Research Article
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Prognostic scores for ursodeoxycholic acid-treated patients predict graft loss and mortality in recurrent primary biliary cholangitis after liver transplantation

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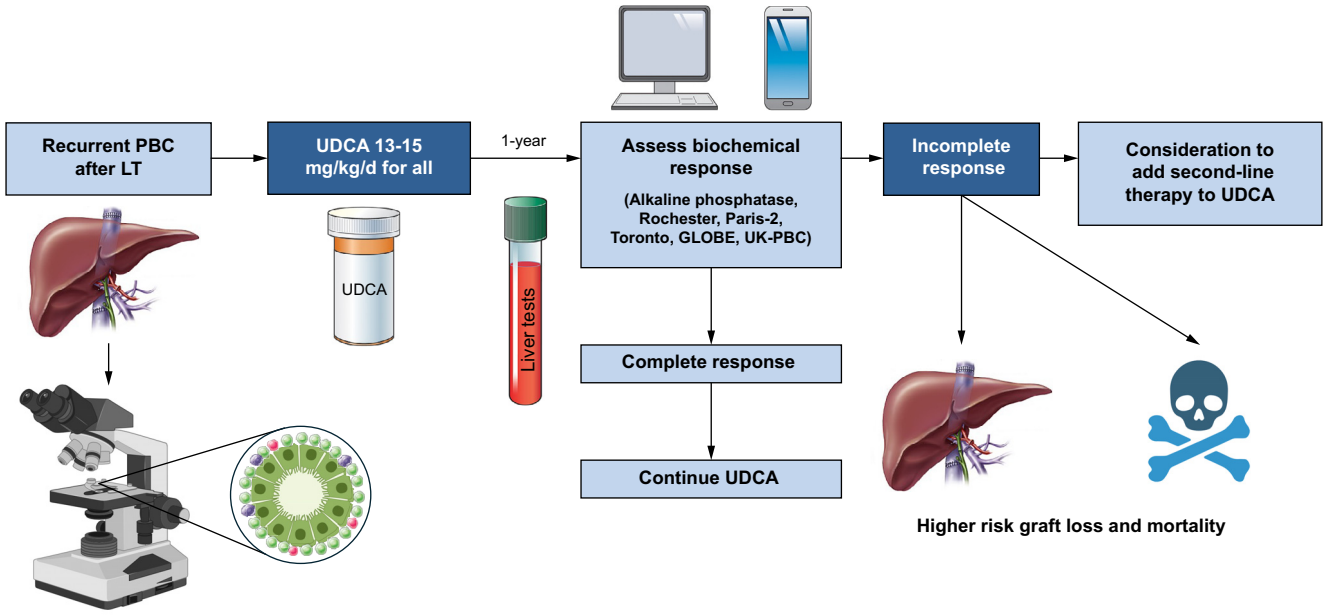
Graphical abstract



Highlights

- Recurrent PBC (*r*PBC) develops in approximately 30% of patients and negatively impacts graft and overall patient survival after LT.
- Levels of alkaline phosphatase after 1 year of UDCA predict graft loss and mortality in patients with *r*PBC after LT.
- Prognostic scores for UDCA-treated patients predict graft loss and mortality in patients with *r*PBC after LT.
- Future studies to evaluate second-line treatments in patients with *r*PBC and incomplete response to UDCA are warranted.

Impact and implications

One in three people who undergo liver transplantation for primary biliary cholangitis develop recurrent disease in their new liver. Patients with recurrent primary biliary cholangitis and incomplete response to ursodeoxycholic acid, according to conventional prognostic scores, have worse clinical outcomes, with higher risk of graft loss and mortality in similar ways to the disease before liver transplantation. Our results supportsupport efforts to treat recurrent disease in similar ways to pre-transplant primary biliary cholangitis.

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Prognostic scores for ursodeoxycholic acid-treated patients predict graft loss and mortality in recurrent primary biliary cholangitis after liver transplantation

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Background & Aims: Recurrent primary biliary cholangitis (*r*PBC) develops in approximately 30% of patients and negatively impacts graft and overall patient survival after liver transplantation (LT). There is a lack of data regarding the response rate to ursodeoxycholic acid (UDCA) in *r*PBC. We evaluated a large, international, multi-center cohort to assess the performance of PBC scores in predicting the risk of graft and overall survival after LT in patients with *r*PBC.

Methods: A total of 332 patients with *r*PBC after LT were evaluated from 28 centers across Europe, North and South America. The median age at the time of *r*PBC was 58.0 years [IQR 53.2–62.6], and 298 patients (90%) were female. The biochemical response was measured with serum levels of alkaline phosphatase (ALP) and bilirubin, and Paris-2, GLOBE and UK-PBC scores at 1 year after UDCA initiation.

Results: During a median follow-up of 8.7 years [IQR 4.3–12.9] after *r*PBC diagnosis, 52 patients (16%) had graft loss and 103 (31%) died. After 1 year of UDCA initiation the histological stage at *r*PBC (hazard ratio [HR] 3.97, 95% CI 1.36-11.55, $p = 0.01$), use of prednisone (HR 3.18, 95% CI 1.04-9.73, $p = 0.04$), ALP xULN (HR 1.59, 95% CI 1.26-2.01, $p < 0.001$), Paris-2 criteria (HR 4.14, 95% CI 1.57-10.92, $p = 0.004$), GLOBE score (HR 2.82, 95% CI 1.71-4.66, $p < 0.001$), and the UK-PBC score (HR 1.06, 95% CI 1.03-1.09, $p < 0.001$) were associated with graft survival in the multivariate analysis. Similar results were observed for overall survival.

Conclusion: Patients with *r*PBC and disease activity, as indicated by standard PBC risk scores, have impaired outcomes, supporting efforts to treat recurrent disease in similar ways to pre-transplant PBC.

Introduction

Primary biliary cholangitis (PBC) is a chronic cholestatic disease characterized by granulomatous destruction of intrahepatic bile ducts and, in some cases, it can remain a progressive disease even when treated.[1] Approximately 5% of patients who undergo liver transplant(ation) (LT) in Europe and North America have PBC as an underlying liver disease.[2,3] Even though there has been a decrease in PBC as an indication for LT in the last decades related to better disease awareness and widespread treatment with ursodeoxycholic acid (UDCA), the absolute annual number of LTs for PBC has steadied.

The outcome after LT for patients with PBC is generally good, but recurrent PBC (*r*PBC) occurs in more than 20% of patients after 5 years and more than 35% after 10 years.[4] Several risk factors associated with *r*PBC have been reported, including young age at the time of diagnosis with PBC or at LT, use of tacrolimus as immunosuppression, and biochemical markers of cholestasis after LT. Importantly, *r*PBC has a negative impact on graft and patient survival; therefore, strategies to prevent recurrence after LT, such as preventive UDCA are imperative.[5]

Liver function tests[6] and different binary[7–13] and dimensional scores[14,15] have been used to evaluate prognosis in

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patients with PBC, mainly by assessing response to UDCA and helping guide clinical decisions regarding the addition of second-line treatments before LT.[16]

However, there is a lack of data regarding their utility in patients with a diagnosis of *r*PBC after LT. We aimed to evaluate the utility of serum liver function tests and the GLOBEand UK-PBC sc ores to predict graft and overall survival after LT in patients with *r*PBC treated with UDCA.

Patients and methods

Study population

Patients included in this study were selected from an international registry from the GLOBAL PBC study group, consisting of 947 patients with PBC who underwent LT from February 1983 until September 2019 from 28 centers across Asia, Europe, and North and South America, were evaluated (Fig. S1).[4,5] All patients had a diagnosis of PBC as an indication for LT according to the AASLD and EASL guidelines.[1,17] In this study, 332 patients with a histological diagnosis of *r*PBC[4] and at least 1 year of follow-up after diagnosis were included for analysis.

