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A combined Baveno VII and spleen stiffness algorithm to improve the non-invasive diagnosis of clinically significant portal hypertension in patients with compensated advanced chronic liver disease

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Abbreviations: ACLD: advanced chronic liver disease; AUROC: area under ROC curve; cACLD: compensated advanced chronic liver disease; CSPH: clinically significant portal hypertension; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HVPG: hepatic venous pressure gradient; LSM: liver stiffness measurement; MAFLD: metabolism-associated liver disease; MELD: Model for End-stage Liver Disease; NAFLD: non-alcoholic fatty liver disease; NIT: non-invasive test; NPV: negative predictive value; PLT: platelet count; PPV: positive predictive value; SSM: spleen stiffness measurement; TE: transient elastography.

Abstract

Background & Aims: Non-invasive diagnosis of clinically significant portal hypertension (CSPH) has important prognostic and therapeutic implications for patients with compensated advanced chronic liver disease (cACLD). We aimed to validate and improve the available algorithms for the CSPH diagnosis by evaluating spleen stiffness measurement (SSM) in patients with cACLD.

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 (NPV) and positive predictive value (PPV) >90% when ruling-out and 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 + PLT≥150x10^9/L to rule out CSPH and LSM>25 kPa to rule-in CSPH) was validated; however, 40-60% of the patients remained in the grey zone. The addition of SSM (40 kPa) to the model significantly reduced the grey zone to 7-15%, maintaining adequate NPV and PPV. 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.

Conclusion: 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 non-invasively identify candidates for non-selective beta-blocker treatment and patients at high-risk of decompensation.

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 cACLD patients, the establishment of clinically significant portal hypertension (CSPH), defined by a hepatic venous pressure gradient (HVPG) ≥10 mmHg, is a milestone in the natural history, as CSPH is the main driver of the onset of complications, such as variceal bleeding, ascites, and hepatic encephalopathy, and therefore the shift towards the decompensated stages of cirrhosis.(2)

In cACLD patients, 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 non-selective beta-blockers (NSBBs) were efficient not only in reducing the risk of variceal bleeding but also in preventing liver decompensation (mainly ascites) in CSPH patients, 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 non-invasive predictors of CSPH will be needed, as 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 non-invasive test (NITs) 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 + PLT ≥150x10^9/L to rule-out

CSPH in most aetiologies. Although such criteria can radically change the clinical approach to risk stratification in cACLD patients, their application suffers from a critical limitation related to the large "grey zone" (LSM between 15 and 25 kPa), including over 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 non-invasive tests and the Baveno VII consensus endorsed the use of SSM to improve risk stratification for CSPH and esophageal varices. (5,25)

The present study aims: (i) to validate the algorithms proposed by the Baveno VII consensus for CSPH diagnosis; (ii) to improve its performance by including SSM evaluation; 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 centres. 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 ongoing treatment with NSBB at the time of diagnostic workup.

The main demographic, biochemical, endoscopic, radiological and elastosonographic data were collected for each patient at the time of enrolment. Moreover, all patients underwent a standard follow-up in agreement with international guidelines.(26,27) Patient's 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 follow-up were censored at the time of death, liver transplant, or last visit to the study centre. 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 mmHg.

Transient elastography examinations:

The LSM and SSM values were assessed by TE (FibroScan® 502), "M" probe (Echosens, Paris, France) after overnight fasting and an abdominal ultrasound examination. The LSM reliability criteria were in agreement with 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 main three diagnostic algorithms evaluated were the following:

1) The Baveno VII model (5,11): LSM ≤15 kPa + PLT ≥150.000 to rule-out CSPH and LSM >25 kPa to rule-in CSPH.

2) The sequential Baveno VII-SSM 50 kPa model(5): sequential application of cut-offs SSM <21 kPa and SSM >50 kPa to respectively rule-out and rule-in CSPH in patients with indeterminate results ("grey zone") according to the Baveno VII model.

