This item is the archived peer-reviewed author-version of:

Shear-wave elastography of the liver and spleen identifies clinically significant portal hypertension : a prospective multicentre study

Reference:

Jansen Christian, Bogs Christopher, Verlinden Wim, Thiele Maja, Vanwolleghem Thomas, Vonghia Luisa, Francque Sven, Moeller Philipp, Goertzen Jan, Lehmann Jennifer,- Shear-wave elastography of the liver and spleen identifies clinically significant portal hypertension : a prospective multicentre study
Liver international - ISSN 1478-3223 - 37:3(2017), p. 396-405
Full text (Publisher's DOI): <https://doi.org/10.1111/LIV.13243>
To cite this reference: <http://hdl.handle.net/10067/1411080151162165141>

Shear-wave Elastography of the liver and spleen identifies clinically significant portal hypertension: a prospective multi-center study

Short title: Liver and Spleen SWE identifies CSPH

Christian Jansen^{1*}, Christopher Bogs^{1*}, Wim Verlinden², Maja Thiele³, Philipp Möller¹, Jan Görtzen¹, Jennifer Lehmann¹, Thomas Vanwolleghe², Luisa Vonghia², Michael Praktiknjo¹, Johannes Chang¹, Aleksander Krag³, Christian P. Strassburg¹, Sven Francque²⁺, Jonel Trebicka^{1,3+}

¹Department of Internal Medicine I, University of Bonn, Germany.

²Department of Gastroenterology and Hepatology, University Hospital Antwerp, Belgium.

³Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark.

* and + contributed equally to this work.

Key points:

- **Shear-wave Elastography of liver and spleen correlates with portal pressure and complications**
- **Shear-wave Elastography of spleen rules in and rules out clinically significant portal hypertension with similar accuracy as Shear-wave Elastography of liver**
- **Sequential use of Shear-wave Elastography of the liver and spleen predicts with high accuracy the absence or presence of CSPH,**
- **The patients not full-filling the criteria to rule-in or rule-out CSPH should undergo invasive HVP measurement**

Correspondence: Prof. Jonel Trebicka, MD, PhD. Department of Internal Medicine I, University of Bonn, Sigmund-Freud Str. 25, D-53105 Bonn, Germany. jonel.trebicka@ukb.uni-bonn.de, Tel: +49 228 287 15507

Electronic word count: 4880

Figures: 5

Tables: 3

Supplemental Figures: 3

Supplemental Tables: 4

Abbreviations:

Child	Child-Turcotte-Pugh
CRP	C-reactive protein
CSPH	clinically significant portal hypertension
γ T	γ - glutamyltransferase
HVPG	hepatic venous pressure gradient
INR	international normalized ratio
MELD	model for end-stage liver disease
NASH	non-alcoholic steatohepatitis
r_s	Spearman's rank-order correlation
L-SWE	liver-Shear-wave Elastography
S-SWE	spleen-Shear-wave Elastography
TE	transient Elastography

Disclosures: All authors have nothing to disclosure.

Author contributions:

Christian Jansen: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis,

Christopher Bogs: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis,

Wim Verlinden: Acquisition of data; analysis and interpretation of data; statistical analysis,

Maja Thiele: Acquisition of data; analysis and interpretation of data; statistical analysis,

Philipp Möller: Acquisition of data; analysis and interpretation of data; statistical analysis,

Jan Görtzen: Acquisition of data; analysis and interpretation of data; statistical analysis,

Jennifer Lehmann: Acquisition of data; analysis and interpretation of data; statistical analysis,

Thomas Vanwolleggem: Acquisition of data; analysis and interpretation of data; statistical analysis,

Luisa Vonghia: Acquisition of data; analysis and interpretation of data; statistical analysis,

Michael Praktijnjo: Acquisition of data; analysis and interpretation of data; statistical analysis,

Johannes Chang: Acquisition of data; analysis and interpretation of data; statistical analysis,

Aleksander Krag: Acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content,

Christian P. Strassburg: Critical revision of the manuscript for important intellectual content, administrative, technical and material support,

Sven Francque: Study concept and design; acquisition of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content, administrative, technical and material support,

Jonel Trebicka: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content, obtained funding; administrative, technical and material support; study supervision,

Grant support: This study was supported by grants from the Deutsche Forschungsgemeinschaft (SFB TRR57 to P18), the H. J. & W. Hector Stiftung (M60.2), Ernst-Bertha-Grimmke-Stiftung (6/15) and European Union's Horizon 2020 research and innovation programme (No 668031). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background and aims: Clinically significant portal hypertension (CSPH) is associated with severe complications and decompensation of liver cirrhosis. Liver stiffness measured either by transient elastography (TE) or Shear-wave elastography (SWE) and spleen stiffness by TE might be helpful in the diagnosis of CSPH. We recently showed the algorithm to rule-out CSPH by using sequential liver- (L-SWE) and spleen-Shear-wave elastography (S-SWE). This study investigated the diagnostic value of S-SWE for diagnosis of CSPH.

Methods: 158 cirrhotic patients with pressure gradient measurements were included into this prospective multicenter study. L-SWE was measured in 155 patients, S-SWE in 112 patients, and both in 109 patients.

