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# Post-treatment LSM rather than change during treatment predicts decompensation in patients with cACLD after HCV cure

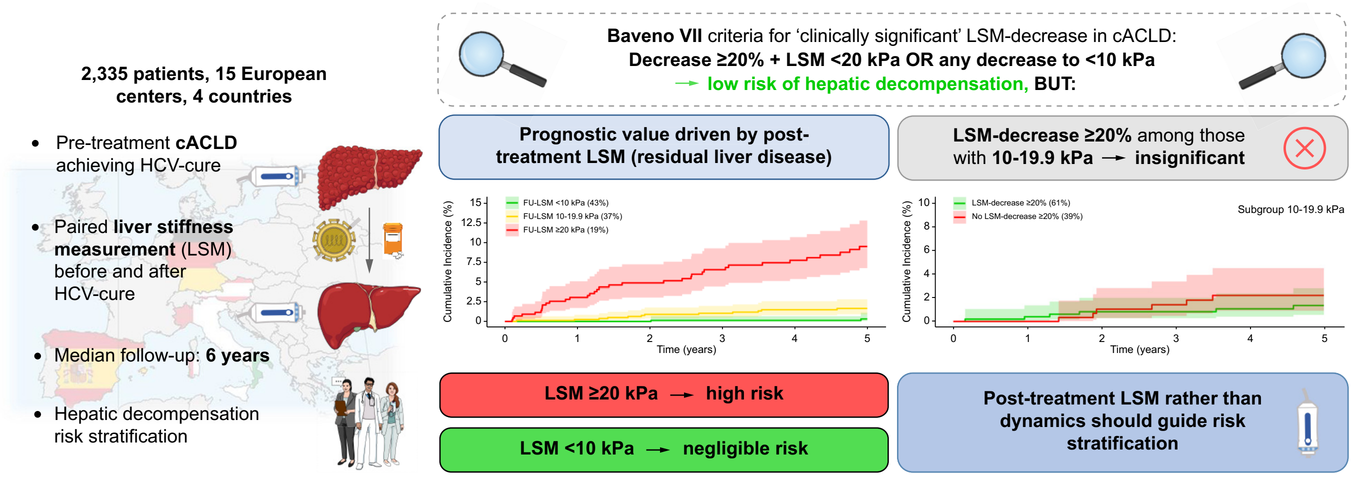
## Authors

**Georg Semmler, Sonia Alonso López,** Monica Pons, …, Joan Genesca, Rafael Bañares, Mattias Mandorfer

## Correspondence

mattias.mandorfer@meduniwien.ac.at (M. Mandorfer).

## Graphical abstract




## Highlights

- Post-treatment LSM is key for risk stratification in patients with compensated advanced chronic liver disease after HCV-cure.
- Changes in LSM during treatment do not hold significant prognostic information in patients with follow-up LSM of 10-19.9 kPa.
- Thus, consideration of LSM dynamics is not of sufficient incremental value in the context of HCV-cure.
- Post-treatment LSM should be used to guide clinical decision making.

## Impact and Implications

Liver stiffness measurement (LSM) is increasingly applied as a prognostic biomarker and commonly decreases in patients with compensated advanced chronic liver disease achieving HCV cure. Although Baveno VII proposed criteria for a clinically significant decrease, little is known about the prognostic utility of LSM dynamics (changes through antiviral therapy). Interestingly, in those with a post-treatment LSM of 10-19.9 kPa, LSM dynamics did not provide incremental information, arguing against the consideration of LSM dynamics as prognostic criteria. Thus, post-treatment LSM should guide the management of patients with compensated advanced chronic liver disease achieving HCV cure.

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# Post-treatment LSM rather than change during treatment predicts decompensation in patients with cACLD after HCV cure

**Georg Semmler**[1,2,†], **Sonia Alonso López**[3,4,5,6,†], Monica Pons[7], Sabela Lens[6,8], Elton Dajti[9], Marie Griemsmann[10], Alberto Zanetto[11], Lukas Burghart[1,12], Stefanie Hametner-Schreil[13], Lukas Hartl[1,2], Marisa Manzano[14], Sergio Rodriguez-Tajes[6,8], Paola Zanaga[11], Michael Schwarz[1,2,12], María Luisa Gutierrez[15], Mathias Jachs[1,2], Anna Pocurull[6,8], Benjamín Polo[16], Dominik Ecker[13], Beatriz Mateos[17], Sonia Izquierdo[18], Yolanda Real[19], Adriana Ahumada[3], David Josef Maria Bauer[1,12], Jim Benjamin Mauz[10], Michelle Casanova-Cabral[16], Michael Gschwantler[12], Francesco Paolo Russo[11], Francesco Azzaroli[9], Benjamin Maasoumy[10], Thomas Reiberger[1,2], Xavier Forns[6,8], Joan Genesca[6,7], Rafael Bañares[3,4,5,6], Mattias Mandorfer[1,2,*], cACLD-SVR Study Group

