Accuracy of spleen stiffness measurement for the diagnosis of clinically significant portal hypertension in patients with compensated advanced chronic liver disease: a systematic review and individual patient data meta-analysis

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Authors: Elton Dajti, MD[1,2]; Federico Ravaioli, PhD[1,2,3], Romanas Zykus, PhD[4]; Pierre-Emmanuel Rautou, PhD (Full Professor)[5,6]; Laure Elkrief, PhD[7]; Ivica Grgurevic, PhD[8], Horia Stefanescu, PhD[9]; Masashi Hirooka, PhD[10]; Mirella Fraquelli, PhD[11]; Matteo Rosselli, PhD[12,13]; Pik Eu Jason Chang, MD[14]; Fabio Piscaglia, PhD (Full Professor) [1,2]; Thomas Reiberger, MD[15]; Elba Llop, PhD[16]; Sebastian Mueller, PhD (Full Professor)[17]; Giovanni Marasco, PhD[1,2], Annalisa Berzigotti, PhD (Full Professor)[18]; Agostino Colli, MD[19]; Davide Festi, MD (Full Professor)[2]; Antonio Colecchia, MD (Full Professor)[3], on behalf of the **Spleen Stiffness – IPD-MA Study Group**

Authors' affiliation:

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, European Reference Network on Hepatological Diseases (ERN RARE-LIVER), Bologna, Italy.

[2]Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, Italy.

[3]Department of Medical Specialities, University Hospital of Modena, University of Modena & Reggio Emilia, Modena, Italy.

[4]Department of Gastroenterology, Lithuanian University of Health Sciences, Kaunas, Lithuania.

[5]Centre de recherche sur l'inflammation, Inserm, Université Paris-Cité, Paris, France.

[6]Service d'Hépatologie, Hôpital Beaujon, Centre de Référence des Maladies Vasculaires du Foie, FILFOIE, ERN RARE-LIVER, Clichy, France.

[7]Hepatogastroenterology Unit, Hôpital Trousseau, CHRU de Tours, Tours, France.

[8]Department of Gastroenterology, Hepatology and Clinical Nutrition, University Hospital Dubrava, University of Zagreb School of Medicine and Faculty of Pharmacy and Biochemistry, Zagreb, Croatia.

[9] Hepatology Department , "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, "luliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.

[10]Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan.

[11]Gastroenterology and Endoscopy Unit, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy.

[12]Department of Internal Medicine, Ospedale San Giuseppe, Empoli, Italy.

[13]Division of Medicine, Institute for Liver and Digestive Health, University College London, Royal Free Hospital, London, United Kingdom.

[14]Department of Gastroenterology & Hepatology, Singapore General Hospital, Singapore, Singapore.

[15]Department of Internal Medicine III, Vienna Hepatic Hemodynamic Lab, Medical University of Vienna, Vienna, Austria.

[16]Liver Unit, Hospital Universitario Puerta De Hierro Majadahonda, Universidad Autònoma de Madrid, Madrid, Spain.

[17] Department of Internal Medicine, Center for Alcohol Research, University of Heidelberg, Heidelberg, Germany.

[18]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, Bern, Switzerland.

[19]Department of Transfusion Medicine and Haematology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano, Italy.

Corresponding author: Prof. Antonio Colecchia MD, Gastroenterology Unit, Department of Medical Specialities, University Hospital of Modena, University of Modena & Reggio Emilia, 41125 Modena, Italy,; e-mail: antonio.colecchia@unimore.it

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Research in context

Evidence before this study

Diagnosing clinically significant portal hypertension (CSPH) is paramount in patients with compensated advanced chronic liver disease (cACLD), and it could guide treatment with non-selective beta-blockers in such patients. CSPH is best diagnosed by measuring the hepatic venous pressure gradient (HVPG), but its measurement is invasive and only readily available in some centres. The Baveno VII Consensus has proposed new non-invasive criteria based on liver stiffness measurement (LSM) and platelet count (PLT) to diagnose CSPH, but up to 50% of the patients have indeterminate results and fall in the "grey zone" of CSPH. The spleen stiffness measurement (SSM) has been proposed as a more accurate surrogate of portal hypertension that could improve CSPH diagnosis and risk stratification. However, available studies evaluating the diagnostic performance of SSM used very heterogeneous cut-offs that have not been validated in large studies and often included patients with decompensation. These limits led us to perform an individual patient data meta-analysis to establish the role of SSM in diagnosing CSPH.

We performed a systematic review, searching articles on PubMed, Scopus, Embase, and Cochrane Library between database inception and December 31st, 2022, and using keywords such as "spleen stiffness", "portal hypertension", and "hepatic venous pressure gradient", with no restriction on language or publication type. After study selection, we requested individual patient data from the investigators. Using different elastography techniques, we pooled data from 17 studies comprising 1245 patients undergoing HVPG and SSM.

Added value of this study

We validated SSM, evaluated by transient elastography, as an accurate and performant non-invasive test to diagnose CSPH in both viral and non-viral patients. The combination of the Baveno VII criteria with SSM drastically reduced the rate of patients with indeterminate results (up to <10%) and increased the number of patients with CSPH correctly included in the rule-in zone (up to 90%) while maintaining an adequate performance (positive predictive value >90%). These results were consistent in different sensitivity analyses. We also proposed a diagnostic algorithm for CSPH based on LSM and SSM evaluated by two-dimensional shear-wave elastography, while data on other elastography techniques were insufficient to recommend their use in clinical practice.

