Preventive Administration of Ursodeoxycholic Acid after Liver Transplantation for Primary Biliary Cholangitis Prevents Disease Recurrence and Prolongs Graft Survival

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The preventive use of ursodeoxycholic acid after transplantation for primary biliary cholangitis: an international cohort study

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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 859 patients transplanted for PBC from 1983 to 2017 in 16 centers and 9 countries and followed-up for a median time of 10 years. Among them, 204 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 proportional-hazards 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, 0.29 –0.60; p<0.0001), graft loss (0.43; 0.20 – 0.92; p<0.05), and liver-related death (0.45; 0.21 – 0.96; p<0.05), but not all-cause death (0.85; 0.62 –1.17). The survival gains without PBC recurrence, graft loss, or liver-related death associated with preventive UDCA were 1.43 years (95%CI, 0.82 – 2.03; p<0.0001) at 12 years and 3.40 years (2.18 – 4.62; p<0.0001) at 20 years. Exposure to cyclosporine rather than to tacrolimus added to the preventive effect of UDCA against PBC recurrence (p<0.0001). Conclusions Preventive exposure to UDCA after LT for PBC is associated with reduced risk for PBC recurrence, graft loss, and liver-related death. Regimen combining cyclosporine, as opposed to tacrolimus, and preventive UDCA is associated with the lowest risk of PBC recurrence.

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December 19, 2019, Paris, France

Professor Rajiv Jalan
Editor-in-Chief
Journal of Hepatology – Editorial Board

Dear Prof. Rajiv Jalan,
Dear Editor-in-Chief,

Attached to this letter, you will find a manuscript entitled "The preventive use of ursodeoxycholic acid after liver transplantation for primary biliary cholangitis: an international cohort study" that we wish to submit to *Journal of Hepatology*.

Our group previously showed that ursodeoxycholic acid (UDCA) therapy may prevent recurrence of primary biliary cholangitis (PBC) after liver transplantation (Bosch et al. J Hepatol 2015). However, these findings were supported by very limited data and the study was not powered enough to assess the potential impact of preventive UDCA on long-term outcomes.

In the present, largest ever cohort of transplanted patients with PBC (n=859, including 204 treated with preventive UDCA), we showed that, while recurrence of PBC significantly shortens graft and patient survivals, preventive administration of UDCA after liver transplantation is associated with reduced risk for disease recurrence, graft loss, and liver-related death. We further showed that exposure to cyclosporine rather than to tacrolimus as main immunosuppressive regimen after transplantation adds to the preventive effect of UDCA against PBC recurrence.

The clinical efficacy of UDCA in PBC has long been a matter of debate until long-term and large-scale follow-up data of both UDCA-treated and untreated patients recently provide convincing findings supporting UDCA as the standard of care in this disease (Harms et al. J Hepatol 2019). The present results strongly reinforce this statement and provide new insights on the potential of UDCA to treat PBC efficiently, in particular in early, preclinical stages of the disease when intrahepatic retention of bile acids (cholestasis), on which UDCA is mainly supposed to act, has not yet occurred.

Finally, we believe that these results may impact the management of transplanted patients with PBC since UDCA is an inexpensive and quite well tolerated drug, and definite confirmation of these data would need large and long-term, histology-based, placebo-controlled trials that are very unlikely to be conducted in the near future.

We sincerely hope that you will find this study of interest and are looking forward to hearing from you.

With our best regards,

Christophe Corpechot, MD.
Jérôme Dumortier, MD., PhD.

The preventive use of ursodeoxycholic acid after transplantation for primary biliary cholangitis: an international cohort study

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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 859 patients transplanted for PBC from 1983 to 2017 in 16 centers and 9 countries and followed-up for a median time of 10 years. Among them, 204 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 proportional-hazards 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, 0.29 – 0.60; $p<0.0001$), graft loss (0.43; 0.20 – 0.92; $p<0.05$), and liver-related death (0.45; 0.21 – 0.96; $p<0.05$), but not all-cause death (0.85; 0.62 – 1.17). The survival gains without PBC recurrence, graft loss, or liver-related death associated with preventive UDCA were 1.43 years (95%CI, 0.82 – 2.03; $p<0.0001$) at 12 years and 3.40 years (2.18 – 4.62; $p<0.0001$) at 20 years. Exposure to cyclosporine rather than to tacrolimus added to the preventive effect of UDCA against PBC recurrence ($p<0.0001$).

Conclusions

Preventive exposure to UDCA after LT for PBC is associated with reduced risk for PBC recurrence, graft loss, and liver-related death. Regimen combining cyclosporine, as opposed to tacrolimus, and preventive UDCA is associated with the lowest risk of PBC recurrence.

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 mortality. Regimen combining cyclosporine and preventive ursodeoxycholic acid was associated with the lowest risk of disease recurrence.

