

# Predicting hepatic decompensation using non-invasive tests in a contemporary multicentre cohort of patients with cACLD

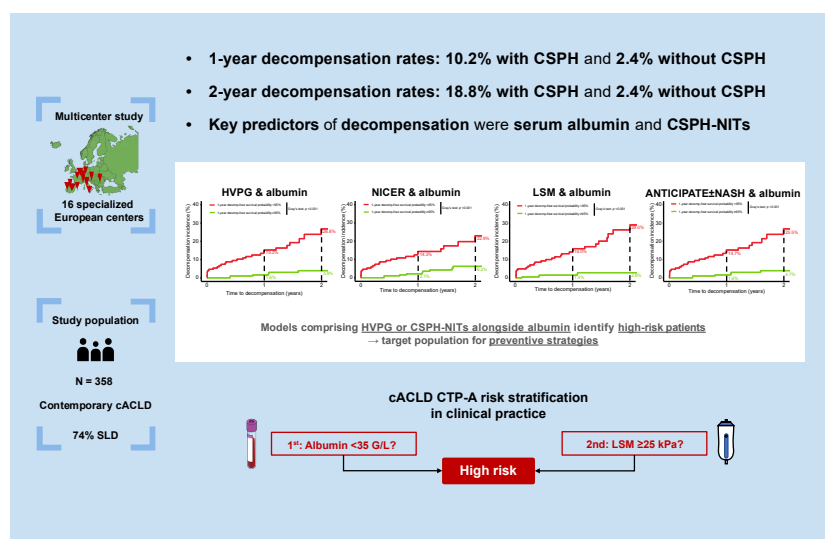
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## Graphical abstract



## Highlights

- HVPG and non-invasive tests were similarly predictive of decompensation in patients with CTP-A cirrhosis.
- Consideration of albumin levels improved the prognostic utility of HVPG and non-invasive tests.
- Novel models identify patients at high risk of decompensation within up to 2 years of follow-up.
- Liver stiffness  $\geq 25$  kPa and/or albumin  $< 35$  mg/dl indicate high risk for decompensation in clinical routine.

## Impact and implications

Non-invasive tests (NITs) facilitate the early diagnosis and management of clinically significant portal hypertension in patients with compensated advanced chronic liver disease (cACLD). In our contemporary cohort of patients with cACLD, mainly steatotic liver disease, recruited at 16 European expert centres, the hepatic venous pressure gradient and NITs were similarly predictive of decompensation within 1 to 2 years of follow-up. Serum albumin levels were identified as the second main predictor of decompensation after hepatic venous pressure gradient or NITs for clinically significant portal hypertension. Novel models were developed that could accurately predict the risk of decompensation, thereby refining point-of-care risk stratification and informing clinical trial design for patients with CTP-A cACLD.

# Predicting hepatic decompensation using non-invasive tests in a contemporary multicentre cohort of patients with cACLD

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**Background & Aims:** The NICER (liver and spleen stiffness by vibration-controlled transient elastography, platelet count, and BMI) and the ANTICIPATE±NASH models predict clinically significant portal hypertension (CSPH) in compensated advanced chronic liver disease (cACLD). This study reports follow-up data from the NICER cohort, comparing the prognostic utility of non-invasive tests for CSPH (CSPH-NITs) and hepatic venous pressure gradient (HVPG).

**Methods:** Patients with Child-Turcotte-Pugh A cACLD (liver stiffness  $\geq 10$  kPa and/or F3/4) from 16 European centres undergoing paired HVPG and CSPH-NIT assessment between 2020–2023 were included and followed until incident hepatic decompensation, hepatocellular carcinoma, death, or last visit.

**Results:** Three hundred and fifty-eight patients with cACLD were included (MASLD: 40.7%; MetALD/ALD: 32.1%; viral: 16.2%), with a CSPH prevalence of 62.0%. The cumulative 1-year and 2-year incidences of decompensation were 7.3 (95% CI 5.9–8.7%) and 12.6 (10.3–14.9%). Albumin levels were a key predictor of decompensation (subdistribution hazard ratio [sHR] 0.836; 95% CI 0.779–0.897), alongside HVPG (albumin-adjusted SHR 1.126; 95% CI 1.059–1.198), NICER (albumin-adjusted SHR 1.207; 95% CI 1.043–1.397), or ANTICIPATE±NASH (albumin-adjusted SHR 1.174; 95% CI 1.003–1.374). Models incorporating albumin alongside HVPG or CSPH-NIT achieved high C-indices for decompensation (0.772–0.806). Stratifying patients by a predicted 1-year decompensation-free survival probability of  $\geq 95\%$  or  $< 95\%$  identified approximately 60% of patients as being at negligible 1-year risk (1.4–2.1%), while the remaining patients were at high risk of decompensation (14.3–16.0%).

**Conclusion:** In our multicentre study of contemporary European patients with cACLD, non-invasively estimated CSPH risk was as predictive for decompensation as HVPG. Models comprising indicators of portal hypertension and albumin discriminated between patients at negligible decompensation risk and those with a 1-year risk of approximately 15%, *i.e.* the potential target population for preventive strategies.

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## Introduction

Patients with compensated advanced chronic liver disease (cACLD) are at high risk of hepatic decompensation if clinically significant portal hypertension (CSPH) is present.<sup>1</sup> The gold standard for the diagnosis of CSPH is the minimally invasive measurement of hepatic venous pressure gradient (HVPG), where values  $\geq 10$  mmHg denote CSPH, which is often unavailable outside specialized centres.<sup>1</sup> Meanwhile, highly accurate non-invasive tests (NITs) for ruling-in/ruling-out CSPH

have been introduced in recent years.<sup>2</sup> The Baveno VII consensus endorsed the application of liver stiffness measurement (LSM) via vibration-controlled transient elastography (VCTE) in combination with platelet count (PLT) for ruling-in (LSM  $\geq 25$  kPa) and ruling-out (LSM  $\leq 15$  kPa and PLT  $\geq 150$  G/L) CSPH based on the results of the ANTICIPATE<sup>3</sup> and subsequent ANTICIPATE-NASH<sup>4</sup> studies, summarized herein as ANTICIPATE±NASH. Spleen stiffness measurement (SSM) by VCTE, an emerging NIT for CSPH, improved the diagnostic

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yield of Baveno VII criteria in terms of an increase in the proportion of correctly classifiable patients.<sup>5</sup> However, previous data on SSM has been generated by repurposing the VCTE probe used for LSM, operating at 50 Hz, which is associated with a high failure rate when applied for SSM.<sup>5</sup> The combination of the recently introduced SSM by VCTE at 100 Hz alongside LSM, PLT and BMI in a composite model ('non-invasive CSPH estimated risk' = NICER) was associated with higher discriminative ability than the ANTICIPATE±NASH model.<sup>6</sup> Meanwhile, the prognostic relevance of SSM in general – and SSM via VCTE at 100 Hz in particular – as well as of scores considering this emergent biomarker remain poorly studied. Moreover, data on the prognostic performance of NITs for CSPH in contemporary cohorts comprising mainly patients with steatotic liver disease (SLD) are scarce, limiting their utility for both clinical decision-making and planning clinical trials.

In this report, we provide follow-up data from a contemporary, multicentre European cohort of patients with cACLD, predominantly with SLD, with the aim of developing prognostic models that incorporate either HVPG or NITs for CSPH alongside routine laboratory tests.

## Patients and methods

### Study design and definitions

This is a retrospective analysis of clinical follow-up data from a large multicentre European cohort study comprising 16 different centres. Cross-sectional data on the prediction of CSPH via NITs in this cohort have previously been reported.<sup>6</sup> Patients who were characterised by paired assessment of the HVPG and NITs, most importantly LSM and SSM, at one of the contributing centres between January 2020 and December 2023 were included.<sup>6</sup>

The original cohort included patients who were ≥18 years old and had Child-Turcotte-Pugh stage A (CTP-A) cACLD, defined as LSM ≥10 kPa and/or F3/F4 fibrosis on liver histology.<sup>6</sup> Patients were excluded from the study cohort if they had a history of splenectomy, portal or splanchnic vein thrombosis or portosinusoidal vascular disorder, transjugular intrahepatic portosystemic shunt placement, liver transplantation, or hepatocellular carcinoma (HCC) outside Milan criteria potentially interfering with LSM.<sup>6</sup> Furthermore, patients were excluded if the HVPG measurement was deemed unreliable owing to the presence of vein-vein communications or if information on PLT were unavailable.<sup>6</sup> For this analysis, we excluded patients with a history of HCC of any stage, as it may alter the natural history of cACLD, as well as those without follow-up data or with incomplete laboratory information for model for end-stage liver disease (MELD) score variables and/or serum albumin levels. The main outcome of this study was the development of first hepatic decompensation, as defined by Baveno VII, *i.e.* the development of clinically apparent ascites, variceal haemorrhage, or overt hepatic encephalopathy.

Notably, the study was designed before the new SLD nomenclature was introduced.<sup>7</sup> Thus, metabolic dysfunction-associated liver disease (MASLD) is used in place of non-alcoholic fatty liver disease in this report, while metabolic- and alcohol-related (MetALD) and alcohol-related liver disease (ALD) could not be distinguished retrospectively.

### Measurement of HVPG, LSM, SSM, and laboratory data

A maximum interval of 3 months was encouraged between NITs and HVPG assessment.<sup>6</sup> One centre also included some patients who were characterised within a time interval of up to 12 months. However, these patients did not exhibit evident changes in the activity of the primary aetiological factor or start/discontinue non-selective beta blocker (NSBB) treatment between the assessments.<sup>6</sup>

HVPG was measured in a fasted state via liver vein catheterization according to international guidelines using a balloon catheter. CSPH was defined as HVPG ≥10 mmHg.<sup>1</sup> The recommendation was to pause NSBB treatment 3 to 5 days prior the examination, if applicable.<sup>8</sup> The FibroScan Expert® 630 device (Echosens, Paris, France) was used for the assessment of LSM at 50 Hz and SSM 100 Hz. LSM was conducted according to international guidelines, using the M or XL probe as suggested by the device.<sup>9</sup> SSM was performed as previously described after determination of the optimal site via the machine's B-mode probe.<sup>6</sup> Laboratory values including PLT, MELD score variables, and serum albumin levels were assessed in clinical routine by local laboratories.

