1980 until 2000 and plateaued thereafter (panel b). In our study, donor type or total ischaemic time was not found to have an effect on patient survival.

Graft survival after LT for PSC

In total, 1,879 grafts were transplanted in this study population of 1,549 patients. Of these grafts, 804 (42.8%) were lost after a median time of 1.2 years (range 0.0–27.6). Causes of graft loss were stratified in liver related (*n* = 360, 44.8%), nonliver related (*n* = 262, 32.6%) and unknown (*n* = 182, 22.6%). Graft survival (including re-transplants) for PSC at 1, 5, 10

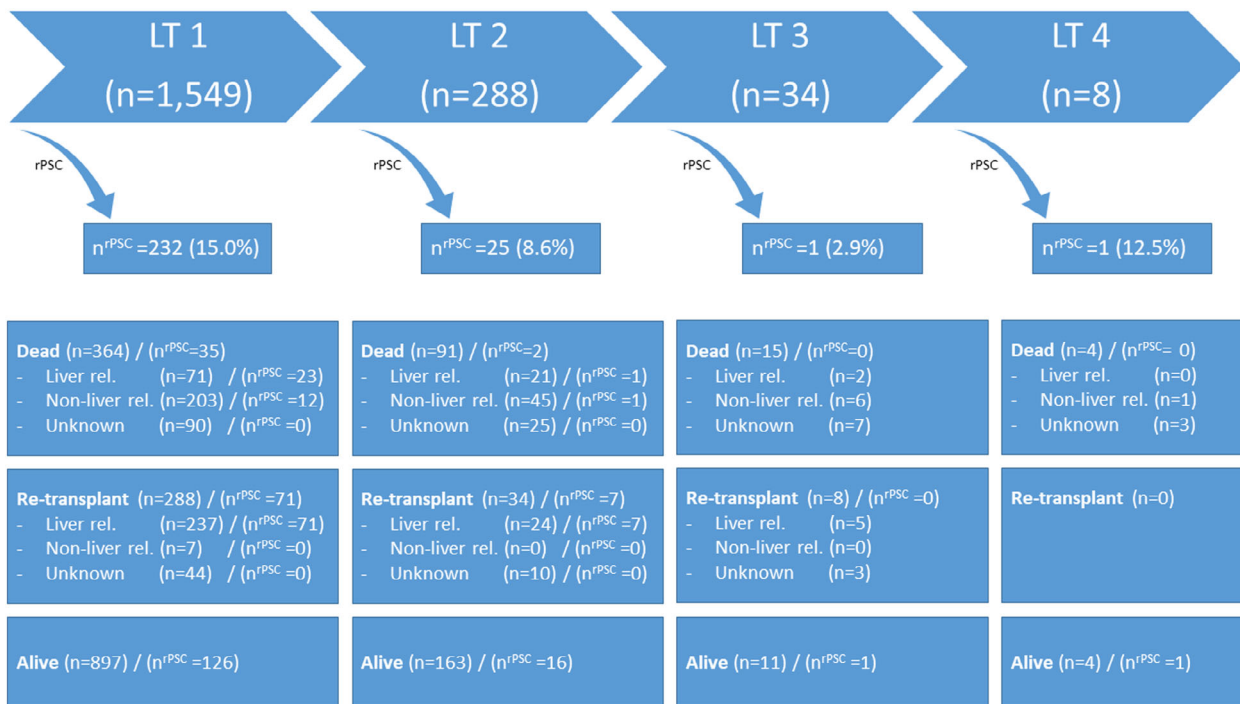


Figure 2 Flowchart of the 1,879 transplants performed in 1,549 patients. The flowchart shows the number of first, second, third and fourth transplants performed. The rPSC cases are displayed throughout the chart as n^{rPSC}, and the outcomes are shown stratified by cause; liver related (liver rel.), nonliver related (nonliver rel.), and unknown.

and 20 years was 80%, 70%, 60% and 41%, respectively (Fig. 3).

Multivariable analysis, corrected for all available potentially confounding factors, showed that rPSC had a significant negative impact on graft survival (HR 6.66; 95% CI: 4.92–9.07, Table 2 b). The impact of this increase in hazard depends on when rPSC occurs and the duration of follow-up afterwards (Fig. 6). When rPSC occurs relatively early (within 5 years) in the post-transplant course (panel a), the estimated 15-year graft survival probability drops from 81% (95% CI: 75%–85%) to 25% (95% CI: 16%–36%). When rPSC is diagnosed after five (panel b) or after ten years (panel c) after LT, the effect is still strong but less profound with a 15-year survival of 38% (95% CI: 27%–49%) and 51% (95% CI: 41%–61%), respectively.

Graft survival of the individual subsequent grafts, with and without the effect of rPSC, is shown in Fig. S2. Without rPSC, the 10-year graft survival of first, second and third grafts is 87% (95% CI: 83%–90%), 79% (95% CI: 66%–88%) and 76% (95% CI: 69%–78%). In contrast, rPSC diagnosed after 5 years showed lower 10-year survival of first, second and third grafts of 61% (95% CI: 52%–69%), 77% (95% CI: 67%–85%) and 43% (95% CI: 16%–68%).

