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Global PBC Study Group

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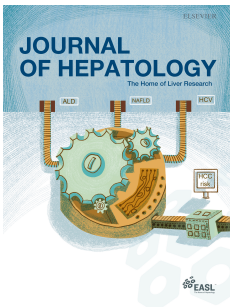

Long-term impact of preventive UDCA therapy after transplantation for primary biliary cholangitis

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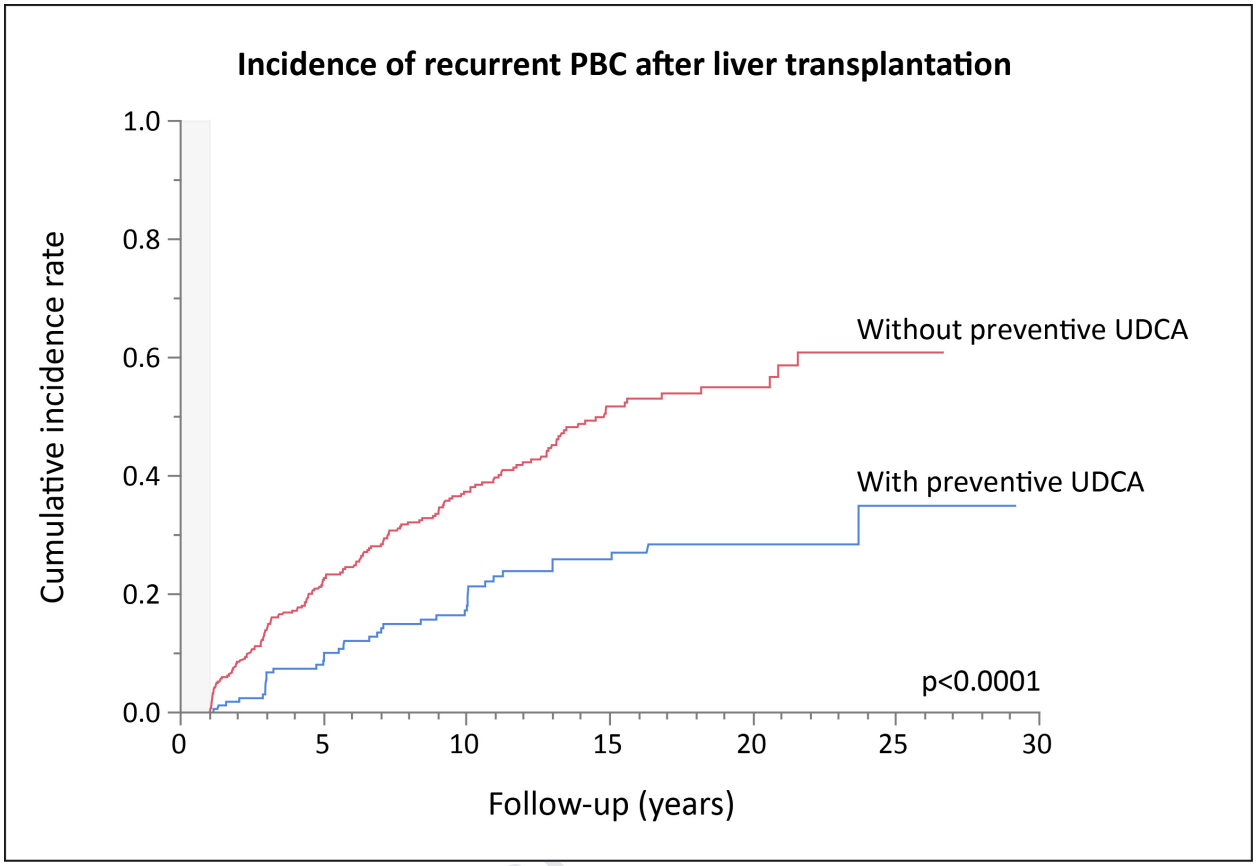
Incidence of recurrent PBC after liver transplantation
Cumulative incidence rate
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
30
Follow-up (years)
Without preventive UDCA
With preventive UDCA
p<0.0001

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Abstract

Background & Aims

Recurrence of primary biliary cholangitis (PBC) after liver transplantation (LT) is frequent and able to impair graft and patient survival. Ursodeoxycholic acid (UDCA) is the current standard therapy for PBC. We investigated the effect of preventive exposure to UDCA on the incidence and long-term consequences of PBC recurrence after LT.

Methods

We did a retrospective cohort study including 780 patients transplanted for PBC from 1983 to 2017 in 16 centers and 9 countries and followed-up for a median time of 11 years. Among them, 190 received UDCA (10-15 mg/kg/d) preventively. The primary outcome was PBC recurrence as proven by histology. The secondary outcomes were graft loss, liver-related death, and all-cause death. The association between preventive UDCA and outcomes was quantified using multivariable-adjusted Cox and restricted mean survival time (RMST) models.

Results

While recurrence of PBC significantly shortened graft and patient survivals, preventive exposure to UDCA was associated with reduced risk for PBC recurrence (adjusted hazard ratio, 0.41; 95%CI, 0.28 – 0.61; p<0.0001), graft loss (0.33; 0.13 – 0.82; p<0.05), liver-related death (0.46; 0.22 – 0.98; p<0.05), and all-cause death (0.69; 0.49 – 0.96; p<0.05). RMST analysis showed consistent results with a survival gain of 2.26 years (95%CI 1.28 – 3.25) over 20 years. Exposure to cyclosporine rather than to tacrolimus added to the preventive effect of UDCA against PBC recurrence and all-cause death.

