Noninvasive Detection of Clinically Significant Portal Hypertension in Compensated Advanced Chronic Liver Disease

Élise Vuille-Lessard, MD, MSc[a,b], Susana G. Rodrigues, MD[a,b], Annalisa Berzigotti, MD, PhD[a,b,*]

KEYWORDS

• Elastography • Cirrhosis • Varices • Spleen • Decompensation

KEY POINTS

- Clinically significant portal hypertension can be identified noninvasively (liver stiffness >21 kPa; portosystemic collaterals on imaging), but cannot be ruled out with confidence.
- Endoscopic screening of varices can be safely avoided if liver stiffness is less than 20 kPa and platelet count is greater than 150 g/L, because varices needing treatment are rare in these patients.
- Spleen stiffness is a novel promising parameter for the noninvasive assessment of portal hypertension.

INTRODUCTION

The natural history of chronic liver disease is characterized by a long asymptomatic or compensated phase. During this long phase, fibrosis progresses eventually leading to cirrhosis, which is histologically defined by marked anatomic changes encompassing septae formation, hepatocyte extinction and regeneration, and angiogenesis. Portal pressure increases progressively as well, and in patients with bridging fibrosis and cirrhosis the hepatic venous pressure gradient (HVPG; the best method to assess portal hypertension in cirrhosis) is over the normal threshold of 5 mm Hg.[1] Once the HVPG doubles its normal values, namely, once it exceeds 10 mm Hg, portosystemic collateralization becomes relevant, gastroesophageal varices can develop, and patients are

Funding: Élise Vuille-Lessard is supported by a Clinical Hepatology Fellowship of the Canadian Association for the Study of the Liver - Canadian Liver Foundation (CASL-CLF 2020-2021).

[a] Hepatology, University Clinic for Visceral Surgery and Medicine (UVCM), Inselspital, University Hospital of Bern, Freiburgstrasse, 3010 Bern, Switzerland; [b] Department of Biomedical Research, University of Bern, Switzerland

* Corresponding author. MEM F807, Maurice Müller Haus, Murtenstrasse 35, Bern 3008, Switzerland.

E-mail address: Annalisa.berzigotti@insel.ch

Clin Liver Dis 25 (2021) 253–289

https://doi.org/10.1016/j.cld.2021.01.005 **liver.theclinics.com**

prone to experience clinical decompensation, including ascites, bleeding from portal hypertensive sources, and hepatic encephalopathy. This is why an HVPG of 10 mm Hg or higher is as defined clinically significant portal hypertension (CSPH). As discussed, liver fibrosis progression is a slow, dynamic process, often not completely homogenous within the liver, and distinguishing between severe fibrosis and cirrhosis in a compensated patients is not trivial. This led to propose the term compensated advanced chronic liver disease (cACLD).[2,3] The HVPG measurement remains the reference standard to identify CSPH and to further stratify the risk of complications in cACLD, but is relatively expensive, not point of care, is available only in specialized centers with personnel with adequate training, and can be (rarely) associated with complications.[1]

Given the strong prognostic value of CSPH and owing to its therapeutic implications, noninvasive tests to detect this hemodynamic threshold in a simple and accurate manner have been object of an increasing number of studies in the last 20 years. Ideally, noninvasive tests should reflect exactly the HVPG, or should at least correctly classify patients as having or not CSPH, and as having or not varices needing treatment.

From a logical point of view, noninvasive tests should be used stepwise to identify CSPH first, and then to identify patients who require endoscopy owing to a negligible risk of varices needing treatment. Within the compensated stage, the presence of gastroesophageal varices identify patients at further risk of complications[4–7] (**Fig. 1**). It is very important to underline that the field of action of noninvasive tests for the detection of CSPH and varices is restricted to patients with compensated ACLD, who can have or not have these conditions and are object of the present review. In patients with decompensated cirrhosis, portal hypertension is per definition present,[1] and screening of CSPH is therefore superfluous.

Noninvasive tests investigated in this field include laboratory tests, imaging tests, and elastography. These modalities complement the clinical history and physical examination of patients, and have different costs and complexities.

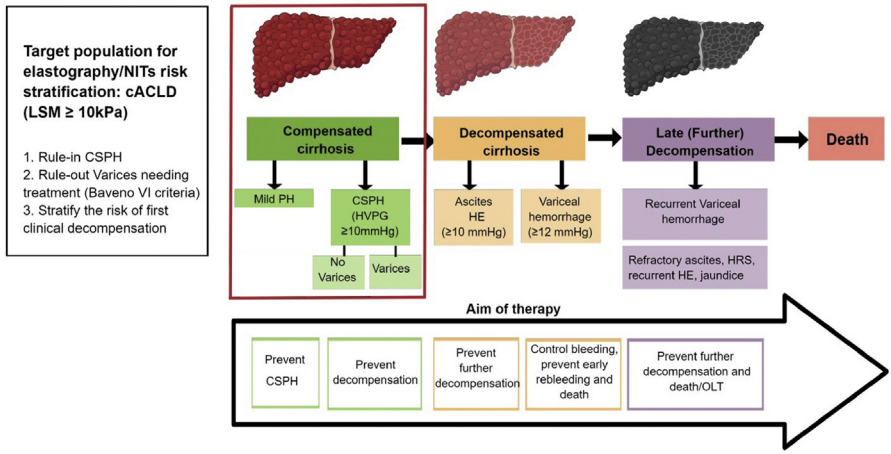

Fig. 1. Stages of cACLD according to D'Amico (D'Amico, 2014 #62). As shown, noninvasive tests (NITs) play a role in the compensated stage of the disease, when the patient is asymptomatic but at risk of carrying CSPH and varices. HE, hepatic encephalopathy; HRS, hepatorenal syndrome; OLT, orthotopic liver transplantation.

LABORATORY TESTS AND PHYSICAL SIGNS

The physical examination can reveal signs of CSPH, including ascites (sometimes associated with abdominal hernias), splenomegaly, spider nevi, visible abdominal portosystemic collaterals, pleural effusions, and lower limb edema. However, their absence cannot rule out CSPH. Of note, the presence of subclinical ascites (ascites sole detected by ultrasound examination) has been shown to be associated with similar HVPG values than clinical ascites, and to an intermediary survival compared with patients without ascites and with clinical ascites,[6] suggesting a subclinical decompensated stage.

In terms of laboratory data, serum biomarkers have initially been introduced to detect liver fibrosis and cirrhosis noninvasively and are classified as direct when reflecting matrix deposition and as indirect when reflecting liver dysfunction. A subset of them has been correlated to portal hypertension and its complications.[8] The advantages of using laboratory tests to noninvasively assess portal hypertension include their high applicability, good interlaboratory reproducibility, and availability.[9]

However, serum biomarkers need to be interpreted critically because some of their individual components can be affected by a variety of comorbidities. Overall, their diagnostic accuracy to detect CSPH and gastroesophageal varices, when used alone, remains modest. Moreover, none of them has been validated to monitor portal pressure and HVPG changes with or without treatment, limiting further their clinical usefulness.[10]

A low platelet count, the most common hematologic abnormality in cirrhosis,[11] has been consistently shown to correlate with HVPG[12] and a platelet count of less than 100×10^9/L strongly suggests CSPH. Von Willebrand factor antigen, produced by activated endothelial cells, also correlates with HVPG and was shown to be an independent predictor of CSPH (area under the receiver operating characteristic curve [AUROC] 0.85 using a cut-off value of $\geq$241%).[13] The derived VITRO score (Von Willebrand factor antigen/thrombocyte ratio) had an AUROC of 0.86 to detect CSPH in one study[14] and a VITRO score 2.5 or higher was recently associated with a higher 1-year probability of decompensation (9% vs 0%).[15]

A variety of biomarkers based on a combination of routine liver blood tests including aspartate aminotransferase (AST)-to-alanine aminotransferase ratio, AST to platelet ratio index, Fibrosis index, Fibrosis 4 index, Forns index, King's score, and the Lok index (**Table 1**) have shown a moderate diagnostic accuracy in predicting CSPH. A recent study showed that King's score, AST to platelet ratio index, and the Lok index had the best diagnostic accuracy, but that the latter was modest, with AUROCs of 0.755 and 0.742, 0.740 and 0.742, and 0.722 and 0.717, for CSPH, and severe portal hypertension, respectively.[16]

Some scores combining direct and indirect biomarkers with the use of patented formulas were also shown to be able to detect CSPH. For instance, the FibroTest (Biopredictive, Paris, France) had in 1 study an AUROC of 0.79 for severe portal hypertension; however, it correlated weakly with the HVPG in patients with cirrhosis.[17]

Numerous other individual biomarkers have shown a correlation with CSPH, such as the prothrombin index (Pearson correlation coefficient, −0.72; AUROC 0.89 with a cut-off value of 82.5%),[18] soluble CD163 (alone or combined with the Enhanced Liver Fibrosis test),[19,20] inflammatory markers such as IL-1β and its receptor IL-1Rα, Fas-R, serum VCAM-1[21] and osteopontin,[22] serum bile acids,[23] chemerin,[24] apelin,[25] hyaluronic acid and laminin,[26,27] and fragments of extracellular matrix,[28] as well as the indocyanine green retention test.[29] Despite some interesting data, the evidence is currently not strong enough to recommend the use of these markers in clinical practice.

Table 1
Available serum biomarkers for the noninvasive evaluation of portal hypertension

Score	Formula
AST to platelet ratio index	(AST/ULN)/PLT(10^9/L) × 100
AST-to-ALT ratio	AST/ALT
Fibrosis 4 index	(age × AST)/(PLT × $ALT^{½}$)
FibroIndex	1.738–0.064 × PLT + 0.005 × AST + 0.463 × gamma globulin
Fibrosis index	8–0.01 × PLT– ALB
Forns index	7.811–3.131 × ln(PLT) + 0.781 × ln(GGT) + 3.467 × ln(age) – 0.014 × (cholesterol)
King's score	Age × AST × INR/PLT
Lok index	−5.56–0.0089 × PLT + 1.26 × AST/ALT + 5.27 × INR

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; INR, international normalized ratio; PLT, platelet count; ULN, upper limit of normal.

Looking specifically at the diagnosis of gastroesophageal varices, the platelet count is usually lower in patients with gastroesophageal varices, but no absolute cut-off value used alone has a satisfactory performance to detect them, with AUROCs in the 0.60 to 0.75 range.[30,31] A systematic review and meta-analysis concluded that AST to platelet ratio index, AST-to-alanine aminotransferase ratio, Fibrosis 4 index, and Lok and Forns scores had low to moderate diagnostic accuracy in predicting the presence of varices and large varices in cirrhosis, with AUROCs of 0.65 to 0.79 overall and summary sensitivities and specificities of 0.60 to 0.78 and 0.56 to 0.68, respectively.[32] The FibroTest was shown to be a good predictor of large esophageal varices (AUROC, 0.77) and had an 86% negative predictive value at a cut-off of 0.80.[33] The prothrombin index,[18] indocyanine green retention test,[34] and soluble CD163[35] have also been showed to predict the presence of gastroesophageal varices, contrary to hyaluronic acid, laminin, amino-terminal propeptide of type III procollagen, and collagen IV.[36]

Despite data showing that individual laboratory tests have a moderate performance in detecting CSPH and gastroesophageal varices, their use alone cannot currently be recommended. Nevertheless, their combination with other noninvasive methods has shown promising results.

IMAGING

Imaging methods used for portal hypertension include ultrasound (complemented by color, power, and pulsed Doppler, and contrast-enhanced techniques), computed tomography (CT) scan and magnetic resonance (MR). All these methods are able to depict the macroscopic changes occurring in the liver, spleen, and vessels of the portal venous system as a consequence of the progression of liver disease and portal hypertension. Some recent studies reported that the nodularity of the liver surface (as quantified by using a specific software) by ultrasound examination[37] and by CT scan (Liver Surface Nodularity Score)[38] is able to detect the presence of cirrhosis confidently and correlates with the HVPG, so allowing the identification of patients with likely CSPH

(AUROC, 0.88; cut-off, 2.8; positive predictive value, 88%). The advantage of this simple method is that it could be implemented automatically in CT scans.

The portal vein, splenic vein, and superior mesenteric vein progressively dilate, splenomegaly often appears, and portosystemic collaterals (**Fig. 2**) can be evident. Particular attention should be paid to portosystemic collaterals, because they are pathognomonic signs of portal hypertension in cACLD,[3] and are associated with higher HVPG[39] and poorer outcomes;[40,41] in addition, large gastroesophageal varices can be detected on CT scans with about 90% accuracy.[42]

Doppler measurements are not sufficiently accurate for CSPH; however, a very low velocity of flow in the portal vein (<12 cm/s) has been associated consistently to the presence of gastroesophageal varices, and is a risk factor for developing portal vein thrombosis.

