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Dynamics in Liver Stiffness Measurements Predict Outcomes in Advanced Chronic Liver Disease

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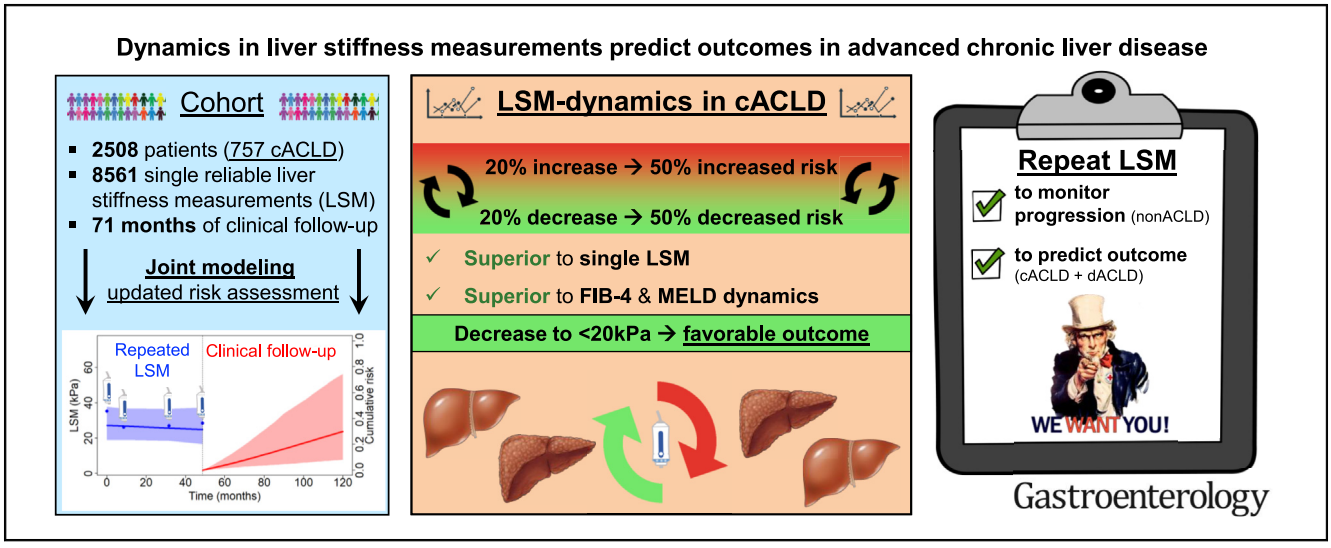

BACKGROUND & AIMS: Liver stiffness measurements (LSMs) provide an opportunity to monitor liver disease progression and regression noninvasively. We aimed to determine the prognostic relevance of LSM dynamics over time for liver-related events and death in patients with chronic liver disease. **METHODS:** Patients with chronic liver disease undergoing 2 or more reliable LSMs at least 180 days apart were included in this retrospective cohort study and stratified at baseline (BL) as nonadvanced chronic liver disease (non-ACLD, BL-LSM $<$ 10 kPa), compensated ACLD (cACLD; BL-LSM $\geq$ 10 kPa), and decompensated ACLD. Data on all consecutive LSMs and clinical outcomes were collected. **RESULTS:** There were 2508 patients with 8561 reliable LSMs (3 per patient; interquartile range, 2–4) included: 1647 (65.7%) with non-ACLD, 757 (30.2%) with cACLD, and 104 (4.1%) with decompensated ACLD. Seven non-ACLD patients (0.4%) and 83 patients with cACLD (10.9%) developed hepatic decompensation (median follow-up, 71 months). A 20% increase in LSM at any time was associated with an approximately 50% increased risk of hepatic decompensation (hazard ratio, 1.58; 95% CI, 1.41–1.79; $P < .001$) and liver-related death (hazard ratio, 1.45; 95% CI, 1.28–1.68; $P < .001$) in patients with cACLD. LSM dynamics yielded a high accuracy to predict hepatic decompensation in the following 12 months (area under the receiver operating characteristics curve = 0.933). The performance of LSM dynamics was numerically better than dynamics in Fibrosis-4 score (0.873), Model for End-Stage Liver Disease (0.835), and single time-point LSM (BL-LSM: 0.846; second LSM: 0.880). Any LSM decrease to $<$20 kPa identified patients with cACLD with a substantially lower risk of hepatic decompensation (hazard ratio, 0.13; 95% CI, 0.07–0.24). If reliable, LSM also confers prognostic information in decompensated ACLD. **CONCLUSIONS:** Repeating LSM enables an individual and updated risk assessment for decompensation and liver-related mortality in ACLD.

Keywords: Vibration-Controlled Transient Elastography; LSM; ACLD; Cirrhosis.

Liver stiffness measurement (LSM) is a well-established surrogate for hepatic fibrosis.[1] Beyond staging of fibrosis, LSM has clinical value for the noninvasive diagnosis of clinically significant portal hypertension (ie, hepatic venous pressure gradient ≥10 mm Hg).[2,3] Importantly, LSM is also linked to the risk of subsequent liver-related events in patients with chronic liver disease.[4–9]

Advanced chronic liver disease (ACLD) is noninvasively defined as "the continuum of severe fibrosis and cirrhosis" to stratify the risk of hepatic decompensation.[10,11] Thus, ACLD is a highly dynamic condition. Although liver disease may progress in case of ongoing liver injury,[12] it may stabilize if the etiology is controlled, or even regress in case of removal of the (primary) etiologic factor.[13] Consequently, the focus of using LSM in patients with ACLD has shifted toward risk stratification, as also suggested by the Baveno VII "rule-of-5" recommendation.[11]

LSM, as compared with liver biopsy or hepatic venous pressure gradient measurement, offers the key advantages of broad clinical availability and noninvasiveness, therefore, enabling longitudinal assessment of liver disease severity within an individual patient.[14] In this regard, current guidelines recommend repeating LSM every 12 months in patients with compensated ACLD (cACLD),[11,15] and monitoring disease severity in specific etiologies (eg, autoimmune liver diseases).[15] With emerging etiologic therapies, noninvasive methods for monitoring disease regression are of increasing importance. Baveno VII proposed a "clinically significant decrease in LSM" at ≥20% associated with LSM <20 kPa or any decrease <10 kPa, however, indicated that this criterion still requires validation.[11] Thus, we aimed to assess the prognostic relevance of LSM dynamics for hepatic decompensation and liver-related death in patients with liver disease.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

It is currently unclear how dynamics in liver stiffness measurement (LSM) should be interpreted regarding prognosis in advanced chronic liver disease.