3) The combined Baveno VII-SSM 40 kPa model: rule-out CSPH if at least two of the following criteria were present: LSM ≤15 kPa, PLT ≥150.000, SSM ≤40 kPa; rule-in CSPH if at least two of the following criteria were present: LSM >25 kPa, PLT <150.000, SSM >40 kPa. We chose the SSM cut-off of 40 kPa based on our previously published data (28).

We also tested the following additional algorithms: 4) the broader Baveno VII criteria for patients at high-risk of CSPH based on LSM values according to the "rule-of-five" and PLT(5); 5) a sequential Baveno VII-SSM 40 kPa algorithm; 6) a combined Baveno VII-SSM model using the SSM cut-off 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, Chi-square test or Mann-Whitney test and McNemar's 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 NPV ≥90% for ruling out CSPH and PPV ≥90% for ruling in CSPH. We built an a priori logistic regression model based on LSM, SSM and platelet count as continuous variables for the diagnosis of CSPH and, based on this model, we drew a nomogram. Model discrimination was assessed by calculating the 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 two or more AUROCs. The secondary outcome was the rate of 5-years decompensation event, stratified according to risk groups identified by the different algorithms. Kaplan-Meier (KM) curves were used to depict the risk of hepatic decompensation development during follow-up. All p values referred to two-tailed tests of significance. P<0.05 was considered significant. The statistical analysis was carried out using Stata/SE (Version 14.0; Stata Corp, Texas, U.S.A.).

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 male (76, 67%), and the median age of 56 (48-68) years. The most common etiologies were viral (66, 58%) and metabolic dysfunction associated fatty liver disease (MAFLD) (36, 32%). The median HVPG was 10 (8-14) mmHg, and 71 (62%) patients had 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 x 10^9/L, and none presented CSPH; sensitivity and NPV were 100% for ruling out CSPH (**Supplementary Material 1**). As for ruling in CSPH, 35 (31%) patients had LSM >25 kPa (of whom 33 had CSPH); the specificity was 95% and the PPV 94% (**Supplementary Material 2**). However, 68 (60%) of the patients were in the "grey zone" and would have required invasive HVPG measurement for CSPH diagnosis; noteworthy, 38 out 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 cut-offs (model 2) to diagnose CSPH (**Table 2**). Applying the <21 kPa cut-off in the "grey zone" patients, 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 cut-off, CSPH could be ruled-in in 30 additional patients, increasing the "rule-in" zone (31% vs 57%, and significantly decreasing the "grey zone", but showing suboptimal PPV (86%).

Second, we evaluated the performance of combined Baveno VII-SSM algorithm (model 3), using the previously described SSM cut-off of 40 kPa, and ruling-out/in CSPH if at least two 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 "rule-out" (9.7% vs 26%) and the "rule-in" zone (31% vs 50%) CSPH, while maintaining adequate NPV (97%) and PPV (93%), respectively. The resulting "grey zone" was significantly reduced to 17 (15%) patients ($p<0.001$).

Other algorithms (model 4-6) were tested, but with lower diagnostic performance (**Supplementary Material 3-5**).

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 latter significantly decreased the rate of patients within the "grey 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 cACLD patients

Based on logistic multivariate regression analysis, LSM, SSM, and platelet count were independently associated with the presence of CSPH (**Supplemental Material 6**); the AUROC of the model was excellent (0.940, 95%-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 platelet count (0.904, 95%-CI. 0.862-0.945, *p-value= 0.021*) (**Figure 2a**). Then, we built a nomogram 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 three risk groups (rule-out, grey zone, and rule-in) were associated with the 5-year decompensation risk. During a median follow-up of 42 (21-54) months, 19/165 (9.7%) patients developed a first decompensation event, mainly ascites (in 14 cases).

