# A Combined Baveno VII and Spleen Stiffness Algorithm to Improve the Noninvasive Diagnosis of Clinically Significant Portal Hypertension in Patients With Compensated Advanced Chronic Liver Disease

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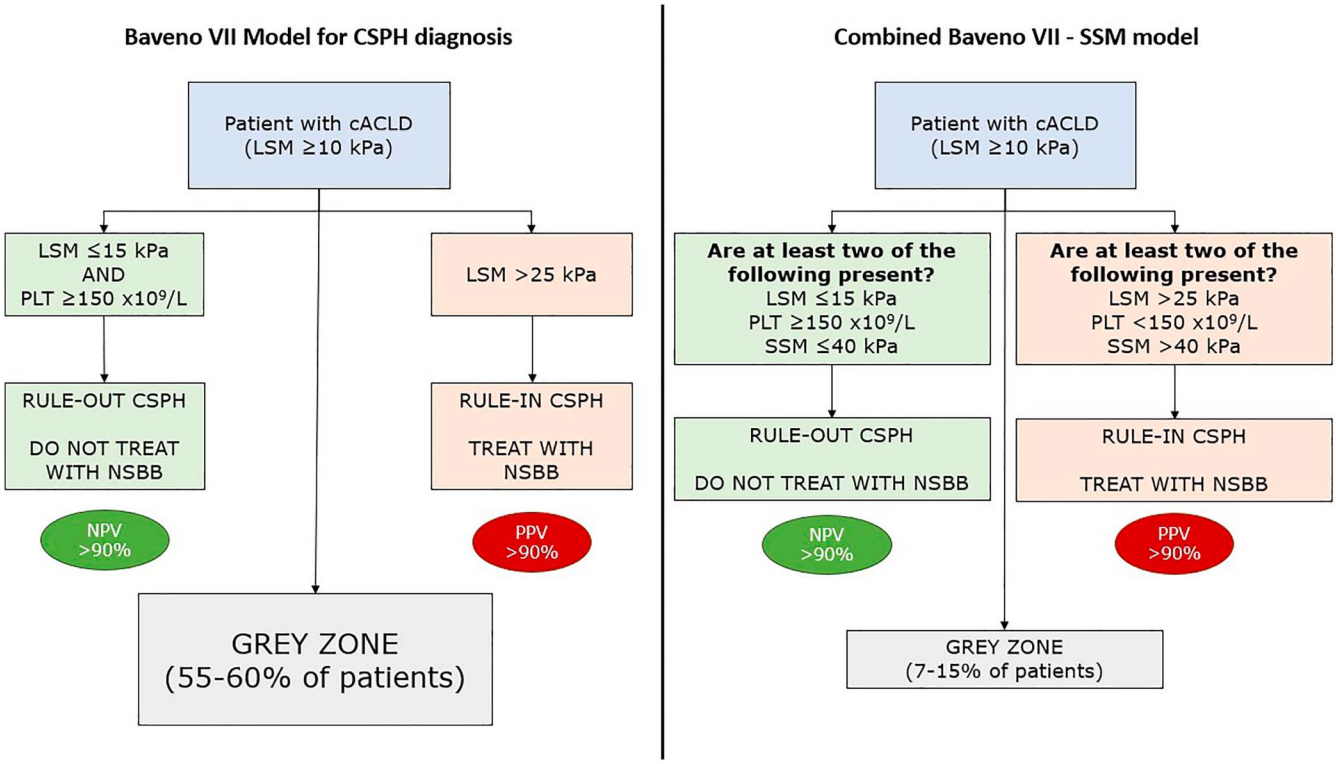
INTRODUCTION: **A noninvasive diagnosis of clinically significant portal hypertension (CSPH) has important prognostic and therapeutic implications for patients with compensated advanced chronic liver disease. We aimed to validate and improve the available algorithms for the CSPH diagnosis by evaluating spleen stiffness measurement (SSM) in patients with compensated advanced chronic liver disease.**

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METHODS: **This is a retrospective study including patients with liver stiffness measurement (LSM) ≥10 kPa, no previous decompensation, and available measurements of hepatic venous pressure gradient, LSM, and SSM by transient elastography referring to our center in Bologna. The diagnostic algorithms were adequate if negative and positive predictive values were >90% when ruling out and ruling in CSPH, respectively; these models were validated in a cohort from Verona. The 5-year decompensation rate was reported.**

RESULTS: **One hundred fourteen patients were included in the derivation cohort. The Baveno VII diagnostic algorithm (LSM ≤15 kPa + platelet count ≥150 × $10^9$/L to rule out CSPH and LSM >25 kPa to rule in CSPH) was validated; however, 40%–60% of the patients remained in the gray zone. The addition of SSM (40 kPa) to the model significantly reduced the gray zone to 7%–15%, maintaining adequate negative and positive predictive values. The diagnostic algorithms were validated in a cohort of 81 patients from Verona. All first decompensation events occurred in the "rule-in" zone of the model including SSM.**

DISCUSSION: **The addition of SSM significantly improves the clinical applicability of the algorithm based on LSM and platelet count for CSPH diagnosis. Our models can be used to noninvasively identify candidates for nonselective beta-blocker treatment and patients at a high risk of decompensation.**

**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/AJG/C591

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## INTRODUCTION

In the Baveno VI consensus, the term compensated advanced chronic liver disease (cACLD) was proposed to reflect the continuum of severe fibrosis and cirrhosis and to allow an early identification of patients at risk of developing portal hypertension complications and liver-related death (1). Among patients with cACLD, the establishment of clinically significant portal hypertension (CSPH), defined by a hepatic venous pressure gradient (HVPG) ≥10 mm Hg, is a milestone in the natural history because CSPH is the main driver of the onset of complications, such as variceal bleeding, ascites, and hepatic encephalopathy, and therefore the shift toward the decompensated stages of cirrhosis (2).

