11 Liver Elastography for Prognostication and Monitoring Patients With Compensated Advanced Chronic Liver Disease

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Introduction

Patients with chronic liver disease (CLD) worry about their health: Will their condition deteriorate to symptomatic complaints, decompensation, and life-threatening disease? Will they ever experience improvement? [1] A diagnosis of compensated advanced chronic liver disease (cACLD) worries patients due to the risk of developing symptoms of decompensation that affects daily living, leads to frequent hospital visits, the need for pharmacological therapy, invasive interventions, and worsening in the mental and physical aspects of health-related quality of life. These aspects of chronic liver disease hold more clinical relevance than the diagnosis itself [2].

Baveno VI established the use of liver stiffness measurements (LSM) by transient elastography (TE) to stratify patients with CLD according to their probability of having cACLD, with 10 kPa as the rule out cutoff, and 15 kPa for ruling in cACLD. Baveno VII marks a shift from diagnosis to prognosis, thereby focusing directly on the quality and length of patients' lives. The change from a diagnostic to a prognostic focus is possible due to evidence from meta-analyses and high-quality prospective cohorts, showing the prognostic accuracy of liver stiffness in patients with CLD [3–12]. Most evidence concerns the major liver disease etiologies (HVC, HBV, NAFLD, ALD), but there is also evidence of a comparable prognostic accuracy of TE in more rare CLD etiologies such as primary biliary cholangitis and primary sclerosing cholangitis [13, 14].

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Other elastography techniques than TE (point and two-dimensional shear-wave elastography, pSWE, 2D-SWE) also possess prognostic ability, but the generalizability of those studies is limited by heterogeneity in elastography techniques, cutoffs, and study populations [7, 15, 16]. Further, the pSWE and 2D-SWE elastography systems offered by several manufacturers are not comparable due to differences in both software and hardware [17]. Similarly, it is important to stress that LSM values by TE are not comparable to pSWE or 2D-SWE values [18]. It is therefore not currently possible to make recommendations regarding prognostication with elastography equipment other than transient elastography.

Liver Stiffness by Transient Elastography as a Prognostic Tool

Transient elastography provides a continuous measure of liver stiffness, with increasing liver stiffness indicating higher risk of decompensation and mortality. The dose–response relationship between liver stiffness and outcomes is however not linear, as indicated by two meta-analyses [3, 4]. Both studies find that the relative risk of liver-related events and all-cause mortality increases substantially in patients with LSM above 10 kPa, whereas the slope wanes off after 25 kPa, marking the point where other factors become more important than liver stiffness for progression of portal hypertension and liver dysfunction.

The generalizability of the available meta-analyses is limited by the fact that they were generated from a majority of studies on chronic viral hepatitis: In the most recent, 46% of studies investigated HCV, 32% HBV, while 22% of publications studied a mixed population [3]. Further, not all included patients have cACLD; many have LSM < 10 kPa, others are decompensated at the time of inclusion.

Fortunately, several recent, high-quality single-etiology studies in NAFLD, ALD, or HCV confirm the good prognostic accuracy of baseline LSM by TE to predict decompensation and mortality, all-cause or liver-related [6–9, 11, 12, 19–23]. The cutoffs reported in the various studies converge on roughly four particular points of LSM: 10, 15, 20, and 25 kPa (see Table 11.1). This leads to the "*rule of five,*" as an easy-to-use rule of thumb for the assessment of the relative risk of decompensation or liver-related mortality in a patient with chronic liver disease. The risk of decompensation within 2–5 years is negligible if LSM is below 10 kPa, after which the relative risk increases in steps of 5 kPa.

It is only possible to make generalizations across liver disease etiologies regarding the relative risks of decompensation and death. This is due to large differences in the incidence of decompensation and death between individual disease etiologies. For example, reports in alcohol-related liver disease indicate an 8–10-times higher rate of liver-related mortality than in NAFLD [19, 24].

In CLD patients with decompensation, there are more accurate prognostic scores than LSM, typically the model for end-stage liver disease [25]. Liver stiffness therefore has no current role in patients with decompensated CLD, except for addressing decompensation (see Chap. 47). While some studies indicate a benefit of combining MELD and LSM for prediction of further decompensation, this concept needs to be validated [15, 26].