The risk of graft failure was also influenced by the number of previous grafts transplanted. Second (HR 1.69; 95% CI: 1.11–2.60), and third or fourth (HR 1.74; 95% CI: 0.52–4.98) grafts were more at risk for graft failure than first grafts (Table 2 b).

Similar to the results for patient survival, recipient age at first LT and chronological year of first transplant had a nonlinear, negative effect on graft survival (Fig. S3). There was a gradual worsening of graft survival after recipient age of 45 (panel a) and a gradual improvement of graft survival for transplants performed over time, plateauing after 2000 (panel b).

Donor age was linearly associated with worsened graft survival (HR=1.02; 95% CI: 1.01–1.02), and female recipients showed a trend towards better graft outcome than male recipients (HR= 0.79; 95% CI: 0.61–1.02), as shown in Table 2. Again, we did not find evidence that either donor type or total ischaemic time had an effect on graft survival.

Re-transplantation in patients with and without rPSC

In total, 1,549 patients received 1,879 transplants. Most patients (n = 1,261; 81%) received only one transplant. In total, 288 patients received a second LT, of whom 34

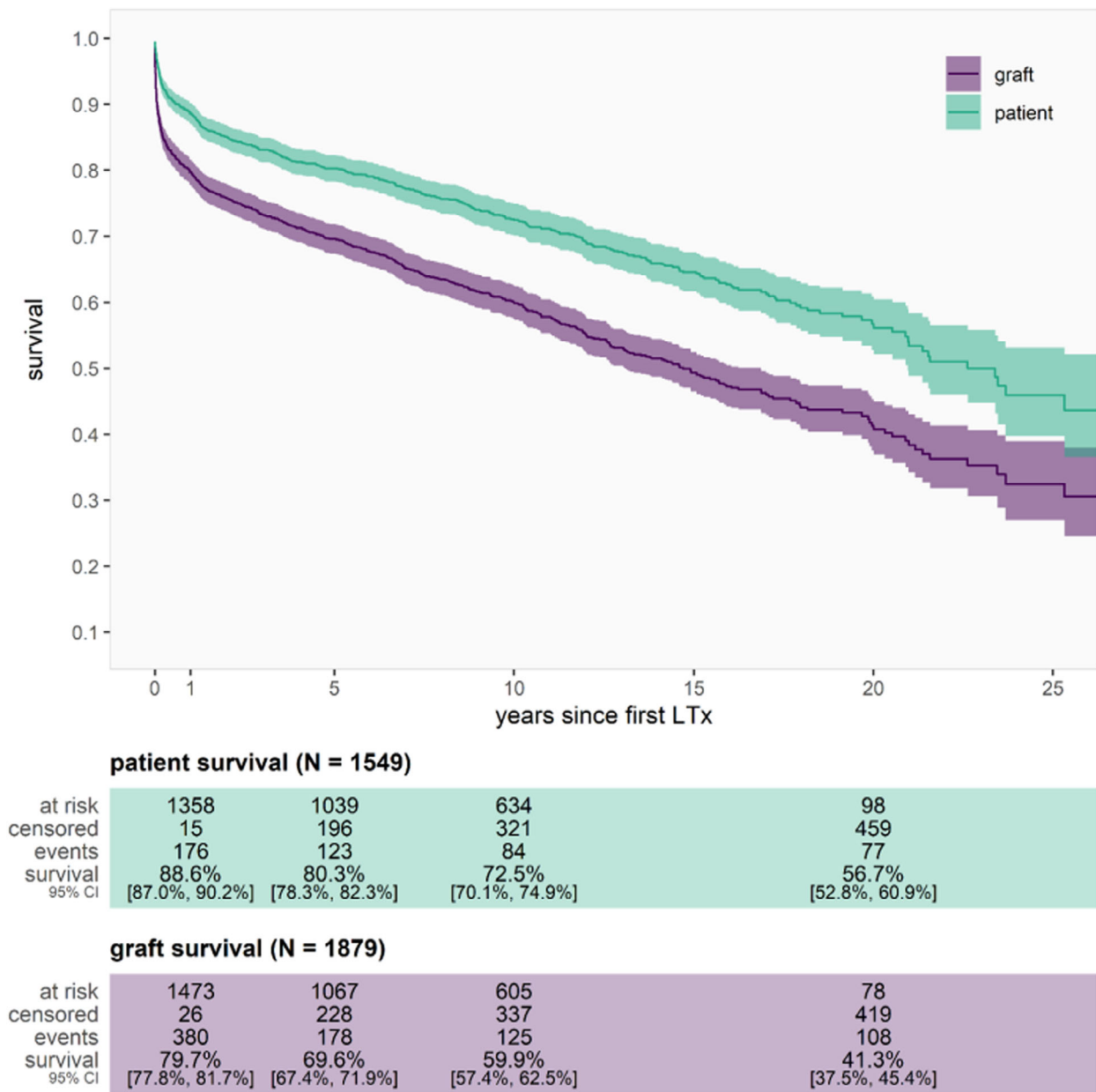


Figure 3 Kaplan–Meier survival curves for patient and graft survival, including all re-transplants.

patients received a third and 8 patients received a fourth LT (Table 3). Of the 288 first re-transplants, 71 (24.7%) were performed for rPSC (Fig. 2). Second ($n = 34$) re-transplants were performed for rPSC in 7 (20.6%) cases. Third re-transplants were performed in 8 patients, none of those were affected by rPSC. None of the patients were reported to have received more than one re-transplant for rPSC.

