Title: Refining the Baveno VII criteria for clinically significant portal hypertension: an individual-patient data meta-analysis

Short title: Baveno VII criteria for CSPH: a meta-analysis

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Abstract

Background and Aims: Clinically significant portal hypertension (CSPH) in compensated advanced chronic liver disease (cACLD) has therapeutic consequences. CSPH may be assessed with the Baveno VII criteria with lower performance in patients with obesity (body mass index ≥30 kg/m^2) and metabolic dysfunction-associated steatotic liver disease (MASLD). The ANTICIPATE±NASH models predict the risk of CSPH. We aimed to validate Baveno VII criteria and refine them with the ANTICIPATE±NASH models.

Methods: Systematic review of studies validating Baveno VII criteria of CSPH (hepatic venous pressure gradient as reference) with search strategy of "CSPH" (AND) "Baveno VII", from Baveno VII consensus until June 2024. A meta-analysis of Baveno VII criteria (ruling in: LSM (liver stiffness measurement) ≥25 kPa and ruling out: LSM ≤15 kPa + platelets ≥150x10^9/L) was performed. Using a risk threshold of CSPH by the ANTICIPATE±NASH for a positive predictive value (PPV) of ≥90% was explored. Individual patient data was used to assess model performance by center.

Results: Five studies with 1433 cACLD patients (CSPH 34% to 62%) of different etiologies were identified. LSM ≥25 kPa had an excellent PPV (92%) pooled by studies and etiologies, except MASLD with obesity. A ≥75% risk of CSPH by the ANTICIPATE±NASH models improved PPV to 95%, including MASLD with obesity (PPV 0.67 to 0.83; p<0.001). The pooled NPV for ruling out was 99% for all etiologies. ANTICIPATE±NASH showed an excellent performance across centers.

Conclusion: Baveno VII criteria for CSPH adequately classify patients across etiologies, except MASLD with obesity. Using a ≥75% risk threshold by ANTICIPATE models to detect CSPH improves global performance, including MASLD with obesity, supporting it can be a simpler way of predicting CSPH in clinical practice.

Impact and implications: This systematic review and meta-analysis confirm the validity for ruling out and ruling in CSPH in cACLD patients with the Baveno VII criteria. Using a threshold of ≥75% of the ANTICIPATE±NASH models, the global performance for detecting CSPH improves regardless of etiology. This represents a very practical approach for general hepatologists to select patients for prophylactic β-blocker therapy as its calculation relies on BMI, liver stiffness and platelet count with an online calculator.

Introduction

Compensated advanced chronic liver disease (cACLD) encompasses a heterogeneous group of patients with different risk of portal hypertension [1]. In the last Baveno VII consensus, new non-invasive criteria for detecting clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg, in the cACLD population were proposed [2]. The need to identify patients with a high probability of CSPH is now more important, as the evidence for the use of non-selective β-blockers to prevent first decompensation is increasing [3-5]. CSPH could be ruled in with a liver stiffness measurement (LSM) by transient elastography (TE) of ≥25 kPa and ruled out with an LSM of ≤15 kPa plus platelet count of ≥150 x 10^9/L with a very good classification accuracy.

Although the proposed ruling in threshold performed optimally for viral hepatitis, alcohol related (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD) patients without obesity, it was suboptimal for MASLD patients with obesity (body mass index-BMI ≥30 kg/m^2) with a positive predictive value (PPV) below 90%. Furthermore, by using these classification rules, a very high proportion of patients (40-50%) remained unclassified, with a mean prevalence of CSPH around 50%. This intermediate zone is an unresolved current challenge for which different alternatives have been proposed, such as the AASLD criteria [6], predictive models for CSPH [2, 7-9], and an upper endoscopy searching for varices [10]. The risk for decompensation of not detecting and treating CSPH in this unclassified population is unknown. In addition, with the current non-invasive strategy, 5 to 10% of patients will be misclassified and might receive β-blockers without having CSPH. If these patients

have progressive disease, CSPH will probably develop in the short-term and initiating therapy would be acceptable.

The ANTICIPATE and the ANTICIPATE-NASH models (ANTICIPATE±NASH models) using LSM plus platelet count with or without BMI were developed for a continuous risk prediction of the probability of having CSPH for patients with viral hepatitis and ALD, and with MASLD, respectively [7-8]. Both models have been validated several times in additional cohorts [11-13], present numerous advantages for clinicians (simple, repeatable, at point-of-care), and have been recommended by the Baveno VII consensus and hepatology societies [2, 6, 14].

Baveno VII recommendations for CSPH were based on a preliminary analysis of a multicenter sample specifically collected to inform the symposium. An expanded version was subsequently published as a full manuscript [8]. Since then, several studies have specifically evaluated Baveno VII criteria with a different composition of etiologies and distinct performance for ruling in and out CSPH [15-21]. On the other hand, it might be possible that by using a different approach utilizing thresholds of predicted values of CSPH by the models, the ruled in group could be improved, especially for MASLD patients, and the indeterminate zone diminished.

We have conducted a systematic review and meta-analysis of the studies published after Baveno VII specifically designed at: 1) validating the consensus recommended criteria for ruling in and ruling out CSPH and assessing their performance of the in the different etiologies of cACLD patients; 2) providing additional improved criteria for ruling in CSPH using the predicted risk of CSPH of the ANTICIPATE±NASH models; and 3) evaluating the robustness of the performance of ANTICIPATE±NASH models taking into account the clustering by center.

Materials and methods

This study was designed to evaluate the performance of Baveno VII criteria to rule out and rule in CSPH. The review and meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [22]. The study included patients who had previously given informed consent to participate in each study.

Search strategy and eligibility criteria

The search strategy was designed and conducted by JG and JB. This meta-analysis was designed to pool the data of individual cACLD patients who had never been decompensated with suspected CSPH who underwent both HVPG measurement (reference test) and LSM (index test) evaluated by TE (FibroScan, Echosens, Paris, France), in studies designed to evaluate the Baveno VII recommendations for CSPH [2]. Using the databases MEDLINE, EMBASE, Google Scholar and Web of Science [23], we performed the search from October 2021 (date of the Baveno VII workshop) to June 30, 2024. Briefly, the key terms for the search were “clinically significant portal hypertension” and “Baveno VII” (full search strategy is shown in Supplementary Table 1). Cross-sectional studies reporting data on adults (≥18 years) with HVPG and LSM were eligible, including conference abstracts and letters. Only studies with at least 50 patients included were eligible. Excluded studies were case-control studies, case reports, or other non-original work (reviews, expert opinions, or practice guidelines). Further research was conducted through a manual check of references. Regarding

etiologies, in patients with hepatitis C only studies with untreated patients were included.