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. 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 analysis: missing follow-up data; death occurred within 3 months after LT; and diagnosis of rPBC made within 12 months after LT. The latter rule was applied because of an expected high rate of cholangitis lesions and portal inflammation related to acute rejection. When patients underwent retransplantation within the first 3 months after the first LT, the date of retransplantation was used as LT date.

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. These 4 centers accounted for approximately five-sixths (85%) of the patients who received preventive UDCA in this cohort. The remaining sixth (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, time to all-cause death, and time to rPBC, graft loss, or liver-related death (defined as liver-related morbimortality). Patients who did not experience any of these 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 hazard 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 exposure was used in multivariable Cox models. Independent predictive factors were selected using a backward stepwise regression procedure. Results were expressed as hazard ratios (HR) and 95% confidence intervals (CI) illustrated through forest plots. The primary outcome (PBC recurrence) was assessed in the subpopulation of patients with at least 1 follow-up liver biopsy available (n=609, 71% of all patients), while secondary outcomes were assessed in the whole population (n=859). Restricted mean survival time (RMST) was estimated at pre-specified time horizons and differences between groups were expressed as mean survival gain (or life loss) with 95% CI. RMST was notably used when the proportional hazard assumption assessed graphically using Log cumulative hazard functions and Schoenfeld residuals was not met. Several sensitivity analyses were performed including patients with no follow-up liver biopsy, patients with premature recurrence (< 12 mo. post-LT) or deaths (≤ 3 mo. post-LT), and patients transplanted in old (1983-1999) vs. recent (2000-2017) times. Cumulative event rate curves were estimated using the Kaplan-Meier method. 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 859 (91%) out of 947 patients were eligible for analysis. Among eligible patients, 204 (24%) had received preventive UDCA while 655 (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 – 11.0). 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 9.8 yr. (3.6 – 15.9). This time was significantly longer in the preventive-UDCA group than in the no-preventive-UDCA group (13.2 yr. vs. 8.1 yr., p<0.01).

Primary Outcome

During the study period, 238 (28%) patients were diagnosed with rPBC. The rates of PBC recurrence were estimated in patients who had at least 1 follow-up liver biopsy (n=609). The recurrence rates at 5, 10, 15, 20, and 25 years were 0.19, 0.32, 0.44, 0.49, and 0.55, respectively. Recurrence of PBC was associated with lower rates of patient (HR 1.77, 95%CI 1.31 – 2.39; p<0.001) and graft (HR 1.79, 95%CI 1.34 – 2.39; p<0.001) survivals (supplementary Figure S1). The estimated life loss associated with rPBC in a multivariable-adjusted RMST analysis was 1.20 years (95%CI, 0.67 – 1.74; p<0.001) at 12 years and 2.98 years (95%CI, 1.40 – 4.56; p<0.001) at 20 years. Eight factors were associated with rPBC risk in a univariate Cox regression analysis, including 5 factors conferring a decreased risk (exposures to preventive UDCA, cyclosporine, and prednisone, use of protocol biopsies, and recipient age at LT) and 3 factors associated with an increased risk (exposures to tacrolimus and MMF, and transplant performed in recent era) (Supplementary Figure S2). In a multivariable analysis, 3 factors were independently associated with rPBC, including preventive-UDCA exposure (HR 0.41, 95%CI 0.29 – 0.60; p<0.0001), exposure to tacrolimus rather than to cyclosporine (HR 2.13, 95%CI 1.58 – 2.87; p<0.0001), and recipient age at LT (HR per additional decade 0.76, 95%CI, 0.66 – 0.88; p=0.0003). These results remained unchanged when patients with no follow-up biopsy (n=859, supplementary Table S2) or those with premature recurrence or death (n=689, supplementary Table S3) were included in the analysis. Furthermore, this association was significant regardless of whether the patients were transplanted in recent or in old times (supplementary Table S4). **Figure 2** illustrates the effect of preventive-UDCA exposure on the cumulative rates of rPBC. The recurrence rates at 5, 10, 15, 20, and 25 years were 0.10, 0.20, 0.27, 0.29, and 0.36, respectively in the preventive-UDCA group and 0.22, 0.37, 0.51, 0.56, and 0.62, respectively in the no-preventive-UDCA group. Preventive UDCA and cyclosporine exposures showed complementary protective effect against rPBC (**Figure 3**).

Secondary Outcomes

Graft loss

During the study period, 72 graft losses occurred, of which 26 (36%) were related to rPBC. The factors associated with graft-loss risk in a multivariable-adjusted Cox analysis included preventive-UDCA exposure (HR 0.42, 95%CI 0.20 – 0.92; p=0.0293), use of protocol biopsies (HR 0.49, 95%CI 0.28 – 0.85; p=0.0117), and high-volume center (HR 5.00, 95%CI, 2.01 – 12.4; p=0.0005) (supplementary Figure S3). The effect of preventive-UDCA exposure on the cumulative rates of graft loss is shown in supplementary Figure S4.

