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Dynamics of Liver Stiffness Measurement and Clinical Course of Primary Biliary Cholangitis

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Abbreviations used in this paper: **ALP, alkaline phosphatase; CI, confidence interval; HR, hazard ratio; JM, joint model; LSM, liver stiffness measurement; LT, liver transplantation; PBC, primary biliary cholangitis; SCE, serious clinical event; UDCA, ursodeoxycholic acid.**

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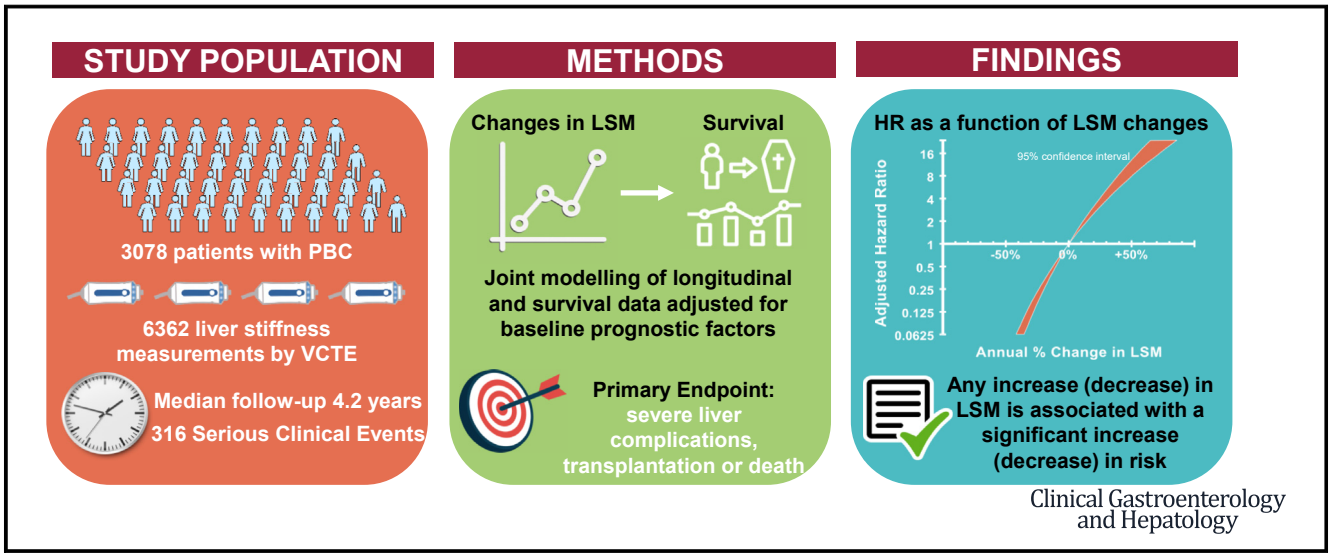


BACKGROUND & AIMS: **In primary biliary cholangitis (PBC), static liver stiffness measurement (LSM) has proven prognostic value. However, the added prognostic value of LSM time course in this disease remains uncertain.**

METHODS: **We conducted an international retrospective cohort study among patients with PBC treated with ursodeoxycholic acid and followed by vibration-controlled transient elastography between 2003 and 2022. Using joint modeling, the association of LSM trajectory and the incidence of serious clinical events (SCE), defined as cirrhosis complications, liver transplantation, or death, was quantified using the hazard ratio and its confidence interval.**

RESULTS: **A total of 6362 LSMs were performed in 3078 patients (2007 on ursodeoxycholic acid alone; 13% with cirrhosis), in whom 316 SCE occurred over 14,445 person-years (median follow-up, 4.2 years; incidence rate, 21.9 per 1000 person-years). LSM progressed in 59% of patients (mean, 0.39 kPa/year). After adjusting for prognostic factors at baseline, including LSM, any relative change in LSM was associated with a significant variation in SCE risk ($P < .001$). For example, the adjusted hazard ratios (95% confidence interval) associated with a 20% annual variation in LSM were 2.13 (1.89–2.45) for the increase and 0.40 (0.33–0.46) for the decrease. The association between LSM trajectory and SCE risk persisted regardless of treatment response or duration, when patients with cirrhosis were excluded, and when only death or liver transplantation was considered.**

CONCLUSIONS: **Tracking longitudinal changes in LSM using vibration-controlled transient elastography provides valuable insights into PBC prognosis, offering a robust predictive measure for the risk of SCE. LSM could be used as a clinically relevant surrogate end point in PBC clinical trials.**

Keywords: PBC; Liver Stiffness; Elastography; FibroScan; Time Course; Prognosis.

Primary biliary cholangitis (PBC) is a slowly progressive, chronic, cholestatic, fibrosing liver disease that, if insufficiently treated, exposes patients to the risk of premature death from cirrhosis-associated liver failure or liver cancer.[1] In addition to blood markers of cholestasis, notably serum levels of alkaline phosphatase (ALP) and total bilirubin, static measurement of liver stiffness (LSM) has been proven to be 1 of the main

prognostic parameters of the disease.[2,3] LSM is currently recommended to risk-stratify patients with PBC and tailor monitoring accordingly.[4] In association with biochemical response criteria, it could also help identify patients in need of second-line therapy.[5] However, the prognostic significance of LSM evolution over time in PBC remains uncertain, and current knowledge of this dynamic aspect of LSM is only based on limited data.[2,6] In particular, it is unclear whether longitudinal changes in LSM could reasonably be used as a clinically meaningful surrogate measure of treatment efficacy in clinical trials.[7] Therefore, in the present study, we sought to assess the association between LSM trajectory over time and long-term PBC outcomes.

What You Need to Know

Background

Static measurement of liver stiffness (LSM) in primary biliary cholangitis (PBC) has established prognostic value. However, the prognostic significance of dynamic changes in LSM in this disease remains uncertain.

