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Noninvasive Tests for Predicting Decompensation in Compensated Advanced Chronic Liver Disease: A Comprehensive Review

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ABSTRACT

Strong non-invasive tests (NITs) are needed to predict decompensation in patients with compensated advanced chronic liver disease (cACLD) and improve personalized patient care. We conducted a comprehensive review of the studies evaluating the effectiveness of NITs in predicting decompensation or liver-related death in patients with cACLD. A literature search was conducted in the PubMed database up to August 2025. Prospective or retrospective studies that included patients with cACLD and evaluated NITs for predicting decompensation or death or liver transplantation were included. Studies evaluating elastography and blood-based tests were analysed separately. The majority of studies assessed liver stiffness measurement (LSM), primarily using transient elastography (TE-LSM). There is a strong association between higher LSM values and an increased risk of decompensation, allowing classification of patients at low risk of decompensation from those with a higher risk. However, none of the studies reported data calibration, thereby limiting the ability to accurately predict the individual risk of decompensation. Higher FIB-4, ELF, and MELD values have been associated with an increased occurrence of decompensation. However, their performance was modest, with an area under the curve (AUC) below 0.75. Innovative approaches to improving the non-invasive prediction of decompensation may include levels of extracellular vesicles, genetic polymorphisms, or imaging-derived variables. Furthermore, since decompensation is the result of numerous interacting factors, artificial intelligence has the potential to improve the clinical relevance of predictive models by incorporating and processing a high-dimensional set of variables that reflect the underlying pathophysiological complexity.

Abbreviations: ACLD, advanced chronic liver disease; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; AUC, area under receiver operating curve; cACLD, compensated advanced chronic liver disease; EVs, extracellular vesicules; FiB-4, fibrosis-4 index; HCC, hepatocellular carcinoma; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; MASH, metabolic dysfunction-associated steatohepatitis; MASLD, metabolic dysfunction-associated steatotic liver disease; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NITs, non-invasives tests; SPSS, spontaneous portosystemic shunts; SSM, spleen stiffness measurements; TE, transient elastography.

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Key Points

- This comprehensive review focuses on the ability of NITs to predict outcomes—decompensation or liver-related death—for individual patients with cACLD. The ideal NIT should ensure strong discrimination, calibration, and predictive accuracy, but calibration data are lacking.
- Higher LSM values consistently predict increased risk of decompensation, with >25 kPa indicating a markedly elevated 5-year risk. The threshold effect of LSM was validated across etiologies.
- FIB-4, ELF, and MELD are associated with decompensation risk but show modest predictive performance (AUC <0.75).
- Emerging biomarkers such as extracellular vesicles, genetic polymorphisms, and imaging-derived variables are promising approaches to enhance individualized prediction.

1 | Introduction

In patients with compensated advanced chronic liver disease (cACLD), decompensation is defined by the occurrence of liver failure or portal-hypertension related clinical complications, namely variceal bleeding, ascites, or encephalopathy. Besides hepatocellular carcinoma, decompensation is the most important event affecting survival [1–3]. To personalize patient care, we need methods that can distinguish patients at high risk of decompensation from those at lower risk. Patients at low risk of decompensation are the ideal population for community-based care, ideally using innovative technologies such as telehealth [1, 4]. On the other hand, patients at high risk of decompensation should ideally be referred to tertiary care centers for close follow-up and inclusion in clinical trials [5]. Furthermore, the latter patients are those likely drawing most benefit from nonselective beta-blockers administration [5–8]. Currently, hepatic venous pressure gradient (HVPG) measurement is the sole reference standard for stratifying the risk of liver decompensation and death in patients with cACLD and no history of decompensation [5, 8–10]. However, the use of HVPG is limited by its invasiveness -although minimal- and limited accessibility [11]. These limitations of HVPG explain the expansion and the profound impact of non-invasive tests (NITs) on the care of patients with cACLD. Indeed, NITs are recommended by international guidelines for the routine diagnosis of cACLD [12, 13]; to rule out oesophageal varices; to estimate the presence of portal hypertension; and consequently to initiate treatment with nonselective beta-blockers [5].

In this article, we present the results of a comprehensive review of the studies of NITs as predictors of decompensation or liver-related death in patients with cACLD. Our focus is on the ability of NITs to predict outcomes for individual patients. We categorized NITs as either elastography-based or blood-based. The final section of the article discusses innovative approaches that could be considered NITs in the future.

1.1 | Which NITs for the Accurate Prediction of Decompensation in Patients With cACLD and How to Evaluate Them?

The clinical utility of NITs depends on the specific question being addressed. The statistical approach should match the clinical utility. The traditional approach separates patients at low risk from those at high risk of an event. This approach usually relies on models derived from observational studies or trials. The performance of such models is assessed using discrimination and calibration.

First, discrimination refers to how well the model differentiates those at higher risk of having an event from those at lower risk. The model performance for discrimination is typically assessed using ROC curves and the C-statistic for binary outcomes. A C-statistic of 0.5 indicates no discriminative ability—equivalent to chance, while a C-statistic above 0.80 is generally considered to represent the minimum acceptable performance criterion [14].

However, beyond the AUROC itself, the selection of thresholds needs to be relevant for the clinical question. For example, a model used to rule out high-risk varices is considered acceptable if it misses fewer than 5% of patients with high-risk oesophageal varices [10]. However, a threshold with a 95% sensitivity may yield a high rate of false positives (especially when the prevalence of the target is very low), thus limiting its clinical utility in excluding low-risk patients and consequently avoiding unnecessary upper gastrointestinal endoscopies. Discrimination alone is insufficient to evaluate a model's predictive performance.

Calibration, which measures how closely predicted risks align with observed outcomes across risk strata, is also essential. Poor calibration leads to over- or underestimation of risk. Statistical tests like the Hosmer-Lemeshow test can assess whether discrepancies between predicted and observed outcomes are due to chance.

Importantly, discrimination depends on the distribution of patient characteristics in the population in which the model is being used. Thus, both discrimination and calibration should be assessed using an external validation cohort. This is critical to determine the model's robustness and its generalizability and accuracy across different patient populations. The ideal NIT should achieve high performance in the key domains of discrimination, calibration, and overall predictive accuracy. The purpose of this review was to evaluate how well currently available NITs meet the criteria for assessing the risk prediction of liver-related events in patients with cACLD (Table 1).