All-cause and liver-related mortality

During the study period, 236 deaths occurred, of which 61 (26%) were liver-related and 13 (6%) were consecutive to rPBC. The patient survival rates at 5, 10, 15, 20, and 25 years were 0.91, 0.83, 0.72, 0.54, and 0.39, respectively. The factors associated with all-cause mortality in a multivariable-adjusted Cox analysis included recipient age at LT (HR per additional decade 1.67, 95%CI 1.42 – 1.96, p<0.0001) and use of protocol biopsies (HR 0.74, 95%CI 0.55 – 0.98; p=0.033) (Supplementary Figure S5). In Cox regression, the association between preventive-UDCA exposure and all-cause mortality was not significant (HR 0.76, 95%CI 0.57 – 1.02; p=0.065) but the proportional hazard assumption was not met (**Figure 4**).

The association was significant in a univariate RMST analysis with a marginal survival gain of 0.52 years (95%CI 0.05 – 0.99; p=0.031) at 12 years and 1.36 years (95%CI 0.38 – 2.33; p=0.006) at 20 years. The significance disappeared after adjusting for recipient age and use of protocol biopsies.

The factors associated with liver-related mortality in a multivariable-adjusted Cox analysis included preventive-UDCA exposure (HR 0.45, 95%CI 0.21 – 0.96; p=0.0388), recipient age at LT (HR per additional decade 1.74, 95%CI 1.27 – 2.38; p=0.0006), and high-volume center (HR 10.08, 95%CI 2.46 – 41.3; p=0.0013) (Supplementary Figure S6). The effect of preventive-UDCA exposure on the cumulative rates of liver-related mortality is shown in supplementary Figure S7.

Liver-related morbimortality

Liver-related morbimortality was defined as disease recurrence, graft loss, or liver-related death. The factors associated with this outcome in a multivariable-adjusted Cox analysis included preventive-UDCA exposure (HR 0.47, 95%CI 0.34 – 0.64; p<0.0001), recipient age at LT (HR per additional decade 0.87, 95%CI 0.77 – 0.99; p=0.0364), and tacrolimus exposure (HR 1.66, 95%CI 1.30 – 2.13; p<0.0001) (Supplementary Figure S8). The effect of preventive-UDCA exposure on liver-related morbimortality is shown in **Figure 5**. In a multivariable-adjusted RMST analysis, preventive UDCA was associated with a survival gain without liver-related morbidity of 1.43 years (95%CI 0.82 – 2.03, p<0.0001) at 12 years and 3.40 years (95%CI 2.18 – 4.62, p<0.0001) at 20 years.

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, was associated with lower rates of disease recurrence, graft loss, and liver-related 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. A decreasing trend in all-cause mortality in patients exposed to preventive UDCA was consistent with this result. 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 at least 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 liver-related mortality 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 long 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 may be protective against 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 or delay 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 crucial role in restoring the bicarbonate protective barrier [25] and, consequently, in preventing cholangiocytes from cell senescence, aberrant expression of immunoreactive antigens, and subsequent domino autoimmune response [26]. At last, one cannot exclude that UDCA therapy may further protect the liver graft from PBC-unrelated biliary and/or vascular injuries [27, 28].

Several, but not all, studies have suggested a protective role of cyclosporine-, as opposed to tacrolimus-, based regimen against recurrence of PBC after LT [12, 16, 17, 29, 30]. Our results are consistent with these findings although it should be noticed that some of the centers that previously reported this association were included in the present study. Cyclosporine vs. tacrolimus exposure was significantly and independently associated with a reduced risk of PBC recurrence. Importantly, this association remained significant after adjusting for an era effect, patients having been mainly exposed to cyclosporine in the 1990s and to tacrolimus after 2000. Interestingly, we found that preventive UDCA and cyclosporine exposures had additive protective effects against rPBC, suggesting that combination of both could be the best appropriate regimen in transplanted patients with PBC. The mechanisms by which cyclosporine may be protective against rPBC are unknown and may involve offtarget effects and complex interactions with genetic and environmental factors linked with PBC [31].

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 difference in outcome rates (disease recurrence, graft loss, all-cause or liver-related mortality) between this center and the other preventive-UDCA providers. In addition, we used multivariable Cox proportional hazards models and sensitivity analyses adjusted for baseline values of all predictor variables and confounders, including era, volume center, liver biopsy use, recipient age, and type of immunosuppression. Immunosuppression regimens were not assessed as time-varying covariates but, instead, the predominant regimens recorded during follow-up were used for analysis. Finally, exposure to preventive UDCA after LT was initiated within a similar time frame (i.e. 2 weeks post-LT) in all exposed patients, so that any immortal time bias can be considered as marginal.

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 mortality than no treatment. The protective effect of UDCA against rPBC was potentiated by cyclosporine-based regimen. Randomized controlled trials are needed to confirm these results. Whether additional treatment with fibrates or obeticholic acid could further improve this effect deserves consideration.

