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Alimentary Tract

Does mucosal inflammation drive recurrence of primary sclerosing cholangitis in liver transplantion recipients with ulcerative colitis?

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ABSTRACT

Background: Liver transplantation remains the only effective evidence based treatment for advanced primary sclerosing cholangitis. However, recurrence of disease occurs in approximately 18%.
Aims: This study aimed to assess risk factors of recurrence of primary sclerosing cholangitis.
Methods: A retrospective cohort study was performed on patients undergoing transplantation for recurrence of primary sclerosing cholangitis in two academic centers (Leuven, Belgium and Leiden, The Netherlands). Besides other risk factors, the degree of mucosal inflammation was assessed as a potential risk factor using histological Geboes scores.
Results: 81 patients were included, of which 62 (76.5%) were diagnosed with ulcerative colitis. Seventeen patients (21.0%) developed rPSC during a median follow-up time of 5.2 years. In a subset of 42 patients no association was found between the degree of mucosal inflammation and recurrence, using both original Geboes scores and multiple cut-off points. In the total cohort, cytomegaloviremia post-transplantation (HR: 4.576, 95%CI 1.688–12.403) and younger receiver age at time of liver transplantation (HR: 0.934, 95%CI 0.881–0.990) were independently associated with an increased risk of recurrence of disease.
Conclusion: This study found no association between the degree of mucosal inflammation and recurrence of primary sclerosing cholangitis. An association with recurrence was found for cytomegaloviremia post-liver transplantation and younger age at time of liver transplantation.

1. Introduction

Primary sclerosing cholangitis (PSC) is a progressive fibro-inflammatory disease of the (intra and/or extra-hepatic) biliary tree and comprises a wide spectrum of presentations going from an asymptomatic stage, overt liver function test disturbance to recurrent cholangitis, hepatogenic pruritus, and/or a progressive form of hepatic fibrosis, in some cases ultimately resulting in biliary cirrhosis [1]. Additionally, PSC patients also have a 10–15% lifetime risk of developing cholangiocarcinoma (CCA), a highly malignant and difficult to detect type of primary liver cancer [2]. The only treatment proven successful to improve quality of life and survival in evolving and therapy-refractory PSC patients is a liver transplantation (LT) [1]. Regrettably, after liver transplantation, PSC is estimated to re-occur in approximately 18% of the patients [3]. Recurrence of PSC is suggested to be associated with a worse patient and graft survival [4,5]. Average patient survival after the diagnosis of rPSC varies between 12 and 17 years [1].

In America and Northern Europe, 70–80% of PSC patients have been or will be diagnosed with inflammatory bowel disease (IBD), mostly ulcerative colitis [6]. Vice versa, 2.4–4% of IBD patients will develop PSC [1]. The phenotype of UC is different in PSC compared to non-PSC patients. In PSC patients, the UC is more often clinically

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quiescent pre-transplant, but the inflammation mostly involves the entire colon with predominant right-sided activity in comparison to UC patients without PSC [7]. After transplantation, the number and severity of UC flares may increase [8] and 30% of the patients will experience an increase in disease activity. Of PSC patients without a diagnosis of IBD at the time of the transplantation, 14–30% will develop IBD post-transplant. It should be kept in mind that, even after LT, IBD-PSC patients have a 10-fold higher risk of Colorectal cancers (CRCs) compared to IBD-patients undergoing a LT for other indications than PSC [9–11]. The risk of CRC development is as high as 30%, at 20 years after the concurrent diagnosis of IBD and PSC [12].

The risk factors associated with rPSC remain a topic of lively scientific discussion. Several associations have been found, such as male gender, younger age at the time of the LT, intercurring acute cellular rejection, co-inciding CMV-viremia post-LT, donor related factors (age, gender-mismatch), international normalized ratio (INR) at LT and CCA pre-transplant [5,7,13–15].

The largest study on this topic, published in 2015, concluded that the presence of UC after LT was associated with a significantly increased risk of rPSC [7]. Intriguingly, a colectomy before or during LT protected for rPSC [14,15]. This suggests that UC might increase the risk of developing rPSC. A German retrospective multicentre analysis, concluded in 2016 that the rate of rPSC was significantly higher in patients with an active colitis after LT compared to patients without IBD, inactive IBD or patients who underwent a colectomy before or during LT [5]. A meta-analysis by Steenstraten et al. also concluded in 2019 that a colectomy before liver transplantation reduced the risk of recurrence [3].

