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Predicting Hepatic Decompensation in Patients With Metabolic Dysfunction Associated Steatotic Liver Disease-Related Cirrhosis: The ABID-LSM Model

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ABSTRACT

Background & Aims: Predicting the risk of hepatic decompensation guides prognostication and therapy; however, it is challenging in patients with cirrhosis due to metabolic dysfunction-associated steatotic liver disease (MASLD). We aimed to improve a previously developed predictive tool of hepatic decompensation in MASLD cirrhosis (ABIDE) by incorporating liver stiffness measurement (LSM).

Methods: A multi-centre retrospective cohort of patients with compensated cirrhosis due to MASLD was identified, with decompensation incidence assessed using competing risk regression. The prognostic accuracy of a modified ABIDE model incorporating LSM (ABID-LSM) was assessed using time-dependent AUC (tAUC) and compared with other predictive models.

Results: Out of 388 patients, 273 (70.4%) had available LSM. Hepatic decompensation occurred in 54 (20%) patients during follow-up (median 31 months, range: 20–60). The predictive accuracy at 5 years of ABID-LSM (tAUC 0.80) was better than ABIDE

Abbreviations: ABIDE, albumin, bilirubin, international normalised ratio, diabetes and oesophageal varices; ALBI, albumin–bilirubin; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; EV, oesophageal varices; HCC, hepatocellular carcinoma; HR, hazard ratio; HVPG, hepatic venous pressure gradient; IDI, integrated discrimination index; INR, international normalised ratio; LSM, liver stiffness measurement; MASH, metabolic associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; Met ALD, metabolic dysfunction-associated steatotic liver disease and increased alcohol intake; NAFLD, non-alcoholic fatty liver disease; NFS, NAFLD fibrosis score; NRI, net reclassification index; sHR, subhazard ratio; tAUC, time dependent area under the curve; TE, transient elastography.

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(tAUC 0.75, $p = 0.03$) and LSM (tAUC 0.63, $p < 0.001$). The ABID-LSM model calibrated well (slope 0.99) with excellent overall performance (Integrated Brier Score 0.15). A cut-off of 8.1 separated those at high and low risk of hepatic decompensation at 5 years (24% vs. 5%, respectively, sHR = 4.8, $p < 0.001$). The ABID-LSM model had better predictive ability at 5 years than ALBI, FIB-4, NAFLD Decompensation Risk Score and ANTICIPATE models (all $p < 0.001$) as well as hepatic vein pressure gradient measurement (tAUC 0.78 vs. 0.71, $p < 0.001$, $n = 60$).

Conclusions: The ABID-LSM model has greater accuracy in predicting hepatic decompensation in patients with cirrhosis due to MASLD than existing predictive models. If externally validated, ABID-LSM may identify those who benefit from pharmacotherapy and close monitoring.

1 | Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously non-alcoholic fatty liver disease (NAFLD), is currently the most prevalent and fastest growing cause of chronic liver disease affecting approximately 38% of the world's population [1]. Consequently, MASLD is a leading aetiology of liver cirrhosis, hepatocellular carcinoma (HCC) and indication for liver transplantation worldwide [2, 3]. It is predicted that within the next few years, MASLD will become the foremost cause of liver-related morbidity and mortality and is thus currently an important and emerging worldwide health priority [4].

MASLD may progress to metabolic dysfunction-associated steatohepatitis (MASH) which will lead to cirrhosis, decompensation and death in some individuals [5, 6]. Approximately 20% of subjects with MASLD will develop MASH, and of those, 20% can progress to cirrhosis [6, 7]. Once cirrhosis is established, the risk of developing a major complication of portal hypertension is approximately 50% at 10 years [8]. Survival and quality of life among patients with MASLD-related cirrhosis fall markedly once decompensation occurs, with a median survival of approximately 2 years [9]. Thus, it is important and clinically relevant to accurately determine the risk of liver decompensation to estimate disease burden and provide counselling regarding prognosis. Furthermore, establishing the risk of decompensation has implications for disease monitoring, the potential use of pharmacological interventions, such as beta-blockers, inclusion in clinical trials and referral for liver transplantation. Notably, the recent Baveno VII statement highlighted the need to validate predictive biomarkers for decompensation, particularly among patients with MASLD [10].

We previously developed and validated a new model which accurately predicted liver decompensation in two large cohorts of biopsy proven MASLD patients with compensated cirrhosis [11]. The model, named ABIDE, consists of the following variables: AST/ALT ratio, bilirubin, international normalised ratio, type 2 diabetes and presence of oesophageal varices.

Further validation and refinement of any prediction model is vital before incorporation into clinical practice. The ABIDE model requires the documentation of oesophageal varices through gastroscopy, an invasive procedure not exempt from complications and cost. The Baveno VII consensus advocates non-invasive assessment of clinically significant portal hypertension (CSPH) to identify patients at risk and avoid unnecessary screening endoscopies [10]. The gold-standard method to assess and stage portal hypertension in compensated advanced chronic liver disease (cACLD) is the measurement of hepatic venous pressure gradient (HVPG) but this is only available in specialised centres [12]. Liver stiffness measurement (LSM) by vibration controlled transient elastography (VCTE) correlates with HVPG and can be used to rule out or rule in CSPH. Society guidelines and the Baveno consensus encourage the use of LSM by VCTE to provide prognostic information at baseline and monitoring of patients with compensated cirrhosis [10, 13, 14].