In patients with cACLD, besides etiological therapy when available and prophylaxis in patients with high-risk varices, no other treatment options are available. Recently, the PREDESCI trial (3) showed how nonselective beta-blockers (NSBB) were efficient not only in reducing the risk of variceal bleeding but also in preventing liver decompensation (mainly ascites) in patients with CSPH, suggesting that a new era could be opened in patients with compensated cirrhosis (4). This evidence was endorsed by the Baveno VII consensus, which suggests treatment with NSBB, preferably carvedilol, for the prevention of decompensation in patients with CSPH (5).

However, to obtain the change in paradigm, safe and noninvasive predictors of CSPH will be needed because the inclusion criterium in the PREDESCI trial was HVPG-driven. Since the Baveno VI consensus, a lot of time and editorial zeal was dedicated to validating and expanding the use of noninvasive test to spare more invasive approaches (6–10). In the last Baveno VII consensus (5), the following criteria were proposed for CSPH diagnosis: LSM >25 kPa to rule in and LSM ≤15 kPa + platelet count (PLT) ≥150 × $10^9$/L to rule out CSPH in most etiologies. Although such criteria can radically change the clinical approach to risk stratification in patients with cACLD, their application suffers from a critical limitation related to the large "gray zone" (LSM between 15 and 25 kPa), including more than 40% of eligible patients (11).

Alongside LSM over the past decade, consistent evidence (7,12–19) and meta-analyses (20–24) have shown the importance of the measurement of spleen stiffness (SSM) as a valuable tool for identifying CSPH and PH-related complications. In support, the latest 2021 EASL guidelines on noninvasive tests and the Baveno VII consensus endorsed the use of SSM to improve risk stratification for CSPH and esophageal varices (5,25).

This study aims the following: (i) to validate the algorithms proposed by the Baveno VII consensus for CSPH diagnosis; (ii) to improve its performance by including SSM evaluation; and (iii) to evaluate whether these diagnostic algorithms can predict the risk of the first hepatic decompensation event.

## MATERIAL AND METHODS

### Study participants and data collection

This is a retrospective study in patients with cACLD (defined by LSM ≥10 kPa), and paired measurements available with HVPG, LSM, and SSM, as measured by transient elastography (TE), referred to our tertiary centers. The derivation cohort was enrolled in 2013–2018 in the Gastroenterology Unit, University of Bologna (Italy), and the validation cohort was enrolled in the Gastroenterology Unit, University of Verona (Italy) in 2017–2019. Exclusion criteria were a previous episode of hepatic decompensation, an interval between HVPG and TE >6 months and an ongoing treatment with NSBB during diagnostic workup.

The main demographic, biochemical, endoscopic, radiological, and elastosonographic data were collected for each patient during enrollment. Moreover, all patients underwent a standard follow-up in agreement with the international guidelines (26,27). Patients' follow-up ended on February 1, 2021; the incidence of events was recorded, such as the first hepatic decompensation (defined as overt ascites, variceal bleeding, and over hepatic encephalopathy), hepatocellular carcinoma, liver transplant, or death. Patients who did not develop the event during the follow-up were censored for events such as death, liver transplant, or

their last visit to the study center. The study was conducted in compliance with the Declaration of Helsinki and approved by the local institutional review board.

### Hepatic venous pressure gradient measurement

The HVPG measurement was performed with the standard balloon catheter technique by experienced personnel, as previously described (12). CSPH was defined as HVPG ≥10 mm Hg.

### Transient elastography examinations

The LSM and SSM values were assessed by TE (FibroScan 502) and "M" probe (Echosens, Paris, France) after overnight fasting and an abdominal ultrasound examination. The LSM reliability criteria were in agreement with the recent guidelines (28). The SSM was assessed on the same day as LSM, as previously described (7,29), and the same reliability criteria for LSM were applied (30).

### Diagnostic algorithms for CSPH

The following 3 main diagnostic algorithms were evaluated: (i) The Baveno VII model (5,11): LSM ≤15 kPa + PLT ≥150,000 to rule out CSPH and LSM >25 kPa to rule in CSPH. (ii) The sequential Baveno VII-SSM 50 kPa model (5): sequential application of cutoff SSM <21 kPa and SSM >50 kPa to rule out and rule in CSPH in patients with indeterminate results, respectively, (gray zone) according to the Baveno VII model. (iii) The combined Baveno VII-SSM 40 kPa model: rule out CSPH if at least 2 of the following criteria were present: LSM ≤15 kPa, PLT ≥150,000, SSM ≤40 kPa; rule in CSPH if at least 2 of the following criteria were present: LSM >25 kPa, PLT <150,000, and SSM >40 kPa. We chose the SSM cutoff of 40 kPa based on our previously published data (28).

