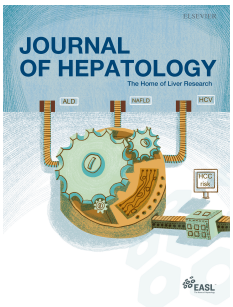

Exploring algorithms to select candidates for non-selective beta-blockers in cirrhosis: a post-hoc analysis of the PREDESCI trial

Elton Dajti, Càndid Villanueva, Annalisa Berzigotti, Anna Brujats, Agustín Albillos, Joan Genescà, Juan C. Garcia-Pagán, Antonio Colecchia, Jaume Bosch, on behalf of the PREDESCI trial investigators, A study by the Baveno Cooperation, an EASL Consortium

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ARE NON-INVASIVE METHODS ACCURATE ENOUGH TO SELECT CANDIDATES TO NSBB TREATMENT?

Prevention of decompensation

Many studies, mostly retrospective

NO DATA from a prospective, trial setting

Design: post-hoc analysis from a RCT (PREDESCI trial)

A study by the Baveno Cooperation, an EASL Consortium

PREDESCI COHORT

Patients with HVPG, endoscopy and LSM available, both from screened for the trial but not randomized since no CSPH (n=52) and from randomized in the trial (n=118)

Prediction rules for CSPH presence

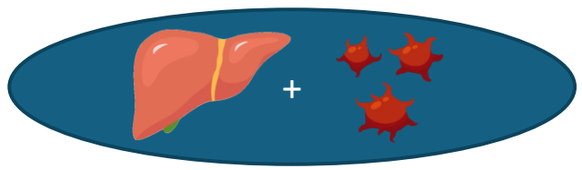
LSM ≥25 kPa — *Baveno VII (rule-in criteria)*

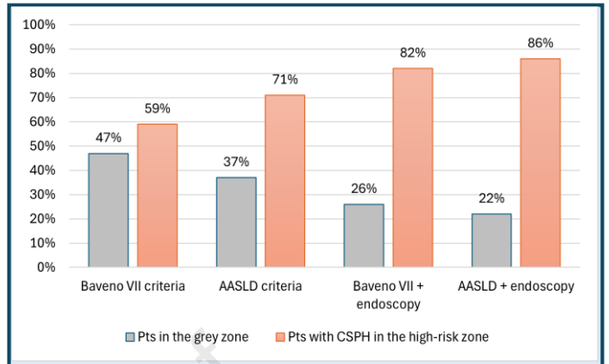
LSM ≥25 kPa *OR*
LSM ≥20 kPa + PLT <150 x 10^9/L — *AASLD (rule-in criteria)*

- Wide "grey zone"
- Many CSPH pts outside rule-in criteria

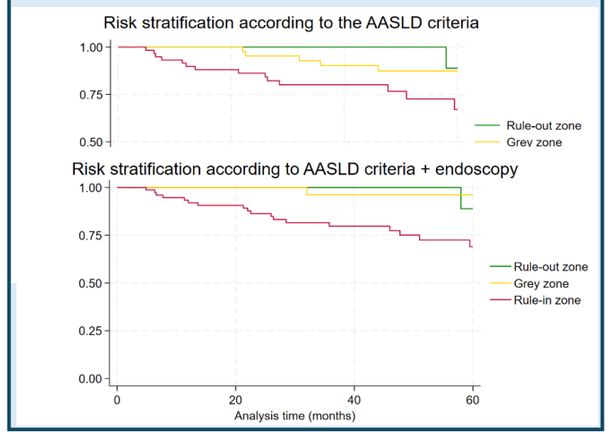
Perform endoscopy in "grey zone" pts

rule-in CSPH if varices





- Significantly reduced grey zone
- More patients with CSPH included, with similar PPV
- Improved risk stratification for decompensation

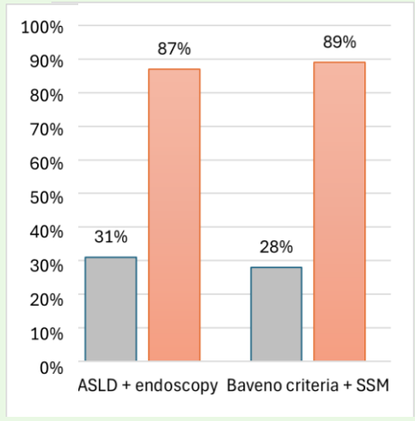


Endoscopy in the Baveno VII grey zone

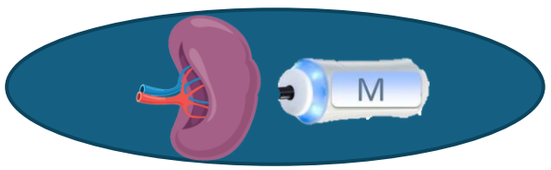
EXTERNAL VALIDATION

Observational cohort

N=195 patients with available LSM, SSM, HPVG, and endoscopy



- Full validation of results
- Comparable results using SSM instead of endoscopy
- Further validation from prospective cohorts required



Exploring algorithms to select candidates for non-selective beta-blockers in cirrhosis: a post-hoc analysis of the PREDESCI trial

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Abbreviations: AASLD: American Association for the study of liver diseases; cACLD: compensated advanced chronic liver disease; CSPH: clinically significant portal hypertension; HVPG: hepatic venous pressure gradient; LSM: liver stiffness measurement; NSBB: non-selective beta-blockers; PBC: primary biliary cholangitis; PLT: platelet count; SSM: spleen stiffness measurement.

Authors' contribution: ED, JB formulated the research questions and developed the study protocol. All authors contributed to the investigations and to the data collection. ED, ABe, CV, JB analysed data and contributed to the drafting and final approval of the manuscript. JB and CV provided overall insight of this study and previous PREDESCI trial- All authors had full access to all the data in the study, reviewed the manuscript, and had final responsibility for the decision to submit for publication.

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Abstract

Background & aims: Whether non-invasive tests (NITs) can accurately select patients with cirrhosis requiring non-selective beta-blockers (NSBB) for clinically significant portal hypertension (CSPH) and prevention of decompensation is unclear. Our aim was to test the performance of NIT-based algorithms for CSPH diagnosis using the prospective PREDESCI cohort. We investigated a new algorithm combining NITs with endoscopy to improve performance.

Methods: We included patients with compensated cirrhosis and available liver elastography who were screened during the trial. The performance of models based on liver stiffness measurement (LSM) and platelet count was evaluated. An algorithm considering endoscopy for patients with inconclusive results (the "grey zone") was then developed and validated in an independent cohort of 195 patients in whom also spleen stiffness was available.