We hypothesized that LSM could replace the need for endoscopy to document the presence of varices in the ABIDE model without impacting its accuracy. To investigate this, we aimed to assess whether the predictive ability of a modified ABIDE model (replacing oesophageal varices with LSM) performed similarly to the original ABIDE model. Secondly, we aimed to compare the modified model with other non-invasive risk prediction models of hepatic decompensation.

2 | Patients and Methods

2.1 | Data Source, Study Design and Participants

The study cohort originated from a multicentre retrospective observational study including eight academic liver units in Catalonia, Spain [15]. The cohort consisted of all patients diagnosed with compensated liver cirrhosis due to MASLD from January 2009 to December 2018. The study was approved by the institutional review board at each participating centre. The study was conducted in compliance with the Declaration of Helsinki (Internal code HCP: 2019/635).

2.2 | Inclusion and Exclusion Criteria

Patients were included on the basis of a diagnosis of liver cirrhosis due to MASLD based on any of the following: (1) Imaging signs of liver cirrhosis with imaging or endoscopic evidence of portal hypertension in subjects with obesity, type 2 diabetes, or metabolic syndrome and no other aetiology of liver disease, (2) a histologically proven diagnosis of cirrhosis in a patient with obesity, type 2 diabetes, or metabolic syndrome and no other detectable aetiology of liver disease, (3) steatosis detected by imaging and LSM ≥ 18 kPa in a patient with obesity, type 2 diabetes or metabolic syndrome in the absence of other etiologies of cirrhosis and heart failure.

All patients fulfilled the MASLD adult criteria of having at least one cardiometabolic factor as per nomenclature [16]. Patients were excluded on the basis of any of the following: alcohol consumption of more than 21 standard drinks (210 g) per week in men and 14 standard drinks (140 g) in women, secondary causes of MASLD or other chronic liver diseases, previous hepatic decompensation, or HCC at the time of inclusion, previous liver transplantation, advanced extrahepatic diseases including metastatic cancer and advanced heart or respiratory failure. The inclusion date was the date of liver cirrhosis diagnosis made by the reference hepatologist. Patients were followed by the same hepatologist in each centre.

2.3 | Variables

The following variables were collected within 6 months of the date of diagnosis of liver cirrhosis: Demographics: (age, sex, race), medical history (obesity, dyslipidemia, hypertension, type 2 diabetes, medications), anthropometric variables (weight, body mass index), serum biochemical parameters (fasting glucose, haemoglobin A1c [HbA1], total cholesterol, high-density and low-density lipoprotein cholesterol, aminotransferases, total bilirubin, albumin, INR, creatinine, platelet count) and others (alcohol, cigarette smoking, presence of gastroesophageal varices). LSM was assessed by VCTE technology (Fibroscan, Echosens, Paris, France) using the standard M or XL probe as per the manufacturer's recommendations. LSM was recorded after obtaining 10 valid measurements and reported using the median in kilo Pascals (kPa). Included scans required a median/inter-quartile range of <0.3. Hepatic vein catheterisation with HVPG measurement was performed by expert hepatologists in a subset of patients ($n=60$) for the assessment of portal hypertension according to local practice.

The following risk predictive tools were computed at baseline based on their original published formulas: ABIDE model, MELD score, FIB-4 score, NAFLD fibrosis score, Albumin-Bilirubin (ALBI), ALBI-FIB-4, NAFLD decompensation risk score, ANTICIPATE and ANTICIPATE-NASH models [11, 17–24]. We also computed the ABIDE model removing oesophageal varices from the original formula (ABID model).

2.4 | Outcome and Follow Up Period

The primary outcome was the first event of hepatic decompensation defined as the occurrence of any of the following: new onset ascites (confirmed or identified by abdominal ultrasound), upper gastrointestinal bleeding secondary to portal hypertension (confirmed by endoscopy in the presence of gastroesophageal varices or portal hypertensive gastropathy), hepatic encephalopathy grade 2 or more according to West Haven criteria. If multiple events occurred in the same patient, only a single and earliest event was considered for the time to event analysis. Patients with HCC and hepatic decompensation at the same time as the diagnosis of liver cirrhosis and patients with previous HCC were excluded from the analysis.

Patients were followed from the day of diagnosis of liver cirrhosis until the occurrence of death, liver transplant, or last visit. All outcomes were assessed and confirmed by an experienced hepatologist in each centre.

2.5 | Statistical Analysis

Patient baseline characteristics were reported using percentage (for categorical variables) and mean and standard deviation (for continuous variables).

