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ORIGINAL ARTICLE

Adequate versus deep response to ursodeoxycholic acid in primary biliary cholangitis: To what extent and under what conditions is normal alkaline phosphatase level associated with complication-free survival gain?

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Abstract

Background and Aims: Normal alkaline phosphatase (ALP) levels in ursodeoxycholic acid (UDCA)-treated patients with primary biliary cholangitis (PBC) are associated with better long-term outcome. However, second-line therapies are currently recommended only when ALP levels remain above 1.5 times the upper limit of normal (×ULN) after 12-month UDCA. We assessed whether, in patients considered good responders to UDCA, normal ALP levels were associated with significant survival gains.

Approach and Results: We performed a retrospective cohort study of 1047 patients with PBC who attained an adequate response to UDCA according to Paris-2 criteria. Time to liver-related complications, liver transplantation, or death was assessed using adjusted restricted mean survival time (RMST) analysis. The overall incidence rate of events was 17.0 (95% CI: 13.7–21.1) per 1000 out of 4763.2 patient-years. On the whole population, normal serum ALP values (but not normal gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), or aspartate aminotransferase (AST); or total bilirubin < 0.6 ×ULN) were associated with a significant absolute complication-free survival gain at 10 years

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; LLN, lower limit of the normal range; LSM, liver stiffness measurement; LT, liver transplantation; PBC, primary biliary cholangitis; RMST, restricted mean survival time; RMTL, restricted mean time lost; UDCA, ursodeoxycholic acid; ULN, upper limit of the normal range; VCTE, vibration-controlled transient elastography.

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(mean 7.6 months, 95% CI: 2.7 - 12.6 mo.; $p = 0.003$). In subgroup analysis, this association was significant in patients with a liver stiffness measurement ≥ 10 kPa and/or age ≤ 62 years, with a 10-year absolute complication-free survival gain of 52.8 months (95% CI: 45.7–59.9, $p < 0.001$) when these 2 conditions were met.

Conclusions: PBC patients with an adequate response to UDCA and persistent ALP elevation between 1.1 and 1.5 ×ULN, particularly those with advanced fibrosis and/or who are sufficiently young, remain at risk of poor outcome. Further therapeutic efforts should be considered for these patients.

INTRODUCTION

Primary biliary cholangitis (PBC) is a slowly progressive, chronic cholestatic liver disease that, if not adequately treated, can lead to cirrhosis and its complications and therefore expose patients to excess mortality or the need for liver transplantation (LT).[1] Its standard treatment is lifelong oral administration of ursodeoxycholic acid (UDCA), which improves biochemical features of cholestasis and long-term survival.[2–4] However, approximately a third of patients, primarily those with an inadequate biochemical response to this treatment, remains at significant risk of liver-related complications and premature death.[5–7] For those inadequate responders, second-line therapies, including obeticholic acid or fibrates, are able to improve biochemical response rates and potentially long-term clinical outcomes.[8–11] Currently, these adjunctive treatments are only considered when serum alkaline phosphatase (ALP) values remain above 1.5 (or 1.67 depending on the criteria used to define inadequate response) times the upper limit of normal (×ULN) or total bilirubin is elevated after 12 months of UDCA therapy.[12–14]

Very recently, it has been shown that, even in patients with an adequate response to UDCA, normal ALP levels or total bilirubin ≤0.6 ×ULN could be associated with a further reduction in the risk of death or LT.[15,16] However, the significance of this deep biochemical response in terms of absolute clinical benefit, that is, real gains in complication-free life expectancy, and not just risk reduction, needs to be further assessed. Indeed, it remains unclear whether UDCA-treated patients with moderate persistent ALP elevation (ie, between 1.0 and 1.5 × ULN) or a bilirubin value between 0.6 and 1.0 × ULN should potentially be considered for second-line therapy. Therefore, the aim of the present study was to evaluate, in a large population of PBC patients who had achieved an adequate response to UDCA over the past 15 years, the complication-free survival gain associated with a deep biochemical response.