NEW FINDINGS

Dynamics in LSM are directly linked to increased and decreased risk of hepatic decompensation in compensated and decompensated advanced chronic liver disease. Updated LSM is not only superior to one-time assessment, but also to established blood-based scores of disease severity. We validated the Baveno VII-proposed rule for "clinically significant LSM decrease" at ≥20% associated with a final LSM <20 kPa, but also found that stratification by "any LSM decrease to <20 kPa" may be of superior value.

LIMITATIONS

This was a single-center retrospective study.

CLINICAL RESEARCH RELEVANCE

Repeated LSMs are useful for updated prognostication in advanced chronic liver disease.

Methods

Patients

All patients with (suspected) chronic parenchymal liver disease who underwent at least 2 LSMs between January 2007 and December 2020 at the Vienna General Hospital were evaluated for inclusion in this retrospective longitudinal cohort study and followed until December 2022. Longitudinal LSM dynamics were studied in patients with 2 or more LSMs that met reliability criteria and were performed at least 180 days apart from each other (ie, a timeframe that allows depicting relevant dynamics in LSM). Patients who either did not have a second reliable LSM or a second LSM 180 days or more apart were included in the group with a single LSM. The full list of exclusion criteria can be found in the Supplementary Material.

Objectives

The primary objective was to assess the association of longitudinal changes in LSM with clinical events of hepatic decompensation in non-ACLD patients and patients with cACLD. Secondary objectives included the comparison of LSM dynamics between different liver disease severity groups, the investigation of the association between LSM dynamics and liver-related mortality, validation of the Baveno VII cutoff for a clinically significant decrease in LSM, and exploratory analysis of the impact of dynamics of LSM on liver-related mortality in decompensated ACLD (dACLD). This study was conducted adhering to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines[16] (see Supplementary Materials).

Data Collection and Definitions

Demographic, clinical, and laboratory data were collected by means of manual retrieval of individual medical records, a systematic readout of laboratory data by the information technology department of the Medical University of Vienna, and a systematic readout of the national death registry (thus, capturing all deaths). Patients were characterized at the time of the first reliable LSM (baseline [BL]-LSM) as non-ACLD (BL-LSM <10 kPa), cACLD (BL-LSM ≥10 kPa, and no current or history of hepatic decompensation), and dACLD (BL-LSM ≥10 kPa with a history of hepatic decompensation).

Data on all consecutive LSM and corresponding laboratory values (eg, platelet count, albumin, Fibrosis-4 score, and Model for End-Stage Liver Disease [MELD] score), as well as data on

Abbreviations used in this paper: **ACLD, advanced chronic liver disease; AUROC, area under the receiver operating characteristics curve; BL, baseline; cACLD, compensated advanced chronic liver disease; dACLD, decompensated advanced chronic liver disease; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; LSM, liver stiffness measurement; MELD, Model for End-Stage Liver Disease.**

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the patient's clinical course, were collected, including first hepatic decompensation (ie, ascites, variceal bleeding, and overt hepatic encephalopathy) in non-ACLD/cACLD patients, hepatocellular carcinoma (HCC), transjugular intrahepatic portosystemic shunt, orthotopic liver transplantation, and (non–) liver-related death. Importantly, hepatic decompensation occurring after HCC diagnosis and HCC were not considered events of interest for prediction because HCC profoundly alters the clinical course independent of fibrosis or portal hypertension.

Liver Stiffness Measurement

All LSMs were performed by experienced operators at a high-volume center using vibration-controlled transient elastography (FibroScan; Echosens, Paris, France), adhering to the local standard operating procedure and established quality criteria.[17,18] Specifically, patients were lying in a dorsal position with the right arm in maximal abduction, and measurements were performed in the right lobe of the liver through intercostal spaces. Patients were instructed to fast for at least 3 hours. The M and XL probes were chosen based on the probe selection tool. We identified patients who underwent LSM as a direct readout from the FibroScan machines in use at our clinic during the study period. LSM data sets that could not be linked to hospital records or with fewer than 10 successful measurements, or if we could not confidently verify that the patient was in a fasted state at the time of the procedure, were excluded from further analyses. In addition, the reliability of LSM was defined by previously established criteria (interquartile range [IQR] or median <0.3 or <7.1 kPa).[17,18] Importantly, only reliable LSMs were considered for assessment of LSM dynamics over time. The same reliability criteria were applied to patients with dACLD (ie, performed in the absence of ascites).

Statistical Analyses

We defined the difference between the first LSM during follow-up after 180 days or more (second LSM) and the BL-LSM as "ΔLSM-First." To incorporate all available LSMs (ie, using all available LSMs within the study period), we used joint modeling, which is an approach that joins a linear mixed-effects model (modeling LSM dynamics over time) and a survival model linking dynamics with the time-to-event outcome of interest.[19] A detailed description of the statistical approach can be found in Supplementary Figure 1 and the Supplementary Materials.

Ethical Statement

The study was approved by the Ethics Committee of the Medical University of Vienna (no. 1531/2022 and no. 1029/2023). The need for informed consent was waived by the Institutional Ethics Committee.