Findings

In this retrospective cohort study of over 3,000 PBC patients, LSM trajectory assessed by vibration-controlled transient elastography was significantly associated with long-term clinical outcome, independent of baseline prognostic factors.

Implications for patient care

LSM evolution in PBC offers an additional predictive measure of risk that could aid treatment decision-making and be used as a clinically meaningful surrogate endpoint in therapeutic trials.

Methods

Study Population and Data

The study population was drawn from a previously reported international, multicenter retrospective cohort, followed between 2003 and 2022 from 24 tertiary centers in 13 countries.[3] The number of patients by country and the participating centers are presented in Supplementary Table 1. All patients had a diagnosis of PBC established according to international guidelines.[8,9] Two populations were distinguished for the analysis: a ursodeoxycholic acid (UDCA)-only cohort of patients with pure, compensated PBC who received treatment with UDCA alone; and a complete cohort comprising all patients with compensated PBC (ie, also including those who received combined treatment with fibrates, obeticholic acid, or corticosteroids at any time during follow-up and those with features of autoimmune hepatitis (AIH) overlap syndrome). Patients in both cohorts were required to have had at least 1 reliable LSM by FibroScan (Echosens, France) at baseline and at least 1 year of follow-up thereafter. The conditions under which FibroScan was performed in this study population have previously been described.[3] All reliable LSMs from the same patient were included in the analysis, regardless of the probe used. A reliable LSM was defined by an interquartile range (IQR)/median ratio $\leq$30%.[10,11] Unreliable results were excluded. Patients with a history of cirrhosis complications or liver transplantation (LT) before the baseline LSM were excluded. Results of blood tests performed within maximally 2 months of LSMs were included in the analyses. Biochemical response to treatment was assessed using the Paris-2 criteria.[12] Advanced disease stage and cirrhosis were defined by LSM $>$10 kPa and LSM $>$15 kPa, respectively, or based on histologic data when available. No data missing at baseline or during follow-up were imputed.

Statistical Analysis

The date of entry into the study was the date of the first available reliable LSM. The primary end point was time to first recorded serious clinical events (SCE), defined as cirrhosis complications (ie, ascites, variceal bleeding, hepatic encephalopathy, or hepatocellular carcinoma), LT, or death. Patients who did not reach this end point were censored at the date of the last recorded visit, so reasons for censoring included loss to follow-up and the end of the study period without the events of interest having occurred.

Time-to-event survival analysis and linear mixed model constitute the 2 submodels and components of the joint models (JMs).[13] In our analyses, the longitudinal changes in LSM were modeled using a linear mixed-effects model, assuming a normal distribution for the random effects. A random intercept and slope (ie, change in LSM per year) were considered in the linear mixed-effects model to individualize the LSM trajectory for each patient. The estimated individual LSM trajectories, characterized by the overall trend (fixed effect) and individual deviations from this trend (random effects), were subsequently incorporated as time-varying covariates in the Cox proportional hazards model (time-to-event analysis). This JM framework allows for the joint estimation of the 2 models, characterizing the relationship between longitudinal data and time-to-event outcomes. Therefore, this approach enables the dynamic prediction of the occurrence of SCE over the follow-up period. The unstandardized coefficients of the JMs and their 95% confidence intervals (CIs) were used to quantify the association between changes in LSM over time and the risk of SCE in different patient populations and with different end points. The origin time was defined as the date of the first visit during which an LSM was recorded for each patient. Schoenfeld residuals were visually inspected to verify the proportional hazards assumption in survival models. LSM measurements were

all log-transformed to satisfy the assumption of normality and to assess the impact of percentage change in LSM (in the natural scale) on the incidence of clinical events.

Using extremely conservative hypotheses to estimate the sample size required, it has been calculated that a minimum of 2328 subjects and 187 outcome events (9.3 events per predictor parameter) were needed to minimize overfitting and ensure precise estimation of key parameters from the complete cohort. This sample size calculation was based on a projected adjusted R^2 of 0.15 for the model, considering 20 predictor parameters, an event rate of 0.02, and aiming for less than 5% shrinkage in predictor effects, with a target shrinkage level of 0.95. For the UDCA-only cohort, we estimated that a minimum of 1918 subjects and 154 outcome events (7.6 events per predictor parameter) were needed with an expected shrinkage of predictor effects by 6% or less to ensure accurate estimation of key parameters in the models.

To verify the linear mixed-effects model assumptions, we analyzed the distribution of residuals versus fitted values to check for linearity and homoscedasticity. We tested the homogeneity of variance of residuals and assessed normality with a QQ plot of residuals. Additionally, we evaluated the linearity between quantitative predictors and the outcome to detect incorrect model specifications or dependencies.

A simple age and sex-adjusted model was first used to assess the significance of the association between changes in LSM and subsequent clinical events, then a fully adjusted model was produced, in which baseline explanatory prognostic variables, including LSM as a continuous variable, abnormal or normal serum levels of total bilirubin, albumin, and platelet count, inadequate or adequate biochemical therapeutic response, and time spent on UDCA treatment ($\leq$3 years or >3 years) before entering the cohort, were additionally included to test the robustness of the association found in the first model. Sensitivity analyses were performed, including an analysis of the UDCA-only cohort after the exclusion of patients with cirrhosis at baseline, and an analysis of the UDCA-only cohort using only LT or death as an end point. The hazard ratio (HR) and its CI were calculated according to the annual percentage change in LSM as follows: $HR = \exp^{(\log(C) \times R)}$, where C is the percentage of change in LSM (ie, 1.2 for a 20% increase) per year and R the unstandardized coefficient quantifying the association between LSM slope and the hazard of clinical events. The predicted survival rates and 95% CIs for specific time horizons were calculated on the basis of LSM values at entry and percentage changes in LSM, generating risk maps. The 95% CIs of incidence rates were estimated using the binomial exact method. The median follow-up time was calculated using the reverse Kaplan-Meier estimator. Quantitative data were expressed as mean $\pm$ standard deviation or median (IQR), depending on whether their distribution was normal or not, and qualitative data as number (%). P values $<$ .05 were considered significant. All statistical analyses were performed using R version 4.3.2 and JMs were developed using JMBayes package.[14]