Several new MR techniques are being tested in patients with portal hypertension and include diffusion-weighted imaging, hepatocellular contrast-enhanced MRI, T1 relaxometry, T1ρ imaging, textural analysis, susceptibility-weighted imaging, and perfusion imaging.[43] They are highly promising, but need further evaluation and clinical validation.

Among the emerging methods, contrast-enhanced ultrasound examination, taking advantage of the physical properties of the inert gas contained in the microbubbles, has been shown to provide information on portal hypertension. In particular, it has been observed that the amplitude of the subharmonic ultrasound waves decreases in parallel (linearly) to the pressure of the liquid surrounding the microbubbles. Hence, by measuring the subharmonic signal amplitude in the liver veins and in the hepatic veins by contrast-enhanced ultrasound examination, a subharmonic gradient reflecting the HVPG can be measured through adequate mathematical modeling. This approach subharmonic aided pressure estimation (SHAPE) has proven successful and allowed an excellent correlation between the SHAPE HVPG and the HVPG

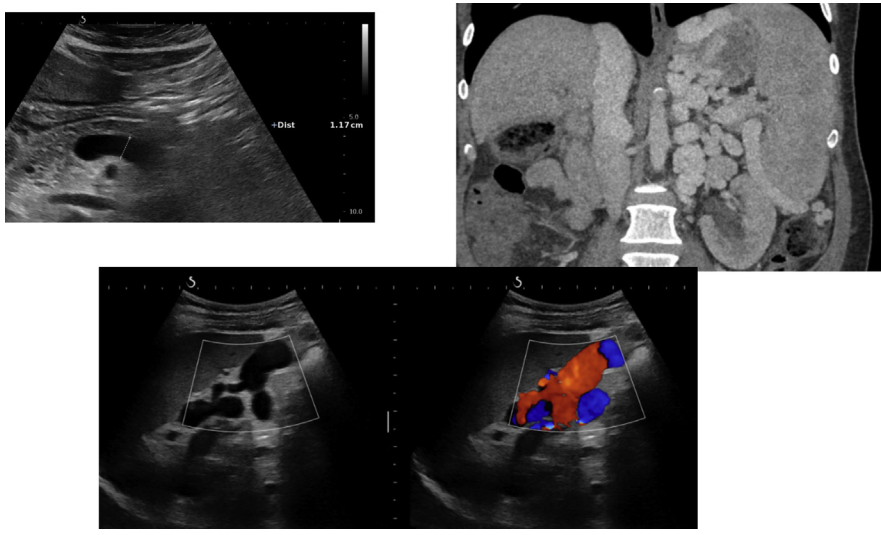

Fig. 2. Imaging signs of portal hypertension. (*Upper left panel*) Dilatation of the splenic vein by ultrasound examination. (*Upper right panel*) Large splenomegaly and numerous large splenorenal collaterals. (*Lower panel*) Large splenorenal collaterals on conventional ultrasound examination (*left*) and color Doppler ultrasound examination (*right*).

measured invasively ($R^2 = 0.82$); the proposed cut-off was greater than 90% accurate for CSPH.[44,45]

Imaging methods, and ultrasound examination in particular, are routinely used to follow-up patients with cACLD. Signs suggesting worsening of portal hypertension in compensated patients include enlargement of the portal venous system, further enlargement of spleen size,[46] and the onset of new portosystemic collaterals.[47]

LIVER ELASTOGRAPHY FOR THE ASSESSMENT OF CLINICALLY SIGNIFICANT PORTAL HYPERTENSION

Transient Elastography

Liver stiffness measurement (LSM) by transient elastography (TE) has been demonstrated to detect CSPH in patients with cACLD owing to different causes, although the majority of data is linked to viral hepatitis (**Table 2**). LSM obtained by TE correlates significantly with the HVPG in patients with cACLD, showing a correlation coefficient ranging between 0.55 to 0.86.[48] As mentioned elsewhere in this article, the correlation between the HVPG and LSM is excellent below the threshold of 10 mm Hg, although it decreases in patients with an HVPG above the threshold for CSPH, likely owing to a flow-dependent increase in portal pressure, not reflected in LSM.[49] Thus, LSM does not provide an accurate estimation of the HVPG value.[50,51] However, LSM is a reliable noninvasive tool to accurately identify patients with CSPH, showing an AUROC ranging between 0.74 and 0.94.[48] A meta-analysis confirmed the diagnostic capability of this method, reporting an AUROC of 0.93 with a sensitivity of 87.5% (95% confidence interval [CI], 75.8%–93.9%) and a specificity of 85.3% (95% CI, 76.9%–90.9%). The summary correlation coefficient was 0.783 (95% CI, 0.737–0.823).[48]

The cut-off of 21 kPa to identify the presence of CSPH demonstrated a high specificity (>90%) for an HVPG of more than 10 mm Hg.[18,49,52] Based on these data, the Baveno VI consensus stated that an LSM greater than 20 to 25 kPa can be used to identify the presence of CSPH (varices) in patients with untreated hepatitis C virus (HCV) or hepatitis B virus cACLD.[3] The specificity of this cut-off was more than 90% in the meta-analysis by You and colleagues.[48] In another recent meta-analysis[53] performed exclusively in patients with chronic viral hepatitis, it was suggested that 2 cut-offs can be used, namely, less than 13.6 kPa to rule out CSPH (pooled sensitivity 96%; CI 95% 93%–97%), and greater than 22 kPa to rule in CSPH (pooled specificity, 94%; 95% CI, 86%–97%), thus confirming Baveno VI consensus recommendations.[53]

After achieving a sustained virological response (SVR) in patients with chronic hepatitis C, LSM quickly and sometimes dramatically decreases.[54–58] Despite being statistically significant, the correlation between the decrease in LSM and HVPG was weak in the largest study published thus far.[57] Consequently, the 13.6 kPa cut-off to rule out CSPH performed poorly after achieving a SVR, because almost one-half of patients with an LSM less than 13.6 kPa still showed an HVPG of 10 mm Hg or greater. In contrast, an LSM of greater than 21 kPa showed to accurately rule in CSPH even after achieving a SVR.[57] Nevertheless, current evidence does indicate an LSM cut-off that could be used to safely rule out persistence of CSPH, in patients with SVR after HCV therapy.

Because the etiology of the underlying liver disease influences LSM, the application of previous described cut-offs, it has been postulated that LSM accuracy may be limited in patients with nonviral cACLD.[59] LSM correlated well with the HVPG in patients with alcohol-related liver disease (ArLD) in a recent retrospective study (correlation coefficient, 0.753; AUROC, 0.925).[60] The cut-off of 30.6 kPa showed the best capacity to rule in CSPH (sensitivity, 81%; specificity, 94%).[60] In a recent meta-

Table 2
Accuracy of LSM for the diagnosis of CSPH

Study, Year	Study Design	Population	Correlation Coefficient Between LSM and HVPG	AUROC for CSPH	Cut-off for CSPH	Sensitivity (%)	Specificity (%)
TE (only studies with ≥100 patients selected)							
Bureau et al,[18] 2008	Prospective	144 patients with HCV or alcoholic cirrhosis	0.858	0.945	21 kPa	89.9	93.2
Colecchia et al,[106] 2012	Prospective	100 patients with HCV cirrhosis	0.836	0.836	24.2 kPa	52.3	97.1
Reiberger et al,[143] 2012	Retrospective	502 patients with/without cirrhosis, some decompensated (mixed etiologies)	0.794	0.871	18 kPa	82.2	83.4
Schwabl et al,[144] 2015	Retrospective	188 patients with chronic liver disease	0.846	0.957	16.1 kPa	94.8	86.9
Cho et al,[145] 2015	Retrospective	219 patients with alcoholic cirrhosis (some decompensated)	n. a.	0.85	n. a.	n. a.	n. a.
Zykus et al,[146] 2015	Prospective	107 patients with cirrhosis (mixed etiologies)	0.750	0.949	17.4 kPa	88	87.5
Hametner et al,[147] 2015	Retrospective	236 patients with cirrhosis (mixed etiologies)	n. a.	0.92	24.8 kPa	81	93
Kumar et al,[148] 2017	Retrospective	326 patients with cirrhosis (mixed etiologies)	n. a.	0.74	21.46 kPa	79	67
Salavrakos et al,[60] 2018	Retrospective	118 patients with alcoholic liver disease	0.753	0.925	30.6 kPa	81	94
Point shear wave elastography							
Salzl et al,[63] 2014	Prospective	88 patients with liver cirrhosis	0.646	0.855	2.58 m/s	71.4	87.5
Attia et al,[64] 2015	Prospective	78 patients with chronic liver disease	0.650	0.93	2.17 m/s	97	89
Takuma et al,[65] 2016	Prospective	60 patients with liver cirrhosis	0.609	0.83	n. a.	n. a.	n. a.
2D-SWE (only studies with >100 patients)							
Jansen et al,[71] 2017	Prospective	158 patients with cirrhosis (mixed etiologies)	0.626	24.6 kPa < 16 kPa rule out > 29.5 kPa rule in	0.86	68.3	80.4

(*continued on next page*)

Table 2
(*continued*)

Study, Year	Study Design	Population	Correlation Coefficient Between LSM and HVPG	AUROC for CSPH	Cut-off for CSPH	Sensitivity (%)	Specificity (%)
Elkrief et al,[72] 2017	Prospective	191 patients with liver cirrhosis (mixed etiologies) 77 included in a previous study[71]	n. a.	n. a.	0.80	n. a.	n. a.
Zhu et al,[69] 2019	Retrospective	104 hepatitis B-related patients with cirrhosis	0.607	16.1 kPa < 13.2 kPa rule out > 24.9 kPa rule in	0.72	81	83
Thiele et al,[68] 2020	Meta-analysis	328 patients with compensated and decompensated cirrhosis (alcohol and viral etiology)	n.a.	Rule out <14 kPa 0.88 (85-91)	0.88	91	37

Abbreviations: ACLD, advanced chronic liver disease; AUROC, area under receiver operator curve; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

analysis focused on ArLD including 9 studies, the authors identified a cut-off value of 21.8 kPa for CSPH.[61] Despite a good pooled sensitivity (0.89; 95% CI, 0.83–0.93), both the specificity (0.71; 95% CI, 0.64–0.78) and positive likelihood ratio (3.1; 95% CI, 2.4–4 were modest.[61] Therefore, the cut-off value of 21.8 kPa has a good performance in ruling out CSPH, but it is not satisfactory in ruling in CSPH (similarly to what described for the 13.6 kPa cut-off in viral ACLD).[53,61] According to these data, the cut-off value to be used to rule in CSPH in ArLD seems to be higher than that for viral ACLD. In a recent meeting, a multicenter study with 786 patients showed that LSM was accurate in diagnosing CSPH in most etiologies, including nonalcoholic steatohepatitis, but not in obese patients with nonalcoholic steatohepatitis.[62] Data on the accuracy of LSM for CSPH in cholestatic liver disease (in which a presinusoidal component of portal hypertension is invariably present) and autoimmune hepatitis are lacking and require targeted studies.