Study identification, selection and data extraction

Criteria for study identification and selection, and the methodology for data extraction are detailed in Supplementary Text 1.

Quality assessment

Two authors (JGA and JB) independently assessed the methodological quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool [24]. The assessed domains of study quality were patient selection, index test, reference standard, and flow and timing. A study was considered at high risk of bias when at least one of the domains of QUADAS-2 showed this risk. Any disagreements were resolved through discussion with a third author (JG).

Definitions and outcome

The criterion to rule in CSPH was LSM of ≥25 kPa, while the criterion to rule out CSPH was a LSM of ≤15 kPa and platelet count ≥150×10⁹/L. If CSPH could be neither ruled in nor ruled out, patients were in an indeterminate (also called “grey”) zone. The main outcome was to assess the performance of the diagnostic algorithms using the individual data from each study for providing positive predictive values (PPV) and negative predictive values (NPV) of ≥90%. According to Baveno consensus and

current recommendations, these targets were considered adequate [2, 25]. In this study, we prioritize selecting patients with CSPH in most of them (90%) to make sure that they are the correct candidates for receiving β-blockers; in other words, we want to avoid false positives, prioritizing a test that predicts a high chance of having CSPH, versus a test with high diagnostic accuracy.

Statistical analysis

Contingency tables were constructed with true positives, true negatives, false positives and false negatives with individual patient data from each study. Sensitivity, specificity, PPV, NPV and their 95% CIs were calculated. With these data, we performed a univariate quantitative meta-analysis of proportions to pool PPVs (for ruling in criteria) and NPVs (for ruling out criteria). In the meta-analysis of studies, two analyses were performed, excluding and including the original paper by Pons, et al. [8]. We used the Freeman-Tukey double arcsine transformation, and a random-effects model with the inverse variance method for pooling the proportions. We did not use bivariate models (which consider the covariance of sensitivity and specificity) in our meta-analysis because bivariate models require continuity correction, which adds a 0.5 to cells with zero value; since the number of zero cells was high in this study, we thought this would substantially bias the estimators. Also, the ruling in and ruling out criteria are very different and were developed to have a high PPV and NPV respectively. It has been argued that prevalence has a major impact on PPV and NPV. This is the case also for sensitivity and specificity [26]. We addressed the issue of the impact of prevalence of CSPH on NPV and PPV in two ways, described in Supplementary Text 2.

Further, in trying to simplify predictions for all etiologies we assessed whether the use of the ANTICIPATE±NASH (https://www.bcn-liverhuvh.com/resources) with a threshold probability of 0.75 of CSPH could be a general threshold to rule in CSPH in all etiologies of cACLD, as explained in Supplementary Text 2 .

We also analyzed the performance in the intermediate zone (patients not ruled in or out) of the AASLD criteria for assuming CSPH published after the Baveno VII consensus [6]. Specifically, CSPH can be presumed if LSM ≥20 and <25 kPa plus platelets <150x10^9/L or if LSM >15 and <20 kPa plus platelets <110x10^9/L. In addition, in a small subset of 216 patients from which we had an upper endoscopy performed at the same time as the other procedures, we analyzed the effect of detecting varices to reclassify patients for CSPH on the intermediate zone, as reported by Dajti, et al. [10].

Finally, since adequate calibration is essential for decision making [27] and considering the proposed use of ANTICIPATE±NASH for clinical practice, there is a need for testing the performance of these models in different centers. The methodological approach for this analysis is explained in Supplementary Text 2.

All analyses were performed in R / R Studio Version 2024.12.1+563 (2024.12.1+563) with the *dplyr*, *pROC*, *ggplot 2*, *randomForest*, *metafor*, *meta*, and *rms* packages [28-35].

Results

Study selection process and quality assessment

Our search strategy identified 801 potential records. Then we proceed with the automatic removal of duplicates, reviewing titles and abstracts and full-text assessment for some studies (Supplementary Figure 1). Of note, four poster abstracts and one published study [15] were included for full review but were finally excluded because of overlapping data with the final selected studies and another study [21] did not have LSM paired with HVPG in all patients (only 49 patients). After manual search of references, we identified and included another relevant work [16]. Six studies [8, 16-20] were eligible and all corresponding authors were contacted; however, no response was received from one author after three attempts. The remaining five authors [8, 16-19] agreed to share their data and participate in the analysis. All studied samples were retrospective. One of them included prospectively collected data for the validation cohort [8], while another one was a retrospective analysis of prospectively collected data [18]. All studies were performed in a hospital setting.

The methodological quality of the studies assessed with the QUADAS-2 too and the characteristics of the studies are summarized in Supplementary Tables 2 and 3.

Patient characteristics

The total sample comprised 1433 patients from five studies. The distribution of etiologies and general characteristics of the patients included in the studies are shown

in Table 1. Mean LSM in the overall sample was 26.9±17.2 kPa. The mean value of ANTICIPATE±NASH was 60.1 (SD 31.7). The prevalence of CSPH in the included studies correlating HVPG and LSM by TE was close to 60% with a mean HVPG of 11.8 (6.1) mmHg. The characteristics and distribution of patients by etiology is shown in Supplementary Table 4 and 5.

Meta-analysis of the ruling in criterion for CSPH of Baveno VII

Figure 1 A and B show the PPVs for ruling in CSPH (LSM ≥25 kPa) corresponding to the analysis excluding and including the original paper by Pons, et al., with similar results. With all studies included, the pooled PPV was 0.92 (0.89-0.94) with low heterogeneity. The lowest PPV was seen in the Odraizola, et al. cohort (0.73), which presented the lowest prevalence of CSPH. The performance of the ruling in criterion for the aggregated data from all studies is shown in Supplementary Table 6.

The forest plot of the same ruling in criterion by etiology of cACLD is depicted in Figure 1C. As seen, for each etiology the pooled PPV was greater than 0.90, except in MASLD patients with obesity (0.67). Supplementary Table 7 shows the performance metrics of the raw data pooled for each etiology. Here additional and mixed etiologies not individually represented in the meta-analysis are analyzed, showing a very high PPV for metabolic dysfunction and increased alcohol intake (MetALD), cholestatic diseases and HCV combinations with other etiologies.

Figure 2 shows the result of meta regression (or moderator analysis) to test the contribution of etiology and prevalence to explain the variation in PPV for CSPH of the

ruling in criteria. Meta-regression showed that cohorts with higher CSPH prevalence tended to have higher PPV (coefficient 0.57, 95% CI 0.20–0.95; p-value= 0.003, Figure 2A). After accounting for etiology, however, this association was attenuated (coefficient 0.20, 95% CI –0.34–0.73, p-value=0.477, Figure 2B).