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**Background & Aims:** Baveno VII has defined a clinically significant (*i.e.*, prognostically meaningful) decrease in liver stiffness measurement (LSM) in cACLD as a decrease of ≥20% associated with a final LSM <20 kPa or any decrease to <10 kPa. However, these rules have not yet been validated against direct clinical endpoints.
**Methods:** We retrospectively analysed patients with cACLD (LSM ≥10 kPa) with paired liver stiffness measurement (LSM) before (BL) and after (FU) HCV cure by interferon-free therapies from 15 European centres. The cumulative incidence of hepatic decompensation was compared according to these criteria, considering hepatocellular carcinoma and non-liver-related death as competing risks.
**Results:** A total of 2,335 patients followed for a median of 6 years were analysed. Median BL-LSM was 16.6 kPa with 37.1% having ≥20 kPa. After HCV cure, FU-LSM decreased to a median of 10.9 kPa (<10 kPa: 1,002 [42.9%], ≥20 kPa: 465 [19.9%]) translating into a median LSM change of -5.3 (-8.8 to -2.4) kPa corresponding to -33.9 (-48.0 to -15.9) %. Patients achieving a clinically significant decrease (65.4%) had a significantly lower risk of hepatic decompensation (subdistribution hazard ratio: 0.12, 95% CI 0.04-0.35, $p$ <0.001). However, these risk differences were primarily driven by a negligible risk in patients with FU-LSM <10 kPa (5-year cumulative incidence: 0.3%) compared to a high risk in patients with FU-LSM ≥20 kPa (16.6%). Patients with FU-LSM 10-19.9 kPa (37.4%) also had a low risk of hepatic decompensation (5-year cumulative incidence: 1.7%), and importantly, the risk of hepatic decompensation did not differ between those with/without an LSM decrease of ≥20% ($p$ = 0.550).
**Conclusions:** FU-LSM is key for risk stratification after HCV cure and should guide clinical decision making. LSM dynamics do not hold significant prognostic information in patients with FU-LSM 10-19.9 kPa, and thus, their consideration is not of sufficient incremental value in the specific context of HCV cure.



## Introduction

Baveno VII has marked a paradigm shift in the definition of compensated advanced chronic liver disease (cACLD): From stage of disease (advanced fibrosis and/or sinusoidal portal hypertension) with Baveno VI[1] to its prognostic implications with Baveno VII.[2] Thus, cACLD now describes the population at risk of complications of advanced chronic liver disease (*i.e.*, development of hepatic decompensation).[2] The definition of cACLD hereby relies on non-invasive tests, especially on liver stiffness measurement (LSM) using vibration-controlled transient elastography (VCTE), to rule-out cACLD (LSM <10 kPa) or rule-in cACLD (LSM ≥15 kPa). Due to the profound prognostic implications of removal/suppression of the primary aetiological factor, risk is dynamic. However, it is unclear clear whether decreases in LSM translate into decreases in risk, and vice-versa. Nevertheless, incorporating the concept of regressive disease is important, as these patients are increasingly encountered in clinical practice, especially after cure from HCV.[3] To facilitate patient management, Baveno VII has defined a 'clinically significant' (*i.e.*, prognostically meaningful) LSM decrease as: a decrease in LSM of ≥20% associated with LSM <20 kPa, or any decrease to a LSM <10 kPa.[2] However,

Keywords: compensated advanced chronic liver disease; liver stiffness measurement; transient elastography; chronic hepatitis C; sustained virological response; SVR; aetiological cure.
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* Corresponding author. Address: Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Währinger Gürtel 18-20, 1090, Vienna, Austria; Tel.: +43 1 40400 47410, fax: +43 1 40400 47350.
*E-mail address:* mattias.mandorfer@meduniwien.ac.at (M. Mandorfer).
† G.S. and S.A.L. contributed equally to the work.
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these criteria are based on limited evidence and have yet to be evaluated in different clinical contexts.

In the setting of aetiological cure, Pons *et al.* (2020)[4] identified pre-treatment LSM ≥20 kPa as the main factor driving hepatic decompensation. Semmler *et al.* (2021)[5] found absolute post-treatment LSM to be more predictive of hepatic decompensation than pre-treatment values, while LSM dynamics were not associated with clinical outcomes.

As both individual studies suffered from limited sample size and follow-up, we aimed to evaluate the Baveno VII criteria[2] for a clinically significant decrease in LSM in a pooled cohort of patients with cACLD who achieved HCV cure and for whom extended follow-up data were available.

## Patients and methods

### Patients

We retrospectively included 2,335 patients with cACLD (as defined by LSM ≥10 kPa[2,6]) undergoing interferon-free therapy with direct-acting antivirals (DAAs) and achieving sustained virologic response from HCV infection between 2012 and 2020 from 15 European centres: nine from Spain (Hospital General Universitario Gregorio Marañón, Hospital Universitario 12 De Octubre, Hospital Universitario Fundación Alcorcón, Hospital Universitario Ramón y Cajal, Hospital Universitario Fundación Jiménez Díaz, Hospital Universitario Clínico San Carlos, and Hospital Universitario La Princesa Madrid [Madrid]; Vall d'Hebron University Hospital and Hospital Clínic [Barcelona]), three from Austria (Medical University of Vienna and Klinik Ottakring [Vienna]; Ordensklinikum Linz Barmherzige Schwestern [Linz]), two from Italy (University of Bologna [Bologna] and Padua University Hospital [Padua]), and one from Germany (Hannover Medical School [Hannover]). Institutional data on the inclusion period as well as LSM by VCTE training and volume per centre can be found in the supplementary information (Table S1). Specifically, only patients with paired LSM and laboratory assessment at baseline (BL, *i.e.*, before) and follow-up (FU, *i.e.*, after HCV cure), but without a pre-treatment history of hepatic decompensation or hepatocellular carcinoma (HCC) were included. Patients with hepatic decompensation or HCC during DAA therapy were excluded.

### Parameters and definitions

Demographic characteristics and data on BMI, diabetes, components of the metabolic syndrome (according to the IDF 2009 definition[7]), and alcohol consumption were retrospectively collected from patient records, together with laboratory parameters and LSM before and after HCV cure. Due to the retrospective design of this study, the timepoints of post-treatment assessment were not standardised, and clustered around 31.3 weeks (IQR 16.0-55.9, Fig. S1A) after end-of-treatment (EoT). Notably, there was considerable variation across countries (Table S2, Fig. S1B). VCTE (FibroScan, Echosens, Paris, France) was used for LSM and performed by experienced operators, as previously described.[8] Changes in LSM were calculated as absolute and relative differences (*i.e.*, FU compared to BL).

Data on the clinical course during follow-up were collected from chart review starting from the EoT until 2022. First hepatic decompensation was defined as the occurrence of variceal bleeding, development of clinically overt ascites (grade 2 or 3), and overt hepatic encephalopathy (West Haven grade ≥2).[2] HCC was diagnosed according to the respective clinical practice guidelines of the European Association for the Study of the Liver.[9] Also, data on transjugular intrahepatic portosystemic shunt placement, orthotopic liver transplantation, and death were collected. For outcome analyses, follow-up started at the time of post-treatment assessment. A graphical illustration of the study design can be found in Fig. 1.