In total, considering all (re-)transplants, 259 (13.8%) grafts and 259 (16.7%) patients were affected by rPSC. Patients diagnosed with rPSC underwent significantly more re-transplants than patients who never

experienced recurrence (OR 3.6, 95% CI: 2.7–4.8). Of the 254 patients who received two LTs, 81 (31.9%) were diagnosed with rPSC (at any time). Half of the patients with three or more LT's had ever been diagnosed with rPSC ($n = 17$, 50.0%).

Discussion

Using data from the ELTR on patients transplanted for PSC, supplemented by the largest series of individual patient data to date, we clearly demonstrated a negative effect of rPSC on patient survival. We also confirmed

Table 2. Multivariable Bayesian models for patient (a; $n = 1,428$) and graft (b; $n = 1,336$) survival.

a) Patient survival	HR	2.5%	97.5%
Female recipient	0.82	0.65	1.03
DBD full graft*	1	1	1
Living donor	1.44	0.76	2.54
DBD split graft	0.58	0.26	1.17
DCD full graft	0.82	0.13	3.18
Recipient age (years) [†]			
Total ischaemic time (hours)	1.03	0.99	1.06
Donor age (years)	1.01	1.00	1.02
Calendar year of first LT [†]			
rPSC [‡]	2.31	1.54	3.33
2nd graft [‡]	2.39	1.73	3.20
3rd and 4th graft [‡]	2.73	0.93	6.42
b) Graft survival	HR	2.5%	97.5%
Female recipient	0.79	0.61	1.02
DBD full graft*	1	1	1
Living donor	1.40	0.70	2.69
DBD split graft	1.32	0.73	2.39
DCD full graft	0.99	0.11	5.39
Recipient age (years) [†]			
Total ischaemic time (hours)	1.02	0.98	1.06
Donor age (years)	1.02	1.01	1.02
Calendar year of first LT [†]			
rPSC [‡]	6.66	4.92	9.07
2nd graft [‡]	1.69	1.11	2.60
3rd and 4th graft [‡]	1.74	0.52	4.98

DBD, donation after brain death; DCD, donation after circulatory death; rPSC, recurrence of primary sclerosing cholangitis.

Results from the multivariable Bayesian models for patient and graft survival.

*Donor graft type DBD full graft as baseline.

[†]Nonlinear effect on survival, therefore HR cannot be displayed in one number.

[‡]Time-varying variable.

the negative impact of rPSC on graft survival and its consequential increased need for re-transplantation. The recurrence rate in our study was 15.0% in first grafts after a median of 4.9 years (0.4–18.5), and 16.7% of patients experienced rPSC in any graft after a median of 5.1 years (0.4–18.5), which is similar to other series [8,13,14,18]. Besides the impact of rPSC, our analysis demonstrated that older donor and recipient age, number of re-transplants and earlier eras of transplantation were negatively associated with the outcome after LT for PSC. Patients with rPSC underwent significantly more re-transplants than those without rPSC (OR 3.6, 95% CI 2.7–4.8), in line with other multicentre studies

[8, 13]. Patients affected by rPSC did, however, benefit from re-transplantation, with patient survival similar to patients without rPSC but re-transplanted for other causes. Overall, graft survival in patients without rPSC was good after first transplant, and acceptable after subsequent transplants. Surprisingly, the negative effect of rPSC on graft survival appeared more pronounced upon a first transplant than upon a second transplant. Unfortunately, we do not have enough specific data for an in-depth analysis of this finding.

An important finding of our study was that rPSC is associated with significantly worsened overall patient survival, independent of several other transplant-related covariates. This negative impact of rPSC on patient survival has, to the best of our knowledge, not been shown before in multivariable fashion. Prior studies reporting on the impact of rPSC on patient survival showed conflicting results, where most reported no effect on patient survival at all [15,18–22], and others reported a negative effect on a combined endpoint of graft and patient survival [8,13]. Two studies have reported a negative effect on patient survival, but only in a sub-analysis after applying significant exclusion criteria [9,23]. The discrepancy in outcomes of these studies can be explained by small sample size [19,22], the use of combined endpoints rather than single endpoints (graft loss and death) [8,13], a short follow-up time [18,21] and by selection bias from applying significant exclusion criteria in (sub) analyses [9,23]. Furthermore, multiple studies did not include rPSC as time-varying covariate and thereby disregarded the impact of survived time until rPSC development on the total survival of the graft or patient [8,15,20]. We strongly believe that this information, however, is crucial and otherwise lost in traditional (time-fixed) analysis. In doing so, our study clearly demonstrated that rPSC has a significant and substantial impact on patient survival (HR=2.3). Without rPSC the estimated 15-year patient survival was 82%, whereas a diagnosis of rPSC at 5 years was associated with a reduction in the estimated 15-year survival to 72%. Besides rPSC, we found that older age of donor and recipient and LTs performed before 2000 were additional covariates impairing patient survival. This impact is in line with results of LT for PSC and for other indications [24–27]. Recipient female sex was associated with a marginal decreased hazard for patient death, in line with a recent ELTR analyses by *Berenguer et al.* [28].