Results

Baseline Characteristics

The flowchart of the study is presented in Figure 1. A total of 3078 and 2007 patients were included in the complete (all compensated PBC, including those with combination treatments and mixed forms) and UDCA-only (pure compensated PBC, UDCA only) cohorts, respectively. The characteristics of these populations at baseline are given in Table 1. They mainly consisted of women in their fifth decade, most of whom (around 75%) had already been treated with UDCA for more than 3 years on average at the time of inclusion. Evidence of advanced fibrosis and cirrhosis was present in approximately 25% and 15% of patients, respectively. In the complete cohort, a third of patients had been exposed, either at the time of inclusion or during follow-up, to a combination therapy with fibrates, obeticholic acid, or corticosteroids, and 8% had been identified as having PBC variant with AIH features.

Follow-up and Events

The median (IQR) follow-up in the 2 cohorts was 4.2 (2.7; 6.8) and 4.0 (2.4; 6.5) years, respectively, corresponding to an observation time of 14,445.0 and 9,060.3 person-years, respectively. During these periods, 6362 and 3881 reliable values of LSM were recorded, respectively. The median number (IQR) of LSM per patient was 2 (1; 3) and 2 (1; 2), respectively. The median time (IQR) between 2 consecutive LSM in the same patient was 2.0 (1.2; 3.1) and 2.0 (1.2; 3.0) years, respectively. The number of SCE was 316 (140 deaths, 44 LTs, 132 cirrhosis complications) and 194 (94 deaths, 26 LTs, 76 cirrhosis complications), respectively, with an incidence rate of 21.9 (95% CI, 19.5–24.4) and 21.4 (95% CI, 18.5–24.6) per 1000 person-years, respectively. The censoring rate was 90%. The distribution of the different complications associated with cirrhosis in the composite end point is presented in Supplementary Table 2. The 5- and 10-year event-free survival rates were 90% (95% CI, 89%–92%) and 79% (95% CI, 76%–82%), respectively, in the complete cohort, and 91% (95% CI, 89%–92%) and 78% (95% CI, 74%–83%), respectively, in the UDCA-only cohort.

Association Between Liver Stiffness Measurement Changes and Event Risk

The scatterplots of LSM values as a function of time elapsed in the complete and UDCA-only cohorts are presented in Supplementary Figure 1. According to the

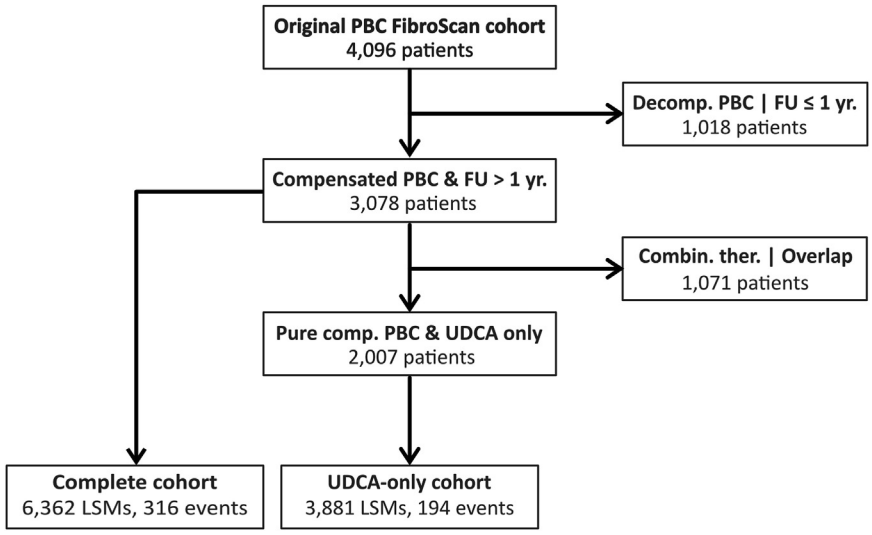


Figure 1. Study flowchart. Combin. ther., combination therapy; Comp., compensated; Decomp., decompensated; FU, follow-up.

linear mixed-effects submodel, the percentage of patients with LSM progression was 59% and 50%, respectively. In these patients, the mean ± standard deviation increase in LSM per unit time was 0.39 ± 0.58 kPa/year and 0.31 ± 0.47 kPa/year, respectively. Conversely, the percentage of patients with no LSM progression was 41% and 50%, respectively. In these patients, the mean ± standard deviation change in LSM per unit time was

Table 1. Patient Characteristics at Inclusion

	Complete cohort (n = 3078)		UDCA-only cohort (n = 2007)	
	Mean/median/freq	Obs	Mean/median/freq	Obs
Age, *y*	57.2 ± 12.2	3078	58.3 ± 12.4	2007
Age ≤45 y	510 (17)	3078	293 (15)	2007
Sex (female)	2793 (91)	3078	1817 (91)	2007
Already on UDCA	2306 (75)	3078	1442 (72)	2007
Time spent on UDCA, *y*	3.8 [0.8; 9.6]	2306	3.7 [0.6; 9.7]	1442
Combination therapy[a]	1023 (33)	3078	0 (0)	2007
Overlap syndrome[a]	242 (8)	3078	0 (0)	2007
LSM, *kPa*	6.9 [5.3; 10.4]	3078	6.7 [5.1; 10.0]	2007
LSM >10 kPa	840 (27)	3078	497 (25)	2007
LSM >15 kPa	412 (13)	3078	249 (12)	2007
Total bilirubin, *μmol/L*	11.9 ± 16.2	2628	11.9 ± 13.9	1716
ALP (xULN)	1.9 ± 7.7	2811	1.8 ± 9.4	1846
GGT (xULN)	4.2 ± 7.3	2378	3.5 ± 4.8	1574
AST (xULN)	1.3 ± 1.3	2747	1.1 ± 1.0	1801
ALT (xULN)	1.4 ± 1.5	2802	1.2 ± 1.3	1853
Albumin, *g/L*	41.6 ± 4.0	2456	41.8 ± 4.0	1620
Platelet count, *G/L*	247.4 ± 84.6	2630	244.0 ± 83.2	1627