### Objectives

The primary objective was to test whether the Baveno VII definition for a 'clinically significant' LSM decrease (decrease of ≥20% associated with LSM <20 kPa, or any decrease to a LSM <10 kPa)[2] identifies patients at lower risk of hepatic decompensation after aetiological cure, considering HCC and non-liver-related death as competing events. Secondary objectives included an investigation on whether LSM dynamics provide independent information on hepatic decompensation, with a specific focus on patients with LSM of 10-19.9 kPa (*i.e.*, the subgroup in which LSM dynamics have been suggested to be prognostically significant by Baveno VII), and on factors associated with LSM dynamics.

### Statistics

Statistical analyses were performed using R 4.3.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were reported as mean ± SD or median (IQR), while categorical variables were reported as proportion of patients with/without a certain characteristic. Student's *t* test was used for group comparisons of normally distributed variables and Mann-Whitney *U* test for non-normally distributed variables, respectively. Group comparisons of categorical variables were performed using either Pearson's Chi-squared test.

Median survival was calculated by applying the reverse Kaplan-Meier method[10] and graphically illustrated as recommended by the STRATOS initiative.[11] The description of liver-related events started from EoT. For all other analyses (*i.e.*, those focusing on the predictive performance of FU-LSM and changes in LSM), follow-up started at the time of post-treatment assessment, and patients with hepatic decompensation (n = 8) or HCC (n = 10) before FU-LSM or no follow-up thereafter were excluded (67 in total [2.9%]). Cumulative incidence functions were computed with the 'cmprsk'-package and plotted with the 'tidycmprsk'-package, and used to assess the incidence of hepatic decompensation during follow-up, while accounting for HCC and non-liver-related death as competing risks for hepatic decompensation, and for death as a competing risk for HCC. Thus, hepatic decompensation occurring after HCC was not considered. Cumulative incidences were compared applying Fine & Gray competing risks regression models with subdistribution hazard ratios (SHRs) adjusted for clustering across centres (mixed effects model) as provided by the 'crrSC'-package. The area under the receiver-operating characteristics curve (AUROC) and respective 95% CIs of receiver-operating characteristic analyses were calculated for hepatic decompensation within 2 years of FU using the 'cutpointr'-package, applying and plotting Youden's J-statistic to obtain the respective optimised

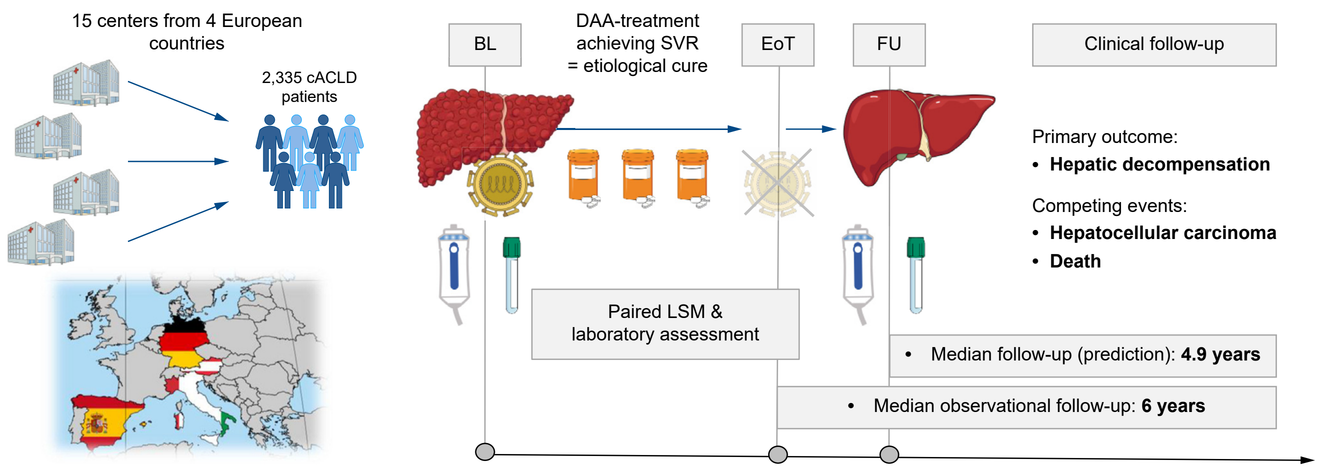


**Fig. 1. Study design.** BL, baseline; cACLD, compensated advanced chronic liver disease; DAA, direct-acting antiviral; EoT, end-of-treatment; FU, follow-up; LSM, liver stiffness measurement; SVR, sustained virologic response. (This figure appears in color on the web.)

cut-offs. To increase the reliability of these analyses, we performed bootstrap resampling of our cohort 500 times. To test for an influence of (i) the time since EoT and (ii) FU-LSM with the association of relative LSM changes and hepatic decompensation, we included interaction terms into cause-specific Cox proportional hazard regression analyses using the R 'survival' package, and assessed overall model discrimination with Harrel's C-indices, again adjusting for clustering across centres. A $p$ value ≤0.05 was considered statistically significant.

### Ethics

This study was approved by the institutional ethics committees of the individual centres. Written informed consent was obtained if the local ethics committees did not waive its requirement.

## Results

### Patient characteristics and dynamics in LSM before and after HCV cure

The mean age of our cohort was 60.2 ± 11.9years, 947 (40.6%) were female, 446 (21.1%) were obese, 495 (21.2%) had diabetes, 318 (15.8%) hypertriglyceridemia (≥150 mg/dl), 313 (22.1%) low high-density lipoprotein cholesterol levels, 854 (40.0%) arterial hypertension, 330 (15.7%) reported any alcohol consumption, and 155 (6.6%) were receiving non-selective beta blockers and 115 (4.9%) statins (Table 1).