Results: L-SWE and S-SWE correlated with clinical events and decompensation. SWE of liver and spleen revealed strong correlations with the pressure gradient and to differentiate between patients with and without CSPH. The best cut-off values were 24.6kPa:L-SWE and 26.3kPa:S-SWE. $L-SWE \leq 16.0 \text{ kPa}$ and $S-SWE \leq 21.7 \text{ kPa}$ were able to rule-out CSPH. Cut-off values of $L-SWE > 29.5 \text{ kPa}$ and $S-SWE > 35.6 \text{ kPa}$ were able to rule-in CSPH (specificity > 92%). Patients with a $L-SWE > 38.0 \text{ kPa}$ had likely CSPH. In patients with $L-SWE \leq 38.0 \text{ kPa}$, a $S-SWE > 27.9 \text{ kPa}$ ruled in CSPH. This algorithm has a sensitivity of 89.2% and a specificity of 91.4% to rule-in CSPH. Patients not full-filling these criteria should undergo HVPg-measurement.

Conclusions: Liver and spleen SWE correlates with portal pressure and can both be used as a non-invasive method to suggest CSPH. Even though external validation is still missing, these algorithms to rule-out and rule-in CSPH using sequential SWE of liver and spleen might change the clinical practice.

Words: 249

Key words: liver; spleen; SWE; portal hypertension

Introduction

Chronic liver injury of different etiologies leads to hepatic fibrosis, which can progress to cirrhosis and end stage liver disease ¹. Decompensation events such as variceal bleeding, refractory ascites and hepato-renal syndrome, mainly related to portal hypertension are responsible for increased morbidity and mortality in patients with liver cirrhosis ^{2,3}. Portal hypertensive complications are likely to occur when the hepatic venous pressure gradient (HVPG) is higher than 10 mmHg, which defines clinically significant portal hypertension (CSPH) ^{4,5}. Invasive measurement of the HVPG is currently considered the gold standard for assessment of portal hypertension, as well as for the evaluation of the therapeutic response to therapy of portal hypertension ^{3,4,6,7}. However, invasiveness, and low availability outside liver units diminish the applicability of HVPG measurements and reinforce the search for noninvasive tools to diagnose CSPH ⁸. The Baveno VI consensus meeting implemented transient elastography (TE) as a tool to rule-in CSPH in viral etiologies and to-rule out varices (need of screening endoscopy for varices ⁹).

Recent studies introduced Shear-wave elastography of the liver (L-SWE) as a promising tool to diagnose portal hypertension ¹⁰⁻¹². These studies find good diagnostic accuracy of L-SWE with specificity and sensitivity ranging between 80% and 90%, which was partly better compared head-to-head with TE. Using two different cut-offs to rule-in and rule-out CSPH, sensitivity and specificity could be increased up to more than 90% ¹¹. However, a significant portion of patients (more than 30%) did fit neither in the rule-in nor in the rule-out group ¹¹. Moreover, the added value of spleen-SWE (S-SWE) was not explored in these studies, probably due to low number of patients receiving S-SWE and the focus on comparison of TE with SWE ^{10,11}. We recently showed that sequential use of L-SWE and S-SWE rules out CSPH with a sensitivity of 98.6% in patients with L-SWE lower 16 kPa ¹³.

However, the proper value of S-SWE in diagnosis of CSPH is unknown to date. In this prospective multi-center study we aimed to compare the diagnostic accuracy of liver and spleen stiffness measured by SWE to diagnose CSPH.

Patients and Methods

Patients and data collection

This prospective multicenter study included 158 patients of which 106 patients had CSPH. Patients were enrolled between September 2013 and May 2015 in the Department of Internal Medicine I, University of Bonn, Bonn, Germany, in the Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark and in the Department of Gastroenterology and Hepatology, University Hospital Antwerp, Antwerp, Belgium. Inclusion criteria were liver cirrhosis, indication for portal pressure gradient measurement, SWE measurements within 48 hours before or after pressure gradient measurement. Patients with cardiac failure were not included into this study. Exclusion criteria were absence of indication for pressure gradient measurement, not accurate SWE measurement (see below), time span between SWE measurement and pressure gradient measurement longer than 48 hour. Healthy subjects were not included in the study. The study population has not been previously used for any other survey. Recruitment overview is presented in Figure 1. The patients gave their written consent for all procedures and the local ethics committee of the University of Bonn (No. 121/14) approved the study in accordance with the Declaration of Helsinki, as well as for Antwerp (15/13/135) and Odense (51872). General clinical and biochemical characteristics are shown in table 1 and supplementary tables 1 and 2 for each center.

SWE procedure

SWE was performed by using the Aixplorer US system (Supersonic Imagine SA; Aixplorer, Aix-en-Provence, France). SWE measurements were performed by three physicians experienced in abdominal ultrasound with an abdominal 3.5-MHz curved-array transducer. Patients were placed in supine position with the right arm or left arm in maximal abduction and were requested to hold his/her breath for about 5 seconds. SWE measurements were performed as previously described^{11,14} in three different regions of interest in the liver and the spleen in fasting state. A SWE measurement was accurate when it fulfilled following criteria: (1) temporal stability of the selected liver area for at least 3 seconds before measurement, (2) two-dimensional quality confirmed by a homogenous color in the region of interest, (3) a measurement region of at least 10 mm and (4) an acquisition depth of ≤ 5.6 cm. Up

to three separate measurements were performed and results are reported as the mean of the total number of valid measurements.