2 | Search Strategy and Publication Selection

Computerized literature research was conducted in the PubMed database up until August 2025. We used the following search strategy for routine noninvasive methods: "(Survival OR death OR decompensation OR ACLF OR mortality OR liver transplantation OR prognosis OR outcomes OR ascites) AND (liver OR cirrhosis OR hepatic) AND (*liver stiffness OR spleen stiffness OR FIB-4 OR ELF OR MELD OR ALBI score OR APRI OR AST/ALT ratio OR NAFLD fibrosis score OR ABIDE Model OR hepascore*

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TABLE 1 | Prognostic biomarkers: statistical tests based on clinical questions.

Clinical question	Expected clinical objective	Metrics	Assessment	Used dataset
Rule out ACLD	Avoid unnecessary and costly intervention	Discrimination	AUROC, C-index	Derivation and validation (confirm generalizability and reliability of the model)
Selection of patients with a low risk of liver related outcomes	Address low risk patients to a community-based care	Discrimination	AUROC, C-index	Derivation and validation (confirm generalizability and reliability of the model)
Selection of patients with a high risk of liver related outcomes	Address high risk patients to a clinical essay or initiating treatment (non selective betablockers)	Discrimination Calibration	AUROC, C-index Calibration plot (observed vs. predicted risk curves), Hosmer-Lemeshow test, Brier Score	Derivation and validation (confirm generalizability and reliability of the model)

OR Fibrotest OR Fibrometer)". Following this, a manual search was conducted to identify additional relevant papers. Two authors (AP and LE) screened all full-text publications in English based on their title and abstract. The same two authors evaluated the full texts of potentially eligible studies against pre-specified inclusion criteria. Duplicate publications were identified and removed. We also reviewed publications in personal reference lists and the bibliography sections of retrieved articles. Any discrepancies were discussed and resolved. Articles reporting animal or paediatric data were excluded. Then, we used the same search strategy for non-routinely used methods, including extracellular vesicles, genetics and imaging.

Studies were included if they met the following criteria: (i) studies including patients with compensated cirrhosis (defined by a combination of clinical, laboratory and imaging features of cirrhosis or liver biopsy) or cACLD (defined according to Baveno VI criteria [15]), either in the main cohort or in sub-group analysis; (ii) decompensation or liver-related death as the main endpoint; and (iii) prospective or retrospective design. Studies using as primary endpoint the following outcomes were not included: liver transplantation alone, HCC, variceal bleeding alone, outcome after SARS CoV2 infection, prediction of post-operative outcomes, or response to therapy. Studies including patients with HCC were excluded. Studies that focused exclusively on patients with cACLD due to rare diseases, including autoimmune, cholestatic or Wilson diseases were also excluded.

In this review, since we relied on the descriptions provided in the original articles analysed. Although according to Baveno VII, the term 'compensated' applies specifically to patients without history of decompensation. In the present review, studies including asymptomatic disease but with a history of decompensation were considered. Recompensated cirrhosis constitutes a separate entity and were not here therefore considered [5].

3 | Elastography

LSM by TE, point shear wave elastography (p-SWE) or two-dimensional SWE (2D-SWE) has been used to identify advanced fibrosis in patients with chronic liver disease [16]. LSM has also been used to identify patients with an HVPG $\geq$10 mmHg. The use of LSM is currently recommended by international guidelines for risk stratification in patients with cACLD [5].

3.1 | Liver Stiffness Measurement Using Transient Elastography (TE-LSM)

We found 29 studies evaluating the association between LSM and patients' outcomes (Table S1 and Figure 1) [17–45]. Most of these studies were retrospective and evaluated the association between baseline LSM and the occurrence of subsequent decompensation [17–28, 30, 32, 34, 36–39, 44]. Recent studies involved large-sized multicentric cohorts, comprising validation samples [24, 25]. Inclusion criteria varied across studies. In some studies patients had been included based on liver biopsy results only [23, 29, 36–39, 45]; while others used pre-specified LSM thresholds ($\geq$10, 12, 12.5 or kPa) [17, 18, 20–22, 24, 26–28, 31, 32, 40, 42–44], A previous history of decompensation was not

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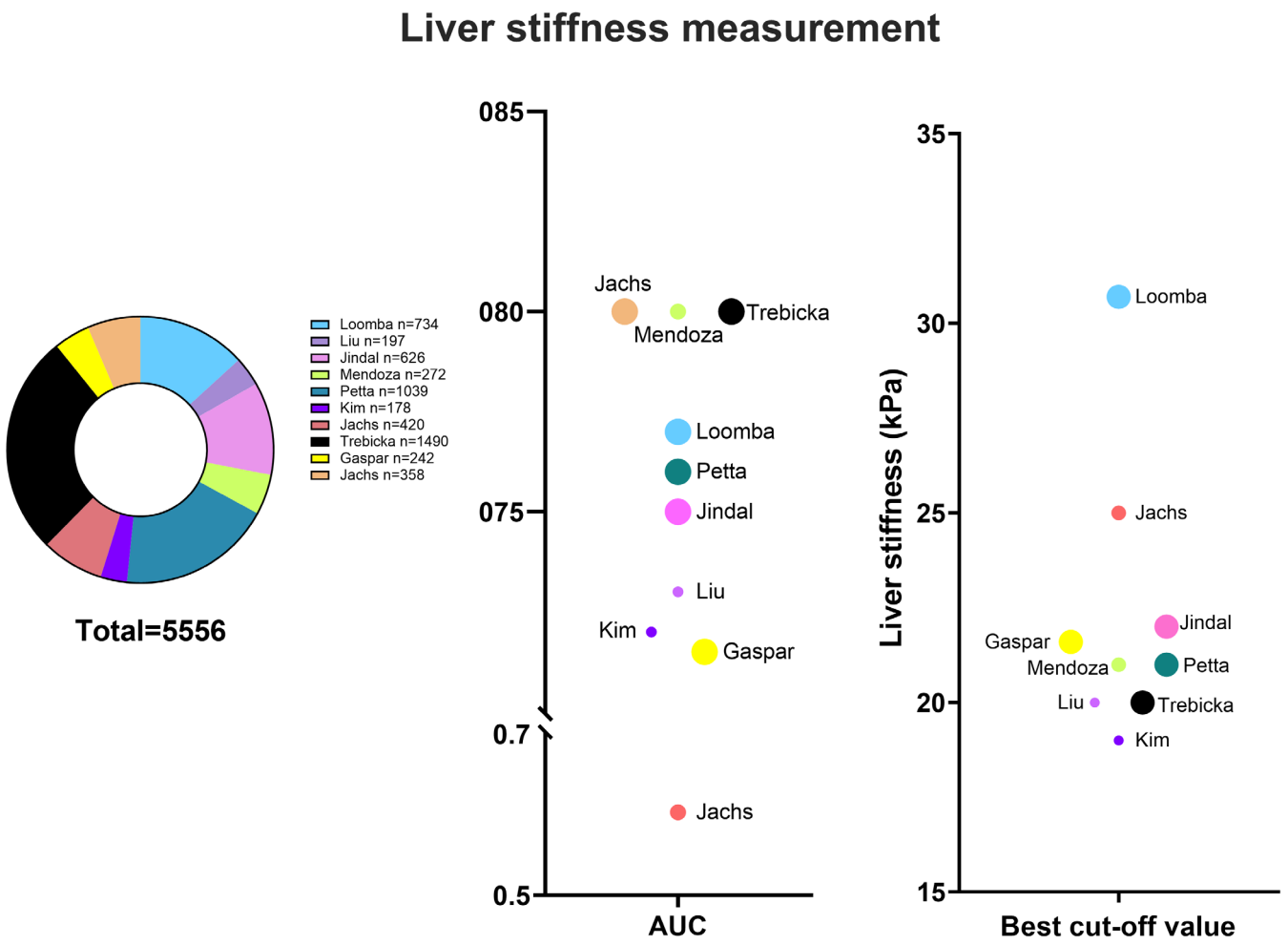