Conclusions

Preventive UDCA after LT for PBC is associated with reduced risk for disease recurrence, graft loss, and death. Regimen combining cyclosporine and preventive UDCA is associated with the lowest risk of PBC recurrence and mortality.

Lay summary

Recurrence of primary biliary cholangitis after liver transplantation is frequent and can impair graft and patient survivals. In this largest ever international study of transplanted patients with primary biliary cholangitis, preventive administration of ursodeoxycholic acid after liver transplantation was associated with reduced risk for disease recurrence, graft loss, and liver-related and all-cause mortalities. Regimen combining cyclosporine and preventive ursodeoxycholic acid was associated with the best outcomes.

Introduction

Primary biliary cholangitis (PBC) is a rare, chronic cholestatic liver disease affecting mainly women, characterized by granulomatous destruction of small intrahepatic bile ducts classically associated with serological markers of autoimmune disease [1]. PBC is a cause of cirrhosis and premature death. Its current standard of care is ursodeoxycholic acid (UDCA) therapy [2, 3]. Long-term treatment with UDCA delays progression of histological stage and prolongs survival free of liver transplantation (LT) [4, 5, 6]. A significant proportion of patients, however, continues to progress to end-stage disease, including patients with cirrhosis and those with an inadequate biochemical response to UDCA [7, 8]. Approximately 200 European patients with PBC undergo LT annually, an absolute number that has not declined in the last 20 years [9].

After LT, the prognosis of patients with PBC is generally good [10, 11, 12, 13]. Recurrent PBC (rPBC), however, is not rare with a range of reported rates between 17% and 53% [10, 13]. Until recently, it was believed that rPBC had little impact on graft function and survival. However, recent data have shown that rPBC is able to affect long-term outcomes [14]. Strategies aimed at preventing rPBC are therefore warranted. The use of cyclosporine vs. tacrolimus has been considered since lower rates of recurrence with this immunosuppression regimen have been reported [15, 16, 17]. While UDCA therapy in established rPBC has been associated with biochemical improvement [11], administration of UDCA soon after LT has been reported to reduce the risk of rPBC [13]. However, evidence to support a preventive effect of UDCA against rPBC is very limited and requires more extensive studies. Accordingly, the present study was aimed to assess UDCA therapy as a preventive strategy against rPBC and its long-term effects. For that purpose, we performed a

longitudinal retrospective analysis of a very large, multicenter, international cohort, adjusted for all predictor variables, including the type of immunosuppressive regimen.

Methods

Study Population

Nine hundred and forty-seven patients with PBC who underwent LT from February 1983 until August 2017 across 16 centers and 9 countries were retrospectively included in the Global PBC Study Group transplant database. Part (nearly 80%) of this multicentric database has previously been described [14]. The numbers (percentages) of patients per center and country are shown in supplementary Table S1. Centers contributing more than 50 patients were defined as high-volume centers. The diagnosis of PBC prior to LT was based on established criteria and subsequently confirmed on liver explant [3]. All patients received ABO-compatible grafts from cadaveric (97%) or living (3%) donors. Following the first year post-LT, the patients were followed-up at least every 6 months. Protocol liver biopsies at 1, 5, 10, 15, 20, and 25 years were routinely performed in 7 (44%) out of 16 centers.

This study was conducted in accordance with the Declaration of Helsinki. It did not involve human participants. It was a retrospective analysis of already-collected routine care data with no opposition by patients. The protocol was approved by the institutional research board of the corresponding center and at each participating center, in accordance with their local regulations.

Study Dataset

The dataset analyzed for this study included the following variables: date of PBC diagnosis, date of LT, demographics of donor and recipient, recipient's biochemical parameters just before LT, immunosuppressive regimen and UDCA treatment (see below), biochemical parameters at 3, 6, and 12 months post-LT, history of rejection, date of rPBC diagnosis, biochemical parameters and histological stage at rPBC diagnosis, date and cause of graft loss, date and cause of death, date of last follow-up visit. Biochemical parameters included serum levels of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), total bilirubin, albumin, IgM, IgG, and creatinine, and international normalized ratio (INR). Model for end-stage liver disease (MELD) score at the time of LT was collected or computed. Positivity of antimitochondrial (AMA) and antinuclear (ANA) antibodies at LT was noted.

Exclusion Criteria

The patients who met one of the following conditions were excluded from primary analysis: follow-up unavailable or < 12 months; death < 12 months; graft loss < 12 months; or diagnosis of rPBC < 12 months. The latter rule was applied because of an expected high rate of cholangitis lesions and portal inflammation related to acute rejection.

Immunosuppression Regimen

The type of immunosuppression during the first year was recorded. The predominant calcineurin inhibitor, either cyclosporine (CYS) or tacrolimus (TAC), and other immunosuppression medications, including prednisone, azathioprine (AZA), mycophenolate mofetil (MMF), and mTOR inhibitors, were all assessed. Changes in the main immunosuppression after the first year of LT were also recorded.

Preventive Ursodeoxycholic Acid

Preventive UDCA was defined as long-term UDCA therapy started within 2 weeks after LT, administered orally at a daily dosage of 10 to 15 milligram per kilogram in two divided doses. This procedure was routinely applied since the 90's in 4 out of 16 centers (3 in Germany: Charité, Berlin; University Hospital, Jena; University Medical Center, Hamburg; and 1 in France: Edouard-Herriot, Lyon) as a protective measure of liver graft for all recipients. The Berlin center accounted for 60% of the patients who received preventive UDCA, and the other 3 centers for 25%. The remaining 15% consisted of patients who received preventive UDCA individually in 6 additional centers and 5 countries.