2.5.1 | Updating the ABIDE Model

In order to obviate the need for gastrointestinal endoscopy (to assess for the presence of oesophageal varices), we developed a new model substituting LSM by Fibroscan (ABID-LSM) for the presence or absence of varices. We confirmed the association of LSM with hepatic decompensation based on competing risk regression analysis. We then removed oesophageal varices from the original ABIDE formula (which included the covariates of AST/ALT ratio, bilirubin, international normalised ratio, type 2 diabetes and oesophageal varices) and tested the association of the ABID (model without oesophageal varices). Lastly, LSM was combined into an algorithm with the ABID variables (AST/ALT ratio, bilirubin, international normalised ratio and type 2 diabetes).

The association between the ABIDE model and the ABID-LSM model with hepatic decompensation was examined using both Cox proportional hazard regression and competing risk regression analysis. The occurrence of non-liver death was considered a competing event for hepatic decompensation. Hazard ratio (HR) and sub-hazard ratios (sHR) with 95% confidence intervals were calculated for each model.

A model cut point was selected to identify a low-risk group with a 5% or less cumulative incidence of the outcome at 5 years, which mirrors the cumulative incidence of liver-related events among patients with a HVPG of <10 mmHg [25, 26]. The cumulative incidence of liver-related events based on cut points was estimated and reported using the cumulative incidence function after competing risk regression analysis based on the Fine and Grey method. Performance characteristics of the ABIDE and ABID-LSM models at selected cut-offs for hepatic decompensation as a binary outcome were assessed using sensitivity, specificity, negative and positive predictive values.

The prognostic performance and classification improvement of both the original ABIDE model and the ABID-LSM model were assessed. Five-year prediction of hepatic decompensation was based on time-dependent area under the curve (tAUC) [27] and overall accuracy based on Harrell's *C*-statistic [28]. Classification improvement was examined using the net reclassification index (NRI) and integrated discrimination index (IDI). IDI is a measure to estimate the ability of the model to rank subjects correctly according to their outcome. The NRI quantifies how well a new model (ABID-LSM) correctly reclassifies subjects compared to the original model (ABIDE) [29]. We additionally assessed the performance of LSM, ABIDE, ABID and ABID-LSM models at 1, 3 and 5 years of follow-up based on tAUC.

2.5.2 | Measures of Discrimination, Calibration and Overall Accuracy

The discrimination, calibration and overall model accuracy of the ABIDE and ABID-LSM models and LSM were compared. Discrimination was examined using Gonen and Keller's (*k* statistic) and Royston and Sauerbrei's (*D*-statistic). Gonen and Heller's *k*-statistic represents a concordance measure where a value of 1 indicates perfect discrimination, whereas a value of 0.5 indicates no discrimination [30]. Sauerbrei's *D*-statistic is a hazard ratio where the greater the value than one indicates the greater discrimination [31]. Model's calibration was based on calibration slope, a method for censoring that ideally takes a value of 1.0. To evaluate overall model performance, we estimated the mean squared difference between the real outcome and the predicted probability based on the Integrated Brier Score [32].

To internal validate the performance of the updated model, we conducted a k-fold cross validation. The sample was randomly split into 10 *k* groups. This technique averages the area under the curves (AUCs) corresponding to each fold and applies the bootstrap procedure to the cross-validated AUC to obtain statistical inference and 95% bias corrected confidence intervals [33]. Additionally, the prognostic accuracy of ABID-LSM was compared with NFS, FIB-4, ALBI, ALBI-FIB-4, the NAFLD decompensation risk score, MELD score, ANTICIPATE and ANTICIPATE-NASH models using tAUC at 5 years.

The performance of the model was additionally explored in subgroups (diabetes vs. no diabetes, age <65 vs. age ≥ 65, obese vs. non-obese), with the age cut-off based on the median age of the cohort. We also assessed the cumulative incidence of hepatic decompensation based on the Baveno VII recommendation of the *rule-of-five* for the cut-off of LSM by VCTE (<15, 15–20, 20–25, >25 kPa) and the combination of LSM by VCTE and platelet count (LSM ≥ 25 kPa, LSM, 20–25 kPa and platelet count <150, LSM, 15–20 kPa and platelet count <110) [10].

Additionally, we conducted a Spearman correlation analysis and a scatter plot with regression line (line of best fit) to illustrate the relationship between HVPG and ABID-LSM in a subgroup with available measurements ($n=60$). The association of both HVPG and ABID-LSM with hepatic decompensation based on Cox regression and competing risk regression was reported. The overall prognostic accuracy and accuracy at 5 years of the ABID-LSM model and HVPG were compared with the *C*-statistic and tAUC, respectively.

Significance tests, confidence intervals, and *p* values results were set to be two-sided, with an alpha level of 0.05. Statistical analyses were carried out using STATA software (release 18.0; College Station, Texas: Stata Corp LP).

3 | Results

3.1 | Cohort Characteristics

Of 388 patients in the original cohort, 273 (70.4%) had LSM available and were thus included in the final cohort (Figure 1). The baseline characteristics of the cohort are shown in Table 1, with a mean age of 64 years and an even sex distribution (52% male). The prevalence of type 2 diabetes (75%) and hypertension (73%) was high. Oesophageal varices were present in 53 subjects (20%). The mean MELD score was 8, and all patients were Child Turcotte Pugh A in keeping with their compensated status.