Results: We included 170 patients from the PREDESCI cohort. An LSM≥25 kPa alone (Baveno VII criteria) or an LSM>20 kPa plus thrombocytopenia (AASLD criteria) ruled-in CSPH with positive predictive value of 88 and 89%, respectively. However, 37%-47% patients fell into the grey zone while at high-risk of decompensation or death. Performing endoscopy in inconclusive cases identified patients with varices that, when re-classified as high-risk for CSPH, significantly reduced the grey zone to 22%. In this algorithm, 86% of CSPH patients were correctly classified as high-risk. The diagnostic performance was confirmed in the external validation cohort, where combining Baveno VII criteria with spleen stiffness showed similar accuracy to the model using endoscopy.

Conclusions: Algorithms based only on LSM and platelet count are suboptimal to identify NSBB treatment candidates. Performing endoscopy in patients with indeterminate findings from NITs improved diagnostic performance and risk stratification. Endoscopy may be substituted by spleen stiffness for stratifying the risk in the grey zone.

Keywords: carvedilol; portal hypertension; decompensation; elastography; liver stiffness; spleen stiffness.

Impact and implications

The PREDESCI trial demonstrated that non-selective beta-blockers prevent decompensation in CSPH patients. Still it is unclear whether we can select treatment candidates using non-invasive tests to assess the presence of CSPH without measuring HVPG. In the prospective cohort of patients screened during the trial, we showed that algorithms based on liver stiffness and platelet count had suboptimal performance, mainly due to a high rate of indeterminate results. Performing endoscopy in the grey zone patients allowed to significantly increase the number of patients with CSPH and improved the risk stratification for decompensation or death on long-term follow-up. These findings were validated in an independent cohort. In addition, a model using spleen stiffness instead of endoscopy showed similar diagnostic performance in the external validation cohort, suggesting that adequate risk stratification to select treatment candidates can be achieved with a fully non-invasive algorithm.

Introduction

Portal hypertension is the major cause of complications in patients with compensated advanced chronic liver disease (cACLD).[1] Values of hepatic venous pressure gradient (HVPG) ≥10 mmHg denote clinically significant portal hypertension (CSPH) and are associated with the development of varices, decompensation, hepatocellular carcinoma, and mortality.[1–4] Recent evidence suggests that treatment with non-selective beta-blockers (NSBB), particularly carvedilol, reduces the risk of decompensation and mortality in patients with CSPH.[5,6] This has led to a paradigm shift in the management of patients with cirrhosis, and treatment with carvedilol is now encouraged in current guidelines to prevent decompensation.[1,7] However, the definition of CSPH in the PREDESCI trial was based on the gold standard, the HVPG measurement during hepatic vein catheterization, which is not only minimally invasive, but also not available or routinely performed in non-academic hepatology centers worldwide. Therefore, how to reliably select patients with an indication for NSBB treatment in everyday clinical practice remains an open question.

The last Baveno VII consensus recommended the use of non-invasive tests (NITs) to stratify for the risk of CSPH in patients with cACLD.[1] Gastroesophageal varices on endoscopy or collaterals on cross-sectional imaging are specific signs of CSPH, but NITs have also been validated for this purpose. The most commonly used NITs are the measurement of liver stiffness (LSM) and spleen stiffness (SSM) by transient elastography (TE), combined with the platelet count (PLT), as these tests have been widely validated for the diagnosis of CSPH, varices, and the prediction of decompensation.[8] In particular, values of LSM ≤15 kPa and PLT ≥150 x 10^9/L are safe to rule-out CSPH, and values of LSM ≥25 kPa are recommended to rule-in CSPH.[1,9] However, these criteria result in a wide range (40-50%)[9–11] of patients with indeterminate results (i.e., those with LSM 15-25 kPa, the so-called "grey zone"), in whom further investigations are required to diagnose CSPH. Therefore, alternative algorithms for identifying patients who require NSBB treatment to prevent decompensation need to be explored, both in clinical practice and for future trial design.

With this in mind, we used the cohort of patients with cACLD screened for inclusion in the PREDESCI trial (a double-blind randomized controlled trial) to evaluate the performance of non-invasive algorithms for the diagnosis of CSPH in a trial setting, thus minimizing the risk of bias. We aimed to develop and validate a new algorithm based on elastography, platelets and

endoscopy to diagnose CSPH in patients with cACLD that performed better than these tests alone.

Material and Methods

Study population

Patients with compensated cirrhosis who were screened during the PREDESCI trial (regardless of enrollment in the trial), were eligible for inclusion in this study. The full description of the selection criteria within the trial has been reported elsewhere (NCT01059396).[5] For the present study, we included all patients with cirrhosis and no previous decompensation who underwent both hemodynamic evaluation and endoscopy as required by the trial protocol, and who had LSM by transient elastography within 3 months before randomization. Specifically, screened patients who did not meet the trial inclusion criteria due to a HVPG <10 mmHg but who had an available LSM were included in the present cohort. Exclusion criteria were (i) absence of LSM by transient elastography; (ii) unreliable LSM measurements (<10 measurements, IQR/median ratio ≥0.3).

Study design and outcomes

The main outcome was the diagnostic performance of NITs and endoscopy in identifying patients with CSPH, as determined by an HVPG measurement ≥10mmHg.

First, we tested the diagnostic performance of the available diagnostic criteria based on LSM and PLT.[9] In this model, CSPH could be ruled out by LSM ≤15 kPa and PLT ≥150 x 10^9/L and ruled in by either (i) LSM ≥25 kPa, as defined by the Baveno VII consensus (hereafter "Baveno VII criteria"),[1] or (ii) LSM ≥25 kPa, or LSM >20 kPa and PLT <150 x 10^9/L, as suggested by the recent AASLD guidance document (hereafter "AASLD criteria").[7]

Second, we evaluated the diagnostic performance of an algorithm combining the Baveno VII/AASLD criteria with endoscopy. In this scenario, endoscopy would only be performed in patients in the grey zone and patients with gastroesophageal varices would be considered at high risk of CSPH, and therefore potential candidates for NSBBs therapy to prevent decompensation.

The secondary outcome was the incidence of decompensation or death, as in the PREDESCI trial.[5] To explore the natural history of cirrhosis, this outcome was assessed only in patients who did not receive NSBB therapy, namely patients included in the control arm of the trial or patients

with screening failure (HVPG <10 mmHg). For the latter group, follow-up was censored at five years after HVPG measurement to allow for a comparable follow-up time between the two groups. The cumulative incidence of decompensation and death at 3 and 5 years was reported for each risk category determined by the algorithms evaluated.

