

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

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## Table of contents

Table S1.....	3
Table S2.....	4
Table S3.....	5
Table S4.....	6
Table S5.....	7
Table S6.....	8
Table S7.....	9
Table S8.....	10
Table S9.....	11
Table S10.....	12
Table S11.....	13

Table S12.....	14
Fig. S1.....	15
Fig. S2.....	16
Fig. S3.....	17
Fig. S4.....	18
Fig. S5.....	19
Fig. S6.....	20
Fig. S7.....	21

**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.

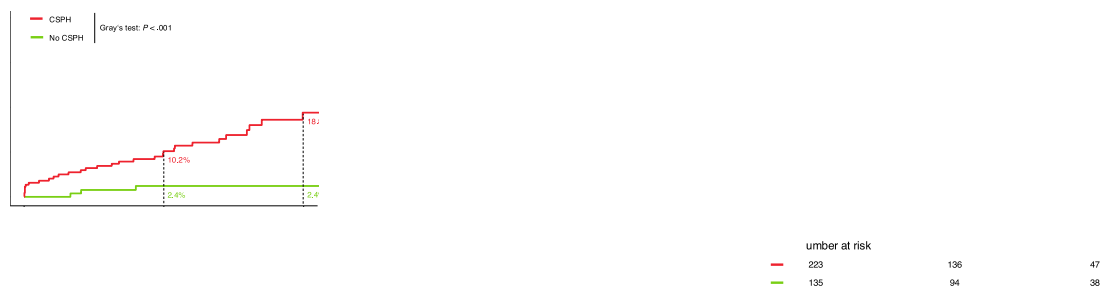
<b>≥95% predicted decompensation-free survival according to model</b>	<b>NPV</b>	<b>Sensitivity</b>	<b>LR -</b>	<b>PPV</b>	<b>Specificity</b>	<b>LR +</b>
HVPG + Albumin	98.6%	87.5%	0.2	13.9%	61.1%	2.2
LSM by VCTE + Albumin	98.6%	87.5%	0.2	14.7%	63.5%	2.4
NICER + Albumin	98.1%	83.3%	0.3	13.2%	60.5%	2.1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