Table 1. Baseline characteristics

Characteristics	All patients (n=859)	No preventive UDCA (n=655)	Preventive UDCA (n=204)	P-value
Recipient				
Age at LT (yr.)†	54.2 ± 9.0	54.3 ± 9.1	53.9 ± 8.66	0.5229
Female gender†	89%	89%	88%	0.8546
Body mass index*†	24.0 ± 4.6	24.4 ± 4.7	22.7 ± 3.7	<0.0001
AMA positivity*	92%	93%	91%	0.7655
Total bilirubin (mg/dL)*	11.3 ± 12.9	12.0 ± 14.7	10.7 ± 10.9	0.4486
ALP (xULN)*	3.0 ± 2.5	2.7 ± 2.5	3.3 ± 2.5	0.0009
AST (xULN)*	3.2 ± 2.6	3.3 ± 2.9	3.2 ± 2.3	0.4923
Albumin (g/L)*	32.9 ± 6.8	32.3 ± 7.1	33.5 ± 6.5	0.0854
MELD score*	17.9 ± 7.7	17.0 ± 6.8	18.8 ± 8.6	0.2931
Donor				
Age (yr.)*†	40.8 ± 17.8	40.8 ± 16.8	40.9 ± 19.7	0.8466
Female gender†	56%	59%	43%	0.0005
Gender mismatch	43%	42%	49%	0.0618
Deceased/Living	97%/3%	96%/4%	97%/3%	0.6891
Immunosuppression				
Tacrolimus/Cyclosporine†	67%/30%	69%/28%	61%/35%	0.0651
Prednisone†	83%	82%	87%	0.0913
MMF or AZA†	62%	65%	52%	0.0009
mTOR inhibitors*†	3%	2%	6%	0.0102
Center				
Protocol biopsies†	44%	34%	75%	<0.0001
High-volume center†	74%	74%	71%	0.3546

†Variables used for multivariable-adjusted analyses.

*Variables with missing data (the number of patients with missing data is shown in supplementary Table S5). 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.

Legends of figures

Figure 1. Flow chart of the study.

Figure 2. Effect of preventive-UDCA exposure on the cumulative rates of PBC recurrence after LT.

The incident rates of PBC recurrence were estimated in the subpopulation of patients who had at least 1 liver biopsy during follow-up (n=609). Shown are the incident curves for PBC recurrence according to whether patients were exposed (blue curve) or not exposed (red curve) to preventive UDCA. aHR, adjusted hazard ratio. CI, confidence interval.

Figure 3. Joint effects of preventive-UDCA and cyclosporine exposures on the cumulative rates of PBC recurrence after LT.

Shown are the incident curves for PBC recurrence after LT according to whether patients were exposed to both preventive UDCA and cyclosporine (CYS) (green curve), either preventive UDCA or CYS (blue curve), or none of both (red curve). aHR, adjusted hazard ratio. CI, confidence interval.

Figure 4. Effect of preventive-UDCA exposure on the cumulative rates of all-cause mortality.

Shown are the incident curves for all-cause mortality according to whether patients were exposed (blue curve) or not exposed (red curve) to preventive UDCA. HR, hazard ratio. CI, confidence interval.

Figure 5. Effect of preventive-UDCA exposure on the cumulative rates of liver-related morbimortality, defined as disease recurrence, graft loss, or liver-related death.

Shown are the incident curves for liver-related morbimortality according to whether patients were exposed (blue curve) or not exposed (red curve) to preventive UDCA. aHR, adjusted hazard ratio. CI, confidence interval.