We also tested the following additional algorithms: (iv) the broader Baveno VII criteria for patients at a high risk of CSPH based on LSM values according to the "rule of five" and PLT (5); (v) a sequential Baveno VII-SSM 40 kPa algorithm; (vi) a combined Baveno VII-SSM model using the SSM cutoff of 50 kPa instead of 40 kPa to rule in CSPH.

### Statistical analysis

Categorical data were expressed as numbers (percentages) and continuous variables as medians (interquartile range); for group comparisons of categorical and continuous variables, the $\chi^2$ test or Mann-Whitney test and McNemar test were used, as appropriate. The primary outcome was the diagnosis of CSPH. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) was reported for each diagnostic test under evaluation; however, we considered as adequate a diagnostic model with an NPV ≥90% for ruling out CSPH and a PPV ≥90% for ruling in CSPH. We built an a priori logistic regression model based on LSM, SSM, and PLT as continuous variables for the diagnosis of CSPH, and based on this model, we drew a nomogram. Model discrimination was assessed by calculating the area under the receiver operating characteristic (AUROC) curve. We repeatedly fitted the model in 1,000 bootstrap samples and evaluated its performance on the original sample, and the DeLong test was used to test the equality of 2 or more AUROC. The secondary outcome was the risk of decompensation at 5 years, stratified according to risk groups identified by the different algorithms. The Kaplan-Meier curves

**Table 1. Characteristics of the included patients with compensated advanced chronic liver disease**

| Variables | All patients (n = 195) | Derivation cohort (Bologna) (n = 114) | Validation cohort (Verona) (n = 81) | *P* |
|---|---|---|---|---|
| Age | 59 (49–70) | 56 (48–68) | 62 (51–71) | 0.136 |
| Sex (male), n (%) | 134 (68.7) | 76 (66.7) | 58 (71.6) | 0.464 |
| Liver disease etiology, n (%) | | | | 0.113 |
| Viral | 109 (55.9) | 66 (57.9) | 43 (53.1) | |
| Alcohol | 35 (17.9) | 14 (12.3) | 21 (25.9) | |
| Other | 11 (5.6) | 8 (7) | 3 (3.7) | |
| Copresence of MAFLD | 69 (35.4) | 36 (31.6) | 33 (40.7) | 0.187 |
| Laboratory test | | | | |
| Platelets ($\times 10^9$/L) | 117 (84–162) | 113 (83–169) | 117 (88–155) | 0.933 |
| Child-Pugh score | 5 (5–6) | 5 (5–6) | 5 (5–6) | 0.796 |
| MELD score | 8 (7–10) | 8 (7–10) | 8 (7–9) | 0.286 |
| Portal hypertension assessment | | | | |
| HVPG (mm Hg) | 11 (9–14) | 10 (8–14) | 11 (9–14) | 0.392 |
| CSPH (%) | 122 (62.5) | 71 (62.3) | 51 (63) | 0.923 |
| Presence of varices | 99 (50.8) | 58 (50.9) | 41 (50.6) | 0.534 |
| LSM (kPa) | 20.5 (15.4–26.6) | 17.9 (15–26.4) | 23.1 (16.1–29.9) | **0.043** |
| SSM (kPa) | 50.2 (38.2–64.4) | 52.9 (38.5–63.9) | 48.5 (38.2–67.3) | 0.687 |

Bold indicates significant $P < 0.05$.
CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; LSM, liver stiffness measurement; MAFLD, metabolic (dysfunction)–associated fatty liver disease; MELD, model for end-stage liver disease; SSM, spleen stiffness measurement.

**Table 2. Overall performance of different models based on LSM, SSM, and PLT for the diagnosis of CSPH**

| | Baveno VII model | | | Sequential Baveno VII-SSM model | | | Combined Baveno VII-SSM model | | |
|---|---|---|---|---|---|---|---|---|---|
| | Rule-out: LSM ≤15 kPa + PLT ≥150,000 | Gray zone | Rule-in: LSM >25 kPa | Rule out: 1°: LSM ≤15 kPa + PLT ≥150,000 2°: SSM <21 kPa | Gray zone | Rule in: 1°: LSM >25 kPa 2°: SSM >50 kPa | Rule-out: Two of: LSM ≤15 kPa PLT ≥150,000 SSM ≤40 kPa | Gray zone | Rule-in: Two of: LSM >25 kPa PLT <150,000 SSM >40 kPa |
| Derivation (Bologna) cohort (n = 114 pts) | | | | | | | | | |
| Pts (%) | 11 (9.7) | 68 (59.6) | 35 (30.7) | 13 (11.4) | 36 (31.6)[a] | 65 (57) | 30 (26.3) | 17 (14.9)[b] | 67 (58.8) |
| CSPH pts | 0 | 38 | 33 | 0 | 15 | 56 | 1 | 8 | 62 |
| Performance | NPV 100% | 53% of pts with CSPH | PPV 94.3% | NPV 100% | 42% of pts with CSPH | PPV 86.2% | NPV 96.7% | 11% of pts with CSPH | PPV 92.5% |
| Validation (Verona) cohort (n = 81 pts) | | | | | | | | | |
| Pts (%) | 7 (8.6) | 45 (55.6) | 29 (35.8) | 10 (90) | 32 (39.5)[a] | 39 (48.2) | 24 (29.6) | 6 (7.4)[b] | 51 (63) |
| CSPH pts | 0 | 24 | 27 | 1 | 15 | 35 | 2 | 2 | 47 |
| Performance | NPV 100% | 47% of pts with CSPH | PPV 93.1% | NPV 90% | 29% of pts with CSPH | PPV 89.7% | NPV 91.7% | 4% of pts with CSPH | PPV 92.2% |