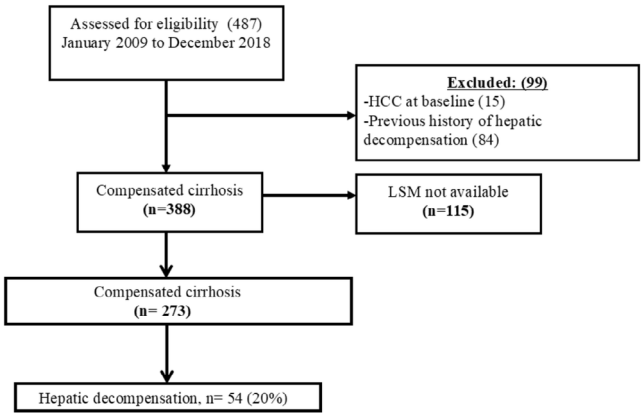


FIGURE 1 | Flow chart and outcomes of enrolled patients.

An initial event of hepatic decompensation occurred in 54/273 (20%) patients during a median follow-up of 31 months (range: 20–60), with the 5-year cumulative incidence being 22% (95% CI: 16–30) as shown in Figure 2. Eight patients died of non-liver-related causes and were analysed as competing events.

3.2 | Development of ABID-LSM Model

Mean LSM was significantly higher among patients with oesophageal varices compared to those without (30 kPa, 95% CI: 25–35 kPa vs. 25 kPa, 95% CI: 23–27 kPa, $p=0.029$), supporting the rationale to substitute oesophageal varices for LSM in the ABIDE model. On competing risk regression analysis, the ABIDE model without the inclusion of oesophageal varices (ABID) was associated with increased risk of hepatic decompensation (sHR, 1.48, 95% CI: 1.24–1.76, $p<0.001$) (Table 2). This set of variables was combined with LSM to build the updated model (ABID-LSM), which was comprised of the following formula: $(2.003 \times \text{INR} + 0.824 \times \text{AST/ALT ratio} + 0.821 \times [\text{Type 2 diabetes: 0 if absent, 1 if present}] + 0.332 \times \text{total bilirubin} + 0.726 \times \text{LSM})$.

3.3 | Accuracy and new ABID-LSM Cut Offs

The original ABIDE model, new ABID (original model without oesophageal varices), ABID-LSM and LSM were all associated with the risk of hepatic decompensation in both Cox and competing risk regression analyses (Table 2), with ABID-LSM providing the highest hazard ratios. In addition, the overall prediction of hepatic decompensation (assessed by *C*-statistic) was better for ABID-LSM than LSM and ABID ($p<0.001$) and similar to ABIDE ($p=0.07$). The ABID-LSM model had more favourable classification indices (NRI and IDI) over ABIDE, ABID and LSM. K-fold cross validation of ABID-LSM displayed a cross-validated mean AUC of 0.79 with bootstrap bias corrected 95% confidence intervals 0.72–0.88 (Figure S1).

TABLE 1 | Baseline characteristics of the cohort with compensated MASLD related cirrhosis ($n = 273$).

Variables	*n* or mean	% or SD
Age, years	64.3	9.9
Gender, male (%)	142	52%
Type 2 diabetes (%)	205	75%
Hypertension (%)	200	73%
Obesity (%)	174	64%
Current smoker (%)	27	10%
Alcohol (%)		
Non drinkers	205	75%
Moderate drinkers[a]	68	25%
BMI (kg/m^2)	32.2	5.1
MELD score	8.0	1.0
Gastroesophageal varices (%)	53	20%
Total bilirubin (mg/dL)	0.87	0.58
Albumin (g/L)	4.1	0.47
INR	1.03	0.20
Platelets ($\times 10^9$/L)	85	19
Cholesterol (mg/day)	178	41
HDL (mg/dL)	50.8	28.8
LDL (mg/dL)	101.3	33.8
Creatinine (mg/dL)	0.84	0.31
ALT (IU/L)	44.3	26.3
AST (IU/L)	46.8	22.8
AST/ALT ratio	1.18	0.47
Fasting glucose (mg/dL)	141	54.5
HbA1c (%)	6.76	1.54
HVPG (mmHg) ($n = 60$)	13.2	0.69
LSM ≥ 25 (kPa)	100	37%
Risk predictive tools of hepatic decompensation		
LSM by VCTE (kPa)	26	16
NAFLD fibrosis score	0.99	1.36
FIB-4	3.9	3.62
ALBI	−0.43	0.16
ALBI-FIB-4	−0.08	0.69
NAFLD decompensation risk score	2.44	1.35

Note: Quantitative data were expressed as mean ± SD.
Abbreviations: ALBI, albumin–bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis 4 index; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; HVPG, hepatic venous pressure gradient; INR, international normalised ratio; LDL, low density lipoprotein; MELD, model for end stage liver disease; VCTE, vibration controlled transient elastography.
[a]Consumption less than 21 standard drinks per week in men and 14 in women.