Table 11.1 Table of evidence for individual studies assessing the prognostic ability of liver stiffness measurements with transient elastography to predict risk of liver-related events, decompensation, and/or mortality

Study	Etiology	N	Events/endpoint	Follow-up	Prognostic intervals			
					<10 kPa	10–15 kPa	15–20 kPa	≥20 kPa
Rasmussen 2021[a] [7]	ALD	462	Total events: 87 LRE	Median 4.1 years (IQR 31–70 months)	Cumulative incidence: 0.2% PY 3 years: 1.1% Event rate: 11/304 (4%)	Cumulative incidence: 2.0% PY 3 years: 10.2% Event rate: 9/42 (21%)	Cumulative incidence: 8.0% PY. 3 years: 24% Event rate: 5/15 (33%)	Cumulative incidence: 10% PY. 3 years 36% Event rate: 48/81 (59%)
Genesca 2021[a]	NAFLD	2638	Total events: 45 LRE	Median 2.2 years (IQR 1.8–2.9)	Cumulative incidence: 0.04% PY. 3 years: 0.11% Event rate: 2/1820 (0.1%)	Cumulative incidence: 0.3% PY. 3 years: 1.03% Event rate: 4/479 (0.8%)	Cumulative incidence (≥15 kPa): 4.2% PY. 3 years: 11.16% Event rate: 8/136 (5.9%)	Event rate: 31/203 (15.3%)
Decraecker 2021 [19]	NAFLD (n = 1698), ALD (n = 1667)	3365	Total events: 563 deaths (510 ALD, 53 NAFLD)	Median 4.5 years (IQR 2.5–7.2)	Cumulative incidence[b] at 3 years: 3%	Cumulative incidence[b] at 3 years: 5%	Cumulative incidence[b] at 3 years: 15%	Cumulative incidence[b] at 3 years: 28%

Study	Etiology	*N*	Events/endpoint	Follow-up	Other cutoffs		
Liu 2021 [12]	cACLD	661	Decompensation, total events not stated	Median 3.4 years (IQR 2.3–5.1)	10–19.9 kPa sHR 9.8 if platelet count <150 × 10^9/L	20–25 kPa sHR 16.8	≥25 kPa sHR 38.0
Mendoza 2021 [11]	NAFLD with cACLD	233	Total events: 14 LRE	Median 1.4 years	10–21 kPa Events 3/147 (2%)	>21 kPa Events 11/86 (13%)	

(continued)

Table 11.1 (continued)

Study	Etiology	*N*	Events/endpoint	Follow-up	Other cutoffs	
Petta 2021 [8]	NAFLD with cACLD	1039	Total events: 71 decompensations	Median 2.9 years (IQR 1.6–5.3)	10–20.9 kPa Event rate: 2% decompensations	≥21 kPa Event rate: 14% decompensations. Cumulative incidence at
Poynard 2014 [23]	HCV	3031	Total events: 104 deaths	Median 5.2 years	<9.5 kPa 39/2344 (1.7%) event rate	9.5–20 kPa 29/486 (6.0%) event rate ≥20 kPa 36/201 (18%) event rate
Robic 2011 [22]	Mixed (65% cirrhosis, 38% ALD)	100	Total events: 18 decompensations	Mean 1.3 years ±0.8	<21.1 kPa: Event rate: 0/57 (0%)	≥21.1 kPa Event rate: 18/43 (53%)
Shili-Masmoudi 2020 [9]	NAFLD	2245	Total events: 55 deaths, 3 LTX, 21 LRE (decomp. And HCC)	Median 2.3 years (IQR 25–38 months)	≤12 kPa Cumulative incidences: Death at 1-3-5 years: 0.5%-2.9%-3.4% LRE at 1-3-5 years: 0.2%-0.2%-0.3%	>12 kPa Cumulative incidences: Death at 1-3-5 years: 2.0%-9.1%-13.8% LRE at 1-3-5 years: 2.1%-2.5%-10.2%

Table of evidence for individual studies assessing the prognostic ability of liver stiffness measurements with transient elastography to predict risk of liver-related events, decompensation, and/or mortality. Focusing only on studies which report cutoffs close to 10, 15, 20, and/or 25 kPa

ALD alcohol-related liver disease, *cACLD* compensated advanced chronic liver disease, *HCC* hepatocellular carcinoma, *HCV* hepatitis C, *LRE* liver-related events, *LTX* liver transplantation, *NAFLD* non-alcoholic fatty liver disease, *PY* person-years

[a] Unpublished data, analyses done for Baveno VII conference

[b] Based on KM-curves

How to Monitor Patients with Chronic Liver Disease Using Liver Stiffness

There are three clinical scenarios where monitoring patients with chronic liver disease using LSM by TE is of relevance: (A) In patients with elevated liver stiffness, but baseline LSM below 10 kPa threshold for ruling out cACLD. (B) In patients with baseline LSM by TE ≥10 kPa, to control for false positives. (C) In the management of cACLD patients, where LSM is monitored to guide decision-making during outpatient care.