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Figure 1

Click here to access/download;Figure;Corpechot_PBC_recurrence_UDCA_Figure1.jpg

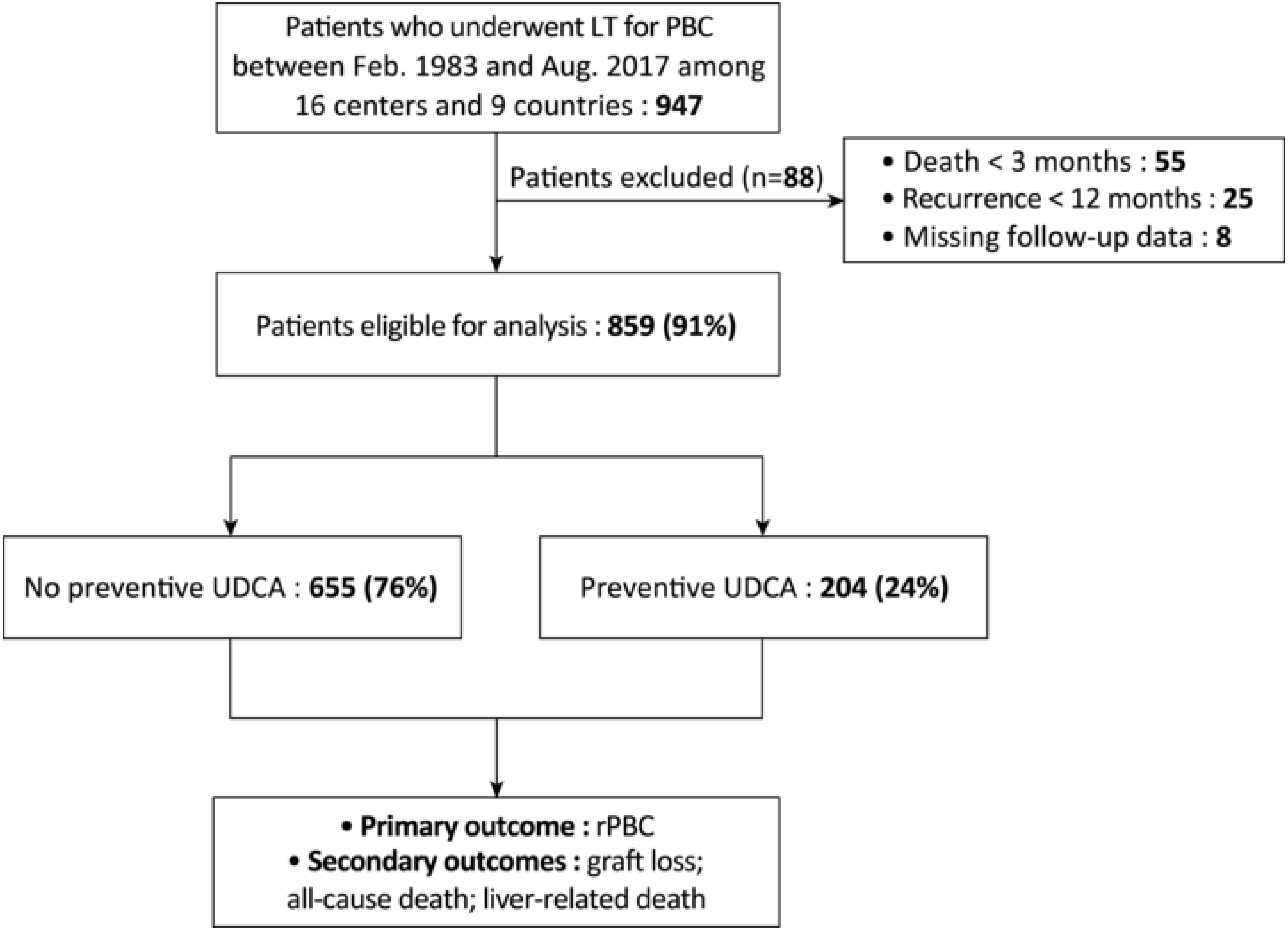
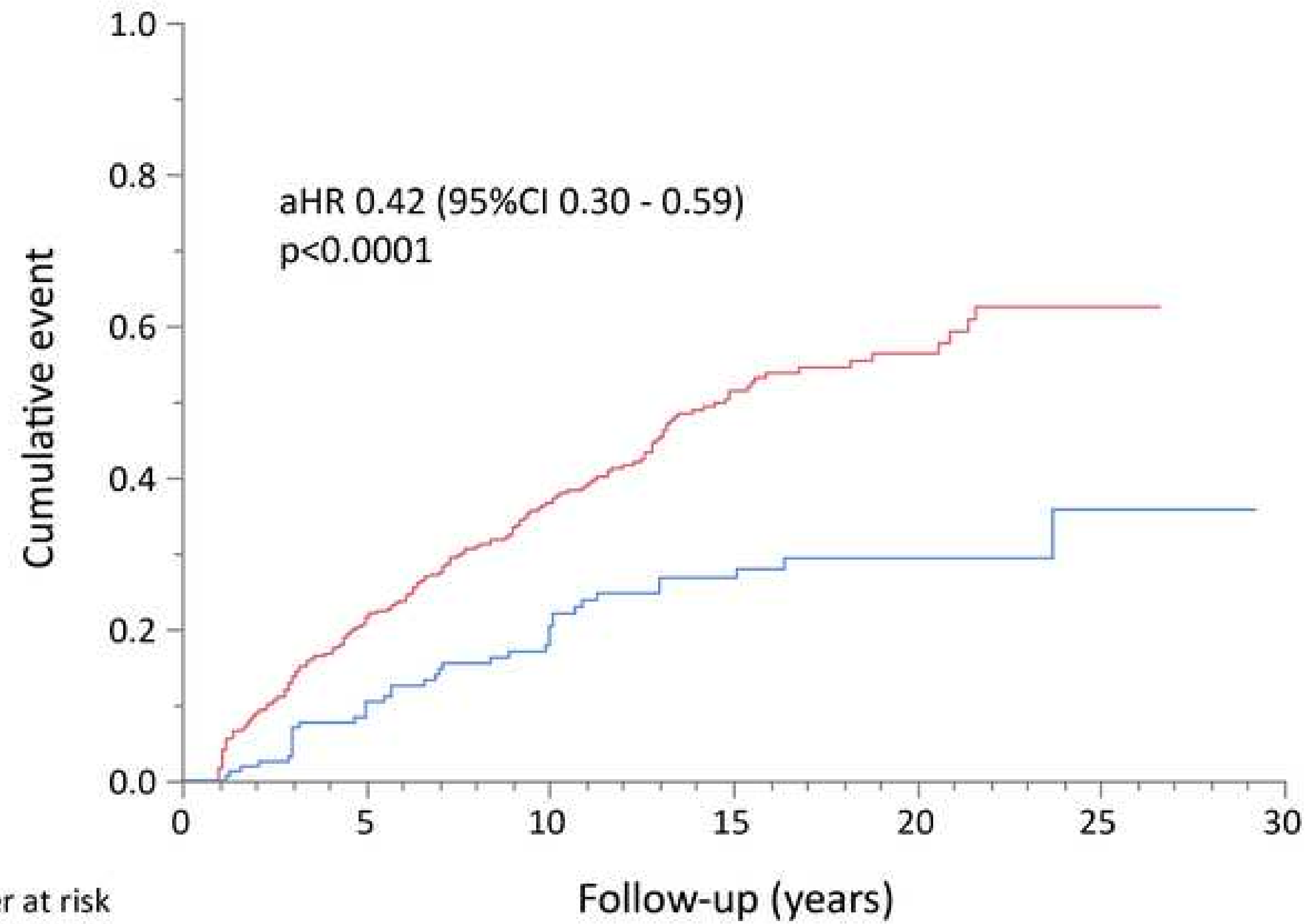
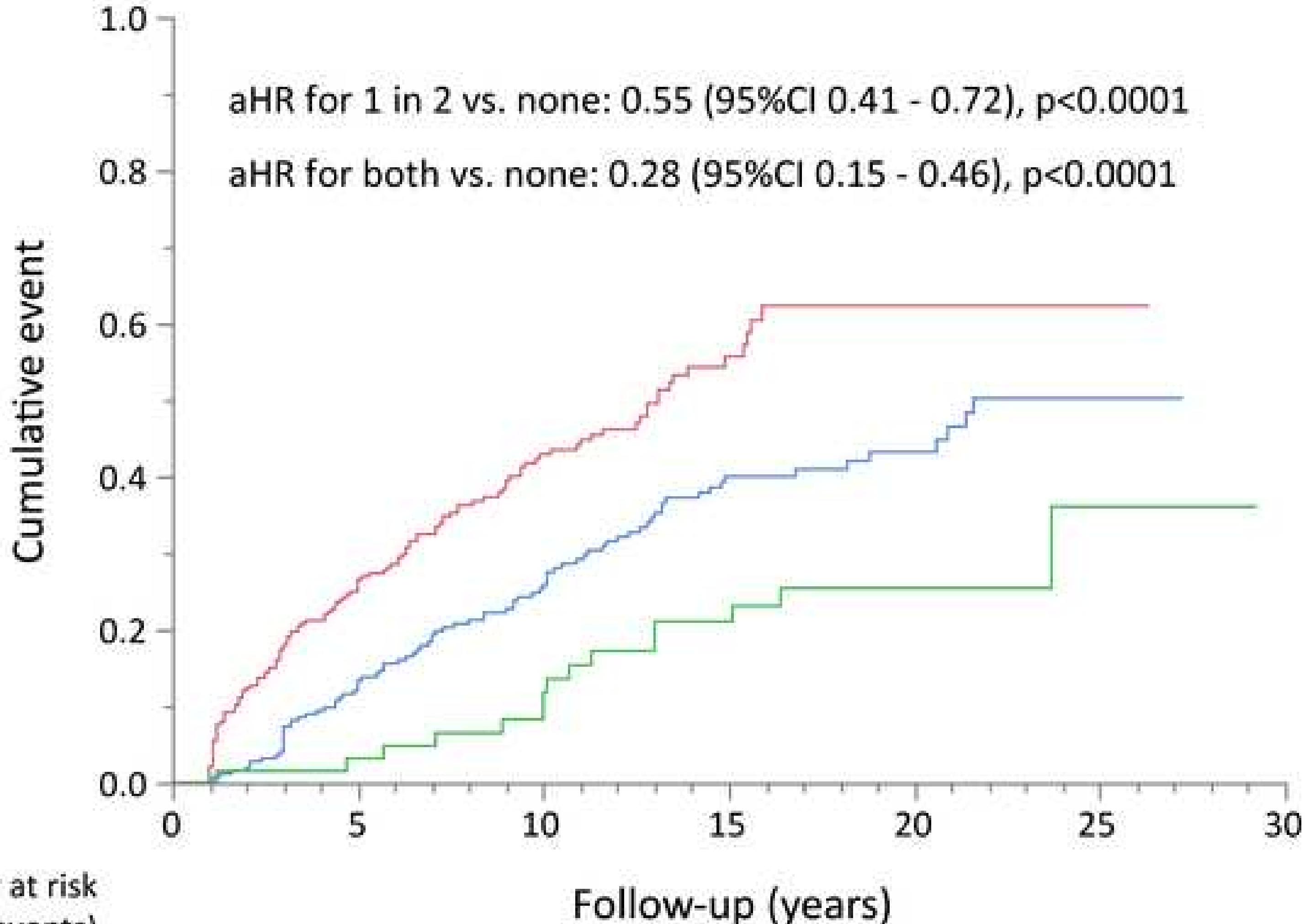