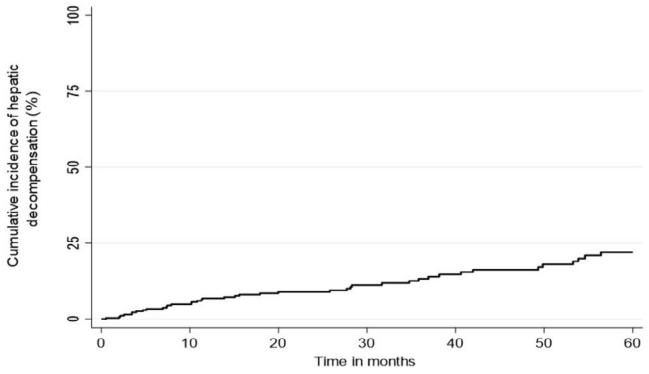


FIGURE 2 | Cumulative incidence of hepatic decompensation in patients with MASLD cirrhosis ($n = 273$).

We assessed the performance of LSM, ABIDE, ABID and ABID-LSM models at 1, 3 and 5 years of follow up (Table 3). The accuracy of ABID-LSM was superior to ABID and ABIDE at 3 and 5 years and similar to ABIDE at 1 year (0.85 vs. 0.84).

An ABID-LSM cut off < 8.1 identified patients with a 5-year cumulative incidence of hepatic decompensation of 5%. In contrast, a cut off of ≥ 8.1 identified subjects at a significantly higher risk of hepatic decompensation (sHR = 4.8, 95% CI: 1.92–9.50, 5-year cumulative incidence 24%) (Figure 3).

Table S1 described the performance of the original ABIDE model and the updated ABID-LSM at selected specific cut-offs. The sensitivity for ABID-LSM and ABIDE was 96% and 48%, respectively. In contrast, the specificity of ABID-LSM and ABIDE was 18% and 77%, respectively.

3.4 | Discrimination, Calibration and Overall Model Accuracy

The ABID-LSM model had higher discriminative ability than both ABIDE and LSM alone, as determined by Gonen and Heller *K*-statistic and *D*-statistic (Table 4). All models calibrated well according to calibration slope, with better calibration for both ABIDE (0.98) and ABID-LSM (0.99). Similarly, the Integrated Brier Score demonstrated good overall accuracy for all models, being best with ABID-LSM.

3.5 | ABID-LSM Accuracy in Comparison With Non-Invasive Tests and Sensitivity Analysis

The accuracy for predicting hepatic decompensation at 5 years was significantly higher for ABID-LSM (tAUC 0.80), compared with NFS and ALBI (tAUC 0.72), FIB-4 and ANTICIPATE-NASH (tAUC 0.74), ALBI-FIB-4 (tAUC 0.73), ANTICIPATE (tAUC 0.69), MELD (tAUC 0.67) and NAFLD decompensation risk score (tAUC 0.65) ($p < 0.001$ for all comparisons) as shown in Table 5. The predictive performance of ABID-LSM was not impacted by the presence of type 2 diabetes, obesity or age (Table S2).

Similarly, all four models were predictive of future hepatic decompensation; however, ABID-LSM (tAUC 0.80) had better discriminative power at 5 years than ABIDE (tAUC 0.75, $p = 0.03$) and LSM (tAUC 0.63, $p < 0.001$).

TABLE 2 | Association, prognostic performance and improvement in discrimination and classification of prognostic models of hepatic decompensation.

	Outcome of hepatic decompensation				
	Risk		Prognostic performance	Classification improvement	
Scores	sHR (95% CI)	HR (95% CI)	Overall prediction: *C* statistic (95% CI)	NRI	IDI
LSM	1.99 (1.13–3.49)[c]	2.06 (1.25–3.39)[c]	0.63 (0.60–0.75)[d]	0.26[f]	0.04[f]
ABIDE	1.47 (1.27–1.72)[c]	1.53 (1.29–1.82)[c]	0.73 (0.70–0.79)[e]	0.44[f]	0.05[f]
ABID[a]	1.48 (1.24–1.76)[c]	1.58 (1.21–2.08)[c]	0.70 (0.68–0.75)[d]	0.03[f]	0.01[f]
ABID-LSM[b]	2.71 (1.72–4.27)[c]	2.76 (1.72–4.42)[c]	0.76 (0.71–0.82)	0.62[f]	0.07[f]

Abbreviations: IDI, integrated discrimination index; NRI, net reclassification index; tAUC, time dependent area under the curve.
[a]Oesophageal varices removed from the equation.
[b]Oesophageal varices removed from the equation and added LSM.
[c]All p values <0.001 (hepatic decompensation).
[d]All p values <0.001 against ABID-LSM.
[e]p value $=0.07$ against ABID-LSM.
[f]All p values <0.001 (against the null hypothesis, NRI or IDI $=0$, ie. no improvement using the model).

TABLE 3 | Hepatic decompensation prognostic performance of ABIDE, ABID and ABID-LSM at 1, 3 and 5 years.