Given the very low rate of decompensation in patients with LSM < 10 kPa from studies with follow-up periods spanning 2 to 5 years, it is probably safe to monitor patients with LSM 7–9.9 kPa every 3 to 5 years [20]. However, management should be on a case-by-case basis. In a mixed etiology cohort study of CLD patients, time-dependent ROC curves showed that the optimal predictive performance of LSM by TE lasted 2–3 years in patients with LSM < 6.7 kPa; compared to 1 year in patients with LSM 6.7–17.6 kPa [27]. A long time interval, or no follow-up in older people, seems relevant in patients at low risk of liver fibrosis progression, whereas patients with several risk factors for progression and LSM close to 10 kPa should probably be monitored more closely.

Due to the risk of false positives, an elevated index LSM should be repeated in a fasting state when feasible [28, 29]. Two consecutively elevated measurements increase sensitivity in both ALD and NAFLD [30, 31]. As the sensitivity of diagnostic tests is always lower in low-prevalence populations, this is particularly important in case LSM is used in primary care or the general population, for referral pathways [32]. If there are reasons to doubt the validity of the index LSM, investigators may also consider a confirmatory test with a blood-based biomarker (Table 11.2). This is in accordance with guidelines on noninvasive tests [33]. In head-to-head comparisons, though, LSM has a better positive-predictive value than both FIB-4, the ELF test, FibroTest or similar serum tests [34, 35].

Patients with cACLD may be monitored using annual LSM measurements, if the longitudinal measurements have implications for patient management, using 12 months as a feasible and preferred interval. Of seven studies evaluating longitudinal LSM by TE, three use annual TE, three repeat after 3 years, and one after 6–12 months (see Table 11.3). In addition, almost two-thirds of the Baveno VII faculty prefer annual monitoring over other time intervals (see Chap. 7).

Table 11.2 Suggested blood-based biomarkers and their cutoffs which can be used complementary to index LSM

	ALD		NAFLD		Viral	
Diagnosis of ≥F3	Sens	Spec	Sens	Spec	Sens	Spec
ELF ≥9.8	89%	77%	65%	86%	60%	91%
FibroTest ≥0.58	66%	89%	–	–	67%	88%
FibroTest ≥0.48	75%	86%	37%	90%	–	–
FIB-4 ≥ 2.67	70%	89%	30%	94%	–	–

Suggested blood-based biomarkers and their cutoffs which can be used complementary to index LSM. Selected based on diagnostic studies using biopsy-controlled advanced fibrosis as outcome [34, 36–40]. The cutoffs also show prognostic accuracy [5, 6, 11, 38, 41, 42]

Table 11.3 Studies that have investigated the prognostic value of longitudinal LSM

Study	Etiology	N	Endpoint	Follow-up	Changes in LSM as prognostic indicator
Wang 2014 [21]	93% viral	220	Portal hypertension progression	Median 37 months LSM every 6–12 months	Baseline LSM < 17 kPa and no worsening: 11/149 (7%) events Baseline LSM < 17 kPa but worsening: 2/12 (17%) events Baseline LSM ≥ 17 kPa regardless of LSM during FU: 17/59 (29%) events
Vergniol 2014 [44]	HCV	1025	Death or LTX	Median 38 months. LSM after 3 years	<7 kPa or 7–14 kPa without worsening: Very low cumulative risk (4 years <5%). 7–14 kPa and worsening, or ≥ 14 kPa and improvement: Moderate cumulative risk (4 years 20%) ≥14 kPa and increase: High cumulative risk (4 years 50%)
Kamaraj 2018 [45]	NAFLD	90	Liver-related events	Median 37 months LSM after 1 year	All four events happened in patients with LSM ≥ 15 kPa at baseline and no improvement
Pons 2019 [10]	HCV after DAA, baseline LSM ≥ 10 kPa	572	Portal hypertension-related events	Median 2.9 years LSM after 1 year	All seven patients with portal hypertension related events had LSM > 20 kPa at baseline and 4/5 (80%) did not improve ≥20% from baseline during FU

Table 11.3 (continued)

Study	Etiology	N	Endpoint	Follow-up	Changes in LSM as prognostic indicator
Semmler 2021 [43]	HCV after DAA	276	12 with hepatic decompensation, 5 liver-related deaths	Median 37 months	Baseline LSM cutoff of 25 kPa for predicting decompensation. Patients without decompensation decreased on average 21% in LSM, versus a 22% increase in patients with decompensation. LSM at follow-up ≤12.4 kPa: No decompensations LSM at follow-up 12.4–25.3 kPa: 2.6% 3-year cumulative risk of decompensation LSM at follow-up ≥25.3 kPa: 17.4% 3-year cumulative risk of decompensation
Rasmussen 2021[a]	ALD	219	Liver-related events	Median 49 months LSM after 3.1 years (IQR 2.1–4.1)	If LSM < 10 kPa at follow-up, regardless of baseline: 1/167 (0.6%) events. Baseline LSM < 10 kPa and worsening to LSM ≥ 10: 1/10 (10%) events Baseline LSM ≥ 10 kPa, but improvement ≥20% and LSM < 20 kPa at follow-up; or decrease to LSM <10 kPa: 3/178 (1.7%) LRE. Baseline LSM ≥ 10 kPa and no response: 7/39 (18%) LRE