Implications of all the available evidence

The findings in this study support the use of SSM in clinical practice to improve the diagnosis of CSPH in patients with compensated cirrhosis. The combined Baveno VII-SSM algorithms could be used in the future for identifying patients benefitting from non-selective beta-blocker treatment.

Summary

Background: Clinically significant portal hypertension (CSPH) is critical for the prognosis and treatment guidance in compensated advanced chronic liver disease (cACLD). We performed an individual patient data (IPD) meta-analysis to investigate the performance of spleen stiffness measurement (SSM) and SSM-based algorithms using different elastography techniques to diagnose CSPH.

Methods: We performed an IPD meta-analysis, in which we systematically researched databases (PubMed, Embase, Scopus, Web of Science, Cochrane Library) from database inception until December 31st, 2022 with no restriction on language and publication type. Studies reporting hepatic venous pressure gradient and SSM in adult patients were eligible for inclusion. The main outcome was the diagnosic performance of the SSM-based algorithms, estimating summary sensitivity and specificity using the bivariate model, as well as the summary negative (NPV) and positive predictive values (PPV): The Baveno VII-SSM single cut-off (40 kPa) model ruled-out CSPH if at least two were present: liver stiffness measurement (LSM≤15 kPa), platelet count (PLT≥150x10^9/L) and SSM≤40 kPa; CSPH was ruled-in if at least two criteria were met: LSM>25 kPa, PLT<150x10^9/L, SSM>40 kPa). The Baveno VII-SSM dual cut-off model used the same "best-of-three" rule, but SSM<21 kPa cut-off to rule-out and SSM>50 kPa to rule-in CSPH. This study is registered with PROSPERO, CRD42019127164.

Findings: From the 44 articles assessed for eligibility, seventeen studies (with 1245 patients) were included in the meta-analysis. In the transient elastography cohort (600 patients), the Baveno VII algorithm was validated for both ruling-out (NPV 100%, 95%-CI: 64-100%) and ruling-in (PPV 95%, 95%-CI: 85-98%) CSPH, but the grey zone was up to 48% (44-52%). The BavenoVII-SSM dual cut-off model was also validated for the first time, showing adequate NPV (98%, 95%-CI: 58-100%) and PPV (93%, 95%-CI: 84-97%) in the whole cohort and after multiple sensitivity analyses. The Baveno VII-SSM single-cut-off model was the best-performing model in ruling-in CSPH (PPV 92%, 95%-CI: 83-95%, with up to 66% of patients in this category) while safely ruling-out CSPH only in viral etiology (overall NPV 85%, 95%-CI; 60-96%, NPV in viral etiology 91%, 95%-CI: 85-95%). Importantly, the SSM-based algorithms progressively reduced the rate of patients with indeterminate results from 48% (Baveno VII) to 32% (28-36%, Baveno-VII-SSM dual cut-off model) and less than 10% (7-12%, Baveno-VII-SSM single cut-off model). In the two-dimensional-shear-wave elastography cohort (225 patients), these algorithms could safely rule-in CSPH with adequate PPV (>90%) for all three models, while the results were inconclusive for CSPH rule-out. The current data

available was inadequate to evaluate the performance of SSM assessed by point-shear-wave elastography. The heterogeneity was low (I^2<25%) for the majority of the estimates.

Interpretation: This large, multicenter, international study validated SSM as an accurate test for the diagnosis of CSPH. The combined Baveno VII-SSM algorithms showed excellent performance and reduced the diagnostic "grey zone" for CSPH presence. Future studies should evaluate if SSM-based CSPH diagnosis allows for identifying patients benefitting from non-selective beta-blocker treatment.

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Keywords: spleen stiffness, SSM, elastography, portal hypertension, CSPH, meta-analysis, Baveno.

Introduction

Clinically significant portal hypertension (CSPH) is the main driver of portal hypertension complications in patients with compensated advanced chronic liver disease (cACLD). [1,2] Identifying patients with CSPH is of utmost importance in cACLD patients, as it bears both prognostic and therapeutical implications. [3,4] Recent studies have demonstrated that treating CSPH patients with non-selective beta-blockers (NSBB), especially carvedilol, can reduce the risk of decompensation and improve overall survival. [5,6]

CSPH is best diagnosed by measuring the hepatic venous pressure gradient (HVPG), but its measurement is invasive and only readily available in some centres. Several non-invasive tests have been developed and validated recently to identify patients with portal hypertension and its complications. [7–9] In the last Baveno VII consensus [1], the following criteria were proposed to diagnose CSPH in most etiologies: liver stiffness measurement (LSM) by transient elastography (TE) >25 kPa to rule-in and LSM ≤15 kPa + platelet count (PLT) ≥150x10^9/L to rule-out of CSPH. Despite the promising diagnostic performance, including these criteria in clinical practice still faces many issues, such as lack of validation and a very wide (40-60%) grey zone of patients with indeterminate results for CSPH and suboptimal performance in some etiologies. Moreover, the role of LSM evaluation by techniques other than TE is still to be clarified.