METHODS

Study population and design

This was an international multicenter retrospective cohort study involving 24 tertiary centers in 13 countries in Europe, North, and South America, and the Middle East. The characteristics of the original cohort from which this study was drawn have recently been published.[17] As this cohort was specifically set up to evaluate the prognostic value of liver stiffness measurement (LSM) assessed by vibration-controlled transient elastography (VCTE, Fibroscan), all patients were initially selected on the basis of at least one available LSM. To be eligible for the current study, the patients in this cohort had to meet the following criteria: (1) long-term treatment with UDCA of ≥12 months; (2) no second-line therapy, including obeticholic acid, fibrates (bezafibrate, fenofibrate, or others) or corticosteroids (including budesonide); (3) no diagnosis of autoimmune hepatitis-PBC overlap syndrome; (4) no signs of decompensated cirrhosis at entry; (5) at least one occurrence of adequate biochemical response as defined by the Paris-2 criteria [ie, ALP and aspartate aminotransferase (AST) levels ≤1.5 × ULN, and total bilirubin normal] after 12 months of UDCA therapy, the first occurrence defining the landmark (time zero) for survival analysis. All available blood test results over time in the same patient were taken into account. Fibrosis stage was defined at entry based on LSM as follows: advanced fibrosis stage, LSM ≥10 kPa; nonadvanced fibrosis stage, LSM <10 kPa.[18]

The study was conducted in accordance with the Declaration of Helsinki. It was a retrospective

observational analysis based on previously collected routine care data with no expressed opposition by patients. The protocol was approved by the institutional research board of each participating center in accordance with their local regulations.

Statistical analysis

The primary end point was survival without serious clinical events, defined as death, LT, or severe liver-related complications, including variceal bleeding, ascites, hepatic encephalopathy, and HCC, when no death or LT was recorded at the time of the last follow-up. Because 95% of patients had follow-up ≤11 years after entry into observation (ie, from time zero), survival data were right-censored at 10 years.

We first performed a Cox proportional hazards regression analysis to identify among all standard biochemical liver tests the simple binary conditions [ie, ALP ≤ 1.0 × ULN, gamma-glutamyl transpeptidase (GGT) ≤ 1.0 × ULN, alanine aminotransferase (ALT) ≤1.0 × ULN, AST ≤1.0 × ULN, and total bilirubin ≤0.6 × ULN] that could be associated with prolonged survival. These conditions were assessed as time-dependent categorical variables and models were adjusted for age, sex, duration of UDCA therapy, LSM, albumin level, total bilirubin level, and platelet count, with the latter 4 variables studied as continuous time-dependent variables. The proportional hazards assumption was tested based on the Schoenfeld residuals. To test for potential delayed entry bias (ie, left censoring), a Cox model with late entry, defined as the time between 1 year of UDCA and entry into the cohort, was evaluated in parallel. In addition, we performed 2 sensitivity analyses by changing the primary end point as follows: (1) liver-related (and not all-cause) deaths, LT, or liver-related complications; (2) all-cause deaths or LT. Unadjusted and adjusted HRs and corresponding CIs were calculated for each condition evaluated. For those who remained significantly associated with survival in adjusted analysis, the relationship between HR and the biochemical variable was assessed in a continuous way using a fractional polynomial function.

To determine the absolute clinical benefit (ie, gross gain in life expectancy), the liver test conditions associated with improved survival in Cox analysis were next studied using restricted mean survival time (RMST) and restricted mean time lost (RMTL) nonparametric analyses. These methods of survival analysis determine absolute (difference in RMST) and relative (RMST ratio) gains in event-free survival time at a given horizon, as well as an HR equivalent (RMTL ratio). As for Cox analyses, all analyses were adjusted for age, sex, duration of UDCA therapy, LSM, albumin level, total bilirubin level, and platelet count to control for the main prognostic and confounding factors. With the exception of sex, all of these variables were studied as continuous parameters assessed at entry. A truncation time of 10 years was specified, which corresponded to the minimum of the largest observed event time among groups. Because age and LSM were independently associated with complication-free survival gains in multivariable-adjusted RMST, analyses were subsequently stratified by these 2 parameters, whose optimal discriminating thresholds (62 y and 10 kPa, respectively) were determined using receiver-operating characteristic analysis with the Youden index.

Survival curves were constructed using Kaplan–Meier estimates and compared using the log-rank test. All tests were 2-tailed and a p-value <0.05 was considered significant. Statistical analyses were performed using Stata 14.1 (Stata Corp LLC).