Recurrent Primary Biliary Cholangitis

Recurrent PBC was diagnosed histologically from liver biopsies performed at least 12 months after LT in a patient with or without biochemical features of cholestasis, and in the absence of any infectious, ischemic, toxic, or obstructive conditions of biliary tract. Diagnosis of rPBC was defined by the presence of portal features typical of or consistent with PBC (i.e. lymphoid infiltrates associated with granulomatous or lymphocytic destructive cholangitis with or without granulomas, ductular reaction, or ductopenia) with no parallel sign of acute rejection (absence of portal and centrilobular endothelialitis). When assessed, histological stage of rPBC was evaluated according to the Ludwig or Scheuer's classification system.

Statistical Analysis

The primary outcome was time to rPBC. The secondary outcomes included time to graft loss, time to liver-related death, and time to all-cause death. A landmark analysis at 12

months was performed. Patients who did not experience any events during follow-up were censored at the time of last visit. The groups exposed and non-exposed to preventive UDCA were compared at baseline using the Student's t-test, or the Wilcoxon-Mann-Whitney test when appropriate, and the Chi-square test, or the Fisher's exact test when appropriate. The effect of rPBC on graft and patient survivals was assessed using a Cox proportional hazards model considering rPBC as a time-dependent covariate. The primary and secondary outcomes were assessed using Cox proportional hazards and restricted mean survival time (RMST) models adjusted for risk and potential confounding factors, including recipient factors (age at LT, gender, body mass index, exposures to tacrolimus, cyclosporine, prednisone, azathioprine, mycophenolate mofetil, and mTOR inhibitors), donor factors (age, gender), center factors (protocol vs. clinically driven biopsies, high vs. low volume centers), and era factor (old vs. recent times split by the median year of 2000). Multiple imputation was applied to correct for missing data in body mass index and donor age. Missing data in mTOR inhibitors exposure were imputed as no exposure. Because tacrolimus and cyclosporine exposures were mutually exclusive covariates, tacrolimus but not cyclosporine was used in multivariable Cox models. Independent predictive factors were selected using a backward stepwise regression procedure. Results were expressed as hazard ratios (HR) with 95% confidence intervals (CI) and differences of RMST with 95% CI at pre-specified truncation times. The primary outcome (PBC recurrence) was assessed in the subpopulation of patients with at least 1 follow-up liver biopsy available (n=571, 73% of all patients), while secondary outcomes were assessed in the whole population (n=780). Several sensitivity analyses were performed: analysis including all patients (n=947); analysis using transplant year instead of transplant era; analysis by time quartiles or periods of equal population size; analysis excluding Berlin center. Cumulative event rate curves were estimated using the

Kaplan-Meier method. Survival curves according to rPBC status were drawn using a clock reset procedure for patients who developed rPBC. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) when appropriate. All tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. Analyses were performed with R software version 3.5.3 (R foundation).

Results

Population Description

The flow chart of the study is shown in **Figure 1**. A total of 780 (82%) out of 947 patients were eligible for analysis. Among eligible patients, 190 (24%) had received preventive UDCA while 590 (76%) had not. The main characteristics of the patients are shown in **Table 1**. As expected, they were mainly women of fifty years old presenting at LT with high bilirubin level and MELD score. Median time from diagnosis until LT was 6.2 yr. (2.9 – 11.1). The groups with and without preventive UDCA were comparable at baseline with respect to recipient demographics, time from diagnosis, bilirubin and albumin levels, and MELD score. Patients in the preventive-UDCA group had lower body mass index and higher serum ALP level. The rate of male donors was higher in this group. Patients from the preventive-UDCA group had lower exposure to antimetabolites (MMF, AZA) and higher exposure to mTOR inhibitors. Protocol biopsies were more frequently used in the preventive-UDCA group than in the no-preventive-UDCA group. On the whole cohort, the median follow-up from LT until last visit or death was 10.7 yr. (4.6 – 16.3). This time was significantly longer in the preventive-UDCA group than in the no-preventive-UDCA group (13.9 ± 7.4 yr. vs. 10.4 ± 7.0 yr., $p<0.0001$).

Primary Outcome

During the study period, 233 (30%) patients were diagnosed with rPBC. The rates of PBC recurrence were estimated in patients who had at least 1 follow-up liver biopsy (n=571). The recurrence rates at 5, 10, 15, 20, and 25 years were 0.18, 0.31, 0.44, 0.46, and 0.52, respectively. Assessed as a time-dependent variable, recurrence of PBC was associated with lower rates of patient (HR 1.93, 95%CI 1.42 – 2.63; p<0.0001) and graft (HR 1.96, 95%CI 1.45 – 2.65; p<0.0001) survivals (supplementary Figure S1). Eight factors were associated with rPBC risk in a univariate Cox regression analysis, including 5 factors conferring a decreased risk (exposures to preventive UDCA and cyclosporine, use of protocol biopsies, and recipient ages at diagnosis and LT) and 3 factors associated with an increased risk (exposures to tacrolimus and MMF, and transplant year ≥ 2000) (Supplementary Figure S2). In a multivariable-adjusted Cox model, 2 factors were independently associated with rPBC: preventive-UDCA exposure (HR 0.41, 95%CI 0.28 – 0.61; p<0.0001), and exposure to tacrolimus (HR 2.06, 95%CI 1.44 – 2.94; p<0.0001). These results did not change when the year of LT was assessed as a continuous variable. In a RMST analysis adjusted for the same factors, exposure to preventive UDCA was associated with a protective effect, while exposure to tacrolimus and LT year ≥ 2000 were associated with higher risk of disease recurrence (Supplementary Table S2). The results regarding UDCA remained unchanged when all patients were included in the analysis (supplementary Table S3). Results were also consistent with a protective effect of preventive UDCA across time periods (supplementary Table S4). The effect of preventive-UDCA exposure on the cumulative rates of rPBC is shown in Figure 2. The recurrence rates at 5, 10, 15, 20, and 25 years were 0.09, 0.18, 0.26, 0.28, and 0.35, respectively in the preventive-UDCA group and 0.22, 0.37, 0.52, 0.55, and 0.61,

respectively in the no-preventive-UDCA group. Preventive UDCA and cyclosporine exposures showed complementary protective effect against rPBC (Supplementary Figure S3).