NOTE. Quantitative variables are expressed as mean ± standard deviation for those with a normal distribution, and as median [interquartile range] for the others. Qualitative variables are expressed as number (%).
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyl transpeptidase; LSM, liver stiffness measurement; Obs, observation available; UDCA, ursodeoxycholic acid; ULN, upper limit of the normal range.
[a]At inclusion or any time during follow-up.

Table 2. Results of the Joint Models

	Unst. Coef.	2.5th Perc.	97.5th Perc.	*P* value
Complete cohort				
Simple model	1.64	1.54	1.74	< .001
Full model	4.15	3.49	4.93	< .001
UDCA-only cohort				
Simple model	3.48	2.99	3.96	< .001
Full model	2.85	2.46	3.25	< .001

NOTE. Unstandardized coefficient refers to the log HR per 1 unit increase. HR = $\exp^{(\text{Unstd. Coef.})}$ for time fixed covariates. The HR associated with the changes in LSM over time is estimated as follows: HR = $\exp^{(\log(1 + \% \text{ change in LSM/year}) * \text{Unstd. Coef.})}$.

The simple model was adjusted for age and sex. The full model was additionally adjusted for LSM and the following dichotomized prognostic variables at baseline: time on UDCA (≤3 years; >3 years), baseline levels of total bilirubin (normal; abnormal), albumin (normal; abnormal), and platelet count (normal; abnormal), and Paris-2 response (adequate; inadequate).

HR, hazard ratio; LSM, liver stiffness measurement; UDCA, ursodeoxycholic acid; Unst. Coef, unstandardized coefficient.

-0.07 ± 0.05 kPa/year and -0.07 ± 0.04 kPa/year, respectively. In both cohorts, the unstandardized coefficient of the JM, which quantifies the association between LSM slope and SCE risk, was highly significant, even after full adjustment for risk factors, at 4.15 (95% CI, 3.49–4.93; $P < .001$) and 2.85 (95% CI, 2.46–3.25; $P < .001$), respectively (Table 2). This association remained highly significant when patients with cirrhosis at baseline were excluded, and when only LT or death was considered as an end point (Supplementary Figure 2).

The adjusted HR of SCE was calculated in both cohorts as a function of the annual percentage change in LSM (Figure 2). In both cohorts, any increase in LSM with time was associated with a significant increase in the risk of events, whereas, conversely, any decrease in LSM was associated with a significant decrease in risk. In the complete cohort, the adjusted HR associated with a 20% annual variation in LSM was 2.13 (95% CI, 1.89–2.45) for the increase and 0.40 (95% CI, 0.33–0.46) for the decrease. In the UDCA-only cohort, the risk of SCE varied less with LSM changes than in the complete cohort, reflecting a patient population with overall less active disease, with the adjusted HR associated with a ± 20% annual variation in LSM of 1.68 (95% CI, 1.56–1.81) and 0.53 (95% CI, 0.48–0.58), respectively.

Finally, because the initial LSM value and the percentage change in LSM over time were independent predictors of clinical outcomes in multivariable-adjusted analyses, we calculated the 10-year probabilities (ie, the 10-year absolute risk) of SCE as a function of these 2 parameters, 1 static (initial LSM), the other dynamic (variation in LSM), based on the UDCA-only cohort. The matrix of results has been represented in the form of a risk heat map, enabling a simple visual assessment of the 10-year absolute risk of a SCE based on the kinetic profile of LSM and its initial value (Figure 3).

Discussion

In this large, retrospective, multicenter study with a median follow-up of more than 4 years, we confirm that, in PBC, the overtime variation of LSM, as assessed by vibration-controlled transient elastography, was strongly and independently associated with the risk of SCE, defined as the occurrence of cirrhosis complications, LT, or death. Importantly, this association was independent of initial LSM, treatment response or duration, and persisted when patients with cirrhosis were excluded, indicating that it also applies to early stages of the disease, and when only death or LT were taken into account, underscoring the robustness of our findings against more severe and objective clinical end points. In addition, this association was significant whether or not we included patients who received combined treatment or had a PBC-AIH variant of the disease, suggesting it operates independently of disease activity or phenotype. All these data clearly confirm that, as baseline LSM and biochemical response to treatment, LSM evolution in patients with PBC has a high and independent prognostic value and enables a more informed and proactive management of patients with PBC.[2,6]

Until now, the prognostic value of LSM in PBC had only been studied using static or time-dependent Cox regression models.[2,3] In contrast to these models, the dynamic regression approach of the JMs allows prediction of event probabilities over any time horizon using information available at any time point.[15] By establishing the relationship between LSM evolution and the timing of clinical events, joint modeling incorporates individualized longitudinal trajectories of LSM before prediction time *t* into the updated time-event projection, capturing more information than simple Cox models, including those that incorporate time-dependent covariates and assume constant values between 2 measurement times.