CSPH, clinically significant portal hypertension; LSM, liver stiffness measurement; NPV, negative predictive value, PLT, platelet count; PPV, positive predictive value; pts, patients, SSM, spleen stiffness measurement.
[a]Comparison with the Baveno VII model: $P < 0.0001$ and 0.041 in the Derivation (Bologna) and Validation (Verona) cohorts, respectively.
[b]Comparison with the Sequential Baveno VII-SSM model: $P = 0.003$ and <0.0001 in the Derivation (Bologna) and Validation (Verona) cohorts, respectively.

were used to depict the risk of hepatic decompensation development during the follow-up. All $P$ values referred to 2-tailed tests of significance. $P < 0.05$ was considered significant. The statistical analysis was performed using Stata/SE (version 14.0; Stata Corp, College Station, TX).

## RESULTS

### Patient characteristics

In the derivation cohort, a total of 198 patients had paired measurements of HVPG, SSM, and LSM during the study period, of whom 41 presented previous episodes of decompensation, 17 were on NSBB treatment, and 26 patients showed an interval between HVPG and TE measurement >6 months. Therefore, a total of 114 patients were included in the derivation cohort. Most of the patients were men (76, 67%), with a median age of 56 (48–68) years. The most common etiologies were viral (66, 58%) and metabolic dysfunction–associated fatty liver disease (36, 32%). The median HVPG was 10 (8–14) mm Hg, and 71 (62%) patients experienced CSPH; the median time interval between the HVPG and TE evaluation was 1.8 (1–3.9) months. In the validation cohort, after the exclusion of 21 patients with previous decompensation and 17 patients with an inadequate interval between HVPG and TE evaluation, 81 patients were finally included. Patients' characteristics are summarized in Table 1.

### Performance of Baveno VII models for CSPH diagnosis

The Baveno VII model was validated in the Bologna cohort (Table 2). Eleven (9.7%) patients had LSM ≤15 kPa and PLT ≥150 × $10^9$/L, and none presented CSPH; sensitivity and NPV were 100% for ruling out CSPH (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/C591). As for ruling in CSPH, 35 (31%) patients had LSM >25 kPa (of whom 33 had CSPH); the specificity was 95% and PPV 94% (see Supplementary Table 2, Supplementary Digital Content 2, http://links.lww.com/AJG/C591). However, 68 (60%) of the patients were in the gray zone and would have required invasive HVPG measurement for CSPH diagnosis; noteworthy, 38 of these 68 patients had CSPH (53% of overall patients with CSPH).

### Performance of algorithms including spleen stiffness for CSPH diagnosis

First, we evaluated the performance of the Baveno VII proposed SSM cutoffs (model 2) to diagnose CSPH (Table 2). Applying the <21 kPa cutoff in the patients within the gray zone, CSPH could be ruled out in 2 additional patients; the NPV remained 100%, but the benefit was modest (9.7% vs 11.4% in the rule out zone). Applying the >50 kPa cutoff, CSPH could be ruled in in 30 additional patients, increasing the rule-in zone (31% vs 57% and significantly decreasing the gray zone) but showing suboptimal PPV (86%).

Second, we evaluated the performance of combined Baveno VII-SSM algorithm (model 3), using the previously described SSM cutoff of 40 kPa and ruling out/in CSPH if at least 2 of the criteria based on LSM, PLT, and SSM were present (Figure 1). Inclusion of SSM in the algorithm increased the rate of patients in the rule-out (9.7% vs 26%) and rule-in zone (31% vs 50%) CSPH, while maintaining adequate NPV (97%) and PPV (93%), respectively. The resulting gray zone was significantly reduced to 17 (15%) patients ($P < 0.001$). Other algorithms (models 4–6) were tested, but with lower diagnostic performance (see Supplementary Tables 3–5, Supplementary Digital Content 3–5, http://links.lww.com/AJG/C591).