Measurement of the portal systemic pressure gradient

In 109 patients, HVPG data were acquired as formerly described^{4,15}. The right internal jugular was punctured under local anesthesia and ultrasound guidance. Under continuous radiological control, a balloon catheter was placed in a major hepatic vein. To calculate HVPG, three repeated measurements of free and wedged hepatic venous pressure were performed.

In 49 patients pressure measurements were performed during insertion of a transjugular intrahepatic portosystemic shunt. A pressure transducer system (Combitrans, Braun Melsung, Germany) and a multichannel monitor (Sirecust, Siemens, Germany) were used to measure portal and hepatic venous pressure invasively, and three repeated measurements were performed. The difference between these pressures was defined as the portal systemic pressure gradient. Arterial pressure and heart rate were monitored non-invasively. To simplify understanding, we used the term pressure gradient for HVPG and portal systemic pressure gradient.

Statistical analysis

In our study, the non-parametric Wilcoxon test was used to compare paired data, the Mann-Whitney test for unpaired comparisons and the Kruskal-Wallis test if more than two groups were compared. Correlations were analyzed with the Spearman correlation coefficient. Analysis of the area under receiver operating characteristics curve (AUROC) was used to determine potential cut-off-values for predicting pressure gradient values. To detecting differences between areas under two ROC curves, the adapted sample size formula was used as previously described¹⁶. Data are presented as mean $\pm$ standard deviation or standard error of the mean (SEM) and ranges unless otherwise declared. Univariate and multivariate analysis provided information about independent predictors of CSPH. Logistic regression analysis was used for the multifactorial analysis of predictive variables regarding CSPH. P-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc. Chicago, IL, USA).

Results

Clinical, biochemical and hemodynamic characteristics

The patients included in the study were predominantly male (61.4%) with a mean age of 56 years and a range of 18 – 80 years. The etiology of chronic liver disease was alcohol in the majority of the patients (56%), non-alcoholic steatohepatitis (NASH) in 27 patients (17%), chronic viral hepatitis in 12 patients (8%) and other etiologies in the rest of patients (19%). Mean Child-Pugh score was 7 with a majority of patients in Child-Pugh class A (62.7%), 45 patients with Child B and 14 with Child C liver cirrhosis. The mean MELD score was 10 points, with a range of 6–28 points. Mild ascites was present in 25 patients and severe ascites in 43 patients, while 90 had no ascites. Mean spleen size was 13.2 cm, reaching from 5.2 – 22cm (Table 1).

Correlation of SWE with CSPH

Liver stiffness by SWE was measured in 155 patients, spleen stiffness in 112 patients, and 109 patients received both L-SWE and S-SWE (Figure 1). Reasons for the missing S-SWE values were technical failure in 18.8% of the cases (n=24) and missing S-SWE data from one center (n=19). Significant correlations were observed between the pressure gradient and L-SWE, as well as S-SWE ($r_s=0.626$, $p<0.001$; $r_s=0.606$, $p<0.001$, respectively; Figure 2A+B).

Furthermore, L-SWE was significantly higher in patients with CSPH compared to those without (35.2 kPa vs. 15.5 kPa; $p<0.001$; Table 2; Figure 2C). Similarly, S-SWE was also significantly higher in patients with CSPH (42.3 kPa vs. 22.2 kPa; $p<0.001$; Supplemental Table 3; Figure 2D).

Association of SWE of liver and spleen with severity of liver disease

Interestingly, L-SWE was associated with spleen size, ascites, Child score and MELD score, while S-SWE was associated only with MELD Score, Child Score and ascites (Supplemental Figure 1A-D).

L-SWE was further correlated with platelet count, albumin, bilirubin, INR, γ Gt, AST, alkaline phosphatase and inversely with cholinesterase and ALT. S-SWE was correlated with platelet count, albumin, bilirubin, creatinine, INR and inversely with cholinesterase and ALT. Detailed correlations are presented in table 2.

Furthermore, we investigated the previously described ratio of L-SWE/Spleen size/Platelet count for transient elastography¹⁷. Interestingly, this ratio showed high AUCs ranging around 0.90 for the diagnosis of CSPH, which were not significantly different to the SWE technique (Supplemental Figure 2).

Analysis of quality criteria

The median of the SD/mean ratio was 0.18, which is higher than the recommended range of <0.1¹⁸. Therefore, ROC analyses were performed to detect CSPH after stratifying the patients in different classes of SD/mean ratio <0.1, <0.2 and <0.3. Indeed, the best AUCs were found in the SD/mean ratio <0.1 cohort. However, the AUCs of <0.2 and <0.3 were almost equal (Supplemental Figure 3).

Univariate and multivariate analysis using logistic regression

In univariate analysis with logistic regression we observed that the following parameters indicate the presence of CSPH: Meld Score, spleen size, platelet count, Albumin, L- and S-SWE. When applying these parameters to the multivariate regression analysis, L-SWE, S-SWE and platelet count were identified as independent predictors of CSPH (Supplemental Table 4 A+B).

