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Prognostic value of liver stiffness measurement *vs.* biochemical response in primary biliary cholangitis

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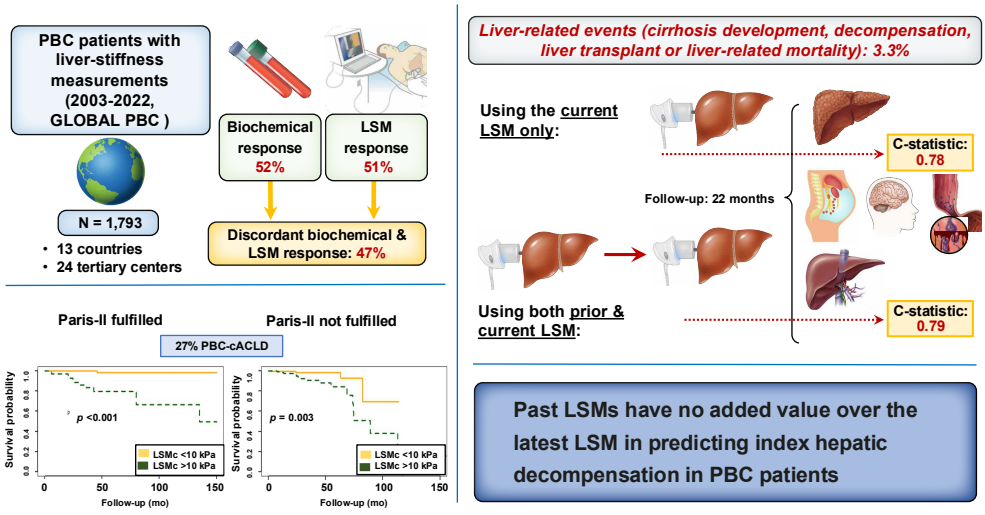
Graphical abstract



Highlights

- Both LSM and biochemical response have prognostic significance in PBC.
- Discordance between LSM and biochemical response is frequent in PBC.
- Latest LSM >10 kPa strongly predicts liver-related events in PBC, irrespective of prior biochemical response or LSM trajectory.

Impact and implications

Both liver stiffness measurement (LSM) and biochemical response have prognostic significance in patients with primary biliary cholangitis. However, the clinical relevance and how discordant biochemical and LSM changes should be best interpreted remain unclear. In this large international multicenter study, we demonstrated that once the current LSM is known, prior LSM trajectories and biochemical changes did not improve the prediction of liver-related events in patients with primary biliary cholangitis. Our finding addresses a common clinical dilemma in risk-stratifying PBC patients with discordant biochemical and LSM responses. Importantly, the use of the latest LSM value for risk prediction significantly simplifies the use of LSM in clinical decision-making for PBC patients with multiple LSM readings.

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Prognostic value of liver stiffness measurement *vs.* biochemical response in primary biliary cholangitis

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Background & Aims: Both liver stiffness measurement (LSM) and biochemical response have prognostic significance in patients with primary biliary cholangitis (PBC). However, the frequency and clinical relevance of discordant biochemical and LSM changes remain unclear. We aim to determine the performance of the most recent or current LSM (LSMc) in predicting first hepatic decompensation (HD) in the setting of discordant biochemical and LSM responses.

Methods: In this international, multicenter study, we included patients with at least two reliable LSM performed at least 6 months apart. Patients with prior HD, liver transplantation or hepatocellular carcinoma were excluded. Biochemical response was based on the Paris-II criteria. LSM response was defined as stable or any reduction in LSM. The primary outcome was the occurrence of the first HD. Secondary outcomes were liver transplantation and liver-related death. The influence of LSM on HD was estimated using Cox regression analysis.

Results: A total of 1,793 patients with PBC were analyzed. Over a median follow-up of 22 (IQR 12-39) months, 3.3% developed HD. Up to 55% of patients with PBC exhibited discordance between LSM and biochemical response. Among patients with LSM response, achieving Paris-II criteria was associated with a lower risk of HD (hazard ratio [HR] 0.25, 95% CI 0.06-0.97, p <0.044). Among patients with biochemical response, LSM response did not influence the risk of developing HD (HR 0.64, 95% CI 0.21-1.96, p = 0.429). The LSMc >10 kPa strongly predicted HD (HR 14.5, 95% CI 6.9-30.6, p <0.001), irrespective of biochemical response and prior LSM trajectories.

Conclusions: Discordance between LSM and biochemical response is frequent. Most recent or current LSM is the strongest predictor of first liver-related events in patients with PBC, irrespective of prior biochemical response or LSM trajectory.