Point Shear Wave Elastography

Similar to TE, point shear wave elastography (pSWE) (acoustic radiation force impulse imaging; Acuson Siemens 2000, Germany) based LSM showed a significant correlation with HVPG (r = 0.609–0.650) and a good diagnostic accuracy for CSPH (AUROC, 0.83–0.93).[63–65] Nevertheless, the data are lacking to establish an accurate cut-off value to rule in and rule out CSPH. The current cut-offs are highly variable (ranging from 2.17 to 2.58 m/s), likely owing to the population. Owing to these limitations, pSWE is not recommended for the diagnosis of CSPH.[50]

Two-Dimensional Shear Wave Elastography

Two-dimensional shear wave elastography (2D-SWE) demonstrated a good discriminative capacity (AUROC, 0.80–0.87), with sensitivity and specificity ranging between 80% and 90% in most of the studies. In a meta-analysis, Suh and colleagues[66] confirmed a good diagnostic performance (AUROC, 0.88; 95% CI, 0.85–0.91). The summary sensitivity and summary specificity were 85% (95% CI 75%–91%) and 85% (95% CI, 77%–90%), respectively. The correlation between LSM by 2D-SWE and HVPG was high with a summary correlation coefficient of 0.741 (95% CI, 0.658–0.825).[66]

In a recent study, 2D-SWE correlated with HVPG (r = 0.704; $P<.0001$), especially if the HVPG was less than 10 mm Hg and was significantly higher in patients with CSPH (15.52 vs 8.14 kPa; $P<.0001$) and not inferior to LSM-TE (0.92; $P = .79$). Furthermore, in the subgroup of compensated patients with ArLD, 2D-SWE classified CSPH better than TE (93.33% vs 85.71%; $P = .039$).[67]

A recent individual patient meta-analysis including 328 patients, 27% with cACLD, showed that LSM using a 2D-SWE of less than 14 kPa may be used to rule out CSPH in patients with cirrhosis.[68]

In the context of hepatitis B virus–related cACLD, a cut-off of less than 13.2 kPa ruled out CSPH with a sensitivity of greater than 90%, and a cut-off greater than 24.9 kPa ruled in CSPH with a specificity of greater than 90%.[69] Jansen and colleagues[70,71] developed 2 algorithms to noninvasively rule in and rule out CSPH using 2D-SWE using LSM followed by spleen stiffness measurement (SSM). An LSM of less than 16 kPa and an SSM of less than 26.6 were able to rule out CSPH with a sensitivity of 98.6%.[70] An LSM of greater than 38 kPa correctly ruled in CSPH in all patients. In patients with an LSM of less than 38 kPa, an SSM of greater than 27.9 kPa was able to rule in CSPH with a specificity of 91.4%. Combining both algorithms, patients were correctly classified as having or not CSPH in 91.6% of cases with a sensitivity of

98.3% and a specificity of 96.3%.[71] A large cohort of 191 patients showed that their accuracy was insufficient for the application in clinical practice.[72]

Overall, LSM performance using 2D-SWE for CSPH is likely consistent with that of TE.[48] However, the heterogeneity of cut-offs (2D-SWE, 16–38 kPa), possibly underlines a lack of standardization. Although currently not implemented in clinical practice, the method seems promising and further data are awaited.[50] **Fig. 3** summarizes the advantages and disadvantages of LSM and SSM using the different available ultrasound elastography techniques.

LIVER ELASTOGRAPHY FOR THE ASSESSMENT OF GASTROESOPHAGEAL VARICES

Screening endoscopy for esophageal varices in patients with a diagnosis of ACLD is a crucial part of the management, because it can precisely identify varices needing treatment aimed at decreasing the risk of bleeding.[73] LSM has been proven extensively to predict varices needing treatment. This section includes more recent studies in this field published after the Baveno VI workshop (**Table 3**).

Transient Elastography

Although it is not as accurate as for defining the presence of CSPH, it is the single best noninvasive method for varices detection.[74] A recent meta-analysis with a total of 3644 patients reported a correct diagnosis of esophageal varices or varices needing treatment after a positive measurement of LSM (with variable cut-offs) did not exceed 70%.[74] The majority of studies including LSM by TE after the publication of the Baveno VI consensus report have been focused on combination tests (see **Table 3**).

Point Shear Wave Elastography

pSWE has been widely evaluated for the prediction of esophageal varices, with varied results. A 2014 cohort study reported an AUROC of 0.743 for the prediction of esophageal varices using pSWE (vs TE with an AUROC of 0.802).[63] Later, a Japanese study showed an AUROC of 0.789 for any varices and an AUROC of 0.788 for varices

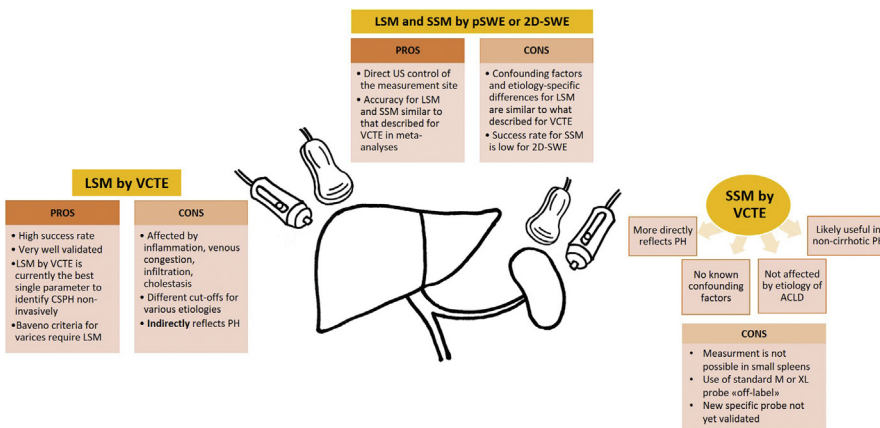

Fig. 3. Advantages and disadvantages of LSM and spleen stiffness measurement (SSM) for portal hypertension using the different available ultrasound elastography techniques. 2D-SWE, 2-dimensional shear wave elastography; ACLD, advanced chronic liver disease; PH, portal hypertension; US, ultrasound examination.

Table 3
Accuracy of LSM using ultrasound elastography techniques (TE, pSWE, and 2D-SWE) for the diagnosis of gastroesophageal varices in the post-Baveno VI era

Study, Year	Design	Type of Ultrasound Elastography Method ± Other Combined	Patient Population; Number of Esophageal Varices, Number Varices Needing Treatment	TE-Cut-offs and AUC Esophageal Varices/ Varices Needing Treatment	Conclusions
TE (studies included $\geq$ 200 patients)					
Maurice et al,[149] 2016	Retrospective	TE + platelet count	310 mixed	LSM: 20 kPa, AUC 0.686 LSM (20 kPa) and PLT (150 G/L): AUC 0.746	SENS. 67%, SPEC. 55%, PPV 7%, NPV 97%; SENS.87%, SPEC. 34%, PPV 6%, NPV 98%
Abraldes et al,[150] 2016	Retrospective	TE + platelet count ± spleen size; LSPS score and platelet-spleen ratio [PSR]	518 mixed	LSM: 14.0 kPa (AUC 0.67) LSM (20 kPa) and PLT (150 G/L): AUC 0.76	LSPS and a model with TE and platelet count identified patients with very low risk (<5%) risk of varices needing treatment
Marot et al,[140] 2017	Meta-analysis	TE ± platelet count or TE alone	3364 mixed	<20 kPa; PLT>150 G/L	LSM + PLT (150 G/L): SENS. 89%, SPEC. 38%, PPV: 43%, NPV: 86% SENS. 93%, SPEC. 30%, PPV 14%, NPV 97%
Pu et al,[151] 2017	Meta-analysis	TE alone	2697 mixed	LSM (pooled): 20 kPa, AUC 0.83; 30 kPa, AUC: 0.83	LSM: Pooled: SENS. 84%, SPEC. 62%, Cut-off 20 kPa: SENS. 83%, SPEC. 68%, Pooled: SENS. 78%, SPEC. 76%, Cut-off 30 kPa: SENS. 73%, SPEC. 74%

(*continued on next page*)

Table 3
(*continued*)

Study, Year	Design	Type of Ultrasound Elastography Method ± Other Combined	Patient Population; Number of Esophageal Varices, Number Varices Needing Treatment	TE-Cut-offs and AUC Esophageal Varices/ Varices Needing Treatment	Conclusions
Jangouk et al,[142] 2017	Retrospective	Baveno VI (LSM 20 kPa, PLT>150 G/L), PLT >150, MELD = 6	262 mixed	LSM (20 kPa) and PLT >150 G/L; MELD = 6 (150 G/L)	Baveno criteria 26% (US) and 16% (Italy) spared. SENS. and NPV were 100%. PLT >150 G/L and MELD = 6, increased the number of endoscopies avoided to 54% (US) while maintaining a SENS. and NPV of 100%.
Agustin et al,[125] 2017	Retrospective	TE ± PLT, expanded Baveno	925 mixed	LSM (25 kPa) and PLT >110 G/L	Expanded-Baveno VI: spare 40%; missing varices needing treatment of 1.6%
Petta et al,[152] 2018	Retrospective analysis of prospective data	Baveno VI and expanded Baveno VI (TE ± PLT)	790 NAFLD/NASH	LSM: 20 kPa + PLT 150 G/L LSM 25 kPa + Plt 110 G/L LSM 30 kPa + Plt 110 G/L	Best cut-offs to rule out varices needing treatment: PLT>110 G/L + LSM <30 kPa (M probe), PLT>110 G/L + LSM <25 kPa (XL probe)

Manatsathit et al,[123] 2018	Meta-analysis 45 studies	LSM alone vs SSM alone vs LSPS	4337 Mixed	AUC SSM and LSPS vs LSM: 0.899 and 0.851 vs 0.817	For esophageal varices detection: SSM and LSPS vs LSM (0.90 and 0.91 vs 0.85), specificity (0.73 and 0.76 vs 0.64) For varices needing treatment: SSM (0.87) > LSM (0.85) > LSPS (0.82); LSM, SSM, and LSPS cannot be recommended for detection of varices needing treatment
Bae et al,[153] 2018	Cross-sectional	TE	282 mixed (60% HBV)	LSM (20 kPa) and PLT >150 G/L LSM (25 kPa) and PLT >110 G/L	Expanded Baveno VI criteria spare more (51.7%) than (27.6%). expanded missed varices needing treatment (6.8%) than the original criteria (3.8%), Baveno VI: NPV HBV: 0.92, HCV: 1.00, ARLD: 1.00, NAFLD:1.00
Lee et al,[154] 2018	Retrospective	Baveno VI and expanded Baveno VI (TE ± PLT)	1218 (40% HBV)	LSM (20 kPa) and PLT >150 G/L; LSM (25 kPa) and PLT >110 G/L AUC LSPS: 0.780 (95% CI: 0.774–0.820)	Baveno VI: 25.7% saved endoscopy; varices needing treatment miss rate: 1.9%. Expanded Baveno VI: saved endoscopy: 39.1%; varices needing treatment miss rate <5%

(*continued on next page*)

Table 3
(*continued*)

Study, Year	Design	Type of Ultrasound Elastography Method ± Other Combined	Patient Population; Number of Esophageal Varices, Number Varices Needing Treatment	TE-Cut-offs and AUC Esophageal Varices/ Varices Needing Treatment	Conclusions
Moctezuma-Velazquez et al,[155] 2018	Cross-sectional	TE ± PLT Baveno VI and expanded Baveno VI	227 cholestatic PBC (n = 147) PSC (n = 80)		Baveno-VI criteria 0% False negative rate in PBC and PSC, saving 39% and 30% of endoscopies. In PBC the other LSM-TE: FNRs >5%. In PSC the expanded Baveno: adequate performance. In both conditions.
Thabut et al,[101] 2019	Prospective ancillary study ANRS CO12 CirVir cohort	TE ± PLT (Baveno VI)	200 HBV- (n = 98) or HCV- (n = 94) or both (n = 8) with SVR to antivirals		Baveno VI valid patients with compensated viral cirrhosis, even SVR. Endoscopy is no longer necessary in the subgroup of low-risk patients
Point shear wave elastography					
Salzl et al,[63] 2014	Cross-sectional	pSWE; Acuson S2000	88 mixed	L-SWE: 2.74 m/s (0.743)	For esophageal varices: 62.5%/89.5 %/PPV: 91.5%/NPV: 56.9%
Takuma et al,[65] 2016	Cross-sectional	pSWE; Acuson S2000	340 mixed	For esophageal varices: AUC: 0.789; varices needing treatment: AUC 0.788	

Attia et al,[64] 2015	Cross-sectional	pSWE; Acuson S2000	78 mixed		LSM in both groups of patients (SSM: 0.90 and 0.93 vs LSM: 0.84 and 0.88, respectively).
Lucchina et al,[156] 2018	Cross-sectional	pSWE; iU22	42 mixed	L-SWE: 12.27 kPa AUC: 0.913	SENS: 100%/SPEC: 66.67%
2D-SWE (only studies with > 100 patients selected)					
Cassinotto et al,[75] 2015	Prospective	2D-SWE, Aixplorer	401 mixed	L-SWE: AUC 0.80 LSM: AUC 0.73	L-SWE: SENS. 92%/SPEC. 36%
Kasai et al,[77] 2015	Retrospective	2D-SWE, Aixplorer	273 mixed	0.807	
Kim et al,[78] 2016	Retrospective	2D-SWE, Aixplorer	103 mixed	For esophageal varices: L-SWE: 13.9 kPa AUC 0.887 varices needing treatment cut-off 16.1 kPa; AUC 0.887 for any esophageal varices and 0.880 varices needing treatment; L-SWE: All patients: 26.3 kPa; AUC:0.683 cACLD:14.2 kPa (0.925)	Esophageal varices: SENS 75%/SPEC 88.9%/ Varices needing treatment: 84.6%/ 85.6%

(*continued on next page*)

Table 3
(*continued*)

Study, Year	Design	Type of Ultrasound Elastography Method ± Other Combined	Patient Population; Number of Esophageal Varices, Number Varices Needing Treatment	TE-Cut-offs and AUC Esophageal Varices/ Varices Needing Treatment	Conclusions
Jansen et al.[71] 2017	Prospective	2D-SWE; Aixplorer SSI	158 mixed		Rule-out for esophageal varices SENS: 0.98; SPEC: 0.50; PPV: 0.80; NPV: 0.93; Diagnostic accuracy: 0.83 Rule-in for esophageal varices SENS: 0.90; SPEC: 0.60; PPV: 0.83; NPV: 0.73; Diagnostic accuracy: 0.81
Petzold G et al,[157] 2019	Prospective	2D-SWE; GE Logiq E9	100 mixed	L-SWE: AUC: 0.781	L-SWE combined with gallbladder wall thickness (GBWT) for esophageal varices: SENS: 86.3% SPEC: 71.4%; At L-SWE >9 kPa or GBWT >4 mm: SENS 100% (NPV 1.0)

Abbreviations: 2D-SWE, bidimensional shear wave elastography; AUC, area under the curve; kPa, kilopascal; LSPS, liver stiffness to spleen/platelet score; L-SWE, liver stiffness by Shear wave elastography; MELD, Model for End-stage Liver Disease; NASH, nonalcoholic steatohepatitis; NPV, negative predictive value; PBC, primary biliary sclerosis; pSWE, point shear wave elastography; SENS, sensibility; SPEC, specificity; SSI, supersonic imaging.

needing treatment, respectively.[65] Currently, evidence is not strong enough to recommend pSWE to rule in or rule out varices needing treatment.