Cut-off values to diagnose portal hypertension

ROC analyses were performed to assess the diagnostic accuracy of SWE measurements to identify patients with a pressure gradient >5 mmHg, indicating elevated portal pressure, >10 mmHg for CSPH and >12 mmHg, indicating respectively increased risk for variceal development and bleeding⁴. Liver and spleen stiffness by SWE revealed a highly predictive value for a pressure gradient > 5 mmHg with AUC of 0.89, $p < 0.001$ for L-SWE (Figure 3A) and AUC of 0.90, $p < 0.001$ for S-SWE (Figure 3B), as well as and cut-off values of 14.6 kPa for L-SWE and 24.0 kPa for S-SWE. The AUC of L-SWE for the diagnosis of CSPH was 0.86 ($p < 0.001$; Table 3; Figure 3C). The AUC of S-SWE for the diagnosis of CSPH was 0.84 ($p < 0.001$; Table 3; Figure 3D). The cut-off values that maximized the sum of sensitivity and specificity for the diagnosis of CSPH were 24.6 kPa for L-SWE (Sensitivity: 68.3%; Specificity: 80.4%) and 26.3 kPa for S-SWE (Sensitivity: 79.7%; Specificity: 84.2%) and are summarized in table 3. L-SWE higher than 28.5 kPa

performed very well with an AUC of 0.81 and $p < 0.001$ to predict a pressure gradient above 12 mmHg (Figure 3E). S-SWE with the same cut-off of 28.5 kPa performed similarly with AUC of 0.81 and $p < 0.001$ to predict a pressure gradient above 12 mmHg (Figure 3F). Importantly, no significant differences between the ROC curves for S-SWE and L-SWE were observed.

Further analyses revealed that L-SWE < 16.0 kPa was able to rule-out CSPH with a sensitivity of $> 90\%$. Cut-off values of L-SWE > 29.5 kPa were able to rule-in CSPH with a specificity of $> 90\%$ (Table 3, Figure 4). 107 (69%) patients had L-SWE values lower than 16.0 kPa and higher than 29.5 kPa. In 48 (30%) patients liver stiffness was between 16.0 kPa and 29.5 kPa. Among these patients, 93 patients were correctly classified (87%). 9 patients had CSPH although L-SWE values were below 16.0 kPa and 5 patients did not have CSPH but had an L-SWE value above 29.5 kPa (Figure 4).

Similarly, S-SWE < 21.7 kPa was able to rule-out CSPH with a sensitivity of 91.9%. Values of S-SWE > 35.6 kPa were able to rule-in CSPH with a specificity of $> 90\%$ (Table 3, Figure 4). 64 patients (57%) had S-SWE values lower than 21.7 kPa and higher than 35.6 kPa. In 45 patients (42%) spleen stiffness was between 21.7 kPa and 35.6 kPa. Among this total, 55 were correctly classified (86%). 6 patients had S-SWE values below 21.7 kPa although having CSPH and 3 patients did not have CSPH but S-SWE values of more than 35.6 kPa (Figure 4).

Algorithm to rule-in CSPH

Additionally to the single cut-off values, an algorithm combining SWE of the liver and spleen was elaborated to rule-in CSPH. Patients with L-SWE > 38.0 kPa had probability of 96.9% of having CSPH. From 109 patients receiving L- and S-SWE measurements in the same session, 77 patients had L-SWE data ≤ 38.0 kPa. In these patients, S-SWE > 27.9 kPa could rule-in CSPH. 67 patients, of which 32 did not have CSPH and 35 had CSPH, were correctly classified and 10 patients were misclassified using this method (Figure 5A). This rule-in algorithm had a sensitivity of 89.2% and a specificity of 91.4% (Table 3). In patients without ascites the specificity was 93.9% and sensitivity 75.0% (Figure 5B).

Furthermore, a combination of both, the rule-in algorithm and our previously published rule-out algorithm¹⁹ was tested and is displayed in Figure 5C. Thereby, 62

1 out of 69 patients were correctly classified in having CSPH by applying the rule-in
2 cut-offs 38.0 kPa for L-SWE and 27.9 kPa for S-SWE. Only one patient was falsely
3 classified as having CSPH with L-SWE values under 16.0 kPa and S-SWE values
4 under 26.3 kPa. By using this method, 14 patients were undetermined in the range of
5 16.0 kPa and 38.0 kPa for L-SWE and between 26.3 kPa and 27.9 kPa for S-SWE. A
6 total of 91.6% of the patients were correctly classified with a sensitivity of 98.3% and
7 specificity of 83.9%.

8

9

Discussion

SWE of liver and spleen revealed strong correlations with the pressure gradient and were equally able to distinguish between patients with and those without CSPH. Recently we showed that sequential L- and S-SWE rules-out CSPH¹³, and the present study shows that S-SWE is similarly useful to predict CSPH as well as proposes an algorithm to rule-in CSPH. Furthermore, L- and S-SWE correlated with clinical events and decompensation.

The presence of CSPH, as the prerequisite for varices, has prognostic value^{4,5}. Importantly, also the success of therapy for portal hypertension might be dependent on the presence of CSPH, as shown recently that non-selective beta-blockers might have a better response in patients with CSPH compared to patients without²⁰. Therefore, the diagnosis of CSPH is important information for clinical decisions.