Introduction

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease which, if insufficiently treated, exposes patients to the risk of cirrhosis, hepatic decompensation and death.[1] Biochemical response in serum alkaline phosphatase (ALP) has been proven to be prognostic in patients with PBC.[2,3] Liver stiffness measurement (LSM) using vibration-controlled transient elastography (VCTE) is increasingly used for risk stratification in patients with chronic liver disease,[4,5] including PBC.[6–8] However, while both LSM and biochemical response have prognostic value in patients with PBC,[6,9] it remains unclear how discordant biochemical and LSM changes should be best interpreted.[10,11]

There is growing interest in the use of serial LSMs to monitor and risk-stratify patients with chronic liver disease because this strategy might capture the impact of both the

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baseline risk of liver-related events and disease modifiers following the index LSM.[12,13] In this respect, it has been shown that monitoring longitudinal changes in LSM provides valuable insights into PBC prognosis, offering a predictive measure for the risk of liver-related events and making LSM a potential surrogate measure of treatment efficacy in clinical trials.[14]

Recently, the Baveno-VII workgroup proposed the concept of "clinically significant improvement" for disease monitoring, which was defined as a reduction in LSM of >20% to <20 kPa, or to less than 10 kPa.[15] However, while the trajectory of LSM may influence the prognosis of PBC, the minimum threshold of "clinically meaningful" improvement in patients with PBC remains unknown. How serial LSM results should be interpreted, and whether the risk reduction is similar for every level of baseline LSM, remains unclear.[10] In addition, this approach requires physicians to consider prior LSMs for accurate prediction of the risk of liver-related events, which is potentially challenging when LSMs might be performed at different levels of care. Importantly, to the best of our knowledge, the relative importance of previous LSM trajectories or biochemical responses compared with predictions based on the current LSM value in patients with PBC has not been investigated.

In the present study, we address these questions by examining the proportion and long-term clinical outcomes in patients with discordant biochemical and LSM responses. Our secondary aim was to determine whether prior LSM trajectories improved the predictive value of the most up-to-date or "current" LSM (LSMc) for predicting clinical outcomes in patients with PBC, as previously described.[10]

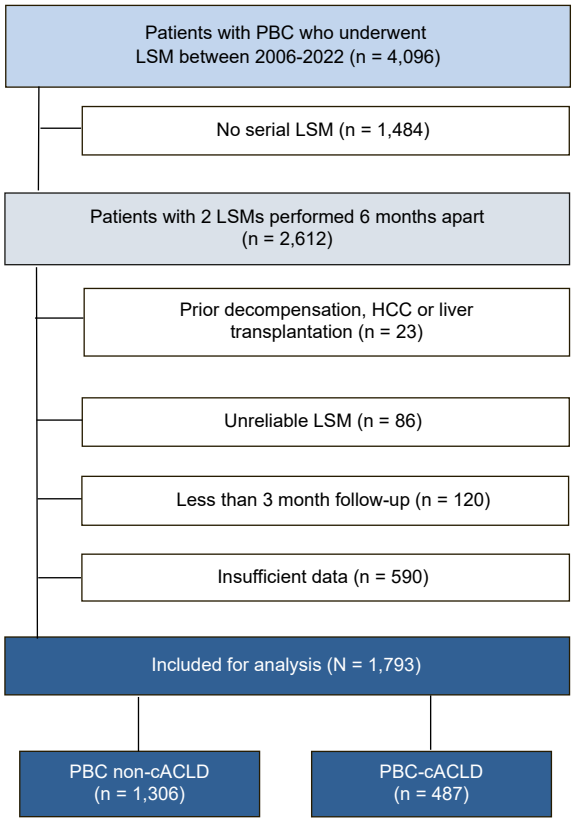

Fig. 1. STROBE flow diagram. cACLD, compensated advanced chronic liver disease; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; PBC, primary biliary cholangitis.

Patients and methods

The study population was derived from an international, multicenter cohort of patients with PBC who underwent at least one LSM by Fibroscan® (Echosens, France) between 2003 and 2022 from 24 tertiary centers in 13 countries, as described in our previous study.[14] Using institutional LSM by VCTE registries, we identified patients with PBC with at least two reliable LSMs performed at least 6 months apart. Patients with unreliable LSM, current or prior decompensating events (ascites, variceal bleeding, or hepatic encephalopathy), liver transplantation prior to obtaining the baseline LSM, and those with missing data were excluded (Fig. 1).

The diagnosis of PBC was made based on international guidelines.[16] Compensated advanced chronic liver disease (cACLD) was used to denominate patients at risk of developing liver-related events based on LSMc, characterized by ≥10 kPa.[15,17]

The earliest LSM (LSM1) was considered the baseline LSM. By setting the landmark time as the time of the LSMc, we then collected longitudinal follow-up data using LSMc as the time of the start of follow-up. Laboratory results performed within 2 months of LSM1 were included. For the purpose of the study, only the first LSM (LSM1) and LSMc were considered. Based on previous evidence suggesting that any increase in LSM in patients with PBC is associated with an increased risk of poor clinical outcomes,[14] we defined LSM response as stable or any decrease in LSMc compared to LSM1. Biochemical response to PBC treatment was determined by the Paris-II criteria.[18] The Paris-II criteria were selected because they were specifically designed for patients with early-stage PBC, are easy to calculate, and have demonstrated prognostic value.[18] Furthermore, the Paris-II criteria have also been extensively validated, both in the Western and Asian populations.[19–21] Sensitivity analysis was performed using different biochemical response criteria including the POISE criteria, normalization of ALP, deep biochemical response (defined as normal serum ALP and serum total bilirubin <0.6x the upper limit of normal), and the Toronto criteria.[2,3,22,23] Furthermore, sensitivity analysis was also performed using the "delta LSM" (defined as the absolute difference between LSM1 and LSMc), and LSM changes by percentages. To distinguish LSM reduction from LSM response, we performed sensitivity analysis by defining "stable LSM" as no change in delta LSM or <15% reduction from the first LSM. To account for the varying duration between two LSMs, we also tested the concept of "LSM slope" (defined as delta LSM divided by the time between two LSM measurements in years).[12] Finally, we explore the prognostic value of the Baveno-VII "clinically significant improvement criteria", defined as a reduction of LSM of more than 20% to <20 kPa, or any LSM reduction to <10 kPa in patients with cACLD.[15]