The suggestion that active colitis after LT might be a risk factor for rPSC implies that recurrence of PSC could be driven by intestinal mucosal inflammation via the concept of the gut-liver axis. This study aims to retrospectively assess this latter and previous mentioned factors in the recurrence of PSC after liver transplantation in Dutch and Belgian LT recipients with UC.

2. Materials and methods

2.1. Design and population

We performed a retrospective cohort study in the Leiden University Medical Centre (LUMC) in the Netherlands and the University Hospitals Leuven (UZ Leuven) in Belgium.

The inclusion criteria are: UC and non-IBD patients receiving their first LT due to PSC between July 1994–August 2–15 (LUMC) and February 1992–July 2015 (Leuven). The exclusion criterium is a follow-up period shorter than 6 months. The following data were systematically obtained from the electronic patient records:

1 Standard demographic patient characteristics.
2 PSC data: Date of diagnosis, occurrence of rPSC and presence and/or occurrence of: CCA, co-inciding autoimmune hepatitis (AIH) and/or CMV infections; defined as a positive Polymerase chain reaction (PCR) for CMV.
3 Transplantation data: Date and indication of liver transplantation, demographic donor data, international normalized ratio (INR), events of rejection and type of immunosuppression.
4 Colitis data: Presence of colitis and date of diagnosis, steroid usage, timing and type of colectomy and adopted medical treatment.
5 Pathology reports; assessment of inflammation and dysplasia.

Ethical approval was obtained from the ethics committees of both the LUMC and UZ Leuven. If follow-up duration was less than 6 months, patients were excluded. However, patients undergoing a re-transplantation within 6 months were included in analysis. Time zero was considered data of index transplantation. Follow-up started at time of transplantation and ended at death, recurrence of PSC or graft failure due to other causes.

2.2. Diagnosis of rPSC

Patients received routine annual check-ups after their liver transplantation. More thorough diagnostic tests (e.g. MRCP, ERCP or biopsies) were performed if either lab results and/or clinical signs suggested cholestasis. Recurrence of PSC was diagnosed in all cases according to the accepted Graziadei or Mayo criteria [6]. With typical findings of bile duct irregularities on cholangiography and/or histological findings in absence of defined causes of secondary sclerosing cholangitis (Established ductopenic rejection, hepatic artery thrombosis/stenosis, anastomotic biliary strictures alone, ABO incompatibility between donor and recipient and non-anastomotic strictures occurring within 90 days after liver transplantation) [6]. To discriminate from ischemic cholangiopathy, histological and/or radiological findings occurring >90 days after transplantation were considered as rPSC, as proposed in an earlier published report on this matter [6].

2.3. Assessment of mucosal inflammation

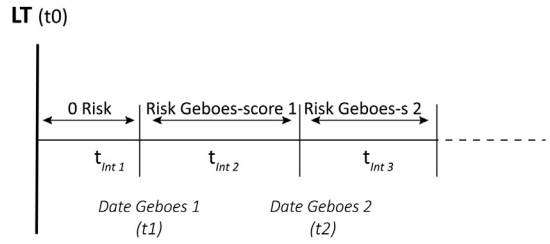
Because of the increased risk of CRC, guidelines suggest performing a colonoscopy yearly or every two years in PSC patients with UC. During most of these colonoscopies, biopsies are taken. These biopsies were used for the assessment of mucosal inflammation; all pathology reports were re-examined by one pathologist specialised in Gastro-intestinal pathology and scored, using the 0–5 Geboes score [16]. A-1 score was added to score biopsies that showed no histological alterations. *The complete Geboes score used for this study is shown in supplementary data (A).* Histological active disease is defined as a Geboes score $\geq$3 [17]. For every biopsy the worst right-sided (Cecum-Flexura Lienalis) and the worst left-sided (Flexura Lienalis-proximal Rectum) score was noted. If a report was insufficient for scoring, archived slides were requested for reassessment and scored by the same pathologist.