Transient elastography (TE) has already been considered not only a good tool for the evaluation of liver fibrosis, but also for diagnosis of portal hypertension²¹⁻²⁵. Therefore, TE measurements have found their way into the guidelines for diagnosing, stratifying and classifying liver diseases²⁵. Also in the last Baveno meeting TE of the liver has been recommended to stratify patients at risk for varices⁹.

Elastography hence represents a useful non-invasive tool for the diagnosis of CSPH. However, TE shows several limitations. First, TE is useless in patients with ascites; second, TE shows high failure rates in obese patients especially in patients with a BMI >30 kg/m²; third, TE offers only a regional elasticity measurement, but no anatomical image; and fourth, the small sample size is by definition not representative for the whole liver²⁶⁻²⁸. Therefore, SWE has already been introduced as a promising and equally accurate tool to diagnose portal hypertension¹⁰⁻¹² and the stage of liver fibrosis and cirrhosis in chronic liver disease^{29,30}.

The present study first of all confirms previous data showing an association and the predictive power of L-SWE to predict CSPH¹⁰⁻¹², but additionally adds a significant amount of knowledge in this regard. The present multi-center study could indeed demonstrate an almost equal association and predictive power of S-SWE with pressure gradient values consistent with the previously described data in two centers, and could validate the previously described cut-offs¹⁰⁻¹², which in turn confirms that

the results obtained in the present study are robust and generally applicable. Furthermore, the study allows the projection of the L-SWE/Spleen size/platelet count ratio from TE to SWE, also showing a very high predictive power for the diagnosis of CSPH.

The present study, however, also yields significant new findings of clinical relevance. First, the present study support the use of S-SWE as an additional read-out to further curtail the group of patients likely to have CSPH. Although some recent data on S-SWE were reported, the authors did not further evaluate S-SWE for the diagnosis of CSPH for practical reasons^{10,11}. Only few patients received S-SWE in these studies and moreover, the distribution of patients did not mirror the full spectrum of HVPG measurements rendering the statistical analysis of these results difficult^{10,11}. Despite these limitations, these recent findings show that SWE is a reliable and reproducible method with high intra- and inter-observer agreement^{31,32}.

By contrast to other studies, in our hands S-SWE appeared to be a good diagnostic tool, similarly accurate compared to L-SWE regarding the correlation with portal pressure and the diagnostic value to detect CSPH. These results were probably obtained due to our higher number of patients with a more balanced distribution throughout the spectrum of HVPG measurements (with CSPH in 67% and 33% without CSPH).

Our study hence showed that S-SWE is a possible tool to assess CSPH, similar to TE^{11,21-25}. On the basis of these significant results, we set for the first time cut-off values for S-SWE to predict accurately porto-systemic pressure gradients of 5 mmHg, 10 mmHg and 12 mmHg. These findings might be very important for the future therapeutic and diagnostic studies, which require follow-up measurements of portal pressure and surrogates of response to specific treatments.

Importantly, we could offer a simple way to rule-in and rule-out CSPH, while patients who do not fulfill these criteria or S-SWE is technically not feasible should undergo invasive HVPG-measurements.

Although our patient cohort was well characterized and balanced, our study has several limitations. First, this was a multi-center study and although a standardized methodology was used, inter-center variability can never be excluded. Moreover, our population was heterogeneous and we did not include a healthy (non-cirrhotic) control group. Finally, due to the data-driven cut-offs, an external validation is

needed. It should be noted, however, that the study cohort was consistent with other studies on SWE as a predictor for CSPH, as shown above. Furthermore, it remains to be assessed if S-SWE can be used as an efficacy of intervention marker i.e. as a surrogate of hemodynamic response to beta-blockers (as was shown for L-SWE³³).

In conclusion, this study demonstrates for the first time that S-SWE provides an accurate diagnostic tool to assess CSPH.

References:

1. Schuppan D, Afdhal NH. Liver cirrhosis. *Lancet*. 2008;371(9615):838-851.
2. Bosch J, Garcia-Pagan JC. Complications of cirrhosis. I. Portal hypertension. *Journal of hepatology*. 2000;32(Suppl 1):141-156.
3. de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of hepatology*. 2010;53(4):762-768.
4. Bosch J, Abraldes JG, Berzigotti A, Garcia-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. *Nature reviews. Gastroenterology & hepatology*. 2009;6(10):573-582.
5. Ripoll C, Groszmann RJ, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *Journal of hepatology*. 2009;50(5):923-928.
6. Garcia-Pagan JC, Di Pascoli M, Caca K, et al. Use of early-TIPS for high-risk variceal bleeding: results of a post-RCT surveillance study. *Journal of hepatology*. 2013;58(1):45-50.
7. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet*. 2014;383(9930):1749-1761.
8. Targownik LE, Spiegel BM, Dulai GS, Karsan HA, Gralnek IM. The cost-effectiveness of hepatic venous pressure gradient monitoring in the prevention of recurrent variceal hemorrhage. *The American journal of gastroenterology*. 2004;99(7):1306-1315.
9. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *Journal of hepatology*. 2015;63(3):743-752.
10. Elkrief L, Rautou PE, Ronot M, et al. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. *Radiology*. 2015;275(2):589-598.
11. Procopet B, Berzigotti A, Abraldes JG, et al. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. *Journal of hepatology*. 2015;62(5):1068-1075.
12. Kim TY, Jeong WK, Sohn JH, Kim J, Kim MY, Kim Y. Evaluation of portal hypertension by real-time shear wave elastography in cirrhotic patients. *Liver international : official journal of the International Association for the Study of the Liver*. 2015;35(11):2416-2424.
13. Jansen C, Bogs C, Verlinden W, et al. Algorithm to rule out clinically significant portal hypertension combining Shear-wave elastography of liver and spleen: a prospective multicentre study. *Gut*. 2016.