Clinical and laboratory assessments

The data extracted from the medical records included age at LT and *r*PBC, sex, type of LT (cadaveric, living donor), BMI, LT period (divided into 6-year periods), time from LT to *r*PBC, UDCA use and dose after *r*PBC, time from *r*PBC to UDCA start date, immunosuppression at *r*PBC, episodes of rejection after *r*PBC, and clinical outcomes. Liver tests including ALT, AST, ALP, bilirubin, and albumin were collected at the time of *r*PBC and 1 year after starting UDCA. The ULN for ALT ranged from 31 to 56 U/L, AST from 30 to 52 U/L, and bilirubin from 18 to 22 μmol/L between the different LT centers. The lower level of normal (LLN) for albumin was 35 g/L and for platelets 140 $x10^9$/L.

Diagnosis of recurrent PBC

The diagnosis of recurrent disease was made histologically and defined by the presence of liver histology compatible with PBC in the absence of other biliary diseases including hepatic artery thrombosis, and anastomosis stricture.[18] All patients with cholestasis and suspicion of recurrence of PBC after LT had an ultrasound Doppler examination to rule out the presence of biliary duct dilation or stricture, and hepatic artery thrombosis as reported elsewhere.[19]

In addition, allograft rejection, the presence of infections, and concomitant use of potentially hepatotoxic drugs were ruled out. Histologic features of *r*PBC were the presence of florid duct lesions or destructive lymphocytic cholangitis with significant portal infiltrate in the absence of endothelialitis.[18] Histological diagnosis of recurrence of PBC was made by liver pathologists in all cases. Histological recurrence of PBC was graded according to Ludwig and Scheuer classification.[20] Overlap syndrome with autoimmune hepatitis was ruled out in all patients with recurrence of PBC according to Paris criteria.[21]

Response to UDCA

Response to UDCA was established at a fixed time point, 1 year after UDCA initiation, and determined by the Paris-2 criteria,[12] GLOBE score,[15] and the 5-year UK-PBC score[14] in those patients who received UDCA (94%). For patients who did not receive UDCA (6%), Paris-2 criteria, GLOBE and 5-year UK-PBC scores were calculated at 1 year after diagnosis of *r*PBC. Other treatments for PBC, such as obeticholic acid and fibrates were also recorded.

Statistical analyses

The Fisher exact probability test was used to compare categorical variables, and the unpaired *t*-test was used to compare differences in means of continuous variables. Variables with a *p* value equal to or less than 0.1 in the univariate analysis were included in the multivariate regression analysis.

To determine whether the response to UDCA in patients with *r*PBC was significantly associated with graft loss and overall survival, the impact of UDCA response *vs.* no response on graft loss and survival was assessed using univariate and multivariate Cox regression analyses. As some patients received preventive UDCA (n = 28) or did not receive UDCA after *r*PBC diagnosis (n = 20), we performed the analysis in two parts. The first part included all patients with *r*PBC. The index date for this part was the date of diagnosis of *r*PBC; however, in this analysis, the time to start UDCA was modelled as a time-dependent covariate and the biochemical parameters at 1 year after UDCA initiation were not included. In the second part of the analysis, we included only patients who received UDCA after *r*PBC (also excluding patients who received preventive UDCA) to evaluate the utility of serum liver function tests and PBC scores to predict graft and overall survival after LT. Variables with a *p* value equal to or less than 0.1 in the univariate analysis and other relevant variables were included in the Cox proportional hazard regression multivariate analysis. Patients who did not develop graft loss and died and those who were lost during follow-up were censored at the time of death or at the time of their last visit. Graft loss was defined using a death-censored definition of graft failure and therefore, graft loss did not include patients who died with a functioning graft. Graft loss only included deaths secondary to or associated with graft failure (*i.e.* cirrhosis development on the graft, recurrent disease, chronic ductopenic rejection, sepsis in patients with biliary or vascular complications, or re-transplantation). The cumulative incidence of graft loss and mortality after *r*PBC were calculated using the Kaplan-Meier method, and they were compared using the Log-Rank (Mantel-Cox) test.[22] Median survival probabilities were presented, unless 50% of the participants developed the event of interest, in which case mean survival was presented. One limitation of Cox proportional hazard models is that they assume competing events are absent and so, they may overestimate the risk. The Fine and Gray competing risks approach assesses the association between variables and outcomes in the presence of competing events. Competing-risk analysis is a more robust approach, compared to the conventional survival analysis, in the presence of competing events.[23] Therefore, as the next step, competing-risk analysis was conducted using the Fine-Gray sub-distribution hazard model for graft survival considering non-graft-loss-related deaths as the competing event.

Lastly, a subanalysis for overall survival was performed for cases classified as liver-related deaths. Continuous data are presented as the median [IQR] and categorical values as n (%) in

tables and text. Statistical analyses were conducted using SPSS 26.0 and SATA 18.0. For handling the missing variables in the analysis, we used mean imputation for continuous variables and allocated a fixed number (99) for categorical variables.

Results

Characteristics of patients with primary biliary cholangitis recurrence

A total of 332 patients who had a liver biopsy-proven diagnosis of *r*PBC after LT from 28 centers across Europe, North and South America were evaluated. The median age at the time of *r*PBC was 58.0 years [IQR 53.2–62.6], and 298 patients (90%) were women (Table 1). Of all the LTs,116 (35%) were performed from 1983 to 1999, and 216 (65%) in the period 2000-2020. The distribution of LTs performed every 6 years is presented in Table 1. Twenty-eight patients (8%) received preventive UDCA before *r*PBC.

The median time from LT to *r*PBC was 5.0 years [IQR 1.8–10.1]. At the time of *r*PBC, 218 patients (66%) were receiving immunosuppression with tacrolimus alone or in combination either with mycophenolate mofetil, sirolimus, prednisone or azathioprine, and 95 (29%) were receiving immunosuppression with cyclosporine alone or in combination either with mycophenolate mofetil, sirolimus, prednisone or azathioprine. Other immunosuppression regimens are presented in Table 1.

The histological stage at the time of PBC recurrence was stage 1 in 227 patients (68%), stage 2 in 76 patients (23%), stage 3 in 21 patients (6%) and stage 4 in eight patients (2%).

Clinical and biochemical features associated with graft loss

A total of 312 patients (94%) received treatment with UDCA after *r*PBC diagnosis. The mean dose was 13 mg/kg/daily [IQR 10-15] and the median time from *r*PBC to the UDCA initiation was 0.4 year [IQR 0–4.8].

During a median follow-up of 8.7 years [IQR 4.3–12.9], 52 patients (16%) had lost grafts, 22 (7%) underwent re-transplantation, and 103 (31%) died. Graft failure was secondary to *r*PBC in 43 of the 52 patients (83%).

Graft survival after *r*PBC was 92% and 85% at 5 and 10 years, respectively (Fig. 1A). Overall survival was 85% and 75%, respectively (Fig. 1B).

In the univariate Cox regression analysis, the LT period and the histological stage at diagnosis of *r*PBC were associated with a higher risk of graft loss. When we analysed the impact of immunosuppression at the time of *r*PBC, the use of tacrolimus was associated with a protective effect on graft survival, whereas patients who received cyclosporine at the time of *r*PBC had a higher risk of graft loss (Table 2).

Regarding biochemical parameters at 1 year after UDCA treatment by univariate Cox analysis, ALP xULN, AST xULN, ALT xULN, bilirubin xULN, and albumin xULN were associated with a higher risk of graft loss.

However, in the multivariate analysis, only the histological stage at diagnosis of *r*PBC (hazard ratio [HR] 2.45, 95% CI 1.18-5.09, $p = 0.01$), the use of prednisone at the time of *r*PBC (HR 3.18, 95% CI 1.04-9.73, $p = 0.04$), and ALP xULN at 1 year

Table 1. Baseline features at the time of diagnosis of *r*PBC.