2.4. Statistical analysis

Data were collected and analysed using SPSS 23.0. Categorical parameters are expressed as n (%), continuous variables, when normally distributed, as mean ± standard deviation and if not as median ± interquartile range (IQR). Follow-up was calculated from date of first LT (or second LT if patients were re-transplanted within 6 months) to recurrence of PSC and censored at: graft loss (i.e. regraft >6 months after initial LT for other reasons than recurrence of disease), death or end of follow-up (July 5th 2016). Univariate analysis of all risk factors, except inflammation, was performed using Cox proportional hazards regression models. All variables close to or under significance level ($p < 0.1$) were included in multivariate analysis, performed by Cox regression analysis. After multivariate analysis, risk factors with a p-value <0.05 were considered statistically significant.

A time-dependent covariate in the Cox proportional hazard regression model was used for the statistical analysis of the risk factor inflammation. The time dependent covariate takes into account the amount of time a patient is exposed to the different risk scores; in this case the degree of intestinal inflammation as defined by the Geboes scores. The proportionality requirement will be verified by plotting log[-log(survival function)] by time and by verifying that there are no lines crossing.

First, all original Geboes scores (−1 to 5) were analysed for both the left side and the right side of the colon. After the original scores,



LT Liver transplantation, t_{int} Time interval, *Geboes-s* Geboes-score

Figure showing the use of the time dependent covariate; for each time period a different risk score is calculated by weighing the risk score of that moment (Risk Geboes-score) to the amount of time a patient is exposed to this amount of inflammation (t_{Int}).

Fig. 1. Time dependent covariate.

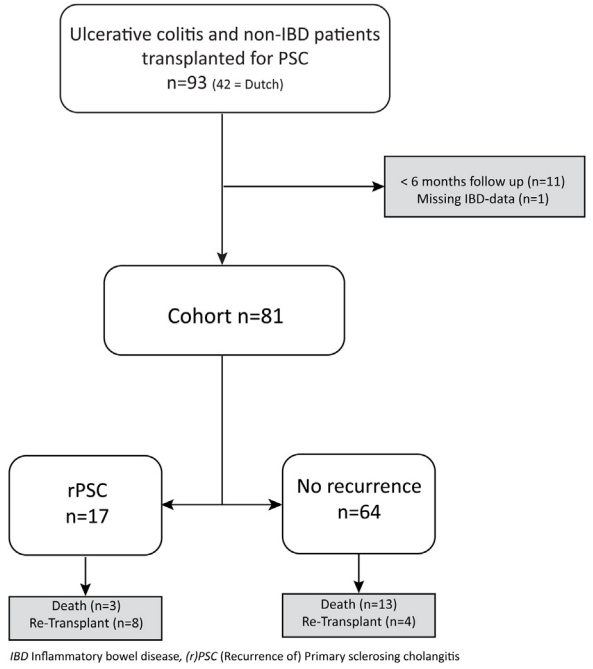
minimum and maximum scores were used for analysis (i.e. the lowest/highest score; so either the left-sided or right-sided score for each of the 13 scoring moments). Lastly, all Geboes scores were divided into two groups, using cut-off points: starting with a cut-off point of Geboes 4 (i.e. all Geboes scores <4 were transformed to 0, all Geboes scores 4 or 5 were transformed to 1). In the time dependent covariate date of LT was stated as t0, appointing every patient a zero risk from this point on until the date of their first biopsy; labelling the LT a reset for the PSC risk. The first Geboes score was applied as the risk factor for the interval between first (t1) and second biopsy date (t2). From t2 until the date of the patient's third biopsy (t3), the second Geboes score was applied as risk factor. The same applies for Geboes score 3 to Geboes score 13 (Fig. 1). For the analysis, using the time dependent covariate, it was necessary that every patient had the same number of Geboes scores. Therefore, we complemented the scores to the point where every patient had the same amount of Geboes scores. For complementing we used the "last observation carried forward" method, with the exception of patients undergoing colectomies during follow-up. After a (sub)total colectomy we rendered the Geboes score, for both right- and left-sided colon, −1. Only patients with at least two biopsies were included in analysis. When patients had missing scores, that side of the colon was excluded from analysis for that specific time point.

3. Results

3.1. Overall study population and outcome

A total of 93 liver transplants were performed for PSC in UC and non-IBD patients. Eleven patients died within 6 months of LT and were therefore excluded from final analysis; the leading causes of death were sepsis and multi-organ failure. In addition, one patient was excluded because of missing data regarding the IBD-diagnosis. From the study cohort of 81, 13 patients were censored at death and three were re-transplanted after six months for other indications than rPSC. A patient flow diagram is shown in Fig. 2.