- 1 14. Sporea I, Gradinaru-Tascau O, Bota S, et al. How many measurements are
2 needed for liver stiffness assessment by 2D-Shear Wave Elastography (2D-
3 SWE) and which value should be used: the mean or median? *Med Ultrason.*
4 2013;15(4):268-272.
- 5 15. Reiberger T, Rutter K, Ferlitsch A, et al. Portal pressure predicts outcome and
6 safety of antiviral therapy in cirrhotic patients with hepatitis C virus infection.
7 *Clinical gastroenterology and hepatology : the official clinical practice journal*
8 *of the American Gastroenterological Association.* 2011;9(7):602-608 e601.
- 9 16. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver
10 operating characteristic (ROC) curve. *Radiology.* 1982;143(1):29-36.
- 11 17. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet
12 count identify portal hypertension in patients with compensated cirrhosis.
13 *Gastroenterology.* 2013;144(1):102-111 e101.
- 14 18. Thiele M, Madsen BS, Procopet B, et al. Reliability Criteria for Liver Stiffness
15 Measurements with Real-Time 2D Shear Wave Elastography in Different
16 Clinical Scenarios of Chronic Liver Disease. *Ultraschall Med.* 2016.
- 17 19. Jansen C, Bogs C, Krag A, Francque S, Trebicka J. Sequential shear-wave
18 elastography of liver and spleen rules out clinically significant portal
19 hypertension in compensated advanced chronic liver disease. *Gut.* 2016.
- 20 20. Villanueva C, Albillos A, Genesca J, et al. Development of hyperdynamic
21 circulation and response to beta-blockers in compensated cirrhosis with portal
22 hypertension. *Hepatology.* 2016;63(1):197-206.
- 23 21. Bureau C, Metivier S, Peron JM, et al. Transient elastography accurately
24 predicts presence of significant portal hypertension in patients with chronic
25 liver disease. *Alimentary pharmacology & therapeutics.* 2008;27(12):1261-
26 1268.
- 27 22. Lemoine M, Katsahian S, Ziol M, et al. Liver stiffness measurement as a
28 predictive tool of clinically significant portal hypertension in patients with
29 compensated hepatitis C virus or alcohol-related cirrhosis. *Alimentary*
30 *pharmacology & therapeutics.* 2008;28(9):1102-1110.
- 31 23. Vizzutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts
32 severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology.*
33 2007;45(5):1290-1297.
- 34 24. Zykus R, Jonaitis L, Petrenkiene V, Pranculis A, Kupcinskas L. Liver and
35 spleen transient elastography predicts portal hypertension in patients with
36 chronic liver disease: a prospective cohort study. *BMC gastroenterology.*
37 2015;15(1):183.
- 38 25. European Association for Study of L, Asociacion Latinoamericana para el
39 Estudio del H. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for
40 evaluation of liver disease severity and prognosis. *Journal of hepatology.*
41 2015;63(1):237-264.
- 42 26. Cosgrove D, Piscaglia F, Bamber J, et al. EFSUMB guidelines and
43 recommendations on the clinical use of ultrasound elastography. Part 2:
44 Clinical applications. *Ultraschall Med.* 2013;34(3):238-253.
- 45 27. Castera L, Foucher J, Bernard PH, et al. Pitfalls of liver stiffness
46 measurement: a 5-year prospective study of 13,369 examinations.
47 *Hepatology.* 2010;51(3):828-835.
- 48 28. Cui XW, Friedrich-Rust M, De Molo C, Ignee A, Schreiber-Dietrich D, Dietrich
49 CF. Liver elastography, comments on EFSUMB elastography guidelines 2013.
50 *World journal of gastroenterology : WJG.* 2013;19(38):6329-6347.

- 1 29. Poynard T, Munteanu M, Luckina E, et al. Liver fibrosis evaluation using real-
2 time shear wave elastography: applicability and diagnostic performance using
3 methods without a gold standard. *Journal of hepatology*. 2013;58(5):928-935.
- 4 30. Thiele M, Detlefsen S, Sevelsted Moller L, et al. Transient and 2-Dimensional
5 Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver
6 Fibrosis and Cirrhosis. *Gastroenterology*. 2016;150(1):123-133.
- 7 31. Ferraioli G, Tinelli C, Dal Bello B, et al. Accuracy of real-time shear wave
8 elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study.
9 *Hepatology*. 2012;56(6):2125-2133.
- 10 32. Ferraioli G, Tinelli C, Zicchetti M, et al. Reproducibility of real-time shear wave
11 elastography in the evaluation of liver elasticity. *Eur J Radiol*.
12 2012;81(11):3102-3106.
- 13 33. Choi SY, Jeong WK, Kim Y, Kim J, Kim TY, Sohn JH. Shear-wave
14 elastography: a noninvasive tool for monitoring changing hepatic venous
15 pressure gradients in patients with cirrhosis. *Radiology*. 2014;273(3):917-926.