### External validation of the diagnostic algorithms for CSPH

In the external validation cohort, the diagnostic performance of the evaluated algorithms was confirmed (Table 2). The Baveno VII and the combined Baveno VII-SSM showed NPV and PPV values >90% for ruling out and ruling in CSPH, respectively, and the

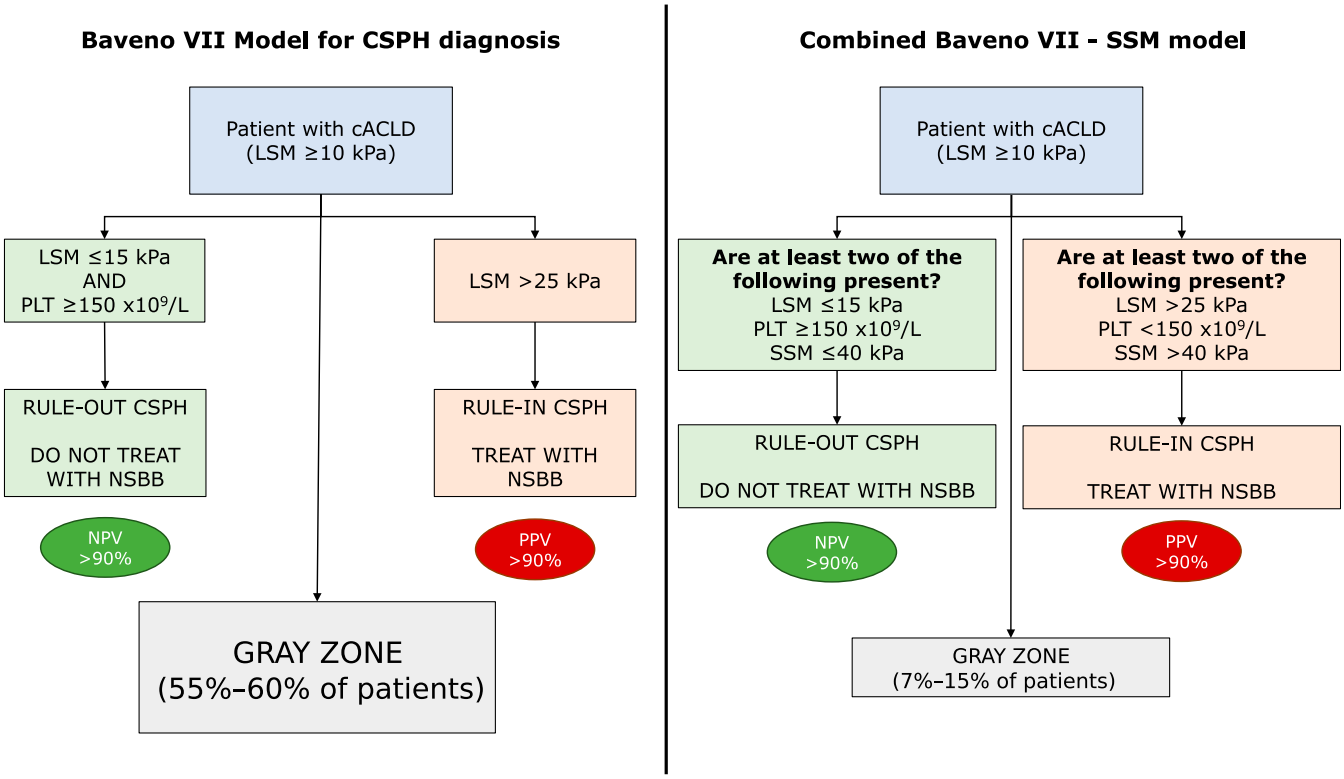


**Figure 1.** Proposed algorithms based on liver stiffness, platelet count, and spleen stiffness for the diagnosis of CSPH in patients with cACLD. cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; LSM, liver stiffness measurement; NPV, negative predictive value; NSBB, nonselective beta-blocker; PLT, platelet count; PPV, positive predictive value; SSM, spleen stiffness measurement.

latter significantly decreased the rate of patients within the gray zone (7.4% vs 56%, $P < 0.0001$). The sequential Baveno VII-SSM model showed a borderline (89.7%) PPV in the validation cohort.

### Nomogram for the prediction of CSPH presence in patients with cACLD

Based on logistic multivariate regression analysis, LSM, SSM, and PLT were independently associated with the presence of CSPH (see Supplementary Table 6, Supplemental Digital Content 6, http://links.lww.com/AJG/C591); the AUROC of the model was excellent (0.940, 95% confidence interval [CI]: 0.909–0.971). The internal validation of the model according to a bootstrap method showed an optimism-corrected AUROC of 0.938 (95% CI: 0.901–0.971), which was significantly superior to that of the ANTICIPATE model (11), based solely on LSM and PLT (0.904, 95% CI. 0.862–0.945, $P = 0.021$) (Figure 2a). Then, we built a nomogram