Baseline patient characteristics are given in Table 1. The median follow-up was 5.2 years (IQR 6.9); there were 529.16 cumulative follow-up years, 70.4% of the cohort consisted of men (n = 57) and the mean age at liver transplantation was 41.9 years (±12.7). Pre-transplant, 57 patients were diagnosed with UC (70.4%), of whom 7 (12.3%) underwent a colectomy pre-LT and 10 (17.5%) post-LT. Three patients (5.3%) were diagnosed with colitis after liver transplantation. Nineteen patients (23.5%) were not diagnosed with IBD prior to transplantation or during follow-up. A total of 3 (3.7%) patients developed CRC during follow-up and 9 (11.1%) other patients had biopsies with definite dysplasia. In addition, 2 other patients had biopsies scored as indefinite for dysplasia.



IBD Inflammatory bowel disease, *(r)PSC* (Recurrence of) Primary sclerosing cholangitis

Fig. 2. Patient flow diagram.

Table 1
Patient baseline characteristics.

Patient characteristics	NL, n = 37	BE, n = 44	Cohort n = 81
Age at LT, mean ± SD	43.2 ± 11.2	40.8 ± 13.8	41.9 ± 12.7
Age at PSC diagnosis, mean ± SD	33.9 ± 11.0	32.8 ± 14.8	33.3 ± 13.0
Gender			
Male, n (%)	25 (67.6%)	32 (72.7%)	57 (70.4%)
Female, n (%)	12 (32.4%)	12 (27.3%)	24 (29.6%)
Follow-up, median (IQR)	4.7 (6.2)	5.4 (8.5)	5.2 (6.9)
UC diagnosed pre-LT, n (%)	32 (86.5%)	25 (56.8%)	57 (70.4%)
Colectomy pre/during LT, n (%)	4 (10.8%)	3 (6.8%)	7 (8.6%)
Colectomy after LT, n (%)	4 (10.8%)	6 (13.6%)	10 (12.3%)
UC diagnosed post-LT, n (%)	1 (2.7%)	4 (9.1%)	5 (6.2%)
Colectomy pre/during LT, n (%)	–	1 (2.2%)	1 (1.2%)
Colectomy after LT, n (%)	–	2 (4.5%)	1 (1.2%)
No-IBD	4 (10.8%)	15 (34.1%)	19 (23.5%)
Colectomy pre-LT, n (%)	1 (2.7%)	–	1 (1.3%)
Colectomy post-LT	1 (2.7%)	–	1 (1.3%)
CCA pre-LT, n (%)	5 (13.5%)	4 (9.3%)	9 (11.1%)
Donor age, mean ± SD	44.2 ± 13.5	46.1 ± 15.3	45.3 ± 1.7
CMV			
Pre, n (%)	9 (24.3%)	15 (34.1%)	24 (29.6%)
Post, n (%)	7 (18.9%)	8 (18.2%)	15 (18.5%)
Gender mismatch, n (%)	13 (35.1%)	14 (31.8%)	27 (33.3%)

LT liver transplantation, *SD* standard deviation, *IQR* interquartile range, *PSC* primary sclerosing cholangitis, *UC* ulcerative colitis, *IBD* inflammatory bowel disease, *CCA* cholangiocarcinoma, *CMV* cytomegalovirus.

3.2. rPSC, graft failure and survival

In this cohort, rPSC was identified in 17 patients (21.0%), of whom 14 had a diagnosis of UC. Ten rPSC patients experienced graft failure (58.8%) of which 2 patients died and 8 were re-grafted after a median of 6.1 (IQR 9.1) years. The 1, 5 and 10 years graft survival was 94%, 61% and 35% respectively.

Graft failure was less common in the 64 patients not experiencing recurrence of PSC, namely in five patients (7.8%). These patients were re-transplanted for autoimmune hepatitis (n = 1), hepatic artery thrombosis (n = 1), chronic rejection (n = 1), ischemic type biliary lesions (n = 1). In one patient graft failure occurred after a suicide attempt. The 1, 5 and 10 year survival was 100%, 89% and 89% respectively. After a liver transplantation for PSC, the 1,5 and

10 year patients' survival was respectively 97.5%, 87.4% and 58.8% in this study cohort (n = 81). The 1,5 and 10 year survival for all patients (n = 91), thus including those who had a follow-up time less than 6 months, was 87.8%, 78.7% and 52.9% respectively. No statistical difference was seen between 10 year survival in rPSC patients vs. non-rPSC patients for the study cohort (p = 0.15) or when patients with a follow-up time shorter than 6 months were included (p = 0.06).