### Assessment of individual CSPH probability according to ANTICIPATE±NASH and NICER

The NICER model as well as the ANTICIPATE, or, in patients with obese MASLD, the ANTICIPATE-NASH model (ANTICIPATE±NASH), were applied to calculate the individual CSPH probability according to the published formulas.<sup>3,4,6</sup> The NICER model incorporates SSM and LSM by VCTE as well as PLT and BMI, while the ANTICIPATE±NASH model incorporates LSM by VCTE, PLT, and, in case of obese MASLD, BMI.

### Longitudinal assessment and outcome prediction

Patients were treated and followed at the discretion of the treating physician according to international recommendations<sup>3</sup> and local standards. Time zero was the assessment of HVPG. Patients were followed until the development of hepatic decompensation, the diagnosis of HCC, non-liver-related death, or last visit at the respective clinic. Follow-up data was recorded by the investigators by manual review of all locally available data until the end of November 2024.

### Statistical analysis

For categorical variables, n (%) of patients are reported, while continuous data are presented as median (IQR).

Group comparisons of categorical variables were conducted applying Fisher's exact test. The medians of continuous data were compared between groups applying Mann-Whitney *U* test.

The cumulative incidence of hepatic decompensation was calculated considering the development of HCC and non-liver-related death as competing events. Moreover, one patient underwent multiorgan transplantation including liver transplantation due to severe CSPH without prior hepatic decompensation nor HCC, which was considered as a competing event. Patients who did not develop one of the mentioned events were censored at the last follow-up visit. Between-

group differences in the incidence of hepatic decompensation were investigated via Gray's test.

To assess the prognostic value of HVP, SSM, LSM, and the composite models ANTICIPATE±NASH and NICER, as well as the MELD score and serum albumin levels, univariable competing risk regression analysis was performed. This variable selection was based on a landmark study in patients with compensated cirrhosis recruited during the 1990s which identified severity of portal hypertension (i.e. HVP), MELD, and serum albumin level as the key independent prognostic factors for hepatic decompensation.<sup>10</sup> The relationship between the prognostic biomarkers that were further evaluated in multivariable models and the cause-specific hazard for hepatic decompensation was visualized in association plots allowing for non-linear terms with restricted cubic splines comprising three knots. Multivariable competing risk regression models considered HVP or one of the investigated NITs for CSPH in addition to serum albumin levels, which yielded superior prognostic utility in comparison to MELD (including its 3.0 derivation<sup>11</sup> and its individual components) as a biomarker for hepatic dysfunction in our CTP-A cACLD cohort. Nomograms were created to illustrate the cause-specific Cox regression models. The models' time-dependent AUCs for decompensation and the overall (apparent and 10-fold cross-validated) C-index were calculated, accounting for competing events. Calibration was assessed by grouped comparison of predicted and actual cumulative incidence of hepatic decompensation at 1 year, considering competing events. Sensitivity analyses were conducted according to NSBB intake status and the underlying liver disease aetiology, and in the subcohort of patients with CTP-A5 cACLD. A landmark analysis accounting for the possibility of prevalent decompensation at baseline was conducted, excluding patients who were censored or developed one of the mentioned events before reaching 1 month of follow-up. Lastly, the prognostic utility of our models was demonstrated by stratifying the cohort according to ≥95% vs. <95% predicted 1-year decompensation-free survival, illustrating a potential application in clinical event-driven trial design using predicted decompensation-free survival as an exclusion/inclusion criterion. We evaluated the value of easy-to-use, clinically oriented decision rules for ruling-in CSPH via NITs, as proposed by the Baveno VII consensus (LSM ≥25 kPa)<sup>1</sup> and/or the recent American Association for the Study of Liver Disease (AASLD) guidelines (LSM ≥25 kPa or LSM 20–25 kPa and PLT <150 G/L or LSM 15–20 kPa and PLT <110 G/L),<sup>12</sup> with or without impaired liver function indicated by albumin levels below the lower limit of normal (<35 mg/dl).

Statistical analyses were performed using the R 4.4.2 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The *cmprsk*<sup>13</sup> package was applied for calculation of cumulative incidences and competing risk regression models ('*cuminc*' and '*crr*' functions). The *rms*<sup>14</sup> package was used for the creation of the prognostic models and respective nomograms ('*cph*' and '*nomogram*' functions), which were further investigated via C-index calculation and cross-validated using the *QHScrnomo* package<sup>15</sup> ('*cindex*' and '*tenf.crr*' functions), which was also used for the creation of the calibration curves ('*groupci*' function). The '*timeROC*' function of the *timeROC* package<sup>16</sup> was used for time-dependent AUC analysis. The models' formulas for predicting 1-year and 2-year decompensation-free survival were provided using the

models' correlation coefficients and the baseline hazard as assessed via the '*basehaz*' function of R's core survival package. A two-sided *p* value of <0.05 was considered statistically significant.

## Ethics

The study was approved by the ethics committees of the Medical University of Vienna (No.1544/2019) and local institutional review boards. Informed consent was obtained, if its requirement had not been waived by the respective institutional review board. The study was performed in accordance with the current version of the Helsinki Declaration.

## Results

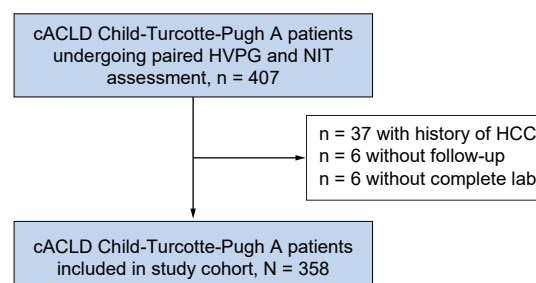
### Study cohort

Four-hundred and seven patients with CTP-A cACLD included in our multicentre observational cohort study<sup>6</sup> were reviewed for inclusion in this analysis. After the exclusion of 37 patients who had a history of HCC, six patients without follow-up data, and six patients with missing lab values, 358 patients were included in the final study cohort, as shown in Fig. 1.

Among these patients, 237 (66.2%) were male, and the median age was 60.0 (IQR 54.0–66.2) years. The predominant aetiology of cACLD was MASLD (42.7%), followed by MetALD/ALD (31.6%), viral disease (16.2%), and other (9.5%). Among patients with MetALD/ALD, 68.1% were abstinent at baseline. In the subcohort of patients with viral disease, 79.3% had achieved control of viral hepatitis, while the remaining patients mostly had uncontrolled HDV-coinfection in addition to controlled HBV. CSPH as determined by HVP was present in 222 (62.0%) patients at baseline. Two-hundred eighty-nine (80.7%) had CTP-A5 cACLD. Detailed information on additional patient characteristics is given in Table 1.

### Treatment and events during follow-up

The median follow-up time among the overall cohort was 1.33 (IQR 0.80–1.97) years. Hepatic decompensation occurred in 36 patients, while 13 patients developed HCC, five patients died of non-liver-related causes, and one patient underwent liver transplantation without prior decompensation, translating into a cumulative incidence of decompensation of 7.3% (95% CI 5.9–8.7%) and 12.6% (10.3–14.9%) at 1 and 2 years of follow-up, respectively. Most patients who decompensated had CSPH, as determined by HVP at baseline (*n* = 32, 88.9%),



**Fig. 1. Study cohort.** cACLD, compensated advanced chronic liver disease; HCC, hepatocellular carcinoma; HVP, hepatic venous pressure gradient; NIT, non-invasive test.



**Table 1. Patient characteristics of the overall patient cohort.**

Parameter	Study cohort N = 358
Age, years (IQR)	60.0 (54.0–66.2)
Sex, male (%)	237 (66.2)
Body mass index, kg/m <sup>2</sup>	28.7 (24.7–33.5)
≥30 kg/m <sup>2</sup> , n (%)	153 (42.7)
Aetiology	
MASLD, n (%)	153 (42.7)
MetALD/ALD, n (%)	113 (31.6)
Viral, n (%)	58 (16.2)
Others, n (%)	34 (9.5)
HVPG, mmHg (IQR)	11.0 (7.5–15.0)
≥10 mmHg, n (%)	222 (62.0)
Varices	
None, n (%)	166 (46.4)
Small, n (%)	94 (26.3)
Large, n (%)	67 (18.7)
Unknown, n (%)	31 (8.7)
LSM by VCTE, kPa (IQR)	21.6 (14.5–33.1)
SSM by VCTE, kPa (IQR)	46.8 (33.9–66.6)
PLT, G/L (IQR)	129 (87–178)
<150 G/L, n (%)	223 (62.3)
MELD score, points (IQR)	9 (7–11)
Albumin, G/L (IQR)	41.3 (37.0–45.0)

ALD, alcohol-related liver disease; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; MetALD, MASLD and increased alcohol intake; PLT, platelet count; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

while four (11.1%) patients had subclinical portal hypertension, *i.e.* elevated but clinically insignificant HVPG values ranging from 6 to 9 mmHg. The most frequent decompensation event was the development of clinically apparent ascites ( $n = 24$ ), followed by variceal haemorrhage ( $n = 8$ ) and overt hepatic encephalopathy ( $n = 4$ ). Among patients with CSPH as determined by HVPG ( $n = 222$ ), 151 (68.0%) were treated with carvedilol ( $n = 124$ ) or propranolol ( $n = 27$ ) during follow-up. Fig. S1 shows a comparison of the cumulative incidence of hepatic decompensation between patients with and without CSPH according to HVPG (year 1 decompensation rate [Y1]: 10.2% [8.1–12.3%] vs. 2.4% [1.0–3.8%]; year 2 decompensation rate [Y2]: 18.8% [15.3–22.3%] vs. 2.4 [1.0–3.8%]; Gray's test  $p < 0.001$ ). Further differences in characteristics between patients who did or did not experience decompensation during follow-up is given in Table S1.