Two-Dimensional Shear Wave Elastography

Three studies showed an AUROC around 0.80 for LSM in patients with cACLD for esophageal varices.[75–77] LSM yielded an AUROC of 0.887 for any esophageal varices and 0.880 (cut-off of 16.1 kPa) for varices needing treatment,[78] which was not confirmed in another study including 79 patients revealing no difference between LSM and SSM values (L-2D-SWE and by TE) between patients for varices needing treatment.[79] Stefanescu and colleagues[80] demonstrated that, with a stepwise approach combining LSM at a cut-off less than 19 kPa with a cut-off of PLT greater than 100 G/L, esophageal varices were ruled out with 83% accuracy. Another cohort study of patients with cACLD supported these data.[71] More recently, diagnostic performance of 2D-SWE was shown to be similar to that of TE for predicting the presence of esophageal varices. The AUROCs for predicting varices needing treatment for 2D-SWE and a modified Liver Stiffness-Spleen Size-To-Platelet Ratio Risk Score were 0.712 (95% CI, 0.621–0.738) and 0.834 (95% CI, 0.785–0.875), respectively.[81] The diagnostic performance of 2D-SWE is similar to that of TE for predicting the presence of esophageal varices.

Overall, larger scale studies are needed to overcome significant discrepancies between among reported cut-offs for both pSWE and 2D-SWE–based LSM. There is solid evidence to support the use of LSM and platelet count, but the future implementation of SSM and other tests to further enhance esophageal varices screening strategies in cACLD is promising.

Liver Stiffness Measurement for the Follow-up of Portal Hypertension

CSPH is a key predictor of risk of clinical decompensation in patients with cACLD.[82] Robic and colleagues[83] showed that LSM and HVPG were similarly accurate in predicting a first episode of decompensation in patients with cACLD. All of the clinical events occurred in patients with an LSM of 21.1 kPa or higher.

Different studies[83–88] have shown that in patients with cACLD, LSM holds prognostic value for liver-related events and death. Recently, this finding was confirmed in a systematic review and meta-analysis[89] of 17 prospective studies, including 7058 patients. In 1 study, an increase of more than 1.5 kPa per year in LSM seemed to add prognostic value to baseline LSM in both primary biliary sclerosis[90] and HCV.[91]

As for the combination of LSM with other noninvasive tests, the liver stiffness to spleen/platelet score predicted first decompensation in an hepatitis B virus cohort better than LSM alone cACLD.[92] Our group recently reported that the liver stiffness to spleen/platelet score was superior to LSM (using an XL probe) and portal hypertension risk score to predict the first clinical decompensation in obese/overweight patients with nonalcoholic steatohepatitis.[93] Furthermore, Wong and colleagues[94] followed 548 patients with cACLD for 3 years and showed that an LSM/SSM–guided screening strategy for varices had a similar low risk of variceal hemorrhage as compared with universal screening endoscopy.

As far as prediction of hepatocellular carcinoma is concerned, a number of prospective studies have identified that LSM in patients with viral cirrhosis is associated with the risk of incidence of hepatocellular carcinoma.[95–99]

Regarding nonselective beta-blockers (NSBB) response, LSM changes in patients with portal hypertension undergoing therapy do not correlate with changes in HVPG.[100]

As for patients with cACLD who did not undergo variceal screening being within the Baveno criteria, LSM should be repeated yearly, and an increase of LSM or more than 10 kPa indicates the need of starting variceal screening.[3] This recommendation has been validated in a recent study from France.[101]

SPLEEN ELASTOGRAPHY

In patients with portal hypertension, the elevated portal pressure is transmitted to the splenic vein and leads to passive congestion in the spleen. Combined with an increased arterial inflow from splanchnic vasodilation, hyperactivation of splenic lymphoid tissue, fibrogenesis and angiogenesis, this causes an increase in spleen stiffness.[102]

The advantages of SSM in comparison with LSM to assess portal hypertension are multiple (see **Fig. 3**). First, SSM is devoid of some of the confounding factors that may affect LSM reliability, such as liver congestion, inflammation, infiltration or cholestasis, although a recent study suggested that liver inflammation could potentially increase SSM.[103] Moreover, SSM takes into account the dynamic component of portal hypertension that is not reflected by LSM and hence correlates better with portal pressure in later stages of liver disease.[104] SSM can also be useful to differentiate between cirrhotic and noncirrhotic (prehepatic, idiopathic, and presinusoidal) portal hypertension, where there is a mismatch between the LSM and the SSM.[105]

However, 2 main disadvantages have made SSM difficult to implement in clinical practice to date. The first is the high failure rate ($\leq$15%–30%) that has been observed with SSM, mostly with TE and 2D-SWE (supersonic imaging) compared with pSWE, which is feasible most of the time (**Table 4**). The absence of splenomegaly, ascites, and obesity, as well as movements caused by the heart beating in the case of 2D-SWE, negatively affect the success rate.[75] SSM by TE was improved significantly with the use of ultrasound examination to localize the spleen[106,107] and with a novel, spleen-dedicated TE examination (SSM at 100 Hz, where the shear wave frequency is set at 100 Hz instead of 50 Hz) (6%–13% and 7.5% failure rate, respectively).[67] All 3 techniques have an excellent reproducibility.[106,108,109]

The second disadvantage of SSM is the ceiling effect at 75 kPa, specific to TE. The spleen is a stiffer organ than the liver, even in normal subjects, and the use of the same probes and software than for LSM may not be appropriate. To overcome this effect, some authors have proposed to use a modified software, where the SSM can be reflected up to 150 kPa[110] and others, as discussed elsewhere in this article, suggested a novel, spleen-dedicated TE examination (SSM at 100 Hz) with values up to 100 kPa.[67]

Spleen Elastography for the Assessment of Portal Hypertension

A number of studies have evaluated the ability of SSM to predict portal hypertension (see **Table 4**). A recent meta-analysis of 9 studies concluded that SSM strongly correlates with HVPG (summary R = 0.72; 95% CI, 0.63–0.80) and has a good accuracy for predicting CSPH (AUROC, summary sensitivity and specificity of 0.92 [95% CI, 0.89–0.94], 0.88 [95% CI, 0.70–0.96], and 0.84 [95% CI, 0.72–0.92], respectively),[111] comparable with LSM,[48] although the heterogeneity of studies included limits the interpretation of these results. Another recent meta-analysis including only studies evaluating 2D-SWE (supersonic imaging) showed a moderate diagnostic accuracy for CSPH.[112] Studies that reported a poor performance of SS to detect CSPH (AUROCs in the 0.60 range) included patients with more advanced CLD.[79,113]

Table 4
Accuracy of SSM using ultrasound elastography techniques for CSPH and esophageal varices in ACLD

Study, Year	Method Used	N Included and Etiology	Failure Rate (%)	End Point	AUROC for the Selected Endpoint	Chosen Cut-off for the Selected Endpoint	Sensitivity (%)	Specificity (%)
Stefanescu et al,[158] 2011	TE	174, mixed	14, 4	Esophageal varices	0.781	46.4 kPa	83.6	71.4
Colecchia et al,[106] 2012	TE	113, HCV, compensated	11.5	CSPH	0.966	40.0 kPa (rule out) 52.8 kPa (rule in)	98.5 76.9	74.3 97.1
				Esophageal varices	0.941	41.3 kPa (rule out) 55.0 kPa (rule in)	98.1 71.7	66.0 95.7
Sharma et al,[113] 2013	TE	200, mixed	13	Esophageal varices	0.898	40.8 kPa	94	76
Calvaruso et al,[110] 2013	TE (modified range)	112, HCV, compensated	14.3	Esophageal varices Large esophageal varices	0.701 0.820	50.0 kPa 54.0 kPa	65 80	61 70
Zykus et al,[146] 2015	TE	107, mixed, most compensated	7.5	CSPH	0.846	47.6 kPa	77.3	79.2
Stefanescu et al,[159] 2015	TE	136, mixed	N/A	High-risk esophageal varices	0.742	53 kPa	89	54
Wong et al,[130] 2016	TE	176, HBV	15.9	Esophageal varices	0.685	21.4 kPa (rule out) 50.5 kPa (rule in)	90.3 45.2	43.4 90.3
Arribas Anta et al,[160] 2019	TE	66, mixed	9.1	Esophageal varices	0.800	48 kPa	87	69
Stefanescu et al,[67] 2020	TE (spleen-dedicated, 100 Hz)	260, mixed	7.5 (*vs.* 24for 50 Hz)	CSPH Esophageal varices High-risk esophageal varices	0.811 0.728 0.756	34.15 kPa 33.3 kPa (rule out) 70 kPa (rule in) 40 kPa (rule out) 79.9 kPa (rule in)	N/A 90.3 29.1 91.3 26.1	N/A 33.7 90.5 40.8 90.1
Rifai et al,[161] 2011	pSWE (VTQ)	100, mixed	22	CSPH	0.680	3.29 m/s	47	73

(*continued on next page*)

Table 4
(*continued*)

Study, Year	Method Used	N Included and Etiology	Failure Rate (%)	End Point	AUROC for the Selected Endpoint	Chosen Cut-off for the Selected Endpoint	Sensitivity (%)	Specificity (%)
Bota et al,[162] 2012	pSWE (VTQ)	145, mixed	2.1	Large esophageal varices	0.578	2.55 m/s	96.7	21.0
Ye et al,[163] 2012	pSWE (VTQ)	204, HBV	N/A	Esophageal varices Large esophageal varices	0.830 0.839	3.16 m/s 3.39 m/s	84.1 78.9	81 78.3
Vermehren et al,[164] 2012	pSWE (VTQ)	166, mixed	0	Large esophageal varices	0.580	3.04 m/s	90	25
Takuma et al,[165] 2013	pSWE (VTQ)	340, mixed	4.5	Esophageal varices High-risk esophageal varices	0.937 (viral) 0.923 (others) 0.930 (all)	3.18 m/s 3.24 m/s 3.30 m/s	98.9 97.7 98.9	59.9 65.2 62.9
Rizzo et al,[166] 2014	pSWE (VTQ)	54, HCV	N/A	Esophageal varices	0.959	3.10 m/s	96.4	88.5
Attia et al,[64] 2015	pSWE (VTQ)	78, mixed, some decompensated, 90CSPH, 76% esophageal varices	0	CSPH	0.968	2.32 m/s	96	89
Kim et al,[167] 2015	pSWE (VTQ)	132, mixed	4.5	Esophageal varices Large esophageal varices	0.785 0.786	3.16 m/s 3.40 m/s	87.0 78.9	60.4 63.0
Park et al,[168] 2016	pSWE (ElastPQ)	366, viral and alcohol	24	Esophageal varices	0.859	29.9 kPa	85.1 kPa	79.1 kPa
Takuma et al,[65] 2016	pSWE (VTQ)	62, mixed, most compensated	3.2	CSPH HVPG $\geq$12 mm Hg Esophageal varices Large esophageal varices	0.943 0.963 0.937 0.955	3.10 m/s 3.15 m/s 3.36 m/s 3.51 m/s	97.1 96.6 95.8 93.8	57.7 61.3 77.8 84.1