Additionally, we showed that rPSC was associated with an increased risk (HR=6.7) of graft loss, independent of available transplant-related covariates. In total,

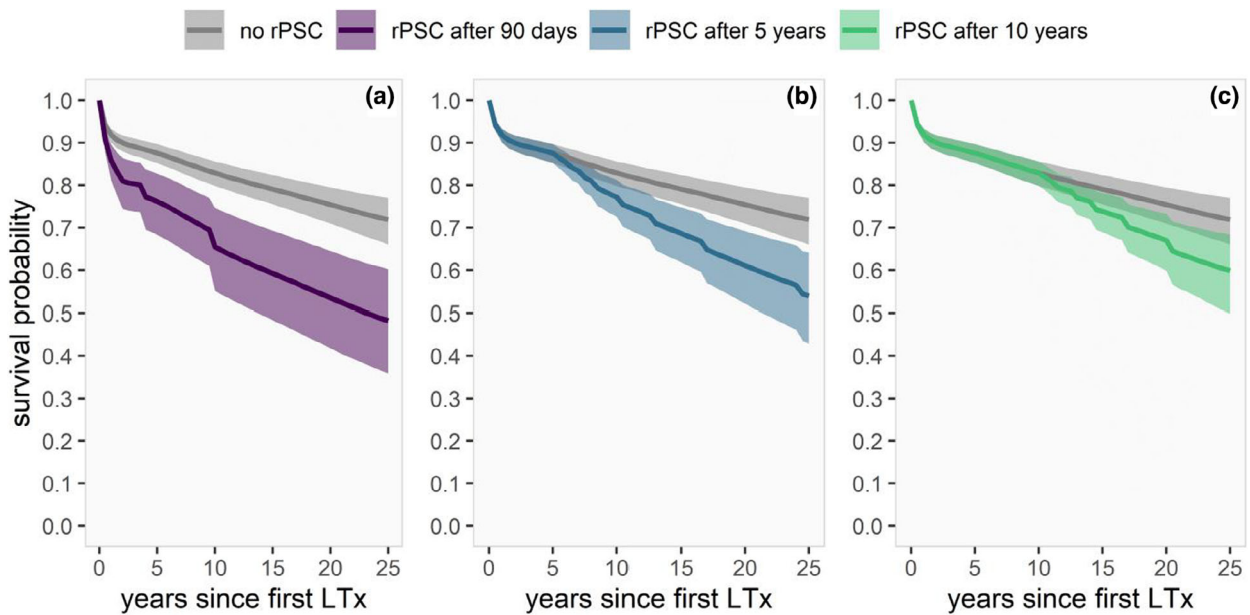


Figure 4 Expected patient survival with and without rPSC. Expected patient survival and corresponding 95% CIs in scenarios with and without rPSC. The curves show the scenarios when rPSC is diagnosed after 90 days (a), 5 years (b) and 10 years (c). The effect of rPSC is more detrimental when diagnosed early after LT, compared with a later onset.