Meta-analysis of a new ruling in criterion based on ANTICIPATE±NASH values

To provide an etiology-agnostic ruling in prediction for CSPH, we tested the performance of a prediction rule based on a risk of CSPH by the ANTICIPATE±NASH model ≥75%. Figure 3A shows the pooled results of PPVs for ruling in CSPH with this criterion. The pooled PPV was 0.95 (0.93-0.97), higher than LSM ≥25 kPa with also low heterogeneity. The performance of this ruling in criterion for the aggregated data from all studies is shown in Supplementary Table 8.

The forest plot of the ANTICIPATE±NASH model ≥75% criterion by etiology of cACLD is depicted in Figure 3B. As observed, the PPV for MASLD patients with obesity notably increased from 0.67 to 0.83 (p<0.001). Supplementary Table 9 shows the performance metrics for the raw data pooled for each etiology, including etiologies not individually represented in the meta-analysis, all of them with very high PPVs.

Finally, in Supplementary Figure 2 we show in a meta regression analysis that with the use of the ANTICIPATE±NASH ≥75% criteria there is no association between the prevalence of CSPH and the PPV for CSPH even without adjusting by etiology, suggesting that this new prediction rule is truly etiology agnostic.

Meta-analysis of the ruling out criteria for CSPH of Baveno VII

Figure 4A shows the pooled results of NPV for ruling out CSPH (LSM ≤15 kPa + platelets ≥150 x 10^9/L). The pooled NPV was 0.99 (0.97-1) with low heterogeneity. The performance of this ruling out criterion for the aggregated data from all studies is shown in Supplementary Table 10.

The forest plot of the same ruling out criteria by etiology of cACLD is depicted in Figure 4B. As seen, for each etiology the pooled NPV was excellent. Supplementary Table 11 shows the performance metrics of the raw data pooled for each etiology. As shown in Supplementary Figure 3, NPVs are not influenced by etiology of cACLD.

We provide at the end of Supplementary Data all contingency tables for all previous analysis.

Intermediate zone and AASLD criteria or endoscopy for CSPH

Table 2 summarizes the distribution of patients and the prevalence of CSPH in the different subgroups determined by the distinct ruling in criteria, including the AASLD classification criteria for the intermediate zone. As seen, patients selected by the AASLD criteria present CSPH prevalences of less than 81%.

Also, in Supplementary Table 12, the results of performing an endoscopy searching for varices in the subset of 216 patients are shown. Using both classification criteria

the percentage of patients with varices in the intermediate zone is similar (22-24%), representing a reduction of 10% in the unclassified patients (from 46% to 36%).

Calibration of the ANTICIPATE±NASH model to predict CSPH clustered by centers

As reported in methods, we tested the robustness of the prediction performance of the ANTICIPATE±NASH across centers. Supplementary Table 13 outlines the general characteristics of all patients available after the addition of the patients provided by two corresponding authors (ED and TR). Figure 5A shows the calibration-in-the-large of the ANTICIPATE±NASH model divided by center. There was an excellent agreement between mean predicted and observed probabilities of CSPH. Furthermore, discrimination (assessed by the C-statistic) was excellent within each center (see Supplementary Table 14). We then used a 2-step meta-analytic approach to test the moderate calibration of ANTICIPATE±NASH considering center clustering. Figure 5B shows the meta-analytic calibration curve, again showing excellent agreement between predicted and observed probabilities of CSPH across all levels of risk.

Discussion

Preventing first decompensation is now a cornerstone of treatment in at-risk patients with cACLD [2-5]. Since patients with CSPH will have the highest benefit from preventive therapies, their identification is becoming increasingly important [3-5]. Screening for CSPH is now possible with non-invasive tests that are simple, repeatable, usable at point-of-care, and recommended by the Baveno VII consensus [2]. In this study, we conducted a systematic review and IPD meta-analysis from data-independent cohorts validating the performance of Baveno VII criteria for detecting CSPH while improving the ruling in criteria with the ANTICIPATE±NASH model.

Baveno VI introduced the possibility to rule in CSPH in virus related cACLD [1] and Baveno VII consolidated a solid recommendation for non-invasive CSPH diagnosis across different etiologies [2], changing clinical decision making in hepatology. The combined LSM ≤15 kPa and platelets ≥150 x 10^9/L and the LSM ≥25 kPa thresholds, confidently divide patients into two groups regarding the presence of CSPH: extremely unlikely and highly probable, respectively. The high performance of these classification rules comes with two drawbacks: First, the ruling in criterion is valid for most etiologies of cACLD except for MASLD patients with obesity, losing the ability to predict CSPH with high BMI. Second, many patients (40-50%) [8, 16-20] fall into an area of uncertainty, the intermediate or gray zone, in which CSPH cannot be excluded or affirmed. Many efforts have been made since the advent of these recommendations to narrow this gap, and some promising tools have risen in the field.

The first key finding of this study is the validation of the Baveno VII criteria. First, the ruling out criterion presents a nearly unbeatable pooled NPV (0.99) with only 4 patients

(out of 203, 1.97%) having CSPH in this group. For this reason, no attempt was made to improve the classification rule. Second, the ruling in criterion (LSM ≥25) has an excellent PPV (0.92) but, as expected, fails to accurately classify MASLD patients with obesity. In the cohort of Odraizola, et al. a study with a high proportion of MASLD patients and obesity- the PPV fell to 0.73 and, when analyzing the PPV by etiology, MASLD patients with obesity had a poor pooled PPV (0.67). This low PPV was not seen in MASLD patients without obesity (0.96).

Improving the ability to detect CSPH in MASLD patients with obesity is needed. The ANTICIPATE models provide an individual risk assessment of CSPH [8] and are currently recommended [2, 6, 14] as valuable diagnostic tools in the increasing population of cACLD patients. Moreover, the ANTICIPATE-NASH model was specifically developed for MASLD patients, considering BMI an important variable. In this study, we propose an ANTICIPATE±NASH ≥75% threshold for ruling in CSPH. First, the overall pooled PPV is greater with the ANTICIPATE±NASH ≥75% (0.95) than with the LSM ≥25 kPa criterion (0.92). Second, in the population of MASLD patients with obesity, the PPV improved notably from 0.67 to 0.83. Third, the ANTICIPATE±NASH criteria render etiology less critical for the prediction of CSPH (as shown in the scatter plots in Figure 2 and Suppl. Figure 2). Fourth, with the new criteria there is a marginal reduction of patients left in the intermediate zone (from 45% to 43%). Lastly, changing from LSM to the ANTICIPATE models does not complicate the process since by using the online tool, the information can be still obtained rapidly at point-of-care by imputing platelet count (in all patients) and BMI (in MASLD patients).