Secondary Outcomes

Graft loss

During the study period, 60 graft losses occurred, of which 24 (40%) were related to rPBC. The factors associated with graft-loss in a multivariable-adjusted Cox analysis included preventive-UDCA exposure (HR 0.33, 95%CI 0.13 – 0.82; p=0.0172), use of protocol biopsies (HR 0.45, 95%CI 0.24 – 0.84; p=0.0114), and high-volume center (HR 3.92, 95%CI, 1.56 – 9.90; p=0.0038) (supplementary Figure S4). In a RMST analysis adjusted for the same factors, exposures to preventive UDCA and cyclosporine were associated with a protective effect, while high-volume center associated with poorer outcomes (Supplementary Table S5). The effect of preventive-UDCA exposure on the cumulative rates of graft loss is shown in **Figure 3**.

Liver-related death

Fifty liver-related death occurred during the study period, of which 13 (26%) were consecutive to rPBC. The factors associated with liver-related death in a multivariable-adjusted Cox analysis included preventive-UDCA exposure (HR 0.46, 95%CI 0.22 – 0.98; p=0.0434) and high-volume center (HR 9.86, 95%CI 2.30 – 42.2; p=0.0020) (Supplementary Figure S5). The effect of preventive-UDCA exposure on the cumulative rates of liver-related death is shown in **Figure 4**. Difference in RMST was non-evaluable.

All-cause death

A total of 202 all-cause deaths occurred during the study period. The patient survival rates at 5, 10, 15, 20, and 25 years were 0.93, 0.84, 0.71, 0.55, and 0.37, respectively. The factors associated with all-cause death in a multivariable-adjusted Cox analysis included recipient age at LT (HR per additional decade 1.75, 95%CI 1.27 – 2.41, p=0.0006), and exposure to preventive UDCA (HR 0.69, 95%CI 0.49 – 0.96; p=0.0278) or cyclosporine (HR 0.73, 95%CI 0.54 – 0.98; p=0.0382) (Supplementary Figure S6). The protective effect of preventive UDCA against all-cause death, or all-cause death or graft loss, remained significant after excluding Berlin center (Supplementary Table S6). In a multivariable-adjusted RMST analysis, exposures to preventive UDCA and cyclosporine were associated with a protective effect, while recipient age at LT and donor age were associated with poorer outcomes (Supplementary Table S7). Exposures to preventive UDCA and cyclosporine were associated with a survival gain of 2.26 years (95%CI 1.28 – 3.25) and 3.51 years (95%CI 2.19 – 4.82), respectively, over 20 years. The effect of preventive-UDCA exposure on the cumulative rates of all-cause death is shown in **Figure 5**. The complementary effects of preventive UDCA and cyclosporine on the cumulative incidence rates of all-cause death are shown in Supplementary Figure S7.

Discussion

In this longitudinal retrospective study of the largest cohort of transplanted patients with PBC to date that confirmed association between PBC recurrence and impaired survival, we showed that preventive administration of UDCA (10-15 mg/kg/d), as compared with no treatment, is associated with lower risk of disease recurrence, graft loss, liver-related death, and all-cause death indicating that UDCA therapy initiated soon after LT has the potential not only to prevent PBC recurrence as previously suggested [13], but also to reduce its long-

term negative effects on graft and patient survival. In addition, we observed an additive beneficial effect of cyclosporine vs. tacrolimus, a result that supports the use of cyclosporine and preventive-UDCA combination therapy in transplanted patients with PBC.

In most liver transplant centers, UDCA is generally employed after the diagnosis of rPBC has been established and has been associated with improvement of biochemical features [11]. However, data documenting a beneficial effect on histologic progression and long-term prognosis is lacking. In the present study, we show that UDCA is able to prevent or delay disease recurrence, a finding that supports a beneficial effect of the drug at very early, subclinical stages of the disease. Furthermore, the parallel decrease observed in graft-loss probability and both liver-related and all-cause mortalities strongly suggests that this effect actually translates into concrete long-term clinical benefits as in LT-naïve patients [6]. These results will need confirmation from clinical trials though significant difficulties in achieving this goal are predictable, notably owing to the larger number of patients and long double-blind study period required. In addition, it would be of interest to know whether current second-line therapies for PBC, in particular fibrates or obeticholic acid, may add to the preventive effect of UDCA therapy against rPBC [18, 19].

The present results raise the question of how and by which pathways UDCA therapy protects from rPBC. UDCA has been shown to target several pathophysiological processes involved in the initiation and progression of PBC, including defective bile secretion (i.e. cholestasis), inflammation, cholangiocytes senescence and apoptosis, and innate and adaptive immune response. The potential of UDCA therapy to prevent rPBC may better reflect its immunomodulatory and/or anti-inflammatory properties than its choleretic and anticholestatic effects [20, 21, 22]. However, reversal by UDCA of defective $Cl^-/HCO3^-$ exchanger AE2 expression on cholangiocytes [23], a hallmark of PBC pathophysiology [24],

may play a key role in restoring the bicarbonate protective barrier [25] and thus preventing cholangiocytes from cell senescence, aberrant expression of immunoreactive antigens, and domino autoimmune response [26]. Finally, UDCA may further protect the liver graft from PBC-independent biliary and/or vascular injuries [27, 28].