Results

Patient Characteristics

A total of 2508 patients were included to study LSM dynamics (non-ACLD: n = 1647 [65.7%], cACLD: n = 757 [30.2%], dACLD: n = 104 [4.1%]) and 4940 patients were included as a comparator group with only a single LSM (non-ACLD: n = 3218 [65.1%], cACLD: n = 1206 [24.6%],

Table 1. Patient Characteristics Across Non-ACLD, cACLD, and dACLD Patients With Repeated Liver Stiffness Measurements

Characteristic	Non-ACLD (n = 1647)	cACLD (n = 757)	dACLD (n = 104)	*P* value
Age, *y*, mean ± SD	46.1 ± 13.7	52.0 ± 12.7	54.1 ± 10.5	<.001
Female sex, n (%)	738 (44.8)	284 (37.5)	39 (37.5)	.002
Body mass index, kg/m^2, mean ± SD	25.6 ± 5.2	27.2 ± 5.7	25.3 ± 4.5	<.001
Diabetes, n (%)	127 (7.7)	178 (23.5)	28 (26.9)	<.001
Etiology, n (%)				<.001
Autoimmune hepatitis /cholestatic	219 (13.3)	107 (14.1)	4 (3.8)	
ALD	19 (1.2)	54 (7.1)	56 (53.8)	
Cryptogenic	30 (1.8)	4 (0.5)	1 (1.0)	
Hepatitis B virus	188 (11.4)	48 (6.3)	5 (4.8)	
HCV	816 (49.5)	384 (50.7)	30 (28.8)	
HCV+ALD	10 (0.6)	26 (3.4)	6 (5.8)	
Nonalcoholic fatty liver disease	299 (18.2)	110 (14.5)	2 (1.9)	
Others	65 (3.9)	24 (3.2)	0 (0)	
Platelet count, *g/L*, median (IQR)	223 (184–266)	169 (119–230)	102 (74–147)	<.001
Albumin, *g/dL*, mean ± SD	44.2 ± 4.7	42.3 ± 4.7	35.4 ± 5.6	<.001
Fibrosis-4 score, median (IQR)	1.10 (0.76–1.60)	2.26 (1.34–3.62)	4.91 (3.17–7.06)	<.001
MELD, *points*, median (IQR)	7 (6–8)	7 (6–9)	11 (9–14)	<.001
BL-LSM, *kPa*, median (IQR)	6.0 (4.8–7.4)	16.3 (11.9–23.9)	42.2 (23.1–75.0)	<.001
BL-LSM ≥25 kPa, n (%)	—	175 (23.1)	76 (73.1)	—

ALD, alcoholic liver disease; HCV, hepatitis C virus.

Table 2. Dynamics in Liver Stiffness Measurements in Patients With Different Liver Disease Severity (Non-ACLD, cACLD, and dACLD)

Variable	Non-ACLD (n = 1647)	cACLD (n = 757)	dACLD (n = 104)	*P* value
No. of reliable LSMs, median (IQR)	3 (2 to 4)	3 (2 to 5)	3 (2 to 4)	<.001
ΔLSM-First[a]				
Time to second LSM, *mo*, median (IQR)	18.1 (11.4 to 31.4)	16.6 (10.1 to 31.2)	18.5 (11.2 to 36.7)	.062
Absolute difference, *kP*, median (IQR)	0 (–1.3 to 1.3)	–4.2 (–7.5 to 0.6)	–5.9 (–25.7 to 4.3)	<.001
Relative difference, %, median (IQR)	0 (–21 to 23)	–26 (–46 to 5)	–22 (–53 to 16)	<.001
Relative difference per year, %, median (IQR)	0 (–12 to 14)	–16 (–36 to 2)	–9 (–32 to 9)	<.001
≥20% decrease, n (%)	431 (26.2)	423 (55.9)	53 (51.0)	<.001
Any increase, n (%)	838 (50.9)	217 (28.7)	37 (35.6)	<.001
LSM maximum, n (%)				
≥10 kPa	274 (16.6)	—	—	—
≥25 kPa	24 (1.5)	259 (34.2)	88 (84.6)	<.001

[a]ΔLSM-First indicates differences in LSM between the second LSM and BL-LSM.

dACLD: n = 516 [10.4%]) after applying exclusion criteria (Supplementary Figure 2)—the single-LSM group is described further in the Supplementary Material. Viral hepatitis C virus (49.5% and 50.7%), nonalcoholic fatty liver disease (18.2% and 14.5%), and autoimmune liver disease (13.3% and 14.1%) were the most prevalent etiologies among non-ACLD and cACLD patients, and patients with dACLD had a high proportion of alcohol-related liver disease (53.8%, Table 1). As per the definition, parameters reflecting liver disease severity significantly differed across ACLD groups.

Liver Stiffness Measurement Dynamics

We evaluated a total of 9551 individual LSMs from 2508 patients. Of these, 8561 (89.6%) were deemed reliable and thus were incorporated into further analyses on LSM dynamics. Each patient underwent a median of 3 (IQR, 2–4) LSMs. Table 2 shows the dynamics of LSM for non-ACLD, cACLD, and dACLD patients. Importantly, the median time to second LSM (ΔLSM-First) clustered around 17 months. Although median LSM remained unchanged in the non-ACLD group (median relative ΔLSM-First, 0; IQR, –21% to 23%), median LSM improved in the cACLD group (–26%; IQR, –46% to 5%) and dACLD group (–22%; IQR, –53% to 16%). A decrease of ≥20% occurred in 26.2% of non-ACLD, 55.9% of cACLD, and 51.0% of dACLD, while any increase occurred in 50.9%, 28.7%, and 35.6% of non-ACLD, cACLD, and dACLD patients, respectively. Patient characteristics between those with any increase and no increase are compared in Supplementary Table 1. Interestingly, patients with cACLD who subsequently improved had less severe liver disease at baseline regardless of etiology, and BL-LSM was comparable.