RESULTS

A total of 1047 patients in the original cohort met the eligibility criteria (ie, had pure nondecompensated PBC with an adequate biochemical response to UDCA alone according to the Paris-2 criteria) for the study (Supplemental Figure S1, http://links.lww.com/HEP/H889). The number of participating centers and countries is shown in the Supporting Information (Supplemental Tables S1, http://links.lww.com/HEP/H889 and S2, http://links.lww.com/HEP/H889). The study population at entry was predominantly female over the age of 45 years with normal total bilirubin level, normal or moderately elevated levels of liver enzymes, and low LSM as evaluated by VCTE (Table 1). The mean duration of UDCA therapy at entry was 7.8 years. The proportions of patients at entry with elevated levels of ALP, GGT, ALT, and AST were 34%, 50%, 17%, and 14%, respectively. One-third had total bilirubin level >0.6 × ULN and 17% had advanced fibrosis by LSM. A comparison with the excluded patient population is shown in Supplemental Table S3 (http://links.lww.com/HEP/H889). The study population was older, with lower bilirubin and liver enzyme levels, and a lower proportion of patients with advanced LSM disease.

A total of 81 serious clinical events occurred during 4763.2 person-years of observation, including 58 deaths, of which 16 were liver-related, 18 patients with cirrhosis complications without death or LT at the last visit, including 12 ascites, 3 HCCs, 2 variceal bleedings, and 1 HE, and 5 LT. The incidence rate of these events was 17.0 (95% CI: 13.7–21.1) per 1000 person-years for the entire cohort, 10.9 (8.1–14.7) per 1000 person-years for patients with nonadvanced fibrosis at entry, and 46.4 (33.8–63.8) per 1000 person-years for those with advanced fibrosis at entry.

In a nonadjusted Cox regression analysis with a time-dependent variable, the 2 liver test conditions that were significantly associated with improved

TABLE 1 Baseline characteristics of the patients

	Obs.	Mean/Frequency	SD/Percent	Min	Max
Year of entry	1047	2013.93	3.92	2004	2021
Age at entry (y)	1047	60.63	11.63	23.1	92.5
Age at entry ≤ 45 y	1047	113	10.79	—	—
Age at diagnosis (y)	869	51.79	11.51	22.0	87.4
Female gender	1047	950	90.74	—	—
Time spent on UDCA (y)	1047	7.83	5.91	1.0	32.7
Total bilirubin (mg/dL)	1047	0.48	0.23	0.1	1.0
Total bilirubin >0.6×ULN	1047	339	32.41	—	—
ALP (×ULN)	1047	0.89	0.28	0.2	1.5
ALP >1.0 ×ULN	1047	360	34.38	—	—
GGT (×ULN)	841	1.53	1.64	0.1	15.2
GGT >1.0 ×ULN	841	424	50.42	—	—
AST (×ULN)	1047	0.76	0.24	0.1	1.5
AST >1.0 ×ULN	1047	149	14.24	—	—
ALT (×ULN)	1043	0.72	0.37	0.1	3.5
ALT >1.0 ×ULN	1043	176	16.87	—	—
Albumin (g/L)	940	42.16	3.45	26.6	51.1
Albumin < 1.0 ×LLN	940	25	2.66	—	—
Platelets (G/L)	1008	243.92	76.08	29.0	620.0
Platelets <1.0 ×LLN	1008	105	10.42	—	—
LSM (kPa)	1047	7.66	5.88	2.0	74.5
LSM ≥ 10 kPa	1047	180	17.19	—	—

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; LLN, lower limit of the normal range; LSM, liver stiffness measurement; Obs; observations; UDCA, ursodeoxycholic acid; ULN, upper limit of the normal range.

complication-free survival at any time were an ALP value ≤1.0 × ULN (HR: 0.46, 95% CI: 0.27–0.77) and a total bilirubin level ≤ 0.6 × ULN (HR: 0.58, 95% CI: 0.38–0.96). After adjustment for time-dependent survival factors and duration of UDCA therapy, the only biochemical condition associated with complication-free survival was a normal ALP level (aHR: 0.57, 95% CI: 0.27–0.99) (Table 2). The results remained consistent

TABLE 2 Time-dependent Cox regression analyses for each liver test condition evaluated