### Predictors of hepatic decompensation

In univariable competing risk regression analysis, the HVPG ( $p < 0.001$ ), LSM ( $p < 0.001$ ), SSM ( $p = 0.040$ ), and BMI ( $p = 0.018$ ), the composite models NICER ( $p < 0.001$ ) and ANTICIPATE±NASH ( $p < 0.001$ ), as well as MELD ( $p = 0.011$ ) and albumin serum levels ( $p < 0.001$ ), were identified as predictors of decompensation (Table S2). In a multivariable competing risk regression model comprising MELD (3.0) variables, *i.e.* sex, serum sodium levels, serum creatinine, bilirubin, international normalized ratio, and serum albumin levels, serum albumin emerged as the only independent predictor of decompensation ( $p < 0.001$ ) (Table S3). Thus, serum albumin levels were considered in further analysis and multivariable prediction models.

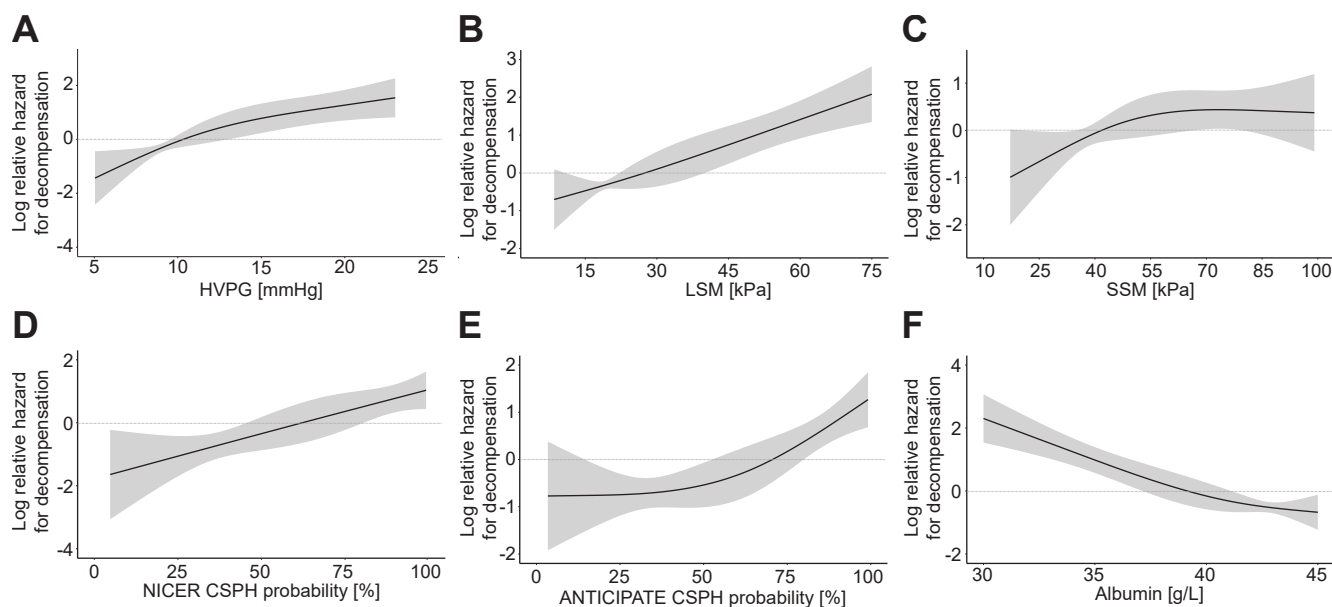
Fig. 2 shows the relation between HVPG, LSM by VCTE, SSM by VCTE, the NICER and ANTICIPATE±NASH models, serum albumin levels, and the relative cause-specific hazard

for decompensation. Of note, serum albumin levels above 45 G/L indicated no further decrease in the risk for decompensation, and only few patients had albumin levels below 30 G/L. Consequently, serum albumin levels were capped at these thresholds for the development of predictive models. HVPG, the investigated NITs for CSPH, and albumin levels demonstrated similar apparent (1 year: 0.701–0.776, 2 years: 0.766–0.810) and cross-validated (1 year: 0.691–0.753, 2 years: 0.710–0.774) time-dependent AUCs and overall C-indices for predicting decompensation (Table S4). Calibration of the respective biomarkers is illustrated in Fig. S2.

### Development and internal validation of models predicting decompensation

In multivariable competing risk regression analysis adjusted for serum albumin levels, HVPG ( $p < 0.001$ ), LSM by VCTE ( $p = 0.001$ ), and the composite models NICER ( $p = 0.011$ ) and ANTICIPATE±NASH ( $p = 0.046$ ), but not SSM by VCTE as an individual parameter ( $p = 0.087$ ), independently predicted decompensation, as shown in Table 2. The observed findings were robust in a landmark analysis excluding patients with less than 1 month of follow-up (Table S5), although ANTICIPATE±NASH could not maintain statistical significance in this subcohort with fewer events. All albumin-considering models demonstrated similarly high apparent (1 year: 0.803–0.844, 2 years: 0.842–0.868) and cross-validated (1 year: 0.791–0.834, 2 years: 0.816 – 0.858) time-dependent AUCs and C-indices (apparent: 0.772–0.806, cross-validated: 0.750–0.791) for decompensation (Table 3). The (apparent) performance of the models was neither influenced by the intake of propranolol/carvedilol during follow-up (Table S6), nor by the sub-aetiology of SLD (MASLD vs. metALD/ALD, Table S7) in sensitivity analyses. Similar results were observed when limiting the population to only CTP-A5 cACLD (Table S8). Of note, LSM predicted decompensation independently of HVPG, which was not the case for SSM (Table S9). Cross-validation was not performed during sensitivity analyses owing to sample size. The corresponding formulas for predicting decompensation-free survival at year 1 and 2 of follow-up are given in Table S10. Nomograms illustrating the models are shown in Fig. 3. Calibration of the models in the overall patient cohort and among the subcohorts of patients with MASLD and ALD/metALD is provided in Figs S3 and S4.

The median predicted 1-year decompensation probability was approximately 5% for all albumin-including models (HVPG: 3.8%, LSM: 4.2%, NICER: 4.0%, ANTICIPATE±NASH: 4.2%). As an example, we stratified the cohort according to a predicted 1-year decompensation-free survival probability ≥95% vs. <95%. Despite identifying approximately 60% of patients as being at negligible/low risk of decompensation, all albumin-including models identified most patients decompensating within the first year of follow-up, missing only a few patients who decompensated (HVPG & albumin, LSM by VCTE & albumin, and ANTICIPATE±NASH & albumin:  $n = 3$ , NICER & albumin:  $n = 4$ ) (Fig. 4). While the 1-year probability of decompensation ranged from 1.4–2.1% in the low-risk group, it was 14.3–16.0% in the high-risk group. Discrimination was maintained at the end of year 2, with probabilities of 2.8–6.2% vs. 22.9–29.0%. The chosen cut-off was associated with high negative predictive values (>98% for all models) and sensitivity (approximately 87% for all models) (Table S11).



**Fig. 2.** Relationship between the individual risk predictors investigated in the study and the  $\log_{10}$  relative hazard ratio for hepatic decompensation. Relationship between (A) HVPG, (B) LSM by VCTE, (C) SSM by VCTE, (D) CSPH probability according to the NICER model, (E) CSPH probability according to the ANTICIPATE $\pm$ NASH model, (F) serum albumin, and the  $\log_{10}$  relative hazard ratio for hepatic decompensation. Models allowed non-linear terms with restricted cubic splines (three knots). CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography; SSM, spleen stiffness measurement.

Similar results were observed in sensitivity analyses among patients with CTP-A5, although the model considering NICER alongside albumin did not maintain statistical significance (Fig. S5). Moreover, a landmark analysis excluding patients with <1 month of follow-up confirmed our findings (Fig. S6).

### NIT cut-offs for risk prediction

The Baveno VII criterion for ruling-in CSPH, *i.e.* LSM  $\geq$ 25 kPa (prevalence: 37.4%), effectively distinguished patients at high risk of decompensation from those with a more favourable prognosis. The cumulative incidence of decompensation among those meeting vs. not meeting the criterion was 13.7% (95% CI 10.6–16.8) vs. 3.3% (2.1–5.5%) at 1 year and 23.3% (18.5–28.1) vs. 5.8% (3.9–7.7%) at 2 years ( $p < 0.001$ ). Similar discrimination was observed for the 40 kPa SSM cut-off

(prevalence: 62.3%; Y1: 8.7% [6.7–10.7] vs. 4.9% [2.9–6.9], Y2: 16.5% [13.1–19.9] vs. 6.5% [4.0–9.0],  $p = 0.029$ ), as well as for exceeding a CSPH probability  $\geq$ 60% according to either the NICER (prevalence: 59.5%; Y1: 9.8% [7.6–12.0] vs. 3.6% [2.0–5.2], Y2: 17.3% [14.8–20.8] vs. 6.1% [3.8–8.4],  $p = 0.004$ ) or the ANTICIPATE $\pm$ NASH model (prevalence: 52.0%; Y1: 11.2% [8.7–13.7] vs. 3.1% [1.7–4.5], Y2: 19.0% [15.1–22.1] vs. 6.0% [3.8–8.2],  $p = 0.002$ ) (Fig. S1).