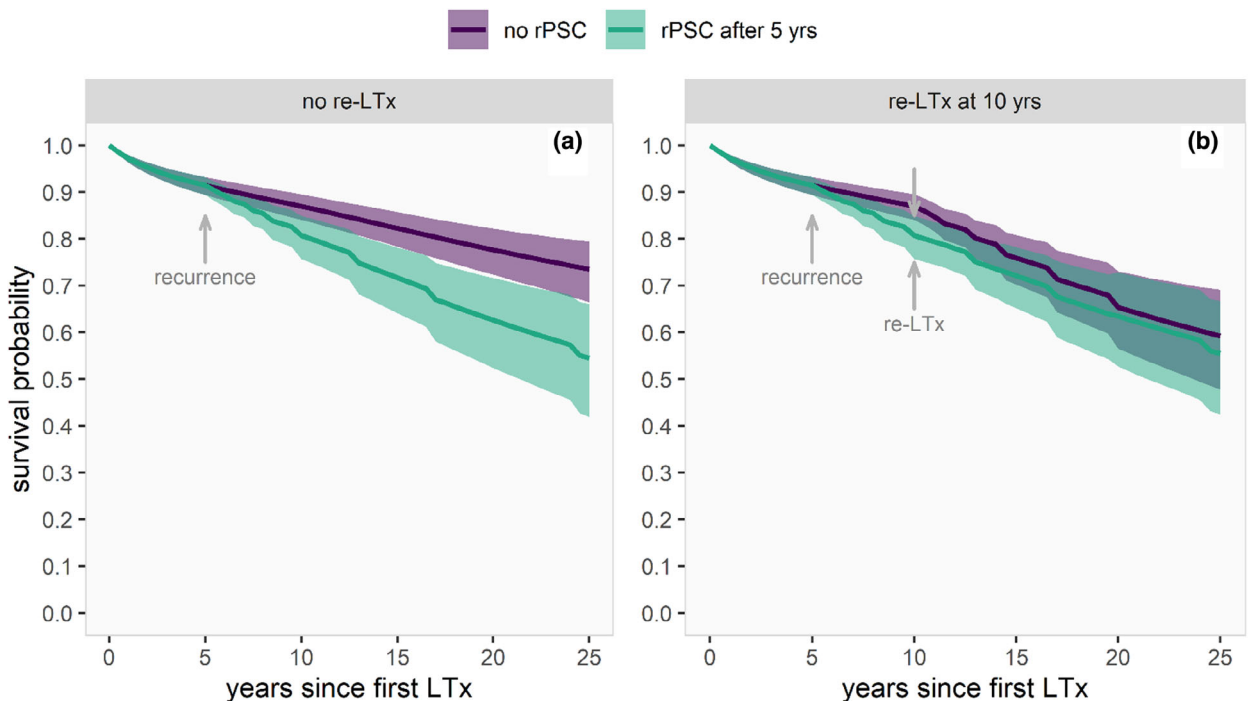


Figure 5 Expected patient survival with and without rPSC, in scenarios with and without re-transplants. Expected patient survival and corresponding 95% CIs in different scenarios of rPSC and re-transplants. Panel a: estimated survival declines faster after rPSC. Panel b: re-transplant does not affect the decline in estimated survival in patients with rPSC, but results in steeper decline for patients without rPSC.

71 (4.6%) patients received a re-transplant for rPSC. These findings are in line with three other multicentre series, with the observed HR being the highest in our

series [8,13,18]. *Ravikumar et al.* [8] showed in 565 transplanted PSC patients in seven UK transplant centres a rPSC rate of 14.3% and an independent HR of

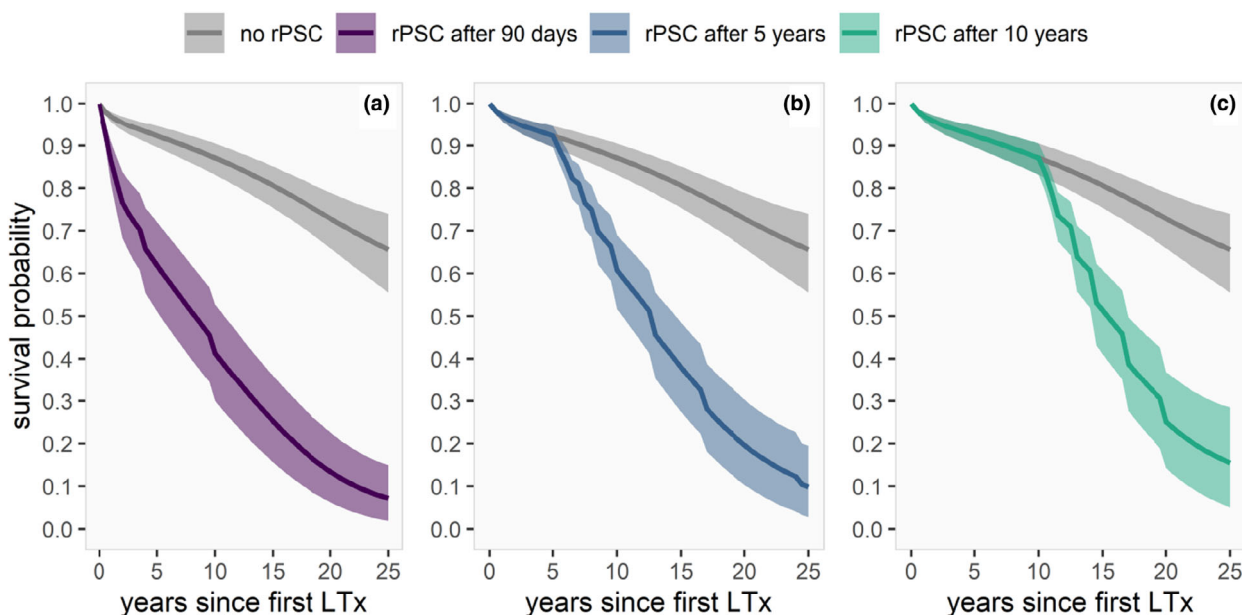


Figure 6 Expected graft survival with and without rPSC. Expected survival of first grafts and corresponding 95% CIs in different scenarios with and without rPSC. The curves show the scenarios when rPSC is diagnosed after 90 days (a), 5 years (b) and 10 years (c). The effect of rPSC is detrimental for graft survival irrespective of timing of recurrence.

2.17 for graft loss or death (combined endpoint). In total, 17 (3.0%) patients received a re-transplant for rPSC. In the study by Lindstrom et al.[13], examining 440 patients with PSC in the Nordic Liver Transplant Registry, a recurrence rate of 19% was found within a mean time of 6.8 years after LT. In this study, rPSC was associated with a HR of 4.26 for graft failure or death (combined endpoint). In total, 32 (7.3%) patients received a re-transplant for rPSC. Finally, in a study on 96 patients with PSC undergoing LDLT in Japan [18], a higher rPSC rate of 27% was found, with a 10-year graft survival of 41%. Thirteen out of the total 16 re-transplants were for rPSC (81%), again showing that rPSC leads to more re-transplantations. In total, 13 (13.5%) patients received a re-transplant for rPSC.

These and our findings are important in the light of shortage of organ donors [29] and reinforce the ongoing need for better understanding of the pathophysiology of (recurrent) PSC and the search for a disease-specific treatment.

Because the seemingly increased incidence of PSC, the need for the already scarce donor organs keeps rising [29]. To extend the donor pool, DCD livers have been used increasingly over the past years, as well as LDLTs. Usage of controlled, Maastricht III DCD donors has been demonstrated to have satisfactory outcomes on graft and patient survival in PSC patients [30,31]. Both DCD and LDLT procedures, however, may be accompanied by biliary complications [32,33]. If these biliary complications are nonanastomotic and diffuse, they can

Table 3. Total of (re-)transplants.

