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

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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 systematically researched databases for studies reporting hepatic venous pressure gradient and SSM in adult patients and collected their IPD. 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, SS>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.

Findings: Seventeen studies (1245 patients) were included in the meta-analysis. In the transient elastography cohort (600 patients), the Baveno VII-SSM dual cut-off model was validated, showing adequate (>90%) negative and positive predictive values (PPV) in the whole cohort and after sensitivity analyses. The Baveno VII-SSM single-cut-off model was the best-performing model in ruling-in CSPH while safely ruling-out CSPH only in viral etiology. The SSM-based algorithms reduced the rate of patients with indeterminate results from 48% to less than 10%. These algorithms showed adequate performance also in the two-dimensional-shear-wave elastography cohort. The current data available was inadequate to evaluate the performance of SSM assessed by point-shear-wave elastography.

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

The meta-analysis was 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).

Study design, aim and eligibility criteria.

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 any either transient elastography (TE, 50 Hz module, FibroScan; Echosens, France), two-dimensional shear wave elastography (2D-SWE) or point shear wave elastography (p-SWE). 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.

Search strategy

We searched MEDLINE via PubMed, Ovid Embase, Scopus, and the Cochrane Library databases up to the 30th of June 2020, and an update was done up to December 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 **Supplemental Material 1**. 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 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, laboratory, elastography, endoscopy, and hemodynamic characteristics, 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 (**Supplemental Material 2**). 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.

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, we created 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 (**Supplementary Material 3**); 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].

Statistical analysis

At baseline, categorical data at baseline were expressed as numbers (percentages), and continuous variables as medians (interquartile range); for group comparisons of categorical and continuous variables, the Chi-square test or Mann-Whitney test and McNemar's test were used, as appropriate. Linear correlation between non-invasive tests and HVPG was evaluated with the Pearson correlation coefficient (r).

An IPD meta-analysis assessing the performance of the diagnostic algorithms was performed using the raw data from each study, using a two-stage approach to the analysis. First, each individual study was analysed independently, and the 2x2 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. 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); 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. 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, 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). We performed leave-one-out meta-analyses to check for influential studies.

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).

Results

The electronic search identified 863 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 of the remaining 21 (19%) 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 **Supplemental Materials 4-5.**

Diagnostic performance of SSM evaluated by TE

After applying the exclusion criteria, 600 patients from six studies were included in the main cohort (**Supplemental Figure 1**) of TE (FibroScan, Echosens, Paris, France). The median age of the included patients was 58 (49-68) years, and they were mostly male (69%) and with viral etiology

(77%). The median HVPG value was 12 (9-17) 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 **Supplemental Material 6.** 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.

Diagnostic performance of the algorithms in the "*main cohort."*

The Baveno VII criteria were validated in the "*main cohort"* (**Table 2, Figure 2, Supplemental Figure 2A**). For the CSPH ruling-out, the summary sensitivity was 100% (95%-CI: 70-100%), and the NPV was 100%. Regarding the CSPH ruling-in, the summary specificity was 94% (95%-CI: 87-97%), and the PPV was 95%. However, 48% 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, Supplemental Figure 2B**). These criteria could accurately rule-out CSPH (summary sensitivity 100%, 95%-CI: 91-100%, NPV 98%), but no superiority compared to Baveno VII criteria alone (9.7% vs 11.2%, p= *NS*) was observed. CSPH could be ruled-in with a summary specificity of 89% (95%-CI: 84-98%) and PPV of 93%; the rate of patients in the "grey zone" was significantly reduced to 32% (*$p<0.0001$*) compared to the Baveno VII model alone **(Figure 3)**.

The Baveno VII-SSM model with a single cut-off (40 kPa) (**Figure 2C, Supplemental Figure 2C**) showed good summary sensitivity (93%, 95%-CI: 85-97%) but suboptimal NPV (85%) 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%. The "grey zone" was minimised to 9%, drastically and significantly lower compared to the other two algorithms (*p<0.0001*) **(Figure 3)**.

Diagnostic performance of the algorithms in the "cACLD cohort".