FIGURE 1 | Summary of the observed performance (estimated by AUC) of liver stiffness measurement using transient or shear-wave elastography in patients with cACLD for the prediction of decompensation. The figure illustrates (i) the number of patients included in each study (each study is identified by the first author and sample size), (ii) the reported AUC values for the prediction of decompensation, and (iii) the reported cut-off values of liver stiffness measurement for this outcome. Circle size reflects the number of patients included in each study (small: < 200; medium: 200–1000; large: > 1000). AUC, area under the receiving operator curve, kPa, kilopascals.

considered as an exclusion criterion in several studies [18–21, 24, 27–34, 36–39, 41, 44, 45]. In addition, study endpoints differed. The heterogeneity of these characteristics likely contributes to the wide variation in reported decompensation rate—ranging from 4% to 40%—which correspond to cumulative proportions over heterogeneous follow-up durations rather than standardized incidence rates.

3.2 | Initial LSM and Risk of Decompensation

As shown in Table S1 LSM measured at "baseline" was consistently a significant predictor of decompensation and/or death. Studies that provided predictive performance metrics constituted a lesser portion of the whole studies. A cut-off value (either derived from analysis or pre-specified) was proposed in 8 studies and varied among studies [23, 24, 27–29, 35, 38, 42]. However, LSM above 20–25 kPa was consistently associated with an increased risk of decompensation. In a study including 3028 patients with cACLD of various etiologies, the 5-year cumulative incidence of liver decompensation was 19% (95% CI, 15.8%–22.4%) among patients with LSM > 25 kPa, significantly higher than in patients with LSM between 15–25 kPa (8.6%) and < 15 kPa (3.7%) [26]. Sixteen studies provided the AUC (or c-statistics) and other metrics of the models such as sensitivity, specificity [18, 20, 21, 23–25, 27–30, 35, 36, 38, 41, 42, 45]. Of note, none of the studies provided data calibration (Table 2).

3.3 | Changes in LSM and Risk of Decompensation

Ten studies evaluated the association of changes in LSM values with decompensation [17, 18, 20, 22, 24, 30, 31, 34, 35, 43]. The majority of these studies included patients with viral hepatitis-related cACLD and focused on LSM changes after antiviral therapy. How LSM changes were defined varied: some studies used the percentage of change from baseline, whereas others analysed the "resolution of ACLD" based on the decrease of LSM below 10 or 12 kPa after therapy [31]. All studies showed that

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TABLE 2 | Summary of the number of studies and performances of the NITs evaluated.

Type of NIT	Studies (*n*)	Type of studies	Studies evaluating AUC (*n*)	Studies with assessment of discrimination and calibration (*n*)	Studies with validation cohort (*n*)
Elastography					
TE-LSM	29	Retrospective 20 Prospective 9	12	1	2
TE-SSM	9	Retrospective 4 Prospective 5	4	None	None
2D-SWE-LSM	2	Retrospective 1 Prospective 1	1	1	1 (internal validation)
MRE-LSM	5	Retrospective 5	0	None	None
Blood-based tests					
FIB-4	11	Retrospective 8 Prospective 3	6	None	2
APRI	3	Retrospective 1 Prospective 2	2	None	None
NAFLD-fibrosis score	3	Retrospective 1 Prospective 2	2	None	None
FibroTest	3	Prospective 3	2	None	None
ELF	4	Prospective 4	3	1	1
MELD	9	Retrospective 7 Prospective 2	7	1	2
ALBI	8	Retrospective 8 Prospective 0	7	None	2

a decrease in LSM over time is associated with a reduced incidence of decompensation or death. In a survey of 1272 patients with HBV-related cACLD receiving antiviral therapy, Yu et al. found that the combination of baseline and follow-up LSM had the best predictive performance for decompensation or death (tAUC (0.737)) [20]. Only one retrospective analysis of a registry of 435 patients (53% of whom had viral hepatitis) found that adding on baseline LSM did not improve the predictive value of follow-up LSM [18].

3.4 | Combining LSM With Other Parameters

Several groups have proposed a combination of LSM with other variables. Studies combining LSM with platelet count are summarized in Table S2. In 2 studies, LSM < 20 kPa together with platelet count $> 150 \times 10^9$/L, was associated with lower risk of decompensation or death than in the other groups of patients [46, 47].