Two hundred and seventy-four patients from the non-ACLD cohort (16.6%) had any LSM ≥10 kPa, indicating progressive disease to cACLD (cACLD progressors), and only a minority of non-ACLD progressed to ≥25 kPa (n = 24

Table 3. Comparison of Clinical Outcomes Across ACLD Groups

Variable	Non-ACLD (n = 1647)	cACLD (n = 757)	dACLD (n = 104)	*P* value
Follow-up, *mo*, median (95% CI)	69.6 (66.9–72.4)	76.0 (71.3–80.0)	72.0 (56.2–81.1)	.110
Decompensation, n (%)	7 (0.4)	83 (10.9)	—	<.001
Incidence[a]	0.07	1.9	—	—
Hepatocellular carcinoma, n (%)	1 (<0.01)	40 (5.3)	11 (10.6)	<.001
Incidence[a]	0.1	0.9	2.0	—
TIPS, n (%)	1 (<0.01)	9 (1.2)	6 (5.8)	<.001
OLT, n (%)	2 (0.1)	19 (2.5)	8 (7.7)	<.001
Death,[b] n (%)	82 (5.0)	98 (12.9)	30 (28.8)	<.001
Liver-related	4 (5)	54 (55)	22 (73)	<.001
Non–liver-related	78 (95)	44 (45)	8 (27)	—

OLT, orthotopic liver transplantation; TIPS, transjugular intrahepatic portosystemic shunt.
[a]Per 100 patient-years.
[b]1 non-ACLD patient, 6 cACLD patients, and 2 dACLD patients died after OLT.

Table 4. Joint Model of LSM for Hepatic Decompensation (n = 720 Patients, 2673 Individual LSM, 62 Events of Hepatic Decompensation) and Liver-Related Mortality (n = 757 Patients, 2798 Individual LSMs, 48 Liver-Related Deaths) in Patients With cACLD

Outcome	Covariable	HR (95% CI)			*P* value	Time-dependent AUROC[b]
		20% Increase[a]	50% Increase[a]	100% Increase (doubling)[a]		
Hepatic decompensation						
	LSM dynamics	1.58 (1.41–1.79)	2.75 (2.13–3.66)	5.65 (3.66–9.17)	<.001	0.933
	LSM dynamics, adjusted for age, PLT, MELD, and albumin	1.54 (1.38–1.76)	2.63 (2.06–3.49)	5.21 (3.44–8.49)	<.001	—
	PLT dynamics	0.75 (0.69–0.82)	0.54 (0.44–0.65)	0.34 (0.25–0.48)	<.001	0.849
	Albumin dynamics	0.14 (0.09–0.22)	0.01 (0.01–0.03)	0 (0–0)	<.001	0.566
	Fibrosis-4 dynamics	1.36 (1.26–1.47)	1.98 (1.68–2.36)	3.20 (2.41–4.33)	<.001	0.873
	MELD dynamics	1.66 (1.37–2.00)	3.09 (2.01–4.69)	6.88 (3.29–14.03)	<.001	0.835
Liver–related death						
	LSM dynamics	1.45 (1.28–1.68)	2.28 (1.72–3.17)	4.08 (2.54–7.20)	<.001	0.886
	LSM dynamics, adjusted for age, PLT, MELD, and albumin	1.47 (1.30–1.71)	2.37 (1.79–3.28)	4.37 (2.71–7.61)	<.001	—

NOTE. Joint models for other laboratory-based biomarkers (PLT, albumin, Fibrosis-4 score, and MELD) at the time of LSM are provided.
PLT, platelet count.
[a]LSM was logarithmically transformed to obtain a normal distribution for all analyses allowing to interpret HR associated with percent increase in LSM (eg, 100% increase: multiplication of coefficient by the factor log 2 ≈ 0.693), 20% increase: multiplication of coefficient by the factor log 1.2) ≈ 0.182).
[b]Time-dependent AUROC curve of respective joint models were derived based on dynamics (ie, trajectories) of LSM or the laboratory-based biomarkers within 24 months to predict hepatic decompensation in the subsequent 12 months.