Eleven (58%) out of the 19 decompensation events occurred in the "grey zone" according to the Baveno VII model, while this number was reduced to 3 (16%) and subsequently to 0 in the "grey zones" according to the two 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 higher risk of decompensation. **Figure 3** depicts the Kaplan-Meier curves of decompensation-free survival in the different risk categories according to the three 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 compensated ACLD compared to Baveno VII diagnostic algorithms based on liver stiffness and platelet count. Our new strategy can non-invasively identify patients that can benefit from treatment with non-selective beta-blockers, minimizing the rate of patients with indeterminate results ("grey-zone") for CSPH presence.

The diagnosis of CSPH among patients with cACLD is essential, as 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, as 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, as 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 non-invasive tests (NITs) 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 cACLD patients, whereas CSPH could be ruled-out if LSM ≤15 kPa and PLT ≥150x10^9/L;(5) these cut-offs were largely based on the findings of a recent large multicentre trial by Pons et al.(11) However, when analysing the data from the Pons et al. study, it was not possible to determine the diagnosis of CSPH non-invasively in 43% of the patients, placing them in the so-called grey 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 SSM <21 kPa and >50 kPa to respectively rule-out and rule-in CSPH, but these cut-offs have not yet been validated.

In our study, we first validated the Baveno VII criteria for the diagnosis 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 cut-offs proposed by the Baveno VII consensus in a sequential manner after the LSM and PLT-based criteria. We found that the sequential Baveno VII-SSM model significantly reduced the grey 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 cohort, 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 cut-off of 40 kPa, together with LSM and PLT, which we called the combined Baveno VII-SSM model, significantly improved the applicability of non-invasive algorithms **(Figure 1)**. When at least two of the following rule-out criteria (LSM≤15 kPa, PLT≥150x10^9/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 two of following rule-in criteria (LSM>25 kPa, PLT<150x10^9/L, SSM>40 kPa) were present. The rate of patients within the grey 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 cut-off 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 (vs. 60% in the model without SSM, p<0.0001).

The main aim of reducing patients within the grey 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 out CSPH, respectively.

We also drew a nomogram for the patient-tailored estimation of CSPH risk in cACLD patients 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.

Lastly, we investigated whether the classification in three groups (rule-out, grey zone, and rule-in) according to the different algorithms provided prognostic information and stratified for the risk of the first decompensation event in cACLD patients **(Table 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. In contrast, the rate of five-year decompensation was similar between the grey zone (9.7%) and the rule-in zone (12.5%) according to Baveno VII model based solely on LSM and platelet counts, as 58% of the hepatic decompensation events occurred in patients within the grey 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 cirrhotic patients (13,16,18,19,31–34). 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 non-invasive screening strategies for portal hypertension and its complications, without requiring additional costs or professional skills. Therefore, the recent EASL guidelines for non-invasive 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 cACLD patients.(5,25) The Baveno VI criteria have consistently been proven safe to exclude high-risk varices (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 HRVs doubled the rate of spared endoscopies maintaining a safe level of missed HRV <5%.(7,16) The results of the present study made no exception and showed that the inclusion of SSM in an algorithm based on LSM and PLT has: i) significantly improved the clinical applicability of non-invasive strategies aimed at defining the presence of CSPH; ii) reduced the need for HVPG measurements in patients with indeterminate results; iii) identified patients at 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 to evaluate the rate of unfeasible SSM examinations. However, patient characteristics and prevalence of CSPH (ca. 60%) are in line with what expected from a cohort of cACLD patients (11,35), and our algorithms have been were externally validated. Moreover, we would expect the rate of technical failure to be <10% (7,34) when: 1) patients have cACLD and usually present with splenomegaly and 2) 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 the present study, but could further improve the non-invasive diagnostic algorithms for CSPH diagnosis (36). 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 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 platelet count. 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.