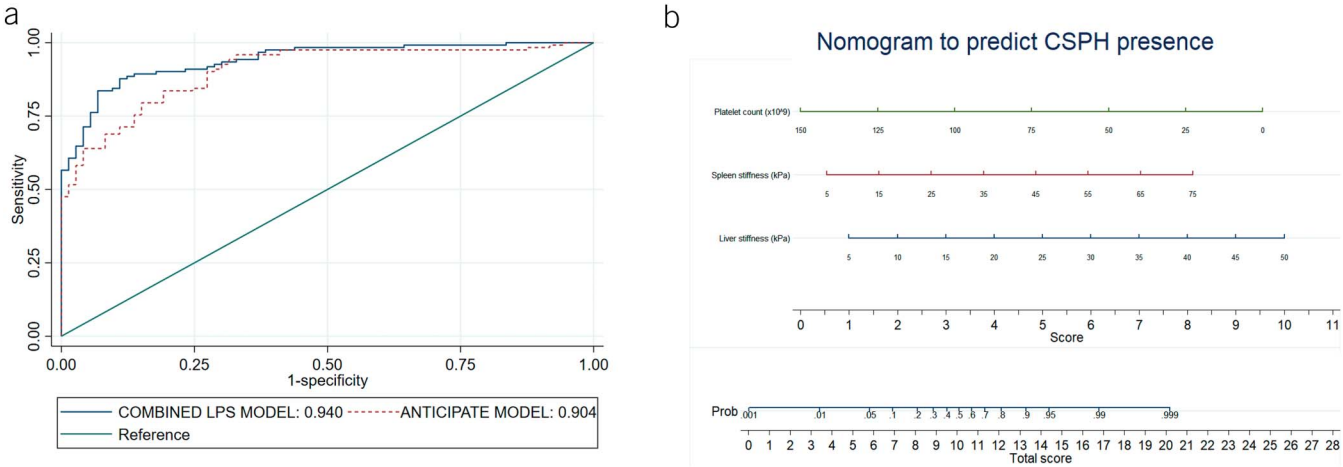


**Figure 2.** Logistic multivariate regression models for the prediction of the individual risk of CSPH in each patient with cACLD. (**a**) AUROC of model including LPS and ANTICIPATE model. (**b**) A nomogram based on liver stiffness, platelet count, and spleen stiffness to predict the risk of CSPH presence. AUROC, area under the receiver operating characteristic; cACLD, compensated advanced chronic liver disease; CSPH, clinically significant portal hypertension; LPS, liver stiffness, platelet count and spleen stiffness.

**Table 3. Risk of the first decompensation event according to the different models based on LSM, SSM, and PLT**

| | Entire cohort | | |
|---|---|---|---|
| | No. of patients (n = 195), n (%) | First decompensation event (n = 19), n (%) | Performance |
| Baveno VII model | | | |
| Rule out group: LSM ≤15 kPa + PLT ≥150,000 | 18 (9.2) | 0 (0) | |
| Gray zone group | 113 (57.9) | 11 (9.7) | 58% of first decompensation events |
| Rule-in group: LSM >25 kPa | 64 (32.9) | 8 (12.5) | |
| Sequential Baveno VII-SSM model | | | |
| Rule-out group: 1°: LSM ≤15 kPa + PLT ≥150,000 2°: SSM <21 kPa | 23 (11.8) | 0 (0) | |
| Gray zone group | 68 (34.9) | 3 (4.4) | 16% of first decompensation events |
| Rule-in group: 1°: LSM >25 kPa 2°: SSM >50 kPa | 104 (53.3) | 16 (15.4) | |
| Combined Baveno VII-SSM model | | | |
| Rule-out group: Two of: LSM ≤15 kPa PLT ≥150,000 SSM ≤40 kPa | 54 (27.7) | 0 (0) | |
| Gray zone group | 23 (11.8) | 0 (0) | 0% of first decompensation events |
| Rule-in group: Two of: LSM >25 kPa PLT <150,000 SSM >40 kPa | 118 (60.5) | 19 (16.1) | |

LSM, liver stiffness measurement; PLT, platelet count; SSM, spleen stiffness measurement.

for tailored-in risk estimation of the CSPH probability in each patient based on LSM, PLT, and SSM (Figure 2b).

### Rate of first decompensation event in the risk groups according to the algorithms

We evaluated whether the different diagnostic algorithms' stratification in 3 risk groups (rule out, gray zone, and rule in) were associated with the 5-year decompensation risk. During a median follow-up of 42 (21–54) months, 19 of the 165 (9.7%) patients developed a first decompensation event, mainly ascites (in 14 cases).

Eleven (58%) of the 19 decompensation events occurred in the gray zone according to the Baveno VII model, while this number was reduced to 3 (16%) and subsequently to 0 in the gray zones according to the 2 models including SSM (Table 3). In fact, all events developed in the rule-in zone according to the combined Baveno VII-SSM model, confirming that these criteria correctly identify the patients with CSPH and at a higher risk of decompensation. Figure 3 depicts the Kaplan-Meier curves of

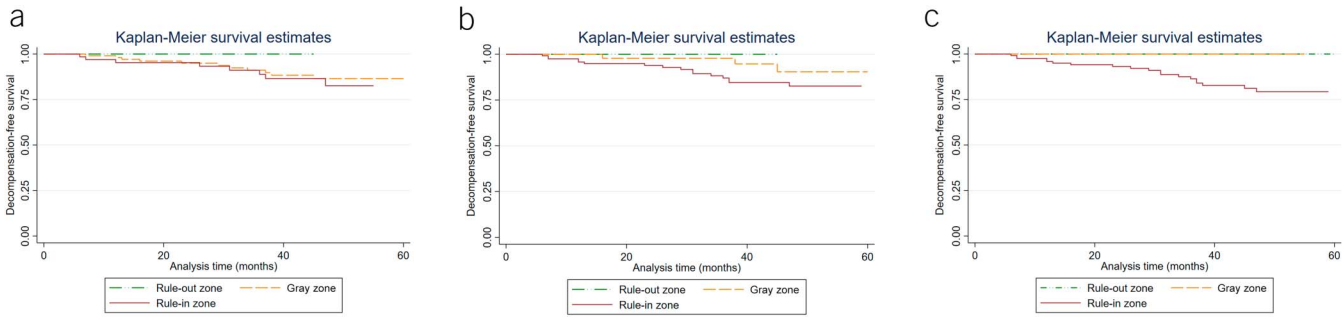


**Figure 3.** The Kaplan-Meier curves of decompensation-free survival in the risk groups identified by the different diagnostic algorithms under evaluation.