Characteristics	N = 332
Sex, female	296 (90)
Age at PBC diagnosis	44.4 [37.7–52.3]
Age at LT	51.8 [44.9–58.9]
LT type	
Cadaveric	297 (89)
Living donor	35 (11)
BMI, kg/m^2	25.2 [22.5–28.4]
Age at *r*PBC (years)	58.0 [53.2–62.6]
Time diagnosis PBC to LT (years)	6.0 [2.9–10.2]
Time from LT to *r*PBC (years)	5.0 [1.8–10.1]
LT period (6-year periods)	
1983-1989	19 (6)
1990-1995	50 (15)
1996-2001	75 (23)
2002-2007	79 (24)
2008-2013	67 (20)
2014-2020	42 (13)
Preventive UDCA	28 (8)
UDCA after *r*PBC	312 (94)
Time from *r*PBC to UDCA initiation (months)*	0.5 [0–4.71]
UDCA dose, mg/kg/day	13 [10–15]
Immunosuppression at *r*PBC	
Tacrolimus monotherapy	77 (23)
Cyclosporine monotherapy	16 (5)
Prednisone monotherapy	5 (1.5)
Mycophenolate mofetil monotherapy	5 (1.5)
Azathioprine monotherapy	1 (0.5)
Sirolimus/everolimus monotherapy	8 (2)
Tacrolimus + mycophenolate mofetil	61 (18)
Tacrolimus + sirolimus	7 (2)
Tacrolimus + prednisone	53 (16)
Tacrolimus + azathioprine	20 (6)
Cyclosporine + prednisone	32 (10)
Cyclosporine + mycophenolate mofetil	26 (8)
Cyclosporine + sirolimus	2 (0.5)
Cyclosporine + azathioprine	19 (6)
Histological stage at *r*PBC	
Stage 1	227 (68)
Stage 2	76 (23)
Stage 3	21 (6)
Stage 4	8 (2)
Biochemical parameters at *r*PBC	
ALP (U/L)	282 [155–282]
AST (U/L)	58 [32–58]
ALT (U/L)	44.0 [27.8–81.3]
Bilirubin (μmol/L)	16.0 [9.9–19.0]
Albumin (g/dl)	39.0 [39.0–41.0]
Platelets (x10^9/L)	193 [162–206]
Biochemical parameters at 1-year after UDCA initiation	
ALP (U/L)	128 [88–240]
AST (U/L)	27 [20–42]
ALT (U/L)	27 [17–43]
Bilirubin (μmol/L)	10 [8–15]
Albumin (g/dl)	40 [38–43]
Platelets (x10^9/L)	183 [143–234]
Rejection after *r*PBC	39 (12)
Graft failure	52 (16)
Related to *r*PBC	43 (13)
Re-transplantation	22 (7)
Death	103 (31)
Follow-up	8.7 [4.3–12.9]

Continuous variables are summarized as medians [IQR 25th-75th] and categorical values as n (%).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LT, liver transplant; PBC, primary biliary cholangitis; *r*PBC, recurrent PBC; UDCA, ursodeoxycholic acid.

Table 2. Clinical and biochemical features associated with graft loss after liver transplantation in patients with recurrent PBC.

	Univariate		Multivariate	
Characteristics (n = 332)	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age at LT	1.01 (0.98-1.05)	0.51		
Age at *r*PBC	1.00 (0.97-1.03)	0.99		
Sex, male	1.51 (0.64-3.56)	0.35		
BMI (kg/m^2)	1.02 (0.96-1.09)	0.54		
LT type[†]	0.95 (0.34-2.67)	0.92		
LT period[*]	**0.75 (0.59-0.95)**	**0.02**	0.98 (0.70-1.38)	0.92
Time diagnosis PBC to LT (years)	0.96 (0.89-1.03)	0.23		
Time LT to *r*PBC (years)	1.05 (0.99-1.11)	0.13		
Time *r*PBC to starting UDCA (months)[¶]	0.97 (0.94-1.01)	0.11		
Histological - stage at *r*PBC (Reference - stage 1-2)	**2.45 (1.18-5.09)**	**0.02**	**3.97 (1.36-11.55)**	**0.01**
Immunosuppression at *r*PBC				
Tacrolimus	**0.48 (0.27-0.86)**	**0.01**	0.82 (0.08-7.91)	0.86
Cyclosporine	**2.21 (1.23-3.96)**	**0.008**	1.16 (0.12-11.59)	0.90
Sirolimus/everolimus	1.97 (0.78-4.99)	0.15		
Prednisone	1.77 (0.96-3.27)	0.07	**3.18 (1.04-9.73)**	**0.04**
Mycophenolate mofetil	0.54 (0.25-1.15)	0.11		
Azathioprine	1.02 (0.43-2.40)	0.97		
Biochemical parameters at 1-year after UDCA initiation (n = 284)[**]				
ALP xULN	**1.72 (1.42-2.09)**	**<0.001**	**1.59 (1.26-2.01)**	**<0.001**
AST xULN	**1.50 (1.22-1.84)**	**<0.001**	2.18 (0.54-8.70)	0.27
ALT xULN	**1.55 (1.22-1.99)**	**<0.001**	0.59 (0.14-2.49)	0.48
Bilirubin xULN	**1.40 (1.20-1.63)**	**<0.001**	1.08 (0.72-1.63)	0.70
Albumin xLLN	**0.01 (0.001-0.22)**	**0.005**	0.03 (0.001-1.16)	0.06
Platelets xLLN	0.43 (0.15-1.29)	0.13		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; LLN, lower limit of normal; LT, liver transplant; PBC, primary biliary cholangitis; *r*PBC, recurrent PBC; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Continuous variables are summarised as medians [IQR] and categorical values as proportions (%). Bold values represent statistically significant results.
[†]LT type (cadaveric *vs*. living donor).
[*]LT period: sexennial periods (1983-1989, 1990-1995, 1996-2001, 2002-2007, 2008-2013, 2014-2020).
[¶]These HRs were obtained with Cox regression analysis by considering time from *r*PBC to starting UDCA as a time-dependent covariate in the analyses.
[**]Excluded 28 (8%) patients who received preventive UDCA, and 20 patients (6%) who did not receive UDCA after *r*PBC.

after UDCA initiation (HR 1.59, 95% CI 1.26-2.01, p <0.001) were independently associated with a higher risk of graft loss (Table 2, Fig. 2A).

In Fine and Gray's competing risks analysis of graft survival considering non-graft-loss-related deaths as the competing event, the results were similar to the Cox analysis and are presented in Table S3.

Mean graft survival was lower in patients with ALP >2x ULN *vs*. ≤2x ULN at 1 year after UDCA initiation (18.02 years, 95% CI 14.88-21.16 *vs.* 23.08 years, 95% CI 22.06-24.11; Log-rank, p = 0.003, Fig. 3A). Similarly, mean graft survival was significantly diminished in patients with bilirubin >1.0x ULN *vs*. ≤1x ULN (14.28 years, 95% CI 9.51-19.06 *vs*. 22.37 years, 95% CI 21.11-23.62; Log-rank, p = 0.003, Fig. 3B).