Table 1 – Characteristics of the included patients with compensated advanced chronic liver disease (cACLD)

Variables	All patients (n=195)	Derivation cohort (Bologna) (n=114)	Validation cohort (Verona) (n=81)	p-value
Age	59 (49-70)	56 (48-68)	62 (51-71)	0.136
Sex (male) (%)	134 (68.7)	76 (66.7)	58 (71.6)	0.464
Liver disease etiology				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)	
Co-presence of MAFLD	69 (35.4)	36 (31.6)	33 (40.7)	0.187
Laboratory Test				
Platelets (x10^9/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 (mmHg)	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

Abbreviations: CSPH: clinically significant portal hypertension; HBV: hepatitis B virus; HCV: hepatitis C virus; 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:		**Rule-in:**	**Rule-out:**		**Rule-in:**	**Rule-out:**		**Rule-in:**
		LSM ≤15 kPa + PLT ≥150.000	**Grey Zone**	LSM >25 kPa	1°: LSM ≤15 kPa + PLT ≥150.000 2°: SSM <21 kPa	**Grey Zone**	1°: LSM >25 kPa 2°: SSM >50 kPa	Two out of: LSM ≤15 kPa PLT ≥150.000 SSM ≤40 kPa	**Grey Zone**	Two out 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%) *	65 (57%)	30 (26.3%)	17 (14.9%) **	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%) *	39 (48.2%)	24 (29.6%)	6 (7.4%) **	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%

*Comparison with the Baveno VII Model: p<0.0001 and 0.041 in the Derivation (Bologna) and Validation (Verona) cohort, respectively.
**Comparison with the Sequential Baveno VII-SSM Model: p=0.003 and <0.0001 in the Derivation (Bologna) and Validation (Verona) cohort, respectively.

Abbreviations: CSPH: clinically significant portal hypertension; LSM: liver stiffness measurement; NPV: negative predictive value, PLT: platelet count; PPV: positive predictive value; SSM: spleen stiffness measurement.

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

	Entire Cohort		
	Nr. Patients (n=195)	*1st decompensation event (n=19)*	*Performance*
Baveno VII Model			
Rule-out group: LSM ≤15 kPa + PLT ≥150.000	18 (9.2%)	0 (0%)	
Grey zone group	113 (57.9%)	11 (9.7%)	58% of 1st 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%)	
Grey zone group	68 (34.9%)	3 (4.4%)	16% of 1st 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 out of: LSM ≤15 kPa PLT ≥150.000 SSM ≤40 kPa	54 (27.7%)	0 (0%)	
Grey zone group	23 (11.8%)	0 (0%)	0% of 1st decompensation events
Rule-in group: Two out 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.

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Author names in bold designate shared co-first authorship.