Relevant clinical data were collected using a unified data template until 30 June 2023. The study was approved by the respective institutional ethics committees with a waiver of consent granted. This study was conducted in compliance with the 1975 Helsinki Declaration and reported according to the STROBE guidelines.[24]

Liver stiffness measurement

All LSMs were performed using VCTE (Fibroscan®, Echosens, Paris, France) in high-volume centers based on established quality criteria. Specifically, all LSM were performed by certified operators on patients who had been fasting for at least 3 h and were in decubitus position. The choice of probe was based on the manufacturer's instructions. LSM was measured as the median of at least 10 successful measurements, expressed in kPa. LSM was considered unreliable when the IQR was >30% of the median LSM value.[25]

Study outcomes

Patients were followed up as per institutional protocol for the onset of index hepatic decompensation (HD). Liver-related events were defined as either the first HD (defined as variceal bleeding, clinically evident ascites or overt hepatic encephalopathy) or hepatocellular carcinoma, whichever occurred earlier. Secondary outcomes included the occurrence of liver transplantation (LT) and death.

Statistical analysis

Descriptive results are presented as frequencies (percentages), mean ± SD, or median (IQR), as appropriate. The normality of data distribution was determined using Kolmogorov-Smirnov test. The influence of LSM (based on both LSM1 and LSMc) on HD was estimated using Cox regression analysis, allowing for non-linear associations with restricted cubic splines (three knots).[26] The added value of previous LSM (captured either as percentage of LSM changes or LSM slope) and changes in LSM on top of LSMc to predict index HD was tested in multivariable Cox regression models with restricted cubic splines (three knots) by introducing them together with LSMc and biochemical response. Finally, we performed competing risk analysis to estimate the cumulative incidence of liver-related events by considering death and liver transplantation as competing events. All statistical tests were two-sided with a 5% significance level. Statistical analysis was performed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) with "rms" and "survival" packages.[26]

Sample size calculation

The sample size calculation was performed using the method described by Riley *et al.*[27]. To develop a multivariable clinical prediction model, including five parameters (three variables modeled with restricted cubic splines with three knots), target shrinkage of 0.9, with a bootstrap-validated R^2 of 0.11, and an incidence of liver-related events of 1.5% per year, the minimum sample size and the number of events required for model development were 396 and 12, respectively.

Results

Baseline characteristics

From 4,096 patients with PBC and available LSM, 1,793 were included in the analysis. The reasons for exclusion are summarized in the STROBE flow diagram (Fig. 1). The median (IQR) model for end-stage liver disease (MELD) scores and GLOBE scores were 7 (6-8) and 0.11 (-0.50 to 0.81), respectively. Overall, 9.6% (172/1,793) had LSM performed with the XL probe. Median (IQR) LSM at baseline and last follow-up were 6.9 kPa (5.3-10.1 kPa) and 6.8 kPa (5.1-10.0), respectively. The baseline characteristics stratified by LSMc and LSM1 are summarized in Tables 1 and S1, respectively.

Liver-related events

Over a median follow-up of 22 months (IQR 12–39) after LSMc, 60 (3.3%) patients developed hepatic decompensation (HD), 68 (3.9%) experienced liver-related events, 80 (4.7%) died, and 34 (1.9%) underwent LT. The most common index liver-related event was ascites (46/1,793; 2.6%), followed by variceal bleeding (10/1,793; 0.6%), hepatocellular carcinoma (9/1,793; 0.5%), and hepatic encephalopathy (3/1,793; 0.2%). Liver-related and non–liver-related deaths occurred in 28 (1.6%) and 52 (2.9%) patients, respectively. Considering death and liver transplantation as competing events, the cumulative incidence of liver-related events based on Fine and Gray's competing risk analysis was 0.7% at 1 year, 1.7% at 2 years, and 3.6% at 3 years.

LSM changes and liver-related events

From a total of 1,793 patients with PBC, 27.2% (487/1,793) fulfilled the definition of cACLD (LSMc ≥10 kPa). The distributions of LSMs for both the LSM1 and LSMc were similar (Fig. S1). The mean (SD) delta LSM was 0.8 kPa (±7.8 kPa), and the median LSM slope of the overall cohort was -1.0 (IQR -2.8 to 0.4) kPa/year. The median duration between the first and the latest LSM was 44 months (IQR 25-69).

Compared to patients without cACLD (LSMc <10 kPa), the patients with cACLD were more likely to be male, have diabetes, and have a worse baseline liver function (as indicated by higher MELD scores, serum bilirubin, alkaline phosphatase, alanine and aspartate aminotransferases) (p <0.05 for all, Table 1). Furthermore, patients with cACLD also had a higher value of LSM1, and a lower proportion of patients attaining biochemical responses by Paris-II criteria, POISE criteria, Toronto criteria, and ALP normalization or deep response (p <0.001) (Table 1). In addition, the cACLD group had greater increase in both the absolute value and percentage changes in LSM, a shorter duration between the two LSMs, a steeper incline in LSM slope (Table 2), and more heterogeneity in delta LSM (Fig. S2).