It is worth mentioning that the compilation of the present large sample of patients has provided the opportunity of analyzing the performance of these different classification criteria for CSPH in other etiologies generally underrepresented in large studies. In that sense, the classification criteria perform very well in all of them, including MetALD, cholestatic diseases and combination of HCV and other etiologies, supporting the universal utility of these classification rules. In addition, we were able to test a potential “center effect", which shows that the performance of the ANTICIPATE±NASH model is robust across the centers involved in the study, both in terms of calibration and discrimination. Finally, we show that the AASLD criteria for classifying CSPH in the intermediate zone present in our study an observed prevalence of CSPH lower than 81%, and that by performing an upper endoscopy in patients in this intermediate zone, 22% of them present gastro-esophageal varices, reducing the proportion of unclassified patients.

There have been other steps forward to improve the detection of CSPH in patients with cACLD since Baveno VII. Notably, the von Willebrand factor antigen to platelet ratio (VITRO) as a non-invasive test alone or applying it sequentially to Baveno VII criteria [18] can detect patients with CSPH with a similar diagnostic accuracy and reduce significantly the intermediate zone. In the last few years, spleen stiffness measurement (SSM) has been establishing its role in the field of noninvasive assessment of portal hypertension. Recently, Jachs, et al. showed that the use of SSM 100Hz in detecting CSPH comparing a combination of SSM, LSM platelet and BMI (NICER model) directly with the ANTICIPATE±NASH, yielded a slightly higher AUC for prediction of CSPH [9], though the new model did not improve the AUC in MASLD

patients. In the classification algorithm proposed by these authors, the performance for MASLD patients with obesity was similar to other etiologies. However, using this algorithm, there is still an intermediate (unclassified) group of patients of 35%, not far from our 43%.

Our study has several strengths. This is an individual patient data meta-analysis of a large cohort of more than 1400 patients with representation of various etiologies of liver disease. Notably 25% of the total cohort are MASLD patients and nearly 20% ALD patients. The IPD approach provides high consistency in collecting the data, more precise estimation, harmonization across studies and stratified subgroup analysis. We validate Baveno VII criteria and further explore the utility of ANTICIPATE±NASH in diagnosing CSPH. The new ruling in criteria using an ANTICIPATE±NASH ≥75% threshold will be a valuable addition to the algorithm of the “rule of five” (Figure 6). In addition, it is important to remark that detecting or not CSPH by these non-invasives rules is clinically relevant since the different subgroups determined by the algorithms carry very different clinical outcomes as evidenced in several reports [36, 37]. Furthermore, the IPD approach allows us to conduct new exploratory analyses and find a relationship between ANTICIPATE±NASH values and HVPG. Our study has some limitations. The analysis is based on a limited number of retrospective studies. Also, any classification rule that includes LSM is a limitation for centers that do not have access to the device, and it might be problematic the performance and interpretation of LSM in patients with important obesity, in which LSM often fails. The new proposed algorithm for ruling in CSPH using the 75% threshold of ANTICIPATE±NASH obtained by using our whole dataset might be affected by overfitting and will need further validation.

In conclusion, Baveno VII criteria have excellent performance in screening in and out CSPH in cACLD patients of different etiologies. Using an ANTICIPATE±NASH value ≥75% as ruling in threshold, the global performance improved, especially in MASLD patients with obesity. Finally, we show stability of the performance of ANTICIPATE±NASH across different centers, suggesting that it can be used as a validated tool to guide clinical practice.

Abbreviations:

ALD = Alcohol-related liver disease

BMI = Body mass index

cACLD = Compensated advanced chronic liver disease

CSPH = Clinically significant portal hypertension

HBV = Hepatitis B virus

HCV = Hepatitis C virus

HVPG = Hepatic venous pressure gradient

IPD-MA = Individual patient data meta-analysis

kPa = Kilopascals

LSM = Liver stiffness measurement

MetALD = MASLD and increased alcohol intake

MASLD = Metabolic dysfunction-associated steatotic liver disease

NPV = Negative predictive value

PPV = Positive predictive value

PRISMA = Preferred reporting Items for Systematic Reviews and Meta-Analyses

QUADAS-2 = Quality assessment of diagnostic accuracy studies 2

SSM = Spleen stiffness measurement

TE = Transient elastography

WoS = Web of Science

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Tables:

Table 1. General characteristics of the overall cohort and of the individual studies

	Pons [8]	Jachs [18]	Dajti [17]	Podrug [16]	Odraizola [19]	Overall
Patients (n)	835	276	195	71	56	1433
Age (mean ± SD)	57.1 ± 11.2	54.2 ± 11.5	58.6 ± 12.7	59.3 ± 10.3	60.2 ± 7.5	57 ± 11.4
Male (%)	533 (63.8%)	191 (69.2%)	134 (68.7%)	55 (77.5%)	56 (66.1%)	950 (66.3%)
Etiology (n, %)						
HCV*	358 (42.8%)	114 (41.3%)	73 (37.4%)	3 (4.2%)	0	548 (38.2%)
HBV	27 (3.2%)	14 (5.1%)	11 (5.6%)	3 (4.2%)	1 (1.8%)	56 (3.9%)
ALD	167 (20%)	47 (17%)	18 (9.2%)	28 (39.4%)	11 (19.6%)	271 (18.9%)
MASLD†	222 (26.6%)	41 (14.8%)	31 (15.9%)	23 (32.4%)	43 (76.8%)	360 (25.1%)
● MASLD with obesity (BMI≥30 kg/m^2)	121 (14.5%)	24 (8.7%)	10 (5.13%)	11 (15.49%)	39 (69.6%)	205 (14.3%)
● MASLD without obesity	87 (10.4%)	17 (6.2%)	21 (10.8%)	12 (16.9%)	4 (7.1%)	141 (9.8%)
Other **	61 (7.3%)	60 (21.7%)	62 (31.8%)	14 (19.7%)	1 (1.8%)	198 (13.8%)
LSM (kPa) (mean, SD)	28.72 ± 18.8	26.51 ± 16	22.83 ± 10	24.71 ± 17	18.72 ± 13.7	26.9 ± 17.2
Platelet count (10^9/L) (mean, SD)	141.8 ± 72.9	130.9 ± 69.4	130.3 ± 67.8	166.9 ± 72.3	183.8 ± 84.1	141 ± 72.9
ANTICIPATE±NASH (%) (mean, SD)	61.2 ± 32.3	63.3 ± 28.7	61.5 ± 27.6	52.1 ± 36.5	32.2 ± 29.4	60.1 ± 31.7
HVPG (mmHg) (mean, SD)	12.2 ± 6.6	11.8 ± 5.6	11.7 ± 4.3	10.5 ± 6	7.7 ± 4.5	11.8 ± 6.1
CSPH (n, %)	493 (59%)	167 (60.5%)	121 (62%)	38 (53.5%)	19 (33.9%)	838 (58.5%)

* All HCV patients had active infection and were assessed prior to therapy

† 14 MASLD patients missed BMI information all in Pons et al [4]

** Other included patients with the following etiologies: MetALD, HCV and ALD, HCV and MASLD, PBC, PSC and other underrepresented etiologies (see Supplementary table 4).