Before DAA treatment (BL), 1,234 (52.8%) showed thrombocytopenia (platelet count [PLT] <150x$10^9$/L), median BL-LSM was 16.6 (12.4-25.0) kPa, and 867 (37.1%) had BL-LSM ≥20 kPa.

After DAA treatment (*i.e.*, at the time of post-treatment assessment, FU), 1,066 (45.7%) had thrombocytopenia, and the median FU-LSM was 10.9 (7.8-17.1) kPa. One thousand and two (42.9%) had FU-LSM <10 kPa, while 465 (19.9%) had FU-LSM ≥20 kPa. This translated into a median LSM change of -5.3 (-8.8 to -2.4) kPa corresponding to -33.9 (-48.0 to -15.9) %. Specifically, 2,019 (86.5%) showed any decrease in LSM of whom 1,632 (69.9%) were ≥20%, 18 (0.8%) remained unchanged and 298 (12.8%) showed an increase in LSM.

Among 867 patients with BL-LSM ≥20 kPa, 100 (11.5%) had a FU-LSM <10 kPa, 357 (41.2%) decreased to 10-19.9 kPa, and 410 (47.3%) remained ≥20 kPa. In the subgroup of patients with BL-LSM≥20 kPa, median LSM change was -9.8 (-14.9 to -4.5) kPa (relative change: -34.8 [-52.2 to -16.2] %), 749 (86.4%) showed a decrease in LSM, and 612 (70.6%) had a decrease ≥20%.

Overall, 1,528 (65.4%) met the proposed criteria for a clinically significant decrease in LSM (FU-LSM<10 kPa: n = 1,002 [42.9%], ≥20% decrease and FU-LSM 10-19.9 kPa: n = 526 [22.5%]), while 807 did not (FU-LSM ≥20 kPa: n = 465 [19.9%], <20% decrease and FU-LSM 10-19.9 kPa: n = 342 [14.6%]).

Importantly, a nearly linear association between the time of post-treatment assessment and relative LSM change (-0.17%/week) was evident, which tended to be more pronounced within the first ∼24 weeks (Fig. S2).

### Factors associated with LSM decrease

See supplementary results.

### Follow-up

During a median follow-up of 6.0 years (range: 0.6-111.6 months, overall: 11,315 patient years, Fig. S3A), 84 (0.04% of all patients) patients developed first hepatic decompensation, with decompensation occurring prior to HCC in 66 (0.03%) after a median of 2.7 years (ascites: n = 39, variceal bleeding: n = 17, hepatic encephalopathy: n = 7, ≥2 events simultaneously: n = 3), 183 (0.08%) patients developed HCC, and 187 (0.08%) patients died, with 73 (0.03%) deaths considered liver-related. In the analyses on the predictive utility of FU-LSM and changes in LSM, the time point of FU-LSM served as an inception point and the median follow-up thereafter was 4.9 years (Fig. S3B). Notably, hepatic decompensation (n = 58, median time between FU-LSM and hepatic decompensation: 27.8 [IQR 11.3-52.8] months) was only considered for outcome prediction if occurring after FU-LSM and prior to HCC diagnosis. A patient flowchart can be found in Fig. S4.

**Table 1. Patient characteristics in the overall cohort (N = 2,335).**

| Patient characteristics | Overall cohort (N = 2,335) |
|---|---|
| Age, years | 60.2 ± 11.9 |
| Female sex | 947 (40.6%) |
| BMI, kg/m$^2$ | 26.8 ± 4.5 |
| Obesity[1] (BMI ≥30 kg/m$^2$) | 446 (21.1%) |
| Diabetes | 495 (21.2%) |
| Hypertriglyceridemia[2] (≥150 mg/dl) | 318 (15.8%) |
| Triglycerides[2] (mg/dl) | 102 (77-135) |
| Low HDL-cholesterol[3] | 313 (22.1%) |
| Cholesterol[4] (mg/dl) | 159 (137-183) |
| Arterial hypertension[5] | 854 (40.0%) |
| Any alcohol consumption[6] | 330 (15.7%) |
| None | 1,778 (84.3%) |
| Yes, below threshold | 172 (8.2%) |
| Yes, above threshold | 158 (7.5%) |
| BL-NSBB intake | 155 (6.6%) |
| BL-statin intake | 115 (4.9%) |
| BL-albumin (mg/dl) | 40.9 ± 4.4 |
| BL-PLT (x10$^9$/L) | 144 (104-191) |
| <150 x 10$^9$/L | 1,234 (52.8%) |
| BL-LSM (kPa) | 16.6 (12.4-25.0) |
| ≥20 kPa | 867 (37.1%) |
| Time to post-treatment assessment (weeks) | 31.3 (16.0-55.9) |
| FU-PLT (x10$^9$/L) | 156 (114-204) |
| <150 x 10$^9$/L | 1,066 (45.7%) |
| FU-LSM (kPa) | 10.9 (7.8-17.1) |
| <10 kPa | 1,002 (42.9%) |
| 10-19.9 kPa | 868 (37.2%) |
| ≥20 kPa | 465 (19.9%) |
| LSM change (absolute, kPa) | -5.3 (-8.8 to -2.4) |
| LSM change (relative, %) | -33.9 (-48.0 to -15.9) |
| LSM decrease | 2,019 (86.5%) |
| LSM decrease ≥20% | 1,632 (69.9%) |
| LSM unchanged | 18 (0.8%) |
| LSM increase | 298 (12.8%) |
| Baveno VII risk groups | |
| High | |
| FU-LSM <10 kPa | 1,002 (42.9%) |
| FU-LSM 10-19.9 kPa + LSM decrease ≥20% | 526 (22.5%) |
| Low | |
| FU-LSM 10-19.9 kPa + LSM decrease <20% | 342 (14.6%) |
| FU-LSM ≥20 kPa | 465 (19.9%) |

[1]Available in 2,107 patients.
[2]Avaiable in 2013.
[3]Available in 1,417, defined as HDL cholesterol <50 mg/dl and <40 mg/dl in males and females, respectively.
[4]Available in 1,781.
[5]Available in 2,136, defined as blood pressure >130/85 mmHg or antihypertensive drug treatment.
[6]Available in 2,108 patients, assessed at baseline as below or above the >30 g/day and >20 g/day threshold for males and females, respectively. BL, baseline; FU, follow-up; HDL, high-density lipoprotein; LSM, liver stiffness measurement; NSBBs, non-selective beta blockers; PLT, platelet count.