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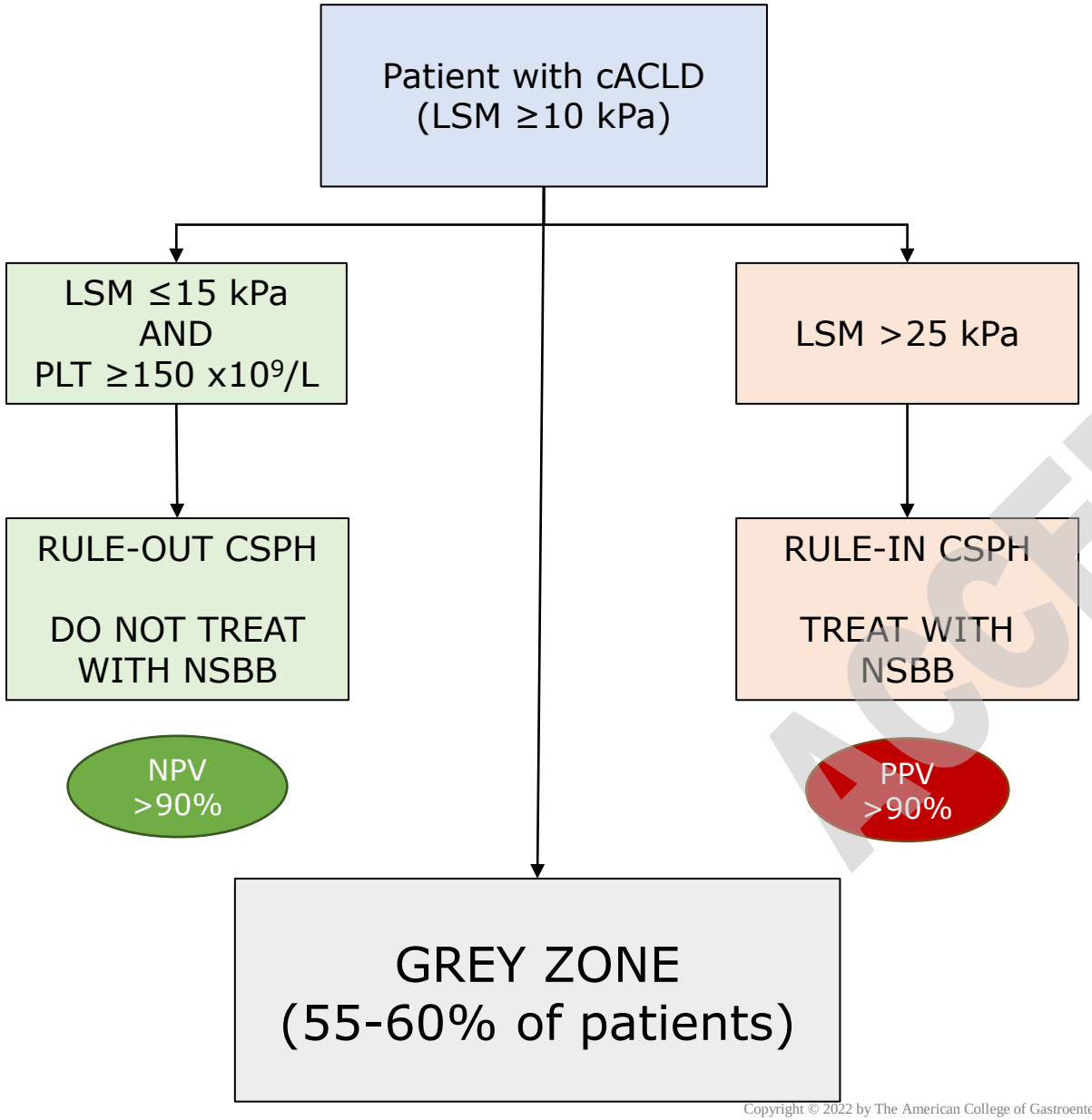
Figure Legend

Figure 1 – Proposed algorithms based on liver stiffness, platelet count and spleen stiffness for the diagnosis of CSPH in cACLD patients