The overall prognostic value of the criteria derived from the ANTICIPATE study, initially proposed by Baveno VII consensus for clinically significant portal hypertension [5, 10] has been recently assessed. Among the 6 available studies, Baveno VII criteria were found to be accurate to discriminate patients with a high risk of decompensation from those with intermediate or low risk of decompensation [21, 25, 48–51]. However, the absolute risk of decompensation was highly variable among studies, suggesting that these features allow stratification but are insufficient for individual risk prediction. Furthermore, calibration was not provided in these studies.

The recently proposed SAVE score [25] and the CHESS-ALARM [46, 52] scores are models combining LSM with simple clinical and laboratory variables, specifically designed for the prediction of decompensation and developed from cohorts of Asian patients with cACLD. They showed excellent ability to identify patients who are at high risk for decompensation in the series they were derived from, but still need external validation (Table S2). In patients with MASLD-related cACLD, the recently proposed ABIDE-LSM model (which includes all ABIDE [53] parameters except varices—AST/ALT ration INR, bilirubin, diabetes—together with TE-LSM), showed a tAUC of 0.85 and 0.84 for predicting decompensation at 1 and 3 years, respectively [45]. In a recent large, retrospective cohort of 358 patients with cACLD from 16 European centers, a model combining the combination of albumin concentration together with TE-LSM achieved a high discriminative ability, with an AUC of 0.84 for decompensation at 1 year, and an excellent calibration [54]. In a study including 5849 patients, the FIB-5 score, combining LSM values to the individual components of the FIB-4 score (i.e., age, aspartate aminotransferase, alanine aminotransferase, and platelet count)

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had a good discriminative ability to predict liver-related events, with AUC of 0.84 to 0.86 [55].

3.5 | LSM Using Shear Wave Elastography

Data on the usefulness of LSM, using either 2D-SWE or p-SWE, to predict decompensation is scarce [56, 57]. The largest survey is a retrospective cohort study of 1490 patients with compensated or decompensated ACLD divided into derivation and validation samples (Table S3). The best predictive value for liver decompensation or death at 2 years was obtained by an algorithm combining 2D-SWE and MELD. In patients with 2D-LSM > 20 kPa and MELD > 10, the risks of death and liver decompensation at 2 years were 39% and 62%, respectively [56]. This M10LS20 model had a C-index of 0.825 and was well calibrated. However, it has never been re-evaluated in subsequent studies.

3.6 | Spleen Stiffness Measurement

In patients with cACLD, spleen stiffness measurement (SSM) has shown a similar or better accuracy than LSM for detecting clinically significant portal hypertension and varices [58]. In patients with cACLD, SSM using TE < 40 kPa could rule out HVPG ≥ 10 mmHg with 97% NPV; whereas SSM ≥ 40 kPa (when LSMs are in the range 15–25 kPa) allows ruling in HVPG ≥ 10 mmHg with 94% PPV [59]. However, the evaluation of the ability of SSM to predict decompensation or liver-related events has thus far been limited. Eight studies evaluated SSM for the prediction of decompensation in patients with cACLD of various aetiology [42, 48, 59–64]. All but two [48, 54], were single-center studies. TE-SSM > 40 kPa was associated with a higher risk of decompensation [59–61] Of note, in the recent study performed by Jachs et al., gathering 358 patients with Child-Pugh Class A cACLD, SSM was not independently associated with the occurrence of decompensation during follow-up [54]. (Table S4).

3.7 | Combination of SSM With Other Parameters

The Baveno VII criteria, criteria combining TE-LSM, platelet count and TE-SSM, to rule-out and rule-in clinically significant portal hypertension, may also be accurate to identify patients at high risk of decompensation. In a recent study, a subgroup of 179 patients with cACLD and concurrent TE-LSM and TE-SSM was retrospectively analysed: the Baveno VII criteria were found to reduce the "grey zone", while maintaining a good ability to identify patients at high risk of decompensation [48]. In another study gathering 1224 patients with HBV-related cACLD, patients in the rule-in groups according to the Baveno VII-SSM models (either using dual or single SSM cut-offs [58]) had a higher risk of decompensation during a 30 months follow-up [64]. None of these studies of SSM provided data on the calibration of the proposed models (Table 2).

3.8 | Magnetic Resonance Elastography (MRE)

In patients with MASLD and cACLD, the predictive value of LSM measured using MRE (MRE-LSM) for further decompensation or death was evaluated in 5 studies. A retrospective study from the Mayo Clinic group, including 277 patients, found an association of MRE-LSM with decompensation or death, with an adjusted hazard ratio of 1.22 [65, 66]. These findings were confirmed in a Korean study including 217 patients with cACLD of various aetiology [67]. Additionally, in patients with MASLD-related cACLD, progression in MRE-LSM over time was predictive of decompensation [68]. In a study of 72 patients with alcohol-related cACLD, Chen et al. found that MRE-LSM ≥ 5.6 kPa could identify patients at high risk of developing decompensation ($p = 0.004$), and that every 1 kPa increment in LSM was associated with a 27% increased risk of developing decompensation [69].

Altogether, these results show that LSM is strongly associated with the risk of decompensation. In patients with cACLD, the 25 kPa cut-off using TE, p-SWE or 2D-SWE allows identifying patients at higher risk of liver decompensation. The combination of LSM with other parameters related to portal hypertension, such as platelet count, albumin or SSM, also improves the accuracy of LSM to predict decompensation. Importantly, the most updated LSM value has a better predictive value than baseline LSM. This highlights the importance of repeating LSM during follow-up, since most patients with cACLD have a relatively low risk of decompensation, and that other factors, especially etiological therapy, can influence patients' prognosis. However, among studies evaluating decompensation prediction using LSM alone, calibration—ensuring accurate estimation of absolute risk—has been assessed in only one study. Thus, LSM cannot be used for individual risk prediction yet. Regarding MRE, the main limitations are its high cost, limited availability, and lengthy examination time.

4 | Blood-Based NITs

Overview of established blood-based NITs is presented in Table S5.