The measurement of spleen stiffness (SSM) could improve the accuracy and clinical applicability of the available non-invasive algorithms for diagnosing CSPH [9]. In fact, since its introduction more than a decade ago, [10] many studies have validated its role in the diagnosis of CSPH and high-risk esophageal varices, [11–13] and SSM is now recommended by both EASL guidelines on non-invasive tests [7] and the Baveno VII consensus [1] as an additional tool to assess portal hypertension in patients

with cACLD. However, the different SSM cut-offs proposed[1,9] for the diagnosis of CSPH are heterogeneous and have still to be validated in a large external cohort.

This study aimed to conduct a systematic review and an individual patient data (IPD) meta-analysis to evaluate the accuracy of SSM and SSM-based algorithms, as measured by different elastography techniques, for diagnosing CSPH in cirrhotic patients.

Material and methods

Search strategy and selection criteria

This is a systematic review and meta-analysis conducted and reported according to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [14] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines. It was registered in PROSPERO (registration number: CRD42019127164). In the current paper, only the data regarding the outcome CSPH will be discussed, while the analyses for the outcome varices are under development.

This meta-analysis was designed to pool the data of individual patients with suspected CSPH that underwent both HVPG measurement (reference test) and SSM (index test), evaluated by either one of the four techniques: transient elastography (TE, 50 Hz module, FibroScan; Echosens, France), two-dimensional shear wave elastography (2D-SWE), point shear wave elastography (p-SWE) by ElastPQ®, or p-SWE by Virtual Touch Quantification. Cross-sectional studies reporting data on adults (≥18 years) with HVPG and SSM were eligible. Studies with any of the following characteristics were excluded: i) case-control studies, case reports, or other non-original work (reviews, expert opinions, practice guidelines); (ii) case series where all patients had definite CSPH at enrollment (candidates for transjugular intrahepatic portosystemic shunt (TIPS) placement, or

patients with high-risk varices before NSBB treatment); iii) studies performed in the pediatric population (age <18 years); iv) unavailability of individual patient data. When studies reported patients with both cACLD and decompensated advanced chronic liver disease (dACLD), only cACLD patients at study enrollment were sought at IPD.

We searched MEDLINE via PubMed, Ovid Embase, Scopus, Web of Science, and the Cochrane Library databases up to the 30th of June 2020, and an update was done up to December 31st, 2022. We used the following keywords: "spleen stiffness", "spleen elastography", "portal hypertension", "hepatic venous pressure gradient", "SSM", and "HVPG". The full search strategy is shown in the Appendix (**see appendix p2-3**). Further research was conducted through a manual check of references. Study search and selection were done by two independent investigators (ED and FR), and a third (AC) arbitrated when any conflict occurred in the suitability of a study for inclusion. Subsequently, they independently performed a detailed full-text assessment of potentially relevant studies. Conference abstracts and letters to the editor were also included. No language restrictions have been applied. The last complete publication was considered when multiple articles were found for a single study to avoid duplication.

Data analysis

Data collection and quality assessment

Among the corresponding authors, the first or last authors of the included studies, at least two were invited by email to participate in the IPD meta-analysis. Authors who did not respond after three occasions were considered non-responders.

Respondents completed a standardised database designed for this study collecting information on clinical (age, sex, body mass index, etiology, status on current or previous decompensation,

antiviral treatment), laboratory (platelet count, Model for end-stage liver disease score, Child-Pugh score), elastography (liver stiffness, spleen stiffness, elastography technique), endoscopy (varices presence and grade), and hemodynamic characteristics (HVPG values, interval between catheterism and elastography), and checked for completeness and internal consistency and amended through correspondence with the principal investigators.

Two authors (FR and ED) independently assessed the methodological quality of the included studies using the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool[15]. We addressed all the aspects regarding study quality involving the participant spectrum, index tests, target conditions, reference standards, and flow and timing. We classified a study as having a high risk of bias if at least one of the domains of QUADAS-2 was at high risk of bias (**see appendix p4**). Any disagreements were resolved through discussion with a third author (AC).

Study cohorts

After receiving the IPD, the following patients were excluded from the analysis: i) lack of paired data for LSM, SSM, PLT, or HVPG; ii) patients with the presence of decompensation at enrolment; iii) patients without ACLD (i.e., LSM <10 kPa). The remaining patients, known as the "*main cohort*", were included in the primary analysis for each of the four elastography techniques.

Since data on prior decompensation events were not available in all included studies, we performed a subgroup analysis in a cohort of patients in whom this information was known, and therefore we were confident of a diagnosis of cACLD, according to the Baveno VII Consensus[1], hereinafter referred to as the "*cACLD cohort*".

Finally, for TE, we performed a sensitivity analysis, creating an "*ideal cohort*" of patients with LSM≥10 kPa, no previous decompensation, no antiviral treatment, and a time interval between HVPG and TE ≤3 months.

Diagnostic algorithms under evaluation

For patients undergoing SSM evaluation by TE, we assessed the diagnostic performance of the following three algorithms:

- *The Baveno VII model* [1,8]: LSM ≤15 kPa + PLT ≥150 x10^9/L to rule-out CSPH and LSM >25 kPa to rule-in CSPH.

- *The combined Baveno VII-SSM single cut-off model (40 kPa)* [9]: rule-out CSPH if at least two of the following criteria were present: LSM ≤15 kPa, PLT ≥150x10^9/L, SSM ≤40 kPa; rule-in if at least two of the following criteria were present: LSM >25 kPa, PLT <150x10^9/L, SSM >40 kPa.