	Free of rPSC (n = 1,290)	rPSC (n = 259)	Total (n = 1,549)
Number of transplants	1,100 (85.3%)	161 (62.2%)	1,261
	2, 173 (13.4%)	81 (31.3%)	254
	3+, 17 (1.3%)	17 (6.5%)	34

rPSC, recurrence of primary sclerosing cholangitis.

The number of patients receiving one or more re-transplants divided into patients (n = 1,549) with and without rPSC. All (re-)transplants are included, irrespective of timing and indication for re-transplant. Patients with the diagnosis rPSC received significantly more re-transplants (OR 3.6, 95% CI 2.7–4.8).

be misclassified as rPSC and vice versa. The widely used Mayo definition hence states that the diagnosis of rPSC can only be made if diffuse nonanastomotic biliary lesions occurred after 90 days and in the absence of vascular complications. For the most part, this rules out profound ischaemia reperfusion injury in DCD, biliary anastomotic problems causing strictures upstream, and ischaemic biliary lesions in the setting of arterial or portal compromise at the anastomosis or elsewhere. Ischaemic lesions can occur even after 90 days, especially in DCD. Given the very small percentages of DCD (0.8%) and LDLT (5.2%) grafts, we believe that this most likely has not influenced the overall outcomes of our study. In addition, the results of this study are all analysed after correcting for graft type in the multivariable models.

A recent meta-analysis of 14 individual studies identified multiple risk factors for rPSC [34], and the effect of a colectomy (with and without ileal pouch-anal anastomosis) has been analysed as well [35]. Aside from the fact that it was outside the scope of our current study to examine individual risk factors for rPSC, the use of registry data with an inheritably limited dataset of covariates did not permit such analysis.

Our study has several strengths and limitations. Strengths of our study are the addition of individual patient data to registry data; the large sample size which makes our study the largest series published so far; the uniform use of the established Mayo criteria for rPSC [10]; inclusion of information on subsequent liver transplants and a very long follow-up of almost 30 years. Moreover, unlike previous studies, we used multivariable Bayesian survival methodology, that allowed us to use rPSC as time-varying covariate and permitted the inclusion of all patients even when in the event of missing data on some covariates. The limitations of our study are in line with the nature of retrospective studies using registry data, such as dealing with missing information on specifics, for example indication for re-transplantation, presence of cholangiocarcinoma and type of biliary reconstruction. Considering our large dataset and high hazard ratios, we expect the influence of these missing factors on our findings to be marginal. That said, the ELTR has implemented both quality control procedures and an external audit to ensure the high quality of the data [36,37].

Finally, notwithstanding our clear instructions to uniformly use the Mayo criteria for diagnosis of rPSC, this diagnosis could not be independently verified as data on explant pathology or imaging were not included. Given the fact that the observed rate of rPSC in our study is in line with other case series, we believe that the chance for

misdiagnosis is very limited and, if anything, represents daily practice in the management of these patients.

This cohort describes a time span of 3.5 decades of experience with patients transplanted for PSC (1980–2015). Since 1980, a lot changed in terms of surgical techniques, immunosuppressant regimes, choice of graft types and pre- and postoperative care. All these factors may affect graft and patient survival, mostly for the better, and perhaps sometimes for the worse (e.g. in case of marginal donor selection). In our attempt to correct for the potential confounding effect of such changes over time, we included the covariable ‘calendar year of first LT’ in all our multivariable models.

In conclusion, in this large European multicentre dataset, we confirm that rPSC has a negative impact on graft survival, which appears independent of other transplant-related factors and leads to a higher number of re-transplantations. The novelty of our study is that we demonstrate that rPSC significantly affects patient survival as well, but that re-transplantation after rPSC has acceptable outcomes. While we seek new and effective treatment strategies for the primary disease of PSC, it is of utmost importance to extend these strategies to post-transplant populations with rPSC in order to improve the outcomes for these patients and to reduce the demand on scarce donor organs.

Authorship

TV, NE, WP, JIJ, HM and SDM involved in study concept and design. RA, VK, FV, BGE, DT, AP, FH, PT, PN, JP and RR involved in acquisition of data. NE involved in statistical analysis of data. TV, NE, HM and SDM involved in interpretation of data. TV, NE, HM and SDM involved in drafting the manuscript. WP, RA, VK, FV, BGE, DT, JIJ, AP, FH, PT, PN, JP, RR, HM, NE and SDM involved in critical revision of the manuscript for important intellectual content. All authors approved the final version.

Funding

The authors have declared no funding.

Conflict of interest

The authors who have taken part in this study declared that they do not have any conflict of interest with respect to this manuscript. Dr. Thorburn reports personal fees from Intercept, Falk Pharma, Mirum, Cymabay, and Engitix, all outside the submitted work.