Scores to evaluate UDCA response and impact on graft loss

All the risk scores evaluated at 1 year after UDCA including, Rochester-II (ALP >2x ULN), Toronto (ALP >1.67x ULN), Paris-2 (ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl [17.1 μmol/L]), GLOBE and UK-PBC scores were significantly

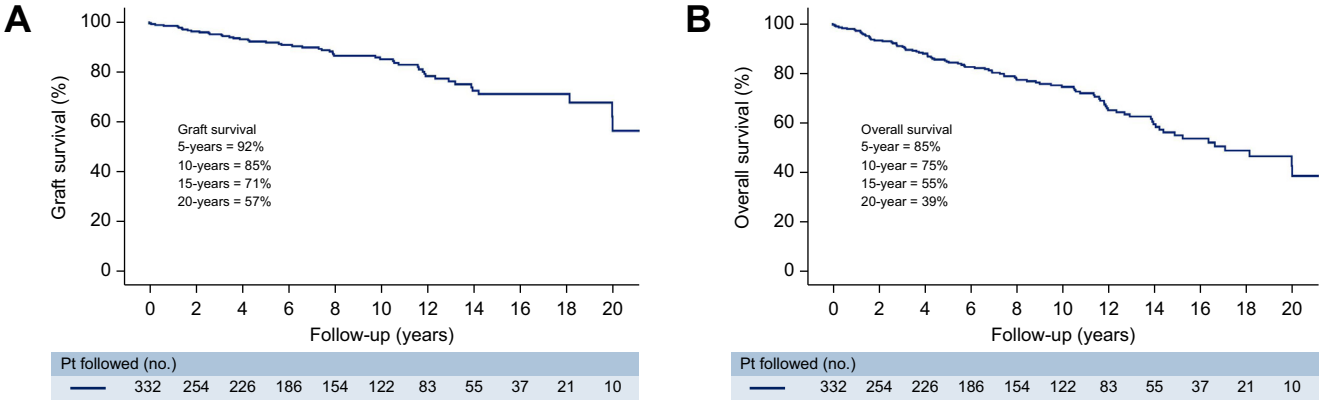

Fig. 1. Survival in patients with recurrent PBC. (A) Graft survival in patients with recurrent PBC. Graft survival after diagnosis of recurrent PBC at 5 years was 92%, and at 10 years was 85%. (B) Overall survival in patients with recurrent PBC. Overall survival after diagnosis of recurrent PBC at 5 years was 85% and at 10 years was 75%. PBC, primary biliary cholangitis.

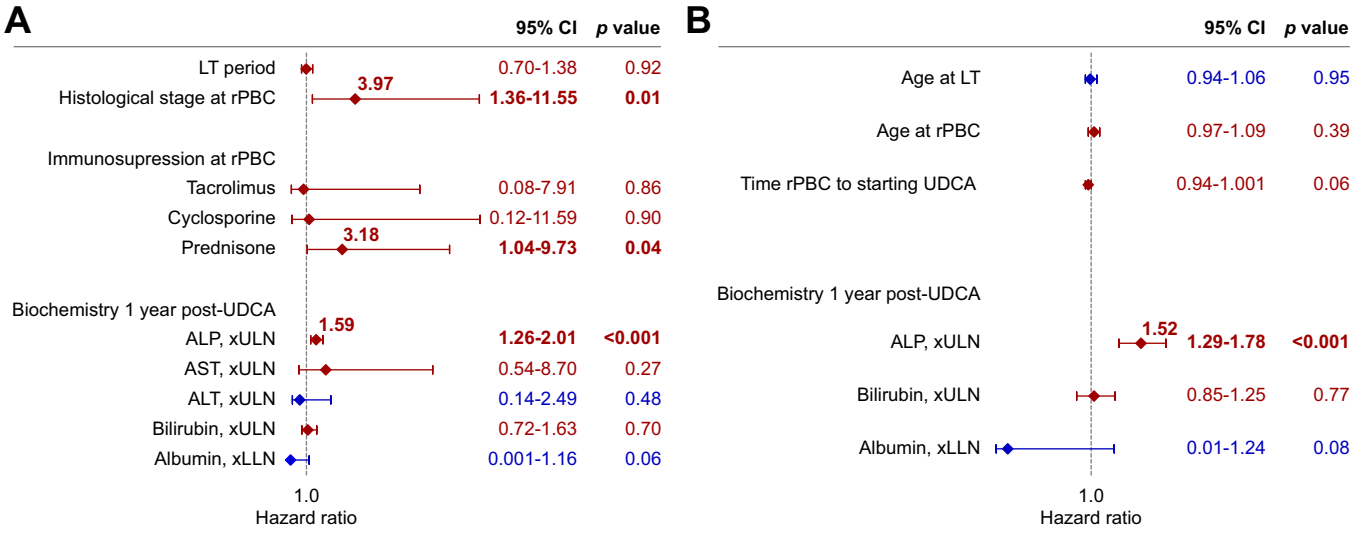

Fig. 2. Forest plot of variables associated with graft loss/overall mortality in multivariate analysis. (A) Forest plot showing variables associated with graft loss in the multivariate analysis. The histological stage at rPBC, use of prednisone, and ALP at 1 year after UDCA initiation were associated with a higher risk of graft loss. (B) Forest plot showing variables associated with overall mortality in the multivariate analysis. ALP at 1 year after UDCA initiation was associated with a higher risk of overall mortality. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LLN, lower limit of normal; LT, liver transplant; PBC, primary biliary cholangitis; rPBC, recurrent PBC; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

associated with graft survival in the univariate and multivariate Cox regression analysis (Table 3).

In Fine and Gray's competing risks approach to evaluate graft survival considering non-graft-loss-related deaths as the competing event, the results were similar to the Cox analysis and are presented in Table S4.

Graft survival was lower in patients with ALP >1.67x ULN *vs.* ≤1.67x ULN at 1 year after UDCA initiation (17.99 years, 95% CI 14.96-21.02 *vs*. 23.19 years, 95% CI 22.17-24.20; Log-rank, $p = 0.002$, Fig. 3C).

Similarly, graft survival was lower in patients who met the criteria for inadequate Paris-2 response *vs*. adequate Paris-2 response (17.39 years, 95% CI 14.49-20.28 *vs.* 23.54 years, 95% CI 22.63-24.45; Log-rank, p <0.001, Fig. 3D).

In addition, graft survival was lower in patients with a GLOBE score >0.3 *vs.* ≤0.3 (19.46 years, 95% CI 17.43-21.49 *vs.* 23.10 years, 95% CI 21.91-24.29; Log-rank, $p = 0.03$, Fig. 3E).

Clinical and biochemical features associated with overall mortality

In Cox regression analysis, age at LT, time from *r*PBC to starting UDCA, ALP xULN, bilirubin xULN, and albumin xULN at 1 year after UDCA initiation were associated with a higher risk of mortality (Table 4). However, in the multivariate analysis only ALP xULN (HR 1.52, 95% CI 1.29-1.78, p <0.001), was associated with a higher risk of mortality (Table 4, Fig. 2B).

The subanalysis for cases classified as liver-related death (n = 48), demonstrated relatively similar results, which are presented in Tables S5 and S6.

Overall survival was lower in patients with ALP >2x ULN *vs*. ALP ≤2x ULN at 1 year after UDCA initiation (11.63 years, 95% CI 9.01-14.27 *vs*. 20.35 years, 95% CI 18.86-21.85; Log-rank, p <0.001, Fig. 4A).

Similarly, overall survival was significantly lower in patients with bilirubin >1.0x ULN *vs.* ≤1x ULN at 1 year after UDCA initiation (9.73 years, 95% CI 6.27-13.19 *vs*. 18.22 years, 95% CI 16.42-20.01; Log-rank, p <0.001, Fig. 4B).

Scores to evaluate UDCA response and impact on overall mortality

All the risk scores evaluated at 1 year after UDCA including, Rochester-II (ALP >2x ULN), Toronto (ALP >1.67x ULN), Paris-2 (ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl [17.1 μmol/L]), GLOBE and UK-PBC scores were significantly associated with overall survival in the univariate and multivariate Cox regression analysis (Table 5).

Overall survival was significantly diminished in patients with ALP >1.67x ULN *vs.* ALP ≤1.67x ULN (11.90 years, 95% CI 9.41-14.40 *vs*. 20.42 years, 95% CI 18.91-21.93; Log-rank, p <0.001, Fig. 4C).

Similarly, overall survival was significantly diminished in patients meeting the criteria for inadequate Paris-2 response *vs*. an adequate Paris-2 response (11.89 years, 95% CI 9.63-14.15 *vs.* 20.82 years, 95% CI 19.33-22.31; Log-rank, p <0.001, Fig. 4D).