Lucchina et al,[156] 2018	pSWE (ElastPQ)	54, mixed (only patients without esophageal varices or with small esophageal varices were included)	22	Esophageal varices	0.675	23.9 kPa	73.8	59.5
Fierbinteanu-Braticevici et al,[169] 2019	pSWE (VTQ)	135, mixed	0	Esophageal varices	0.776	2.5 m/s (rule out) 3.5 m/s (rule in)	92 47	22 96
				High-risk esophageal varices	0.972	3.2 m/s (rule out) 3.8 m/s (rule in)	97 55	69 98
Peagu et al,[170] 2019	pSWE (VTQ)	178, viral	N/A	Esophageal varices Large esophageal varices	0.872 0.969	2.89 m/s 3.30 m/s	91.4 96.4	67.7 88.5
Darweesh et al,[171] 2019	pSWE (VTQ)	200, HCV	1	Esophageal varices	0.760	3.25 m/s	85	58
Giuffrè et al,[103] 2020	pSWE (ElastPQ)	210, mixed, compensated	4.5	Esophageal varices	0.95	31 kPa (rule out) 69 kPa (rule in)	100 14	60 100
				High-risk esophageal varices	N/A	46 kPa (rule out)	100	84
Elkrief et al,[79] 2015	2D-SWE (SSI)	79, mixed, most decompensated, 89 CSPH, 69%	3	CSPH Large esophageal varices	0.640 0.580	34.7 kPa 32.3 kPa	40 48	100 71
	TE	Child-Pugh B-C	58	CSPH Large esophageal varices	0.630 0.650	56.3 kPa 73.5 kPa	73 54	67 78
Procopet et al,[109] 2015	2D-SWE (SSI)	55, mixed, most compensated	34	CSPH	0.725	22.7 kPa (rule out) 40 kPa (rule in)	90 N/A	N/A 90
Cassinotto et al,[75] 2015	2D-SWE (SSI)	401, mixed, some decompensated	29.2	Esophageal varices High-risk esophageal varices	0.80 0.78 (all) 0.75 (compensated)	N/A N/A 25.6 kPa (with NPV >90%)	N/A N/A 94	N/A N/A 36

(*continued on next page*)

Table 4
(*continued*)

Study, Year	Method Used	N Included and Etiology	Failure Rate (%)	End Point	AUROC for the Selected Endpoint	Chosen Cut-off for the Selected Endpoint	Sensitivity (%)	Specificity (%)
Grgurevic et al,[118] 2015	2D-SWE (SSI)	126, mixed	29.4	Esophageal varices	0.790	30.3 kPa	79.6	75.8
Jansen et al,[71] 2017	2D-SWE (SSI)	158, mixed, some decompensated	18.8	CSPH	0.840	26.3 kPa 21.7 kPa (rule out) 35.6 kPa (rule in)	79.7 91.9 51.4	84.2 50 92
Zhu et al,[69] 2019	2D-SWE (SSI)	104, HBV, most compensated	24.6	CSPH	0.810	23.2 kPa (rule out) 34.2 kPa (rule in)	>90 N/A	N/A >90
Karagiannakis et al,[124] 2019	2D-SWE (SSI)	64, mixed, compensated	9.8	High-risk esophageal varices	0.792 (all) 0.854 (excluding cholestatic liver disease)	33.7 kPa (rule out) 35.8 kPa (rule out)	91.7 88.9	60.0 72.4

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value; pSWE, point shear wave elastography; SS, spleen stiffness; SSI, supersonic imagine; SWE, shear wave elastography; VTQ, virtual touch quantification.

As for the prediction of severe portal hypertension, a recent study confirms that the correlation between SSM and HVPG decreases with increasing HVPG, especially greater than 16 mm Hg,[104] where SS is more dependent on the chronic spleen parenchymal remodeling rather than reflecting passive congestion. Thus, SSM is likely not a good tool to identify patients with severe portal hypertension.

Determining the optimal SSM cut-off values to predict CSPH is challenging, as highlighted by the multiple cut-off values proposed in various studies, which depend on the population included (the etiology of liver disease and compensated or decompensated stage) (see **Table 4**). The use of a single cut-off value is usually associated with suboptimal sensitivity and specificity, whereas the use of 2 values (one rule out with high sensitivity and one rule in with high specificity) has the disadvantage of leading to a large number of unclassified patients. As with LSM, the use of specific cut-offs for each etiology of CLD has been proposed,[61] but its importance is probably less than for LSM.

SSM has also been shown to be able to predict clinical decompensation and mortality,[114–118] as well as late hepatocellular carcinoma recurrence.[119] As for the ability of SSM to predict liver failure after hepatectomy, the data are inconclusive.[120,121]

MR elastography (MRE) of the spleen has recently emerged as a potential tool to evaluate portal hypertension. A recent systematic review and meta-analysis of 14 studies (8 studies including spleen MRE) concluded that MRE had a good diagnostic accuracy in detecting portal hypertension with a summary AUROC, sensitivity, and specificity of 0.92 (95% CI, 0.89–0.94), 0.79 (95% CI, 0.61–0.90), and 0.90 (95% CI, 0.80–0.95), respectively.[122] The major inconvenient of MRE remains its limited availability and cost.

Spleen Elastography for the Assessment of Gastroesophageal Varices

Because the development of gastroesophageal varices depends on CSPH, it is not surprising that SSM can predict their presence (see **Table 4**). A recent systematic review and meta-analysis of 45 studies (17 evaluating SS with various techniques) concluded that SSM was superior to LSM in predicting esophageal varices in CLD with AUROC, summary sensitivity, and summary specificity of 0.899, 0.90 (95% CI, 0.87–0.94), and 0.73 (95% CI, 0.65–0.80), respectively, compared with 0.817, 0.85 (95% CI, 0.81–0.89), and 0.64 (95% CI, 0.56–0.71) for LSM.[123] This result is likely attributable to the better performance of SSM compared with LSM in more severe portal hypertension because it reflects better the hemodynamic component of portal hypertension. The diagnostic accuracy was not as good for high-risk esophageal varices (AUROC, 0.807). A study published after showed a slightly better performance for high-risk esophageal varices (AUROC, 0.847).[107] The results of this meta-analysis, however, need to be interpreted carefully given the heterogeneity of the population included, with both compensated and decompensated patients.

As discussed elsewhere in this article, some studies have evaluated new technologies to improve further the diagnostic capacity of SSM. In a recent study, prediction of large esophageal varices was improved with the use of a novel, spleen-dedicated TE with higher shear wave frequency (100 Hz, compared with the traditional 50 Hz).[67] In this study, the use of SSM at 100 Hz alone (with a cut-off of 41.3 kPa) could spare 37.8% esophagogastroduodenoscopy compared with Baveno VI alone (8.1%), with a 4.7% rate of missed high-risk esophageal varices (with the total number of high-risk esophageal varices as denominator). Colecchia and associates[107] with regular TE and Karagiannakis and colleagues[124] with 2D-SWE showed similar rates of spared endoscopy with SSM alone, so did studies on expanded Baveno VI criteria.[125]

As with CSPH, once again, determining optimal rule out and rule in cut-off values is challenging. For SSM by TE, a value of 46 kPa has been accepted as an adequate rule out cut-off, whereas for pSWE and 2D-SWE, no single values can currently be recommended, although they probably are in the range of 2.5 to 3.5 m/s and 21 to 33 kPa, respectively. The Spleen Stiffness Probability Index was recently proposed by Giuffrè and coworkers[103] to establish, instead of cut-offs, a probability of high-risk esophageal varices for each SSM value, supporting the clinician in deciding whom to screen or not and avoiding the issue of false negatives and false positives that occur with cut-offs.

SSM was also found to be a good predictor of esophageal variceal bleeding (cumulative incidence 7.4%), with an AUROC of 0.857 (0.911 in compensated patients) in a prospective study by Takuma and colleagues,[126] where patients were followed for a median duration of 32.7 months. In this study, the SSM with the maximal negative predictive value was 3.64 m/s (3.48 m/s in compensated cirrhosis). A retrospective study using TE showed similar results with a 100% negative predictive value at a cut-off SSM value of 42.6 kPa.[127]

Spleen Elastography for the Follow-up of Portal Hypertension

Given the rationale behind SSM, it can be expected that the most efficient treatment for portal hypertension, liver transplantation, causes a net decline in SSM.[128] Whether SSM could be a useful tool to assess response to other treatments for portal hypertension is a topic of interest. A recent study showed a good performance (AUROC, 0.848) of a model based on dynamic changes in SSM (by pSWE) in predicting the hemodynamic response to NSBB prophylaxis in patients with high-risk esophageal varices.[129] Of note, beta-blockers were previously shown not to affect the diagnostic accuracy of SSM.[130] SSM has also been repeatedly shown to decrease after transjugular intrahepatic portosystemic shunt and, therefore, could be a reliable tool to monitor transjugular intrahepatic portosystemic shunt function,[131–135] except when there is concurrent embolization or thrombosis of competitive shunts, where SSM may increase after transjugular intrahepatic portosystemic shunting.[136] In a recent study by Takuma and colleagues,[137] SSM by virtual touch quantification increased after balloon-occluded retrograde transvenous obliteration and was a predictor of exacerbation of esophageal varices. Studies done in the post-direct-acting antiviral era showed that SSM also decreases after HCV eradication[54,138]

In conclusion, there are now enough solid data to include SSM in the list of standard, noninvasive tools available to assess CSPH. A number of studies have also proven its good performance in detecting the presence of esophageal varices, justifying its integration in algorithms to select patients for screening endoscopy for varices.

COMBINATION TESTS

Strategies combining other noninvasive markers of portal hypertension have been implemented to improve diagnostic accuracy of LSM. In a recent meta-analysis, esophageal varices detection for the liver stiffness to spleen/platelet score and SSM was superior to LSM.[123] Furthermore, in a prospective cohort of patients with cACLD, the liver stiffness to spleen/platelet score correctly classified esophageal varices in around 80% of patients.[139] Subsequently, the Baveno VI Consensus suggested that a platelet count of more than 150 g/L and a LSM of less than 20 kPa could identify patients with cACLD, with a very low risk (<5%) of varices needing treatment.[3]

A meta-analysis concluded that varices needing treatment are found in no more than 4% of patients when the LSM is less than 20 kPa with a normal platelet count.[140]

Moreover, another study tested earlier noninvasive test-based algorithms and Baveno VI and found that esophageal varices misdiagnosed when using platelets in 3.1%, TE in 3.7%, the liver stiffness to spleen/platelet score in 10%, variceal risk index in 11.3%, Baveno VI in 1.8%, and Augustin algorithm in 3.7% of patients. The rate of unnecessary gastroscopies was 46% for platelet count, 25% for TE, 13% for the liver stiffness to spleen/platelet score, 6% for the variceal risk index, 53% for Baveno VI, and 39.1% for the Augustin algorithm.[141]

In an attempt to reduce the number of unnecessary endoscopies, Jangouk and colleagues[142] reported that a strategy using platelet count or more than 150 G/L and a Model for End-stage Liver Disease of 6 without LSM, substantially increased the number of endoscopies avoided to 54%, with a very low rate of missing varices needing treatment. These findings without LSM were not validated because of an unacceptable high rate of missed varices needing treatment.[125] The Expanded Baveno VI criteria used a platelet count or more than 110 G/L and a LSM of less than 25 kPa potentially spared 40% of endoscopies (21% with Baveno VI criteria) with a risk of missing varices needing treatment of 1.6%.[125]

More recently, combined approaches have included SSM. The combination of SSM with Baveno VI criteria could spare 43.8% of endoscopies. The combined Baveno VI/SSM of 46 or less model would have safely spared 37.4% of endoscopies (0 high-risk esophageal varices missed), compared with 16.5% without SSM.[107]

Fig. 4 summarizes the existing strategies combining noninvasive tests to optimize the selection of patients for endoscopy in the context of cACLD.