Figure legends:

Figure 1. Recruitment overview. One hundred and fifty-eight patients were recruited. In all patients pressure gradient measurements were performed. 155 patients had their liver stiffness by SWE measured. In 112 patients, spleen stiffness measurements were performed using SWE. In 109 patients both L- and S-SWE were performed. L- and S-SWE, liver- and spleen-Shear-wave elastography.

Figure 2. Correlation of Shear-wave elastography with clinically significant portal hypertension. (A) L-SWE data correlated significantly with the pressure gradient ($r_s=0.625$; $p<0.001$). Of note, data of two patients lay outside of the shown range, and were not shown to increase readability. (B) S-SWE data correlated significantly with the pressure gradient ($r_s=0.606$; $p<0.001$). Of note, data of four patients lay outside of the shown range, and were not shown to increase readability. Data are presented using Spearman coefficient r_s and p-values for Figure (2A) and (2B). (C) L-SWE was significantly higher in patients with CSPH compared to those without ($p<0.001$). (D) S-SWE was significantly higher in patients with CSPH compared to those without ($p<0.001$). Data are presented using Kruskal-Wallis p-values for Figure (2C) and (2D). CSPH, clinically significant portal hypertension; L- and S-SWE, liver- and spleen-Shear-wave elastography.

Figure 3. Cut-off values to diagnose portal hypertension. ROC analyses demonstrate the predictive value of L- and S-SWE on the pressure gradient >5 mmHg (3A) and (3B), >10 mmHg (3C) and (3D) and >12 mmHg (3E) and (3F). AUC, area under the curve; ROC, receiver operating characteristic L- and S-SWE, liver- and spleen-Shear-wave elastography.

Figure 4. Comparison between L-SWE and SWE-S using single, rule-out and rule-in cut-off. 112 patients had S-SWE measurements. 65 patients had an S-SWE > 26.3 kPa of which 91% were well classified as having CSPH. 47 patients had an S-SWE ≤ 26.3 of which 68% were well classified as having no CSPH. Using rule-in and rule-out cut-off, 93% were well classified as having CSPH, 76% were well classified as having no CSPH. 45 patients could not be classified (Figure 4 A, B). 155 patients had L-SWE measurements. 81 patients had an L-SWE > 24.6 kPa of which 88% were well classified as having CSPH. 74 patients had an L-SWE ≤ 24.6 of which 55% were well classified as having no CSPH. Using rule-in and rule-out cut-off, 92% were well classified as having CSPH and 80% were well classified as having no CSPH. 48 patients could not be classified. CSPH, clinically significant portal hypertension; L- and S-SWE, liver- and spleen-Shear-wave elastography.

Figure 5. Algorithms to rule-in CSPH. (A) 109 patients with and without ascites had simultaneous L- and S-SWE measurements. 32 patients had an L-SWE >38.0 kPa of which 31 were well classified as having CSPH and 1 was not. 77 patients had L-SWE data ≤ 38.0 kPa. In these patients, S-SWE cut-off value of 27.9 kPa was used to further classify them. By doing so, 32 patients without CSPH were well classified

1 while 8 patients were not. 35 patients with S-SWE >27.9 had CSPH, two were
2 misclassified. From the total number of 109 patients, 35 did not have CSPH and 74
3 had CSPH. 98 patients (90%) were well classified whereas 11 patients (10%) were
4 misclassified. **(B)** 57 patients without ascites had simultaneous L- and S-SWE
5 measurements. 6 patients had an L-SWE >38.0 kPa of which all were well classified
6 as having CSPH. 51 patients had L-SWE data $\leq$ 38.0 kPa. In these patients, S-SWE
7 cut-off value of 27.9 kPa was used to further classify them. By doing so, 31 patients
8 without CSPH were well classified while 6 patients were not. 12 patients with S-SWE
9 >27.9 kPa had CSPH, two were misclassified. From the total number of 57 patients,
10 33 did not have CSPH and 24 had CSPH. 49 patients (86.0%) were well classified
11 whereas 8 patients (14%) were misclassified. CSPH, clinically significant portal
12 hypertension; L- and S-SWE, liver- and spleen-Shear-wave elastography. **(C)**
13 Combining the rule-in and our previously published rule-out algorithm, 62 out of 69
14 patients were correctly classified in having CSPH by applying the rule-in cut-offs 38.0
15 kPa for L-SWE and 27.9 kPa for S-SWE. Only one patient was falsely classified as
16 having CSPH with L-SWE values under 16.0 kPa and S-SWE values under 26.3 kPa.
17 By using this method, a grey-zone of 14 patients was created, who should undergo
18 HVPG-measurement. A total of 91.6% of the patients were correctly classified.