Validation cohort

To validate the newly proposed screening algorithm for CSPH, we used data from a previously published cohort of 195 patients with cACLD who underwent HVPG measurement at two Italian centers and had both elastography and clinical follow-up.[12] As SSM was available in this cohort, we investigated whether a completely non-invasive algorithm (Baveno VII + SSM) could diagnose CSPH and compared its diagnostic performance with the model combining Baveno VII/AASLD criteria with endoscopy. We adapted the previously proposed cut-offs in algorithms combining Baveno VII with SSM[13] and used SSM values <21 kPa and >40 kPa to rule-out and rule-in CSPH, respectively, alongside LSM and PLT.

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-squared test or Mann-Whitney test and McNemar test were used, as appropriate.

To assess the primary outcome, we reported the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for each algorithm evaluated.

The secondary outcome was the rate of decompensation or death at 3- and 5-years, stratified according to the risk groups identified by the different algorithms. Kaplan-Meier (KM) curves were used to report the risk of hepatic decompensation development during follow-up. All p-values refer to two-tailed significance tests. $P<0.05$ was considered significant. Statistical analysis was performed using Stata/SE (version 18.0; Stata Corp, Texas, USA).

Ethics

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by the ethics committee and the local institutional review board of each participating center. Informed consent was obtained from each patient included in the study.

Results

Population

Two hundred and seventy-four patients were eligible for inclusion in the study, of whom 69 were excluded because of missing elastography data and 35 because of unreliable measurements (<10 measurements or IQR/median ≥0.3) (**Figure 1**). Finally, 170 patients were included in the study (elastography cohort): 118 had participated in the PREDESCI trial (56 treatment arm, 62 placebo arm) and 52 patients had screening failures due to an HVPG <10 mmHg. The comparison between patients included in the elastography cohort and patients excluded from this study is shown in **Supplementary Table 1**. The characteristics of the patients not included in the trial are shown in **Supplementary Table 2**. Of note, 12 patients had varices despite HVPG <10 mmHg; of these, 8 had HVPG values between >8 and <10 mmHg and 2 additional patients had primary biliary cholangitis (PBC) (with varices and HVPG of 5.5 and 6.5 mmHg).

The median age of the included patients was 60 (51-69) years and half of the patients were men (84; 49%). The median HVPG value was 12 (9-16) mmHg and 119 (70%) had CSPH; 83 (49%) had gastroesophageal varices. The two main etiologies were viral and alcohol-related cirrhosis; however, alcohol consumption and metabolic co-morbidities (i.e. obesity, diabetes, and dyslipidemia) were prevalent cofactors in one third of the patients with viral etiology (**Table 1**). None of the patients with hepatitis C at enrollment received antiviral treatment during follow-up, as required by the trial protocol. Only five patients enrolled had pure MASLD cirrhosis, two of whom had obese MASLD cirrhosis. Comparison of clinical characteristics of patients within and outside the rule-in zone according to non-invasive tests is shown in **Supplementary Table 3**.

Performance of the Baveno VII model

The Baveno VII criteria ruled out CSPH with a sensitivity of 98% (95%-CI: 94-99%) and a NPV of 82% (95%-CI: 50-96%) (**Table 2**). Only one patient in the rule-out zone was decompensated at five years (a PBC patient with LSM 11.9 kPa, HVPG 5.5 mmHg, but with varices, who developed the first decompensation event at 58 months after screening).

The LSM ≥25 kPa cut-off for rule-in CSPH showed a specificity of 82% (95%-CI: 69-92%) and a PPV of 89% (95%-CI: 81-93%); the cumulative incidence of decompensation or death at 3 years in the rule-in group was 21%. Using the Baveno VII criteria, 80 (47%) patients fell into the

grey zone, with a significant risk of decompensation or death (9% at 3 years) (**Figure 2A**). In this scenario, 40% of the patients with CSPH would not have NSSB treatment because they were not included in the high-risk zone.

Performance of the AASLD model

Expanding the rule-in criteria according to the AASLD criteria (LSM ≥25 kPa, or LSM >20 kPa + PLT <150 x 10^9/L), reduced the grey zone to 63 (37%) patients (vs 47%, p=0.062) (**Table 2**). These criteria showed a specificity of 76% (95%-CI: 63-87%) and a PPV of 88% (95%-CI: 50-96%), and 29% of the patients with CSPH were outside the high risk zone (vs 40%, p=0.057). The risk of decompensation or death for patients in the grey zone remained at 9% at the 3 years (**Figure 2B**).

New algorithm combining Baveno VII/AASLD criteria and endoscopy

The diagnostic performance of a strategy based on endoscopy only is shown in **Supplementary Table 4**. In this scenario, all patients would undergo a somehow invasive test, but this would not be sufficient to rule-out CSPH, as patients without varices had CSPH in 55% of the cases and had a 5% risk of decompensation or death at 3 years.

We therefore evaluated the performance of a new algorithm combining non-invasive criteria and endoscopy (**Table 3**). The table shows the performance of both the Baveno VII and AASLD models combined with endoscopy. However, we focused on the AASLD criteria to rule in CSPH (LSM ≥25 kPa, or LSM >20 kPa + thrombocytopenia), as they showed a smaller grey zone compared to the LSM ≥25 kPa rule alone. Performing endoscopy only in patients in the grey zone (n=63; 37%) allowed 26 patients to be reclassified as high risk (those with varices at endoscopy); the patients who remained with inconclusive results had a lower risk of events Overall, the model showed a specificity of 61% (95%-CI: 46-74%) and a PPV of 84% (95%-CI: 78-88%), and the grey zone was significantly reduced to 22% (p=0.002). Most patients with CSPH (86%) were included in the high risk zone. Importantly, the model provided very good discrimination, as none of the patients in the grey or low risk zones decompensated at 3 years (**Figure 3**).

Performance of the new algorithm in the validation cohort

One hundred and ninety-five patients were included in the validation cohort: 122 (63%) had CSPH and 89 (51%) had varices. Median follow-up was 42 (21-54) months; at 3 years, the risk of decompensation or death was 13.3%. The Baveno VII and the AASLD algorithms were validated in this cohort and confirmed the high proportion of patients in the grey zone (57% and 46% respectively) (**Table 4**). By performing endoscopy only in patients with inconclusive results and by re-classifying as high-risk those patients found to have varices, the grey zone was reduced to 31% (p=0.003), while only 13% of the patients with CSPH remained outside the high-risk zone. The cumulative risk of decompensation for patients in the grey zone was zero, but 7% of the patients died at 3 years without having experienced decompensation (two patients with liver cancer, two with pancreatic cancer, one with stroke).