Finally, to provide an easy-to-use approach for risk stratification based on this study's results, we refined the LSM-based ruling-in criteria for CSPH by the Baveno consensus (LSM  $\geq$ 25 kPa) and the AASLD practice guidelines (LSM  $\geq$ 25 kPa or LSM 20–25 & PLT <150 G/L or LSM 15–20 & PLT <110 G/L) by also considering albumin levels. Stratifying the cohort by CSPH status, according to the aforementioned criteria, and/or impaired liver function indicated by below-normal albumin levels (<35 mg/dl) improved discrimination for predicting decompensation, which was paralleled by improved test performance metrics compared to decision rules based on LSM (with or without PLT) alone (Fig. S7; Table S12).

### Discussion

In our study investigating the incidence and predictors of hepatic decompensation in a contemporary, European multi-centre cohort of patients with CTP-A cACLD, predominantly caused by SLD, we confirmed the relevance of CSPH (HVPG  $\geq$ 10 mmHg) and non-invasive estimates of its probability (CSPH-NITs) for risk prediction. Furthermore, we developed prognostic models for decompensation-free survival during 1 to 2 years of follow-up incorporating serum albumin levels, reflecting liver function, as the second key predictor of prognosis in cACLD.

**Table 2.** Multivariable competing risk regression analysis investigating the independent value of HVPG, SSM by VCTE, LSM by VCTE, and the composite CSPH prediction models (ANTICIPATE $\pm$ NASH and NICER) in predicting hepatic decompensation during follow-up ( $n = 36$ ), adjusted for serum albumin levels (ranging from 30–45 G/L).

Parameter	Adjusted subdistribution hazard ratio	95% CI	$p$ value
HVPG, per mmHg	1.126	1.059–1.198	<0.001
LSM by VCTE, per kPa	1.031	1.012–1.050	0.001
SSM by VCTE, per kPa	1.011	0.998–1.025	0.087
NICER, per 10% CSPH risk	1.207	1.043–1.397	0.011
ANTICIPATE $\pm$ NASH, per 10% CSPH risk	1.174	1.003–1.374	0.046

CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

**Table 3. Time-dependent AUCs with 95% CIs and overall C-indices for hepatic decompensation (considering competing events) of the final models including HVPG or a NIT for CSPH alongside albumin levels (ranging from 30–45 G/L).**

Model	Apparent AUC for decompensation at 1 year	Cross-validated AUC for decompensation at 1 year	Apparent AUC for decompensation at 2 years	Cross-validated AUC for decompensation at 2 years	Apparent C-index	Cross-validated C-index
HVPG + albumin	0.844 (0.767–0.921)	0.800 (0.706–0.894)	0.868 (0.801–0.935)	0.858 (0.788–0.929)	0.793	0.775
LSM by VCTE + albumin	0.840 (0.767–0.921)	0.834 (0.756–0.911)	0.865 (0.7933–0.936)	0.844 (0.764–0.925)	0.806	0.791
NICER + albumin	0.803 (0.717–0.895)	0.792 (0.697–0.887)	0.842 (0.767–0.895)	0.816 (0.730–0.901)	0.776	0.759
ANTICIPATE±NASH + albumin	0.815 (0.735–0.894)	0.791 (0.702–0.879)	0.850 (0.764–0.936)	0.825 (0.733–0.917)	0.772	0.750

CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; NIT, non-invasive test; VCTE, vibration-controlled transient elastography.

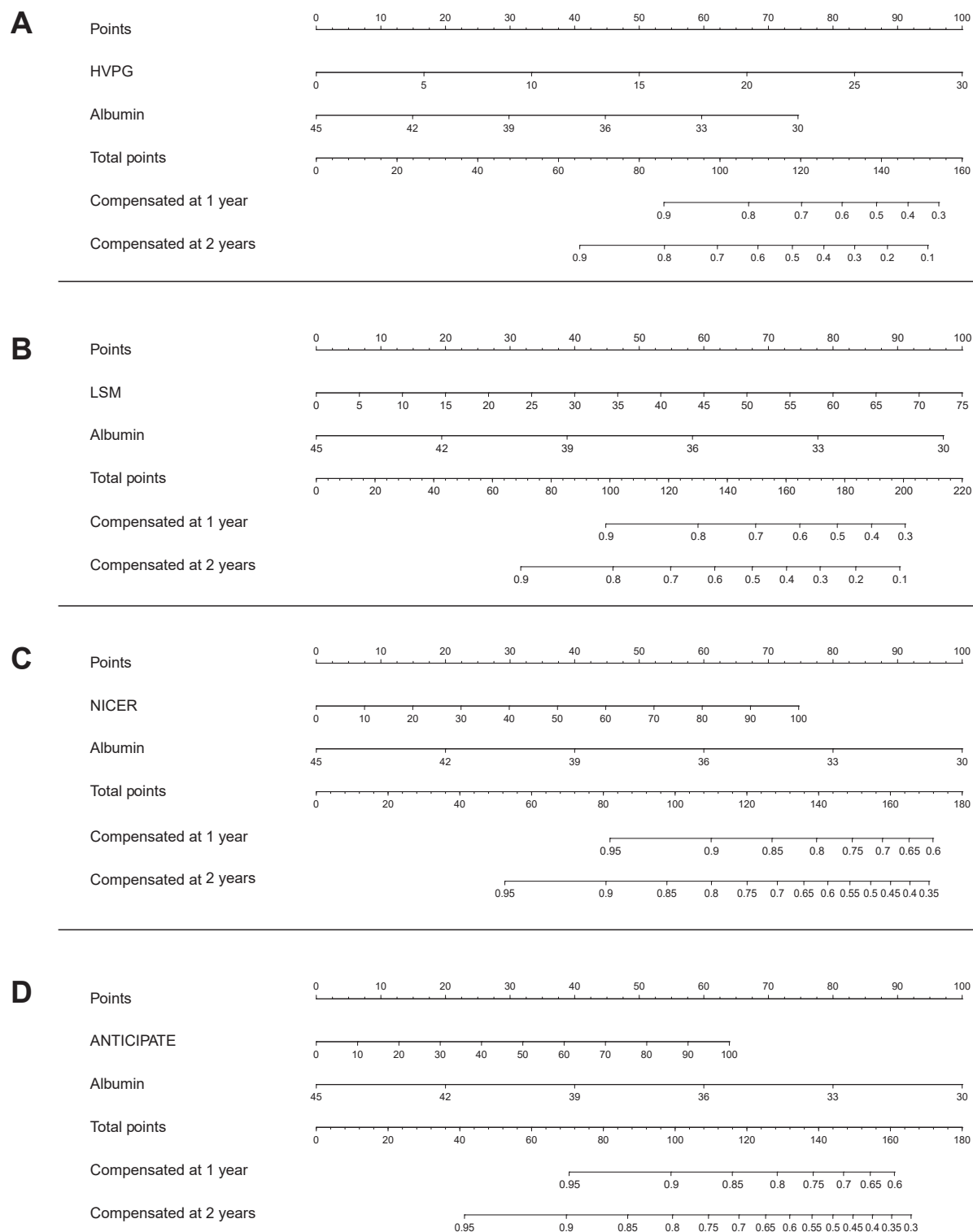
The diagnostic utility of NITs for CSPH has been extensively studied in multinational cohorts, although the generalizability of most of the data (viraemic viral hepatitis) to contemporary clinical practice (SLD and cured/suppressed viral hepatitis) remains unclear.<sup>2–5</sup> While it has been demonstrated that LSM by VCTE-based NITs confer similar prognostic information as the HVPG in patients with cACLD,<sup>17</sup> the prognostic utility of the recently introduced NICER model incorporating SSM by VCTE at 100 Hz remained to be established. In our cohort, in which the NICER model was developed, the NICER and the ANTICIPATE±NASH models showed a similar discriminative ability for hepatic decompensation, compared to HVPG. Intriguingly, when assessed as a standalone NIT, LSM by VCTE performed similarly to HVPG and the composite models. Meanwhile, SSM by VCTE, which has been firmly established as a diagnostic NIT for CSPH in cACLD,<sup>2,5,6</sup> did not independently predict hepatic decompensation. It may be hypothesized that the limited prognostic utility of SSM by VCTE owes to the lack of capturing liver disease activity in addition to portal hypertension, while both are reflected by LSM.<sup>18</sup> Along these lines, it should be noted that LSM by VCTE conferred prognostic information that was at least partly independent from HVPG in our study, which was not the case for SSM by VCTE. Since the consideration of SSM by VCTE improves the non-invasive diagnosis of CSPH as evidenced by the NICER model outperforming other CSPH-NITs,<sup>6</sup> SSM by VCTE has clinical utility as a predictive biomarker for the therapeutic benefit of carvedilol/NSBBs. However, SSM by VCTE does not seem essential for outcome prediction and may be of subordinate relevance (vs. LSM by VCTE) as a prognostic biomarker. However, it should be noted that SSM by VCTE predicted decompensation in univariable analysis, and the previously proposed 40 kPa cut-off could distinguish between patients at low and high risk of decompensation. Considering the limited number of decompensation events for multivariate modelling, validation in larger cohorts would be desirable, which do not necessarily need to be HVPG-characterised. Nonetheless, early reports postulating that SSM may be more informative than LSM in cACLD might have been overly optimistic.<sup>19</sup>

Moreover, it would be of interest to investigate the (prognostic) value of changes in SSM, especially since conflicting data on LSM has been published in this context.<sup>20–23</sup> Currently, it seems that the most recent LSM value rather than its dynamics over time are key for prognostication in cACLD. We would like to hypothesize that the same applies to SSM; however, our study does not provide longitudinal information.