	HR	SE	z	$p>\|z\|$	95% CI
Unadjusted analysis					
ALP ≤ 1.0 ×ULN	0.457	0.120	−2.98	0.003	0.273–0.765
Total bilirubin ≤ 0.6 ×ULN	0.581	0.147	−2.14	0.032	0.353–0.955
AST ≤ 1.0 ×ULN	0.599	0.193	−1.59	0.111	0.319–1.126
GGT ≤ 1.0 ×ULN	0.707	0.202	−1.21	0.225	0.404–1.237
ALT ≤ 1.0 ×ULN	1.524	0.581	1.10	0.269	0.722–3.218
Adjusted analysis					
ALP ≤ 1.0 ×ULN	0.578	0.159	−2.00	0.046	0.226–0.990
T. bilirubin ≤ 0.6 ×ULN	0.513	0.285	−1.20	0.230	0.172–1.526
AST ≤ 1.0 ×ULN	0.569	0.267	−1.20	0.230	0.226–1.430
GGT ≤ 1.0 ×ULN	0.885	0.273	−0.40	0.692	0.484–1.620
ALT ≤ 1.0 ×ULN	0.883	0.573	−0.19	0.848	0.247–3.152

Results were ranked by decreasing level of statistical significance. The proportional hazard assumption was verified for each liver test evaluated (Supporting Information, Supplemental Table S4, http://links.lww.com/HEP/H889).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; ULN, upper limit of the normal range.

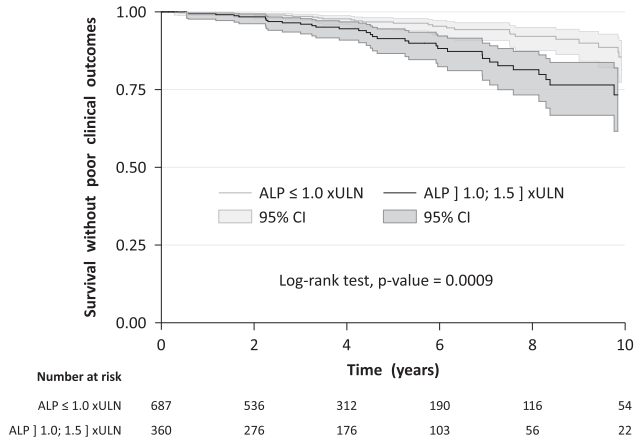

FIGURE 1 Complication-free survival curves of patients with or without normal ALP levels at entry. The Kaplan–Meier curve and its 95% CI for the normal ALP group are in gray and light gray, respectively. Those for the abnormal ALP group are in black and dark gray, respectively. The *p*-value corresponds to the log-rank test. Abbreviations: ALP, alkaline phosphatase; ULN, upper limit of normal.

when a delayed-entry survival model was applied to control for survival bias (Supplemental Table S5, http://links.lww.com/HEP/H889) or when different definitions of the primary end point were used (Supplemental Table S6, http://links.lww.com/HEP/H889, Supplemental Table S7, http://links.lww.com/HEP/H889). The complication-free survival curves of patients with or without normal ALP levels at entry are shown in Figure 1. The 10-year complication-free survival rate was 85.7% (95% CI: 77.7%–91.0%) for patients with normal ALP levels at entry and 73.2% (95% CI: 61.5%–81.9%) for those without (log-rank test, $p < 0.001$). The relationship between the HR and the ALP level at entry is shown in Figure 2. Between 0.9 ×ULN and 1.5 × ULN, the log HR increased as a linear function of the ALP level, indicating the exponential prognostic value of ALP in this range.

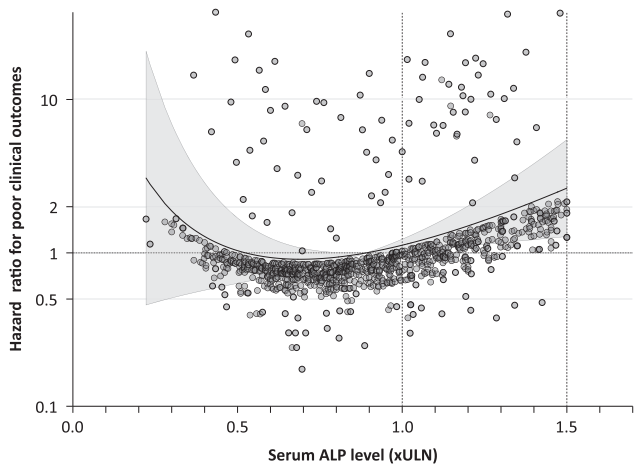

FIGURE 2 The HR for death, liver transplantation, or liver complications as a function of ALP level at entry. Each circle corresponds to a patient. The regression curve and its 95% CI are in black and light gray, respectively. The ordinate scale for HR is logarithmic. Abbreviations: ALP, alkaline phosphatase.