A fully non-invasive algorithm including SSM instead of endoscopy showed comparable results to the model combining AASLD criteria with endoscopy (specificity 86% vs 85%, PPV 92% vs 91%, grey zone 28% vs 31%) (**Figure 4**) and was able to stratify well for the risk of decompensation. Similar to above, three patients (6%) in the grey zone died at 3 years, but none of them experienced decompensation (two with pancreatic cancer and one with liver cancer).

Discussion

The PREDESCI trial introduced a paradigm shift in the management of portal hypertension by showing that treatment with NSBBs reduces the risk of decompensation or death.[5,6] This has led to current guidelines encouraging treatment with NSBBs, particularly carvedilol, in all patients with CSPH.[1,7] Inclusion in the PREDESCI trial[5] was based on demonstration of CSPH by measurement of HVPG, which is the gold standard for assessing portal hypertension. However, HVPG is not well adapted to clinical practice, as it is invasive and not readily available in routine clinical practice, so, a strategy based solely on HVPG to select candidates for treatment with NSBB would not be feasible in many centers, and other more pragmatic options need to be explored for both clinical practice and future trials. This was already recognized at Baveno VII[1] and reinforced at the AASLD 2024 Guidance document[7] for the management of portal hypertension, which suggests that selection for treatment should be based on non-invasive tools (NITs).

The extent to which NITs might be adequate for this purpose is largely unknown, as these tests have mostly been developed in retrospective cohorts, and although widely validated to avoid unnecessary screening endoscopies,[14–16] have not been used to guide patient selection in studies aimed at developing prophylactic strategies to avoid decompensation. In the present study, we used the cohort of patients screened in the PREDESCI trial to investigate how non-invasive algorithms would have performed in identifying cACLD patients with CSPH, and how accurate the prediction of decompensation would have been based on this non-invasive assessment.

First, we evaluated the diagnostic performance of the Baveno VII criteria,[1] as non-invasive strategies based on elastography and platelet count are accurate and recommended by current guidelines for the diagnosis of CSPH.[1,7,17] The overall performance of the Baveno VII criteria was acceptable in our cohort. Liver stiffness ≤15 kPa and absence of thrombocytopenia could rule-out the presence of CSPH with high sensitivity (98%). The rule-in cut-off for liver stiffness (≥25 kPa) showed a PPV of 89% and a specificity of 82%. However, almost half of the patients (47%) were in the grey zone and 40% of the patients with CSPH (who would benefit from NSBB treatment) were outside the rule-in criteria; this translated into a significant risk of

decompensation (9% at 3 years) for patients in the grey zone who did not receive treatment. Expanding the rule-in criteria to include patients with liver stiffness >20 kPa and thrombocytopenia, as suggested by the recent AASLD guidelines[7] and the Baveno VII "rule of 5", improved diagnostic performance by being more inclusive and reducing the grey zone, while maintaining a similar PPV, although 37% of patients still remained in such a grey zone. In addition, the risk of decompensation and death of patients in the grey zone remained relatively high, probably reflecting a still substantial prevalence of CSPH in this category.[11,18,19]

To overcome these limitations, we hypothesized that performing endoscopy in patients with indeterminate results would be informative and improve the applicability of the diagnostic algorithm for CSPH. Indeed, we found that an endoscopy-only screening strategy (or "scope all") would be somewhat invasive, futile in half of the cases, and leave out 55% of patients without varices but with CSPH. A recent retrospective study suggests better performance with NITs than using endoscopy alone to guide NSBB treatment.[18] Furthermore, our study shows that performing an upper endoscopy only in patients with indeterminate results limits the number of invasive investigations and has the potential to improve the overall diagnostic and prognostic performance. It should be noted that endoscopy is clinically indicated in grey zone patients, as many of them may have varices that, even if small, are associated with an increased risk of decompensation.

In the PREDESCI cohort, of the 63 patients in the grey zone according to the AASLD criteria, 26 (41%) had varices and were therefore reclassified as high risk. The algorithm combining non-invasive (LSM and platelet count) plus endoscopy showed a PPV of 84% and significantly reduced the grey zone to 22%, correctly classifying 86% of the patients found to have CSPH on hepatic vein catheterization as high-risk. More importantly, patients outside the high-risk zone according to the new algorithm were at low risk of decompensation or death, demonstrating that its use resulted in an excellent discrimination of outcomes. The performance of the new algorithm was validated in an independent cohort of 195 patients, where the model showed a PPV of 91% and it significantly reduced the grey zone from 46% to 31%.

On a more general note, this prospective cohort of well-characterized cACLD patients screened during the PREDESCI trial gave us the unique opportunity to test different algorithms in a real-world scenario, which led to several relevant considerations. First, the diagnostic performance of the Baveno VII/AASLD criteria was lower than previously reported, as many parameters (specificity/NPV/PPV) were below the established threshold of 90%. Although still within the 95% confidence interval of the original studies, it is likely that the diagnostic accuracy was overestimated in retrospective studies[9,12] where it is conceivable that some patients with unfeasible LSM may have been excluded. Second, the clinical diagnosis of CSPH in real life should be based on the combination of different methods (liver and spleen elastography, platelet count, serum-based tests, endoscopy), as none of them is perfect as a stand-alone approach. Elastography can have false positives, as liver stiffness can be overestimated in the presence of confounders, such as meal ingestion, inflammation, congestion, intrahepatic cholestasis[20] and may be equivocal in obese patients.[9,21] Endoscopy is the gold standard for the diagnosis of varices; however, in this study 15% of the patients with varices had HVPG <10 mmHg, which may in part be due to imperfect interobserver agreement for small varices[22], on the fact that some patients may have partial regression of disease, where collaterals may persist despite an improvement in portal pressure,[23,24] and probably also on the fact that HVPG may underestimate portal pressure in some etiologies with a pre-sinusoidal component of portal hypertension, not captured by HVPG (as suggested by the relatively high risk of events in these patients),[25–27]. For example, 2 of the 12 patients with HVPG <10 mmHg and varices had PBC (where a pre-sinusoidal component is common) and 8 had an elevated HVPG (≥8 but <10 mmHg), which could be due to a mild pre-sinusoidal component, to the presence of intrahepatic veno-venous collaterals, to variability in the HVPG measurement (which is increased in obese patients), or to technical pitfalls.[4,7,28] Third, LSM, platelet count and endoscopy have shown prognostic significance in cACLD, supporting their integrated use in clinical practice. Another relevant finding in our study was that the patients in the grey zone defined by the new algorithm did not experience decompensation at follow-up. This observation suggests that the presence of varices has prognostic impact on top of increased HVPG values, that patients without any of these risk factors have a lower risk of complications. In fact, among cACLD patients with CSPH those with varices have a much higher risk of decompensation than those without,[29,30] which may be due to the presence of a more hyperdynamic circulation and higher portal pressure in patients

with varices as compared with those with CSPH without varices and to those without CSPH.[31] Consistent with this view, the rate of decompensation or death in patients with HVPG values <10 mmHg but in the rule-in zone according to the combined algorithm was high (10% at 3 years and 19% at 5 years).