Our results also highlight the importance of considering surrogates of liver function alongside HVPG or NITs for CSPH for risk prediction in cACLD.<sup>10,24</sup> In previous reports, albumin levels below 40 G/L were predictive of decompensation,

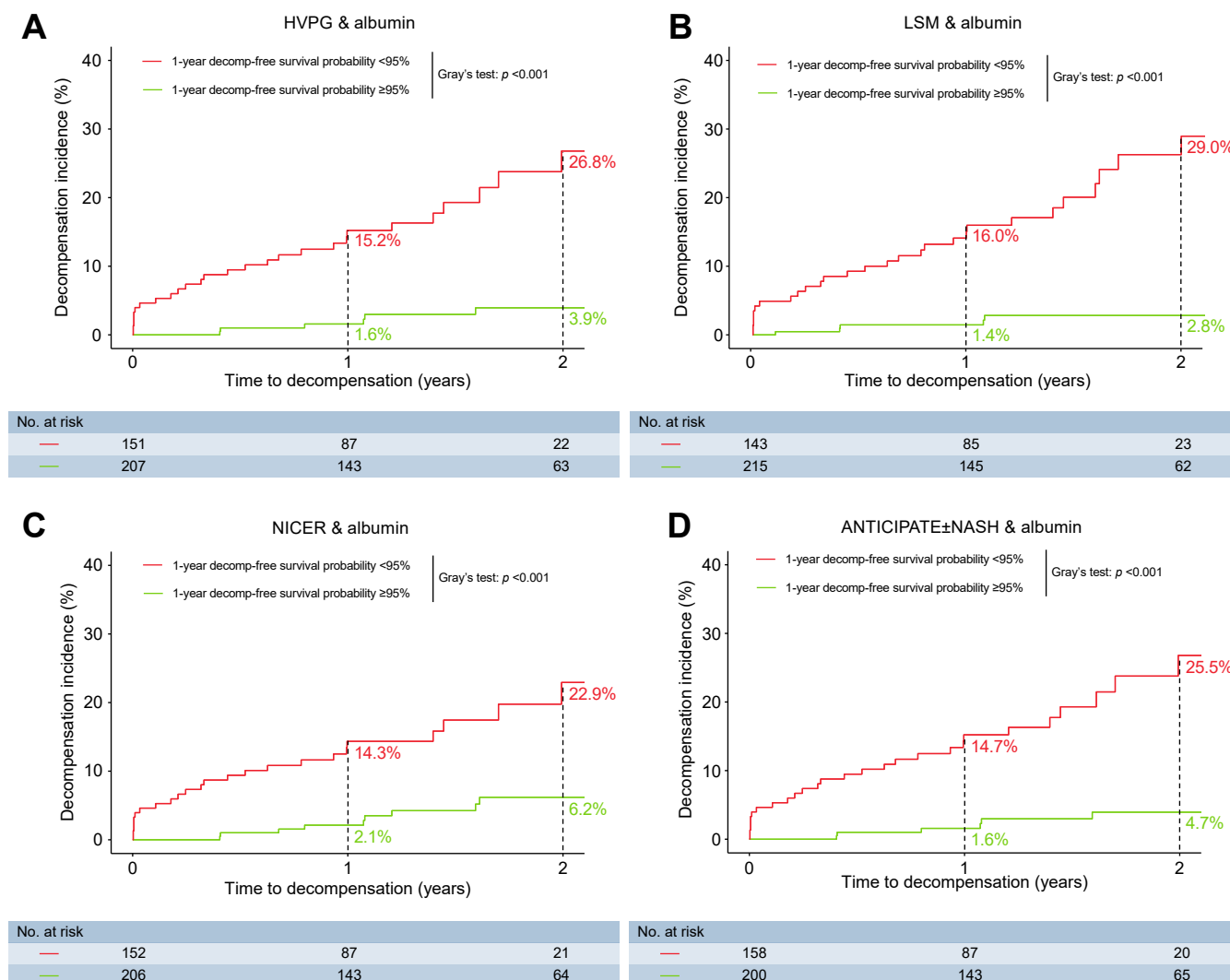
corresponding with the risk prediction inflection point observed for albumin levels in our cohort.<sup>24</sup> To provide an easy-to-use risk prediction algorithm for clinical routine, we decided to investigate a more specific cut-off at 35 G/L, as this threshold aligns with the CTP score. When combined with ruling-in criteria for CSPH put forward by the Baveno VII consensus<sup>1</sup> and the AASLD practice guidelines,<sup>12</sup> patients at high risk for short-term decompensation and those at negligible risk could be accurately distinguished. Intriguingly, the Baveno VII rule-in criterion (LSM ≥25 kPa) performed even better than the AASLD criteria combining LSM with PLT, further corroborating the value of LSM as a prognostic NIT, particularly if albumin levels are considered. While albumin levels were independently predictive of decompensation in our CTP-A patient cohort, which is the target population for the application of CSPH-NITs, MELD seemed of limited prognostic value in this population. Notably, previous studies demonstrating the prognostic value of MELD in compensated cirrhosis also included patients with CTP-B.<sup>10</sup> Despite the restriction to CTP-A patients, our HVPG-characterised cohort was at considerable risk of decompensation during follow-up, and thus, evaluation/validation of the discrimination and calibration of our proposed prediction models in unselected cACLD cohorts is required. Of note, a previous study investigating the prognostic utility of the ANTICIPATE(-NASH) models in patients with MASLD not characterised by HVPG reported convincing results, suggesting that CSPH-NIT-based models developed in HVPG-characterised patients may be broadly applicable.<sup>25</sup> However, the latter study also included patients without cACLD and one may argue that these patients are easier to classify in regard to decompensation risk.

Among the patients who decompensated, most had MetALD/ALD, highlighting the particularly progressive natural history of this entity, which contrasts to the generally more benign course of MASLD or ‘contemporary’ (i.e. suppressed/cured) viral hepatitis.<sup>26</sup> Nevertheless, the observed time-dependent AUCs and C-indices in patients with MASLD were higher than in patients with MetALD/ALD. We would like to hypothesize that in patients with MetALD/ALD, alcohol intake patterns during follow-up contribute to a more heterogeneous natural history, resulting in difficult-to-predict disease trajectories.<sup>17,26</sup> Notably, the CSPH risk according to the NICER model accounting for BMI seems not to be influenced by the aetiology *per se*, as it was well calibrated across different SLD sub-aetiologies in our modelling study.<sup>6</sup> Meanwhile, the ANTICIPATE±NASH model has already been adjusted for use in patients with obese MASLD.<sup>25</sup> Regardless, it may be worth exploring SLD-specific prognostic models in future cohort studies that also capture disease activity, e.g. by monitoring alcohol intake, physical activity, weight loss, and therapies targeting obesity and MASH (e.g. incretin analogues), which was not



**Fig. 3. Nomograms facilitating point-of-care prognostication predicting decompensation-free survival at 1 and 2 years of follow-up.** The nomograms comprise (A) HVPG (B) LSM by VCTE, (C) the NICER model, (D) the ANTICIPATE±NASH model, alongside serum albumin levels (capped at 30 and 45 G/L). HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography.





**Fig. 4. Comparison of the incidence of hepatic decompensation between patients with  $\geq 95\%$  and  $< 95\%$  1-year decompensation-free survival probability according to competing risk regression models comprising serum albumin levels.** Competing risk regression models comprising serum albumin levels and (A) HVPG, (B) LSM by VCTE, (C) the NICER model, and (D) the ANTICIPATE±NASH model. Incident hepatocellular carcinoma and non-liver-related death were considered as competing events. Cumulative incidences were compared via Gray's test. HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; VCTE, vibration-controlled transient elastography. (This figure appears in color on the web.)

feasible within the framework of our cohort that included limited numbers of patients and events. Moreover, we were unable to distinguish MetALD from ALD, as the definition of MetALD only emerged during the conduct of the study.

It should be noted that the landmark studies establishing HVPG as the prognostic gold standard in cACLD recruited patients in the 1990s and included mostly patients with viræmic viral hepatitis,<sup>10</sup> which limits the generalizability of their findings to current clinical practice and reduces their utility for sample size estimations in contemporary clinical trials. Our study provides updated decompensation rates in a multicentre European cohort, reflecting the recent shift in aetiology towards SLD. Importantly, we focused exclusively on the prediction of hepatic decompensation as defined by Baveno VII,<sup>1</sup> which contrasts with previous studies that included incident HCC in their definition of liver-related events.<sup>25</sup> The rationale for this decision is the different clinical consequences of

hepatic decompensation vs. HCC, which limit the interpretability of composite endpoints. Interestingly, in our cohort, three patients with SLD who only had subclinical portal hypertension at baseline decompensated within the first year of follow-up. Albeit anecdotal, this highlights that in the context of progressive SLD, HVPG and NIT may be subject to rapid changes. Particularly, in MetALD/ALD, alcohol consumption may induce rapid increases in HVPG.<sup>27</sup> Moreover, HVPG may slightly underestimate the risk for decompensation in some patients with MASLD,<sup>28</sup> while the prognostic value of CSPH as determined by the HVPG itself has recently been confirmed even in MASLD.<sup>29</sup> While repeating HVPG is not feasible outside clinical studies, NITs can be easily updated. Consequently, the Baveno VII consensus suggests monitoring patients with NIT on a yearly basis.<sup>1</sup> This is supported by our data, because overall C-indices for decompensation were lower than time-dependent AUCs at 1 and 2 years of follow-up,

indicating that NIT-based risk stratification is associated with reduced predictive accuracy after 2 years. It could be argued that even shorter intervals may be justified in case of progressive cACLD aetiology. Meanwhile, although data exists that links dynamics in NITs to clinical endpoints,<sup>21</sup> the last (absolute) value should guide clinical decision-making in the setting of cACLD.<sup>2,20</sup>

Furthermore, we encourage the application of continuous risk prediction models rather than dichotomized decision rules/algorithms to avoid the loss of valuable prognostic information. Quantifying the CSPH probability, and thereby estimating the risk for decompensation, provides physicians and patients with individualized information and enables shared decision-making on strategies to prevent decompensation. Considering serum albumin may further refine decision-making, since those with low baseline risk, including some with HVPG-confirmed CSPH, could require an unacceptably high number-needed-to-treat for carvedilol. For illustrative purposes, we stratified patients by a predicted decompensation-free survival probability of  $\geq 95\%$  or  $< 95\%$ , and identified approximately 60% of patients as being at negligible 1-year risk (1.6–2.1%), while the remaining patients were at substantial risk of decompensation (14.3–16%), *i.e.* the potential target population for preventive strategies. Notably, the proportion of patients identified as being at negligible (predicted) risk exceeded the proportion of patients without haemodynamically confirmed CSPH.