CSPH = Clinically significant portal hypertension, HCV = Hepatitis C virus, HBV = Hepatitis B virus, ALD = Alcohol-related liver disease, MASLD = Metabolic dysfunction-associated steatotic liver disease, LSM = Liver stiffness measurement, HVPG = Hepatic venous pressure gradient, BMI = body mass index

Table 2. Distribution of patients and prevalence of clinically significant portal hypertension (CSPH) in the subgroups based on different classification criteria, including the AASLD criteria for the intermediate zone. In (A) ruling in CSPH with Baveno VII criteria of LSM ≥25 kPa. In (B) ruling in CSPH with ANTICIPATE±NASH ≥75%

(A) RULING IN CSPH WITH LSM ≥25 kPa		
RULING OUT CSPH LSM ≤15 kPa + platelets ≥ 150.000	**INTERMEDIATE ZONE***	**RULING IN CSPH** **LSM ≥ 25kPa**
203 (14.2%) CSPH: 1.97%	**646 (45.1%)** CSPH: 46.9%	584 (40.75%) CSPH: 90.92%
	**LSM 20-25 kPa + < 150.000	
	134 (CSPH 80.6%)	
	**LSM 15-20 kPa + <110.000	
	80 (CSPH 71.25%)	

(B) RULING IN CSPH ANTICIPATE±NASH ≥75%		
RULING OUT CSPH LSM ≤15 kPa + platelets ≥ 150.000	**INTERMEDIATE ZONE***	**RULING IN CSPH** **ANTICIPATE±NASH ≥75%**
203 (14.2%) CSPH: 2%	**616 (43.1%)** CSPH: 42.7%	610 (42.7%) CSPH: 93.5%
	**LSM 20-25 kPa + < 150.000	
	53 (CSPH 71.7%)	
	**LSM 15-20 kPa + <110.000	
	61 (CSPH 67.2%)	

* Intermediate zone refers to patients not ruled in or out.
** Classification criteria based on AASLD recommendations.
LSM = Liver stiffness measurement

Figure legends:

Figure 1. Forest plots for ruling in CSPH with LSM ≥25 kPa criteria. (A) Performance excluding the study by Pons et al., (B) Performance including all studies and (C) Performance by etiology.

Figure 1 footnotes: LSM = Liver stiffness measurement, CSPH = Clinically significant portal hypertension, PPV = Positive predictive value, Prev = Prevalence, HCV = Hepatitis C virus, HBV = Hepatitis B virus, ALD = Alcohol-related liver disease, MASH = Metabolic dysfunction-associated steatohepatitis, Other etiologies include patients classified as such in Table 1 and Supplementary Table 4.

Figure 2. Meta regression showing the association between the prevalence of CSPH (in different etiologies) and the PPV of the Baveno VII ruling in criteria (LSM ≥25 kPa). In univariable meta-regression, higher prevalence was associated with higher PPV (coefficient 0.57, 95% CI 0.20–0.95) (A), but this association was no longer significant after adjustment for etiology (coefficient 0.20, 95% CI –0.34–0.73) (B).

Figure 2 footnotes: PPV = Positive predictive value, CSPH = Clinically significant portal hypertension, ALD = Alcohol-related liver disease, HBV = Hepatitis B virus, HCV = Hepatitis C virus, MASH = Metabolic dysfunction-associated steatohepatitis.

Figure 3. Forest plots for ruling in CSPH with ANTICIPATE±NASH ≥75% criteria. (A) Performance including all studies and (B) Performance by etiology.

Figure 3 footnotes: LSM = Liver stiffness measurement, CSPH = Clinically significant portal hypertension, PPV = Positive predictive value, Prev = Prevalence, HCV = Hepatitis C virus, HBV = Hepatitis B virus, ALD = Alcohol-related liver disease, MASH

= Metabolic dysfunction-associated steatohepatitis, Other etiologies include patients classified as such in Table 1 and Supplementary Table 4.

Figure 4. Forest plots for ruling out CSPH the LSM ≤15 kPa + platelet count ≥150 x 10^9/L criterion. (A) Performance by study and (B) by etiology.

Figure 4 footnotes: LSM = Liver stiffness measurement, CSPH = Clinically significant portal hypertension, NPV = Negative predictive value, Prev = Prevalence, HCV = Hepatitis C virus, HBV = Hepatitis B virus, ALD = Alcohol-related liver disease, MASH = Metabolic dysfunction-associated steatohepatitis. Other etiologies include patients classified as such in Table 1 and Supplementary Table 4.

Figure 5. Calibration of the ANTICIPATE±NASH model to predict CSPH clustered by centers. A) Calibration-at-large across the centers providing patients for the present study. Due to the low numbers, the two centers contributing less patients (Bern and London) were pooled as a single center. The size of the circles represents the number of patients contributed by each center. The plot shows an excellent agreement between the mean predicted risk of CSPH (by ANTICIPATE±NASH) and observed proportion of patients with CSPH. B) 2-step meta-analytic calibration plot. The dark pink area represents the 95% confidence interval of the average calibration curve (CI). The lighter pink areas represent the 95% confidence interval of the prediction intervals (PI) at each level of estimated probability of CSPH.

Figure 6. Updated algorithm for the "rule of 5" for non-invasive determination of cACLD and CSPH.

Figure 6 footnotes: cACLD = compensated advanced chronic liver disease; CSPH = clinically significant portal hypertension; MASLD = metabolic dysfunction-associated steatotic liver disease.