4.1 | Fib-4

FIB-4 is a simple test, based on aspartate aminotransferase (AST), alanine transaminase (ALT), platelets and age, with no additional cost, and therefore has been routinely used in primary care for assessment of chronic liver diseases. In patients with chronic liver diseases (i.e., not specifically cACLD), the Fibrosis-4 Index (FIB-4) has demonstrated ability to risk stratify patients for liver-related morbidity and mortality in patients with MASLD [70], alcohol-related liver disease [71], and after HCV eradication [72]. In patients with cACLD, eleven studies evaluated the usefulness of the FIB-4 to predict decompensation [20, 26, 29, 44, 45, 73–79] (Table S6) (Figure 2). Five out of these eleven studies included patients with cACLD of various aetiology, while 6 studies included patients with a specific cause of cACLD. In all studies, FIB-4 was associated with either decompensation or death. The largest study included a total of 3028 patients with cACLD patients of mixed etiologies [26]. The total follow-up was 9403 patient-years, and a median follow-up of 3.1 years per patient. FIB-4 independently predicted decompensation (HR (95% CI) 1.05 (1.02–1.07) per unit increase) after

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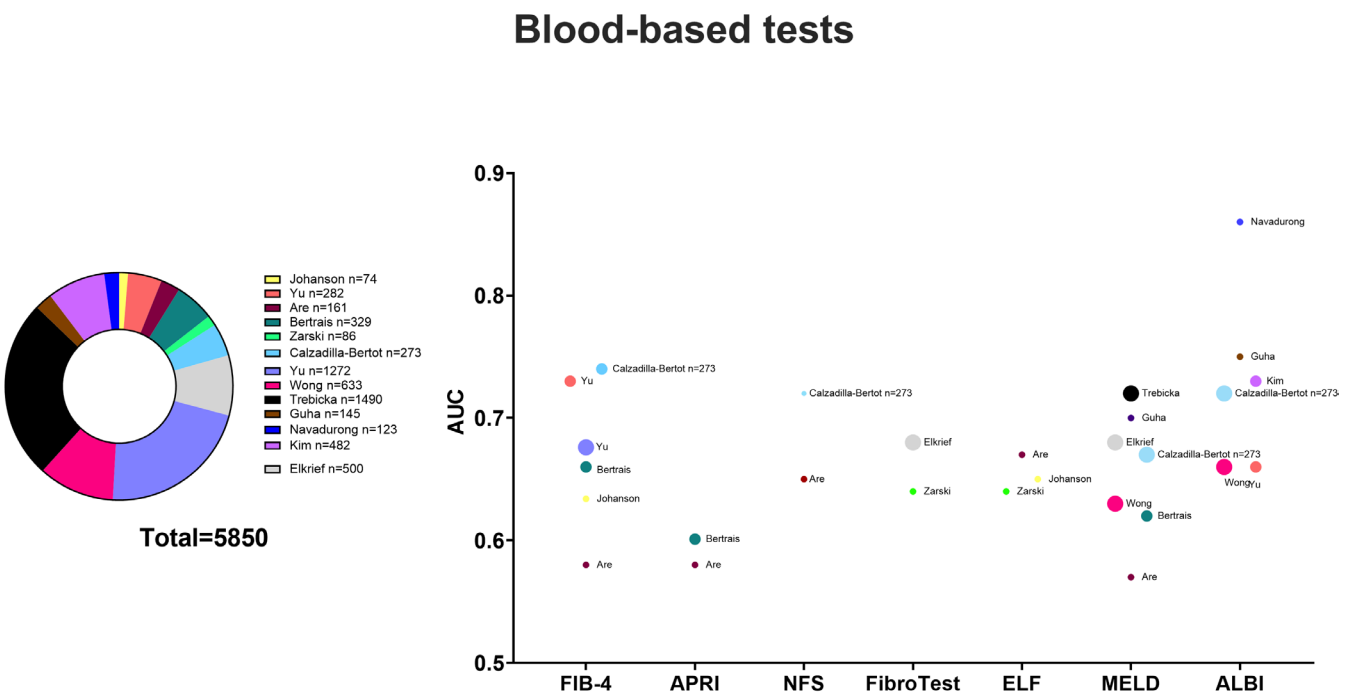

FIGURE 2 | Summary of the observed performance of blood-based tests in patients with cACLD for prediction of decompensation. The figure illustrates (i) the number of patients included in each study (each study is identified by the first author and sample size) and (ii) the reported AUC values of blood-based tests for this outcome. Circle size reflects the number of patients included in each study (small: < 200; medium: 200–1000; large: > 1000). Some studies evaluated multiple tests within the same patient cohort. AUC, area under the receiving operator curve. FiB-4, Fibrosis-4 Index, APRI, AST-to-platelet ratio index, NFS, NAFLD Fibrosis score, ALBI, albumin-bilirubin, ELF, enhanced liver fibrosis, MELD, model for end-stage liver disease.

adjustment for liver stiffness, albumin, platelet count, and aetiology of liver disease. The second largest study, derived from a phase II randomized controlled trial, included 1133 patients with MASH-related cACLD [29]. A FIB-4 ≥ 3.25 had a sensitivity of 71% in predicting decompensation or liver transplantation with a negative predictive value of 77%. The AUC was provided in 6 studies and varied from 0.58 to 0.74 (Figure 2). Among these studies, only one included a large sample of patients from a single center, all with HBV-related cACLD and analysed retrospectively [73]. In that study, the AUC was only 0.676 (0.634–0.718). Time-dependent AUC analyses were provided in 4 studies [45, 73–75], where the predictive performance of FIB-4 remained stable up to 4 years. Of note, besides AUC, these studies did not include sensitivity, specificity, positive and negative predictive value, calibration, clinical validity and utility (Table 2).

4.2 | Enhanced Liver Fibrosis (ELF) Test

ELF is a non-invasive, patented serum-based biomarker panel, which integrates three direct markers of extracellular matrix remodelling—hyaluronic acid (HA), tissue inhibitor of metalloproteinase-1 (TIMP-1), and the amino-terminal peptide of procollagen III (PIIINP)—to generate a composite fibrosis score. Four studies evaluated ELF for assessing the risk of decompensation in patients with cACLD [29, 75, 76, 80] (Table S7) (Table 2). When reported, the tAUC for predicting decompensation did not exceed 0.70 (Figure 2) [75, 76, 80]. In the study by Younossi et al., including 1133 patients with MASH cACLD, both baseline ELF values and longitudinal changes were associated with the occurrence of clinical events, highlighting its potential utility as a dynamic marker [29]. In a cohort of 475 patients with cACLD, an ELF ≥ 11.27 independently predicted outcomes over a median 31 months follow-up, but did not improve by adding change in ELF over time [81]. ELF has also been increasingly used in clinical trials as a treatment-monitoring biomarker [82]. Altogether, these data support a growing role for ELF as a relevant biomarker for risk stratification in cACLD.