Patients with cACLD had a significantly higher risk of hepatic decompensation (10.7% *vs*. 0.6%, p <0.001), liver-related death (4.7% *vs.* 0.4%, p <0.001), and LT (6.4% *vs.* 0.2%, p <0.001) compared to patients without cACLD. In patients without cACLD, eight patients (0.6%) developed HD (all were ascites) (Table 3). Median time to decompensation in patients without cACLD was 26.6 months (18.0-50.0) months. None of the patients without cACLD had heavy alcohol consumption (beyond 7 units/week for females or 14 units/week for males).

Discordant LSM and biochemical response

Overall, biochemical response by Paris-II criteria and LSM response were achieved in 51.1% (359/702) and 51.6% (925/1,793), respectively. Patients achieving biochemical responses by ALP normalization, deep response, and Paris-II criteria had

Table 1. Baseline demographic stratified based on the status of compensated advanced chronic liver disease at LSMc.

Variables	Overall cohort (N = 1,793)	LSMc <10 kPa (n = 1,306)	LSMc ≥10 kPa (n = 487)	*p* values
Age	51 [41, 59]	52 [42, 59]	47 [38, 57]	<0.001
Gender, male	152 (8.5)	96 (7.4)	56 (11.5)	0.007
AMA positive	1,024 (88.0)	730 (86.8)	294 (91.0)	0.06
Diabetes mellitus	120 (8.2)	61 (5.7)	59 (15.0)	<0.001
BMI, kg/m^2	25 [22, 28]	25 [22, 28]	26 [23, 29]	<0.001
MELD score	7.0 [6.0, 8.0]	6.0 [6.0, 7.0]	7.0 [6.0, 9.5]	<0.001
Laboratory				
ALP, IU/L	156 [105, 264]	137 [97, 222]	223 [137, 338]	<0.001
Total bilirubin, mg/dl	0.6 [0.4, 0.9]	0.5 [0.4, 0.7]	0.8 [0.6, 1.2]	<0.001
Albumin, g/L	42 [40, 44]	43 [40, 45]	41 [38, 43]	<0.001
ALT, IU/L	33 [22, 52]	29 [20, 45]	46 [28, 72]	<0.001
AST, IU/L	33 [24, 49]	29 [23, 39]	47 [32, 69]	<0.001
Creatinine, mg/dl	0.8 [0.7, 0.9]	0.8 [0.7, 0.9]	0.7 [0.6, 0.8]	0.004
Platelet, x10^9/L	245 [198, 293]	256 [216, 300]	210 [144, 264]	<0.001
INR	1.0 [0.9, 1.0]	1.0 [0.9, 1.0]	1.0 [1.0, 1.1]	0.001
Biochemical response[^]				
Paris-II	359 (51.1)	294 (60.4)	65 (30.2)	<0.001
Normal ALP	300 (38.6)	236 (44.3)	64 (26.1)	<0.001
Deep response	186 (24.9)	157 (30.7)	29 (12.3)	<0.001
POISE	425 (57.0)	340 (66.5)	85 (36.2)	<0.001
Toronto	423 (58.0)	338 (67.5)	85 (37.3)	<0.001
Baseline LSM, kPa	6.9 [5.3, 10.1]	6.2 [4.9, 7.9]	11.7 [8.4, 17.3]	<0.001
LSM response	925 (51.6)	786 (60.2)	139 (28.5)	<0.001
Medications[&]				
UDCA	1,736 (97.3)	1,270 (97.8)	466 (96.1)	0.073
OCA	158 (9.7)	93 (7.9)	65 (14.5)	<0.001
Fibrate	278 (17.2)	182 (15.5)	96 (21.4)	0.006
Follow-up time, months	22.0 [12.0, 39.0]	118.5 (89.7)	120.8 (89.0)	0.627
Decompensation	60 (3.3)	8 (0.6)	52 (10.7)	<0.001
HCC	16 (0.9)	0 (0.0)	16 (3.3)	<0.001
Liver-related death	28 (1.6)	5 (0.4)	23 (4.7)	<0.001
Liver transplantation	34 (1.9)	3 (0.2)	31 (6.4)	<0.001

Data presented as n (%), median [IQR], or mean (SD), as appropriate.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibody; AST, aspartate aminotransferase; HCC, hepatocellular carcinoma; INR, international normalized ratio; LSM(c), (current) liver stiffness measurement; MELD, model for end-stage liver disease; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.
[^]Biochemical responses were determined at the time of first (baseline) LSM.
[&]Second-line therapy used at any point of time during follow-up, regardless of the duration of exposure.

Table 2. Dynamic changes in liver stiffness parameters between patients without cACLD (LSMc <10 kPa) and those with cACLD (LSMc ≥10 kPa) by the current LSM (landmark time).