Figures:

Figure 1A

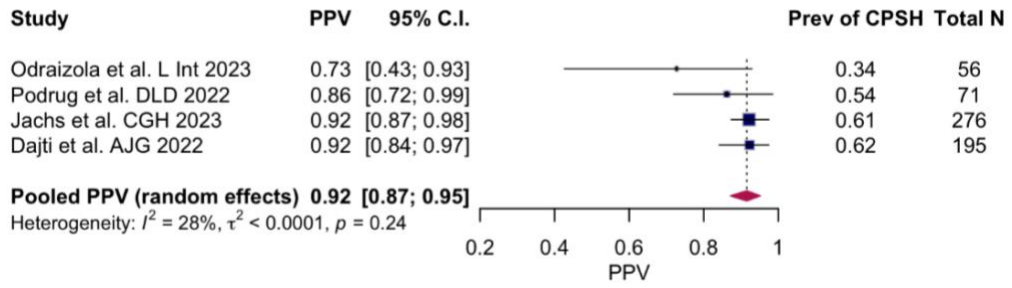
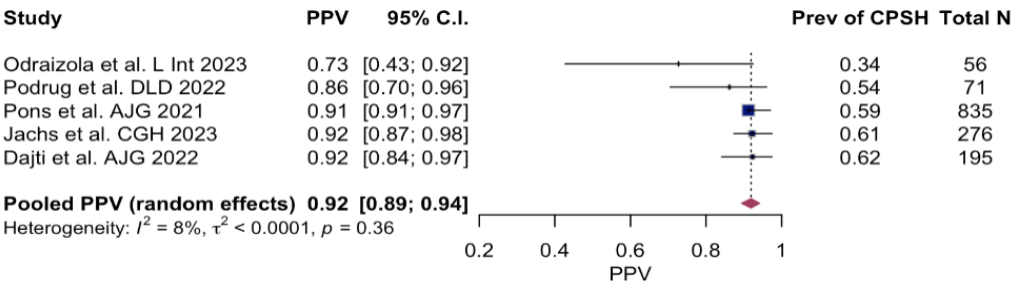


Figure 1B



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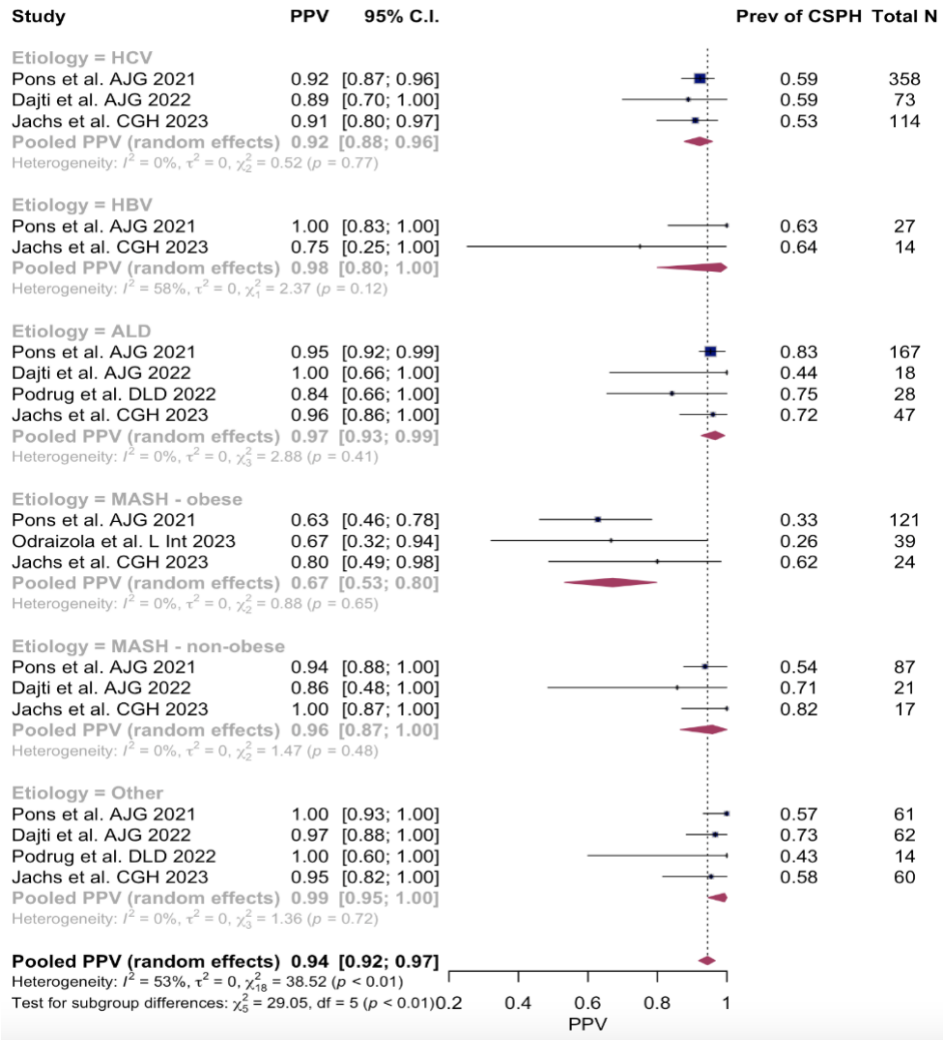
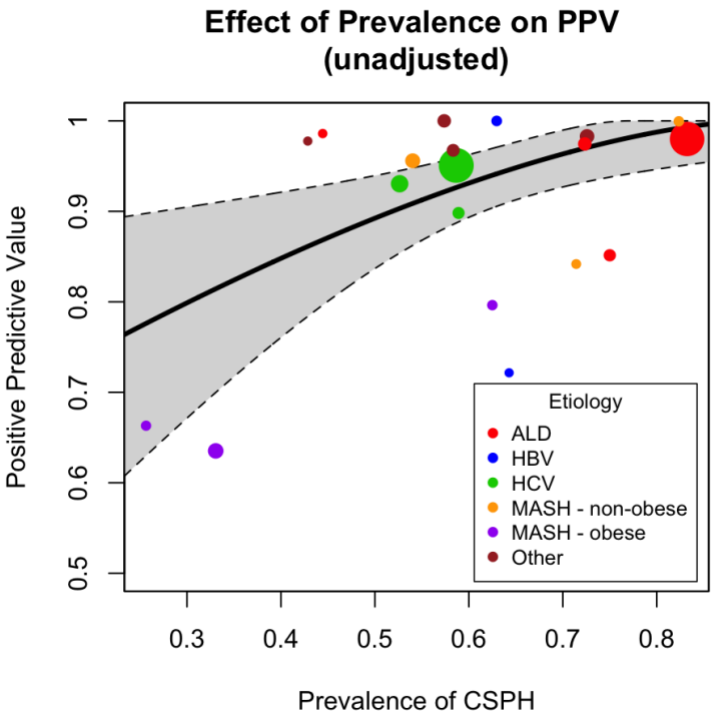