	Outcome of hepatic decompensation		
Scores	1-year tAUC (95% CI)	3-year tAUC (95% CI)	5-year tAUC (95% CI)
LSM	0.73 (0.68–0.76)[a]	0.70 (0.67–0.75)[a]	0.63 (0.60–0.72)[a]
ABIDE	0.84 (0.83–0.88)[b]	0.78 (0.70–0.82)[a]	0.75 (0.73–0.81)[a]
ABID	0.79 (0.71–0.82)[a]	0.72 (0.68–0.74)[a]	0.70 90.65–0.76)[a]
ABID-LSM	0.85 (0.76–0.88)[a]	0.84 (0.78–0.88)[a]	0.80 (0.76–0.83)[a]

[a]All p values <0.001 against ABID-LSM.
[b]p value $=0.23$ against ABID-LSM.

3.6 | ABID-LSM and HVPG Measurement

Overall, there were 60 patients with HVPG available, with 43/60 (72%) having a HVPG ≥ 10 mmHg. Nineteen (32%) developed hepatic decompensation during follow-up (median 31, range: 20–65 months) with 18 (95%) occurring in patients with a HVPG ≥ 10 mmHg. One patient died of a non-liver-related cause and was analysed as a competing event.

ABID-LSM values were significantly correlated with HVPG measurements (Spearman $r=0.51$, 95% CI: 0.29–0.72, $p<0.001$). In addition, a scatter plot with a linear regression line showed a regression coefficient of 0.37, $p=0.003$ (Figure S2).

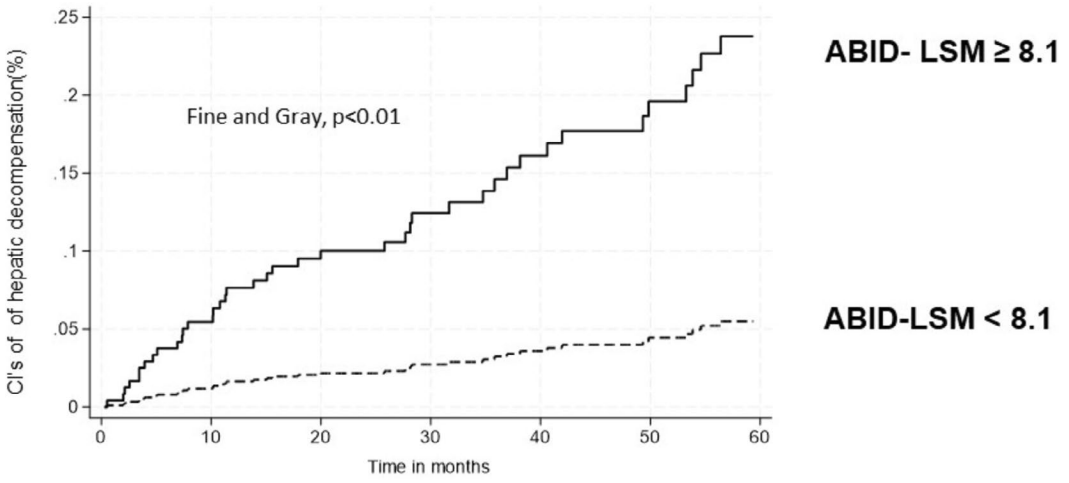
HVPG was associated with the occurrence of hepatic decompensation using Cox regression (HR 1.12; 95% CI: 1.02–1.24, $p<0.001$) and competing risk regression (sHR 1.11; 95% CI: 1.04–1.19, $p<0.001$) analysis. ABID-LSM had greater accuracy at 5-year prediction than HVPG (tAUC 0.78 vs. 0.71, $p<0.001$), the prognostic accuracy of HVPG was superior to ABID-LSM when assessed using Harrell's *C*-statistic (0.85 vs. 0.74, $p<0.001$), shown in Table S3.

Patients with an ABID-LSM score <8.1 ($n=10$) had a mean HVPG value of 7.8 mmHg and no events of liver decompensation on follow-up in contrast to a mean HPVG value of 14 mmHg and a total of 19 events in patients with ABID-LSM ≥ 8.1 ($n=50$) (Figure S3).

3.7 | ABID-LSM and Baveno VII Risk Stratification Tools for Liver Related Events

Figure S4 displays the cumulative incidence of hepatic decompensation based on the Baveno VII 'rule of five' recommendations for LSM by transient elastography. Patients with an LSM value of more than 25 kPa, and between 20 and 25 kPa demonstrated a 5-year cumulative incidence of 28% and 22%, respectively, which is comparative to the cumulative incidence of 24% displayed in high-risk group of the ABID-LSM model (Figure 3). In contrast, LSM was poorer in identifying a group of low-risk patients with those with a LSM of <15 kPa having a 5-year cumulative incidence of decompensation of 14% in comparison to a 5% 5-year incidence in the low risk ABID-LSM group below the cut-off of 8.1.