- *The combined Baveno VII-SSM dual cut-off model (21-50 kPa)* [1]: rule-out CSPH if at least two of the following criteria were present: LSM ≤15 kPa, PLT ≥150x10^9/L, SSM <21 kPa; rule-in if at least two of the following criteria were present: LSM >25 kPa, PLT <150x10^9/L, SSM >50 kPa. If CSPH could be neither ruled-in nor ruled-out, patients were considered the "*grey zone*".

Using the IPD dataset of the *cACLD cohort*, we also identified SSM by TE cut-offs for CSPH by Receiver Operating Characteristic (ROC)-optimisation for rule-out and rule-in based on likelihood ratios and the best cut-off according to Youden's index (**see appendix p5**); which were similar to those mentioned above and already published cut-offs, so the latter were used for the analyses.

For patients undergoing SSM evaluation by other elastography techniques, we tested whether the same TE cut-offs could be applied to diagnose CSPH if no other cut-offs were already available in the current literature. For 2D-SWE, we used an LSM cut-off of 14 kPa instead of 15 kPa to rule-out CSPH, as previously reported[16].

According to current standards, a diagnostic model with NPV ≥90% for ruling out CSPH and PPV ≥90% for ruling in CSPH was considered adequate[1].

Moreover, we tested the performance of previously published nomograms to estimate the individual risk of CSPH presence, namely the ANTICIPATE model[8] and the LPS (LSM-PLT-SSM) model[9]. For 2D-SWE (SSI), since no similar nomograms are available, we developed two new logistic models (with and without SSM) to estimate CSPH risk (ANTICIPATE-SSI and LPS-SSI).

Statistical analysis

At baseline, categorical data were expressed as numbers (percentages), and continuous variables as means (standard deviations); for group comparisons of categorical and continuous variables, the Chi-square test, Mann-Whitney U test, and the McNemar's test for paired data were used, as appropriate (**see appendix p6**). Correlation between non-invasive tests and HVPG was evaluated with the Pearson correlation coefficient (r) (**see appendix p6**).

The main outcome of the IPD meta-analysis was to assess the performance of the diagnostic algorithms using the raw data from each study with a two-stage approach to the analysis. First, each individual study was analysed independently, and the 2-by-2 tables were built for each diagnostic test. In the second stage, these data were combined to provide a summary estimate of the effect. We performed the meta-analyses using the bivariate model and provided summary sensitivity and specificity estimates ("metadta" and "midas" command). Briefly, this model implements the generalized linear model for the binomial family with a logit link, i.e logistic regression for meta-analysis of diagnostic accuracy data, ad allows a joint modelling of both sensitivity and specificity to preserve the two-dimensional nature of diagnostic accuracy. We used the recommended random-effect term, assuming a normal distribution. We presented the Clopper-Pearson (exact) binominal 95%-CI for the evaluated diagnostic performance measures. We used the summary estimates obtained from the fitted models to calculate summary estimates of positive

(LR+) and negative (LR–) likelihood ratios; the LR are not directly estimated. Moreover, we calculated the negative (NPV) and positive predictive values (PPV) with two methods: i) using LR+ and LR– and the median prevalence of CSPH across the included studies (pre-test probability), the 95%-CI was calculated incorporating the uncertainties of both the LR values (95%-CI estimated by the bivariate model with random effects) and the target condition prevalence (95%-CI estimated in 10,000 bootstrap samples) (preferred method); ii) calculating the summary proportion of patients with target condition (CSPH) among patients with a positive test for PPV and summary proportion of patients without CSPH among patients with a negative test for NPV using random effect models. Heterogeneity across the studies was assessed using the Q test and the I^2 statistic. Analyses were done per protocol, as we did not have IPD data of patients with unfeasible SSM for each study.

We explored heterogeneity between studies through the following sensitivity subgroup analysis for study design (retrospective or prospective), study centre (excluding the cohort[9] where some of the tested algorithms were developed), study size (≥100 patients vs <100 patients), patients' characteristics (etiology, obesity, cACLD definition), the interval between HVPG and elastography (≤3 months vs >3 months or unknown). The "ideal" cohort was created to perform part of these sensitivity analyses (cACLD definition; interval). For study-level potential confounders, we maintained the two-stage meta-analytic approach using the bivariate model. For patient-level potential confounders, we used IPD to create subgroups of patients, which were considered as a single multicenter cohort for the diagnostic test accuracy analysis. Finally, we planned to perform leave-one-out meta-analyses to check for influential studies.

We assessed model discrimination by calculating the area under the receiver operating characteristic (AUROC) curve. To test the equality of the AUROCs, the DeLong test was

performed. For the newly proposed logistic regressions models, we first assessed the linearity assumption underlying logistic regression model for quantitative predictors (**see appendix p6**). We repeatedly fitted the model in 1,000 bootstrap samples and evaluated its performance on the original sample. Model calibration was determined by Hosmer-Lemeshow technique, and the command "calibrationbelt" was used to visually assess the calibration plot.

We did not investigate publication bias as standard funnel plots and tests for publication bias are not recommended in the meta-analysis of diagnostic test accuracy. All analyses were performed with STATA version 16 (StataCorp, College Station, TX, USA) and R-Project version 4.1.1 (R Core Team 2021, Vienna, Austria).