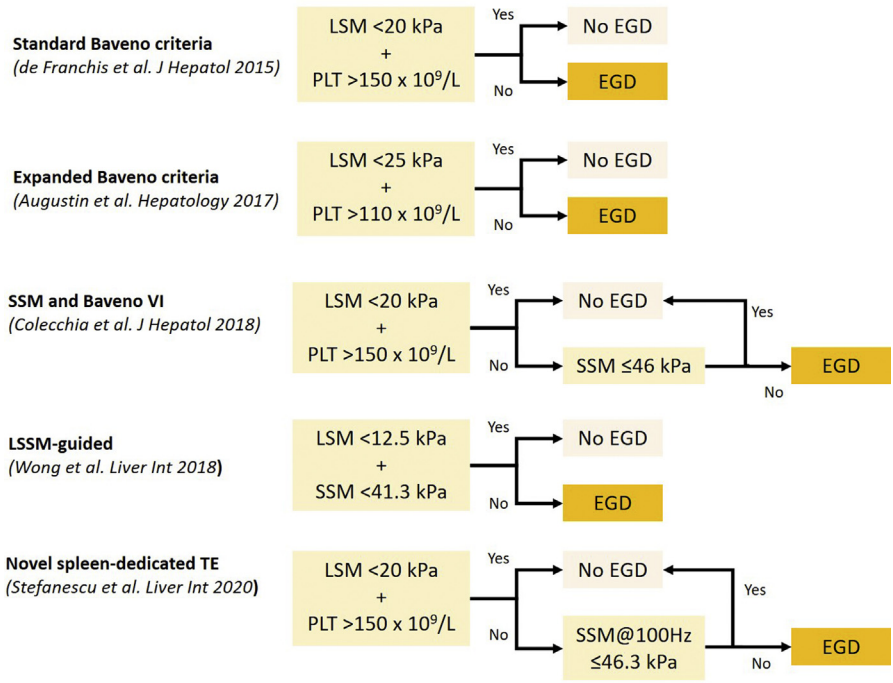

Fig. 4. Existing strategies based on noninvasive tests to decrease the need of screening for varices treatment (VNT). EGD, esophagogastroduodenoscopy; PLT, platelet count; SSM, spleen stiffness measurement; TE, transient elastography.

SUMMARY

Noninvasive tests, and in particular liver elastography, have represented a major advantage in the assessment of patients with cACLD in the last years. Although a perfect method to quantify noninvasively the HVPG is still lacking, novel techniques such as MR-based techniques and SHAPE by contrast-enhanced ultrasound examination have a large potential to become game-changers in this field within the next 5 years. The authors expect also radiomics to expand and become a novel strategy integrating the existing imaging data into robust algorithms allowing better identifying in a completely automated way the presence of CSPH and varices. Given the new data regarding a protective role of NSBB on the onset of decompensation (and not just variceal bleeding), a quick and accurate way of diagnosing CSPH noninvasively will become the standard of care. Awaiting for the validation of these methods, LSM and SSM used in combination, and combined to unrelated methods such as spleen size by imaging and platelet count, already allow to rule in CSPH with an accuracy exceeding 90%.

Recent data showing that the hemodynamic response to NSBB can be mirrored by changes in SSM by pSWE are awaiting validation and, if confirmed, would represent a major advantage in the management of patients with portal hypertension. The HVPG measurement remains the reference standard and it should be used whenever noninvasive tests provide inconsistent results or whenever the clinical decision based on the result implies possible risks for patients (eg, selection of candidates to liver resection for hepatocellular carcinoma; identification of patients nonresponding to medical therapy of portal hypertension after variceal bleeding, potential candidate to transjugular intrahepatic portosystemic shunt).

CLINICS CARE POINTS

- CSPH can be diagnosed noninvasively in patients with cACLD by the following findings: portosystemic collaterals on imaging and a LSM of more than 20 to 25 kPa.
- Splenomegaly, thrombocytopenia, and a SSM of more than 46 kPa further increase the likelihood of CSPH.
- Patients presenting any of the signs discussed in this article while compensated should undergo endoscopy for screening of varices requiring treatment according to the existing guidelines.
- In the future, patients with signs of CSPH on noninvasive tests might be started on carvedilol straight away to decrease the risk of a first clinical decompensation.

DISCLOSURE

The authors have nothing to disclose.

REFERENCES

1. Bosch J, Abraldes JG, Berzigotti A, et al. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6:573–82.
2. Rosselli M, MacNaughtan J, Jalan R, et al. Beyond scoring: a modern interpretation of disease progression in chronic liver disease. Gut 2013;62:1234–41.

3. 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. J Hepatol 2015;63:743–52.
4. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017;65:310–35.
5. Bruno S, Zuin M, Crosignani A, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. Am J Gastroenterol 2009;104:1147–58.
6. Zipprich A, Garcia-Tsao G, Rogowski S, et al. Prognostic indicators of survival in patients with compensated and decompensated cirrhosis. Liver Int 2012;32:1407–14.
7. D'Amico G, Pasta L, Morabito A, et al. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014;39:1180–93.
8. Colecchia A, Marasco G, Taddia M, et al. Liver and spleen stiffness and other noninvasive methods to assess portal hypertension in cirrhotic patients: a review of the literature. Eur J Gastroenterol Hepatol 2015;27:992–1001.
9. European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del H. EASL-ALEH clinical practice guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63:237–64.
10. Qi X, Berzigotti A, Cardenas A, et al. Emerging non-invasive approaches for diagnosis and monitoring of portal hypertension. Lancet Gastroenterol Hepatol 2018;3:708–19.
11. Qamar AA, Grace ND, Groszmann RJ, et al. Incidence, prevalence, and clinical significance of abnormal hematologic indices in compensated cirrhosis. Clin Gastroenterol Hepatol 2009;7:689–95.
12. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 2013;144:102–11.e101.
13. Ferlitsch M, Reiberger T, Hoke M, et al. von Willebrand factor as new noninvasive predictor of portal hypertension, decompensation and mortality in patients with liver cirrhosis. Hepatology 2012;56:1439–47.
14. Hametner S, Ferlitsch A, Ferlitsch M, et al. The VITRO Score (Von Willebrand Factor Antigen/Thrombocyte Ratio) as a new marker for clinically significant portal hypertension in comparison to other non-invasive parameters of fibrosis including ELF test. PLoS One 2016;11:e0149230.
15. Schwarzer R, Reiberger T, Mandorfer M, et al. The von Willebrand Factor antigen to platelet ratio (VITRO) score predicts hepatic decompensation and mortality in cirrhosis. J Gastroenterol 2020;55(5):533–42.
16. Wang L, Feng Y, Ma X, et al. Diagnostic efficacy of noninvasive liver fibrosis indexes in predicting portal hypertension in patients with cirrhosis. PLoS One 2017;12:e0182969.
17. Thabut D, Imbert-Bismut F, Cazals-Hatem D, et al. Relationship between the Fibrotest and portal hypertension in patients with liver disease. Aliment Pharmacol Ther 2007;26:359–68.
18. Bureau C, Metivier S, Peron JM, et al. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. Aliment Pharmacol Ther 2008;27:1261–8.

19. Waidmann O, Brunner F, Herrmann E, et al. Macrophage activation is a prognostic parameter for variceal bleeding and overall survival in patients with liver cirrhosis. J Hepatol 2013;58:956–61.
20. Sandahl TD, McGrail R, Moller HJ, et al. The macrophage activation marker sCD163 combined with markers of the Enhanced Liver Fibrosis (ELF) score predicts clinically significant portal hypertension in patients with cirrhosis. Aliment Pharmacol Ther 2016;43:1222–31.
21. Buck M, Garcia-Tsao G, Groszmann RJ, et al. Novel inflammatory biomarkers of portal pressure in compensated cirrhosis patients. Hepatology 2014;59:1052–9.
22. Bruha R, Jachymova M, Petrtyl J, et al. Osteopontin: a non-invasive parameter of portal hypertension and prognostic marker of cirrhosis. World J Gastroenterol 2016;22:3441–50.
23. Horvatits T, Drolz A, Roedl K, et al. Serum bile acids as marker for acute decompensation and acute-on-chronic liver failure in patients with non-cholestatic cirrhosis. Liver Int 2017;37:224–31.
24. Horn P, von Loeffelholz C, Forkert F, et al. Low circulating chemerin levels correlate with hepatic dysfunction and increased mortality in decompensated liver cirrhosis. Sci Rep 2018;8:9242.
25. Lim YL, Choi E, Jang YO, et al. Clinical implications of the serum apelin level on portal hypertension and prognosis of liver cirrhosis. Gut Liver 2016;10:109–16.
26. Kondo M, Miszputen SJ, Leite-mor MM, et al. The predictive value of serum laminin for the risk of variceal bleeding related to portal pressure levels. Hepatogastroenterology 1995;42:542–5.
27. Kropf J, Gressner AM, Tittor W. Logistic-regression model for assessing portal hypertension by measuring hyaluronic acid (hyaluronan) and laminin in serum. Clin Chem 1991;37:30–5.
28. Leeming DJ, Karsdal MA, Byrjalsen I, et al. Novel serological neo-epitope markers of extracellular matrix proteins for the detection of portal hypertension. Aliment Pharmacol Ther 2013;38:1086–96.
29. Moller S, la Cour Sibbesen E, Madsen JL, et al. Indocyanine green retention test in cirrhosis and portal hypertension: accuracy and relation to severity of disease. J Gastroenterol Hepatol 2019;34:1093–9.
30. Qamar AA, Grace ND, Groszmann RJ, et al. Platelet count is not a predictor of the presence or development of gastroesophageal varices in cirrhosis. Hepatology 2008;47:153–9.
31. Sebastiani G, Tempesta D, Fattovich G, et al. Prediction of oesophageal varices in hepatic cirrhosis by simple serum non-invasive markers: results of a multicenter, large-scale study. J Hepatol 2010;53:630–8.
32. Deng H, Qi X, Guo X. Diagnostic accuracy of APRI, AAR, FIB-4, FI, King, Lok, Forns, and FibroIndex scores in predicting the presence of esophageal varices in liver cirrhosis: a systematic review and meta-analysis. Medicine (Baltimore) 2015;94:e1795.
33. Thabut D, Trabut JB, Massard J, et al. Non-invasive diagnosis of large oesophageal varices with FibroTest in patients with cirrhosis: a preliminary retrospective study. Liver Int 2006;26:271–8.
34. Pind ML, Bendtsen F, Kallemose T, et al. Indocyanine green retention test (ICGr15) as a noninvasive predictor of portal hypertension in patients with different severity of cirrhosis. Eur J Gastroenterol Hepatol 2016;28:948–54.
35. Fouad R, Hamza I, Khairy M, et al. Role of serum soluble CD163 in the diagnosis, risk of bleeding, and prognosis of gastro-esophageal varices in cirrhotic patients. J Interferon Cytokine Res 2017;37:112–8.

36. Qi X, Li H, Chen J, et al. Serum liver fibrosis markers for predicting the presence of gastroesophageal varices in liver cirrhosis: a retrospective cross-sectional study. Gastroenterol Res Pract 2015;2015:274534.
37. Berzigotti A, Abraldes JG, Tandon P, et al. Ultrasonographic evaluation of liver surface and transient elastography in clinically doubtful cirrhosis. J Hepatol 2010;52:846–53.
38. Sartoris R, Rautou PE, Elkrief L, et al. Quantification of liver surface nodularity at CT: utility for detection of portal hypertension. Radiology 2018;289:698–707.
39. Berzigotti A, Rossi V, Tiani C, et al. Prognostic value of a single HVPG measurement and Doppler-ultrasound evaluation in patients with cirrhosis and portal hypertension. J Gastroenterol 2011;46:687–95.
40. Praktiknjo M, Simon-Talero M, Romer J, et al. Total area of spontaneous portosystemic shunts independently predicts hepatic encephalopathy and mortality in liver cirrhosis. J Hepatol 2020;72:1140–50.
41. Simon-Talero M, Roccarina D, Martinez J, et al. Association between portosystemic shunts and increased complications and mortality in patients with cirrhosis. Gastroenterology 2018;154:1694–705.e1694.
42. Deng H, Qi X, Guo X. Computed tomography for the diagnosis of varices in liver cirrhosis: a systematic review and meta-analysis of observational studies. Postgrad Med 2017;129:318–28.
43. Palaniyappan N, Cox E, Bradley C, et al. Non-invasive assessment of portal hypertension using quantitative magnetic resonance imaging. J Hepatol 2016;65:1131–9.
44. Halldorsdottir VG, Dave JK, Leodore LM, et al. Subharmonic contrast microbubble signals for noninvasive pressure estimation under static and dynamic flow conditions. Ultrason Imaging 2011;33:153–64.
45. Eisenbrey JR, Dave JK, Halldorsdottir VG, et al. Chronic liver disease: noninvasive subharmonic aided pressure estimation of hepatic venous pressure gradient. Radiology 2013;268:581–8.
46. Berzigotti A, Zappoli P, Magalotti D, et al. Spleen enlargement on follow-up evaluation: a noninvasive predictor of complications of portal hypertension in cirrhosis. Clin Gastroenterol Hepatol 2008;6:1129–34.
47. Berzigotti A, Merkel C, Magalotti D, et al. New abdominal collaterals at ultrasound: a clue of progression of portal hypertension. Dig Liver Dis 2008;40:62–7.
48. You MW, Kim KW, Pyo J, et al. A meta-analysis for the diagnostic performance of transient elastography for clinically significant portal hypertension. Ultrasound Med Biol 2017;43:59–68.
49. Vizzutti F, Arena U, Romanelli RG, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology 2007;45:1290–7.
50. Ferraioli G, Wong VW, Castera L, et al. Liver ultrasound elastography: an update to the world federation for ultrasound in medicine and biology guidelines and recommendations. Ultrasound Med Biol 2018;44:2419–40.
51. Berzigotti A. Non-invasive evaluation of portal hypertension using ultrasound elastography. J Hepatol 2017;67:399–411.
52. Llop E, Berzigotti A, Reig M, et al. Assessment of portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable liver tumors. J Hepatol 2012;56:103–8.
53. Song J, Ma Z, Huang J, et al. Comparison of three cut-offs to diagnose clinically significant portal hypertension by liver stiffness in chronic viral liver diseases: a meta-analysis. Eur Radiol 2018;28:5221–30.