Variables	LSMc <10 kPa[†] (n = 1,306)	LSMc ≥10 kPa[†] (n = 487)	*p* values
Current LSM, kPa	5.9 [4.7, 7.4]	15.1 [11.6, 24.5]	<0.001
Delta LSM, kPa	-0.4 [-1.8, 0.8]	3.5 [0, 8.1]	<0.001
5% LSM decrease	76 (5.8)	46 (9.4)	0.009
10% LSM decrease	17 (1.3)	27 (5.5)	<0.001
20% LSM decrease	3 (0.2)	13 (2.7)	<0.001
30% LSM decrease	1 (0.1)	5 (1.0)	0.008
Delta LSM, %	-6.0 [-25.0, 15.0]	26.0 [-1.0, 84.0]	<0.001
LSM slope	0.0 [-3.8, 1.0]	6.0 [0.0, 20.5]	<0.001
Any LSM decrease from LSM1	727 (55.7)	129 (26.5)	<0.001
Time between LSM1 & LSMc, months	52.8 (31.7)	47.3 (32.8)	0.001

cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement.
[†]LSMc was defined as landmark LSM; LSM1 was defined as earliest LSM before LSMc; LSM slope was defined as delta LSM (kPa) divided over time between LSM1 and LSMc (in months). Units presented as n (%), or median [IQR].

a lower risk of HD (Fig. S3). The risk of HD was similar between patients with stable LSM or a decrease in LSM (Fig. S4).

Discordant biochemical and LSM responses occurred in up to 52% of patients with PBC (Table S1). We did not identify any baseline characteristics that could predict discordant biochemical and LSM response. In patients without LSM response, achieving ALP normalization (hazard ratio [HR] 0.19, 95% CI 0.06-0.64, p = 0.007) and deep response (HR 0.22, 95% CI 0.05-0.96, p = 0.044) was associated with a lower risk of HD. However, attaining biochemical response by Paris-II, Toronto or POISE criteria were not associated with a lower risk of HD. In patients achieving LSM response, only patients achieving Paris-II criteria had a lower risk of HD. In the setting of discordant biochemical and LSM responses, neither biochemical nor LSM responses in isolation were predictive of HD. In the setting of concordant LSM responses with various biochemical responses, none were predictive of HD (p >0.05 for all).

While LSM response was not predictive of HD, both LSM reduction by percentages, the Baveno-VII "clinically

Table 3. Clinical outcomes in patients with and without cACLD.

	Overall cohort N = 1,793	Without cACLD* (LSMc <10) n = 1,306	cACLD (LSMc ≥10) n = 487	*p* values
Liver-related events[†]	68 (3.3)	8 (0.6)	60 (12.3)	<0.001
Ascites	46 (2.6)	8 (0.6)	38 (7.8)	<0.001
Variceal bleeding	10 (0.6)	0 (0)	10 (2.1)	<0.001
Hepatic encephalopathy	3 (0.2)	0 (0)	3 (0.6)	0.005
HCC	9 (0.9)	0 (0)	9 (1.8)	0.323
Transplant	34 (1.9)	3 (0.2)	31 (6.4)	<0.001
Death	80 (4.5)	46 (3.5)	34 (7.0)	0.014
Liver-related	28 (1.6)	5 (0.4)	23 (4.7)	<0.001
Non-liver-related	52 (2.9)	41 (3.1)	11 (2.3)	0.368

cACLD, compensated advanced chronic liver disease; HCC, hepatocellular carcinoma; LSMc, current liver stiffness measurement. Comparison across groups was analyzed using Chi-square or Fisher's test as appropriate.
[†]Reported in n (%); only the first liver-related events are reported.

significant improvement criteria" (Fig. S5), and LSMc being <10 kPa were associated with a significantly lower risk of HD. LSMc was the strongest predictor of HD compared to LSM response and biochemical responses (Table S2). Notably, LSMc >10 kPa was strongly predictive of the development of HD (HR 14.5, 95% CI 6.9-30.6, p <0.001) (Fig. 2), irrespective of biochemical response or concordance between biochemical and LSM responses (Fig. S6). Subgroup analysis among 378 patients with PBC who received second-line treatment at any time during follow-up (278 fibrates, 158 obeticholic acid, and 58 received both) showed LSMc ≥10 kPa was associated with a significantly higher risk of decompensation (HR 8.0, 95% CI 2.3-27.6, p <0.001). Among patients who received second-line treatment, the proportions of patients attaining LSM response (50.8% *vs*. 51.8%, p = 0.727) or developing HD (HR 1.6, 95% CI 0.9-2.7, p = 0.08) were similar to patients who only received ursodeoxycholic acid.