Role of the funding source

There was no funding source for this study.

Results

The electronic search identified 1173 records after removing duplicates, of which 44 were assessed for eligibility. Of the 44 articles, 15 were excluded because included patients had all CSPH (12 studies in patients undergoing TIPS placement, 3 studies in patients with high-risk varices) and 8 because of overlapping cohorts. Four (19%) of the remaining 21 eligible studies (including 400 patients with SSM assessed by p-SWE and/or 2D-SWE) did not provide IPD data. Finally, 17 studies met the criteria for inclusion in the review, of which 11 were full-texts [9,10,25,17–24] and 6 abstracts [26–31], for a total of 1245 patients. Of note, 3 records were initially included as abstracts but later published as full texts. [9,23,24] **Figure 1** shows the flowchart for the selection process and details the reasons for excluding studies that were not included. The methodological quality of the included studies is summarised in the Appendix (**see appendix p7-9**).

After applying the exclusion criteria, 600 patients from seven studies were included in the main cohort (**see appendix p20**) of TE (FibroScan, Echosens, Paris, France); one study was excluded because it did not include any compensated patient. [29] The median rate of SSM failure was 16% (95%-CI: 7-24%). The mean age of the included patients was 58 (12) years, and they were mostly male (69%) and with viral etiology (77%). The mean HVPG value was 13 (5) mmHg, and 155 (28%) patients had large varices. The correlation of SSM and LSM with HVPG and the accuracy of the CSPH diagnosis in summarised in the Appendix (**see appendix p10).** The two nomograms for predicting the individual risk of CSPH, namely the ANTICIPATE and LPS model, were validated in the main cohort, showing AUROCs of 0.904 (95%-CI: 0.878-0.930) and 0.918 (95%-CI: 0.893-0.943), respectively.

The Baveno VII criteria were validated in the "*main cohort"* (**Table 2, Figure 2, appendix p21**). For the CSPH ruling-out, the summary sensitivity was 100% (95%-CI: 70-100%), and the NPV was 100% (95%-CI: 64-100%). Regarding the CSPH ruling-in, the summary specificity was 94% (95%-CI: 87-97%), and the PPV was 95% (95%-CI: 85-98%). The rate of patients in the rule-out and rule-in zone was 10% (7-12%) and 42% (38-46%), respectively; 57% (52-62%) of the patients with CSPH were included in the rule-in zone. Therefore, 48% (44-52%) of the patients fell under the "grey zone" and had indeterminate results for CSPH diagnosis.

The Baveno VII-SSM model with a dual cut-off (SSM 21 kPa and 50 kPa) was also validated in the "*main cohort"* (**Figure 2B, appendix p22**). These criteria could accurately rule-out CSPH (summary sensitivity 100%, 95%-CI: 91-100%, NPV 98%, 95%.CI: 58-100%), but the rate of patients in this zone was similar: 10% (7-12%) vs 11% (9-14%), p= 0.723). CSPH could be ruled-in with a summary specificity of 89% (95%-CI: 84-98%) and PPV of 93% (95%-CI: 84-97%). The

rate of patients in the rule-in zone was 57% (53-61%), and it included 76% (72-80%) of the patients with CSPH. The rate of patients in the "grey zone" was reduced to 32% (28-36%) compared to the Baveno VII model alone (48%, 44-52%) **(Figure 3)**.

The Baveno VII-SSM model with a single cut-off (40 kPa) (**Figure 2C, appendix p23**) showed good summary sensitivity (93%, 95%-CI: 85-97%) but suboptimal NPV (85%, 95%-60-96%) for ruling-out CSPH. On the other hand, CSPH could be ruled-in with a summary specificity of 86% (95%-CI: 80-91%) and a PPV of 92% (95%-CI: 83-95%). The rate of patients in the rule-out and rule-in zone was 25% (21-28%) and 66% (62-70%), respectively; 88% (84-91%) of the patients with CSPH were included in the rule-in zone. Therefore, the "grey zone" was minimised to 9% (7-12%) **(Figure 3)**.

After excluding patients with known or without data on prior decompensation, 403 patients were included in the "cACLD cohort". Patients' characteristics were summarised in **Table 1,** and the performance of the diagnostic algorithms in **Table 2**.

The diagnostic performance of the Baveno VII criteria and the Baveno VII-SSM model with a dual cut-off was confirmed in this cohort, as sensitivity/NPV and specificity/PPV were all >90%, respectively for ruling-out/in CSPH (**see appendix p24-26**). The rate of patients in the "grey zone" was again lower in the Baveno VII-SSM model than in Baveno VII alone: 54% (49-59%) vs 38% (34-43%) (p=0.0001). As for the Baveno VII-SSM model with a single cut-off (**see appendix p24, p27)**, the rule-out performance was better than in the main cohort, with borderline NPV (88%, 95%-CI: 56-98%), whereas the PPV for CSPH rule-in was confirmed >90% (92%, 95%-CI: 88-95%); the grey zone was 11% (8-14%, p= 0.0001 for pairwise comparisons with other models).