3.3. Inflammation as a risk factor for rPSC

In total, 42 patients had a sufficient number of biopsies taken from either left, right or both sides of their colon and were included into analysis. Recurrence of disease occurred in 10 patients (23.8%). As stated above, scores of all patients were complemented to the amount of 13 Geboes scores. In some patients only biopsies were taken from the sigmoid colon, therefore data from the right side of the colon were missing. These patients were excluded from analysis of the right side, leaving 32 patients for analysis. *Complemented original scores are shown in supplementary data (B.1).*

No association was found between histological inflammation and rPSC in this cohort (Table 2). When using original Geboes scores, using values −1 to 5, left-sided inflammation appeared to increase the risk of rPSC with 19.6% (HR: 1.196, 95% CI 0.885–1.616), whereas right-sided inflammation reduced the rate of recurrence (HR 0.557, 95% CI 0.254–1.219). Neither reached statistical significance (respectively p = 0.41, p = 0.14). There was also no association found when using the maximum scores or just the minimum of the Geboes scores for each of the 13 scoring moments. Furthermore no association was found in this cohort when using different cut-off points; for instance looking at microscopic active disease (i.e. Geboes score ≥3). Also the cumulative right-sided score, (p 0.274, HR 0.964, 95% CI 0.902–1.030) the cumulative left-sided score (p 0.432, HR 1.011, 95% CI 0.984–1.039) and total cumulative score (p 0.228, HR 0.976, 95% CI 0.937–1.016) showed no association with recurrence of disease. *Scores recoded for histological active colitis are shown in supplementary data (B.2).*

3.4. Risk factors for rPSC

The strongest predictor for rPSC was intercurrent CMV viremia post-LT (Table 3). Interestingly, older recipient age was found to be a protective factor against rPSC; with each 10 year increment in age there was a risk reduction for rPSC of 6.5% (HR: 0.935, 95% CI 0.890–0.982). Univariate analysis showed age at PSC diagnosis to be protective for rPSC. Similar to recipient age it decreases the recurrence risk with an increment of age (HR: 0.942 95% CI 0.893–0.993, p = 0.03). However, age at PSC diagnosis appeared to be dependent of the risk factor recipient age at LT (r 0.86) and was therefore left out of multivariate analysis. An association was furthermore observed for non-heart-beating (NHB) donors; showing an increased risk of 265% of rPSC (HR: 3.653, 95% CI 0.914–14.60), although did not reach statistical significance (p = 0.07). No association was found between rPSC and the interval between date of PSC diagnosis and LT (p = 0.77) or the interval between IBD diagnosis and LT (p = 0.29).

Multivariate analysis showed an independent association between recipient age at LT and post-LT CMV viremia with rPSC (Table 4). Every 10 year increment of the recipient age showed a risk reduction of 6.6% for rPSC (HR: 0.934, 95% CI 0.881–0.990). Patients suffering from a post-LT CMV viremia showed an increased risk of 357% in multivariate analysis (HR: 4.576, 95% CI 1.688–12.403). An increased risk was furthermore seen for non-heart-beating donors (HR: 4.258, 95% CI 0.989–18.329), this however did not reach statistical significance (p = 0.05).

4. Discussion

In UC and non-IBD patients transplanted for PSC, this multicentre retrospective cohort study identified CMV viremia post-LT and a younger recipient age at time of LT as independent risk factors for recurrence of PSC after liver transplantation. The extent and severity of mucosal inflammation was not found related to rPSC.

To the best of our knowledge, this study is the first to assess the association of the histological degree of mucosal inflammation with rPSC. We used the validated Geboes score [16] as a measure of mucosal inflammation. Either when using the Geboes score value, or when using cut-off points of active mucosal inflammation (Geboes score of three or higher), or when using cumulative scores, no relation was observed with PSC recurrence, which opposed our initial hypothesis. Also when the Geboes scores were rendered 5 after a colectomy (Instead of the previously described −1 after), because you could argue these patients are exposed to the maximum inflammatory amount, no association was found. Interestingly, Hildebrand et al. also did not find an association between (merely clinically-endoscopically defined) active IBD disease and recurrence of PSC in multivariate analysis. In the study of Hildebrand only endoscopic (and clinical) activity were reported without histological confirmation [5]. These findings are also in line with the results from Lindström et al. where also no association was found between IBD-activity and recurrence of PSC [18]. Lindström et al. stated the IBD activity was measured by the number of IBD flares, endoscopic activity and microscopic activity. The assessment of microscopic activity was however, not explained. We chose to exclude patients with Crohn's disease because the Geboes score isn't validated for this disease.