### Baveno VII strata and hepatic decompensation

Patients meeting the Baveno VII criteria for a clinically significant decrease in LSM had a significantly lower risk of hepatic decompensation (SHR 0.12, 95% CI 0.04-0.35, *p* <0.001, Fig. 2A), which was valid in those with FU-assessment <33.1 weeks and ≥33.1 weeks after EoT (Fig. S5). Although the SHR was numerically higher in the latter group, the 95% CI of both strata were overlapping. Importantly, risk differences were predominantly achieved by a negligible risk in patients with FU-LSM <10 kPa (cumulative incidence after 5 years: 0.3%) compared to a substantial risk in patients with FU-LSM ≥20 kPa (cumulative incidence after 5 years: 16.6%, Fig. 2B). Notably, in both of these FU-LSM strata (<10 kPa, ≥20 kPa), the assignment to the risk groups occurs irrespective of the magnitude of LSM changes according to Baveno VII (any decrease to <10 kPa = low risk, any change to ≥20 kPa = high risk).

While those with FU-LSM 10-19.9 kPa (n = 849, 37.4%) also had a comparatively low risk of hepatic decompensation (cumulative incidence after 5 years: 1.7%), it was still significantly higher than the risk of patients with FU-LSM <10 kPa (SHR 5.43, 95% CI 2.31-12.70, *p* <0.001, Fig. 2B).

### LSM dynamics and hepatic decompensation in the overall cohort

In the overall cohort, relative LSM changes achieved a moderate accuracy to predict hepatic decompensation within 2 years (AUROC 0.75, 95% CI 0.68-0.81) with a Youden's index optimised cut-off of -31.2% (Fig. S6A). In comparison, FU-LSM had an AUROC of 0.88 (95% CI 0.86-0.92) with a Youden's index optimised cut-off of ≥15.8 kPa (Fig. S6B).

When comparing patient outcomes according to strata of relative LSM change, patients with an LSM decrease ≥20% (n = 1,595, 70.3%) had a favourable outcome (cumulative incidence after 5 years: 1.4%, Fig. 3A). However, patients with any LSM decrease (n = 1,970, 86.9%) had a similarly low incidence of hepatic decompensation (after 5 years: 1.8%, Fig. 3B). Consecutively, patients with a <20% decrease (SHR *vs*. ≥20% decrease: 2.01, 95% CI 0.94-4.30, *p* = 0.074) had a comparable risk of hepatic decompensation while patients with unchanged/increased LSM (SHR 4.60, 95% CI 2.41-8.82, *p* <0.001) had a significantly higher risk of hepatic decompensation than their counterparts (Fig. 3C).

Notably, there was no evidence for an interaction between the timing of post-treatment assessment and the prognostic implications of FU-LSM or relative changes in LSM (Table S3), suggesting that the timing of post-treatment assessment did not modify its predictive utility.

### LSM dynamics and hepatic decompensation in patients with FU-LSM 10-19.9 kPa

In patients with FU-LSM 10-19.9 kPa, relative LSM change (AUROC 0.59, 95% CI 0.37-0.85) was unable to predict hepatic decompensation within 2 years, although these findings must be interpreted in the context of the low number of events in this subgroup. Therefore, no optimal cut-off could be determined.

Of note, patients with an LSM decrease ≥20% had a comparable risk of hepatic decompensation compared to those with a <20% decrease (*p* = 0.550, Fig. S7A). However, patients with any decrease in LSM (n = 712, 83.9%) had a slightly lower risk of hepatic decompensation (SHR 0.48, 95% CI 0.28-0.83, *p* = 0.009) compared to those with stable or increasing LSM (n = 137, 16.1%, Fig. S7B).

### Exploratory analyses on the association between LSM dynamics and hepatic decompensation

See supplementary results and supplementary discussion.

### HCC occurrence according to Baveno VII strata and LSM dynamics in the overall cohort

See supplementary results.