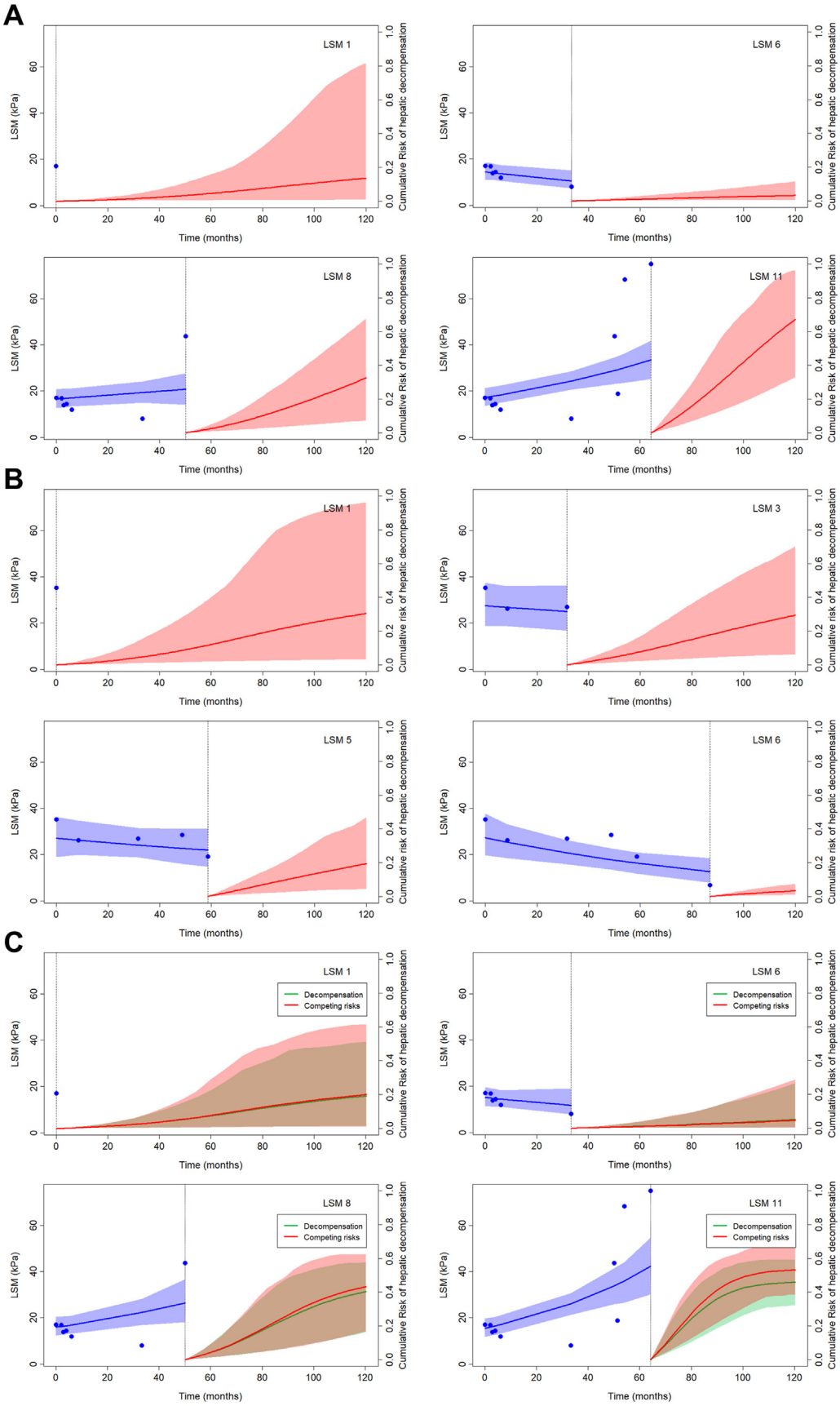

Figure 1. Estimated individual risk of hepatic decompensation updated by consecutive LSM: Example patient (*A*) demonstrates the effects of an increase in LSM on predicted risk of hepatic decompensation. Example patient (*B*) demonstrates that an initial decrease and subsequent stabilization leads to a low estimated risk with high certainty. *Panel C* shows an estimate for hepatic decompensation in the presence of competing risks (HCC or death) for example patient (*A*).

[1.5%]). These patients were more often male, older, had a higher BMI, higher prevalence of diabetes, and more severe liver disease at baseline (Supplementary Table 2). Two hundred and fifty-nine cACLD patients (34.2%) progressed to ≥25 kPa at any time during follow-up.

Clinical Outcomes

During a median follow-up of 71.2 months (95% CI, 69.1–73.4 months) (Supplementary Figure 3), 7 non-ACLD patients (0.4%, cumulative incidence per 100 patient-years = 0.07) and 83 patients with cACLD (10.9%, 1.9/100 patient-years) developed any first hepatic decompensation (Table 3). Furthermore, 40 patients with cACLD (5.3%) and 11 patients with dACLD (10.6%) developed HCC and 19 (2.5%) and 8 (7.7%) underwent orthotopic liver transplantation, respectively. Eighty-two non-ACLD patients (5.0%) died, of which only 3 deaths (0.2%) were liver-related. In contrast, among 98 (12.9%) and 30 (28.8%) deaths in patients with cACLD and dACLD, respectively; 54 (7.1%) and 22 (21.2%) were considered to be liver-related.

Because both hepatic decompensation and liver-related death were extremely rare in non-ACLD patients, we did not perform further outcome analyses in these patients. Importantly, overall survival was comparable in cACLD progressors and patients that remained <10 kPa (Supplementary Figure 4). A detailed description of the events in the non-ACLD group can be found in the Supplementary Material.

Joint Modeling of Liver Stiffness Measurements Dynamics and Hepatic Decompensation in Compensated Advanced Chronic Liver Disease

To link the dynamics in LSM (linear mixed effects model) with the risk of subsequent hepatic decompensation (survival model), we fitted univariable and multivariable joint models using LSM dynamics in the overall cohort (model A), considering HCC and death as competing risks (model B), adjusting for etiologic cure as a time-dependent covariable (model C) and adjusting both for competing risks and etiologic cure (model D, Table 4 and Supplementary Table 3).

Following this approach, a 20% increase in LSM, at any time, was associated with an approximately 50% increased risk of developing hepatic decompensation (HR, 1.58; 95% CI, 1.41–1.79; $P < .001$). When adjusting for age and disease severity (ie, platelet count, MELD, and albumin at baseline), the association was nearly identical. When adjusting for competing risks (HCC or death, model B), the effect size of LSM dynamics on the prediction of the first hepatic decompensation was even more pronounced (HR, 2.24; 95% CI, 1.50–3.11; $P < .001$).

After including etiologic cure as a time-dependent covariable (model C), LSM dynamics in LSM showed a significant association with hepatic decompensation before etiologic cure (HR, 1.57; 95% CI, 1.39–1.82, which was even stronger after etiologic cure (HR, 1.94; 95% CI, 1.68–2.32; $P < .001$).

Finally, we studied a combined model with etiologic cure as a time-dependent covariable, and HCC and death as competing events (model D). Here, a striking increase in the effect size of LSM dynamics was evident (HR for 20% increase before etiological cure: 10.70; 95% CI, 7.11–32.75; $P < .001$; after etiologic cure: 15.73; 95% CI, 8.54–33.47; $P < .001$), corresponding to an approximately 10 times and approximately 15 times increased risk of hepatic decompensation before and after etiologic cure when considering that competing events (HCC or death) may precede the occurrence of hepatic decompensation.

Importantly, the predictive value of LSM dynamics for liver-related death reached comparable effect sizes (Table 4 and Supplementary Table 4). At the same time, using alternative parameterizations of LSM (such as the area under the LSM curve or the slope of the LSM curve within the last 12 months), did not enhance the accuracy of the model. Subsequently, these were not explored further due to their limited clinical applicability and complex interpretation (data not shown). Also, applying a polynomial fit to account for nonlinearity did not improve the models (data not shown).