54. Pons M, Santos B, Simon-Talero M, et al. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals. Therap Adv Gastroenterol 2017;10:619–29.
55. Mandorfer M, Kozbial K, Schwabl P, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. J Hepatol 2016;65:692–9.
56. Rincon D, Ripoll C, Lo Iacono O, et al. Antiviral therapy decreases hepatic venous pressure gradient in patients with chronic hepatitis C and advanced fibrosis. Am J Gastroenterol 2006;101:2269–74.
57. Lens S, Alvarado-Tapias E, Marino Z, et al. Effects of all-oral anti-viral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis. Gastroenterology 2017;153:1273–83.e1.
58. Radu C, Stancu O, Sav R, et al. Liver stiffness better predicts portal hypertension after HCV eradication. J Gastrointestin Liver Dis 2018;27:204.
59. Dietrich CF, Bamber J, Berzigotti A, et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (long version). Ultraschall Med 2017;38:e48.
60. Salavrakos M, Piessevaux H, Komuta M, et al. Fibroscan reliably rules out advanced liver fibrosis and significant portal hypertension in alcoholic patients. J Clin Gastroenterol 2019;53(10):772–8.
61. Song J, Ma Z, Huang J, et al. Reliability of transient elastography-based liver stiffness for diagnosing portal hypertension in patients with alcoholic liver disease: a diagnostic meta-analysis with specific cut-off values. Ultraschall Med 2020;41(1):60–8.
62. Pons M, Augustin S, Scheiner B, et al. Validation of the Baveno VI criteria for noninvasive diagnosis of CacId and clinically significant portal hypertension by transient elastography. Hepatology 2018;68:610–611A.
63. Salzl P, Reiberger T, Ferlitsch M, et al. Evaluation of portal hypertension and varices by acoustic radiation force impulse imaging of the liver compared to transient elastography and AST to platelet ratio index. Ultraschall Med 2014;35:528–33.
64. Attia D, Schoenemeier B, Rodt T, et al. Evaluation of liver and spleen stiffness with acoustic radiation force impulse quantification elastography for diagnosing clinically significant portal hypertension. Ultraschall Med 2015;36:603–10.
65. Takuma Y, Nouso K, Morimoto Y, et al. Portal hypertension in patients with liver cirrhosis: diagnostic accuracy of spleen stiffness. Radiology 2016;279:609–19.
66. Suh CH, Kim KW, Park SH, et al. Shear wave elastography as a quantitative biomarker of clinically significant portal hypertension: a systematic review and meta-analysis. AJR Am J Roentgenol 2018;210:W185–95.
67. Stefanescu H, Marasco G, Cales P, et al. A novel spleen-dedicated stiffness measurement by FibroScan(R) improves the screening of high-risk oesophageal varices. Liver Int 2020;40:175–85.
68. Thiele M, Hugger MB, Kim Y, et al. 2D shear wave liver elastography by Aixplorer to detect portal hypertension in cirrhosis: an individual patient data meta-analysis. Liver Int 2020;40:1435–46.
69. Zhu YL, Ding H, Fu TT, et al. Portal hypertension in hepatitis B-related cirrhosis: diagnostic accuracy of liver and spleen stiffness by 2-D shear-wave elastography. Hepatol Res 2019;49(5):540–9.
70. 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;65:1057–8.

71. Jansen C, Bogs C, Verlinden W, et al. Shear-wave elastography of the liver and spleen identifies clinically significant portal hypertension: a prospective multicentre study. Liver Int 2017;37:396–405.
72. Elkrief L, Ronot M, Andrade F, et al. Non-invasive evaluation of portal hypertension using shear-wave elastography: analysis of two algorithms combining liver and spleen stiffness in 191 patients with cirrhosis. Aliment Pharmacol Ther 2018; 47:621–30.
73. European Association for the Study of the Liver, Electronic address eee, European Association for the Study of the L. EASL Clinical practice guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018; 69:406–60.
74. Shi KQ, Fan YC, Pan ZZ, et al. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. Liver Int 2013;33:62–71.
75. Cassinotto C, Charrie A, Mouries A, et al. Liver and spleen elastography using supersonic shear imaging for the non-invasive diagnosis of cirrhosis severity and oesophageal varices. Dig Liver Dis 2015;47:695–701.
76. Grgurevic I, Bokun T, Mustapic S, et al. Real-time two-dimensional shear wave ultrasound elastography of the liver is a reliable predictor of clinical outcomes and the presence of esophageal varices in patients with compensated liver cirrhosis. Croat Med J 2015;56:470–81.
77. Kasai Y, Moriyasu F, Saito K, et al. Value of shear wave elastography for predicting hepatocellular carcinoma and esophagogastric varices in patients with chronic liver disease. J Med Ultrason (2001) 2015;42:349–55.
78. Kim TY, Kim TY, Kim Y, et al. Diagnostic performance of shear wave elastography for predicting esophageal varices in patients with compensated liver cirrhosis. J Ultrasound Med 2016;35:1373–81.
79. 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;275:589–98.
80. Stefanescu H, Allegretti G, Salvatore V, et al. Bidimensional shear wave ultrasound elastography with supersonic imaging to predict presence of oesophageal varices in cirrhosis. Liver Int 2017;37:1405.
81. Yoo HW, Kim YS, Kim SG, et al. Usefulness of noninvasive methods including assessment of liver stiffness by 2-dimensional shear wave elastography for predicting esophageal varices. Dig Liver Dis 2019;51:1706–12.
82. Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology 2007;133:481–8.
83. Robic MA, Procopet B, Metivier S, et al. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. J Hepatol 2011;55:1017–24.
84. Merchante N, Rivero-Juárez A, Téllez F, et al. Liver stiffness predicts clinical outcome in human immunodeficiency virus/hepatitis C virus-coinfected patients with compensated liver cirrhosis. Hepatology 2012;56:228–38.
85. Macías J, Camacho A, Von Wichmann MA, et al. Liver stiffness measurement versus liver biopsy to predict survival and decompensations of cirrhosis among HIV/hepatitis C virus-coinfected patients. AIDS 2013;27:2541–9.
86. Wang JH, Chuah SK, Lu SN, et al. Baseline and serial liver stiffness measurement in prediction of portal hypertension progression for patients with compensated cirrhosis. Liver Int 2014;34:1340–8.

87. Kitson MT, Roberts SK, Colman JC, et al. Liver stiffness and the prediction of clinically significant portal hypertension and portal hypertensive complications. Scand J Gastroenterol 2015;50:462–9.
88. Merchante N, Rivero-Juárez A, Téllez F, et al. Liver stiffness predicts variceal bleeding in HIV/HCV-coinfected patients with compensated cirrhosis. AIDS 2017;31:493–500.
89. Singh S, Fujii LL, Murad MH, et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11: 1573–84.e1571-2 [quiz: e1588–9].
90. Corpechot C, Gaouar F, El Naggar A, et al. Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis. Gastroenterology 2014;146:970–9 [quiz: e915–76].
91. Vergniol J, Boursier J, Coutzac C, et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatology 2014;60:65–76.
92. Kim BK, Park YN, Kim DY, et al. Risk assessment of development of hepatic decompensation in histologically proven hepatitis B viral cirrhosis using liver stiffness measurement. Digestion 2012;85:219–27.
93. Mendoza Y, CS, Murgia G, et al. Simple non-invasive surrogates of portal hypertension predict clinical decompensation in overweight/obese patients with cACLD. 2019;70:e664.
94. Wong GL, Liang LY, Kwok R, et al. Low risk of variceal bleeding in patients with cirrhosis after variceal screening stratified by liver/spleen stiffness. Hepatology 2019;70(3):971–81.
95. Masuzaki R, Tateishi R, Yoshida H, et al. Prospective risk assessment for hepatocellular carcinoma development in patients with chronic hepatitis C by transient elastography. Hepatology 2009;49:1954–61.
96. Narita Y, Genda T, Tsuzura H, et al. Prediction of liver stiffness hepatocellular carcinoma in chronic hepatitis C patients on interferon-based anti-viral therapy. J Gastroenterol Hepatol 2014;29:137–43.
97. Wang HM, Hung CH, Lu SN, et al. Liver stiffness measurement as an alternative to fibrotic stage in risk assessment of hepatocellular carcinoma incidence for chronic hepatitis C patients. Liver Int 2013;33:756–61.
98. Kim DY, Song KJ, Kim SU, et al. Transient elastography-based risk estimation of hepatitis B virus-related occurrence of hepatocellular carcinoma: development and validation of a predictive model. Onco Targets Ther 2013;6:1463–9.
99. Jung KS, Kim SU, Ahn SH, et al. Risk assessment of hepatitis B virus-related hepatocellular carcinoma development using liver stiffness measurement (FibroScan). Hepatology 2011;53:885–94.
100. Reiberger T, Ferlitsch A, Payer BA, et al, Vienna Hepatic Hemodynamic L. Non-selective beta-blockers improve the correlation of liver stiffness and portal pressure in advanced cirrhosis. J Gastroenterol 2012;47:561–8.
101. Thabut D, Bureau C, Layese R, et al. Validation of Baveno VI criteria for screening and surveillance of esophageal varices in patients with compensated cirrhosis and a sustained response to antiviral therapy. Gastroenterology 2019; 156:997–1009.e1005.
102. Mejias M, Garcia-Pras E, Gallego J, et al. Relevance of the mTOR signaling pathway in the pathophysiology of splenomegaly in rats with chronic portal hypertension. J Hepatol 2010;52:529–39.

103. Giuffre M, Macor D, Masutti F, et al. Spleen Stiffness Probability Index (SSPI): a simple and accurate method to detect esophageal varices in patients with compensated liver cirrhosis. Ann Hepatol 2020;19:53–61.
104. Tseng Y, Li F, Wang J, et al. Spleen and liver stiffness for noninvasive assessment of portal hypertension in cirrhotic patients with large esophageal varices. J Clin Ultrasound 2018;46:442–9.
105. Seijo S, Reverter E, Miquel R, et al. Role of hepatic vein catheterisation and transient elastography in the diagnosis of idiopathic portal hypertension. Dig Liver Dis 2012;44:855–60.
106. Colecchia A, Montrone L, Scaioli E, et al. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. Gastroenterology 2012;143:646–54.
107. Colecchia A, Ravaioli F, Marasco G, et al. A combined model based on spleen stiffness measurement and Baveno VI criteria to rule out high-risk varices in advanced chronic liver disease. J Hepatol 2018;69:308–17.
108. Balakrishnan M, Souza F, Munoz C, et al. Liver and spleen stiffness measurements by point shear wave elastography via acoustic radiation force impulse: intraobserver and interobserver variability and predictors of variability in a US population. J Ultrasound Med 2016;35:2373–80.
109. Procopet B, Berzigotti A, Abraldes JG, et al. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. J Hepatol 2015;62:1068–75.
110. Calvaruso V, Bronte F, Conte E, et al. Modified spleen stiffness measurement by transient elastography is associated with presence of large oesophageal varices in patients with compensated hepatitis C virus cirrhosis. J Viral Hepat 2013;20:867–74.
111. Song J, Huang J, Huang H, et al. Performance of spleen stiffness measurement in prediction of clinical significant portal hypertension: a meta-analysis. Clin Res Hepatol Gastroenterol 2018;42:216–26.
112. Deng H, Qi X, Zhang T, et al. Supersonic shear imaging for the diagnosis of liver fibrosis and portal hypertension in liver diseases: a meta-analysis. Expert Rev Gastroenterol Hepatol 2018;12:91–8.
113. Sharma P, Kirnake V, Tyagi P, et al. Spleen stiffness in patients with cirrhosis in predicting esophageal varices. Am J Gastroenterol 2013;108:1101–7.
114. Meister P, Dechêne A, Büchter M, et al. Spleen stiffness differentiates between acute and chronic liver damage and predicts hepatic decompensation. J Clin Gastroenterol 2019;53(6):457–63.
115. Takuma Y, Morimoto Y, Takabatake H, et al. Measurement of spleen stiffness with acoustic radiation force impulse imaging predicts mortality and hepatic decompensation in patients with liver cirrhosis. Clin Gastroenterol Hepatol 2017;15:1782–90.e1784.
116. Zhang Y, Mao DF, Zhang MW, et al. Clinical value of liver and spleen shear wave velocity in predicting the prognosis of patients with portal hypertension. World J Gastroenterol 2017;23:8044–52.
117. Colecchia A, Colli A, Casazza G, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. J Hepatol 2014;60:1158–64.
118. Grgurević I, Bokun T, Mustapić S, et al. Real-time two-dimensional shear wave ultrasound elastography of the liver is a reliable predictor of clinical outcomes and the presence of esophageal varices in patients with compensated liver cirrhosis. Croat Med J 2015;56:470–81.