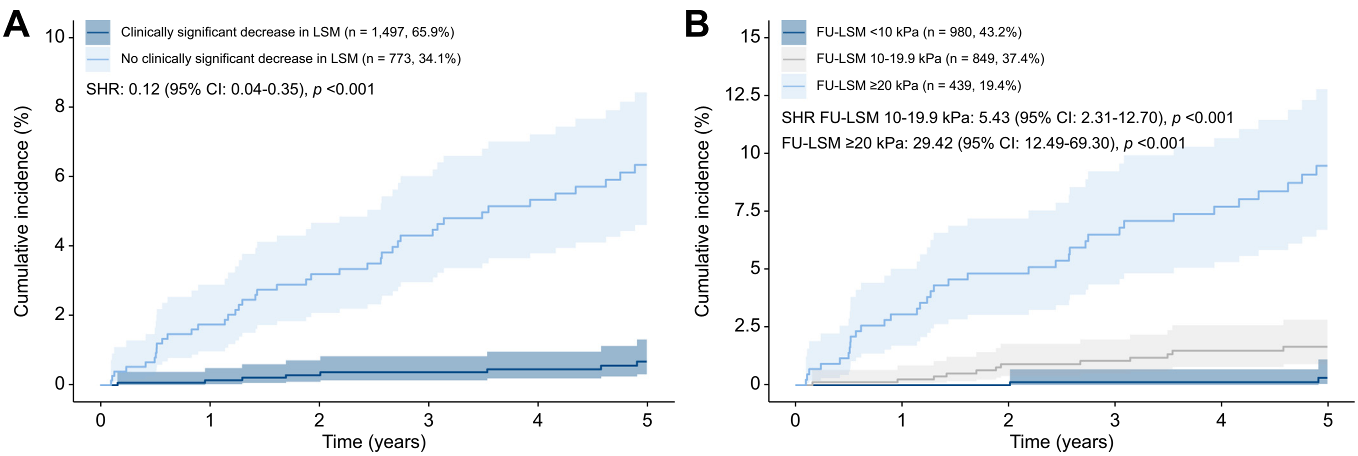


**Fig. 2. Hepatic decompensation in patients with cACLD stratified according to Baveno VII criteria for a clinically significant decrease in LSM.** Cumulative incidence curves for hepatic decompensation in cACLD patients stratified according to Baveno VII criteria for a clinically significant decrease in LSM (A), and according to FU-LSM strata: <10 kPa, 10-19.9 kPa, and ≥20 kPa (B). HCC and non-liver-related death were considered competing events. Outcomes were assessed starting from FU-LSM. In (B), SHR are compared vs. FU-LSM <10 kPa. (Fine & Gray competing risk regression analysis, Gray's test). cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement; HCC, hepatocellular carcinoma; SHR, subdistribution hazard ratio.

## Discussion

Baveno VII has introduced simple rules to facilitate the interpretation of dynamics in LSM in patients with cACLD in clinical practice by defining a decrease in LSM ≥20% which is accompanied by an LSM <20 kPa, or any decrease to a LSM <10 kPa as 'clinically significant'. Although the concept of cACLD has primarily been developed in the presence of ongoing liver injury, decreases in LSM are nowadays commonly achieved by removal/suppression of the primary aetiological factor, raising the question of whether these criteria are applicable in this setting.[2]

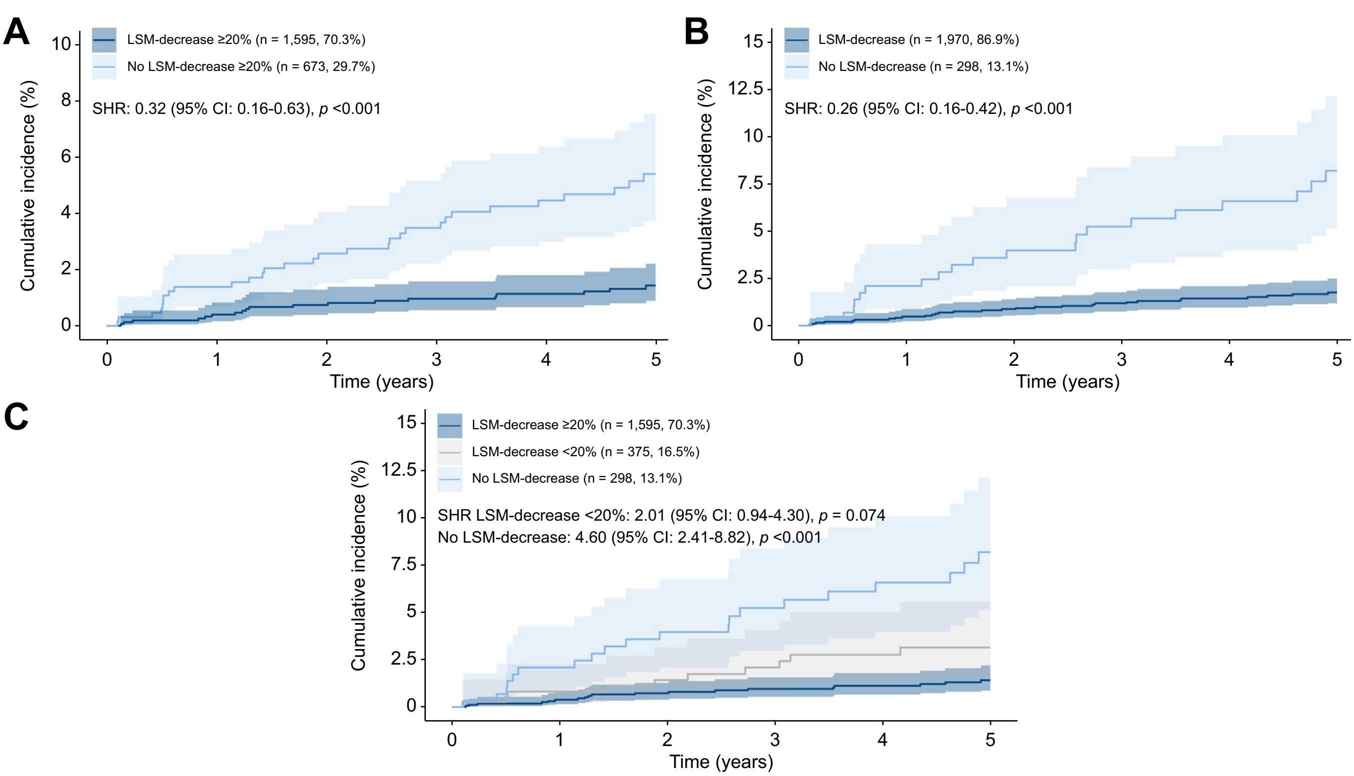


**Fig. 3. Hepatic decompensation in patients with cACLD stratified according to dynamics in LSM after HCV cure.** Cumulative incidence curves for hepatic decompensation in cACLD patients stratified according to dynamics in LSM after HCV cure: Any LSM decrease (A), LSM decrease ≥20% (B), or stratified into decrease ≥20%, decrease of <20%, and no decrease (C). HCC and non-liver-related death were considered competing events. Outcomes were assessed starting from FU-LSM. (Fine & Gray competing risk regression analysis, Gray's test). cACLD, compensated advanced chronic liver disease; LSM, liver stiffness measurement; HCC, hepatocellular carcinoma; SHR, subdistribution hazard ratio.