4.3 | MELD

The Model for End Stage Liver Disease (MELD) was initially developed to assess the risk of death within 90 days after TIPS placement; it was subsequently used for allocating cadaveric liver grafts to patients listed for liver transplantation. Nine studies evaluated MELD for predicting decompensation or death in patients with cACLD (Table S8) [45, 46, 56, 63, 74, 75, 78, 83, 84]. The 2 largest studies included 633 and 1490 patients with cACLD of various aetiology, respectively [46, 56]. The tAUC of MELD for decompensation (at 1 or 3 years in one study, and at 2 years in the other study) was in the same range in both studies (0.74 and 0.63 at 1 and 3 years, respectively; and 0.73 at 2 years) (Figure 2). Of note, calibration was only assessed in the study performed by Trebicka et al., who used 10-fold cross-validation with 200 times of bootstrapping (Table 2) [56].

4.4 | Albumin-Bilirubin Score (ALBI)

The Albumin-Bilirubin score (ALBI), routinely used in HCC, was evaluated in 8 studies for decompensation/death prediction in

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cACLD (Table S9) [26, 45, 46, 52, 73, 78, 84, 85]. Harrell's c-statistic/AUC ranged 0.6–0.8 across 6 studies [45, 46, 52, 73, 78, 85], with stable time-dependent AUC in 3 studies (Figure 2) [45, 46, 73]. No studies proposed cut-offs or calibration data for decompensation prediction (Table 2).

4.5 | Other Blood-Based Tests

Various blood-based tests have been used over the years to estimate liver fibrosis, especially in patients with chronic viral hepatitis or MASLD. However, data evaluating their relevance for prediction of decompensation in patients with cACLD remain limited.

In patients with cACLD, only three studies evaluated the usefulness of the Aspartate-aminotransferase-to-Platelet-Ratio-Index (APRI) to predict decompensation [29, 74, 75] (Table S10), yielding AUCs < 0.60 (Figure 2). In addition, none of these studies provided data on sensitivity, specificity, PPV, and NPV (Table 2).

The NAFLD fibrosis score (NFS) has demonstrated the ability to risk stratify patients with MASLD for liver-related morbidity and mortality, a NFS > 0.676 having the same discriminative ability as an F4 liver fibrosis stage to predict liver-related events [70]. Three studies evaluated the ability of NFS to discriminate patients at higher risk of decompensation among patients with cACLD (Table S11) (Figure 2) [29, 45, 75].

The aspartate aminotransferase activity (AST)/alanine aminotransferase activity (ALT) ratio was originally proposed to assess liver fibrosis in hepatitis C and later applied to hepatitis B and other liver conditions. The AST/ALT ratio predicted decompensation in one study of 543 MASLD-related cACLD patients (median FU 5.6 years; derivation $n = 299$, validation $n = 244$) [53]. AST/ALT ratio contributed to the ABIDE model (AST/ALT + bilirubin, INR, diabetes, varices), and was identified as a significant predictor of hepatic decompensation in patients with MASLD-related cACLD. Its inclusion in the multivariable ABIDE model contributed to a time-dependent AUC of 0.71 (95% CI, 0.67–0.73). The ABIDE model demonstrated strong 5-year predictive performance (tAUC 0.80 in derivation; 0.78 in validation cohorts). A modified ABIDE (LSM replacing varices) showed superior performance in MASLD-cACLD but lacks external validation in non-MASLD [45].

Three studies assessed the performance of the FibroTest in predicting decompensation in cACLD, showing modest results (tAUC ≤ 0.70) (Table S12) (Figure 2) [29, 80, 83]. In a study of 1133 patients with MASH-related cACLD, baseline FibroTest value was associated with clinical events, but its changes over time were not (Table 2) [29]. Two studies evaluated the Fibrometer in cACLD (HCV or mixed etiologies), reporting tAUC values of around 0.68 for liver-related mortality. Hepascore showed similar results (Table S12) [74, 80].

Altogether, these results show that blood-based tests initially designed for other purposes also have the ability to discriminate patients with cACLD at a greater risk of decompensation. This is particularly true for FIB-4, ELF and MELD. Except for MELD and its cut-off of 10, other blood-based tests do not provide a validated cut-off, hampering their use for risk-stratification in clinical studies. Furthermore, they cannot be used for individual risk prediction. Thus, the development of an easily available blood-based test for decompensation able to reliably quantify the risk of decompensation in the individual patient remains an unmet need.

5 | Perspectives on Improving Noninvasive Prediction of Decompensation

5.1 | Standard and Functional Imaging

The presence and size of spontaneous portosystemic shunts appears to help identify a subgroup of patients with cACLD who are at a higher risk of liver decompensation. In a study by the Baveno group which included 1729 patients with cACLD and preserved liver function (MELD score 6–9 or Child-Pugh Class A), the presence of spontaneous portosystemic shunt vessels ≥ 8 mm in diameter was associated with a higher risk of liver decompensation (variceal bleeding and ascites) or death than shunt vessels < 8 mm in diameter [86]. This is in line with a recent study of 235 patients with cACLD, were the presence of spontaneous portosystemic shunt vessels was independently associated with the development of decompensation (SHR: 2.264, 95%-CI: 1.259–4.071) after adjustment for age, MELD score, presence of ascites, hepatic encephalopathy, and oesophageal varices [87]. Liver surface nodularity can be quantified digitally from CT or MRI images. Such a quantification has been proposed for the noninvasive diagnosis of cACLD [88] and for estimating HVPG ≥ 10 mmHg [89]. A retrospective study of 830 patients with cACLD showed that liver surface nodularity quantification score was a strong predictor of liver-related events. Indeed, in patients with cACLD, after adjusting for such concurrent risk factors as the MELD score, the liver surface nodularity score independently predicted hepatic decompensation (hazard ratio 1.38, 95% CI 1.06–1.79) [90]. As these results were derived from a single center study, they need independent validation. Functional liver imaging score—derived from gadoxetic acid-enhanced MRI—correlates with liver function. A study of 397 patients with cACLD of mixed etiologies, a functional liver imaging score of 0–3 points was at increased risk of hepatic decompensation (aHR 3.07; 95% CI 1.43–6.59; $p = 0.004$). Although not yet implemented in routine practice, such emerging imaging-based methods may still hold promise for future risk stratification [91].