Our study has several strengths, including, first and foremost, its multicentre design, resulting in the inclusion of a contemporary cohort from 16 expert centres across Europe. This allowed for a thorough investigation of the (comparative) value of NITs for CSPH that were initially developed for diagnostic purposes. While previous studies have shown that HVPG and NITs for CSPH confer comparable prognostic information, these data were generated in historic cohorts of

patients with mostly viraemic hepatitis C, a group that is no longer clinically relevant.<sup>17</sup> Meanwhile, validation of these findings in contemporary patients with SLD was lacking. With regards to SSM (at 100 Hz), this cohort is the first that allowed for a detailed appraisal of its prognostic utility following the development of the diagnostic NICER model based on cross-sectional information.<sup>6</sup> However, the uniqueness of this cohort precluded external validation of our findings at this point. Thus, adjustments may be necessary to refine our model for use in lower-risk, non-HVPG-characterised cohorts. Reassuringly, the observed C-statistics of our models are well in line with previous studies modelling decompensation risk based on CSPH-NITs in cohorts with cACLD.<sup>25</sup> We observed a high number of patients on prophylactic treatment with carvedilol or propranolol, which is nowadays the standard of care in (NIT-suspected) CSPH, particularly in the presence of varices.<sup>1,12</sup> Two out of three patients with HVPG-confirmed CSPH received prophylactic treatment, which may have influenced the relationship between clinical risk and NITs, potentially even lowering their discriminative ability, as clinical risk was mitigated in those at higher predicted risk. However, this limitation likely affected all investigated NITs similarly and therefore would not have influenced their comparison. Notably, the derived risk estimates are representative of the current standard of care, and thus, may be most informative for sample size calculations.

In our multicentre study of contemporary European patients with cACLD, with SLD as the predominant aetiology, non-invasively estimated CSPH risk was as predictive for decompensation as HVPG. Models and simple clinical decision algorithms based on non-invasive indicators of portal hypertension and albumin may discriminate between patients at negligible decompensation risk and those with a 1-year risk of approximately 15%, and subsequent external validation may identify the target population for preventive strategies.

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### Abbreviations

ALD, alcohol-related liver disease; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; HVPG, hepatic venous

pressure gradient; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; MetALD, metabolic- and alcohol-related liver disease; NIT, non-invasive test; PLT, platelet count; SHR, subdistribution hazard ratio; SLD, steatotic liver

disease; SSM, spleen stiffness measurement; VCTE, vibration-controlled transient elastography.

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### Conflict of interest

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The authors declare no conflict of interest regarding this study. Outside the submitted work, the authors declare the following potential conflicts of interest: M.J. served as a speaker and/or consultant for Gilead. P.T. no conflict of interest. A.O. no conflict of interest. F.T. served as speaker for W. L. Gore & Associates. L. M. no conflict of interest. L.T. served as speaker and/or consultant and/or advisory board member for AbbVie, Eisai, Gilead, Janssen, and W. L. Gore & Associates and received travel support from AbbVie, Janssen, Roche, and Gilead. P.F. no conflict of interest. D.S. no conflict of interest. W.K. served as speaker for the PanNASH initiative and received travel grants from Ipsen and Norgine. He is a co-inventor patent on the use of lipopigment imaging for disease (filed by MGH/MIT: US 20190307390). M.G. no conflicts to declare. E.L. n no conflicts to declare. Y.P.M. no conflicts to declare. A.A. no conflicts to declare. J. T. no conflicts to declare. C.P. no conflicts to declare. A.C. served as speaker and/or consultant for Jazz Pharmaceuticals. F.R. no conflict of interest. B.M. received grants/research support from Abbott, Fujirebio, Evimed, Roche; and personal fees from Abbott, AbbVie, BMS, Janssen, Luvos, Merck/MSD, Roche, Fujirebio, Norgine, Gilead, Astellas. W.L. served as consultant for Cook Medical, Boston Scientific, CSL Behring, MRM Health. J.P. served as speaker and/or consultant and/or advisory board member for AbbVie, Gilead, Advanz, MSD, Roche, Astra-Zeneca, Eisai, Orphan and Sobi. J.M.S. served as consultant and/or advisory board member for AbbVie, honorarium from Apollo Endoscopy, Boehringer Ingelheim, Gilead, Advanz Sciences, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal Pharmaceuticals, MSD, Northsea Therapeutics, Novartis, Novo Nordisk, Pfizer, Roche, Astra-Zeneca, Eisai, Orphan/Sanofi, and Siemens Healthineers, research funding from Boehringer Ingelheim, Siemens Healthcare GmbH, and speaker honoraria from Boehringer Ingelheim, Echosens, MedPublico GmbH, Novo Nordisk, Madrigal Pharmaceuticals, Histoindex, MedPublico GmbH; Stockholder options: AGED diagnostics, and Sobi JHepta Bio. A.B. served as consultant and/or speaker for Boehringer Ingelheim, GE Healthcare; Hologic; W. L. Gore & Associates. J.L.C. no conflicts to declare. V.C. served as a speaker and/or consultant and/or advisory board member for Advanz, Ipsen, AbbVie, Echosens, Gilead, and Roche and received grants/research support from Advanz, MSD. S.F. served as speaker and/or consultant for W.L. Gore & Associates, Cook Medical, Echosens; and received grants/research support from W.L. Gore & Associates and Cook Medical. F.S. served as speaker and/or consultant for W.L. Gore & Associates, Cook Medical and Echosens; received grants/research support from W.L. Gore and Cook Medical. B.P. served as speaker for AbbVie and Echosens. A.A. has received fellowship funding from UEWG. P-E.R. has received research funding from Terrafirma and served as speaker and/or consultant for Abbelight, AbbVie, Hemostod, Mursla, Genfit, Boehringer Ingelheim and Tillots Pharma. J.C.G.-P. served as advisory board member for W. L. Gore & Associates and Cook, and received grant support from Mallinckrodt, VIFOR and Astra-Zeneca. A.P. no conflict of interest. J.I. F. served as a speaker for Grifols and received travel support from Gilead. T.R. served as a speaker and/or consultant and/or advisory board member for AbbVie, Bayer, Boehringer Ingelheim, Gilead, Intercept, MSD, Siemens, and W. L. Gore & Associates and received grants/research support from AbbVie, Boehringer Ingelheim, Gilead, Intercept, MSD, Myr Pharmaceuticals, Pliant, Philips, Siemens, and W. L. Gore & Associates as well as travel support from AbbVie, Boehringer Ingelheim, Gilead and Roche. M.M. served as a speaker and/or consultant and/or advisory board member for AbbVie, Echosens, Eli Lilly, Gilead, Ipsen, Takeda, and W. L. Gore & Associates and received travel support from AbbVie and Gilead. P.A. no conflicts to declare. A.F.S. no conflicts to

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

### Authors' contributions

All authors contributed to conceptualization (M.J. and M.M.), data curation (all authors), formal analysis and visualization (M.J., P.T.), writing of the original draft (M.J., P.T. and M.M.), reviewing and editing (all authors), or supervision (M.M.).

### Data availability

Data are available in pseudonymised manner upon request to the corresponding author after approval by the coauthors.

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## Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2025.10.019>.

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Author names in bold designate shared co-first authorship

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## **Supplemental information**

### **Predicting hepatic decompensation using non-invasive tests in a contemporary multicentre cohort of patients with cACLD**

**Mathias Jachs, Paul Thöne, Aitor Odriozola, Fanny Turon, Lucile Moga, Luis Téllez, Petra Fischer, Dario Saltini, Wilhelmus J. Kwanten, Maria Grasso, Elba Llop, Yuly P. Mendoza, Angelo Armandi, Carlos Pardo, Antonio Colecchia, Federico Ravaioli, Benjamin Maasoumy, Wim Laleman, José Presa, Jörn M. Schattenberg, Annalisa Berzigotti, José L. Calleja, Vincenza Calvaruso, Thomas Vanwolleghem, Filippo Schepis, Bogdan Procopet, Agustín Albillos, Pierre-Emmanuel Rautou, Juan C. Garcia-Pagan, Ángela Puente, José I. Fortea, Thomas Reiberger, Mattias Mandorfer, and SSM-100Hz/ACLD Study Group of the Baveno Cooperation: an EASL consortium**

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**Table S1.** Differences in patient characteristics between patients experiencing hepatic decompensation during follow-up and patients who remained compensated. Fisher's exact and Mann-Whitney U test were used for comparisons.