Figure 2



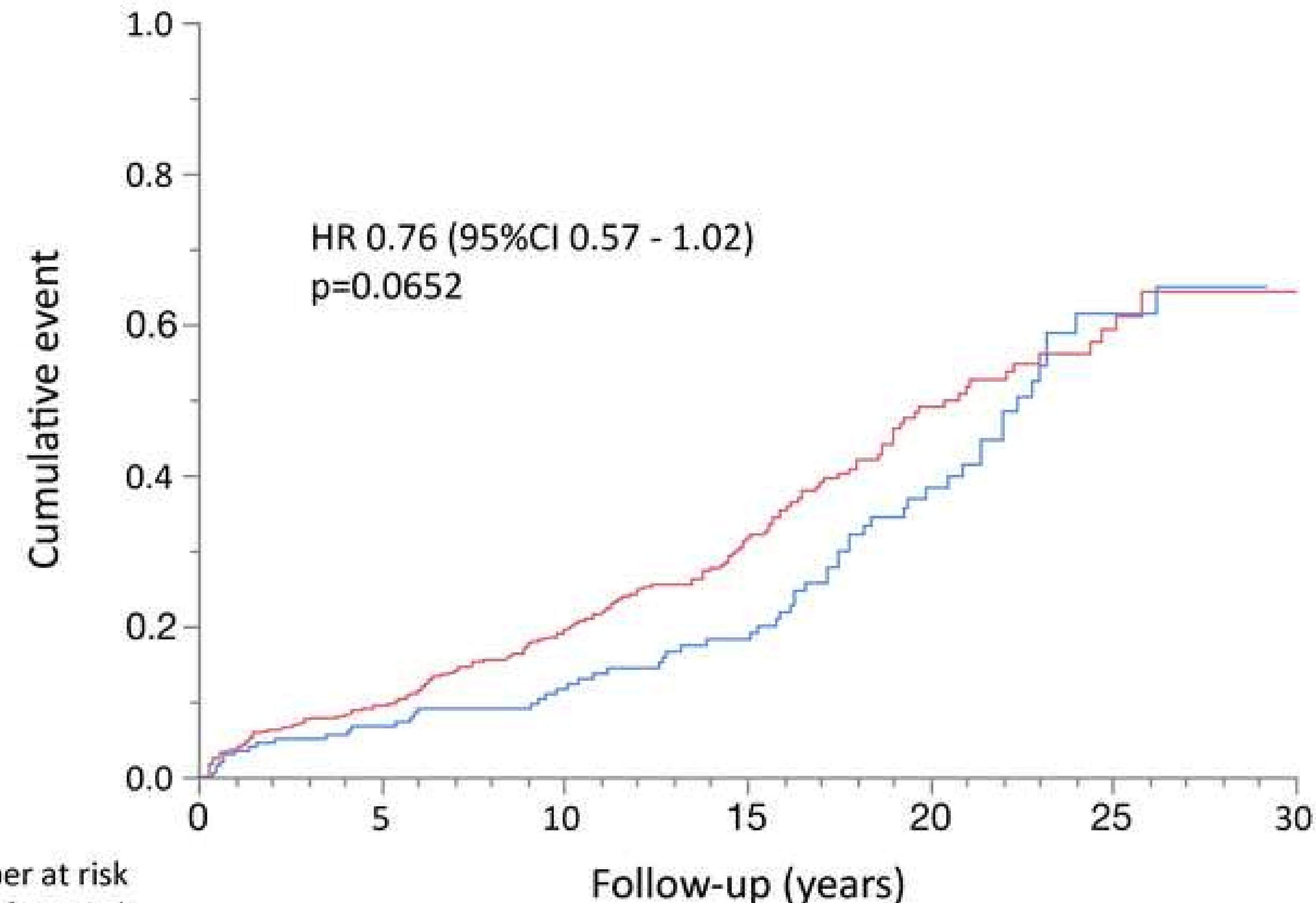
Number at risk (number of events)	0	5	10	15	20	25	30
No preventive UDCA (red curve)	434 (0)	258 (89)	161 (133)	75 (163)	31 (167)	9 (170)	0 (170)
Preventive UDCA (blue curve)	175 (0)	136 (14)	102 (27)	66 (36)	29 (38)	7 (39)	0 (39)