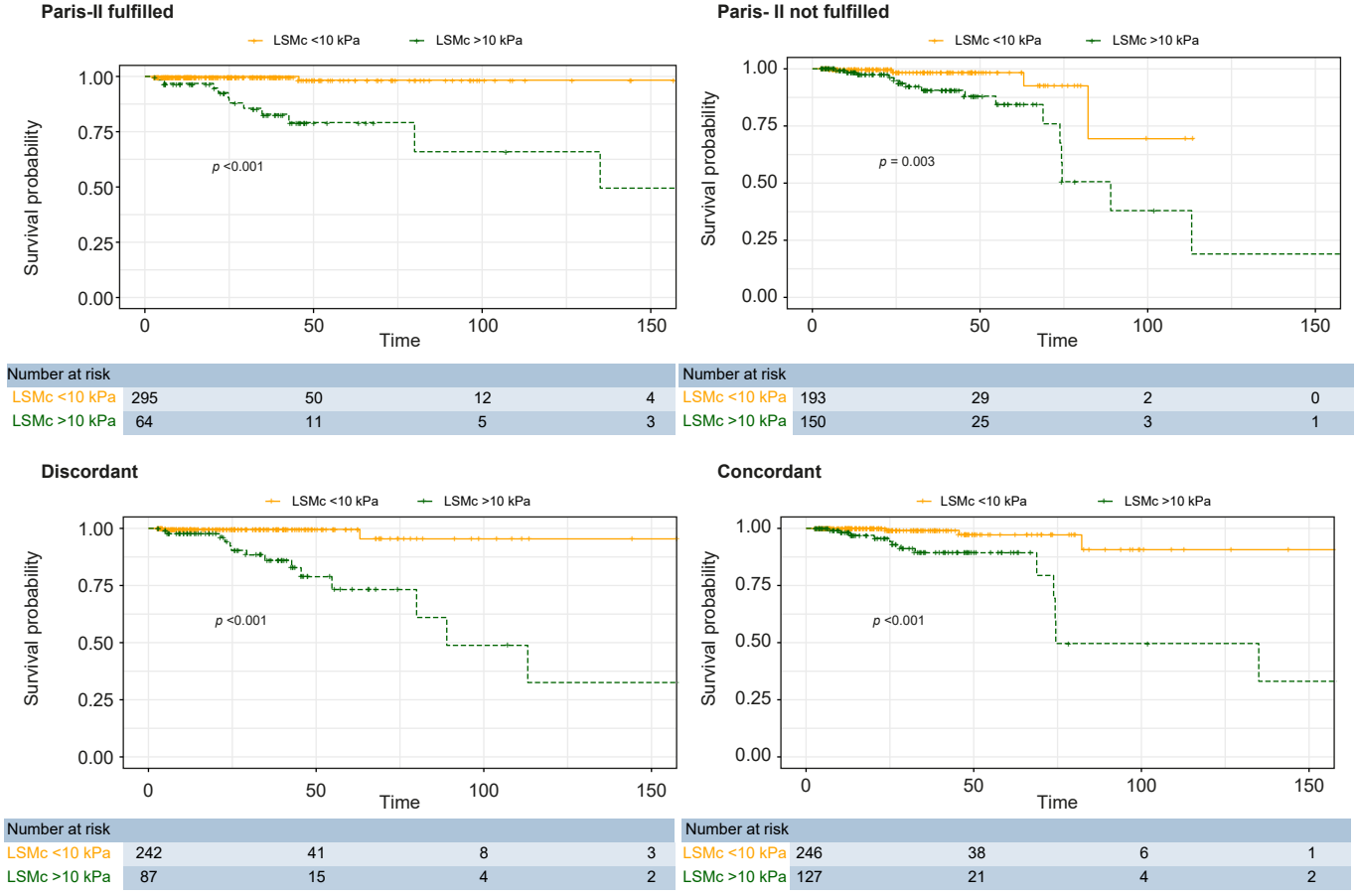

Fig. 2. LSMc remained prognostic in patients with primary biliary cholangitis, irrespective of prior biochemical response (Paris-II criteria), or concordance between LSM and biochemical responses. Time to event analysis was performed using competing risk analysis, with death and liver transplantation as competing events. LSM(c), (current) liver stiffness measurement. (This figure appears in color on the web.)

The risk of developing HD increased proportionally with the "rule-of-five" based on both the current LSM (LSMc <10 kPa: reference, LSMc 10-15 kPa: HR 7.4, 95% CI 3.2-17.2; LSMc 15.1-20 kPa: HR 17.9, 95% CI 7.4-43.2; LSMc ≥20 kPa: HR 35.8, 95% CI 17.2-74.3; p <0.0001), and prior LSM (LSM1 <10 kPa: reference; LSM1 10-15 kPa: HR 6.4, 95% CI 3.2-12.9; LSM1 15.1-20 kPa: HR 25.2, 95% CI 10.3-61.4; LSM1 ≥20 kPa: HR 31.3, 95% CI 15.6-62.7; p <0.001). The association between LSM1, LSMc, and the log-HR for HD was shown in Figs. S7 and 3, respectively. While the log-HR of HD increased exponentially with higher LSMc, the increase gradually plateaued beyond LSMc >15 kPa.

Value of adding previous LSMs to LSMc

To determine if prior LSM changes add predictive value to the LSMc in predicting HD, we included LSMc along with either LSM1 or LSM slope in a multivariable Cox regression model. When including either LSM1, LSM slope, or biochemical responses with LSMc in the model (Table 4), neither added predictive value to LSMc. LSMc alone has a C-statistic of 0.86. In a sensitivity analysis using LT and death as secondary endpoints, this association remained significant for LSMc (Table S3, Models 2 and 3).

Discussion

LSM by VCTE is increasingly used to risk-stratify and guide clinical management of patients with chronic liver disease.[4,12] However, how to interpret and utilize serial LSMs to predict clinical outcomes, specifically in patients with PBC, remains unclear.[14] In this international cohort of patients with PBC, we showed that the LSMc has important prognostic value, irrespective of prior biochemical response or LSM trajectory. Furthermore, when the current LSM is available, knowing previous LSM values and trajectory has little added value in improving the prediction of HD in patients with PBC.

In addition, we found that the prognostic role of LSM responses was limited to patients with PBC who did not achieve ALP normalization or deep response. In patients with discordant biochemical and LSM responses, observed in about half of the cohort, LSMc showed the strongest predictive value for the occurrence of index hepatic decompensation, regardless of biochemical or LSM response status. Notably, the predictive value of LSMc remained robust even when considering LT and death as secondary outcomes. These findings align with previous data from Wong *et al.*,[12] again supporting that prior LSM trajectories and LSM responses add little value when the current LSM is known.