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Table 11.3 (continued)

Study	Etiology	N	Endpoint	Follow-up	Changes in LSM as prognostic indicator
Petta 2021 [8]	NAFLD	533 with cACLD	Decompensation, HCC and liver-related death	Median 35 months (19–63). LSM after 1 year	Baseline and delta-LSM both predicted liver decompensation. Delta-LSM also predicted all-cause mortality. Improvement (>20% reduction in LSM): 3.8% decompensation event rate (0% if baseline LSM < 21 kPa) Stable (between 20% reduction and 20% increase in LSM): 6.2% decompensation event rate (3.2% if baseline LSM < 21 kPa). Impairment (>20% increase in LSM): 14.4% decompensation rate (10% if LSM < 21 kPa at baseline)

ALD alcohol-related liver disease, *cACLD* compensated advanced chronic liver disease, *DAA* direct acting antivirals, *HCC* hepatocellular carcinoma, *HCV* hepatitis C, *LRE* liver-related events, *LSM* liver stiffness measurement by TE, *LTX* liver transplantation, *NAFLD* non-alcoholic fatty liver disease

[a] Unpublished data, analyses done for Baveno VII conference based on data from [7]

The Clinical Relevance of Changes in Liver Stiffness in Patients with Chronic Liver Disease

There is a widespread availability of pharmaceutical, dietary, or psychosocial interventions that can attenuate or reverse liver disease progression: antivirals for chronic hepatitis, weight loss for NAFLD, and alcohol rehabilitation for ALD are the most common. Combined with a widespread availability of LSM, it has become a pressing need to map the prognostic relevance of longitudinal changes in liver stiffness. So far, six studies have investigated the prognostic value of longitudinal LSM (Table 11.3). Four studies investigated LSM in chronic viral hepatitis (two including

HCV patients before and after DAA), and another two are in NAFLD patients following the natural history of disease. A seventh set of analyses, on ALD, were conducted for the Baveno VII conference, but have not yet been published.

Some overall trends can be deduced from the six published monitoring studies. First, *a* ≥ 20% change in LSM seems to be clinically relevant: two studies used it as a predefined endpoint, while a third study found an average 22% increase in LSM in HCV patients who decompensated during follow-up, while patients free of decompensation showed a 21% decrease in LSM [8, 10, 43]. Second, highly elevated liver stiffnesses at follow-up, above 17–25 kPa, result in a substantial risk of decompensation or death regardless of whether LSM improved or worsened from baseline. Consequently, a CLD patient with a LSM decrease of 20% or more is at very low risk of LRE, if the LSM at follow-up is below approximately 20 kPa. If the follow-up LSM in cACLD patients improves to below 10 kPa, the prognostic evidence shown first in this chapter indicates a negligible risk of decompensation, regardless of the proportional change.

An effective intervention to reverse disease progression in cACLD patients should result in a very low risk of liver-related events or liver-related mortality. Such a significant improvement in LSM may consequently be defined as a reduction ≥20% and LSM < 20 kPa, or any improvement to LSM < 10 kPa.

For Baveno VII, we tested this definition in a cohort of 219 ALD patients without decompensation at baseline, and repeated LSM measurements after 1–4 years (see Table 11.3). Of the patients with cACLD at baseline, 1.7% (3/178) experienced an event if LSM improved ≥20% and LSM was <20 kPa at follow-up, or if LSM decreased to <10 kPa. In comparison, 10% (1/10) of patients with baseline LSM < 10 kPa but worsening to LSM ≥ 10 experienced events, and so did 18% (7/39) of patients with cACLD and no substantial improvement in LSM. The suggested definition of a clinically relevant response in LSM is probably a conservative estimate, especially for NAFLD patients achieving weight decrease and HCV patients after DAA. Higher LSM values during follow-up monitoring may be acceptable for these patient groups.

An important exception to LSM as a monitoring tool is for changes in HVPG after non-selective beta-blockers or Carvedilol. Changes in LSM do not correlate with HVPG after NSBB, nor with a clinically significant response to NSBB [46, 47]. LSM can therefore not be recommended for evaluation of changes in portal pressure after NSBB treatment.

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