A final relevant consideration is the fact that spleen stiffness was available in the validation cohort, giving us the opportunity to assess the performance of a combined Baveno VII-SSM algorithm. This is of obvious interest in the search for a completely non-invasive and simple risk assessment strategy. Interestingly, our findings support the view that the use of SSM allows a completely non-invasive risk-stratification algorithm based on an accurate estimation of the presence of CSPH. Indeed, the performance of an algorithm combining the Baveno VII criteria and SSM showed comparable results to the algorithm combining the Baveno VII/AASLD criteria with endoscopy. The inclusion of SSM may also mitigate the risk of underestimating portal hypertension due to a pre-sinusoidal component in some etiologies, including PBC.[32] Indeed, data from studies using the 100 Hz module specifically designed for SSM support this view.[33–35]. It would be desirable for confirmatory studies to be performed in prospective cohorts of patients with contemporary etiology of liver disease, with sufficient follow-up time to observe clinically meaningful events.

Our study has limitations. First, elastography was not available in all patients screened during the trial, which may have introduced a selection bias. In fact, patients excluded from the TE cohort were less likely to have a viral etiology, a higher BMI, a higher prevalence of diabetes, and worse liver function. However, it should be noted that the trial was started in 2010, when elastography was not routinely used to assess portal hypertension. Second, the median follow-up of patients not included in the trial was longer than that of randomized patients, and changes in treatment (initiation of NSBB, antiviral therapy) cannot be excluded in this group of patients with longer follow-up. However, to mitigate this risk, we censored events occurring after five years and used cumulative incidence at fixed time points to account for this limitation. Third, we were not able to test and validate recently proposed tests to refine the risk of CSPH in patients who fall into the grey zone using the Baveno VII criteria, such as adding the VITRO score.[11] Whether the inclusion of collaterals at imaging could improve the diagnostic algorithm remains an open question. Collaterals are specific for the presence of CSPH, but ultrasound is operator-

dependent and less sensitive than cross-sectional imaging (computed tomography, magnetic resonance), which is not suitable as a screening tool in every patient with suspected cACLD. The number of patients with MASLD-related cirrhosis may have been underestimated in our study, and the accuracy of non-invasive tests for this etiology could not be specifically assessed. Similarly, we could not assess how the algorithms perform in patients with cured HCV. Finally, the validation cohort was retrospective and, unlike the trial population, it also included patients with high-risk varices who received primary prophylaxis for variceal bleeding with NSBBs.

In conclusion, the Baveno VII/AASLD criteria alone showed a suboptimal performance in identifying patients with compensated cirrhosis who could be started on non-selective beta-blockers to prevent decompensation. Using these criteria alone to select patients would leave a very substantial number of patients at risk untreated. However, their combination with endoscopy for patients in the grey zone provides is a valid strategy that allows both a significant reduction in the grey zone and better risk stratification by identifying a risk category of patients at high risk of decompensation not captured by the Baveno VII/AASLD criteria. Spleen stiffness appears to be an attractive alternative to endoscopy for reducing the grey zone and improving patient selection in a completely non-invasive manner, but this requires further study.

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Author names in bold designate shared co-first authorship.

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Figure 1 – Flowchart of patients' selection in the present study. (HVPG: hepatic venous pressure gradient; LSM: liver stiffness measurement).

Figure 2 – Kaplan-Meier curves for depicting decompensation-free survival according to the (A) Baveno VII criteria and (B) AASLD criteria.

Figure 3 - Kaplan-Meier curve for depicting decompensation-free survival according to a combined strategy using both non-invasive tests (AASLD criteria) and endoscopy.

Figure 4 – Summary performance of the evaluated algorithms in the derivation (A) and the validation (B) cohort.

Table 1 – Characteristics of patients in the transient elastography population.

Variable	**TE cohort N=170**
Age (years)	60 (51-69)
Gender (male)	84 (49)
Body mass index (kg/m^2)	25.9 (24.1-28.4)
Obesity (%)[#]	31 (18)
Etiology	
Viral etiology (%)	126 (74)
Only viral (%)	83 (66)
Concomitant alcohol (%)	13 (10)
Concomitant metabolic[§] (%)	30 (24)
Alcohol-related cirrhosis (%)	23 (14)
MASLD-related cirrhosis (%)	5 (3)
Primary biliary cholangitis (%)	9 (5)
Other (%)	7 (4)
Diabetes mellitus (%)	24 (14)
Arterial hypertension (%)	56 (33)
Dyslipidemia (%)	20 (12)
Bilirubin (mg/dL)	0.88 (0.64-1.29)
Albumin (g/dL)	3.98 (3.6-4.2)
Child-Pugh B (%)	11 (6.5)
ALBI grade >1 (%)	87 (51)
HVPG (mmHg)	12 (9-16)
CSPH (%)	119 (70)
Presence of varices (%)	83 (49)
LSM (kPa)	22.5 (16-34.9)
Platelet count (x 10^9)	110 (80-141)

[#]Only two patients had metabolic dysfunction-associated steatotic liver disease and obesity.

[§]Defined by the presence of diabetes, obesity, or dyslipidemia.

Abbreviations: *ALBI: albumin-bilirubin score; CSPH: clinically significant portal hypertension; HVPG: hepatic venous pressure gradient; LSM: liver*

stiffness measurement; MASLD: metabolic dysfunction-associated steatotic liver disease; TE: transient elastography.

Table 2 – Algorithm based only on non-invasive tests to select treatment candidates for non-selective beta-blockers.