Consistent with existing literature, ascites was the most common cause of HD, even after accounting for liver-related events with concomitant HCC in this multinational cohort of patients with PBC. In contrast to previous studies involving patients with cACLD (primarily due to viral hepatitis or MASLD), where no decompensating events were observed at LSM values <10 kPa, eight patients with PBC (0.6%) developed decompensation at LSM values <10 kPa, presenting with ascites in all cases. This might be related to the presinusoidal component of portal hypertension in patients with PBC without cirrhosis, as shown in an earlier study.[28] However, the risk of decompensation was considered negligible when compared to PBC-cACLD where the risk was 10-fold higher. Lowering the LSM cut-off to 8 kPa had limited clinical utility since it only marginally reduced the number of patients (0.5%) developing HD, which was at the expense of classifying 40% of patients with PBC as having cACLD. These findings support the use of 10 kPa as the LSM threshold for

Table 4. Added value of prior LSM trajectory or biochemical response to current LSM in predicting liver-related events.

Overall cohort (N = 1,793)					
Liver decompensation					
Models	**Parameters**	**Chi-square**	**sHR (95% CI)**	***p* value**	**Harrell's c-statistics**
Model 1	LSMc	136.5	1.06 (1.05-1.07)	**<0.001**	0.8935
Model 2	LSMc	90.8	1.06 (1.05-1.07)	**<0.001**	0.8913
	LSM response	0.2	1.16 (0.61-2.20)	0.659	
Model 3	LSMc	166.2	1.06 (1.05-1.07)	**<0.001**	0.8983
	LSM slope	32.3	0.996 (0.997-0.998)	**<0.001**	
Model 4	LSMc	121.2	1.07 (1.06-1.09)	**<0.001**	0.8935
	LSM delta	9.8	0.98 (0.96-0.99)	**0.0017**	
Model 5	LSMc	62.4	1.06 (1.04-1.07)	**<0.001**	0.8656
	Paris-II criteria	0.001	1.01 (0.50-2.04)	0.98	
Model 6	LSMc	61.1	1.06 (1.04-1.07)	**<0.001**	0.8623
	Paris-II criteria	0.003	1.02 (0.48-2.16)	0.956	
	10% reduction in LSM	0.27	1.36 (0.43-4.26)	0.603	
Model 7	LSMc	58.7	1.06 (1.04-1.07)	**<0.001**	0.867
	Paris-II criteria	0.001	1.01 (0.50-2.05)	0.978	
	20% reduction in LSM	0.42	1.72 (0.34-8.85)	0.517	
Model 8	LSMc	131	1.06 (1.05-1.07)	**<0.001**	0.8892
	10% reduction in LSM	4.2	2.46 (1.05-5.81)	0.038	
Model 9	LSMc	126.4	1.06 (1.05-1.07)	**<0.001**	0.8941
	20% reduction in LSM	5.14	3.89 (1.20-12.62)	0.02	
Model 10	LSMc	28.4	1.04 (1.03-1.05)	**<0.001**	0.8845
	20% reduction to <20 kPa or <10 kPa	19.7	0.20 (0.10-0.41)	**<0.001**	

LSM(c), (current) liver stiffness measurement; sHR, sub-distributional hazard ratio.
Note: [†]Chi-square reflects the quantitative contribution of the variable to the model. sHR estimated from competing risk analysis, with death and liver transplantation as competing events, c-statistics at month 36.

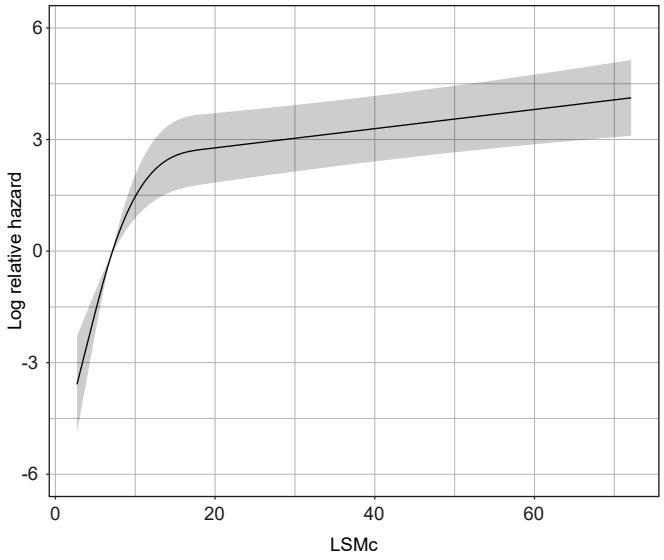

Fig. 3. Association between Log-hazard ratio of liver-related events with LSMc, analysed using Cox regression analysis allowing for non-linear association using restricted cubic splines (3 knots). While the Log-hazard ratio of liver-related events increases exponentially with LSMc, this positive association began to plateau beyond values of 15 kPa (plots show unadjusted associations, modeling one variable at a time). LSM(c), (current) liver stiffness measurement.

identifying cACLD in patients with PBC, which is in line with the Baveno-VII consensus for other chronic liver disease etiologies.[15]

Our current study showed that discordance between LSM and biochemical responses is common (Table S1). We postulate that the high discordance rate may be due to disparities between the timing of LSM and the assessment of biochemical responses, as well as operator variability in LSM measurements.