decompensation-free survival in the different risk categories according to the 3 diagnostic algorithms evaluated.

## DISCUSSION

We have developed and externally validated an algorithm including the spleen stiffness that significantly improved the diagnosis of CSPH in patients with cACLD compared with Baveno VII diagnostic algorithms based on liver stiffness and platelet count. Our new strategy can non-nvasively identify patients who can benefit from treatment with nonselective beta-blockers, minimizing the rate of patients with indeterminate results (gray zone) for CSPH presence.

The diagnosis of CSPH among patients with cACLD is essential because it bears valuable prognostic information regarding the risk of developing portal hypertension–related complications and liver-related death (5). Following the PREDESCI trial, CSPH diagnosis could have also therapeutic implications because this landmark study showed for the first time that treatment with NSBB in patients with CSPH significantly reduced the risk of the first decompensation event by mainly reducing the incidence of ascites development (3). The application of the PREDESCI findings, as recently suggested (4), would lead to a crucial change in paradigm in the management of cACLD because the main aim of NSBB treatment would no longer be only the prevention of variceal bleeding in the subgroup of patients with high-risk varices (1) but the prevention of progression to the decompensated state of cirrhosis in all patients with CSPH. In agreement with the Baveno VII consensus (5), NSBB treatment is now recommended in cACLD patients with CSPH to prevent decompensation, offering a chance to significantly affect the natural history, patient management, and healthcare costs associated with this condition.

The main limit of the applicability of PREDESCI trial is the identification of treatment candidates through HVPG measurement. This limit could be overcome by applying noninvasive tests developed and validated over the last years to identify patients with portal hypertension and its complications (1,25). The Baveno VII Consensus suggested that LSM values >25 kPa were sufficient to rule in CSPH in patients with cACLD, whereas CSPH could be ruled out if LSM ≤15 kPa and PLT ≥150 × $10^9$/L (5); these cutoffs were largely based on the findings of a recent large multicenter trial conducted by Pons et al. (11). However, when analyzing the data from the study conducted by Pons et al., it was not possible to determine the diagnosis of CSPH noninvasively in 43% of the patients, placing them in the so-called gray zone. This would lead to the use of invasive measurements such as HVPG in almost half of the patients in routine clinical practice. Moreover, the Baveno VII suggested the use of SSM <21 and >50 kPa to rule out and rule in CSPH, respectively, but these cutoffs have not yet been validated.

In our study, we first validated the Baveno VII criteria for the diagnosis of CSPH. They could safely rule in (PPV >90%) and rule out (NPV >90%) CSPH in 31% and 10% of the patients, respectively. However, the rate of patients with undetermined risk remained substantial (60%), decreasing the clinical applicability of this strategy. Second, we applied the SSM cutoffs proposed by the Baveno VII consensus in a sequential manner after the LSM-based and PLT-based criteria. We found that the sequential Baveno VII-SSM model significantly reduced the gray area to 23%, mostly by increasing the rate of patients in the rule-in zone, but with the price of a suboptimal PPV (86.2% and 89.7% in the derivation and validation cohorts, respectively). Therefore, improving the current algorithms for better risk stratification and identification of patients with CSPH is an imminent clinical necessity.

The main finding of our study is that the application of spleen stiffness with a cutoff of 40 kPa, together with LSM and PLT, which we called the combined Baveno VII-SSM model, significantly improved the applicability of noninvasive algorithms (Figure 1). When at least 2 of the following rule out criteria (LSM ≤15 kPa, PLT ≥150 × $10^9$/L, SSM ≤40 kPa) were present, CSPH could be safely excluded in 26% of patients; likewise, it could be accurately ruled in in 59% of the patients when at least 2 of following rule in criteria (LSM >25 kPa, PLT <150 × $10^9$/L, SSM >40 kPa) were present. The rate of patients within the gray zone in the new Baveno VII-SSM model was significantly reduced to 15%; in this case, only 11% of patients with CSPH remained unidentified by this novel diagnostic algorithm. Alternatively, using the more conservative cutoff of 50 kPa to rule in CSPH, together with LSM and PLT in best-of-three algorithm, the model reached both PPV and specificity >90%, with indeterminate results only in 23% of the patients (compared with 60% in the model without SSM, $P < 0.0001$).

The main aim of reducing patients within the gray zone was successfully met also in the external validation cohort (Verona); indeed, our diagnostic algorithms performed similarly to what was shown in the derivation cohort and maintained the required PPV >90% and NPV >90% for ruling in and ruling out CSPH, respectively.