Parameter	No decompensation n=322	Decompensation n=36	p-value
<b>Age, years (IQR)</b>	60.0 (55.0-66.2)	59.0 (46.8-65.6)	0.314
<b>Sex, male (%)</b>	213 (66.1)	24 (66.7)	1.000
<b>Body mass index, kg/m<sup>2</sup></b>	29.1 (24.8-33.6)	27.0 (24.3-31.3)	0.066
≥30 kg/m <sup>2</sup> , n (%)	142 (44.1)	11 (30.6)	0.168
<b>Aetiology</b>			0.005
MASLD, n (%)	141 (43.8)	12 (33.3)	
MetALD/ALD, n (%)	93 (28.9)	20 (55.6)	
Viral, n (%)	57 (17.7)	1 (2.8)	
Others, n (%)	31 (9.6)	3 (8.3)	
<b>HVPG, mmHg (IQR)</b>	10.5 (7.5-14.0)	14 (11.0-20.0)	<0.001
≥10 mmHg, n (%)	190 (59.0)	32 (88.9)	0.001
<b>Varices</b>			0.078
None, n (%)	154 (47.8)	12 (33.3)	
Small, n (%)	82 (25.5)	12 (33.3)	
Large, n (%)	56 (17.4)	11 (30.6)	
Unknown, n (%)	30 (9.3)	1 (2.8)	
<b>LSM by VCTE, kPa (IQR)</b>	20.9 (14.3-29.9)	40.5 (23.9-57.5)	<0.001
<b>SSM by VCTE, kPa (IQR)</b>	45.7 (33.2-65.4)	50.2 (42.2-75.6)	0.039
<b>PLT, G/L (IQR)</b>	130 (88-178)	123 (73-185)	0.690
<150 G/L, n (%)	201 (62.4)	22 (61.1)	1.000
<b>MELD score, points (IQR)</b>	9 (7-10)	10 (9-12)	0.011
<b>Albumin, g/L (IQR)</b>	42.0 (37.9-45.0)	37.0 (32.0-41.4)	<0.001

MASLD = metabolic dysfunction-associated steatotic liver disease, MetALD = MASLD and increased alcohol intake, ALD = alcohol-related liver disease, SSM = spleen stiffness measurement, LSM = liver stiffness measurement, PLT = platelet count, MELD = model for end-stage liver disease, VCTE = vibration-controlled transient elastography



**Table S2.** Univariable competing risk regression analysis investigating the value of hepatic venous pressure gradient (HVPG), spleen stiffness measurement (SSM) by vibration-controlled transient elastography (VCTE), liver stiffness measurement (LSM) by VCTE, platelet count (PLT), body mass index (BMI), MELD score, serum albumin levels (ranging from 30-45 g/L), and the composite clinically significant portal hypertension (CSPH) prediction models (ANTICIPATE±NASH and NICER) in predicting hepatic decompensation during follow-up (n=36).

Parameter	Subdistribution hazard ratio	95% confidence interval	p-value
HVPG, per mmHg	1.148	1.090-1.210	<0.001
LSM by VCTE, per kPa	1.042	1.026-1.057	<0.001
SSM by VCTE, per kPa	1.013	1.001-1.026	0.040
PLT, per G/L	0.998	0.992-1.003	0.370
BMI, per kg/m <sup>2</sup>	0.933	0.881-0.988	0.018
BMI ≥30 kg/m <sup>2</sup> , yes vs. no	0.523	0.258-1.057	0.071
NICER, per 10% CSPH risk	1.315	1.135-1.523	<0.001
ANTICIPATE±NASH, per 10% CSPH risk	1.296	1.117-1.504	<0.001
MELD, per point	1.093	1.020-1.170	0.011
Albumin, per g/L	0.836	0.779-0.897	<0.001

**Table S3.** Uni- and multivariable competing risk regression analysis investigating the independent value of serum albumin levels (ranging from 30-45 g/L) from MELD variables, including those considered in its 3.0 iteration, for predicting hepatic decompensation during follow-up (n=36).

<b>Parameter (univariable)</b>	<b>Subdistribution hazard ratio</b>	<b>95% confidence interval</b>	<b>p-value</b>
Albumin, per g/L	0.822	0.762-0.886	<0.001
INR, per 0.1 unit	1.302	1.041-1.627	0.021
Bilirubin, per mg/dL	1.456	0.819-2.589	0.200
Serum creatinine, per mg/dL	0.574	0.184-1.790	0.340
Serum sodium, per mmol/L	1.014	0.929-1.106	0.760
Sex, female vs. male	0.953	0.478-1.899	0.890
<b>Parameter (multivariable)</b>	<b>Adjusted subdistribution hazard ratio</b>	<b>95% confidence interval</b>	<b>p-value</b>
Albumin, per g/L	0.834	0.767-0.906	<0.001
INR, per 0.1 unit	1.189	0.914-1.547	0.200

**Table S4.** Time-dependent areas under the curve (AUC) with 95% confidence intervals and overall C-indices for hepatic decompensation (considering competing events) of HVPG, NITs for CSPH, and albumin levels (ranging from 30-45 g/L). Thirty-six patients developed hepatic decompensation during follow-up.

<b>Model</b>	<b>Apparent AUC for decompensation at 1 year</b>	<b>Cross-validated AUC for decompensation at 1 year</b>	<b>Apparent AUC for decompensation at 2 years</b>	<b>Cross-validated AUC for decompensation at 2 years</b>	<b>Apparent C-index</b>	<b>Cross- validated C-index</b>
HVPG	0.701 (0.595-0.872)	0.691 (0.586-0.796)	0.787 (0.698-0.875)	0.774 (0.681-0.867)	0.696	0.696
LSM by VCTE	0.726 (0.599-0.853)	0.708 (0.566-0.850)	0.743 (0.639-0.847)	0.710 (0.583-0.837)	0.708	0.694
NICER	0.720 (0.620-0.820)	0.691 (0.583-0.799)	0.766 (0.662-0.870)	0.720 (0.612-0.828)	0.705	0.681
ANTICIPATE±NASH	0.730 (0.601-0.854)	0.699 (0.579-0.819)	0.774 (0.677-0.872)	0.735 (0.631-0.838)	0.706	0.683
Albumin	0.776 (0.671-0.880)	0.753 (0.617-0.888)	0.810 (0.718-0.902)	0.767 (0.651-0.883)	0.713	0.713

**Table S5.** Multivariable competing risk regression analyses investigating the independent value of hepatic venous pressure gradient (HVPG), spleen stiffness measurement (SSM) by vibration-controlled transient elastography (VCTE), liver stiffness measurement (LSM) by VCTE, and the composite clinically significant portal hypertension (CSPH) prediction models (ANTICIPATE±NASH and NICER) in predicting hepatic decompensation during follow-up (n=29), adjusted for serum albumin levels (ranging from 30-45 g/L). Patients who did not reach the chosen landmark for this analysis (one month after HVPG measurement) were excluded (n=11).

Parameter	Adjusted subdistribution hazard ratio	95% confidence interval	p-value
HVPG, per mmHg	1.137	1.060-1.219	<0.001
LSM by VCTE, per kPa	1.030	1.009-1.052	0.006
SSM by VCTE, per kPa	1.007	0.994-1.021	0.300
NICER, per 10% CSPH risk	1.178	1.012-1.370	0.034
ANTICIPATE±NASH, per 10% CSPH risk	1.154	0.967-1.376	0.110



**Table S6.** Time-dependent areas under the curve (AUC) with 95% confidence intervals and overall C-indices for hepatic decompensation (considering competing events) of models including HVPG or a CSPH-NIT alongside albumin levels (ranging from 30-45 g/L), stratified by non-selective betablocker (NSBB) intake status during follow-up. Twenty-five patients on NSBB and eleven without NSBB developed decompensation during follow-up.

	No NSBB (N=170)			NSBB (N=188)		
Model	Apparent AUC for decompensation at 1 year	Apparent AUC for decompensation at 2 years	Apparent C-index	Apparent AUC for decompensation at 1 year	Apparent AUC for decompensation at 2 years	Apparent C-index
HVPG + Albumin	0.837 (0.679-0.995)	0.884 (0.796-0.971)	0.799	0.794 (0.681-0.907)	0.831 (0.719-0.944)	0.752
LSM by VCTE + Albumin	0.839 (0.672-1.0)	0.868 (0.758-0.977)	0.793	0.824 (0.731-0.917)	0.803 (0.688-0.919)	0.776
NICER + Albumin	0.810 (0.597-1.0)	0.844 (0.723-0.965)	0.782	0.769 (0.664-0.697)	0.814 (0.697-0.931)	0.729
ANTICIPATE±NASH + Albumin	0.843 (0.752-1.0)	0.862 (0.752-0.973)	0.794	0.766 (0.661-0.870)	0.808 (0.691-0.925)	0.719

**Table S7.** Time-dependent areas under the curve (AUC) with 95% confidence intervals and overall C-indices for hepatic decompensation considering competing events of the final models including HVPG or a NIT for CSPH alongside albumin levels (ranging from 30-45 g/L), stratified by the underlying aetiology of liver disease (MASLD vs. MetALD/ALD). Viral and other aetiologies could not be considered owing to limited patient and event numbers. Twelve MASLD and 20 MetALD/ALD patients developed hepatic decompensation.

	MASLD (N=153)			MetALD/ALD (N=113)		
Model	Apparent AUC for decompensation at 1 year	Apparent AUC for decompensation. at 2 years	Apparent C-index	Apparent AUC for decompensation at 1 year	Apparent AUC for decompensation at 2 years	Apparent C-index
HVPG + Albumin	0.886 (0.734-1.0)	0.940 (0.863-1.0)	0.846	0.774 (0.638-0.910)	0.722 (0.568-0.877)	0.743
LSM by VCTE + Albumin	0.889 (0.777-1.0)	0.952 (0.899-1.0)	0.869	0.805 (0.679-0.931)	0.704 (0.544-0.864)	0.750
NICER + Albumin	0.898 (0.784-1.0)	0.939 (0.870-1.0)	0.858	0.741 (0.592-0.891)	0.659 (0.493-0.825)	0.705
ANTICIPATE±NASH + Albumin	0.898 (0.794-1.0)	0.933 (0.868-0.999)	0.855	0.740 (0.602-0.879)	0.667 (0.500-0.833)	0.701

**Table S8.** Time-dependent areas under the curve (AUC) with 95% confidence intervals and overall C-indices for hepatic decompensation considering competing events of the final models including HVPG or a NIT for CSPH alongside serumalbumin levels (ranging from 35-45 g/L) in CTP-A5 patients. Seventeen patients developed hepatic decompensation.