Several, but not all studies have suggested a protective role of cyclosporine as opposed to tacrolimus against rPBC [12, 16, 17, 29, 30]. Our results are consistent with these findings though it should be noticed that some of the centers that previously reported this association were included in the present study. We confirm that cyclosporine vs. tacrolimus exposure was significantly and independently associated with a reduced risk of rPBC. This association was strong and remained significant after controlling for an era effect. These results, therefore, definitively support the use of cyclosporine instead of tacrolimus in transplanted patients with PBC. The mechanisms by which cyclosporine prevents rPBC are unknown and may involve off-target effects and complex interactions with genetic and environmental factors linked with PBC [31]. Importantly, cyclosporine and preventive UDCA were found to have additive effects against rPBC and all-cause mortality, suggesting that this combination is the best appropriate regimen in transplanted patients with PBC.

A limitation of our study is that preventive-UDCA treatment strongly depended on center-specific policies and, accordingly, propensity score methods were not applicable. Since the Berlin center contributed more than half the preventive-UDCA group, a cluster effect could potentially have biased results. However, there was no significant differences in event rates between this center and the other preventive-UDCA providers, and results on graft loss and all-cause mortalities did not change after excluding this center. Furthermore, after adjusting for baseline values of all predictors and confounders, including era, volume center, protocol liver biopsy use, recipient age, and type of immunosuppression, results

from both Cox and RMST multivariate models were consistent. Finally, exposure to preventive UDCA after LT was initiated within a similar time frame for all exposed patients, which precluded any potential immortal time bias.

In conclusion, in this large international retrospective cohort study of transplanted patients with PBC, preventive administration of UDCA after LT resulted in lower rates of disease recurrence, graft loss, and liver-related or all-cause mortalities than no treatment. The protective effect of UDCA was potentiated by cyclosporine-based regimen.

Table 1. Baseline characteristics

Characteristics	All patients (n=780)	No preventive UDCA (n=590)	Preventive UDCA (n=190)	P-value‡
Recipient				
Age at LT (yr.)†	54.0 ± 9.0	54.0 ± 9.1	53.9 ± 8.5	0.8687
Female gender†	89%	89%	88%	0.6789
Body mass index*†	23.9 ± 4.6	24.4 ± 4.7	22.6 ± 3.5	<0.0001
AMA positivity*	92%	92%	91%	0.7664
Total bilirubin (mg/dL)*	11.2 ± 13.0	12.0 ± 14.8	10.4 ± 10.6	0.2607
ALP (xULN)*	3.0 ± 2.5	2.7 ± 2.5	3.3 ± 2.4	0.0483
AST (xULN)*	3.3 ± 2.7	3.3 ± 3.0	3.2 ± 2.3	0.8825
Albumin (g/L)*	32.9 ± 6.8	32.4 ± 7.1	33.5 ± 6.5	0.1858
MELD score*	17.5 ± 7.4	16.8 ± 6.5	18.3 ± 8.3	0.1770
Donor				
Age (yr.)*†	40.1 ± 17.5	40.3 ± 16.5	39.6 ± 19.6	0.6890
Female gender†	55%	58%	45%	0.0018
Gender mismatch	44%	42%	49%	0.1280
Deceased/Living	97%/3%	97%/3%	98%/2%	0.6224
Immunosuppression				
Tacrolimus/Cyclosporine†	66%/31%	68%/29%	60%/37%	0.0651
Prednisone†	83%	82%	86%	0.1862
MMF or AZA†	60%	63%	52%	0.0102
mTOR inhibitors*†	3%	2%	6%	0.0085
Center				
Protocol biopsies†	47%	37%	77%	<0.0001
High-volume center†	73%	73%	72%	0.6251

†Variables used for multivariable-adjusted analyses.

*Variables with missing data (the number of patients with missing data is shown in supplementary Table S8). Missing data for body mass index, donor age, and exposure to mTOR inhibitors were imputed before these variables were used in multivariable-adjusted analyses. AMA positivity, total bilirubin, ALP, AST, albumin, and MELD score are shown as descriptive variables at baseline. These variables were not used for multivariable-adjusted analyses.

‡P-values for the Student's t-test or Fisher's exact test. P-values <0.05 are considered statistically significant.

Legends of figures

Figure 1. Flow chart of the study.

Figure 2. Cumulative incidence rates of rPBC according to preventive-UDCA status.
Shown are the incidence curves of rPBC according to whether the patients were exposed (blue curve) or not exposed (red curve) to preventive UDCA. aHR, adjusted hazard ratio. CI, confidence interval. The gray area corresponds to the 12-month post-LT period before the landmark point. P-value for the multivariable-adjusted Cox proportional hazards model. A P-value < 0.05 is considered statistically significant.

Figure 3. Cumulative incidence rates of graft loss according to preventive-UDCA status.
Shown are the incidence curves of graft loss according to whether the patients were exposed (blue curve) or not exposed (red curve) to preventive UDCA. HR, hazard ratio. CI, confidence interval. The gray area corresponds to the 12-month post-LT period before the landmark point. P-value for the multivariable-adjusted Cox proportional hazards model. A P-value < 0.05 is considered statistically significant.