Predictions from liver stiffness measurements dynamics. The predictions derived from the model incorporating LSM dynamics (models A and B) can be found in Figure 1, depicting the individual course of LSM in 2 examples of patients with cACLD with either progressive or regressive disease demonstrating updated risk estimations of hepatic decompensation with consecutive LSM: Although a decrease in LSM is associated with a subsequent lower risk (ie, flattened cumulative incidence curve), an increase is conversely associated with a higher risk. To demonstrate the differences between models A and B, the same patient is shown in *panel A* (derived from model A) and in *panel C* (derived from model B).

Discriminatory ability vs laboratory values and single time-point liver stiffness measurement. The discriminatory ability of joint models (model A) can be indicated by the AUROC incorporating dynamics in the first 24 months to predict hepatic decompensation within the subsequent 12 months. Here, LSM dynamics achieved an excellent prediction of hepatic decompensation with an AUROC of 0.933. At the same time, the AUROC for decompensation within the next 12 months was 0.846 (95% CI, 0.759–0.937) using absolute LSM-BL and 0.880 (95% CI, 0.826–0.934) for second LSM, indicating that the more recent LSM is more accurate. Both single-LSM models, however, were inferior to the model incorporating LSM dynamics.

In parallel to dynamics in LSM, we studied the dynamics of established surrogates of liver disease severity (ie, platelet count, albumin, Fibrosis-4 score, and MELD). As shown in Table 4, their dynamics were also linked with a change in the risk for subsequent hepatic decompensation. However, they displayed a numerically lower AUROC (ranging between 0.566 and 0.873) compared with LSM for predicting hepatic decompensation within the following 12 months.

Validation of the Baveno VII Cutoff for a Clinically Significant Decrease in Liver Stiffness Measurement

When applying the proposed cutoff for a clinically significant decrease in LSM (ie, decrease ≥20% to <20 kPa, or any

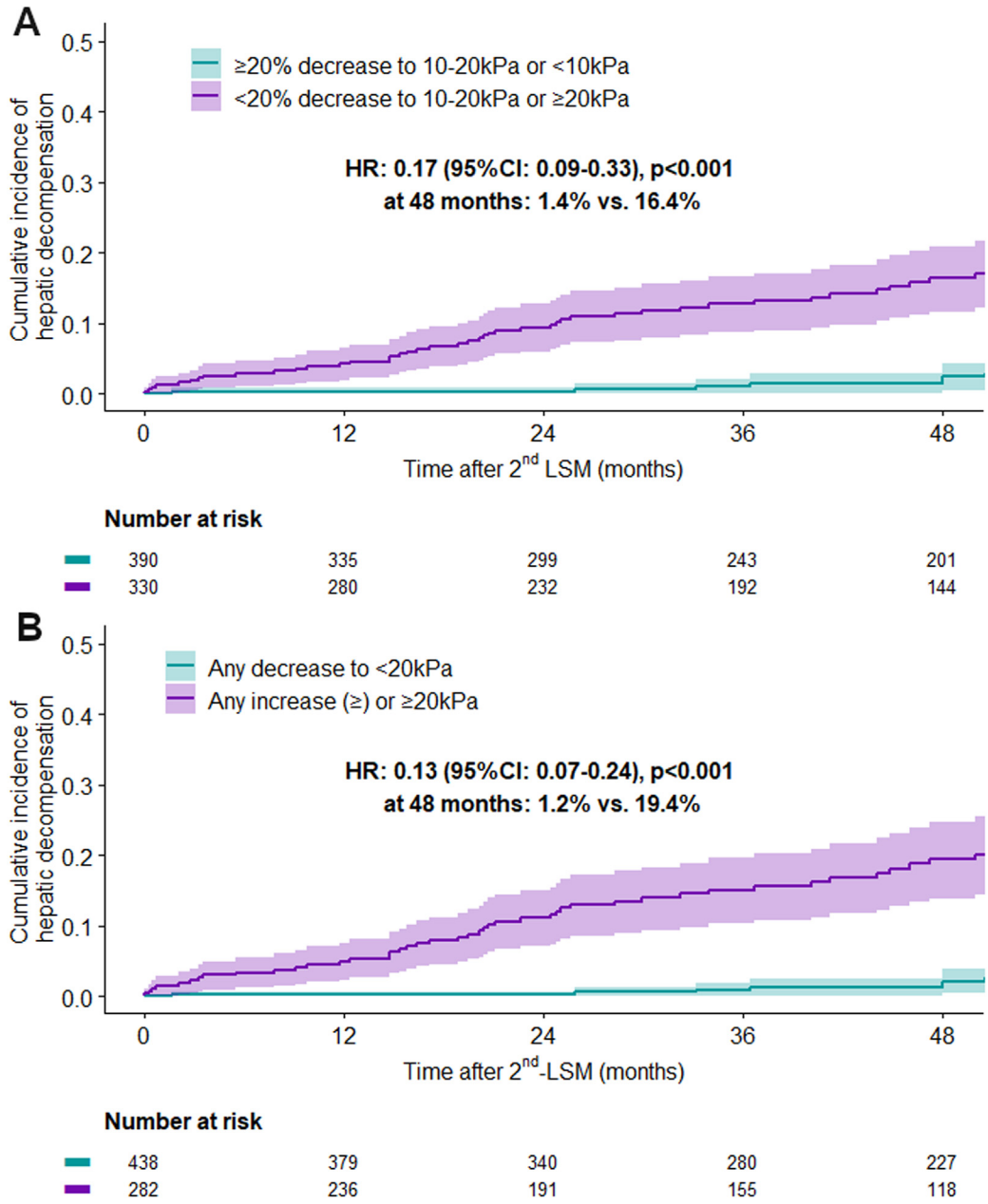

Figure 2. Comparison of the cumulative incidence of hepatic decompensation in patients with cACLD (*A*) without vs with a relative decrease of ≥20% associated with LSM <20 kPa, or any decrease to an LSM <10 kPa (ie, the Baveno VII criteria for a clinically significant decrease in LSM) and (*B*) patients with any decrease to an LSM <20 kPa. Relative differences were calculated between the second LSM and the BL-LSM (ΔLSM-First). Follow-up started after the second LSM.