	CTP-A5 (N=289)		
Model	Apparent AUC for decompensation at 1 year	Apparent AUC for decompensation at 2 years	Apparent C-index
HVPG + Albumin	0.712 (0.537-0.888)	0.795 (0.693-0.904)	0.721
LSM by VCTE + Albumin	0.779 (0.608-0.949)	0.776 (0.640-0.913)	0.726
NICER + Albumin	0.689 (0.526-0.852)	0.736 (0.612-0.860)	0.670
ANTICIPATE±NASH + Albumin	0.773 (0.637-0.910)	0.783 (0.664-0.903)	0.707

**Table S9.** Multivariable competing risk regression analysis investigating the independent value liver stiffness measurement (LSM) and spleen stiffness measurement (SSM) from the hepatic venous pressure gradient (HVPG) for predicting hepatic decompensation during follow-up (n=36).

<b>HVPG &amp; LSM</b>	<b>Adjusted subdistribution hazard ratio</b>	<b>95% confidence interval</b>	<b>p-value</b>
HVPG, per mmHg	1.094	1.017-1.177	0.016
LSM, per kPa	1.029	1.009-1.048	0.004
<b>HVPG &amp; SSM</b>	<b>Adjusted subdistribution hazard ratio</b>	<b>95% confidence interval</b>	<b>p-value</b>
HVPG, per mmHg	1.151	1.085-1.220	<0.001
SSM, per kPa	0.999	0.984-1.014	0.860



**Table S10.** Formulas based on the cause-specific Cox regression models estimating decompensation-free survival (h) at years 1 and 2 of follow-up. Serum albumin levels below and above 30 and 45 g/L should be introduced as 30 and 45 g/L, respectively. ‘NICER’ and ‘ANTICIPATE±NASH’ should be introduced as % probability for clinically significant portal hypertension (CSPH), ranging from 0-100%.

Model	Equation
<b>HVPG &amp; Albumin</b>	
<i>Year 1</i>	$h(1) = 0.9575030 \wedge \exp (0.1192229 \times \text{HVPG} - 0.1778297 \times \text{Albumin} + 5.808664265)$
<i>Year 2</i>	$h(2) = 0.9125354 \wedge \exp (0.1192229 \times \text{HVPG} - 0.1778297 \times \text{Albumin} + 5.808664265)$
<b>LSM &amp; Albumin</b>	
<i>Year 1</i>	$h(1) = 0.9534805 \wedge \exp (0.0318556 \times \text{LSM} - 0.1546125 \times \text{Albumin} + 5.3954794)$
<i>Year 2</i>	$h(2) = 0.9092280 \wedge \exp (0.0318556 \times \text{LSM} - 0.1546125 \times \text{Albumin} + 5.3954794)$
<b>NICER &amp; Albumin</b>	
<i>Year 1</i>	$h(1) = 0.9552423 \wedge \exp (0.0190711 \times \text{NICER} - 0.1702358 \times \text{Albumin} + 5.6840323)$
<i>Year 2</i>	$h(2) = 0.9077619 \wedge \exp (0.0190711 \times \text{NICER} - 0.1702358 \times \text{Albumin} + 5.6840323)$
<b>ANTICIPATE±NASH &amp; Albumin</b>	
<i>Year 1</i>	$h(1) = 0.9528990 \wedge \exp (0.0162151 \times \text{ANTICIPATE}\pm\text{NASH} - 0.1690443 \times \text{Albumin} + -5.8814436)$
<i>Year 2</i>	$h(2) = 0.9038618 \wedge \exp (0.0162151 \times \text{ANTICIPATE}\pm\text{NASH} - 0.1690443 \times \text{Albumin} + 5.8814436)$

**Table S11.** Performance metrics of the chosen 95% cutoff for 1-year predicted decompensation-free survival for the final models incorporating HVPG or a NIT for CSPH alongside levels (ranging from 30-45 g/L) for decompensation within one year of follow-up. Negative predictive value (NPV), sensitivity, negative likelihood ratio (LR -), positive predictive value (PPV), specificity, and positive likelihood ratio (LR +) are shown for each model.

<b>≥95% predicted decompensation-free survival according to model</b>	<b>NPV</b>	<b>Sensitivity</b>	<b>LR -</b>	<b>PPV</b>	<b>Specificity</b>	<b>LR +</b>
HVPG + Albumin	98.6%	87.5%	0.2	13.9%	61.1%	2.2
LSM by VCTE + Albumin	98.6%	87.5%	0.2	14.7%	63.5%	2.4
NICER + Albumin	98.1%	83.3%	0.3	13.2%	60.5%	2.1
ANTICIPATE±NASH + Albumin	98.5%	87.5%	0.2	13.3%	59.0%	2.1

**Table S12.** Performance metrics of clinically oriented non-invasive biomarker/algorithm cutoffs for decompensation within one year of follow-up. Negative predictive value (NPV), sensitivity, negative likelihood ratio (LR -), positive predictive value (PPV), specificity, and positive likelihood ratio (LR +) are shown for each biomarkers/model.

<b>≥95% predicted decompensation-free survival according to model</b>	<b>NPV</b>	<b>Sensitivity</b>	<b>LR -</b>	<b>PPV</b>	<b>Specificity</b>	<b>LR +</b>
LSM >25 kPa	96.9%	66.7%	0.5	10.7%	65.0%	1.9
AASLD CSPH rule-in <sup>\$</sup>	96.2%	75.0%	0.5	9.0%	45.8%	1.4
Albumin <35 mg/dL	96.4%	54.2%	0.5	24.1%	87.7%	4.4
LSM >25 kPa AND/OR Albumin <35 mg/dL	98.1%	83.3%	0.3	13.4%	61.4%	2.2
AASLD CSPH rule-in <sup>\$</sup> AND/OR Albumin <35 mg/dL	97.3%	83.3%	0.4	9.6%	43.7%	1.5

<sup>\$</sup> LSM ≥25 kPa OR LSM 20-25 kPa & PLT <110 G/L OR LSM 15-20 kPa & PLT <90 G/L

**Fig. S1.** Comparison of the incidence of hepatic decompensation between patients (A) with and without clinically significant portal hypertension (CSPH), (B) with liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE)  $\geq 25$  kPa and  $< 25$  kPa, (C) with spleen stiffness measurement (SSM) by VCTE  $\geq 40$  kPa and  $< 40$  kPa, (D) CSPH probability  $\geq 60\%$  and  $< 60\%$  according to the NICER model, (E) CSPH probability  $\geq 60\%$  and  $< 60\%$  according to the ANTICIPATE $\pm$ NASH model. Incident hepatocellular carcinoma and non-liver related death were considered as competing events. Incidences were compared between groups using Gray's test.



**Fig. S2.** Calibration of (A) hepatic venous pressure gradient (HVPG), (B) liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), (C) the NICER model, (D) the ANTICIPATE±NASH model, and (E) albumin on first hepatic decompensation. Incident hepatocellular carcinoma and non-liver related death were considered as competing events.

**Fig. S3.** Calibration of the models predicting 1-year decompensation risk based on albumin and (A) hepatic venous pressure gradient (HVPG), (B) liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), (C) the NICER model, (D) the ANTICIPATE±NASH model. Incident hepatocellular carcinoma and non-liver related death were considered as competing events.

**Fig. S4.** Calibration of the models predicting 1-year decompensation risk based on albumin and (A-B) hepatic venous pressure gradient (HVPG), (C-D) liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), (E-F) the NICER model, (G-H) the ANTICIPATE±NASH model according to underlying metabolic dysfunction-associated steatotic liver disease (MASLD) or MASLD and increase alcohol intake (MetALD) / alcohol-related liver disease (ALD). Incident hepatocellular carcinoma and non-liver related death were considered as competing events.

**Fig. S5.** Comparison of the incidence of hepatic decompensation between patients with  $\geq 95\%$  and  $< 95\%$  1-year decompensation free survival probability according to cause-specific Cox regression models comprising serum albumin levels and (A) hepatic venous pressure gradient (HVPG), (B) liver stiffness measurement (LSM) by VCTE, (C) the NICER model, and (D) the ANTICIPATE $\pm$ NASH model in patients with CTP A5 (n=289). Incident hepatocellular carcinoma and non-liver related death were considered as competing events. Incidences were compared between groups using Gray's test.



**Fig. S6.** Landmark analysis comparing the incidence of hepatic decompensation between patients with  $\geq 95\%$  and  $< 95\%$  1-year decompensation free survival probability according to cause-specific Cox regression models comprising serum albumin levels and (A) hepatic venous pressure gradient (HVPG), (B) liver stiffness measurement (LSM) by VCTE, (C) the NICER model, and (D) the ANTICIPATE $\pm$ NASH model (n=347). Incident hepatocellular carcinoma and non-liver related death were considered as competing events. Patients who had  $< 1$  month of follow-up available, i.e., those who were censored or developed events before the chosen landmark, were not considered for this analysis (n=11). Incidences were compared between groups using Gray's test.

**Fig. S7.** Comparison of the incidence of hepatic decompensation among the overall cohort patients as stratified by a simple algorithm targeting at the identification of patients with either impaired liver function (albumin  $\leq 35$  mg/dL) and/or high probability for clinically significant portal hypertension, as evident from liver stiffness measurement (LSM)  $\geq 25$  kPa. Incident hepatocellular carcinoma and non-liver related death were considered as competing events. Incidences were compared between groups using Gray's test.