Tracking longitudinal changes in LSM has recently emerged as a noninvasive means of assessing therapeutic effects, particularly of hepatitis C and hepatitis B antiviral drugs, and predicting their long-term clinical impact in patients with chronic liver disease.[16–19] In a recent single-center study of 78 patients with PBC followed by vibration-controlled transient elastography, LSM remained stable in 84%, and none of these patients experienced liver-related events during a median follow-up of 15 months.[6] More generally, LSM dynamics have been shown to more accurately predict the risk of hepatic decompensation and liver-related death in patients with compensated advanced chronic liver disease.[20] In the latter study, only a minority of patients had autoimmune and/or cholestatic chronic liver disease. Interestingly, in this etiology-independent study, a 20% increase in LSM at any time was associated with an approximately 50% increased risk of hepatic decompensation or liver-related death. Our results are consistent with this, with an approximately 70% increase in the

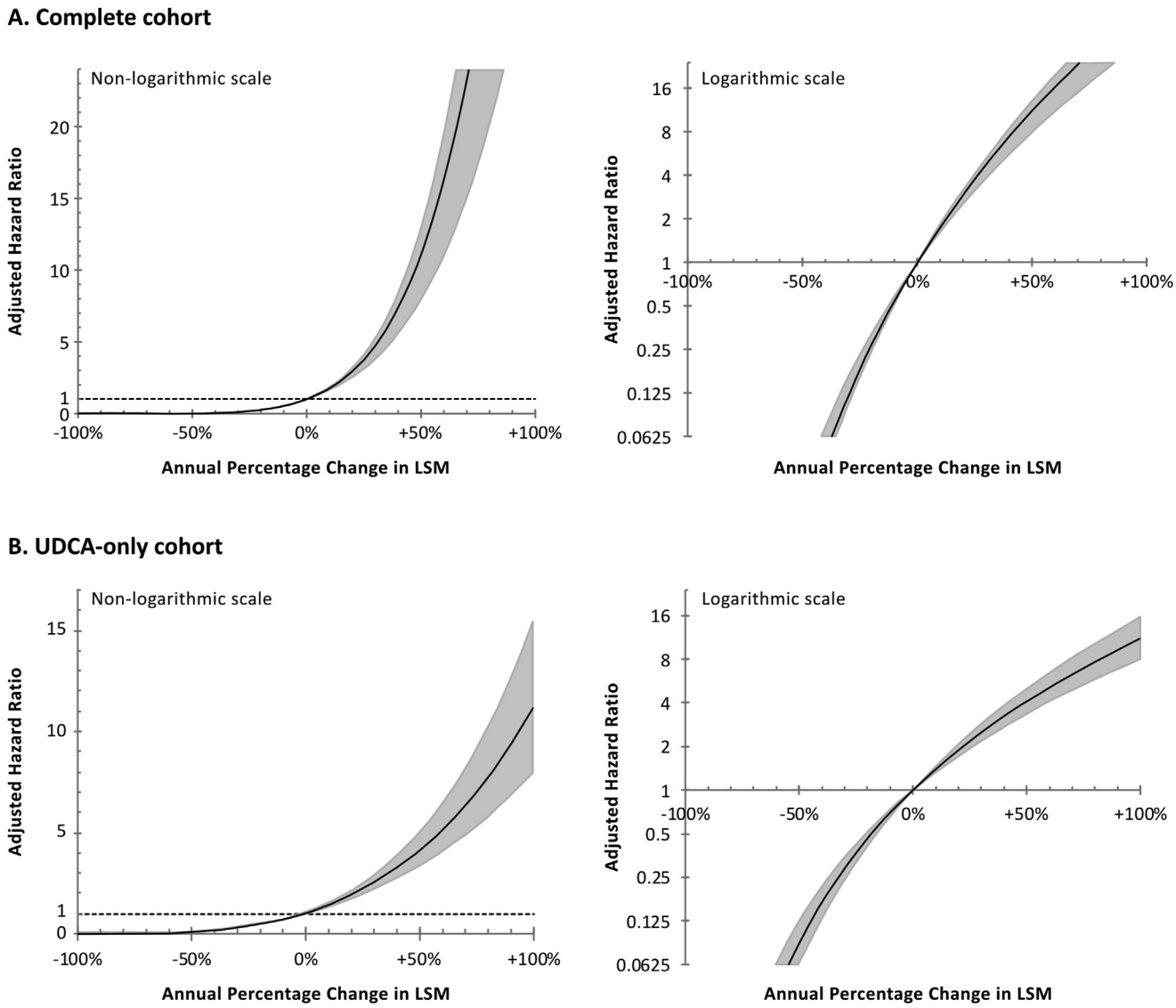
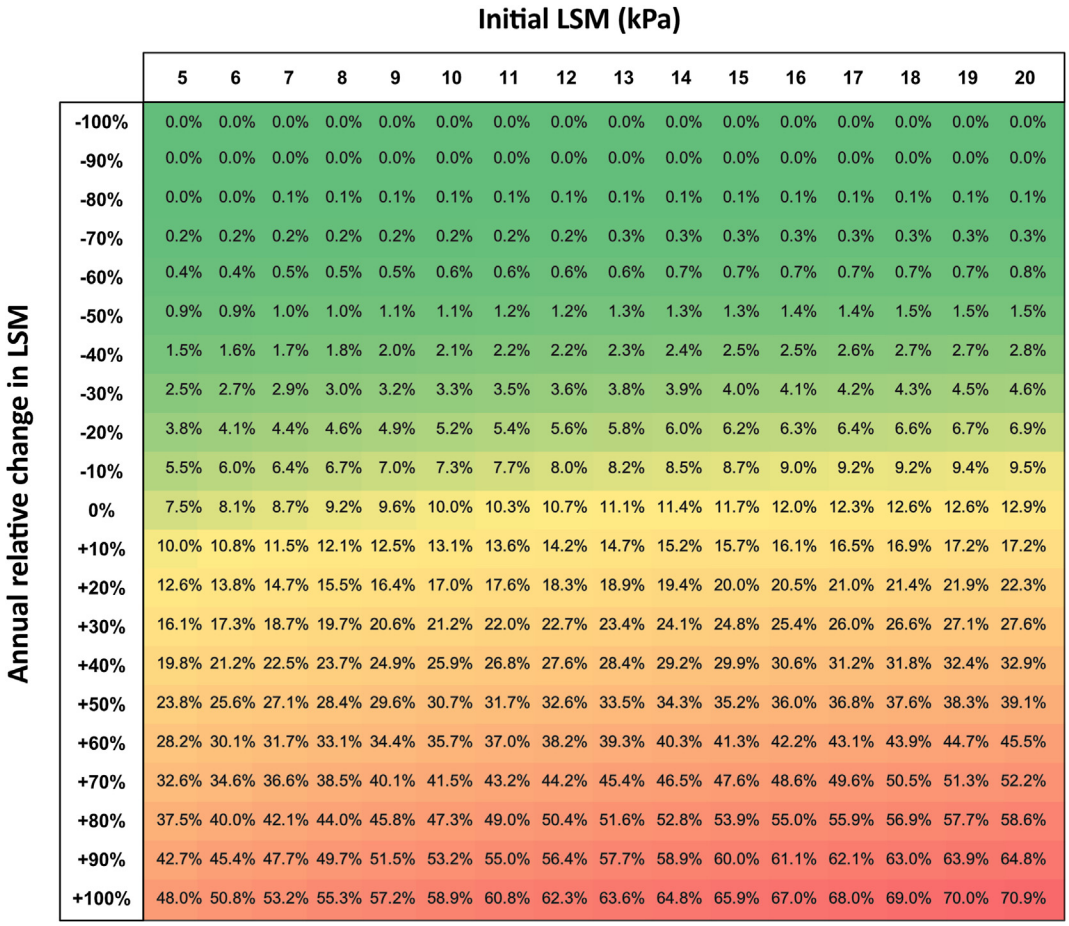