We also drew a nomogram for the patient-tailored estimation of CSPH risk in patients with cACLD based on LSM, PLT, and SSM values (Figure 2); the logistic model's accuracy was excellent (AUROC 0.940) and outperformed that of the ANTICIPATE model.

Last, we investigated whether the classification in 3 groups (rule out, gray zone, and rule in) according to the different algorithms provided prognostic information and stratified for the risk of the first decompensation event in patients with cACLD (Table 3 and Figure 3). We found that all hepatic decompensation events at 5 years of follow-up occurred in the high-risk group (rule in) according to the combined Baveno VII-SSM model, confirming that the algorithms correctly identified the patients who would benefit most from NSBB treatment. By contrast, the rate of 5-year decompensation was similar between the gray zone (9.7%) and the rule-in zone (12.5%) according to the Baveno VII model based solely on LSM and PLT because 58% of the hepatic decompensation events occurred in patients within the gray zone for CSPH.

In recent years, SSM has been extensively proposed as a more accurate and direct surrogate of portal hypertension than LSM, with a better diagnostic performance in diagnosing CSPH and varices in patients with cirrhosis (13,16,18–20,31–33). Going beyond the LSM comparison, the addition of SSM in models that include LSM and PLT has been shown to significantly improve the performance of noninvasive screening strategies for portal hypertension and its complications, without requiring additional costs or professional skills. Therefore, the recent EASL guidelines for noninvasive testing and the Baveno VII consensus recommended for the first time the use of SSM as an additional tool to refine further the risk of high-risk varices (HRV) and CSPH in patients with cACLD (5,25). The Baveno VI criteria have consistently been proven safe to exclude HRV, but their application was limited by a rate of spared endoscopies of only 15%–25% (10). The inclusion of the SSM ≤46 kPa criterion to further rule out

HRV doubled the rate of spared endoscopies maintaining a safe level of missed HRV <5% (7,16). The results of this study made no exception and showed that the inclusion of SSM in an algorithm based on LSM and PLT has yielded the following: (i) it significantly improved the clinical applicability of noninvasive strategies aimed at defining the presence of CSPH; (ii) it reduced the need for HVPG measurements in patients with indeterminate results; and (iii) it identified patients at the highest risk of hepatic decompensation at 5 years who could therefore benefit most from treatment with NSBB.

The main limitation is the retrospective design of the study, which could have introduced a selection bias and did not allow evaluating the rate of unfeasible SSM examinations. However, patient characteristics and the prevalence of CSPH (ca. 60%) are in line with what was expected from a cohort of patients with cACLD (11,34), and our algorithms have been were externally validated. Moreover, we would expect the rate of technical failure to be <10% (7,33) when: (i) patients experience cACLD and usually present with splenomegaly and (ii) the examination is performed under ultrasound guidance (whether with a standard US device or with the novel SSM-dedicated TE device). The use of broadly available serum-based surrogates of CSPH, such as von Willebrand factor, was not investigated in this study but could further improve the noninvasive diagnostic algorithms for CSPH diagnosis (35). Another known limitation was the predominance of viral hepatitis and our cohorts' relatively low number of NAFLD-only patients. It is known that viral eradication can change the course of patient outcomes, and this could explain the very low event rate in the time-to-event analysis. These data should be interpreted with caution; however, the prevalence of viral etiology did not differ between the at-risk groups identified by the new diagnostic algorithms and therefore should not affect differently the decompensation rate among the at-risk groups.

In conclusion, we validated the Baveno VII models for CSPH stratification and demonstrated that the addition of spleen stiffness significantly improves the performance and applicability of these algorithms based on liver stiffness and PLT. In particular, the combined Baveno VII-SSM can substantially reduce uncertainty and decrease the use of invasive methods, such as HVPG. Consistently, given the concordance between patients at high risk and those who experienced a 5-year hepatic decompensation event, the new combined model can be used to identify candidates for NSBB treatment and provide helpful information on the risk of hepatic decompensation in patients with cACLD.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Antonio Colecchia, PhD.

**Specific author contributions:** E.D. and F.R.: collected data, analyzed data, wrote the manuscript, and approved the final manuscript. E.D., F.R., G.M., L.V.A., L.C., A.F., C.C., S.G., A.V., M.R., and R.G.: analyzed data and contributed to the drafting and final approval of the manuscript. A.C. and D.F.: provided overall oversight of the study and contributed to the drafting and final approval of the manuscript.

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## Study Highlights

### WHAT IS KNOWN

- ✓ The diagnosis of clinically significant portal hypertension (CSPH) is crucial in patients with compensated cirrhosis.
- ✓ The Baveno VII algorithm based on liver stiffness and platelet count could noninvasively diagnose CSPH.

### WHAT IS NEW HERE

- ✓ The Baveno VII algorithm is validated, but up to 60% of the patients have indeterminate results.
- ✓ The addition of spleen stiffness to the algorithm is safe and reduces the gray area for CSPH presence.
- ✓ The combined Baveno VII-SSM algorithm can identify cACLD patients at high risk of decompensation.

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