Figure 2A



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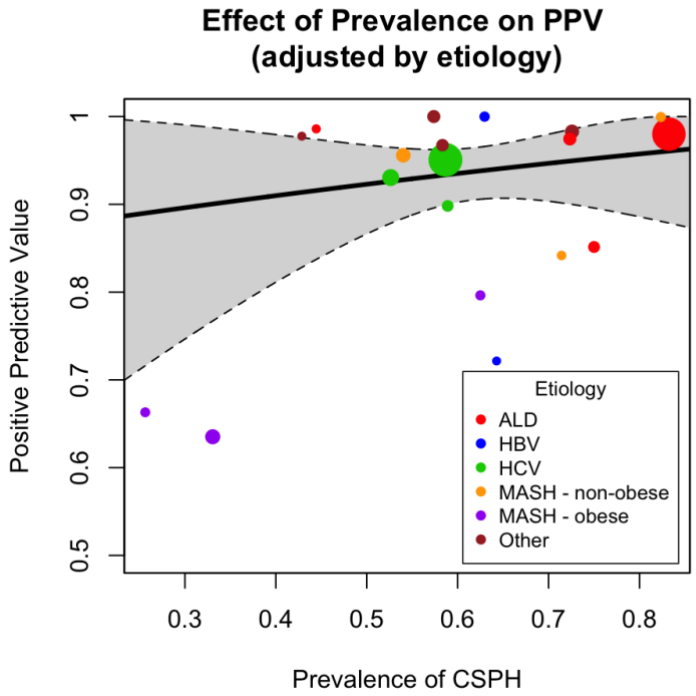

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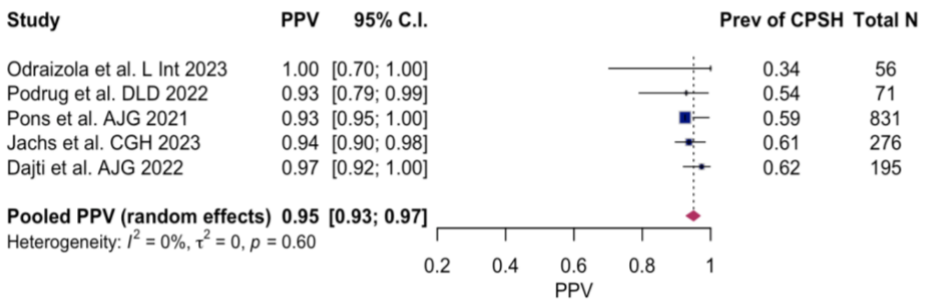


Figure 3B.