Figure 2. (*A, B*) Hazard ratio of SCE as a function of LSM time course. The *shaded area* corresponds to the 95% CI.

risk of SCE (ie, cirrhosis complications, LT, or all-cause death) associated with a 20% increase in LSM in patients with PBC treated with UDCA alone. Data from Semmler et al[20] also indicated that any LSM decrease to a final value <20 kPa identified patients at lower risk. Again, our results are consistent with these data, proving that any reduction in LSM, whatever the cause and whatever the other associated prognostic factors, including initial LSM, is associated with a better clinical outcome.

PBC on UDCA is a very slowly progressing disease, making phase 3 trials unable to capture the effect of treatment on clinical outcomes within an acceptable timeframe. The recent experience of the COBALT trial of obeticholic acid in PBC illustrates this pitfall.[21] This underlines the need of developing alternative outcomes (ie, true surrogate end points for PBC). A surrogate end point is intended to be a correlate of the true clinical outcome; and fully capture the effect of treatment on the clinical outcome.[22] To date, no biomarker in patients with PBC fully meets these criteria, not even serum ALP levels, which are nevertheless used as the main efficacy end point in trials. Indeed, although ALP levels are associated with clinical outcomes and can be modified by pharmacotherapy, so far, no interventional study has proven that the effect of a treatment on ALP translates directly into a better clinical outcome. Thus, ALP levels in PBC are considered to be a "reasonable" rather than a "true" surrogate end point.[23] The same applies here to LSM. LSM is associated with clinical outcomes and can be modified by pharmacotherapy, as highlighted by the BEZURSO trial.[7] However, as with ALP, there is no evidence that treatment-induced changes in LSM directly affect clinical outcomes. Based on our results, we propose that ALP and LSM be used together as a "reasonable" composite surrogate end point for PBC trials, in which normalization of ALP levels AND any decrease or lack of increase in LSM would be the 2 key objectives to be achieved.



	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
-100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
-90%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
-80%	0.0%	0.0%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
-70%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%
-60%	0.4%	0.4%	0.5%	0.5%	0.5%	0.6%	0.6%	0.6%	0.6%	0.7%	0.7%	0.7%	0.7%	0.7%	0.7%	0.8%
-50%	0.9%	0.9%	1.0%	1.0%	1.1%	1.1%	1.2%	1.2%	1.3%	1.3%	1.3%	1.4%	1.4%	1.5%	1.5%	1.5%
-40%	1.5%	1.6%	1.7%	1.8%	2.0%	2.1%	2.2%	2.2%	2.3%	2.4%	2.5%	2.5%	2.6%	2.7%	2.7%	2.8%
-30%	2.5%	2.7%	2.9%	3.0%	3.2%	3.3%	3.5%	3.6%	3.8%	3.9%	4.0%	4.1%	4.2%	4.3%	4.5%	4.6%
-20%	3.8%	4.1%	4.4%	4.6%	4.9%	5.2%	5.4%	5.6%	5.8%	6.0%	6.2%	6.3%	6.4%	6.6%	6.7%	6.9%
-10%	5.5%	6.0%	6.4%	6.7%	7.0%	7.3%	7.7%	8.0%	8.2%	8.5%	8.7%	9.0%	9.2%	9.2%	9.4%	9.5%
0%	7.5%	8.1%	8.7%	9.2%	9.6%	10.0%	10.3%	10.7%	11.1%	11.4%	11.7%	12.0%	12.3%	12.6%	12.6%	12.9%
+10%	10.0%	10.8%	11.5%	12.1%	12.5%	13.1%	13.6%	14.2%	14.7%	15.2%	15.7%	16.1%	16.5%	16.9%	17.2%	17.2%
+20%	12.6%	13.8%	14.7%	15.5%	16.4%	17.0%	17.6%	18.3%	18.9%	19.4%	20.0%	20.5%	21.0%	21.4%	21.9%	22.3%
+30%	16.1%	17.3%	18.7%	19.7%	20.6%	21.2%	22.0%	22.7%	23.4%	24.1%	24.8%	25.4%	26.0%	26.6%	27.1%	27.6%
+40%	19.8%	21.2%	22.5%	23.7%	24.9%	25.9%	26.8%	27.6%	28.4%	29.2%	29.9%	30.6%	31.2%	31.8%	32.4%	32.9%
+50%	23.8%	25.6%	27.1%	28.4%	29.6%	30.7%	31.7%	32.6%	33.5%	34.3%	35.2%	36.0%	36.8%	37.6%	38.3%	39.1%
+60%	28.2%	30.1%	31.7%	33.1%	34.4%	35.7%	37.0%	38.2%	39.3%	40.3%	41.3%	42.2%	43.1%	43.9%	44.7%	45.5%
+70%	32.6%	34.6%	36.6%	38.5%	40.1%	41.5%	43.2%	44.2%	45.4%	46.5%	47.6%	48.6%	49.6%	50.5%	51.3%	52.2%
+80%	37.5%	40.0%	42.1%	44.0%	45.8%	47.3%	49.0%	50.4%	51.6%	52.8%	53.9%	55.0%	55.9%	56.9%	57.7%	58.6%
+90%	42.7%	45.4%	47.7%	49.7%	51.5%	53.2%	55.0%	56.4%	57.7%	58.9%	60.0%	61.1%	62.1%	63.0%	63.9%	64.8%
+100%	48.0%	50.8%	53.2%	55.3%	57.2%	58.9%	60.8%	62.3%	63.6%	64.8%	65.9%	67.0%	68.0%	69.0%	70.0%	70.9%