After the exclusion of the study by Dajti et al. [9], where the Baveno VII-SSM combined models were first developed, the diagnostic performance of all algorithms was evaluated in this "validation" cohort and was comparable to that of the *"main cohort":* good for Baveno VII and Baveno VII-SSM dual cut-off model, suboptimal for Baveno VII-SSM single cut-off model in terms of CSPH ruling-out (NPV 83%, 95%-CI: 62-93%), but not ruling-in CSPH (PPV 93%, 95%-CI: 86-97%). Moreover, **Table 3** summarises the sensitivity analysis according to the patient's etiology and BMI. All three algorithms were validated with good performance (all NPV and PPV >90%) in patients with viral etiology, and the grey zone reduced progressively across the three algorithms: 53% (48-58%) vs 33% (28-38%) vs 10 (8-15%) (**see appendix p11**). Otherwise, in patients with non-viral etiology, the Baveno VII-SSM 40 kPa model showed low NPV (67%, 95%-CI: 55-78%), whereas all other criteria were validated (Baveno VII alone, Baveno VII-SSM with a dual cut-off model, Baveno VII-SSM 40 kPa for ruling-in CSPH). Similar findings were also observed in non-obese patients, while in obese patients, all three algorithms could rule-in CSPH with a PPV >90%, but none could safely rule-out CSPH (NPV <90%); however, given few patients included in this subgroup analysis (n=69), these data should be interpreted with caution.

We also evaluated the "ideal" cohort (n=358), where the accuracy of SSM and SSM-based nomogram for the diagnosis of CSPH was higher than that of LSM and the ANTICIPATE models, respectively (**see appendix p10**). Moreover, the diagnostic performance of all three algorithms measured (sensitivity, specificity, NPV, and PPV) was adequate (>90%).

Finally, we performed a leave-one-out meta-analysis to check for outliers, but no study was deemed as particularly influential (**see appendix p12**). The NPV of the Baveno VII-SSM 40 kPa model was the only parameter that showed some variability, dropping to 80% after excluding a

study that included exclusively patients with viral etiology.[10] We did not perform sensitivity analyses for study design or size, as only one study[9] had >100 patients and a retrospective design.

Of the 397 patients with available HVPG, we included 225 patients from five studies [17,19,22,24,25] in the *"main cohort"* of 2D-SWE SSI Aixplorer (Supersonic Imagine, Aix-en-Provence, France) (**see appendix p28**). The patient's characteristics and the correlation between elastography and HVPG are summarised in the Appendix **(see appendix p13-14)**, respectively.

Since no specific algorithms are available for 2D-SWE, we tested the same three models derived for TE, except for the LSM cut-off of 14 kPa, to rule-out CSPH. The modified Baveno VII and both combined Baveno VII-SSM models showed excellent performance in ruling-in CSPH, with specificity and PPV >90% in both the *"main cohort*" and the *"cACLD cohort"* (**Table 4, appendix p29-31**); all models showed suboptimal NPV (<90%) for ruling-out CSPH.

The sensitivity analysis by leave-one-out meta-analysis showed that one study [17] was particularly influential, as its exclusion led to an improvement in the diagnostic performance of the three algorithms, with all performance measures (sensitivity/NPV for ruling-out, specificity/PPV for ruling-in CSPH) being above 90% (**see appendix p15**). This study, [17] which accounted for almost half of the 2D-SWE cohort, also included patients with previous decompensation, and showed an uncertain correlation between SSM and HVPG (r=0.070, 95%-CI: -0.140, 0.274; p=0.514), whereas it was moderate in the other studies (r=0.480, 95%-CI: 0.339, 0.599; p<0.0001). We did not perform sensitivity analyses neither for study size, as no study included >100 patients, nor for study design, because only one study [25] was retrospective.

Finally, we developed two logistic models for estimating the individual risk of CSPH, namely the ANTICIPATE-SSI and LPS-SSI, which showed good discrimination and calibration (**see appendix p6, p16, p32-33**).

We considered 112 compensated cirrhotic patients from four studies [20,27,28,30] with available SSM evaluated by p-SWE ElastPQ® (Philips Healthcare, Bothell, WA) (**see appendix p17, p34)**. However, i) the correlation between SSM and HVPG was weak (0.179, 95%-CI: 0.006, 0.353), whereas the correlation between LSM and HVPG was uncertain (**see appendix p18**); ii) the AUROC for the diagnosis of CSPH was suboptimal (<0.70 for both parameters; iii) the median prevalence of CSPH in the four cohorts was 76-91%. Thus, we decided that this cohort was suboptimal and insufficient to evaluate and eventually develop new algorithms for the diagnosis of CSPH. Similarly, 65 patients from two abstracts[26,31] were included in the cohort of the patients with SSM by p-SWE ARFI (Acoustic Radiation Force Impulse, Siemens, Erlangen, Germany) (**see appendix p17,p35**). The correlation between SSM and HVPG was moderate and its accuracy for predicting CSPH was good and apparently higher than that of LSM (**see appendix p18**); however, the limited number of studies precluded further analyses.

Discussion

Our individual patient meta-analysis established that non-invasive algorithms, including spleen stiffness by transient elastography, are safe and perform better than the Baveno VII Criteria alone in diagnosing CSPH. Adding the SSM with a cut-off of 40 and 50 kPa markedly increased the number of patients with CSPH that were included in the rule-in zone and, therefore, could be started on non-selective beta-blockers, maintaining a robust PPV >90% in all sensitivity analyses according to etiology, body mass index, and study centre. We also developed an algorithm and nomogram for the diagnosis of CSPH based on LSM and SSM evaluated by 2D-SWE.