In addition, overall survival was significantly diminished in patients with a GLOBE score >0.3 *vs.* ≤0.3 (14.77 years, 95% CI 12.57-16.96 *vs.* 20.41 years, 95% CI 18.70-22.13; Log-rank, p <0.001, Fig. 4E).

Discontinuation of UDCA and use of second-line treatments in patients with incomplete response

Twenty-one patients (6%) discontinued UDCA after a median follow-up of 57 months [IQR 17-93]. Ten patients discontinued UDCA due to intolerance, five for no response, and six for unknown reasons.

Only 22 patients (7%) were started on second-line treatments. Nineteen patients (6%) were started on fibrates (bezafibrate, fenofibrate), and three patients (1%) on obeticholic acid.

Of the patients who received second-line treatment, 12 (55%) had an ALP <2x ULN after 1 year of starting the second-

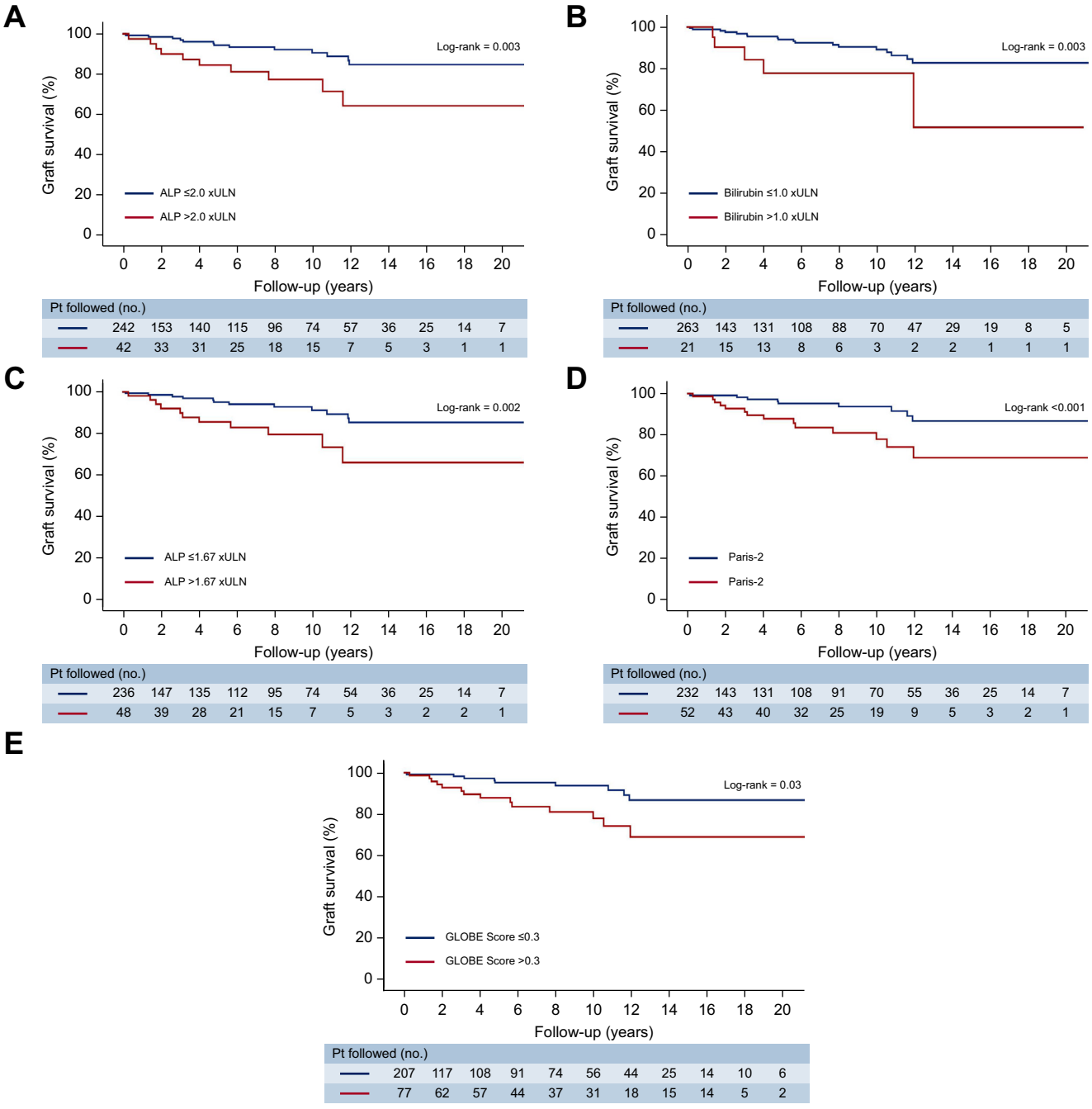

Fig. 3. Graft survival after 1 year of UDCA and response according to ALP or bilirubin levels, or Toronto, Paris-2, or GLOBE scores. (A) Graft survival in recurrent PBC after 1 year of UDCA treatment and response according to ALP levels. Graft survival according to ALP at 1 year after UDCA was started. Patients who had an ALP ≤2x ULN after 1 year of treatment with UDCA are represented by the blue line, and ALP >2x ULN after 1 year of treatment with UDCA by the red line. The 5-year probability was 96% and 86%, respectively (p = 0.003, log-rank test). (B) Graft survival in recurrent PBC after 1 year of UDCA treatment and response according to bilirubin levels. Graft survival according to bilirubin at 1 year after UDCA was started. Patients who had bilirubin ≤1x ULN after 1 year of treatment with UDCA are represented by the blue line, and bilirubin >1x ULN after 1 year of treatment with UDCA by the red line. The 5-year probability was 96% and 77%, respectively (p = 0.003, log-rank test). (C) Graft survival in recurrent PBC after 1 year of UDCA treatment and response according to Toronto score. Graft survival according to ALP 1 year after UDCA was started. Patients who had an ALP ≤1.67x ULN after 1 year of treatment with UDCA are represented by the blue line, and ALP >1.67x ULN after 1 year of treatment with UDCA by the red line. The 5-year probability was 97% and 88%, respectively (p = 0.002, log-rank test). (D) Graft survival in recurrent PBC after 1 year of UDCA treatment and response according to Paris-2 score. Graft survival according to Paris-2 score at 1 year after UDCA was started. Patients with criteria for response according to Paris-2 after 1 year of treatment with UDCA are represented by the blue line, and non-responders after 1 year of treatment with UDCA by the red line. The 5-year probability was 97% and 89%, respectively (p <0.001, log-rank test). (E) Graft survival in recurrent PBC after 1 year of UDCA treatment and response according to GLOBE score. Graft survival according to GLOBE score at 1 year after UDCA was started. Patients who had a GLOBE score ≤0.3 at 1 year of treatment with UDCA are represented by the blue line, and patients who had a GLOBE score >0.3 after 1 year of treatment with UDCA by the red line. The 5-year probability was 97% and 91%, respectively (p = 0.03, log-rank test). ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Table 3. Risk scores associated with graft loss after LT in patients with *r*PBC.

	Univariate		*Multivariate	
Scores for PBC (n = 284)**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Rochester-II (ALP >2x ULN) at 1-year after UDCA initiation	3.01 (1.32-6.89)	0.009	2.79 (1.09-7.15)	0.03
Toronto (ALP >1.67x ULN) at 1-year after UDCA initiation	3.90 (1.57-9.66)	0.003	2.85 (1.11-7.32)	0.03
Paris-2 (ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl [17.1 μmol/L]) at 1-year after UDCA initiation	5.04 (1.98-12.85)	<0.001	4.14 (1.57-10.92)	0.004
GLOBE score at 1-year after UDCA initiation	2.64 (1.72-4.06)	<0.001	2.82 (1.71-4.66)	<0.001
GLOBE score >0.3 at 1-year after UDCA initiation	2.78 (1.09-76.76)	0.03	2.68 (1.04-6.92)	0.04
UK-PBC score (5-years) at 1-year after UDCA initiation	1.06 (1.03-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
UK-PBC score (10-years) at 1-year after UDCA initiation	1.04 (1.02-1.06)	<0.001	1.04 (1.02-1.06)	<0.001
UK-PBC score (15-years) at 1-year after UDCA initiation	1.03 (1.02-1.05)	<0.001	1.03 (1.01-1.05)	<0.001

Biochemical parameters and PBC scores were not included in the same model to avoid collinearity.