Acknowledgements

We are extremely indebted to and grateful for the efforts of the following people at the contributing centres who kindly provided us with additional data on rPSC, hereby mentioned in order of sample size:

Florian Vondran, Hannover, Germany; Annika Bergquist & Lina Lindström, Huddinge, Sweden; Victoria Snowdon, London, U.K.; Andreas Paul, Essen, Germany; Frans van der Heide, Groningen, The Netherlands; Pavel Trunecka, Prague, Czech Republic; Petr Nemeč, Brno, Czech Republic; Jacques Pirenne, Louvain, Belgium; Mauro Salizzoni, Torino, Italy; Andreas Arendtsen Rostved, Copenhagen, Denmark; Chetana Lim, Creteil, France; Giuseppe Arenga, Pisa, Italy; Gabriela ABERLAKOVICH, Wien, Austria; Daniel Candinas, Bern, Switzerland; Sasa Markovic, Ljubljana, Slovenia; Roberto Troisi, Ghent, Belgium; Bart van Hoek, Leiden, The Netherlands; Turan Kanmaz, Istanbul, Turkey; Murat Dayangac, Istanbul, Turkey; Thierry Berney, Genève, Switzerland; Daniele Sforza, Roma, Italy; Bruno Gridelli, Palermo, Italy; Pierre-Alain Clavien, Zurich, Switzerland; Maria Hoppe-Lotichius, Mainz, Germany; Norbert Senninger, Münster, Germany; Thomas Lorf, Göttingen, Germany; Utz Settmacher, Jena, Germany; Valentín Cuervas-Mons, Madrid, Spain; Aylin Bacakoğlu, Izmir, Turkey; Silvio Nadalin, Tübingen, Germany; Valentina Serra, Modena, Italy; Marek Pacholczyk, Warsaw, Poland; Umberto Baccarani, Udine, Italy; Cristina Dopazo Taboada, Barcelona, Spain; Marina Berenguer & Fernando San Juan, Valencia, Spain; Olivier Detry, Liege, Belgium; Dirk Stippel, Köln, Germany; Philippe Evrard, Besancon, France; Jean Gugenheim, Nice, France; Murat Kiliç, Izmir, Turkey; Carlos Fernández

Selles, La Coruna, Spain; Luis Antonio Herrera Norena, Santander, Spain; Fabio Melandro, Roma, Italy; Ignacio Gonzalez-Pinto, Oviedo, Spain; Daniele Nicolini, Ancona, Italy; Fernando Pardo Sánchez, Pamplona, Spain; Christoph Neumann-Haefelin, Freiburg, Germany.

The ELTR is supported by a grant from Astellas, Novartis, Institut Georges Lopez, Sandoz and logistic support from the Paul Brousse Hospital (Assistance Publique – Hôpitaux de Paris). The Organ Sharing Organizations: the French ABM (Sami Djabbour), the Dutch NTS (Maaïke de Wolf), the Eurotransplant Foundation (Marieke Van Meel), the Spanish RETH (Gloria de la Rosa), the UK-Ireland NHSBT (Michael Daynes) and the Scandiatransplant (Ilse Duus Weinreich) are acknowledged for the data cross-check and sharing with the ELTR.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Expected patient survival and corresponding 95% CI by recipient age (a) and year of transplant (b) for a hypothetical patient with reference values for all other covariates.

Figure S2. Expected graft survival and corresponding 95% CI for first, second and third grafts in scenarios with and without rPSC.

Figure S3. Expected graft survival and corresponding 95% CI by recipient age (a) and year of transplant (b) for a hypothetical case with reference values for all other covariates.

REFERENCES

- Hirschfield GM, Karlsen TH, Lindor KD, Adams DH. Primary sclerosing cholangitis. *Lancet* 2013; **382**: 1587.
- Ponsioen CY, Vrouenraets SM, Prawirodirdjo W, et al. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. *Gut* 2002; **51**: 562.
- Karlsen TH, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. *J Hepatol* 2017; **67**: 1298.
- Boonstra K, Weersma RK, van Erpecum KJ, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology* 2013; **58**: 2045.
- Lindkvist B, Benito de Valle M, Gullberg B, Björnsson E. Incidence and prevalence of primary sclerosing cholangitis in a defined adult population in Sweden. *Hepatology* 2010; **52**: 571.
- Bambha K, Kim WR, Talwalkar J, et al. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. *Gastroenterology* 2003; **125**: 1364.
- Goet JC, Hansen BE, Tieleman M, et al. Current policy for allocation of donor livers in the Netherlands advances primary sclerosing cholangitis patients on the liver transplantation waiting list - a retrospective study. *Transpl Int* 2018; **31**: 590.
- Ravikumar R, Tsochatzis E, Jose S, et al. Risk factors for recurrent primary sclerosing cholangitis after liver transplantation. *J Hepatol* 2015; **63**: 1139.
- Alabraba E, Nightingale P, Gunson B, et al. A re-evaluation of the risk factors for the recurrence of primary sclerosing cholangitis in liver allografts. *Liver Transpl* 2009; **15**: 330.
- Graziadei IW, Wiesner RH, Batts KP, et al. Recurrence of primary sclerosing cholangitis following liver transplantation. *Hepatology* 1999; **29**: 1050.