decrease to <10 kPa, calculated from second LSM [ΔLSM-First]) in our cACLD cohort, patients with a significantly lower risk of hepatic decompensation could be identified (HR, 0.17; 95% CI, 0.09–0.33; $P < .001$, Figure 2*A*). However, applying other cutoffs for the relative decrease in LSM (eg, any decrease, ≥10%, and ≥30%) resulted in similar discriminatory abilities, as assessed by Harrell's C-indices (Supplementary Table 5). Importantly, stratifying patients by "any decrease to <20 kPa" achieved the highest discrimination (Harrell's C-index: 0.747 [SE 0.022]) that was superior to Baveno VII rules identifying a comparatively small, at-risk population (39.2%) with a high risk of subsequent hepatic decompensation (cumulative incidence at 48 months: 19.4% vs 1.2%; $P < .001$, Figure 2*B*).

Liver-Related Mortality in Decompensated Advanced Chronic Liver Disease

Finally, we investigated whether dynamics in LSM are associated with liver-related death (n = 21) in patients with dACLD (n = 104 with 341 individual LSM, Supplementary Table 6). Interestingly, LSM dynamics were clearly linked

to liver-related death (HR for 20% increase: 1.62; 95% CI, 1.24–2.17; $P < .001$) in patients with dACLD, indicating that increasing and decreasing LSM is linked to higher and lower risk of subsequent liver-related death with an excellent AUROC of 0.915 when using predictions from 24 months for subsequent 12 months).

Subgroup Analysis of Patients With Hepatitis C Virus

See results in the Supplementary Material.

Discussion

In this study, we have provided comprehensive evidence for the important clinical value of longitudinally monitoring LSM in patients with ACLD, as it refines risk prediction. Studying a large cohort of 2508 patients with liver disease (including 757 patients with cACLD), considering 8561 reliable LSM, and following patients for a median of more than 70 months, this represents the largest cohort study on LSM dynamics so far.

Applying a joint modeling approach as the best-suited statistical method to link longitudinally measured biomarkers to clinical outcomes, we could show that dynamics in LSM are highly indicative of prognosis in patients with cACLD, but might also confer important information in dACLD (see Supplementary Material). In brief, the following interpretations should be considered:

1. Dynamics in LSM provide important information on clinical outcomes in cACLD: a 20% increase in LSM—at any time point at least 180 days after the BL-LSM—is associated with an approximately 50% increased risk of hepatic decompensation and liver-related death. Conversely, regression of LSM by 20% also indicates an approximately 50% reduced risk of hepatic decompensation or liver-related death. This is relevant as it allows individualized interpretation of LSM dynamics. However, the absolute risk of the patient must still be considered: Although the risk of an individual patient progressing from 10 kPa to 12 kPa (20%) is increasing by approximately 50%, the overall risk of another patient increasing from 50 kPa to 60 kPa (20%) is increasing similarly, yet undoubtedly higher.

2. The association of LSM dynamics with clinical outcomes remains robust after adjusting for laboratory-based biomarkers of liver disease severity. Here, LSM dynamics provide strong, robust estimates when correcting for established prognostic factors, such as platelet count, MELD, and albumin across all models. This highlights the crucial clinical relevance of dynamics in LSM. They offer continually updated information on the risk of forthcoming hepatic decompensation, independent of liver function (as indicated by MELD or albumin) or hypersplenism (represented by platelet count). We believe that individual changes in LSM, more effectively than other biomarkers, signify increased intrahepatic vascular resistance[20]—a primary factor of portal hypertension in cACLD. Consequently, they robustly forecast decompensation events related to portal hypertension.

3. Repeated LSM hold higher prognostic accuracy in forecasting hepatic decompensation in contrast to a single LSM: By integrating all accessible LSM, we achieved exceptional accuracy in predicting hepatic decompensation within the following 12 months (AUROC = 0.933). Although this AUROC cannot be statistically compared with single time-point LSM (BL-LSM: 0.836; second LSM: 0.880), it becomes evident that updated information on LSM should always be obtained in cACLD, as it provides the most accurate prediction of hepatic decompensation within the forthcoming 12 months.

4. The association of LSM dynamics with hepatic decompensation is even stronger when adjusting for competing risks: Given that other events (such as the occurrence of HCC or non–liver-related death) alter the clinical course and management, the relevance of LSM dynamics for hepatic decompensation was even higher.

5. After etiologic cure, LSM dynamics are even more important for hepatic decompensation or liver-related death: This is in line with experience from clinical practice in patients with hepatitis C virus in whom a decrease in LSM (eg, to <12 kPa with normal platelet count) indicates protection from liver-related adverse outcomes.[21] At the same time, if patients do not decrease in LSM after the etiologic cure, this suggests a "point-of-no-return" at which etiologic cure does not confer protection from hepatic decompensation. However, the numerically stronger association seems to be driven mostly by the profoundly decreased risk of hepatic decompensation in patients that regress to low LSM (eg, to <10 kPa) after etiologic cure.

6. Dynamics in LSM seem to be more important in cACLD than changes in other established prognostic markers, such as Fibrosis-4 score, albumin, or MELD: We found that LSM dynamics have numerically higher prognostic accuracy than the dynamics of blood-based biomarkers. Especially at the earlier stage of ACLD (ie, cACLD) in which prognostication is key, LSM seems to be particularly valuable, probably due to the limited association of MELD and albumin with portal hypertension—the main driver of first hepatic decompensation[22]—with deterioration in MELD and albumin being mostly observed only at later stages (ie, dACLD).[12] However, this analysis and conclusion are limited by methodology (ie, the current technical inability to calculate 95% CI or directly compare derived AUROCs).