In the TE cohort, the Baveno VII Criteria (LSM≤15 kPa + PLT≥150x10^9/L) and SSM<21 kPa cut-off were both validated for ruling-out CSPH in our study, with a similar rate of patients included in this zone (10% vs 11%). Instead, the SSM<40 kPa cut-off markedly increased the rate of patients in the rule-out zone (10% vs 25%), but it was accurate (NPV >90%) only in patients with viral etiology of liver disease.

Regarding CSPH rule-in, all three algorithms consistently showed a PPV>90% in the main and the sensitivity analyses according to etiology, BMI, and centre, and therefore can be safely recommended to rule-in CSPH. However, the rate of patients in the rule-in zone progressive increased across the three algorithms (42% vs 57% vs 66%). More importantly, the percentage of patients with CSPH that would have been correctly identified as high-risk (i.e., included in the rule-in zone) and started on carvedilol based on non-invasive algorithms significantly increased in the SSM-based models (57% vs 76% vs 88%). Therefore, the rule-in criteria of the combined Baveno VII-SSM 40 kPa model are the most efficient for identifying patients with CSPH.

The grey zone was progressively and significantly reduced in the SSM-based algorithms (48% vs 32% vs 9%), which was also valid in the "cACLD" cohort. This remarkable reduction in the grey zone could meaningfully improve the applicability of non-invasive algorithms in routine clinical practice for risk stratification and hepatic decompensation prevention.

Overall, the Baveno VII algorithm is validated in its largest cohort to date, as it showed robust accuracy in both ruling-out and ruling-in CSPH. However, its clinical application may be limited, as half of the patients have indeterminate results (grey zone), and less than 60% of the patients with CSPH (i.e., candidates for treatment with carvedilol) are included in the rule-in zone. Including SSM in the algorithms significantly reduced the rate of patients with indeterminate results and increased the number of patients with CSPH correctly included in the rule-in zone. In particular, the Baveno VII-SSM with dual cut-off (21-50 kPa) is validated for the first time and showed robust performance across all sensitivity analyses; both sensitivity/NPV and specificity/PPV were >90% in the "cACLD cohort". The Baveno VII-SSM 40 kPa model is a powerful and safe tool to rule-in CSPH in all etiologies and maximise the number of patients with CSPH that could start treatment with carvedilol based on non-invasive tests. In patients with viral etiology, this model can also safely rule-out CSPH and safely reduce the grey one to <12%. However, its rule-out ability was lower in non-viral etiology as the NPV falls <90% in this category, so further studies are warranted before applying this criterion to these patients to rule-out CSPH.

In the 2D-SWE (SSI Aixplorer) cohort, we developed new algorithms based on LSM and SSM for the diagnosis of CSPH, using cut-offs similar to those proposed for TE in a large cohort of mixed etiology (only 40% viral). LSM >25 kPa and the model including SSM >40 kPa could safely rule-

in CSPH. On the other hand, LSM ≤14 kPa + PLT <150x10^9/L, and the model, including SSM <21 kPa, showed an NPV >90% only in sensitivity analysis after the exclusion of an influential study [17]. We also developed two nomograms based on LSM, PLT, and SSM to estimate CSPH risk in each patient (ANTICIPATE-SSI and LPS-SSI models).

As for p-SWE by ElastPQ and Virtual Touch Quantification, the data collected were insufficient to develop new diagnostic algorithms based on p-SWE, despite SSM-ARFI showing promising accuracy for CSPH diagnosis.

To our knowledge, this is the first IPD meta-analysis to evaluate the diagnostic accuracy of SSM for the diagnosis of CSPH in compensated cirrhotic patients. Many meta-analyses have been performed on this topic [11,12,32,33] demonstrates an excellent accuracy of SSM. However, the clinical applicability was always questioned due to the heterogeneity in elastography techniques, cut-offs used, and inclusion of decompensated patients. The IPD approach provided the following strength points to our meta-analysis, among others: i) exclusion of patients either with LSM<10 kPa (negligible risk of decompensation) or with decompensation at the time of elastography (who have CSPH per definition); ii) creation of a subpopulation of definite cACLD after exclusion of patients with a previous episode of decompensation or no data on this outcome; iii) validation of previously proposed cut-offs for TE [1,9] in the largest to date cohort (600 patients), overcoming the issue of heterogeneous cut-offs in previous studies; iv) evaluation of the diagnostic accuracy in subgroups according to liver disease etiology, presence of obesity, or study centre, confirming the robustness of the evaluated algorithms. Finally, another strength of our meta-analysis is that we performed a systematic literature search without language or type of publication restrictions.

A possible weakness of our study is that four study groups did not provide individual patient data, so not all eligible patients were included in the present meta-analysis. We did not dispose of patients' data with available HVPG but unfeasible SSM for all studies, so an intention-to-diagnose approach was impossible. However, the median rate of SSM failure by TE was acceptable (16%, 95%-CI: 7-24%). Viral etiology remained the most common cause of liver disease among the included patients. Despite the validation of our algorithms also in patients with non-viral etiology, future studies should specifically address the diagnostic performance of these tests in patients with metabolic dysfunction-associated liver disease and obesity. Regarding TE evaluation, no study used the novel spleen-dedicated module (100 Hz), so studies using this device are awaited. As for 2D-SWE, we developed algorithms and nomograms in the largest cohort to date, but they need to be validated by future studies. Due to the population characteristics and the limited number of patients, we could not evaluate the diagnostic performance of SSM by p-SWE, so their use for CSPH in clinical practice still needs to be improved. Finally, another area for improvement of the meta-analysis is that the results are based on eligible studies with an overall acceptable, but not optimal, methodological quality. However, we mitigated this limit by using an IPD approach to the analysis that allowed us to exclude decompensated patients for the definite cACLD cohort.