We also explored the Baveno VII criteria to stratify the risk of liver related events associated with CSPH for subjects with cACLD, which include the combination of platelet count and LSM [10] (Figure S5). Subjects with an LSM between 20 and 25 kPa and a platelet count less than 150, and those with LSM values more than 25 kPa, exhibited a 5-year cumulative incidence of 40% and 28%, respectively. This is comparable to the high-risk group of ABID-LSM and confirms the validity of both strategies to identify a selected group of patients at a higher risk of decompensation. Subjects within the third category proposed by Baveno VII (LSM 15–20 kPa and platelet count <110) had a 5-year cumulative incidence of 22%.



Model	Number of patients/events	Category	5 Year Cumulative Incidence (95% CI)	P value
ABIDLSM	42/2 231/52	< 8.1 >= 8.1	5 (1.5-17) 24 (18-33)	<0.001

* Analysis and graph based on competing risk regression.

FIGURE 3 | Hepatic decompensation in MASLD cirrhosis. Stratification by ABID-LSM score categories ($n = 273$). Cumulative incidence curve indicates predictions calculated by competing-risks regression.

TABLE 4 | Discrimination & calibration & overall accuracy of predictive models of hepatic decompensation.

	Discrimination		Calibration	Overall accuracy
	Gonen and Heller's *k*-statistic	Royston and Sauerbrei's *D*-statistic	Calibration slope	Integrated Brier Score
LSM	0.68	1.65	0.96	0.18
ABIDE	0.71	1.77	0.98	0.20
ABID-LSM	0.73	1.91	0.99	0.15

Note: Gonen and Heller's *k*-statistic is a concordance measure and a value of 1 indicates perfect discrimination, whereas a value of 0.5 indicates no discrimination. Royston and Sauerbrei's *D*-statistic is a hazard ratio and the greater than 1, the greater the discrimination. A calibration slope of 1 indicates perfect calibration. An Integrated Brier Score of 0 indicates perfect accuracy.

Interestingly, 45% of the cohort ($n = 124$) were classified outside the proposed categories (having for example an LSM between 15 and 20 kPa and a platelet count between 110 and 150 or LSM < 15 kPa). These subjects had a 5-year cumulative incidence of decompensation of 13%, in contrast to the low-risk category of ABID-LSM (< 8.1) which had only a 5% 5-year cumulative incidence.

4 | Discussion

Undertaking risk stratification of patients with compensated cirrhosis is a fundamental part of patient assessment and management given an episode of hepatic decompensation is associated with a substantive increase in health-care utilisation and mortality risk. In this cohort study conducted in MASLD patients with compensated cirrhosis, the modified ABID-LSM score accurately predicted the risk of hepatic decompensation over a 5-year time period. The model demonstrated good discrimination and calibration with better net benefit compared to the original ABIDE and the model without oesophageal varices. In addition, ABID-LSM was more accurate in the prediction of future decompensation in comparison with two non-invasive fibrosis scores (NFS and FIB-4) and five prognostic scores of liver decompensation (ALBI, ALBI-FIB-4, NAFLD decompensation risk score, ANTICIPATE and ANTICIPATE-NASH models) and a predictive model of survival (MELD).

Oesophageal varices are an important marker of portal hypertension; however, assessment requires gastroscopy, which is relatively invasive and costly. LSM by VCTE is a non-invasive and widely available and validated diagnostic tool for advanced liver

TABLE 5 | Comparative accuracy of non-invasive models for the prediction of hepatic decompensation over 5 years in patients with cirrhosis due to MASLD.

		5-year prediction of hepatic decompensation
Models	**tAUC (95% CI)**	***p* vs. ABID-LSM**
ABID-LSM	0.80 (0.76–0.83)	—
vs. NFS	0.72 (0.66–0.78)	< 0.001
vs. FIB-4	0.74 (0.70–0.79)	< 0.001
vs. ALBI	0.72 (0.62–0.84)	< 0.001
vs. ALBI-FIB-4	0.73 (0.66–0.79)	< 0.001
vs. ANTICIPATE-NASH	0.74 (0.70–0.82)	< 0.001
vs. ANTICIPATE	0.69 (0.64–0.78)	< 0.001
vs. MELD	0.67 (0.64–0.70)	< 0.001
vs. NAFLD decompensation risk score	0.65 (0.57–0.70)	< 0.001

fibrosis and is also used to identify patients at low risk of oesophageal varices, avoiding the need for gastroscopy screening [34, 35]. Thus, the substitution of LSM for oesophageal varices increases the ease of implementing the prognostic model in the clinic at the point of care.

It is also reported that baseline and follow up LSM can stratify the risk of development of future liver decompensation in patients with MASLD and cACLD [36]. In our study, we found the ABID-LSM model was significantly better at predicting liver decompensation at 5 years than the ABIDE model and LSM alone. This is likely related to the inclusion of variables that are independently associated with hepatic decompensation in patients with chronic liver disease.

In clinical practice, the cut-off value of 8.1 for the ABID-LSM score can identify subjects at low or higher risk of decompensation at 5 years (5% vs. 24%, respectively). With this information, health care practitioners can counsel patients regarding prognosis and likelihood of significant complications in the medium term. Furthermore, information derived from ABID-LSM may be informative to guide patient monitoring and follow-up intervals. In addition, ABID-LSM may aid in sample size calculations and defining inclusion criteria for clinical trials in patients with MASLD-related cirrhosis where liver decompensation is an endpoint.