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 (**Supplemental Figure 3A-B, 4A-B**). The rate of patients in the "grey zone" was again significantly lower in the Baveno VII-SSM model than in Baveno VII alone (*54% vs 38%, p=0.0001*). As for the Baveno VII-SSM model with a single cut-off (**Supplemental Figure 3C,4C)**, the rule-out performance was better than in the main cohort, with borderline NPV (88%), whereas the PPV for CSPH rule-in was confirmed >90%; the grey zone was 11%, significantly lower than in the other models (*p=0.0001*).

Sensitivity analyses

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":* excellent 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%), but not ruling-in CSPH (PPV 93%). 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; otherwise, in patients with non-viral etiology, the Baveno VII-SSM 40 kPa model showed low NPV (67%), 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 significantly higher than that of LSM and the ANTICIPATE models, respectively (**Supplemental Material 6**). Moreover, the diagnostic performance of all three algorithms measured (sensitivity, specificity, NPV, and PPV) was excellent (>90%).

Finally, we performed a leave-one-out meta-analysis to check for outliers, but no study was deemed as particularly influential (**Supplemental Material 7**). 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 exclusive patients with viral etiology.[10]

Diagnostic performance of SSM evaluated by 2D-SWE-SSI

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) (**Supplemental Figure 5**). The patient's characteristics and the correlation between elastography and HVPG are summarised in **Supplemental Materials 8 & 9**, 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, Supplemental Figure 6A-C**); 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% (**Supplemental Material 10**). This study, [17] which accounted for almost half of the 2D-SWE cohort, also included patients with previous decompensation, and showed a non-significant correlation between SSM and HVPG (r=0.070, p=NS), whereas it was moderate in the other studies (r=0.480, p<0.0001).

Finally, we developed two logistic models for estimating the individual risk of CSPH, namely the ANTICIPATE-SSI and LPS-SSI, which showed excellent discrimination and calibration (**Supplemental Material 11 and Supplemental Figure 7A-B**).

Diagnostic performance of SSM evaluated by p-SWE

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) (**Supplemental Material 12, Supplemental Figure 8)**. However, i) the correlation between SSM and HVPG was weak (0.179), whereas the correlation between LSM and HVPG was non-significant (**Supplemental Material 12**); 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 90%. 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) (**Supplemental Material 12, Supplemental Figure 9**). Even though the correlation between SSM and HVPG was moderate and its accuracy for predicting CSPH was excellent and significantly higher than that of LSM (**Supplemental Material 13**); 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 significantly 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.

Transient elastography

CSPH rule-out

The Baveno VII Criteria (LSM≤15 kPa + PLT≥150x10^9/L) and SSM<21 kPa cut-off were both validated in our study, with a similar rate of patients included in the rule-out zone (9% vs 11%). Instead, the SSM<40 kPa cut-off markedly increased the rate of patients in the rule-out zone (9% vs 24%), but it was accurate (NPV >90%) only in patients with viral etiology of liver disease.

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 (45% 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.

Grey Zone

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 significantly improve the applicability of non-invasive algorithms in routine clinical practice for risk stratification and hepatic decompensation prevention.

Overall diagnostic performance

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 drastically reduce the grey zone to <12%. However, its rule-out ability was lower in non-viral etiology as the NPV falls <90% in this cater, so further studies are warranted before applying this criterion in this category of patients to rule-out CSPH.

Other elastography techniques

2D-SWE by SSI Aixplorer

We developed new algorithms based on LSM and SSM evaluated with 2D-SWE 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).

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.

Strengths and weaknesses of the study

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. Moreover, we did not dispose of patients' data with available HVPG but unfeasible SSM for all studies, so an intention-to-diagnose approach was impossible. Moreover, the heterogeneity among studies was low for most analyses. 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 and perform a sensitivity analysis in the definite cACLD cohort.

Conclusion and implications

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).

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Legend of figures and tables

Figure 1 – PRISMA flowchart of literature search.

Figure 2 – Forest plot of summary negative (NPV) and positive (PPV) 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.

Figure 3 – Summary report of the diagnostic performance of the Baveno VII and the combined Baveno VII-SSM algorithms for diagnosing CSPH.