Figure 4. Cumulative incidence rates of liver-related death according to preventive-UDCA status.
Shown are the incidence curves of liver-related death according to whether the patients were exposed (blue curve) or not exposed (red curve) to preventive UDCA. HR, hazard ratio. CI, confidence interval. The gray area corresponds to the 12-month post-LT period before the landmark point. P-value for the multivariable-adjusted Cox proportional hazards model. A P-value < 0.05 is considered statistically significant.

Figure 5. Cumulative incidence rates of all-cause death according to preventive-UDCA status.
Shown are the incidence curves of all-cause death according to whether the patients were exposed (blue curve) or not exposed (red curve) to preventive UDCA. HR, hazard ratio. CI, confidence interval. The gray area corresponds to the 12-month post-LT period before the

landmark point. P-value for the multivariable-adjusted Cox proportional hazards model. A P-value < 0.05 is considered statistically significant.

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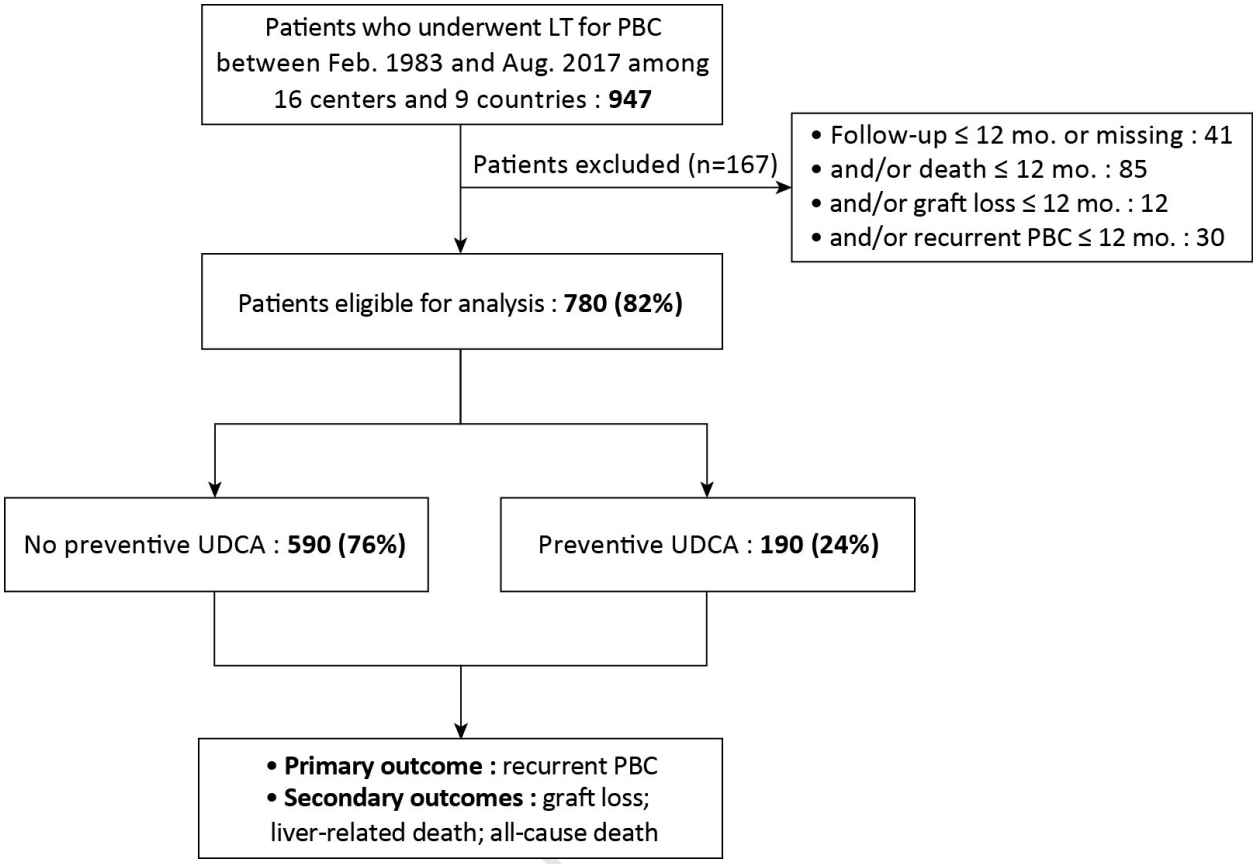
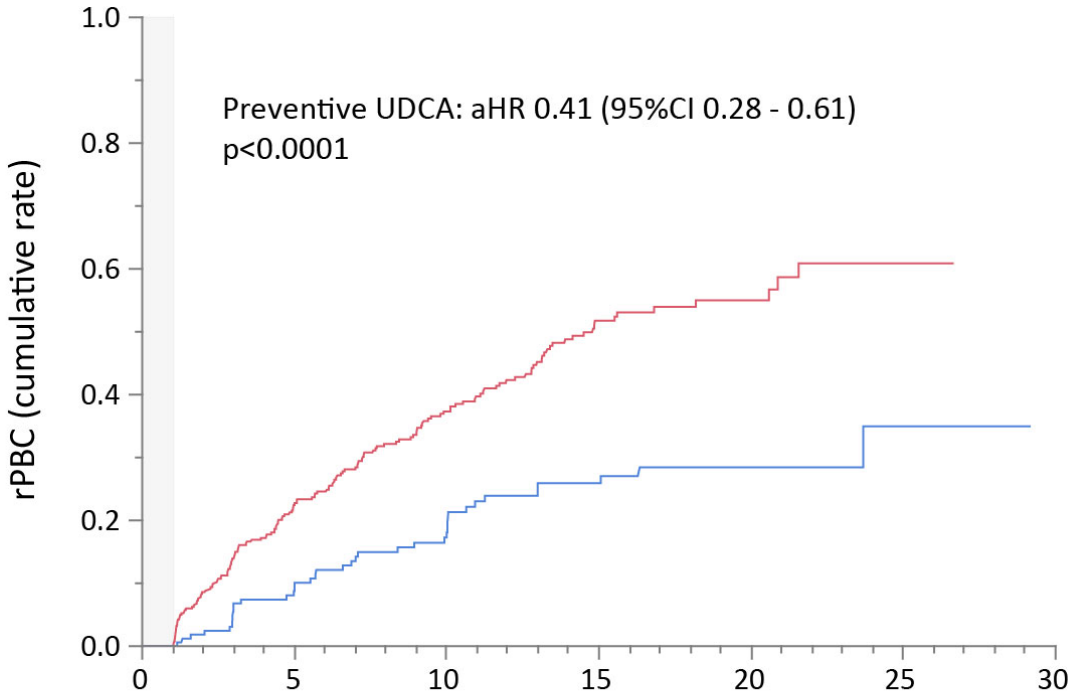
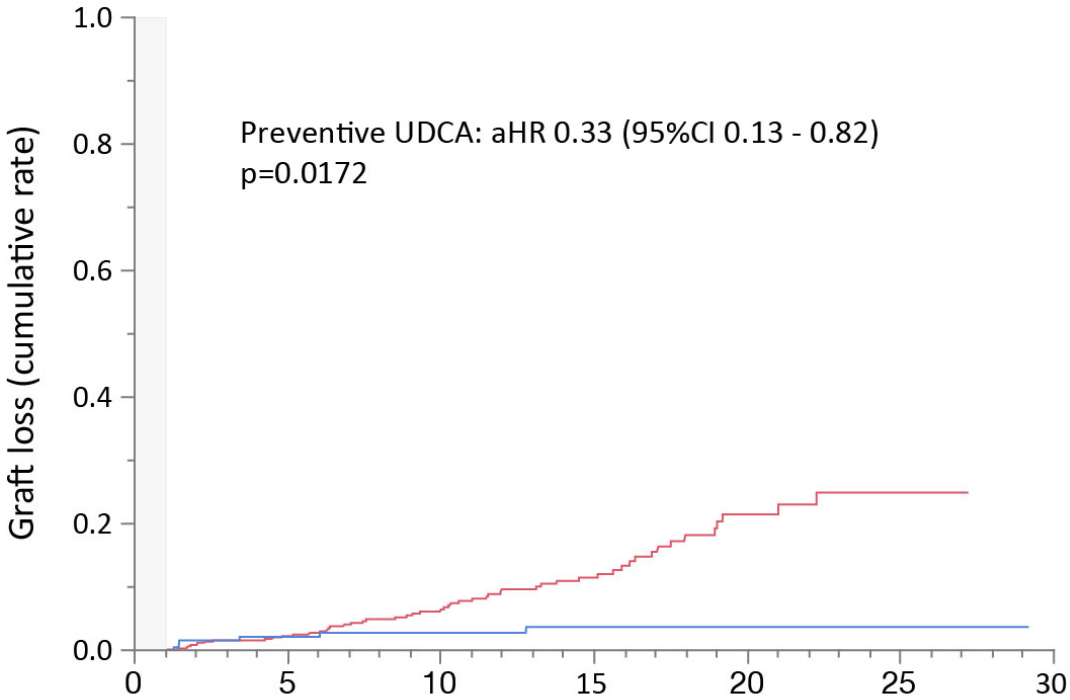
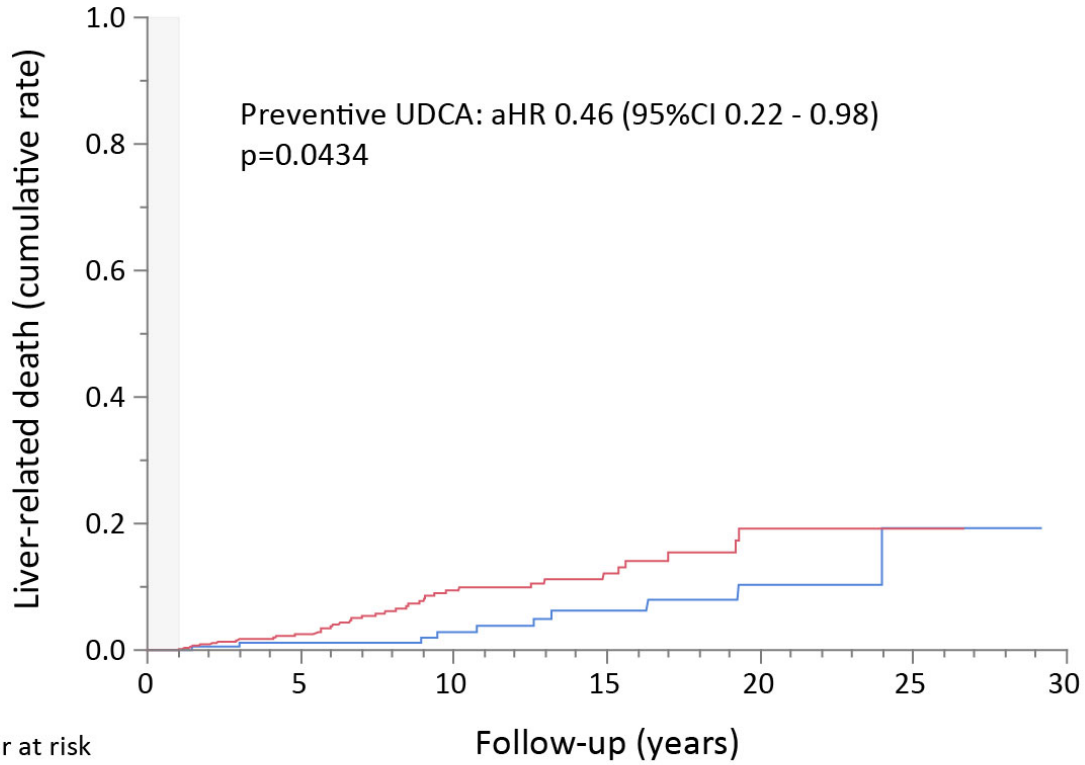