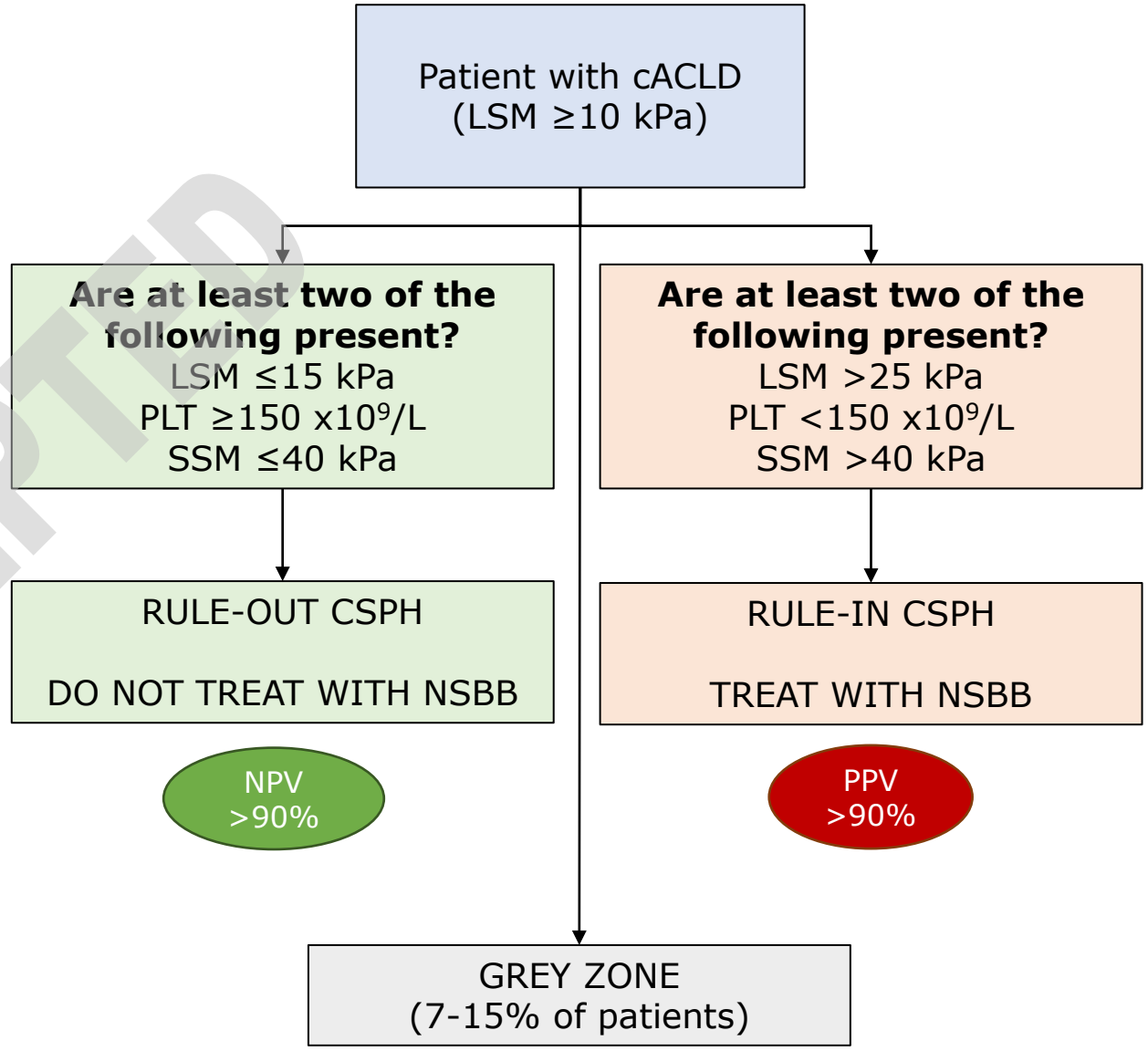
Figure 2 – Logistic multivariate regression models for the prediction of the individual risk of CSPH in each cACLD patient. A) AUROC of model including liver stiffness, platelet count and spleen stiffness (LPS) and ANTICIPATE model; B) A nomogram based on liver stiffness, platelet count and spleen stiffness to predict the risk of CSPH presence.