Figure 3



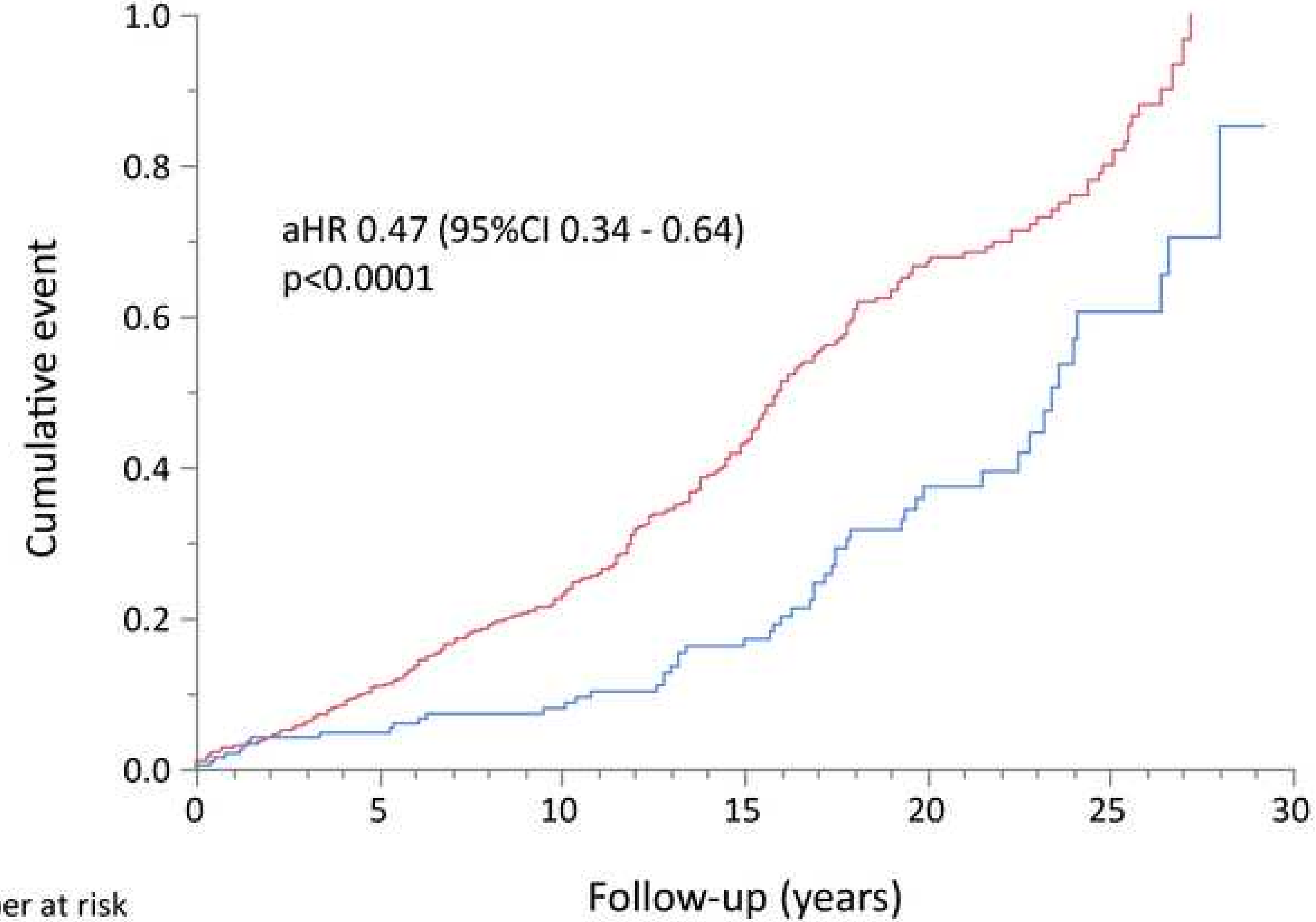
Number at risk (number of events)							
prev-UDCA / CYS: none (red curve)	355 (0)	191 (129)	99 (163)	33 (178)	6 (182)	2 (182)	0 (182)
prev-UDCA / CYS: 1 in 2 (blue curve)	283 (0)	198 (32)	137 (58)	84 (81)	42 (84)	13 (88)	0 (88)
prev-UDCA / CYS: both (green curve)	69 (0)	60 (2)	52 (7)	40 (12)	20 (14)	4 (15)	0 (15)

Figure 4



Number at risk (number of events)							
No preventive UDCA (red curve)	655 (0)	417 (56)	293 (97)	164 (133)	66 (163)	24 (172)	0 (172)
Preventive UDCA (blue curve)	204 (0)	164 (13)	134 (21)	97 (30)	43 (49)	13 (61)	0 (61)

Figure 5



Number at risk (number of events)							
No preventive UDCA (red curve)	655 (0)	403 (60)	282 (109)	154 (173)	59 (227)	21 (242)	0 (242)
Preventive UDCA (blue curve)	204 (0)	155 (9)	127 (14)	91 (25)	41 (42)	11 (50)	0 (50)

Highlights

- Recurrence of PBC after liver transplantation impairs graft and patient survivals.
- Preventive administration of UDCA after transplantation for PBC is associated with reduced risk of disease recurrence, graft loss, and liver-related death.
- Cyclosporine rather than tacrolimus use adds to the preventive effect of UDCA against PBC recurrence.