We studied 2,335 patients with cACLD achieving HCV cure at 15 European centres who have been evaluated by paired LSM, *i.e.*, one of the most comprehensive cACLD cohorts to date. Together with long-term follow-up data, this cohort provides an ideal basis for evaluating the Baveno VII criteria for a clinically significant decrease in LSM after HCV cure, or more generally, for guiding the interpretation of LSM dynamics after removal of the primary aetiological factor. In the present study, we demonstrate that the Baveno VII criteria for a clinically significant decrease in LSM identify patients at substantially reduced risk of hepatic decompensation. However, this is due to the post-treatment disease severity/stage (*i.e.*, absolute FU-LSM) incorporated into these composite criteria: Patients with FU-LSM <10 kPa are at negligible risk, while those with FU-LSM ≥20 kPa are at high risk of hepatic decompensation. In those with FU-LSM of 10-19.9 kPa, the cut-off of ≥20% decrease – as proposed by Baveno VII – was not capable of identifying patients with a better prognosis. Thus, in the setting of aetiological cure, residual liver disease severity/stage seems to be considerably more important than the magnitude of LSM improvement. In this regard, a recent pooled analysis confirmed the accuracy of PLT and LSM for diagnosing CSPH after aetiological cure,[12] which remains the key driver of hepatic decompensation in this context.[13–17] Here, simple rules assessing solely the severity of liver disease/portal hypertension (LSM <12 kPa and PLT >150 x $10^9$/L) can reliably exclude post-treatment CSPH, and thus, identify a large proportion (*e.g.*, 42.5%[12]) of patients with cACLD who are not at risk of hepatic decompensation. Notably, these criteria have already been implemented in international[2] and national[6] recommendations.

Baveno VII has proposed a ≥20% cut-off for LSM decrease to be clinically significant based on a single retrospective study in 533 patients with metabolic dysfunction-associated steatotic liver disease, categorising LSM change according to ±20% change.[18] This cut-off was intended to minimise noise created by smaller variations in LSM that may fall below the 'smallest detectable difference' that is inherent to the technique and might not translate into changes in risk. However, this limit of detection has not yet been defined. In the current study, this cut-off (≥20% decrease) does not provide prognostic information in patients after aetiological cure. In contrast, we observed a comparable risk in those with any LSM decrease, and thus, a better discrimination if using LSM as a surrogate of progression (any LSM increase) or regression (any LSM decrease). Importantly, this is in line with a recent study from our group in a multi-etiological cohort[19] and patients with cholestatic liver disease.[20] Most importantly, however, all three studies emphasise that LSM dynamics (*i.e.*, degree of change) can only be interpreted in the context of absolute LSM values (*i.e.*, severity/stage of disease), with the latter being the decisive factor for prognostication after aetiological cure. A detailed discussion on further analyses regarding their relationship can be found in the supplement.

The current study has several strengths. First, we provide the largest cohort of patients with cACLD (*i.e.*, those at risk for complications) undergoing repeated LSM so far that is linked to long-term follow-up (median 6 years after EoT). Despite the high overall number of 11,315 patient years, the low event rate in patients with FU-LSM 10-19.9 kPa limited statistical power to detect small effects in this subgroup. However, we are confident that additionally considering LSM dynamics in this stratum is not of sufficient incremental value in the specific context of HCV cure. The latter is explained by the fact that if the prognostic utility of the LSM decrease ≥20%-criterion cannot be established in the subgroup of 868 patients with FU-LSM 10-19.9 kPa, it becomes obvious that the benefit of its consideration in clinical practice is negligible, while substantially complicating the risk stratification criteria. Notably, little is known about the test-retest reliability of LSM by VCTE (particularly in cACLD); however, such knowledge is instrumental for interpreting LSM change on an individual patient level, and thus, this should be a priority for further research. Second, we report on a homogenous cohort comprising a single aetiology of liver disease characterised within a relatively narrow time window, and thus, limited variation in care. Third, the effectiveness of DAA therapies reduces additional complexity that would be introduced due to variation in the efficacy of an intervention to a minimum, being an ideal model to study disease regression. Fourth, patients were included from four European countries and 15 centres, maximising the representativeness for European patients with HCV, and thus, the generalisability of our findings.

However, this study also has limitations. First, analyses were restricted to patients with paired LSM before and after HCV cure, which could give rise to selection bias. However, we have demonstrated that most pre- and post-treatment characteristics, and more importantly, clinical outcomes (across LSM strata) were comparable between Viennese centres with a particularly low and high rate of FU-LSM. Second, the time of FU-LSM was not standardised due to the retrospective design and logistical differences across centres. While there was no evidence of an influence of the time of post-treatment assessment on the main outcomes (*e.g.*, prognostic utility of risk strata), the timing of post-treatment assessment relative to EoT influenced the magnitude of LSM decrease, and therefore, also to some extent the allocation to risk strata. Third, although not all patients at each institution underwent FU-LSM, reassessment rates were around 85% or higher in all but one of the 15 contributing centres, rendering major selection bias very unlikely. Fourth, dynamics of LSM were only assessed at a single time point after HCV cure. Here, sequential post-treatment LSM assessments may improve prognostic accuracy.[19] Fifth, data on alcohol consumption and metabolic comorbidities were not systematically assessed during post-treatment follow-up, limiting potential analyses.

In conclusion, post-treatment LSM (*i.e.*, residual liver disease severity) provides prognostic information on the risk of hepatic decompensation in cACLD. As Baveno VII criteria for a clinically significant LSM decrease include prognostically meaningful LSM thresholds (<10 kPa, ≥20 kPa), they are capable of stratifying risk. However, LSM dynamics do not hold significant prognostic information in patients with LSM 10-19.9 kPa, and thus, considering LSM dynamics in this stratum is not of sufficient incremental value in the specific context of HCV cure. Thus, post-treatment LSM is sufficient to guide risk stratification and clinical decision making.