The complication-free survival curves associated with the other liver test conditions are shown in the Supporting Information (Supplemental Figure S2, http://links.lww.com/HEP/H889). Compared with normal ALP levels, a complete biochemical response with normal ALP, GGT, AST, and ALT was not associated with higher survival rates (Supplemental Figure S3, http://links.lww.com/HEP/H889). Furthermore, patients with normal ALP levels had similar survival rates whether total bilirubin was ≤ or >0.6 ×ULN (Supplemental Figure S4, http://links.lww.com/HEP/H889). The relationship between the HR and total bilirubin level at entry is shown in Supplemental Figure S5 (http://links.lww.com/HEP/H889).

The absolute and relative gains in complication-free survival associated with normal ALP levels at baseline were then determined using RMST analysis. In a univariate analysis, an ALP level ≤ 1.0 × ULN at entry was associated with an overall absolute complication-free survival gain at 10 years of 6.9 months (95% CI: 2.6–11.1 mo, $p = 0.002$) corresponding to a relative complication-free survival gain of 6.4% (95% CI: 2.3%–10.6%, $p = 0.002$). After controlling for prognostic factors and duration of UDCA treatment, these gains were 7.6 months (95% CI: 2.7–12.6 mo, $p = 0.003$) and 7.2% (95% CI: 2.3%–12.4%, $p = 0.004$), respectively, and were associated with an overall HR (time-lost ratio) of 0.44 (95% CI: 0.29–0.65, $p < 0.001$) (Table 3). Because age and LSM were independently associated with gains in complication-free survival associated with normal ALP levels, the analyses were subsequently stratified by these 2 parameters.

When stratified according to the optimal LSM threshold (10 kPa) at entry, absolute, and relative complication-free survival gains associated with normal ALP levels were greater in patients in the high-LSM group (19.4 mo, 95% CI: 6.9–31.8 mo, $p = 0.002$ and 20.0%, 95% CI: 3.2%–39.6%, $p = 0.018$, respectively) than in the low-LSM group (5.7 mo, 95% CI: 1.1–10.2 mo, $p = 0.015$ and 5.1%, 95% CI: 0.9%–9.6%, $p = 0.018$, respectively) (Supplemental Table S8, http://links.lww.com/HEP/H889). The estimated complication-free survival functions for normal and abnormal ALP groups according to LSM threshold at entry are shown in Figure 3. Gains in complication-free survival were also stratified according to the optimal age threshold (62 y). While absolute and relative complication-free survival gains related to normal ALP levels were significant in younger patients, they were not in older patients (Supplemental Table S9, http://links.lww.com/HEP/H889). When LSM and age conditions were considered together, the patients with the greatest gains in complication-free survival were those (8%) who were both younger and had higher LSM, in whom absolute and relative gains at 10 years were 52.8 months (95% CI: 45.7–59.9, $p < 0.001$) and 138.9% (95% CI:

TABLE 3 Adjusted 10-year restricted mean complication-free survival time analysis for alkaline phosphatase level ≤ 1.0 ×ULN at entry (n = 914)

	Mean	SE	Z	$p > \|z\|$	95% CI
Difference in RMST (mo)	7.620	2.520	3.02	0.003	2.664–12.564
Ratio of RMST (relative gain)	1.072	0.027	2.89	0.004	1.023–1.124
Ratio of RMTL (HR)	0.437	0.111	−4.03	0.000	0.293–0.654

Difference in RMST is the absolute survival gain. Ratio of RMST is the relative survival gain. Ratio of RMTL is the HR.
Abbreviations: RMST, restricted mean survival time; RMTL, restricted mean time lost.

130.5%–147.6%, $p < 0.001$), respectively. Those (52%) who met only one condition among young age and high LSM had significant intermediate gains in complication-free survival, and those (40%) who met neither condition had no significant gains despite a significant decrease in HR (Table 4). Consistent results were obtained when different definitions of the primary end point were used (Supplemental Table S10, http://links.lww.com/HEP/H889, Supplemental Table S11, http://links.lww.com/HEP/H889).