	TE population (n=170)			Natural history cohort[#] (n=114)	
	Nr pts with CSPH	**Performance**	**CSPH pts eligible for treatment°**	**Decompensation or death**	
				Risk at 3 years	**Risk at 5 years**
Model #1 (Baveno VII criteria)					
LSM ≥25 kPa (high-risk zone) (n=79)	70 (89%)	Spec 82% (69-92%) PPV 89% (81-93%)	59%	10/47 (21%)	13/47 (28%)
Grey zone (n=80)	47 (59%)	*Grey zone 47%*		5/57 (9%)	6/57 (11%)
LSM ≤15 kPa + PLT ≥150 x 10^9/L (low-risk zone) (n=11)	2 (18%)	Sens 98% (94-99%) NPV 82% (50-96%)		0/10 (0%)	1/10 (10%)
Model #2 (AASLD criteria)					
LSM ≥25 kPa *OR* LSM ≥20 kPa + PLT <150 x 10^9/L (n=96)	84 (88%)	Spec 76% (63-87%) PPV 88% (81-92%)	71%	11/59 (19%)	14/59 (24%)
Grey zone (n=63)	33 (52%)	*Grey zone 37%*		4/45 (9%)	5/45 (11%)
LSM ≤15 kPa + PLT ≥150 x 10^9/L (n=11)	2 (18%)	Sens 98% (94-99%) NPV 82% (50-96%)		0/10 (0%)	1/10 (10%)

[#]Patients that did not receive treatment with non-selective beta-blockers (placebo group or patients with HVPG <10 mmHg at screening).
°The rate corresponds to the sensitivity of the high-risk zone, as it reflects the rate of patients with CSPH that were included in the rule-in zone and that could hypothetically be treated with non-selective beta-blockers.
Abbreviations: *AASLD: American Association for the study of the liver diseases; CSPH: clinically significant portal hypertension; LSM: liver stiffness measurement; NPV: negative predictive value; PLT: platelet count; PPV: positive predictive value*

Table 3 – Algorithm based on non-invasive tests and endoscopy to select treatment candidates for non-selective beta-blockers.

	TE population (n=170)			Natural history cohort[#] (n=114)	
	Nr pts with CSPH	Performance	CSPH pts eligible for treatment°	Decompensation or death	
				Risk at 3 years	Risk at 5 years
Model #3 (Baveno VII + endoscopy)					
1° LSM ≥25 kPa 2° Varices at endoscopy (n=115)	97 (84%)	Spec 65% (50-78%) PPV 84% (79-89%)	82%	14/70 (20%)	18/70 (26%)
Grey zone (n=44)	20 (45%)	*Grey zone 26%*		1/34 (3%)	1/34 (3%)
LSM ≤15 kPa + PLT ≥150 x 10^9/L (n=11)	2 (18%)	Sens 98% (94-99%) NPV 82% (50-96%)		0/10 (0%)	1/10 (10%)
Model #4 (AASLD + endoscopy)					
1° LSM ≥25 kPa *OR* LSM ≥20 kPa + PLT <150 x 10^9/L 2° Varices at endoscopy (n=122)	102 (84%)	Spec 61% (46-74%) PPV 84% (78-88%)	86%	14/75 (19%)	18/75 (24%)
Grey zone (n=37)	15 (40%)	*Grey zone 22%*		1/29 (3%)	1/29 (3%)
LSM ≤15 kPa + PLT ≥150 x 10^9/L (n=11)	2 (18%)	Sens 98% (94-99%) NPV 82% (50-96%)		0/10 (0%)	1/10 (10%)

[#]Patients that did not receive treatment with non-selective beta-blockers (placebo group or patients with HVPG <10 mmHg at screening).
°The rate corresponds to the sensitivity of the high-risk zone, as it reflects the rate of patients with CSPH that were included in the rule-in zone and that could hypothetically be treated with non-selective beta-blockers.
Abbreviations: *AASLD: American Association for the study of the liver diseases; CSPH: clinically significant portal hypertension; LSM: liver stiffness measurement; NPV: negative predictive value; PLT: platelet count; PPV: positive predictive value*

Table 4 – Validation cohrot: Performance of different algorithms based on non-invasive tests and endoscopy to select treatment candidates for non-selective beta-blockers.