19 CSPH, clinically significant portal hypertension; L- and S-SWE, liver- and spleen-
20 Shear-wave elastography.
21

- 1
- 2

1 **Tables:**2 **Table 1.** Clinical and biochemical parameters of the patients (n=158) at baseline.

Parameters	All patients
Sex [male / female]	97 / 61
Age	56 ± 12 (18 – 80)
Etiology of liver disease alcohol / viral hepatitis / NASH / others	89 / 12 / 27 / 30
Child-Pugh score	7 ± 2 (5 – 12)
Child-Pugh class A / B / C	99 / 45 / 14
MELD score	10.42 ± 4.53 (6 – 28)
Ascites [absent / mild / severe]	90 / 25 / 43
Spleen size [cm]	13.2 ± 2.9 (5.2 – 22)
L-SWE [kPa]	28.7 ± 20.1 (5 – 130)
S-SWE [kPa]	35.5 ± 22.9 (7 – 131.5)
Pressure gradient [mmHg]	13.2 ± 7.6 (0.7 – 30)
Sodium [mmol/L]	138 ± 4 (127 – 146)
Creatinine [mg/dL]	1.01 ± 0.67 (0.52 – 7.61)
Bilirubin [mg/dL]	1.72 ± 2.44 (0.16 – 18.00)
Albumin [g/L]	33.3 ± 7.5 (12 – 49.2)
INR	1.20 ± 0.33 (0.63 – 3.41)
YGT [IU/L]	199 ± 196 (20 – 1013)
ALT [IU/L]	59 ± 124 (6 – 1412)
AST [IU/L]	59 ± 74 (13 – 687)
Cholinesterase [IU/L]	6884 ± 3942 (1366 – 14000)
Alkaline phosphatase [IU/L]	158 ± 123 (40 – 1315)
CRP [mg/L]	14 ± 22 (0.43 – 153)

3 Data are means ± standard deviation (ranges). ALT, alanine aminotransferase; AST,
4 aspartate aminotransferase; CRP, C-reactive protein; yGT, gamma-
5 glutamyltranspeptidase; INR, International Normalized Ratio; MELD, model of end-
6 stage liver disease; NASH, non-alcoholic steatohepatitis; L- and S-SWE, liver- and
7 spleen-Shear-wave elastography.

8

1

2 **Table 2.** Correlations of baseline parameters with L-SWE and S-SWE.

	Parameters	L-SWE		S-SWE	
		r_s	p	r_s	p
Clinical	CHILD Score	0.407	<0.001	0.221	0.023
	MELD Score	0.341	<0.001	0.190	0.049
	Spleen size	0.283	0.001	0.484	<0.001
	Ascites	0.474	<0.001	0.488	<0.001
Biochemical	Platelet Count	-0.263	0.001	-0.470	<0.001
	Bilirubin	0.473	<0.001	0.344	<0.001
	Albumin	-0.442	<0.001	-0.314	0.001
	Creatinine	-	-	0.208	0.030
	INR	0.406	<0.001	0.280	0.003
	yGT	0.177	0.031	-	-
	ALT	-0.214	0.008	-0.188	0.049
	AST	0.186	0.032	-	-
	Cholinesterase	-0.470	<0.001	-0.327	0.003
	Alkaline Phosphatase	0.240	0.003	-	-

3 ALT, alanine aminotransferase; AST, aspartate aminotransferase; yGT, gamma-
4 glutamyltranspeptidase; INR, International Normalized Ratio; MELD, model of end-
5 stage liver disease; r_s , Spearman's rank correlation coefficient, L- and S-SWE, liver-
6 and spleen-Shear-wave elastography.

Table 3. Diagnostic performance of L-SWE (n=155) and S-SWE (n=112) for the diagnosis of CSPH.

	Parameters	Cut-off value [kPa]	AUC	Sensitivity [%]	Specificity [%]	Positive predictive value [%]	Negative predictive value [%]	Diagnostic accuracy [%]
one cut-off*	S-SWE [kPa]	26.3	0.84 (0.76 – 0.92)	79.7	84.2	90.8	68.0	81.3
	L-SWE [kPa]	24.6	0.86 (0.80 – 0.94)	68.3	80.4	87.7	55.4	72.3
rule-out**	S-SWE [kPa]	21.7	0.84 (0.76 – 0.92)	91.9	50	86	85.7	85.9
	L-SWE [kPa]	16.0	0.86 (0.80 – 0.94)	91.3	68.6	85.6	79.5	83.9
rule-in***	S-SWE [kPa]	35.6	0.84 (0.76 – 0.92)	51.4	92	92	76	67.9
	L-SWE [kPa]	29.5	0.86 (0.80 – 0.94)	56.7	90.2	92.2	50.5	67.7
Rule-in algorithm				89.2	91.4	95.7	80.0	89.9
Rule-in algorithm without ascites				75.0	93.9	90.0	83.8	89.5
Combined algorithms				98.3	83.9	92.1	96.3	91.6

* Cut-off values that maximized the sum of sensitivity and specificity were chosen. ** Cut-off values that optimized sensitivity were chosen. *** Cut-off values that optimized specificity were chosen. AUC, area under the curve; CSPH, clinically significant portal hypertension; L- and S-SWE, liver- and spleen-Shear-wave elastography.