DISCUSSION

In this large retrospective cohort study of patients with pure PBC and adequate biochemical response to UDCA followed up over the past 15 years, normal ALP levels were associated with significant absolute and relative gains in complication-free survival at 10 years, particularly in patients with advanced fibrosis (LSM ≥ 10 kPa) and/or younger age (≤ 62 y). These results suggest that PBC patients previously considered as adequate responders to UDCA but with moderate persistent ALP elevation, that is, one-third of them, may benefit from therapeutic escalation with second-line therapies, as fibrates or obeticholic acid, especially younger patients with advanced compensated disease

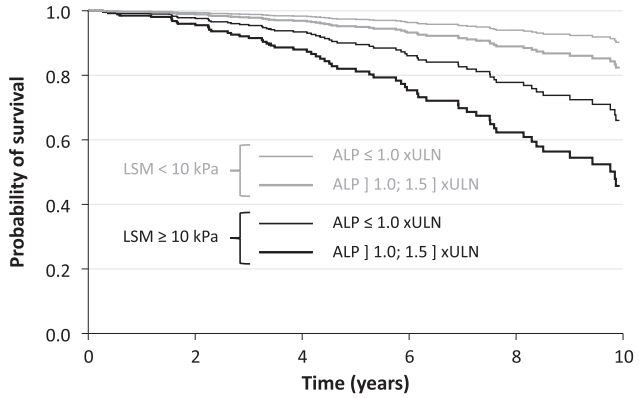

FIGURE 3 Estimated complication-free survival functions for the normal-ALP and abnormal-ALP groups depending on LSM at entry. Kaplan–Meier curves for the normal ALP group are in thin lines. Those for the abnormal ALP group are in thick lines. Kaplan–Meier curves for the lower LSM group are in gray. Those for the higher LSM group are in black. Abbreviations: ALP, alkaline phosphatase; LSM, liver stiffness measurement; ULN, upper limit of normal.

(nearly 10% of this population), in whom the survival benefit associated with normal ALP values is greatest.

In a previous study based on older data,[15] bilirubin levels ≤ 0.6 ×ULN or normal ALP values were associated with the lowest risk of death or LT in PBC, with a 10% and 7% reduction, respectively, in 10-year LT-free survival. However, the actual survival gain associated with this risk reduction was not evaluated, nor was the interactions with liver fibrosis extension and age, thus limiting the clinical interpretability of these data. In the present study, we used RMST analysis, which is an alternative that can overcome some of the limitations of proportional hazards modeling.[19] The difference in RMST, the mean absolute difference of event-free time until a milestone time point, does not depend on model assumptions and helps determine whether a benefit is clinically meaningful, as opposed to the relative information provided by the HR. Using this, we show that patients who attained normal ALP values had overall 8 additional months of life free of serious clinical events at 10 years (ie, ~7% relative gain), a result that increased to 19 months (20% relative gain) for patients with advanced fibrosis and to 53 months (ie, more than 4 y over 10 y of follow-up) for those with both advanced fibrosis and age ≤ 62 years at entry. Of note, similar significant differences were found when the composite end point was restricted to liver-related events, thus limiting the risk of a possible confounding effect of ALP reduction on extrahepatic mortality, particularly cardiometabolic mortality. The results were also consistent when only death or LT was considered. In addition, we found that, between 0.9 ×ULN and 1.5 ×ULN, that is, in a relatively low range of ALP values, the HR increased as an exponential function of ALP level. All these results support the use of normal ALP values as a primary therapeutic end point goal, most notably in younger patients with PBC and elevated LSM.

In contrast to Murillo Perez et al,[15] we did not find total bilirubin levels ≤ 0.6 ×ULN as an independent predictor of long-term outcomes. The fact that this condition was found to be associated with improved complication-free survival in univariate but not multivariate analysis, and that patients at the upper end of the normal range for total bilirubin appeared to have an increased HR, may suggest a lack of statistical power and insufficient follow-up, particularly in patients with advanced disease, who represented only a small

TABLE 4 Adjusted 10-year restricted mean complication-free survival time analysis for alkaline phosphatase level ≤ 1.0 ×ULN at entry stratified by age and LSM

	Mean	SE	Z	$p > \|z\|$	95% CI
2 conditions met among age ≤ 62 y and LSM ≥ 10 kPa (n = 67)					
Difference in RMST (mo)	52.812	3.180	14.51	0.000	45.672–59.940
Ratio of RMST (relative gain)	2.389	0.043	47.61	0.000	2.305–2.476
Ratio of RMTL (HR)	0.003	0.001	−21.78	0.000	0.001–0.004
Only 1 condition met among age ≤ 62 y and LSM ≥ 10 kPa (n = 477)					
Difference in RMST (mo)	8.928	3.576	2.49	0.013	1.908–15.948
Ratio of RMST (relative gain)	1.085	0.036	2.36	0.018	1.014–1.160
Ratio of RMTL (HR)	0.429	0.185	−2.71	0.007	0.233–0.792
No conditions met among age ≤ 62 y and LSM ≥ 10 kPa (n = 373)					
Difference in RMST (mo)	1.812	3.504	0.52	0.603	−5.040, 8.676
Ratio of RMST (relative gain)	1.013	0.034	0.40	0.691	0.951–1.079
Ratio of RMTL (HR)	0.486	0.124	−3.47	0.001	0.323–0.730