In our study, both intercurring CMV viremia post-transplant and a younger age at liver transplantation were identified as risk factors for PSC recurrence. Both factors have been identified before. In the largest study published so far on this subject, Ravikumar et al. [7] explained the association between younger receiver age at LT and rPSC by the fact that being in need of a LT at a younger age reflects a more aggressive/relentless course of disease at that point that might resurface by reactivation of "residual immune memory" after transplantation (in accordance with the homing lymphocyte hypothesis [19]).

A CMV viremia within 3 months after LT has also been described earlier as a risk factor for rPSC in a small single centre cohort study (n = 20) [13]. No explanation was given for their findings. Purely hypothetical, one could consider the initial hepatobiliary inflammation and damage caused by the acute CMV viremia to instigate recurrence of the chronic fibro-inflammatory cascade leading to PSC [20,21]. A different explanation for this association might be that the dosage of immune suppressive therapy is increased when there is suspicion of rejection because of elevated liver enzymes, increasing the risk of a CMV viremia. A recent meta-analysis on risk factors of rPSC did not find a relation between CMV infection and rPSC [3]. This may also have been the consequence of the different definitions for CMV-infection in the reviewed papers.

Finally, we also evaluated whether the presence of IBD increased the risk of developing rPSC. In our study, although recurrence of PSC was numerically higher in IBD patients (22% Diagnosis of IBD pre-transplant vs. 15% of patients without UC), no significant relation was found between presence and/or activity of UC presence and rPSC recurrence. A previous systematic review by Gautam et al., also found no relation between rPSC and IBD presence [4] where other studies did [5,7]. A meta-analysis by our group did find a relation between presence of IBD and recurrence of PSC [3].

The limitations of our study are in line with the nature of all retrospective studies, namely that selection bias cannot be excluded despite the cohort showing fairly representative characteristics

Table 2
Risk assessment of Geboes scores using the time dependent covariate.

Scoring used for analysis	Right-sided (n = 32)		Left-sided (n = 42)	
	Hazard ratio (95% CI)	p-Value	Hazard ratio (95% CI)	p-Value
Original Geboes	0.669 (0.340–1.314)	0.243	1.196 (0.885–1.616)	0.24
Geboes ≥ 0	0.459 (0.084–2.510)	0.369	2.137 (0.619–7.373)	0.23
Geboes ≥ 1	0.486 (0.088–2.682)	0.408	1.776(0.534–5.909)	0.35
Geboes ≥ 2	0.026 (0.000–36.777)	0.325	1.283 (0.339–4.855)	0.71
Geboes ≥ 3	0.606 (0.069–5.306)	0.651	2.309 (0.603–8.845)	0.22
Geboes ≥ 4	0.042 (0.000–182 × 10^4)	0.723	1.219 (0.150–9.888)	0.85
	Right-sided and left-sided (n = 32)			
	Hazard ratio (95% CI)	p-Value		
Minimum score	0.632 (0.325–1.231)	0.18		
Maximal score	0.719 (0.346–1.497)	0.38		

CI confidence interval.

Table 3
Univariate analysis using Cox proportional hazards model.