119. Marasco G, Colecchia A, Colli A, et al. Role of liver and spleen stiffness in predicting the recurrence of hepatocellular carcinoma after resection. J Hepatol 2019;70:440–8.
120. Wu D, Chen E, Liang T, et al. Predicting the risk of postoperative liver failure and overall survival using liver and spleen stiffness measurements in patients with hepatocellular carcinoma. Medicine (Baltimore) 2017;96:e7864.
121. Peng W, Li JW, Zhang XY, et al. A novel model for predicting posthepatectomy liver failure in patients with hepatocellular carcinoma. PLoS One 2019;14: e0219219.
122. Singh R, Wilson MP, Katlariwala P, et al. Accuracy of liver and spleen stiffness on magnetic resonance elastography for detecting portal hypertension: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol 2021;32(2):237–45.
123. Manatsathit W, Samant H, Kapur S, et al. Accuracy of liver stiffness, spleen stiffness, and LS-spleen diameter to platelet ratio score in detection of esophageal varices: systemic review and meta-analysis. J Gastroenterol Hepatol 2018;33: 1696–706.
124. Karagiannakis DS, Voulgaris T, Koureta E, et al. Role of spleen stiffness measurement by 2D-shear wave elastography in ruling out the presence of high-risk varices in cirrhotic patients. Dig Dis Sci 2019;64:2653–60.
125. Augustin S, Pons M, Maurice JB, et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology 2017;66:1980–8.
126. Takuma Y, Nouso K, Morimoto Y, et al. Prediction of oesophageal variceal bleeding by measuring spleen stiffness in patients with liver cirrhosis. Gut 2016;65:354–5.
127. Buechter M, Kahraman A, Manka P, et al. Spleen and liver stiffness is positively correlated with the risk of esophageal variceal bleeding. Digestion 2016;94: 138–44.
128. Chin JL, Chan G, Ryan JD, et al. Spleen stiffness can non-invasively assess resolution of portal hypertension after liver transplantation. Liver Int 2015;35: 518–23.
129. Kim HY, So YH, Kim W, et al. Non-invasive response prediction in prophylactic carvedilol therapy for cirrhotic patients with esophageal varices. J Hepatol 2019; 70:412–22.
130. Wong GL, Kwok R, Chan HL, et al. Measuring spleen stiffness to predict varices in chronic hepatitis B cirrhotic patients with or without receiving non-selective beta-blockers. J Dig Dis 2016;17:538–46.
131. Ran HT, Ye XP, Zheng YY, et al. Spleen stiffness and splenoportal venous flow: assessment before and after transjugular intrahepatic portosystemic shunt placement. J Ultrasound Med 2013;32:221–8.
132. Gao J, Zheng X, Zheng YY, et al. Shear wave elastography of the spleen for monitoring transjugular intrahepatic portosystemic shunt function: a pilot study. J Ultrasound Med 2016;35:951–8.
133. De Santis A, Nardelli S, Bassanelli C, et al. Modification of splenic stiffness on acoustic radiation force impulse parallels the variation of portal pressure induced by transjugular intrahepatic portosystemic shunt. J Gastroenterol Hepatol 2018;33:704–9.
134. Buechter M, Manka P, Theysohn JM, et al. Spleen stiffness is positively correlated with HVPG and decreases significantly after TIPS implantation. Dig Liver Dis 2018;50:54–60.

135. Attia D, Rodt T, Marquardt S, et al. Shear wave elastography prior to transjugular intrahepatic portosystemic shunt may predict the decrease in hepatic vein pressure gradient. Abdom Radiol (NY) 2019;44:1127–34.
136. Novelli PM, Cho K, Rubin JM. Sonographic assessment of spleen stiffness before and after transjugular intrahepatic portosystemic shunt placement with or without concurrent embolization of portal systemic collateral veins in patients with cirrhosis and portal hypertension: a feasibility study. J Ultrasound Med 2015;34:443–9.
137. Takuma Y, Morimoto Y, Takabatake H, et al. Changes in liver and spleen stiffness by virtual touch quantification technique after balloon-occluded retrograde transvenous obliteration of gastric varices and exacerbation of esophageal varices: a preliminary study. Ultraschall Med 2020;41:157–66.
138. Ravaioli F, Colecchia A, Dajti E, et al. Spleen stiffness mirrors changes in portal hypertension after successful interferon-free therapy in chronic-hepatitis C virus patients. World J Hepatol 2018;10:731–42.
139. Berzigotti A, Seijo S, Arena U, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 2013;144:102–11.e1.
140. Marot A, Trepo E, Doerig C, et al. Liver stiffness and platelet count for identifying patients with compensated liver disease at low risk of variceal bleeding. Liver Int 2017;37:707–16.
141. Llop E, Lopez M, de la Revilla J, et al. Validation of noninvasive methods to predict the presence of gastroesophageal varices in a cohort of patients with compensated advanced chronic liver disease. J Gastroenterol Hepatol 2017; 32:1867–72.
142. Jangouk P, Turco L, De Oliveira A, et al. Validating, deconstructing and refining Baveno criteria for ruling out high-risk varices in patients with compensated cirrhosis. Liver Int 2017;37:1177–83.
143. Reiberger T, Ferlitsch A, Payer BA, et al. Noninvasive screening for liver fibrosis and portal hypertension by transient elastography–a large single center experience. Wien Klin Wochenschr 2012;124:395–402.
144. Schwabl P, Bota S, Salzl P, et al. New reliability criteria for transient elastography increase the number of accurate measurements for screening of cirrhosis and portal hypertension. Liver Int 2015;35:381–90.
145. Cho EJ, Kim MY, Lee JH, et al. Diagnostic and prognostic values of noninvasive predictors of portal hypertension in patients with alcoholic cirrhosis. PLoS One 2015;10:e0133935.
146. Zykus R, Jonaitis L, Petrenkiene V, et al. Liver and spleen transient elastography predicts portal hypertension in patients with chronic liver disease: a prospective cohort study. BMC Gastroenterol 2015;15:183.
147. Hametner S, Ferlitsch A, Ferlitsch M, et al. The VITRO Score (Von Willebrand Factor Antigen/Thrombocyte Ratio) as a new marker for clinically significant portal hypertension in comparison to other non-invasive parameters of fibrosis including ELF test. PLoS One 2016;11:e0149230.
148. Kumar A, Khan NM, Anikhindi SA, et al. Correlation of transient elastography with hepatic venous pressure gradient in patients with cirrhotic portal hypertension: a study of 326 patients from India. World J Gastroenterol 2017;23:687–96.
149. Maurice JB, Brodkin E, Arnold F, et al. Validation of the Baveno VI criteria to identify low risk cirrhotic patients not requiring endoscopic surveillance for varices. J Hepatol 2016;65:899–905.

150. Abraldes JG, Bureau C, Stefanescu H, et al. Noninvasive tools and risk of clinically significant portal hypertension and varices in compensated cirrhosis: the "Anticipate" study. Hepatology 2016;64:2173–84.
151. Pu K, Shi JH, Wang X, et al. Diagnostic accuracy of transient elastography (FibroScan) in detection of esophageal varices in patients with cirrhosis: a meta-analysis. World J Gastroenterol 2017;23:345–56.
152. Petta S, Sebastiani G, Bugianesi E, et al. Non-invasive prediction of esophageal varices by stiffness and platelet in non-alcoholic fatty liver disease cirrhosis. J Hepatol 2018;69:878–85.
153. Bae J, Sinn DH, Kang W, et al. Validation of the Baveno VI and the expanded Baveno VI criteria to identify patients who could avoid screening endoscopy. Liver Int 2018;38:1442–8.
154. Lee HA, Kim SU, Seo YS, et al. Prediction of the varices needing treatment with non-invasive tests in patients with compensated advanced chronic liver disease. Liver Int 2019;39(6):1071–9.
155. Moctezuma-Velazquez C, Saffioti F, Tasayco-Huaman S, et al. Non-invasive prediction of high-risk varices in patients with primary biliary cholangitis and primary sclerosing cholangitis. Am J Gastroenterol 2019;114:446–52.
156. Lucchina N, Recaldini C, Macchi M, et al. Point shear wave elastography of the spleen: its role in patients with portal hypertension. Ultrasound Med Biol 2018;44:771–8.
157. Petzold G, Tsaknakis B, Bremer SCB, et al. Evaluation of liver stiffness by 2D-SWE in combination with non-invasive parameters as predictors for esophageal varices in patients with advanced chronic liver disease. Scand J Gastroenterol 2019;1–8.
158. Stefanescu H, Grigorescu M, Lupsor M, et al. Spleen stiffness measurement using Fibroscan for the noninvasive assessment of esophageal varices in liver cirrhosis patients. J Gastroenterol Hepatol 2011;26:164–70.
159. Stefanescu H, Radu C, Procopet B, et al. Non-invasive ménage à trois for the prediction of high-risk varices: stepwise algorithm using lok score, liver and spleen stiffness. Liver Int 2015;35:317–25.
160. Arribas Anta J, Garcia Gonzalez M, Torres Guerrero ME, et al. Prediction of the presence of esophageal varices using spleen stiffness measurement by transient elastography in cirrhotic patients. Acta Gastroenterol Belg 2018;81:496–501.
161. Rifai K, Cornberg J, Bahr M, et al. ARFI elastography of the spleen is inferior to liver elastography for the detection of portal hypertension. Ultraschall Med 2011;32(Suppl 2):E24–30.
162. Bota S, Sporea I, Sirli R, et al. Can ARFI elastography predict the presence of significant esophageal varices in newly diagnosed cirrhotic patients? Ann Hepatol 2012;11:519–25.
163. Ye XP, Ran HT, Cheng J, et al. Liver and spleen stiffness measured by acoustic radiation force impulse elastography for noninvasive assessment of liver fibrosis and esophageal varices in patients with chronic hepatitis B. J Ultrasound Med 2012;31:1245–53.
164. Vermehren J, Polta A, Zimmermann O, et al. Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis. Liver Int 2012;32:852–8.
165. Takuma Y, Nouso K, Morimoto Y, et al. Measurement of spleen stiffness by acoustic radiation force impulse imaging identifies cirrhotic patients with esophageal varices. Gastroenterology 2013;144:92–101.e102.

166. Rizzo L, Attanasio M, Pinzone MR, et al. A new sampling method for spleen stiffness measurement based on quantitative acoustic radiation force impulse elastography for noninvasive assessment of esophageal varices in newly diagnosed HCV-related cirrhosis. Biomed Res Int 2014;2014:365982.
167. Kim HY, Jin EH, Kim W, et al. The role of spleen stiffness in determining the severity and bleeding risk of esophageal varices in cirrhotic patients. Medicine (Baltimore) 2015;94:e1031.
168. Park J, Kwon H, Cho J, et al. Is the spleen stiffness value acquired using acoustic radiation force impulse (ARFI) technology predictive of the presence of esophageal varices in patients with cirrhosis of various etiologies? Med Ultrason 2016;18:11–7.
169. Fierbinteanu-Braticevici C, Tribus L, Peagu R, et al. Spleen stiffness as predictor of esophageal varices in cirrhosis of different etiologies. Sci Rep 2019;9:16190.
170. Peagu R, Sararu R, Necula A, et al. The role of spleen stiffness using ARFI in predicting esophageal varices in patients with Hepatitis B and C virus-related cirrhosis. Rom J Intern Med 2019;57:334–40.
171. Darweesh SK, Yosry A, Salah M, et al. Acoustic radiation forced impulse-based splenic prediction model using data mining for the noninvasive prediction of esophageal varices in hepatitis C virus advanced fibrosis. Eur J Gastroenterol Hepatol 2019;31:1533–9.