## Affiliations

[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [2]Vienna Hepatic Hemodynamic Lab, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria; [3]Liver Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [4]Instituto De Investigación Sanitaria Gregorio Marañón (IiSGM), Madrid, Spain; [5]Universidad Complutense de Madrid, Madrid, Spain; [6]Centro de Investigación Biomédica En Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain; [7]Liver Unit, Vall d'Hebron University Hospital, Vall d'Hebron Institut of Research (VHIR), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona, Barcelona, Spain; [8]Liver Unit, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain; [9]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Italy; IRCCS Azienda Ospedaliero-Universitaria di Bologna, European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Bologna, Italy; [10]Hannover Medical School, Department of Gastroenterology, Hepatology, Infectious diseases and Endocrinology, Hannover, Germany; [11]Gastroenterology and Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, Padua University Hospital, Padua, Italy; [12]Department of Internal Medicine IV, Klinik Ottakring, Vienna, Austria; [13]Department of Internal Medicine IV, Ordensklinikum Linz Barmherzige Schwestern, Linz, Austria; [14]Liver Unit, Hospital Universitario 12 De Octubre, Madrid, Spain; [15]Gastroenterology Unit, Hospital Universitario Fundación Alcorcón, Madrid, Spain; [16]Gastroenterology Unit, Hospital Universitario Fundación Jimenez Díaz, Madrid, Spain; [17]Liver Unit, Hospital Universitario Ramón y Cajal, Madrid, Spain; [18]Gastroenterology Unit, Hospital Universitario Clínico San Carlos, Madrid, Spain; [19]Gastroenterology Unit, Hospital Universitario La Princesa, Madrid, Spain

## cACLD-SVR Study Group

Sofia Maria Agostini, Lorenz Balcar, Sara Battistella, David Chromy, Markus Cornberg, Katja Deterding, Inmaculada Fernandez, Conrado Fernandez-Rodriguez, Francisco Gea, Fiona Koeck, Julia Krawanja, Daniela Neumayer, Daniel Riado, Diego Rincón, Philipp Schwabl, Benedikt Simbrunner, Michael Trauner, Clara Uson, Heiner Wedemeyer.

## Abbreviations

AUROC, area under the receiver-operating characteristics curve; BL, baseline; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; DAAs, direct-acting antivirals; EoT, end-of-treatment; FU, follow-up; HCC, hepatocellular carcinoma; LSM, liver stiffness measurement; PLT, platelet count; SHR, subdistribution hazard ratio; VCTE, vibration-controlled transient elastography.

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## Conflict of interest

G.S. received travel support from Amgen. S.A.L. received grant support from AbbVie and Gilead, and served as a speaker and/or consultant and/or advisory board member for AbbVie, and Gilead. S.L. received grant support from Gilead and served as a speaker and/or consultant and/or advisory board member for AbbVie, Gilead, and MSD. S.H.-S. served as a speaker and/or consultant and/or advisory board member for AbbVie, Bristol-Myers Squibb, Eisai, Gilead, and Intercept and received travel support from AbbVie and Gilead. S.R.-T. served as a speaker for AbbVie, Advanz, and Gilead, and received travel support from AbbVie, Advanz, and Gilead. M.S. received travel support from MSD, Sandoz, BMS, AbbVie and Gilead, and speaking honoraria from BMS. M.J. served as a speaker and consultant for Gilead. A.P. received travel support from AbbVie and Gilead. D.B. received travel support from Gilead and Siemens, speaker honoraria from Siemens, as well as grant support from Philips, Siemens, and Gilead. M.G. received grants from AbbVie, Gilead, and MSD, speaking honoraria/advisory board fees from AbbVie, Gilead, MSD, Janssen, BMS, Roche, Intercept, Alnylam, Norgine, AstraZeneca, Falk, Gebro Pharma and Shionogi, and travel support from AbbVie and Gilead. F.P.R. served as a speaker and/or consultant and/or advisory board member for AbbVie, Biotest, Gilead, and GSK, and received travel support from AbbVie, Biotest, and Gilead. B.M. served as a speaker and/or consultant for Roche, AbbVie, Fujirebio, MSD, and Gilead, received grant support from Fujirebio, Altona Diganostics, and Roche, and received travel support form AbbVie, and Gilead. T.R. received grant support from AbbVie, Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Myr Pharmaceuticals, Philips Healthcare, Pliant, Siemens and W. L. Gore & Associates, served as a consultant for Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Resolution Therapeutics, and Siemens, received speaking honoraria from AbbVie, Gilead, Intercept/Advanz Pharma, Roche, MSD, and W. L. Gore & Associates, served as advisory board member for Boehringer Ingelheim, Gilead, Intercept/Advanz Pharma, MSD, Resolution Therapeutics, and Siemens, and received travel support from AbbVie, Boehringer Ingelheim, Dr. Falk Pharma, Gilead and Roche. X.F. served as a consultant for Gilead, and as a speaker for AbbVie and Gilead. J.G. served as a consultant for Boehringer Ingelheim, and speaker for Echosens. R.B. served as a speaker and/or consultant and/or advisory board member for AbbVie, Gilead, and Janssen. M.M. received grant support from Echosens, served as a speaker and/or consultant and/or advisory board member for AbbVie, Collective Acumen, Echosens, Gilead, Ipsen, Takeda, and W. L. Gore & Associates and received travel support from AbbVie and Gilead. M.P., E.D., M.G., A.Z., L.B. L.H., M.M., P.Z., M.L.G., B.P., D.E., B.M., S.I., Y.R., A.A., J.M., M.C., and F.A. have nothing to disclose.

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

## Authors' contributions

Study concept and design (G.S. and M.M.), acquisition of data (all authors), analysis and interpretation of data (G.S., S.A.L., and M.M.), drafting of the manuscript (G.S. and M.M.), critical revision of the manuscript for important intellectual content (all authors).

## Data availability statement

Data are available from the corresponding author upon reasonable request.

## Supplementary data

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*Author names in bold designate shared co-first authorship*

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