The Baveno VII criteria for the diagnosis of CSPH were validated in a large cohort but showed suboptimal clinical applicability due to the high number of patients with indeterminate results (up to 50%). The inclusion of the SSM in algorithms significantly reduced the rate of patients in the grey zone and increased the number of patients with CSPH that were correctly included in the rule-in zone, as almost 90% of the patients with CSPH fell under this category in the Baveno VII-SSM 40 kPa model while maintaining a PPV >90% in all analyses. Therefore, the combined Baveno VII-SSM models are excellent non-invasive algorithms to identify and maximise the number of

patients who could be started on carvedilol, a treatment that could improve their survival [6]. Further studies are required to evaluate the diagnostic performance of these models in specific etiologies, validate the diagnostic algorithms for 2D-SWE, and especially validate the use of SSM measured with the novel spleen-dedicated module (100 Hz).

The Spleen Stiffness – IPD-MA Study Group: Luigina Vanessa Alemanni (Gastroenterology and Digestive Endoscopy Unit, Forlì-Cesena Hospitals, AUSL Romagna, Italy; University of Bologna, Italy), Amanda Vestito (IRCCS AOUBO, Bologna, Italy), Matteo Renzulli (IRCCS AOUBO, ERN RARE-LIVER, Bologna, Italy), Francesco Azzaroli (IRCCS AOUBO, ERN RARE-LIVER, Bologna, Italy; DIMEC, University of Bologna, Italy.), Luigi Colecchia (University of Bologna, Italy), Laurent Castera (Department of Hepatology, Hospital Beaujon, INSERM, Université Paris Cité, Clichy, France.), Maxime Ronot (Université Paris Cité, France & Service de Radiologie, Hôpital Beaujon, Clichy, France.), Monica Platon-Lupsor (Hepatology Department, "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, "luliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania), Oana Nicoara-Farcau (Hepatology Department, "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, "luliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania), Mina Ignat (Hepatology Department, "Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, "luliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania), Yoichi Hias (Department of Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan), Anna Fichera (Section of Gastroenterology and Hepatology, University of Palermo, Palermo, Italy.), Chin Chin Ooi (Radiography Department, Allied Health Division, Singapore General Hospital, Singapore, Singapore), Alberto Borghi (Internal Medicine Department, Faenza Hospital, Faenza, Italy), David Bauer (Department of Internal Medicine III, Vienna Hepatic Hemodynamic Lab, Medical University of Vienna, Vienna, Austria), Georg Semmler (Department of Internal Medicine III, Vienna Hepatic Hemodynamic Lab, Medical University of Vienna, Vienna, Austria.), Mattias Mandorfer (Department of Internal Medicine III, Vienna Hepatic Hemodynamic Lab, Medical University of Vienna, Vienna, Austria), José Luis Calleja (Liver Unit, Hospital Universitario Puerta De Hierro Majadahonda, Universidad Autònoma de Madrid, Madrid, Spain.), Omar Elshaarawy (Hepatology and Gastroenterology Department, National Liver Institute, Menoufia University, Shebeen El-Kom, Egypt; Department of Internal Medicine, Salem Medical

Center and Center for Alcohol Research and Liver Disease, University of Heidelberg, Heidelberg, Germany), Dante Romagnoli (Department of Medical Specialities, University Hospital of Modena, University of Modena & Reggio Emilia, Modena, Italy).

Contributors

ED, FR, GM, DF, AB, AgC, AnC were responsible for study concept and design, literature search, collecting data from participating centres, data review, verification and analysis, interpretation of data, drafting of the manuscript, statistical analysis. The remaining authors were responsible for obtaining original data, coding and providing data, interpretation of data, and critical revision of the manuscript. All authors critically revised the manuscript and approved of the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Because this is an individual patient data meta-analysis, data cannot be provided without the consent of all parties involved. Individual datasets should be requested from the authors of the relevant papers.

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Legend of figures and tables

Figure 1 – PRISMA flowchart of literature search.

TIPS: transjugular intrahepatic portosystemic shunt.**Figure 2 –** Forest plot of summary negative and positive predictive values for CSPH diagnosis according to (A) Baveno VII criteria; (B) Baveno VII-SSM (dual cut-off) algorithm; (C) Baveno VII-SSM (single cut-off) algorithm. The Clopper-Pearson (exact) binominal 95%-CI is presented in this figure.

CI: confidence interval; CSPH: clinically significant portal hypertension; NPV: negative predictive value, PPV: positive predictive value; SSM: spleen stiffness measurement.

Figure 3 – A) Summary report of the diagnostic performance of the Baveno VII and the combined Baveno VII-SSM algorithms for diagnosing CSPH; B) Rate of patients with CSPH included in the rule-in zone of the different diagnostic algorithms evaluated.

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