Study variable	n (missing)	Recurrence of disease		Hazard ratio (95% CI)	p-Value
		rPSC, % (n = 17, 21%)	no rPSC, % (n = 64, 79%)		
Gender					
Male, n (%)	57	14 (82.3%)	43 (67.2%)	1.844 (0.528–6.441)	0.34
Female, n (%)	24	3 (17.6%)	21 (32.8%)	1.0	
Age at LT in years, median (IQR)	**81**	**34.6 (11.2)**	**43.0 (16.0)**	**0.935 (0.890–0.982)**	**0.01**
Age at PSC diagnosis, mean ± SD	**77(4)**	**26.9 ± 11.50**	**34.87 ± 13.03**	**0.942 (0.893–0.99)**	**0.03**
CMV Total	80(1)	12 (70.6%)	27 (42.2%)	3.111 (1.090–8.880)	0.03
Pre-LT, n (%)	24	3 (17.6%)	21 (32.8%)	0.586 (0.168–2.043)	0.40
Post-LT, n (%)	15	**9 (52.9%)**	**6 (9.4%)**	**5.535 (2.122–14.437)**	**<0.001**
Donor age, mean ± SD	76(5)	42.437 ± 17.0	46.03 ± 13.8	0.989 (0.954–1.025)	0.55
INR, median (IQR)	59(22)	12 (4.75)	12 (3.00)	0.965 (0.795–1.172)	0.72
NHB, n (%)	81	**3 (17.6%)**	**8 (12.5%)**	**3.653 (0.914–14.60)**	**0.07**
CCA pre-LT	81	–	9 (14.1%)	0.044 (0.000–109.93)	0.43
Gender mismatch	72(9)	6 (40%)	21 (36.8%)	0.983 (0.349–2.770)	0.97
Acute rejection	81	9 (52.9%)	31 (48.4%)	1.273 (0.488–3.322)	0.62
Timing colectomy	81				
No colectomy	57	12 (21%)	45 (79.4%)	1.0	
Pre-LT, n (%)	9	1 (11%)	8 (89%)	0.719 (0.092–5.595)	0.75
Post-LT, n (%)	13	2 (16.4%)	11 (84.6%)	0.411 (0.093–1.824)	0.24
UC diagnosed	81				
Never, n (%)	19	3 (15.8%)	16 (84.2%)	1.0	
Pre-LT, n (%)	57	13 (22.8%)	44 (77.2%)	1.509 (0.430–5.301)	0.52
Post-LT, n (%)	5	1 (5.9%)	4 (80%)	0.903 (0.094–8.700)	0.93
Interval: PSC diagnosis and LT, median (IQR)	77(4)	6.522 (7.94)	6.337 (8.7)	0.989 (0.919–1.065)	0.77
Interval: IBD diagnosis and LT, median (IQR)	54(27)	11.2 (11.7)	17.2 (18.8)	0.975 (0.931–1.022)	0.29

rPSC recurrence of primary sclerosing cholangitis, *CI* confidence interval, *LT* liver transplantation, *IQR* interquartile range, *SD* standard deviation, *CMV* cytomegalovirus, *INR* international normalized ratio, *NHB* non-heart-beating, *CCA* cholangiocarcinoma, *UC* ulcerative colitis.

Table 4
Multivariate analysis using Cox proportional hazards model.

Patient characteristics	Hazard ratio (95% CI)	p-Value
CMV viremia post-LT	4.576 (1.688–12.403)	0.01
Age at LT	0.934 (0.881–0.990)	0.02
NHB procedure	4.258 (0.989–18.329)	0.05

CI confidence interval, *CMV* cytomegalovirus, *LT* liver transplantation, *NHB* non-heart-beating.

in accordance with other reported cohorts of transplanted PSC patients. Other shortcomings relate to the size and duration of follow-up. Due to the limited sample size (numbers of events) the study may suffer from lack of power. However, our cohort of 81 patients surpassed the numbers of most previously reported cohorts [13,22–25] and reported a rPSC rate of 21.0% in accordance with larger cohort studies [6,7,15]. In analogy with the latter, our cohort also had a comparable median follow-up time of 5.2 years and a maximum follow-up time of 17.1 years. An item applicable to all rPSC studies at present is the definition of PSC recurrence. Although the criteria by Graziadei et al. [6] are generally accepted and were also used to define recurrence in this study, these criteria still leave some uncertainty with regards to distinguishing between ischemic type biliary lesions (ITBL) and rPSC given the lack of diagnostic tools to distinguish between these entities except for timing of arisal post-transplantation. The medical treatments patients were exposed to was often poorly reported. Since the assessment of drug exposure would not be reliable due to the very small sample size we chose not to analyse these data.

In conclusion, this multicentre cohort study is the first to have assessed the histological extent of mucosal inflammation as potential risk factor for rPSC and found no association between the two. An association between younger receiver age at time of LT and CMV viremia post-LT and the risk for post-transplant PSC recurrence was found adding weight to the awareness for and clinical suspicion of this entity by transplant clinicians when facing recurrent cholestasis and/or biliary tree abnormalities. Further studies, designed to optimally analyse these risk factors in a prospective setting, are necessary to confirm our findings.

Conflicts of interest
None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dld.2020.02.006.

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