Difference in RMST is the absolute survival gain. Ratio of RMST is the relative survival gain. Ratio of RMTL is the HR.
Abbreviations: LSM, liver stiffness measurement; RMST, restricted mean survival time; RMTL, restricted mean time lost.

proportion of the study population. Unlike the study by Murillo Perez and colleagues, all patients in our study were adequate responders to UDCA and thus had normal bilirubin levels at entry, a situation that may have reduced the prognostic range of this variable. It would have been meaningful to study conjugated rather than total bilirubin levels, because bilirubin conjugates are likely to better reflect the severity of PBC and may be more closely related to its prognosis.[20] Unfortunately, this parameter, which is often overlooked in routine practice, especially in patients with normal bilirubin level, was not available in our database.

We also found no significant associations in this specific cohort between normal levels of aminotransferases or GGT and long-term prognosis. It should be noted, however, that patients diagnosed with an autoimmune hepatitis overlap syndrome, or alternatively, the inflammatory PBC phenotype, both of which usually require combination therapies and corticosteroids, had been excluded from the study, and only a small minority of patients at entry had elevated ALT or AST levels. As a consequence, we do not exclude that our results on aminotransferases may be due to a lack of statistical power. Half of the patients had elevated GGT levels at entry. Normal GGT in this population was not associated with a better clinical outcome. This contrasts with the findings of Gerussi et al,[21] who suggested that in patients with low ALP level, a GGT level > 3.2 ×ULN may identify those who might require treatment optimization. In our study, GGT was only slightly elevated, with an average level at entry of 2.45 ×ULN in those with an abnormal test.

Our results are consistent with those of Harms et al[22] suggesting that the absolute clinical benefit from UDCA therapy in patients with PBC is greater for those with the most advanced disease. Indeed, we found that both absolute and relative gains in complication-free survival associated with normal ALP values were greater in patients with advanced fibrosis, as evaluated with VCTE, than in those with less severe disease. This result is not unexpected since PBC is a slowly progressive disease and the effect of a treatment on hard clinical end points, such as LT, death, or liver decompensations over a limited observation period is more likely to be observed in the late stages than in the early stages of the disease. Nevertheless, our study suggests that therapeutic goals in PBC, especially in terms of biochemical response and ALP reduction, should be more stringent for patients with extensive fibrosis, in particular cirrhosis.

These results also highlight that a significant decrease in HR is not necessarily clinically relevant when considering specifically a slowly progressive disease with few long-term clinical events, as PBC is, particularly in patients with adequate response to UDCA. Indeed, whereas normal ALP values in this population were consistently associated with a significant decrease in HR in the different subgroups studied, a concrete clinical benefit (ie, a significant increase in life expectancy without complications) was mainly found in the youngest patients, that is, before the age of 62 years, or those with high LSM, that is, ≥10 kPa, who together account for 60% of the study population. This inverse relationship between age and prognostic value of ALP under UDCA has been recently suggested.[16] The added value of a second-line therapy in PBC is likely to decrease with age, particularly beyond 70, especially if any ALP elevation is considered as a potential indication regardless of disease stage. It also depends, of course, on the relationship between the drug's safety profile and its expected benefits. The point is that hepatologists should be proactive in identifying at-risk PBC patients (before or during treatment) and treating well generally, to achieve the best overall outcomes. In this regard, ALP level under UDCA, LSM, and age are undoubtedly key elements for therapeutic decision making in PBC.