ALP, alkaline phosphatase; AST, aspartate aminotransferase; HR, hazard ratio; LT, liver transplant; PBC, primary biliary cholangitis; *r*PBC, recurrent PBC; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

*Adjusted for LT period (Sexennial periods: 1983-1989, 1990-1995, 1996-2001, 2002-2007, 2008-2013, 2014-2020), histological stage at *r*PBC (Stage 3-4), use of tacrolimus, cyclosporine or prednisone at the time for *r*PBC.

**Excluded 28 (8%) patients who received preventive UDCA, and 20 patients (6%) who did not receive UDCA after *r*PBC. These HRs were obtained with Cox regression analysis.

line treatment. Similarly, 14 patients (64%) had bilirubin <1x ULN after 1 year of starting the second-line treatment. In addition, 11 patients (50%) had an adequate response according to Paris-2 criteria and 14 (64%) patients had a GLOBE score <0.3 after 1 year of starting the second-line treatment.

Of the patients who started second-line treatments, two patients (9%) lost their graft and three patients (14%) died during a mean time of 7.99 years [IQR 5.31-9.72].

Discussion

In the largest cohort of patients with a diagnosis of *r*PBC after LT to date, we are the first to demonstrate that disease activity indicated by standard PBC risk scores is associated with impaired outcomes, supporting efforts to treat recurrent disease in similar ways to pre-transplant PBC.

To our knowledge, this is the first study to demonstrate the utility of conventional scores in patients with *r*PBC after LT. Our study challenges current paradigms and perceptions emphasizing the importance of stratification of risk in *r*PBC, as even when treated with UDCA, *r*PBC can remain a progressive disease leading to graft loss and mortality. This study highlights the importance of individual assessments for the risk of developing progressive *r*PBC and, consequently, the potential need for second-line treatments.

It is currently well established that PBC management is based on initiating UDCA for all patients and performing risk stratification according to both the characteristics at baseline

Table 4. Clinical and biochemical features associated with overall mortality after liver transplantation in patients with recurrent PBC.

	Univariate		Multivariate	
Characteristics (n = 332)	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Age at LT	**1.04 (1.01-1.06)**	**0.006**	0.99 (0.94-1.06)	0.95
Age at *r*PBC	1.02 (0.99-1.05)	0.08	1.03 (0.97-1.09)	0.39
Sex, male	1.05 (0.54-2.03)	0.87		
BMI (kg/m^2)	1.03 (0.97-1.05)	0.89		
LT type†	1.62 (0.88-2.99)	0.12		
LT period*	0.98 (0.83-1.15)	0.80		
Time diagnosis PBC to LT	1.03 (0.99-1.07)	0.16		
Time LT to *r*PBC	1.05 (0.99-1.11)	0.13		
Time *r*PBC to starting UDCA (months)¶	**0.98 (0.97-0.99)**	**0.02**	0.97 (0.94-1.001)	0.06
Histological stage at *r*PBC (Stage 3-4)	1.08 (0.53-2.21)	0.84		
Immunosuppression at *r*PBC				
Tacrolimus	0.93 (0.61-1.41)	0.72		
Cyclosporine	1.16 (0.75-1.78)	0.51		
Sirolimus/everolimus	1.37 (0.55-3.45)	0.50		
Prednisone	1.42 (0.91-2.22)	0.12		
Mycophenolate mofetil	0.69 (0.41-1.14)	0.69		
Azathioprine	0.96 (0.52-1.76)	0.89		
Biochemical parameters (n = 284)**				
ALP xULN	**1.70 (1.47-1.96)**	**<0.001**	**1.52 (1.29-1.78)**	**<0.001**
AST xULN	1.13 (0.96-1.33)	0.15		
ALT xULN	1.09 (0.87-1.37)	0.44		
Bilirubin xULN	**1.14 (1.04-1.25)**	**0.007**	1.03 (0.85-1.25)	0.77
Albumin xLLN	**0.05 (0.005-0.48)**	**0.01**	0.13 (0.01-1.24)	0.08
Platelets xLLN	0.93 (0.65-1.32)	0.67		

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; LLN, lower limit of normal; LT, liver transplant; PBC, primary biliary cholangitis; *r*PBC, recurrent PBC; UDCA, ursodeoxycholic acid; ULN, upper limit of normal. Bold values represent statistically significant results.

†LT type (cadaveric *vs.* living donor).

*LT period: sexennial periods (1983-1989, 1990-1995, 1996-2001, 2002-2007, 2008-2013, 2014-2020).

¶These HRs were obtained with Cox regression analysis by considering time from *r*PBC to starting UDCA as a time-dependent covariate in the analyses.