Current Baveno guidelines recommend the consideration of treatment with non-selective beta-blocker medications for patients with CSPH [10]. This is based on evidence from clinical trials and an individual patient data meta-analysis that suggests long-term use of non-selective beta-blockers reduced hepatic decompensation in compensated cirrhosis patients with CSPH [37]. In this context, ABID-LSM may be a useful tool to identify those patients at risk of future liver decompensation who may benefit from the use of beta-blockers. Notably, the low-risk population identified by an ABID-LSM cut-off value of < 8.1 had a lower 5-year risk of decompensation compared with a cohort of patients with MASLD and a HVPG of < 10 mmHg (5% vs. 9.4% at 5 years) [26]. Conversely, in this European study, MASLD patients with a HVPG between 10 and 15 mmHg had a 29% cumulative incidence of decompensation over 5 years which is similar to that found in patients in the current study with an ABID-LSM score ≥ 8.1 (28%). In this cohort, HVPG showed superior overall accuracy compared to ABID-LSM, but the updated model was better at predicting 5-year risk of decompensation. Interestingly, in a recent multicentre cohort study of advanced MASLD patients, 15 (9%) of subjects with clinical decompensation had HVPG values less than 10 mmHg [38]. This may suggest that classical HVPG cut-offs may not accurately identify MASLD patients at risk of hepatic decompensation. In this context, ABID-LSM may have similar prognostic ability compared with HVPG; however, further validation with a bigger sample size and enough events is needed to confirm this observation.

The 'rule of five' based on LSM cut-offs proposed by the Baveno VII consensus is recommended to estimate the risk of decompensation regardless of liver disease aetiology. In this cohort study, the cumulative incidence of decompensation at 5 years based the rule of five cut off of 25 kPa was comparative to the incidence of clinical decompensation in the high risk ABID-LSM group (28% vs. 24%, respectively). In contrast, the ABID-LSM model was able to better identify a subgroup of patients with a very low risk of decompensation at 5 years compared to those with an LSM < 15 kPa (5% vs. 14%, respectively). Furthermore, the ABID-LSM model outperformed the ANTICIPATE-NASH model, which was specifically developed to predict outcomes in patients with MASLD. This finding highlights the ability of the ABID-LSM score to identify low-risk patients who may not benefit from pharmacotherapy.

The study has a number of strengths, including the inclusion of a well-characterised multi-centre cohort that had a significant number of study endpoints. Nonetheless, the limitations need to be acknowledged, including a relatively small sample size, lack of data on variables that may impact liver decompensation, including non-selective beta-blocker use, band ligation for varices, statins, antidiabetic drugs and alcohol consumption over time. In addition, despite being compensated, two thirds of subjects in our cohort had signs of portal hypertension, indicating a population at higher risk of decompensation. Validation in an external cohort is required, and inclusion of patients with cACLD would increase the utility of the score. Furthermore, the validity of ABID-LSM in subjects without type 2 diabetes should be investigated further, given the small proportion in our cohort, and the score should not be used in patients with MASLD cirrhosis and concomitant HCC.

In conclusion, the ABID-LSM score, which incorporates liver stiffness in conjunction with easily obtainable clinical and laboratory factors, can accurately predict the risk of hepatic decompensation in patients with MASLD and cirrhosis. Estimation of the future risk of liver decompensation based on the ABID-LSM model is relevant for patient counselling, with implications for

monitoring and individualising treatment as well as for clinical trial design. Further study should validate the model and explore the role of ABID-LSM in identifying those who may benefit from beta-blockade.

Author Contributions

Luis Calzadilla Bertot: conceptualization, writing – original draft, methodology, data curation, writing – review and editing, validation, visualization, formal analysis, investigation. **Anna Sòria:** writing – review and editing, data curation, resources. **Alba Jimenez-Masip:** writing – review and editing, data curation, resources. **Isabel Serra:** writing – review and editing, data curation, resources. **Teresa Broquetas:** writing – review and editing, data curation, resources. **Mercedes Vergara:** writing – review and editing, data curation, resources. **Adrià Rodriguez:** writing – review and editing, data curation, resources. **Carles Aracil:** writing – review and editing, data curation, resources. **Cautar El Maimouni:** writing – review and editing, data curation, resources. **Sergio Muñoz-Martinez:** writing – review and editing, data curation, resources. **Jose A. Carrión:** writing – review and editing, data curation, resources. **Albert Pardo:** writing – review and editing, data curation, resources. **Juan M. Pericàs:** conceptualization, validation, visualization, writing – review and editing, funding acquisition, resources, data curation. **Isabel Graupera:** conceptualization, supervision, validation, data curation, project administration, funding acquisition, writing – review and editing. **Leon A. Adams:** conceptualization, validation, writing – review and editing, supervision, resources, project administration.

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Data Availability Statement

Research data are not shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.