Our study has several limitations. Because of its retrospective design, and although analyses were adjusted for major prognostic factors and duration of UDCA treatment, and survival bias was accounted for by using delayed-entry models, we cannot fully exclude the misleading effects of selection biases and undetected confounders. Of course, this population with adequate response to UDCA was made up of older, less severely affected patients. If we could control for the duration of UDCA exposure, we were unable to do the same for the dose, nor could we control for other confounders such as metabolic-associated fatty liver disease or alcohol consumption. Data completeness was not optimal for some of the parameters analyzed and the low number of events may limit the accuracy and generalizability of the findings. It was also not possible to look for a center effect because of the large number of centers and the low number of events per center. Finally, because the original cohort from which this study was conducted was initially designed to evaluate in PBC the prognostic role of LSM by VCTE, a device primarily available in Western tertiary centers, this cohort might not be fully representative of a PBC real-world population.

In conclusion, among PBC patients with an adequate response to UDCA, those who achieve normal ALP values have a significantly longer life expectancy without liver complications than patients who do not. This survival advantage associated with normal ALP is particularly noticeable in younger patients with advanced fibrosis. Therefore, additional therapeutic efforts should be considered in UDCA-treated PBC patients with persistent ALP elevations between 1.1 and 1.5 ×ULN, particularly in those with advanced disease and/or sufficiently young age.

AUTHOR CONTRIBUTIONS

Christophe Corpechot is acting as the submission's guarantor. Christophe Corpechot: study co-designer, coordinating investigator, data acquisition, data analysis and interpretation, drafting manuscript. Fabrice Carrat: statistical analysis, data interpretation, critical revision. Victor de Lédinghen: study co-designer, data acquisition, critical revision. Remaining authors: data acquisition, critical revision. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

Christophe Corpechot consults and received grants from Intercept. He received grants from Arrow. He has other interests with Biotest and Gilead. Sara Lemoinne consults for Albireo. Bettina Hansen consults, advises, and received grants from Albireo, Calliditas Therapeutics, CymaBay, Intercept, and Mirum. Consults and advises HighTide, Ipsen, and Pliant. Gideon Hirschfield consults and is on the speakers' board for Ipsen. He consults for CymaBay, Intercept, and Plaint. He is on the speakers' bureau for GlaxoSmithKline. Aliya Gulamhusein consults and is on the speakers' board for Advanz. She consults for CymaBay. Albert Pares consults for Calliditas Therapeutics, Intercept, and Kowa. Frederik Nevens consults for Calliditas Therapeutics, CymaBay, Intercept, and Mayoly. Francesco Paolo Russo is on the speakers' bureau for AbbVie and Gilead. Annarosa Floreani consults and received grants from Advanz. Nadir Abbas is on the speakers' bureau and received grants from Advanz. He is on the speakers' bureau for Dr Falk Pharma. Vicenza Calvaruso advises, is on the speakers' bureau, and received grants from Advanz. She consults and is on the speakers' bureau for AbbVie. She advises Ipsen. She is on the speakers' bureau for Echosens. She received grants from Gilead. Alan Bonder consults and received grants from CymaBay and Intercept. He received grants from Chemobab-101, Gilead, Mirium, and Vistas. He has other interests with Dynamed and Up to Date. Pietro Invernizzi Advises and received grants from Intercept. He advises Zydus. He received grants from AbbVie. Laura Cristoferi received grants from Albireo. She is on the speakers' bureau for Advanz and Echosens. Adriaan van der Meer consults for and is on the speakers' bureau for AOP Health. He is on the speakers' bureau and received grants from Zambon. He consults for Intercept. He is on the speakers' bureau for AbbVie. He received grants from CymaBay and Gilead. Andreas E. Kremer consults, advises, is on the speakers' bureau, and received grants from Intercept. He consults, advises, and is on the speakers' bureau for AbbVie, Bayer, CymaBay, Gilead, GlaxoSmithKline, and MSD. He is on the speakers' bureau for AOP Orphan, Beiersdorf, Bristol Myers Squibb, CMS, Eisai, Escient, Falk, FMC, Guidepoint, Janssen, Lilly, Medscape, Mirum, Myr, Newbridge, Novartis, Roche, Viofor, and Zambon. Tony Bruns consults for Advanz, Grifols, and Sobi. He has other interests with CSL Behring, Falk Foundation, Gilead, and Gore. Jessica Katharine Dyson is on the speakers' bureau and received grants from Falk Pharma and GlaxoSmithKline. She consults for NICE. She received grants from Umecrine. David Jones consults, advises, is on the speakers' bureau, and received grants from Intercept. He consults for Ipsen and Umecrine. He is on the speakers' bureau for Advanz, Falk Pharma, and GlaxoSmithKline. The remaining authors have no conflicts to report.

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