Figure 3. The 10-year probability of SCE as a function of initial value and time course of LSM (UDCA-only cohort).

Our results show that PBC progression, assessed on the basis of LSM dynamics, could affect half of patients over a median follow-up of 4 years, making LSM-based clinical trials credible and feasible. Importantly, our data also suggest that the association between LSM changes and SCE risk is independent of the biochemical response to treatment and can therefore be dissociated from it for patient assessment. This could represent a new paradigm in the rationale for initiating combination therapy in PBC, because until now, only an insufficient decrease in ALP levels was taken into account in this decision or in the selection of patients for trials.[8 9] If these results are confirmed by prospective studies, this could be particularly important for patients with PBC with advanced compensated disease on UDCA, in whom ALP levels on treatment are often low, while the disease remains at risk of progression and decompensation.[5,24] As a result, the baseline value and time course of LSM should become decisive parameters in the therapeutic management of patients with PBC, alongside biochemical response, paving the way for the evaluation of new treatment strategies, notably based on nonspecific antifibrotic agents.[25]

This study has some limitations. First, it is critical to acknowledge the inherent limitations of our observational study design, in particular the potential impact of unmeasured confounding factors on our analysis. Moreover, its retrospective nature implies an intrinsic selection bias in favor of the most compliant patients, which may artificially overestimate the ability of LSM variations to predict clinical outcomes.[26] In addition, we excluded unreliable and failed results of LSM to ensure quality control of data. This approach was aimed at reducing the likelihood of associations resulting from measurement errors, but therefore did not allow us to assess the performance of LSM changes from an "intent-to-predict" perspective. We did not analyze the results according to the probe used, because the number of measurements with the XL probe was limited. Another potential limitation is the limited number of measurements per patient and the relatively short duration of follow-up (median, 4 years), which undoubtedly penalizes the prognostic evaluation of early forms of the disease. Finally, another pitfall is that what is true and reproducible at the level of a population (average trends) is not necessarily generalizable to a single patient. Although LSM autocorrelation was taken into account in the analysis, the intrinsic variability of LSM by vibration-controlled transient elastography, which depends on various factors at the time of measurement, such as the absence of fasting, transient intrahepatic hemodynamic changes caused by clinostatism, inhomogeneous

distribution of lesions within the liver, or subinflammatory flare-ups of the disease, is unavoidable and incompressible. Therefore, caution should be exercised when interpreting LSM variations on an individual basis, and we can only recommend always checking any result that might seem unusual in a given patient, and the conditions under which it was obtained, and always confronting it with other markers of disease.

In conclusion, LSM in PBC is not only a robust measure of disease stage and a useful tool for risk stratification, but also a surrogate marker of clinical course that could be used to evaluate treatments in clinical trials, alongside biochemical response. As part of routine management, monitoring LSM variations in patients with PBC also offers a predictive measure of risk that could facilitate decision-making on treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.06.035.