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

Baveno VII Model for CSPH diagnosis



Combined Baveno VII - SSM model



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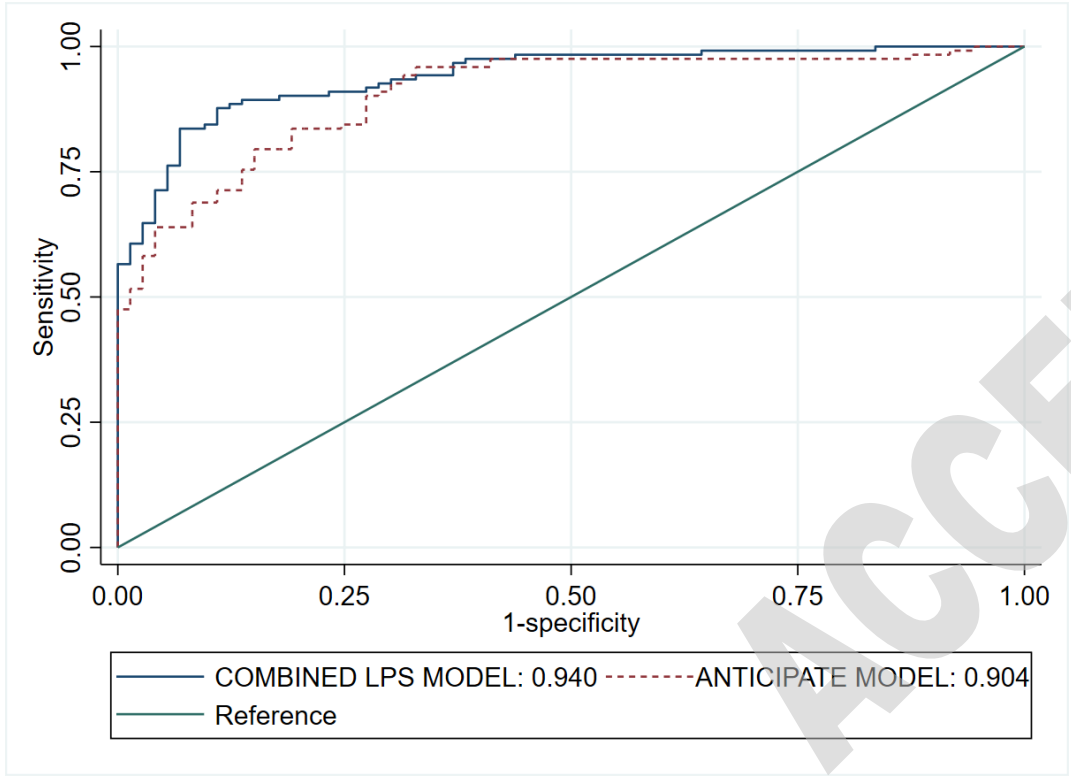

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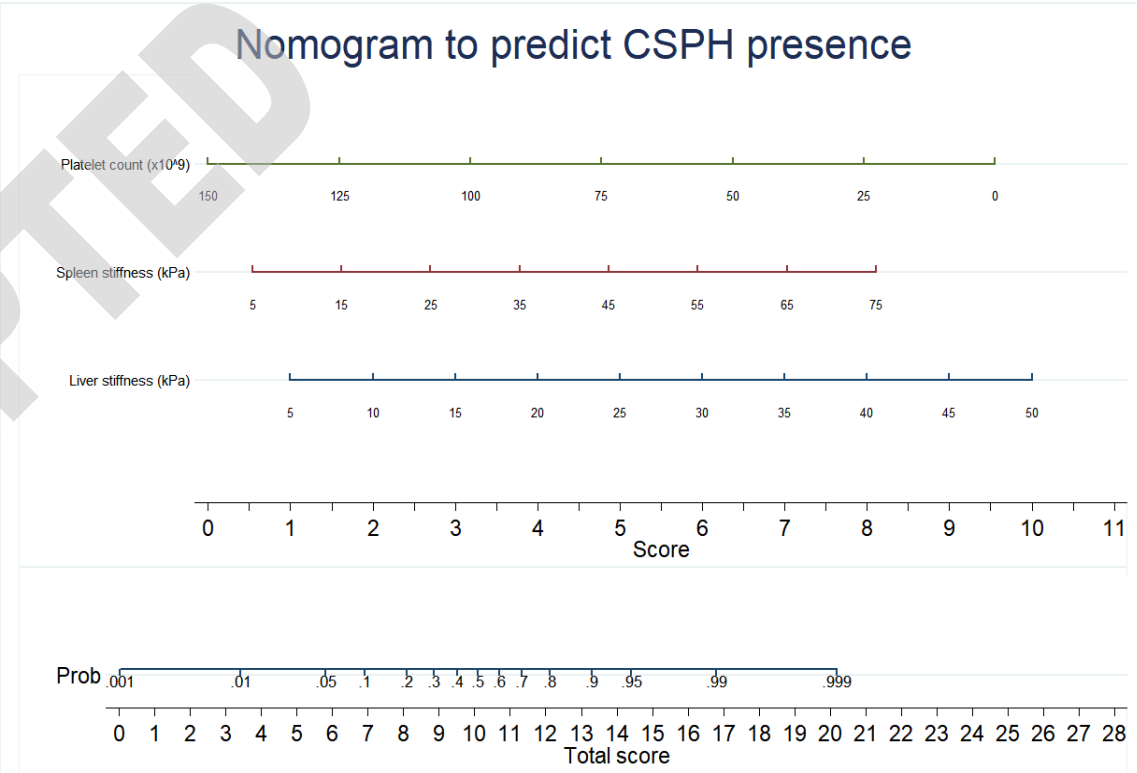