**Excluded 28 (8%) patients who received preventive UDCA, and 20 patients (6%) who did not receive UDCA after *r*PBC.

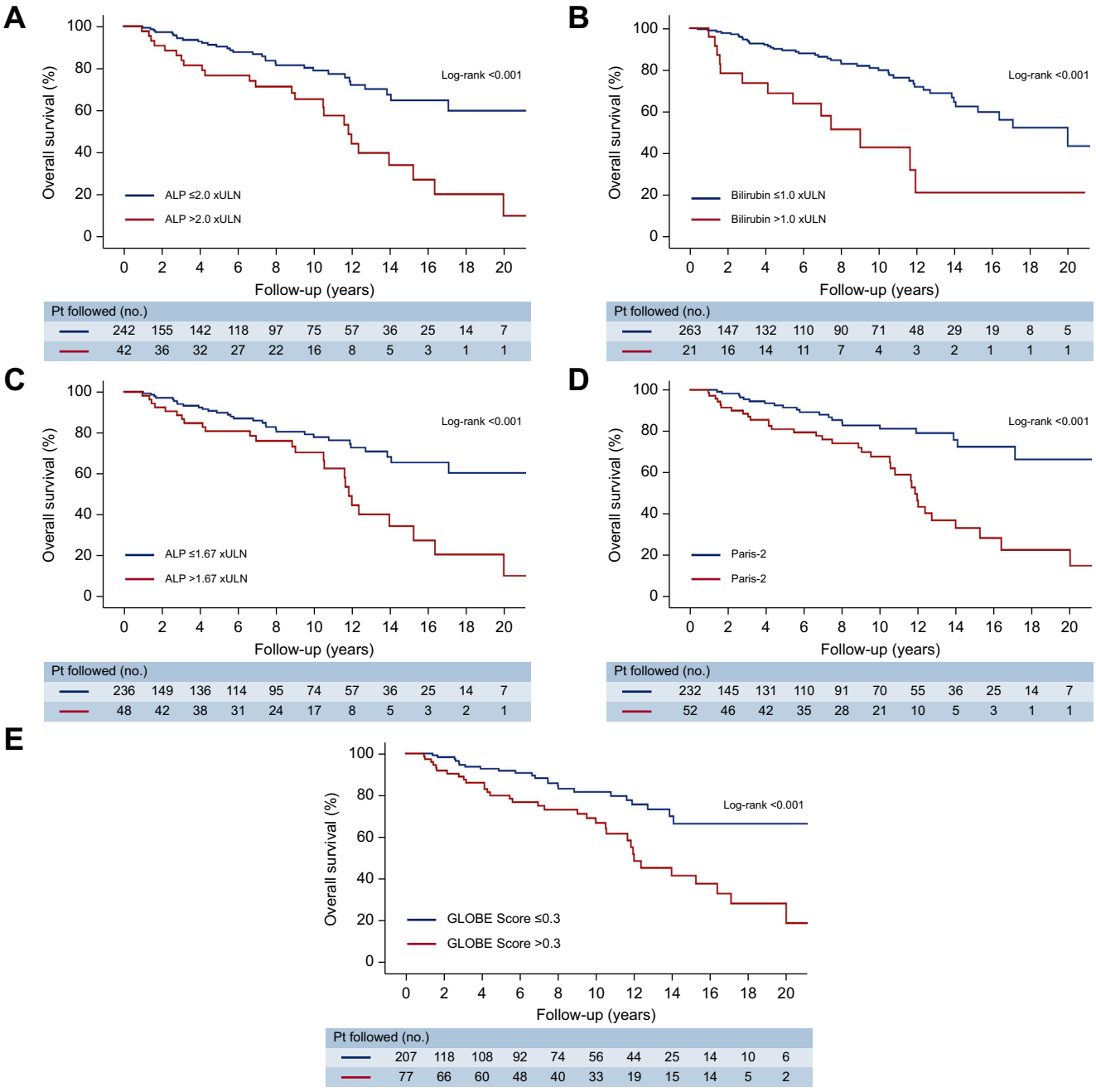

Fig. 4. Overall survival after 1 year of UDCA and response according to ALP or bilirubin levels, or Toronto, Paris-2, or GLOBE scores. (A) Overall survival in recurrent PBC after 1 year of UDCA treatment and response according to ALP levels. Overall survival according to ALP at 1 year after UDCA was started. Patients who had an ALP ≤2x ULN after 1 year of treatment with UDCA are represented by the blue line, and ALP >2x ULN after 1 year of treatment with UDCA by the red line. The 5-year probability was 93% and 85%, respectively (p <0.001, log-rank test). (B) Overall survival in recurrent PBC after 1 year of UDCA treatment and response according to bilirubin levels. Overall survival according to bilirubin at 1 year after UDCA was started. Patients who had bilirubin ≤1x ULN after 1 year of treatment with UDCA represented by the blue line, and bilirubin >1x ULN after 1 year of treatment with UDCA by the red line. The 5-year probability was 90% and 70%, respectively (p <0.001, log-rank test). (C) Overall survival in recurrent PBC after 1 year of UDCA treatment and response according to Toronto score. Overall survival according to ALP at 1 year after UDCA was started. Patients who had an ALP ≤1.67x ULN after 1 year of treatment with UDCA are represented by the blue line, and ALP >1.67x ULN after 1 year of treatment with UDCA by the red line. The 5-year probability was 93% and 78%, respectively (p <0.001, log-rank test). (D) Overall survival in recurrent PBC after 1 year of UDCA treatment and response according to Paris-2 score. Overall survival according to Paris-2 score at 1 year after UDCA was started. Patients with criteria for response according to Paris-2 after 1 year of treatment with UDCA are represented by the blue line, and non-responders after 1 year of treatment with UDCA by the red line. The 5-year probability was 92% and 80%, respectively (p <0.001, log-rank test). (E) Overall survival in recurrent PBC after 1 year of UDCA treatment and response according to GLOBE score. Overall survival according to GLOBE score at 1 year after UDCA was started. Patients who had a GLOBE score ≤0.3 at 1 year of treatment with UDCA are represented by the blue line, and patients who had a GLOBE score >0.3 after 1 year of treatment with UDCA by the red line. The 5-year probability was 93% and 81%, respectively (p <0.001, log-rank test). ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

Table 5. Risk scores associated with overall mortality after LT in patients with *r*PBC.

	Univariate		*Multivariate	
Scores for PBC (n = 284)**	**HR (95% CI)**	***p* value**	**HR (95% CI)**	***p* value**
Rochester-II (ALP >2x ULN) at 1-year after UDCA initiation	3.89 (2.22-6.82)	<0.001	3.47 (1.97-6.10)	<0.001
Toronto (ALP >1.67x ULN) at 1-year after UDCA initiation	3.69 (2.10-6.47)	0.002	3.28 (1.86-5.77)	<0.001
Paris-2 (ALP ≥1.5x ULN or AST ≥1.5x ULN or bilirubin >1 mg/dl [17.1 μmol/L]) at 1-year after UDCA initiation	4.82 (2.71-8.57)	<0.001	3.35 (1.90-5.92)	<0.001
GLOBE score at 1-year after UDCA initiation	2.05 (1.52-2.76)	<0.001	2.04 (1.50-2.68)	<0.001
GLOBE score >0.3 at 1-year after UDCA initiation	2.61 (1.48-4.58)	<0.001	2.55 (1.41-4.63)	0.002
UK-PBC score (5-years) at 1-year after UDCA initiation	1.02 (1.01-1.04)	0.002	1.03 (1.01-1.04)	0.002
UK-PBC score (10-years) at 1-year after UDCA initiation	1.03 (1.01-1.04)	<0.001	1.03 (1.01-1.04)	<0.001
UK-PBC score (15-years) at 1-year after UDCA initiation	1.02 (1.12-1.04)	<0.001	1.02 (1.01-1.04)	<0.001

ALP, alkaline phosphatase; AST, aspartate aminotransferase; HR, hazard ratio; LT, liver transplant; PBC, primary biliary cholangitis; *r*PBC, recurrent PBC; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Biochemical parameters and PBC scores were not included in the same model to avoid collinearity.
*Adjusted for age at LT and *r*PBC, and time from *r*PBC to starting UDCA as a time-dependent covariate in the analysis.
**Excluded 28 (8%) patients who received preventive UDCA, and 20 patients (6%) who did not receive UDCA after *r*PBC. These HRs were obtained with Cox regression analysis.

and the response to treatment. However, this assessment could be overseen in patients with a diagnosis of *r*PBC, given the complexity of the management of LT recipients, and sometimes the fallacious idea that recurrent disease does not have a negative impact on graft or patient survival.[4]

In this study, we demonstrated that patients with histological diagnosis of *r*PBC and incomplete response to UDCA evaluated by different categorical or dimensional scores had from 2 to 3-fold-times higher risk of graft loss or mortality.

We consider our results to be important, as they shed light on the individualised care after LT for PBC. Along the same line, all patients who receive a LT for PBC should receive preventive UDCA as this strategy reduces the risk of *r*PBC and improves graft and patient outcomes.[5]

Our study underlines the definition and management of patients at risk and is a fundamental part of the evaluation of patients with *r*PBC, similar to patients before LT.[16] The assessment of biochemical response to UDCA is typically performed at 12 months; however, a recent study showed that identification of patients for second-line therapy could be done at 6 months using an ALP threshold of 1.9x ULN, as approximately 90% of these patients are non-responders according to POISE criteria.[24]

Interestingly, we found that bilirubin at 1 year after UDCA was associated with graft loss and mortality in the univariate analysis (Tables 2 and 4); however, the association was lost in the multivariate analysis. We recognize that bilirubin is an established predictor of prognosis in PBC[25]; however, we consider that only patients with relatively advanced disease are likely to show meaningful changes in bilirubin levels that will independently predict the risk of graft loss and mortality.[6]

Our results suggest that response criteria to UDCA in *r*PBC must include ALP and bilirubin levels (Paris-2, GLOBE, UK-score), and abnormal levels of total and conjugated bilirubin or ALP level >1.5x ULN should be the minimal thresholds above which second-line therapies should be considered. In addition, we demonstrated that many of the current scores/response definitions, including Paris-2, Toronto, Rochester-II, GLOBE and UK-score can identify patients with a higher risk of graft loss and mortality after LT.

Patients with *r*PBC and adequate biochemical response can be maintained on UDCA monotherapy. In contrast, patients with *r*PBC and no or inadequate response to UDCA should be considered for second-line therapy, among which obeticholic acid (licensed) or fibrates (at present unlicensed), in addition to continued treatment with UDCA, are currently the main options.

Notably, as the prognostic scores for UDCA-treated patients with PBC include variables such as bilirubin and albumin, these might predict graft loss and mortality in LT recipients for different etiologies other than PBC. However, this should be evaluated in other studies.