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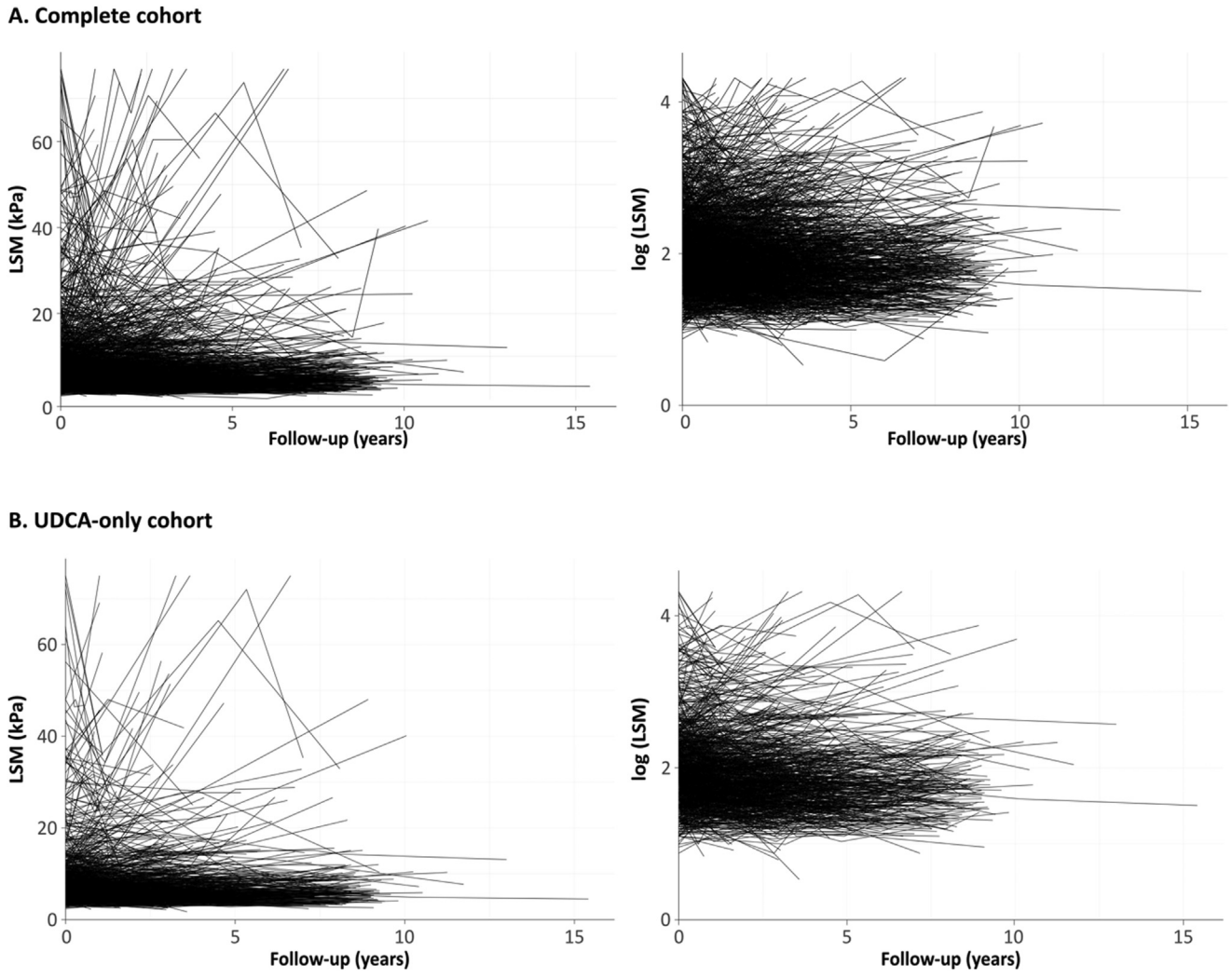
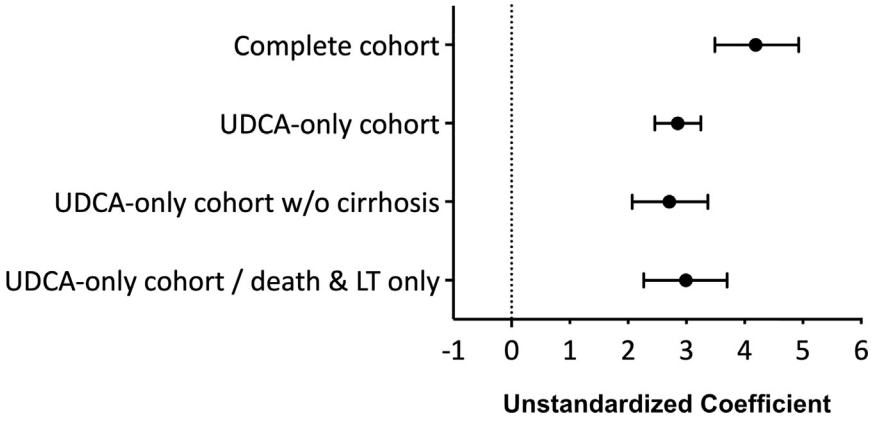
Conflicts of interest

This author discloses the following: Christophe Corpechot declares having received lecture fees from Echosens. The remaining authors disclose no conflicts.



Supplementary Figure 1. Scatterplots of LSM values versus time.



Supplementary Figure 2. Unstandardized coefficient of the fully adjusted joint model for different patient populations and end points. The unstandardized coefficient quantifies the association between changes of LSM over time and the risk of serious clinical events.

Supplementary Table 1. Number of Patients by Country

Country	Participating centers	Patients
Canada	Toronto, Edmonton	779
France	Paris, Bordeaux, Lyon, Montpellier	716
Italy	Padova, Palermo, Novara, Monza	502
United States	Rochester, Boston	419
United Kingdom	Birmingham, London, New Castle	324
Germany	Hamburg, Aachen	295
Spain	Barcelona	292
Greece	Larissa	275
Belgium	Leuven	156
Argentina	Buenos Aires	114
Netherlands	Rotterdam	86
Israel	Tel Aviv	74
Switzerland	Zurich	64

Supplementary Table 2. Number of Cirrhosis-Related Complications in the Primary Composite End Point

	Complete cohort (n = 3078)	UDCA-only cohort (n = 2007)
Ascites	85	50
Variceal bleeding	26	15
Hepatic encephalopathy	15	7
Hepatocellular carcinoma	13	7
Patient with any complication	132	76

NOTE. Several patients experienced simultaneous complications as follows. (1) In the complete cohort, 2 patients had ascites and variceal bleeding; 2 had variceal bleeding and hepatic encephalopathy; 1 patient had ascites, variceal bleeding, and hepatic encephalopathy; 1 patient had ascites and hepatic encephalopathy; and 1 patient had ascites and hepatocellular carcinoma. (2) In the UDCA-only cohort, 1 patient had ascites and variceal bleeding; and 1 patient had ascites, variceal bleeding, and hepatic encephalopathy.
UDCA, ursodeoxycholic acid.