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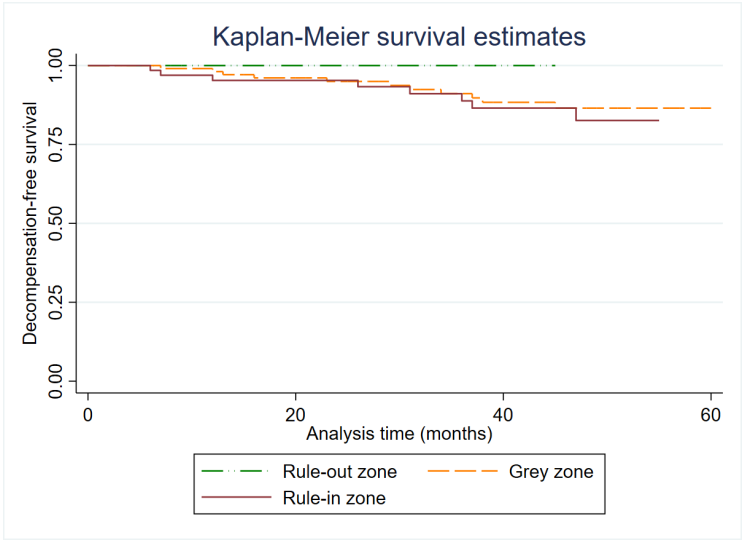

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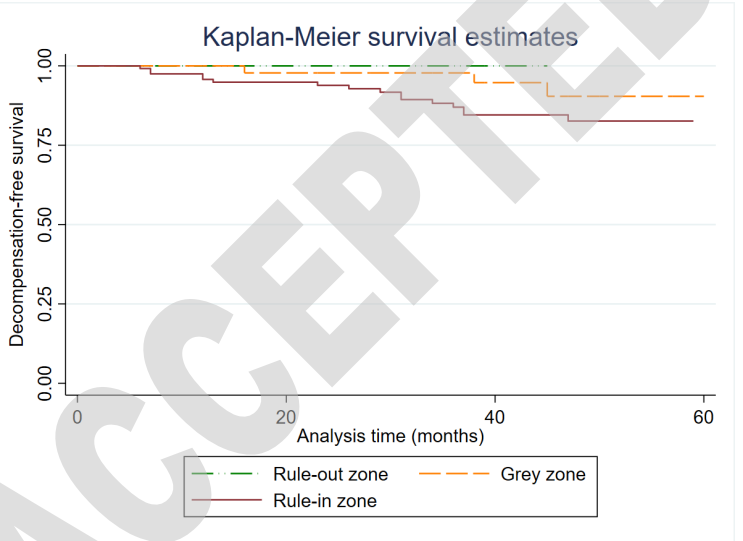

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