11. Cholongitas E, Shusang V, Papatheodoridis GV, *et al.* Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl* 2008; **14**: 138.
12. Alexander J, Lord JD, Yeh MM, Cuevas C, Bakthavatsalam R, Kowdley KV. Risk factors for recurrence of primary sclerosing cholangitis after liver transplantation. *Liver Transpl* 2008; **14**: 245.
13. Lindstrom L, Jorgensen KK, Boberg KM, *et al.* Risk factors and prognosis for recurrent primary sclerosing cholangitis after liver transplantation: a Nordic Multicentre Study. *Scand J Gastroenterol* 2018; **53**: 297.
14. Visseren T, Darwish MS. Recurrence of primary sclerosing cholangitis, primary biliary cholangitis and autoimmune hepatitis after liver transplantation. *Best Pract Res Clin Gastroenterol* 2017; **31**: 187.
15. Dekkers N, Westerouen van Meeteren M, Wolterbeek R, *et al.* Does mucosal inflammation drive recurrence of primary sclerosing cholangitis in liver transplantation recipients with ulcerative colitis? *Dig Liver Dis* 2020; **52**: 528.
16. Erler NS, Rizopoulos D, Jaddoe VW, Franco OH, Lesaffre EM. Bayesian imputation of time-varying covariates in linear mixed models. *Stat Methods Med Res* 2019; **28**: 555.
17. Erler NS, Rizopoulos D, JointAI LEM. JointAI: Joint Analysis and Imputation of Incomplete Data in R. 2019; arXiv e-prints, arXiv:1907.10867.
18. Egawa H, Ueda Y, Ichida T, *et al.* Risk factors for recurrence of primary sclerosing cholangitis after living donor liver transplantation in Japanese registry. *Am J Transplant* 2011; **11**: 518.
19. Moncrief KJ, Savu A, Ma MM, Bain VG, Wong WW, Tandon P. The natural history of inflammatory bowel disease and primary sclerosing cholangitis after liver transplantation—a single-centre experience. *Can J Gastroenterol* 2010; **24**: 40.
20. Campsen J, Zimmerman MA, Trotter JF, *et al.* Clinically recurrent primary sclerosing cholangitis following liver transplantation: a time course. *Liver Transpl* 2008; **14**: 181.
21. Goss JA, Shackleton CR, Farmer DG, *et al.* Orthotopic liver transplantation for primary sclerosing cholangitis. A 12-year single center experience. *Ann Surg* 1997; **225**: 472.
22. Khettry U, Keaveny A, Goldar-Najafi A, *et al.* Liver transplantation for primary sclerosing cholangitis: a long-term clinicopathologic study. *Hum Pathol* 2003; **34**: 1127.
23. Hildebrand T, Pannicke N, Dechene A, *et al.* Biliary strictures and recurrence after liver transplantation for primary sclerosing cholangitis: A retrospective multicenter analysis. *Liver Transpl* 2016; **22**: 42.
24. Burra P, Senzolo M, Adam R, *et al.* Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). *Am J Transplant* 2010; **10**: 138.
25. Germani G, Zeni N, Zanetto A, *et al.* Influence of donor and recipient gender on liver transplantation outcomes in Europe. *Liver Int* 2020; **40**: 1961.
26. Haldar D, Kern B, Hodson J, *et al.* Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study. *J Hepatol* 2019; **71**: 313.
27. Holmer M, Melum E, Isoniemi H, *et al.* Nonalcoholic fatty liver disease is an increasing indication for liver transplantation in the Nordic countries. *Liver Int* 2018; **38**: 2082.
28. Berenguer M, Di Maira T, Baumann U, *et al.* Characteristics, trends and outcomes of liver transplantation for primary sclerosing cholangitis in female vs male patients: An analysis from the European Liver Transplant Registry. *Transplantation* 2020. [Epub ahead of print].
29. Boonstra K, Beuers U, Ponsioen CY. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012; **56**: 1181.
30. Kootstra G, Daemen JH, Oomen AP. Categories of non-heart-beating donors. *Transplant Proc* 1995; **27**: 2893–2894.
31. Trivedi PJ, Scalera I, Slaney E, *et al.* Clinical outcomes of donation after circulatory death liver transplantation in primary sclerosing cholangitis. *J Hepatol* 2017; **67**: 957.
32. Nemes B, Gaman G, Polak WG, *et al.* Extended-criteria donors in liver transplantation Part II: reviewing the impact of extended-criteria donors on the complications and outcomes of liver transplantation. *Expert Rev Gastroenterol Hepatol* 2016; **10**: 841.
33. Ziogas IA, Alexopoulos SP, Matsuoaka LK, *et al.* Living vs deceased donor liver transplantation in cholestatic liver disease: An analysis of the OPTN database. *Clin Transplant* 2020; **34**: e14031.
34. Steenstraten IC, Sebib Korkmaz K, Trivedi PJ, *et al.* Systematic review with meta-analysis: risk factors for recurrent primary sclerosing cholangitis after liver transplantation. *Aliment Pharmacol Ther* 2019; **49**: 636.
35. Trivedi PJ, Reece J, Laing RW, *et al.* The impact of ileal pouch-anal anastomosis on graft survival following liver transplantation for primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2018; **48**: 322.
36. Karam V, Gunson B, Roggen F, *et al.* Quality control of the European Liver Transplant Registry: results of audit visits to the contributing centers. *Transplantation* 2003; **75**: 2167.
37. Adam R, Karam V, Cailliez V, *et al.* 2018 annual report of the European liver transplant registry (ELTR) - 50-year evolution of liver transplantation. *Transpl Int* 2018; **31**: 1293.