7. Baveno VII criteria for a clinically significant decrease in LSM are capable of identifying patients at low risk.

However, a simplified rule attributing a low risk to patients who decrease in LSM to <20 kPa might be of superior accuracy: As several binary cutoffs for LSM (≥10%, ≥20%, and ≥30% decrease) seem equally accurate in stratifying decompensation risk in cACLD, the universal interpretation of a decrease of ≥20% as "clinically relevant" might not be fully justified (see Discussion). Although the results of our joint models generally support the statement "the larger the decrease, the better the prognosis," a cutoff of ≥20% might be arbitrary. In contrast to pathophysiological principles, it seems intuitive to treat any patient with LSM ≥20 kPa, or in whom the LSM remains steady or even increases, as a patient at risk, as this indicates that the patient's liver disease remains active or insufficiently controlled. At the same time, the high accuracy of our joint model highlights the importance of incorporating all LSMs into risk stratification rather than using less flexible "high- vs low-risk criteria" assessed at a single time point.

8. In non-ACLD patients, monitoring LSM seems important to detect progression of disease (eg, to cACLD): Although the absolute risk of hepatic decompensation is very low in these patients, hepatic decompensation does occur in the follow-up of (our) non-ACLD patients (see Supplementary Material), which highlight the opportunities that noninvasive and readily available LSM offers, if repeated on a regular basis.

9. In patients with dACLD, reliable LSM dynamics predict liver-related death: Because an increasing number of etiologic therapies are available, and recompensation is possible in selected patients,[23–25] dynamics in LSM could offer an opportunity to monitor disease progression and regression, even at this late stage of liver disease (discussed further in the Supplementary Material). Importantly, because ascites can impact the results of LSM, adherence to applicability and reliability criteria for LSM are of particular relevance in patients with dACLD.

Although clinical practice guidelines currently encourage LSM at yearly intervals,[11,15] robust evidence to support this recommendation is lacking, especially regarding the value of repeated LSM for the prediction of clinical events. This might be due to the small number of studies on this topic, being mostly etiology-specific, of limited sample size, and lacking a standard on how to assess dynamics in LSM,[26–30] in turn, complicating the interpretation of individual LSM dynamics in clinical practice. Here, easily applicable results of widely available tests derived from multietiologic cohorts harbor the potential of broad utility, as they can be applied without comprehensive evaluation or knowledge of a patient's disease etiology. Therefore, we deliberately focused on a large cACLD cohort of diverse liver disease etiologies to investigate the value of LSM in clinical practice, as limiting cohorts to selected etiologies with a small sample size would drastically decrease the precision and generalizability of the study results and the derived recommendations. In this regard, the recommendation for applying the "rule-of-5" by Baveno VII in all liver disease etiologies underscores this principle of easy and broad use in clinical practice, which, for instance, contrasts previously applied diagnostic criteria for cirrhosis with a plethora of varying cutoffs throughout different etiologies, thereby limiting clinical applicability.

Finally, we could validate the Baveno VII criteria for a clinically significant decrease in LSM (≥20% decrease associated with 10–20 kPa or to absolute LSM <10 kPa), but propose a, in our opinion, more intuitive approach to treat any patient as high-risk/at risk that remains ≥20 kPa or fails to decrease in LSM. Although a previous study showed that categorization into >20% increase, +20% to −20% (ie, stable LSM), and >20% decrease in LSM identified patients with a distinct prognosis,[30] differences in patient characteristics, but also methodological aspects call for further studies to validate theses cutoffs (see Supplementary Materials).

This study has limitations: First, we studied a multietiologic cohort. Although etiology-specific studies might identify distinct, liver disease–specific associations of LSM-dynamics and respective risks (ie, HR) for clinical events, the link between increasing or decreasing LSM and associated increasing or decreasing risk of liver-related events will undoubtedly remain valid. However, as discussed above, etiology-independent data also have important advantages. Second, due to the retrospective design, a selection toward adherent patients is inherited. However, we clearly want to emphasize that results from this study can, in real-world clinical practice, by nature, never be applied to incompliant patients or those who die before a follow-up visit (both cACLD and dACLD). Third, individual LSM results, and thus, LSM dynamics over time, might have been influenced by active alcohol consumption or hepatic necroinflammation at the specific time of LSM. However, increasing LSM by hepatic necroinflammation may even hold prognostic value. Fourth, laboratory values were collected at the time of LSM, and it is unclear whether the inclusion of all longitudinally available laboratory values increases their prognostic accuracy. Fifth, the current study can only insufficiently portray the value of LSM for risk prediction in non-ACLD patients, as the incidence of hepatic decompensation in this group was very low, and progression to cACLD could not be used as the outcome (dependent variable), given that cACLD is defined by LSM (independent variable in the current study). Lastly, the current state of the methodology does neither allow for direct statistical comparison between AUROCs of different joint models or the calculation of 95% CI, preventing direct statistical comparison.

In conclusion, we provide evidence for the prognostic relevance of LSM changes in a large cohort of patients with chronic liver disease. The longitudinal dynamics in LSM over time enable an updated and more accurate risk prediction for hepatic decompensation and liver-related death. Specifically, a 20% increase or decrease in patients with cACLD indicates an approximately 50% increased or decreased risk of hepatic decompensation and liver-related death. Finally,

the threshold for a clinically meaningful LSM decrease by Baveno VII identified patients with cACLD with a substantially lower risk of hepatic decompensation—still, our simplified approach stratifying according to "any decrease to LSM <20 kPa" seems to allow for improved identification of a population at remaining risk for liver-related complications. These results strongly encourage the broad use of repeated LSMs for the clinical management of patients with liver disease.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2023.06.030.

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Data Availability
Data are available from the authors upon reasonable request.