5.2 | Von Willebrand Factor and VITRO Model

In patients with ACLD, elevated levels of von Willebrand factor are deemed to result from endothelial alterations due to hemodynamic changes and bacterial translocation/systemic inflammation [92]. In a study on 346 patients with cACLD and a median follow-up of 54 months, von Willebrand factor concentration was a predictor of decompensation or liver-related death independent from MELD score, HVPG, CHILD-Pugh score and platelet count (HR (95% CI) 1.04 (1.02–1.07), tAUC 0.68 to 0.70) [93]. A score combining von Willebrand

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factor and C reactive protein yielded similar performance as HVPG-based models to predict decompensation. In a study from the same single center, the VITRO model (combining von Willebrand factor and platelet count) was evaluated in 420 patients with cACLD of various aetiology and a median follow-up of 1.6 (0.5–3.8) years [94]. VITRO was able to predict decompensation (HR (95% CI) 1.134 (1.062–1.211) per unit; $p < 0.001$) both in the derivation and the validation cohort. HVPG, VITRO, ANTICIPATE±NASH-CSPH probability, and LSM to PLT ratio yielded similar AUROCs (0.739, 0.811, 0.683, and 0.699, respectively) for the risk of hepatic decompensation at 1 year. Combining the VITRO model with simple tests such as FIB-4 was suggested as facilitating the CSPH stratification in patients with suspected liver disease [95].

5.3 | Extracellular Vesicles

Extracellular vesicles (EVs) are small-sized particles naturally released from presumably all types of cells in the extracellular space. EVs contain part of the cytoplasm of the parental cell. The release and the content of EVs depend on the origin and on the pathophysiological state of the parental cell [96, 97]. The release of EVs changes in response to liver injury and its mechanisms. Circulating EV concentrations are thus potential biomarkers for decompensation of liver diseases [97]. One study evaluated the association between large, hepatocyte-derived EVs concentration and liver-related events in patients with cACLD [83]. In the latter study, including 500 patients with alcohol-related Child-Pugh Class A ACLD, hepatocyte-derived large EV concentrations were related to the risk of liver-related events at 2 years in patients with active alcohol consumption, after adjustment for MELD and Fibrotest (HR 3.1; 95% CI 0.99–9.6) [83]. The combination of Fibrotest > 0.74 and hepatocyte large EV > 50 U/L could identify a subset of patients with a 62% risk of liver-related events at 2 years. An independent validation in larger cohorts of patients with cACLD of various aetiology is needed.

5.4 | Co-Factors That Influence the Progression of Liver Disease

The prognostic value of several factors, known to influence the course of liver diseases independently from the main causes, has been evaluated. They mainly include obesity, sarcopenia, and genetic polymorphisms.

In a study of 161 patients with cACLD, the incidence of decompensation was significantly higher in patients with overweight or obesity ($p = 0.022$). In a multivariable model that included HVPG, albumin, MELD, aetiology and treatment group, BMI [HR 1.06 (1.01–1.12), $p = 0.02$] was an independent predictor of decompensation, together with HVPG and albumin [98].

In a study including 209 patients with cACLD and a median follow-up of 37 [20–63] months, sarcopenia was identified as a predictive factor for the occurrence or worsening of ascites (SHR 2.083, 95% CI 1.091–3.978), independently of clinically significant portal hypertension. Sarcopenia (SHR 2.744, 95% CI 1.105–6.816) and liver stiffness measurement (LSM) ≥ 21 kPa (SHR 3.973, 95% CI 1.548–10.197) were also independent risk factors for increased mortality [99]. However, this cohort included approximately one third of decompensated patients, limiting extrapolation to cACLD. Prospective studies restricted to compensated or predominantly compensated cirrhosis have shown that adverse body composition, particularly sarcopenia, predicts first decompensation and mortality, supporting an early prognostic impact of sarcopenia in cACLD [100, 101].

Four genetic polymorphisms have been associated with an increased risk of decompensation: (i) T allele of *TM6F2* [102], (ii) Z allele of *SERPINA1* [103, 104], (iii) G allele of *PNPLA3* [105–108] and (iv) TA allele of *HSD17B13* [109, 110] (Table S13). (i) In a study involving 938 patients diagnosed with ACLD of diverse aetiology, including 63% of patients classified as Child Pugh Class A, individuals with the T allele of *TM6SF2* had a higher risk (adjusted HR 1.40 (1.09–1.8)) of decompensation, liver transplantation, or liver-related death [102]. (ii) Two recent single center retrospective studies have evaluated the prognostic role of harbouring at least one Pi*Z allele of the *SERPINA1* gene (responsible for alpha-1 antitrypsin deficiency) in 118 and 576 patients with cACLD, respectively [103, 104]. Patients with at least one *Pi*Z* allele were at higher risk of requiring a liver transplantation or dying from a liver disease, even after adjusting for the severity of liver disease. (iii) In two retrospective monocentric studies involving a total of 534 patients, the majority of whom had cACLD related to alcohol or MASLD, it was observed that individuals carrying the *G* allele of *PNPLA3* (rs738409; C > G) had a 2 fold higher risk of decompensation [105, 108]. (iv) Harbouring at least one TA variant in *HSD17B13* gene was associated with a higher incidence of decompensation and liver related death in a total of more than 800 patients with cACLD of various aetiology in two retrospective studies [109, 110]. Overall, these findings suggest that genetic factors help identifying individuals with cACLD at a higher risk of disease progression. These preliminary data need to be further combined with other imaging or blood-based tests for predicting decompensation.

5.5 | Other

Isolated studies have focused on the novel use of serum markers to predict liver-related clinical events in cACLD: PRO-C3 [76, 111], biomarkers of immunity such as IL6 [112] or even serum microRNA (miRNA) signature (miR-181b-5p) [113]. Available data, however, must still be considered as preliminary.

The relationship between gut microbiome and occurrence of decompensation in patients with cACLD has been addressed by a recent study [114]. Changes in viral, bacterial, and archaeal α-diversity (diversity within a sampled environment), β-diversity (diversity between communities), and differential microbial features at baseline and longitudinally between/within groups who remained stable or developed further outcomes were assessed in 157 cACLD outpatients who provided stool twice. At baseline, no α/β diversity differences were seen between those who remained stable or developed the outcome. However, commensals were lower and pathobionts were higher in the patients who developed decompensation [114]. Further evaluation is obviously needed.