It is important to emphasize that patients with cholestasis after LT should be evaluated for other potential etiologies, including hepatic arterial stenosis, ischemic cholangiopathy or chronic ductopenic rejection among others. All the patients evaluated in this study had a histological diagnosis of *r*PBC and had a clinical and radiological evaluation to rule out other etiologies of cholestasis.

Notably, in the univariate analysis, we found that the use of tacrolimus at the time of *r*PBC was associated with a lower risk of graft loss (HR 0.48, $p = 0.01$), and cyclosporine was associated with a higher risk (HR 2.21, $p = 0.008$). Interestingly, previous studies have demonstrated that tacrolimus is associated with a higher risk of *r*PBC after LT, whereas cyclosporine was associated with a protective effect for *r*PBC.[4,26] However, in this cohort, similar to other studies,[27] the use of tacrolimus at the time of *r*PBC was associated with better graft survival, whereas cyclosporine was associated with worse graft survival. Overall tacrolimus provides better immunosuppression and is considered the backbone of most anti-rejection regimens after LT.[28]

The association of prednisone with graft loss is interesting. Previous randomized placebo-controlled trials with steroids as add-on therapy to UDCA in patients with early-stage PBC exhibited a significant reduction in serum ALP as well as improvement in liver histology.[29] In addition, a recent trial with budesonide add-on therapy was not associated with improved liver histology in patients with PBC and insufficient response to UDCA,[30] but these trials did not demonstrate an association of steroids with worse clinical outcomes. We found that patients who had episodes of T cell-mediated rejection after *r*PBC had a higher frequency of prednisone use at the time of *r*PBC (16% *vs.* 9.6%, $p = 0.02$). This could at least partially explain the higher risk of graft loss (Table 2).

Recent experience has demonstrated that vibration-controlled transient elastography (VCTE) is a useful tool to predict clinical outcomes in patients with PBC.[31] In this study, we only had information for VCTE in 27 patients (8%) at the time of *r*PBC. Despite the small number, increasing VCTE was associated with a higher risk of graft loss (HR 1.14, 95% CI 1.02-1.28). Therefore, future studies should evaluate the utility of VCTE in addition to biochemical response in patients with *r*PBC.

We acknowledge there are limitations in this study, mainly related to its retrospective nature. For example, we did not have information regarding the management of PBC before LT, which could have an impact on clinical outcomes in *r*PBC. In the same line, up to 25% of patients had missing data; however, the median percentage of missing data was 6.5% for all the variables (range 0-25%; Table S2). In addition, the diagnosis of *r*PBC was based on liver biopsies in a non-protocol fashion. This could explain why more than 31% of patients had histological stages 2 to 4. However, our results emphasize the need for clinical trials testing approaches to minimize the risk of graft loss related to *r*PBC. Combination therapy in patients with incomplete responses to UDCA should be prospectively assessed and it will be important to evaluate the pharmacodynamics and the interaction of obeticholic acid and fibrates in patients with *r*PBC and incomplete response to UDCA.

In conclusion, patients with *r*PBC and disease activity as indicated by standard PBC risk scores have impaired outcomes, supporting efforts to treat recurrent disease in similar ways to pre-transplant PBC. Future studies for patients with *r*PBC and incomplete response to UDCA, to evaluate the benefit of the addition of second-line treatment such as obeticholic acid, and fibrates are warranted.

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Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; INR, international normalised ratio; MELD, model for end-stage liver disease; LT, liver transplantation; OCA, obeticholic acid; PBC, primary biliary cholangitis; *r*PBC, recurrent PBC; UDCA, ursodeoxycholic acid.

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Conflicts of interest

These authors disclose the following: A.J. Montano-Loza has served on advisory boards for Intercept Pharmaceuticals. B.E. Hansen reports grants from Intercept Pharmaceuticals and Zambon Nederland B.V. and consulting work for Intercept Pharmaceuticals and Novartis. A.E. Kremer reports consulting work for CymaBay, GSK, Intercept Pharmaceuticals, and Mirum and grants from Intercept Pharmaceuticals. A. Parés consults for Intercept and Novartis. A. Floreani reports consulting activities for Intercept Pharmaceuticals. P. Trivedi has received grant support from the Wellcome Trust, the Medical Research Foundation, GlaxoSmithKline, Guts UK, PSC Support, LifeArc, NIHR, Intercept Pharma, Dr Falk Pharma, Gilead Sciences, and Bristol-Myers Squibb. He has also received speaker fees from Albireo/IPSEN, Advanz/Intercept and Dr. Falk, and advisory board/consultancy fees from ChemoMab, Cymabay, Intercept, Dr. Falk Pharma, Albireo/Ipsen, Pliant Pharma and GlaxoSmithKline. A. Mason consults for, is on the speakers' bureau of, and received grants from Intercept. He received grants from Merck. C. Corpechot reports grants from Intercept Pharmaceuticals, and consulting work for Cymabay, Ipsen, Calliditas, and Intercept Pharmaceuticals. J. Dyson has received speaker fees from Intercept Pharmaceuticals and Dr. Falk Pharma and acted as a scientific expert for NICE. The remaining authors disclose no conflicts.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Aldo J. Montano-Loza, study design, analyses of the data, creation of the first draft of the manuscript and final version; Ellina Lytvyak, analyses of the data, creation of the first draft of the manuscript and final version and submitting the manuscript for review; Bettina E. Hansen, analyses of the data, creation of the first draft of the manuscript and final version; Gideon Hirschfield, analyses of the data, creation of the first draft of the manuscript and final version; Thierry Berney, critical revision of the manuscript for important intellectual content; Christian Toso, critical revision of the manuscript for important intellectual content; Giulia Magini, critical revision of the manuscript for important intellectual content; Alejandra Villamil, critical revision of the manuscript for important intellectual content; Frederik Nevens, critical revision of the manuscript for important intellectual content; Natalie Van den Ende, critical revision of the manuscript for important intellectual content; Albert Pares, critical revision of the manuscript for important intellectual content; Pablo Ruiz, critical revision of the manuscript for important intellectual content; Débora Terrabuio, critical revision of the manuscript for important intellectual content; Palak Trivedi, critical revision of the manuscript for important intellectual content; Nadir Abbas, critical revision of the manuscript for important intellectual content; Maria Francesca Donato, critical revision of the manuscript for important intellectual content; Lei Yu, critical revision of the manuscript for important intellectual content; Charles Landis, critical revision of the manuscript for important intellectual content; Jérôme Dumortier, critical revision of the manuscript for important intellectual content; Jessica Dyson, Adriaan J. van der Meer, critical revision of the manuscript for important intellectual content; Rozanne de Veer, critical revision of the manuscript for important intellectual content; Mark Pedersen, critical revision of the manuscript for important intellectual content; Marlyn Mayo, critical revision of the manuscript for important intellectual content; Michael P. Manns, critical revision of the manuscript for important intellectual content; Richard Taubert, critical revision of the manuscript for important intellectual content; Kirchner Theresa, Luca S Belli, critical revision of the manuscript for important intellectual content; Chiara Mazzarelli, critical revision of the manuscript for important intellectual content; Guido Stirnimann, critical revision of the manuscript for important intellectual content; Annarosa Floreani, critical revision of the manuscript for important intellectual content; Nora Cazzagon, critical revision of the manuscript for important intellectual content; Francesco Paolo Russo, critical revision of the manuscript for important intellectual content; Patrizia Burra, critical revision of the manuscript for important intellectual content; Udi Zigmound, critical revision of the manuscript for important intellectual content; Inbal Houri, critical revision of the manuscript for important intellectual content; Marco Carbone, critical revision of the manuscript for important intellectual content; Giacomo Mulinacci, critical revision of the manuscript for important intellectual content; Stefano Fagiuoli, critical revision of the manuscript for important intellectual content; Daniel Stephan Pratt, critical

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Data availability statement

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author at reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2024.05.010.

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