The present results do not contradict our previous data showing that the LSM trajectory in PBC has prognostic value independent of the baseline LSM.[14] In the previous study, we showed that dynamic changes in LSM could be used, alongside biochemical response, as a potential surrogate measure of disease outcome. The fact that the last available LSM has a stronger prognostic value than either the LSM trajectory itself or the previous LSM does not call this conclusion into doubt. These should be considered as two different aspects of the potential usefulness of LSM for PBC assessment, one for risk stratification (LSMc) and the other for the evaluation of therapeutic intervention (LSM changes in association with biochemical response). Strengths of our study include a large number of patients and multinational design that adds to the generalizability of our findings. With the increasing use of repeated LSMs in routine clinical practice, our findings provide valuable insights to interpret serial LSM changes in patients with PBC. The use of the latest LSM value for risk prediction considerably simplifies the use of LSM in clinical decision-making for patients with PBC. Importantly, our finding addresses a common clinical dilemma on how to risk-stratify patients with PBC with discordant biochemical and LSM responses. To our knowledge, this is the first study elucidating the added value of prior LSM and biochemical response when risk-stratifying patients using LSMc.

A key limitation of our study is its retrospective design, which makes it subject to selection bias. In addition, the timing of repeated LSM was not standardized across different institutions; however, this limitation was accounted for, in part, by introducing the LSM slope. As the study cohort only included patients with PBC who underwent serial VCTE, there are concerns regarding whether the cohort may be skewed towards patients with more advanced liver disease. However, the current study included all LSM within the project period from each institution and thus represents local practice. As the proportion of patients with LSM >10 kPa between the overall cohort and the final cohort was similar (27.5% *vs.* 27.2%, $p = 0.76$), we feel the patients with LSM <10 kPa are equally represented in the current study. That said, in the real-world setting, patients who are offered a Fibroscan in clinical practice may be more likely to have ACLD or be referred to tertiary expert centers; therefore, we cannot entirely exclude potential selection bias towards more advanced liver disease. We were unable to exclude survivorship bias among patients with a high first LSM who might have decompensated and not undergone a second LSM after decompensation, primarily because the current guidelines did not recommend repeating LSM in patients with decompensated cirrhosis. We believe this is unlikely to profoundly influence our findings because only a small proportion of patients were excluded for this reason, and the odds of developing HD were similar between LSM1 and LSMc (Figs 3 and S3). Unlike our previous study,[14] we used only the first and last LSM value, and not all the available values for the same patient to define LSM trajectory. However, this restriction probably had only a limited impact on the results, as the mean number of LSMs in patients with ≥2 LSMs in this cohort was only 2.6. Only about one-third of our cohort had the controlled attenuation parameter score recorded. Finally, the biochemical response was assessed in most cases on data prior to the last LSM value, and we therefore had to assume that this response was stable over time.

In summary, the LSMc seems to be the strongest predictor of first HD in patients with PBC, irrespective of prior biochemical response or LSM trajectory. In patients with PBC and serial LSM values, knowing prior LSM value and trajectory appears of little added value over the latest LSM in predicting HD. Once the current LSM is known, the previous LSM trajectory or biochemical response does not add to the prediction of liver-related events in patients with PBC.

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Abbreviations

ALP, alkaline phosphatase; (c)ACLD, (compensated) advanced chronic liver disease; HD, hepatic decompensation; HR, hazard ratio; LSM, liver stiffness measurement; LT, liver transplantation; PBC, primary biliary cholangitis; VCTE, vibration-controlled transient elastography.

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Conflicts of interest

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

Authors' contributions

Yu Jun Wong study design, analyses of the data, creation of the first draft of the manuscript and final version; Bettina Hansen analysis of the data and critical revision of the manuscript for important intellectual content; Laurent Lam, Pierre-Antoine Soret, Sara Lemoinne, Gideon Hirschfield, Aliya Gulamhusein, Ellina Lytvyak, Albert Pares, Ignasi Olivas, John E. Eaton, Karim T. Osman, Christoph Schramm, Marcial Sebode, Ansgar W. Lohse, George Dalekos, Nikolaos Gatselis, Frederik Nevens, Nora Cazzagon, Alessandra Zago, Francesco Paolo Russo, Annarosa Floreani, Nadir Abbas, Palak Trivedi, Douglas Thorburn, Francesca Saffioti, Laszlo Barkai, Davide Roccarina, Vicenza Calvaruso, Anna Fichera, Adèle Delamarre, Natalia Sobenko, Alejandra Maria Villamil, Esli Medina-Morales, Alan Bonder, Vilas Patwardhan, Cristina Rigamonti, Marco Carbone, Pietro Invernizzi, Laura Cristoferi, Adriaan van der Meer, Rozanne de Veer, Ehud Zigmond, Eyal Yehezkel, Andreas E. Kremer, Ansgar Deibel, Tony Bruns, Karsten Große, Aaron Wetten, Jessica Katharine Dyson, David Jones, Jérôme Dumortier, Georges-Philippe Pageaux, Victor de Lédinghen, Fabrice Carrat, Olivier Chazouillères critical revision of the manuscript for important intellectual content; Christophe Corpechot and Aldo J. Montano-Loza study design, analyses of the data, creation of the first draft of the manuscript and final version.

Data availability

The datasets generated and analyzed 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.2025.09.024.

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