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5.6 | Integration of Multiple Data Using Artificial Intelligence

Technological evolution in the field of computing and data storage allows the formation of huge databases including any type of data produced in clinical practice. The availability of such types of information in large patient populations is also raising the interest towards clinical research in the field of personalized clinical management, using artificial intelligence. Artificial intelligence (AI)-based models are intended to produce a decision rule directly from data, without any (human) predefined behaviour. They may also disclose more granularity in the course of cACLD through the sophisticated analyses of the huge amount of explorable data which was inaccessible until recently [115, 116].

6 | Discussion

Several systematic reviews and meta-analysis recently assessed the value of NITs to predict decompensation [117, 118]. Although the present review is not a systematic review, we also show that the method carrying the highest of evidence for its ability to predict decompensation in patients with cACLD is LSM, measured using transient elastography in the majority of the studies. Multivariable models, combining LSM with various other parameters, have been published, with some achieving an AUC > 0.80, which is admitted as the minimal expected for diagnostic or prognostic methods. By contrast, data on available blood-based tests to predict decompensation are limited, and their performance to predict decompensation were sufficient to used them in clinical practice. Despite wide variability among the studies, the results consistently showed that LSM can discriminate patients at greater risk of decompensation. This suggests that a model or score using LSM is a promising approach. Combining LSM with other parameters related to portal hypertension, such as platelet count, as well as SSM, improve TE-LSM's ability to identify patients at higher risk of decompensation.

However, it is important to keep in mind that patients included varies widely among studies. Some studies included patients with strictly compensated disease, while other included patients with history of decompensation. In addition, in some studies patients with cACLD were included (according to Baveno definition), while in others, patients with features of cirrhosis were included. We deliberately decided not to limit this review to patients with strictly cACLD (i.e., patients with LSM > 10 kPa and without a history of decompensation). Finally, most models were developed on historical cohorts. Whether these models relying on "historical" data should be considered as fit for use in contemporary patients is questionable. Indeed, the natural history of ACLD in general has changed due to shifts in aetiology and the increasing availability of etiological therapies. Thus, restricting this review to patients with strict cACLD would have limited the analysis to a small proportion of the landscape of patients with ACLD and no (current or previous) symptoms. Furthermore, whether patients with a history of decompensation and long-lasting cured aetiology have a different prognosis from those with strictly compensated disease is unknown. For example, half of the 650 patients included in the CIRRAL study, including patients with asymptomatic alcohol-related cirrhosis, had a history of previous decompensation of cirrhosis. However, only alcohol consumption was associated with decompensation and death, but not previous history of decompensation [119, 120].

Except studies focusing on the dynamics of LSM with HCV cure, the models usually do not take into account the control of the aetiology of cirrhosis. It has been suggested that future models should be developed in cohorts of patients with controlled etiological factor [121]. However, such strategies may limit the applicability of the use of these models in real life, especially in regions where alcohol remains the first cause of CLD. In addition, follow-up periods were often short, which restricts the ability to robustly link NIT values to hard clinical outcomes such as first decompensation, liver-related mortality, or transplant-free survival. Repeating NIT and using the most updated value for short-term or mid-term prognostication could be a more appropriate follow-up strategy.

Furthermore, only a minority of the studies assessed calibration. This underscores that NITs, while valuable at the population level, do not yet permit confident prediction of decompensation risk at the individual patient level in routine clinical practice. Further well-designed, prospective studies with standardized criteria and robust validation are warranted to advance their clinical utility. Given the multifactorial drivers of decompensation in advanced chronic liver disease, integrating multiple parameters via artificial intelligence-based models may improve prognostic precision.

In conclusion, LSM-based NITs are currently the most validated method of identifying patients at higher risk of decompensation. Future studies should focus on the development of models able to predict individual risk of decompensation, and therefore guide clinical practice inclusion in clinical trials.

Author Contributions

Conceptualization of the manuscript: A.P., L.E., P.-E.R., J.B., D.V. All authors contributed to the writing, review, and editing of the initial draft.

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Conflicts of Interest

Laurent Castéra served as a consultant for Boehringer Ingelheim, Boston pharmaceutical, Echosens, Gilead, GSK, Madrigal, MSD, Novo Nordisk, Pfizer, Sagimet, and Siemens Healthineers; and as a speaker for AstraZeneca, Boehringer Ingelheim, Echosens, Gilead, Madrigal, and Novo Nordisk. Jérome Boursier served as a consultant for

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Results of the studies evaluating the performance of liver stiffness using transient elastography to predict liver decompensation or death. **Table S2:** Results of the studies evaluating the performance of liver stiffness using transient elastography combined with other variables to predict decompensation or death.

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Table S3: Results of the studies evaluating the performance of liver stiffness using 2-dimensional-shearwave elastography to predict decompensation or death. **Table S4:** Results of the studies evaluating the performance of spleen stiffness measurement to predict liver decompensation or death. **Table S5:** Established Blood-based Non-Invasive Tests, definitions and calculation methods. **Table S6:** Results of the studies evaluating the performance of the FIB-4 index to predict decompensation or death in patient with compensated cirrhosis. **Table S7:** Results of the studies evaluating the performance of Enhanced Liver Fibrosis (ELF) test to predict decompensation or death in patient with compensatedcirrhosis. **Table S8:** Results of the studies evaluating the performance of the Model for End stage Liver Disease (MELD) to predict decompensation or death in patient with compensated cirrhosis. **Table S9:** Results of the studies evaluating the performance of the ALBI score to predict decompensation or death in patient with compensated cirrhosis. **Table S10:** Results of the studies evaluating the performance of the APRI to predict decompensation or death in patient with compensated cirrhosis. **Table S11:** Results of the studies evaluating the performance of the NAFLD fibrosis score to predict decompensation or death in patient with compensated cirrhosis. **Table S12:** Results of the studies evaluating the performance of FibroTest, Fibrometer and Hepascore to predict decompensation or death in patient with compensated cirrhosis. **Table S13:** Results of the studies evaluating the performance of genetic polymorphisms to predict liver decompensation or death in patient with cirrhosis.

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