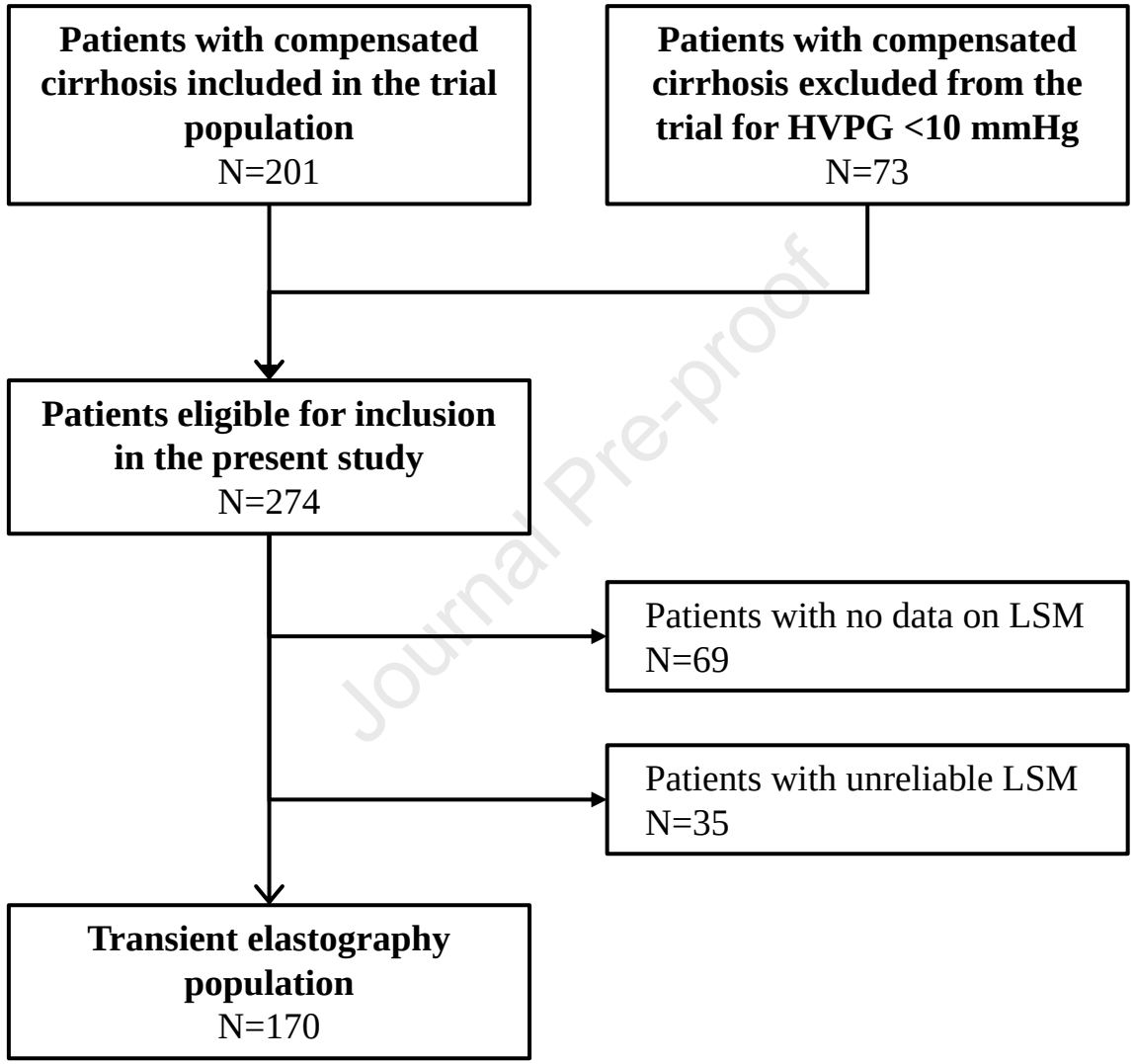
Model	Nr. pts with CSPH	Performance	CSPH pts eligible for treatment°	Decompensation or death at 3 years
Model #1 (Baveno VII criteria)				
LSM ≥25 kPa (n=65)	60 (92%)	Spec 93% (85-98%) PPV 92% (83-97%)	49%	11 (17%)
Grey zone (n=112)	62 (55%)	*Grey zone 57%*		15 (14%)
LSM ≤15 kPa + PLT ≥150 x 10^9/L (n=18)	0 (0%)	Sens 100% (97-100%) NPV 100% (81-100%)		0 (0%)
Model #2 (AASLD criteria)				
LSM ≥25 kPa *OR* LSM ≥20 kPa + PLT <150 x 10^9/L (n=88)	80 (91%)	Spec 89% (80-95%) PPV 91% (84-95%)	66%	19 (22%)
Grey zone (n=89)	42 (47%)	*Grey zone 46%*		7 (8%)
LSM ≤15 kPa + PLT ≥150 x 10^9/L (n=18)	0 (0%)	Sens 100% (97-100%) NPV 100% (81-100%)		0 (0%)
Model #3 (Baveno VII + endoscopy)				
1° LSM ≥25 kPa 2° Varices at endoscopy (n=109)	101 (93%)	Spec 89% (80-95%) PPV 93% (87-96%)	83%	21 (19%)
Grey zone (n=68)	21 (31%)	*Grey zone 35%*		5 (7%)[#]
LSM ≤15 kPa + PLT ≥150 x 10^9/L (n=18)	0 (0%)	Sens 100% (97-100%) NPV 100% (81-100%)		0 (0%)
Model #4 (AASLD + endoscopy)				
1° LSM ≥25 kPa *OR* LSM ≥20 kPa + PLT <150 2° Varices at endoscopy (n=117)	106 (91%)	Spec 85% (75-92%) PPV 91% (85-94%)	87%	22 (19%)
Grey zone (n=60)	16 (27%)	*Grey zone 31%*		4 (7%)
LSM ≤15 kPa + PLT ≥150 x 10^9/L (n=18)	0 (0%)	Sens 100% (97-100%) NPV 100% (81-100%)		0 (0%)
Model #5 – Baveno VII + SSM				
Two out three: LSM ≥25 kPa PLT <150 SSM >40 kPa (n=119)	109 (92%)	Spec 86% (76-93%) PPV 92% (86-95%)	89%	23 (19%)
Grey zone (n=54)	13 (24%)	*Grey zone 28%*		3 (6%)

Two out three: LSM ≤15 kPa PLT ≥150 SSM <21 kPa (n=22)	0 (0%)	Sens 100% (97-100%) NPV 100% (85-100%)		0 (0%)

°The rate corresponds to the sensitivity of the high-risk zone, as it reflects the rate of patients with CSPH that were included in the rule-in zone and that could hypothetically be treated with non-selective beta-blockers.

#Two patients died because of liver cancer, two because of pancreatic cancer, and one because of stroke.

Abbreviations: *AASLD: American Association for the study of the liver diseases; CSPH: clinically significant portal hypertension; LSM: liver stiffness measurement; NPV: negative predictive value; PLT: platelet count; PPV: positive predictive value; SSM: spleen stiffness measurement.*



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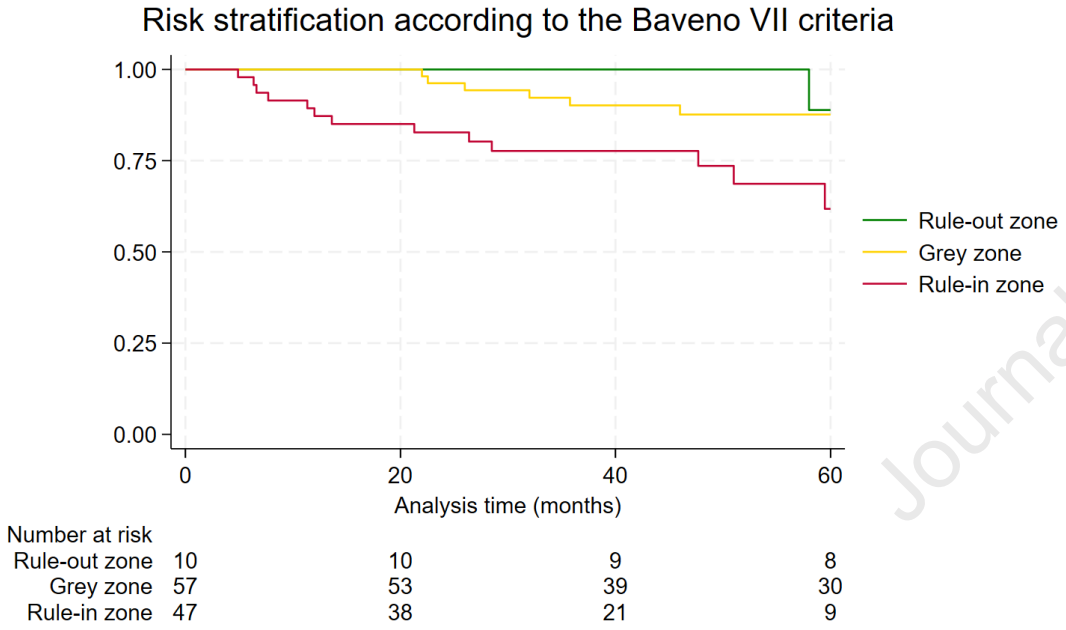