Patients who underwent LT for PBC between Feb. 1983 and Aug. 2017 among 16 centers and 9 countries : **947**
Patients excluded (n=167)
• Follow-up ≤ 12 mo. or missing : 41
• and/or death ≤ 12 mo. : 85
• and/or graft loss ≤ 12 mo. : 12
• and/or recurrent PBC ≤ 12 mo. : 30
Patients eligible for analysis : **780 (82%)**
No preventive UDCA : **590 (76%)**
Preventive UDCA : **190 (24%)**
• **Primary outcome :** recurrent PBC
• **Secondary outcomes :** graft loss; liver-related death; all-cause death



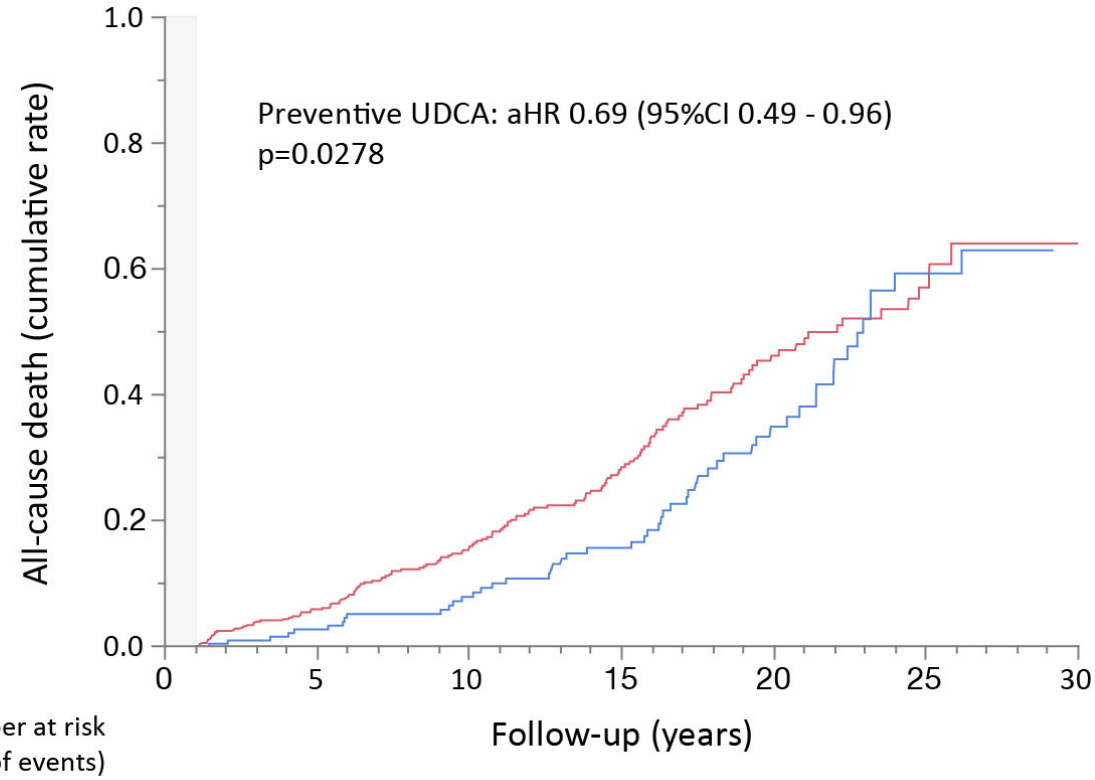
Number at risk (number of events)							
No preventive UDCA (red curve)	404 (0)	260 (84)	163 (128)	76 (158)	32 (162)	10 (165)	0 (165)
Preventive UDCA (blue curve)	167 (0)	137 (14)	102 (27)	67 (36)	30 (38)	8 (39)	0 (39)



Number at risk (number of events)							
No preventive UDCA (red curve)	590 (0)	407 (12)	287 (27)	158 (40)	63 (52)	22 (54)	0 (54)
Preventive UDCA (blue curve)	190 (0)	162 (4)	129 (5)	94 (6)	40 (6)	11 (6)	0 (6)



Number at risk (number of events)							
No preventive UDCA (red curve)	590 (0)	338 (12)	198 (31)	93 (35)	39 (40)	11 (40)	0 (40)
Preventive UDCA (blue curve)	190 (0)	149 (2)	107 (4)	70 (7)	31 (9)	8 (10)	0 (10)



Number at risk (number of events)							
No preventive UDCA (red curve)	590 (0)	411 (32)	290 (71)	160 (107)	67 (137)	25 (146)	2 (149)
Preventive UDCA (blue curve)	190 (0)	163 (5)	131 (13)	96 (23)	42 (40)	13 (52)	0 (53)

Highlights

- Preventive administration of ursodeoxycholic acid after liver transplantation for primary biliary cholangitis is associated with a reduced risk of disease recurrence.
- This protective effect is associated with a parallel reduction in the long-term risk of graft loss, liver-related death, and all-cause death.