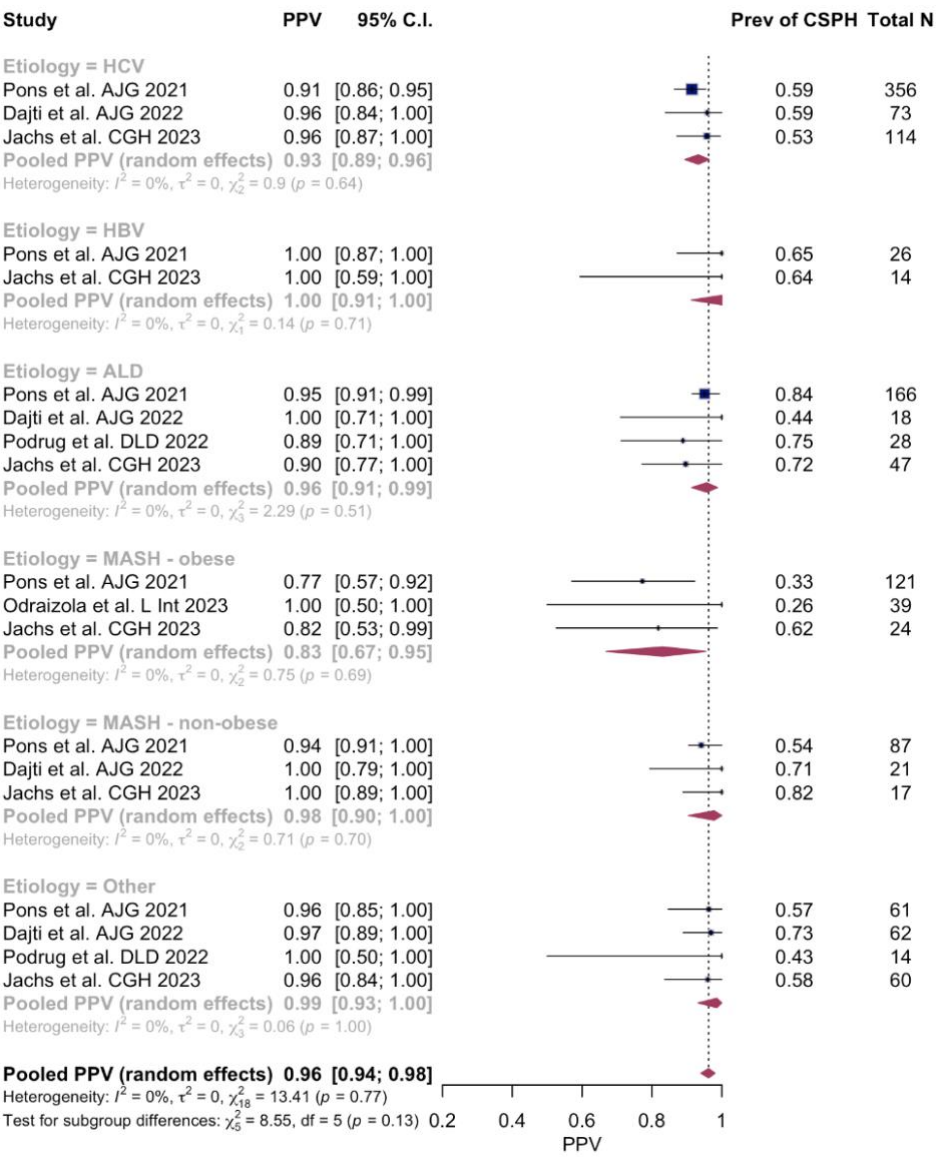


Figure 4A

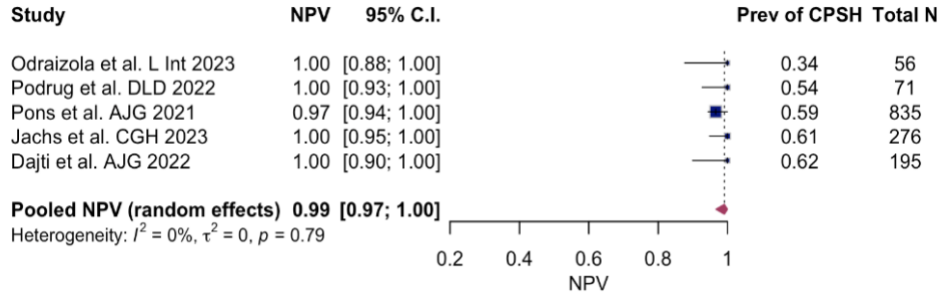


Figure 4B

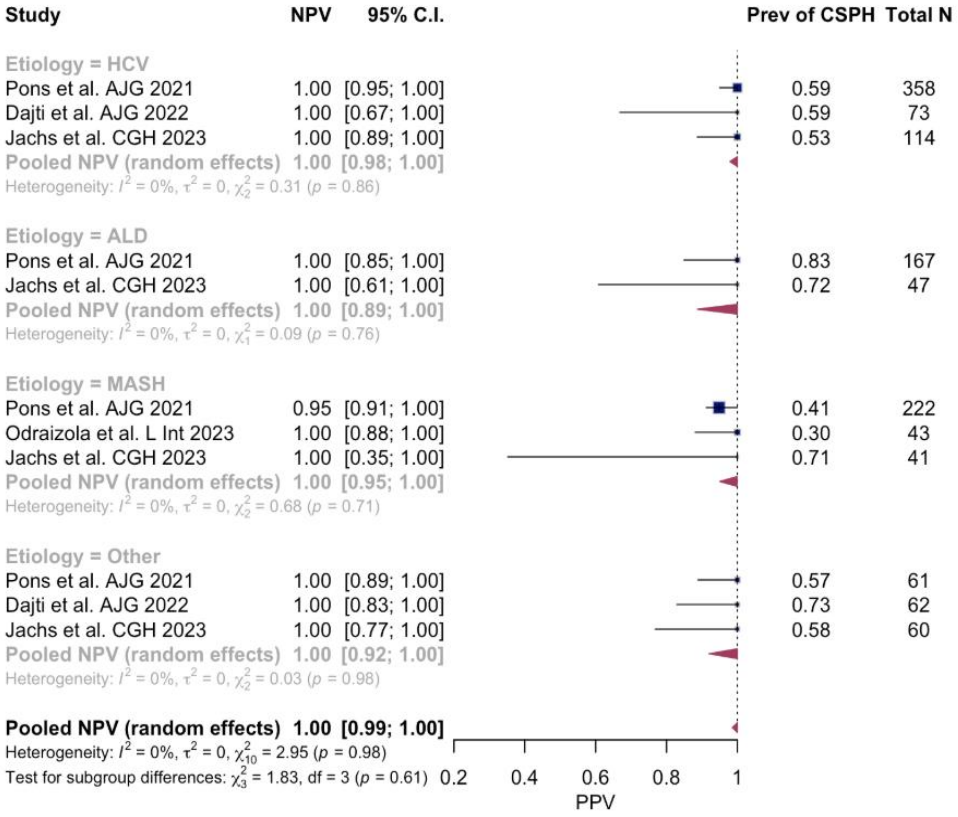


Figure 5

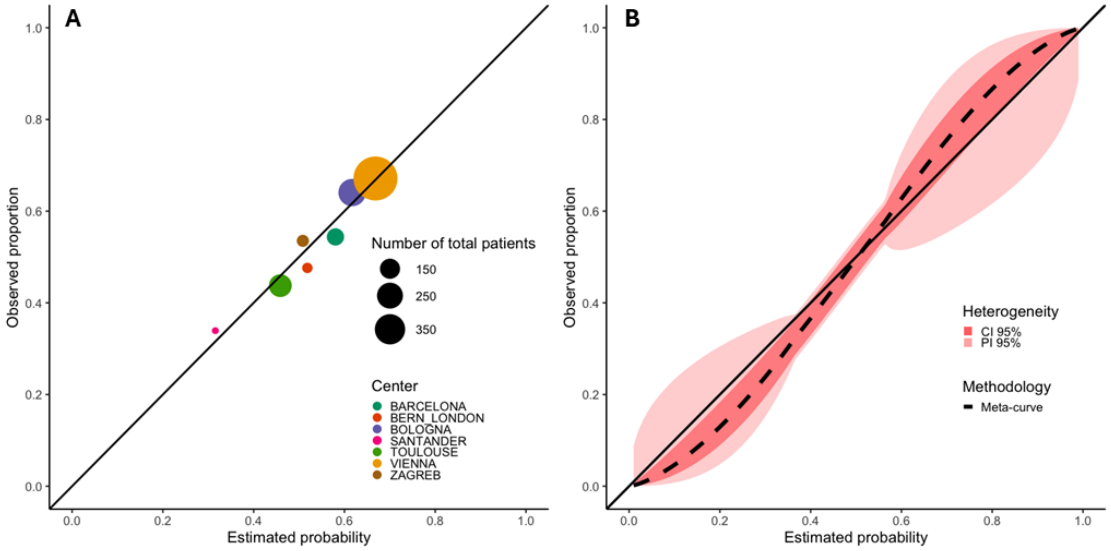
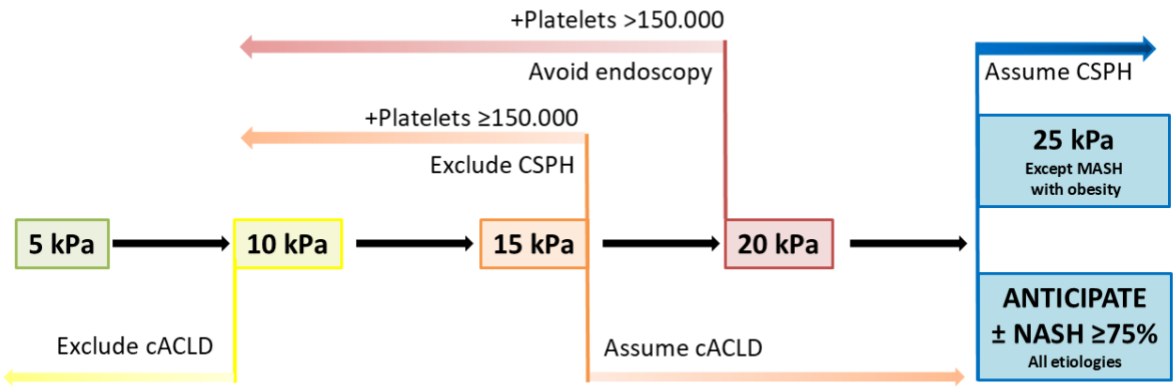

A
B
Observed proportion
Estimated probability
0.0
0.2
0.4
0.6
0.8
1.0
Number of total patients
150
250
350
Center
BARCELONA
BERN_LONDON
BOLOGNA
SANTANDER
TOULOUSE
VIENNA
ZAGREB
Heterogeneity
CI 95%
PI 95%
Methodology
Meta-curve

Figure 6


+Platelets >150.000
Avoid endoscopy
+Platelets ≥150.000
Exclude CSPH
Assume CSPH
25 kPa
Except MASH with obesity
5 kPa
10 kPa
15 kPa
20 kPa
ANTICIPATE
± NASH ≥75%
All etiologies
Exclude cACLD
Assume cACLD