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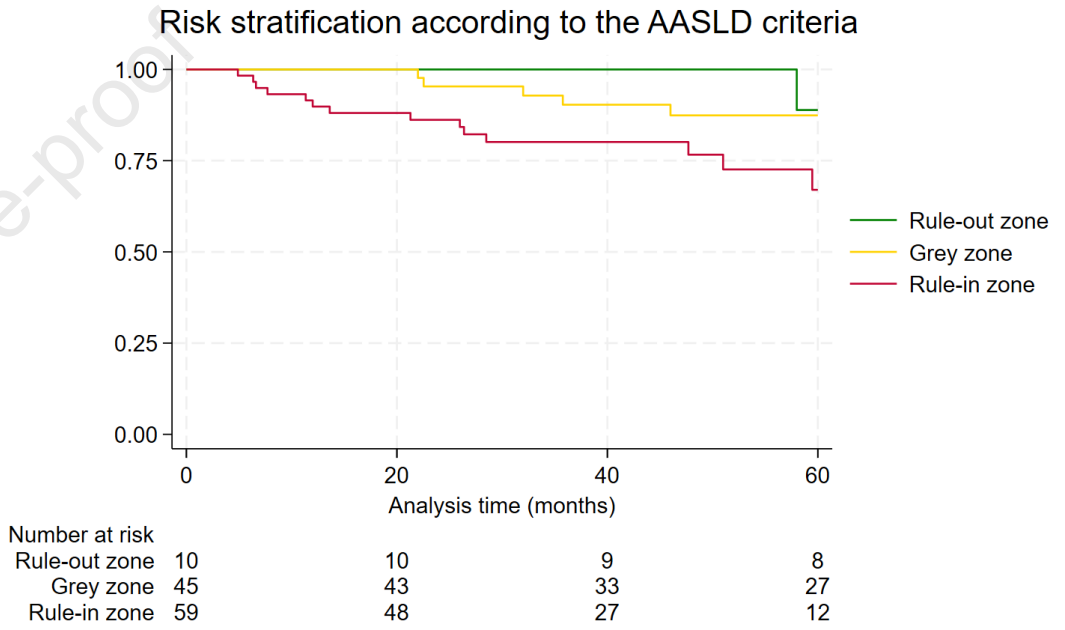
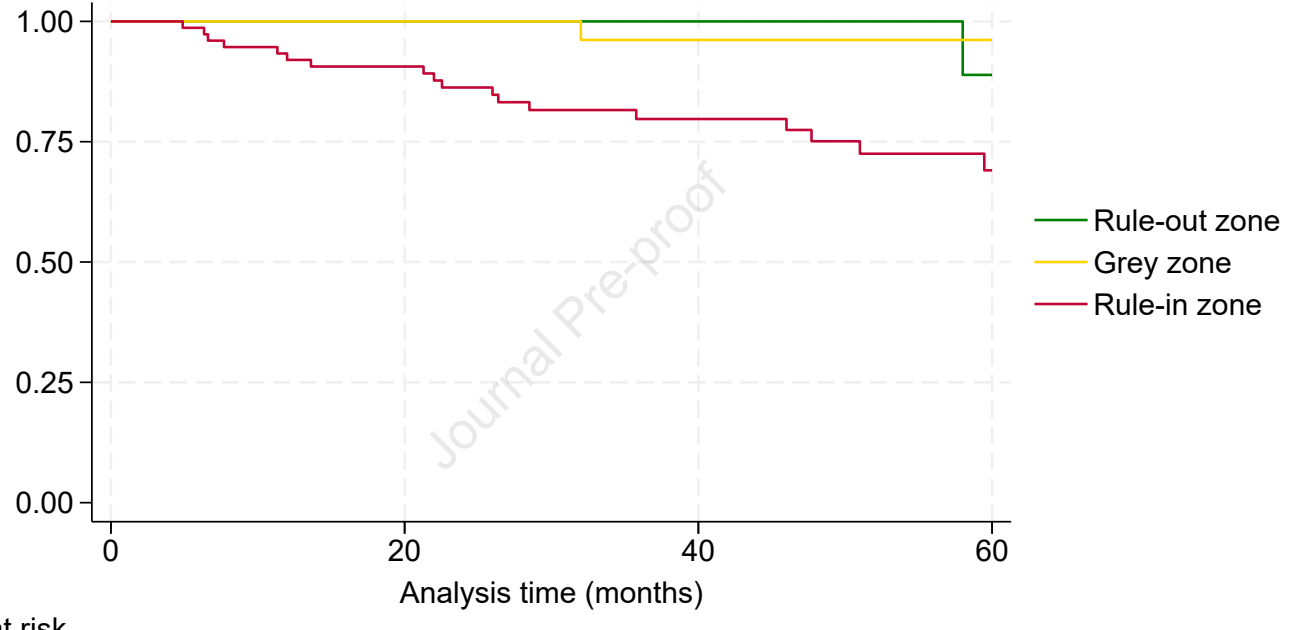
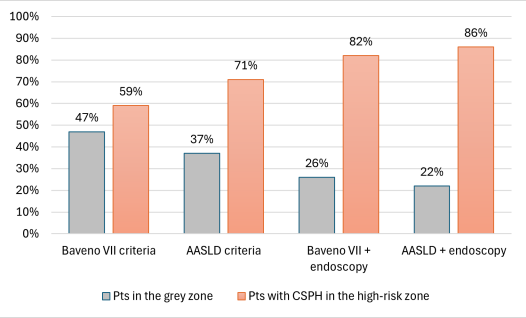
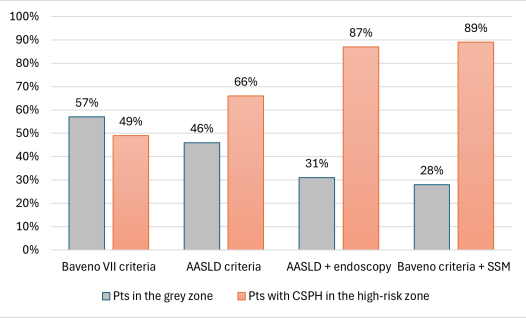


Risk stratification according to AASLD criteria + endoscopy



Number at risk				
Rule-out zone	10	10	9	8
Grey zone	29	27	22	19
Rule-in zone	75	64	38	20





Highlights

- Non-invasive diagnosis of CSPH based only on liver stiffness and platelet count showed suboptimal performance (grey zone 41%).

- Performing endoscopy in the patients with indeterminate results could reduce the grey zone to 22% and improve risk stratification.

- A combined Baveno VII and endoscopy algorithm not only improved the performance of CSPH diagnosis but also correctly predicted the risk of decompensation.

- Combining Baveno VII with spleen stiffness could be an effective strategy for a fully non-invasive diagnosis of CSPH.