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Review

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Abstract

Introduction: The gold standard to assess the presence and severity of portal hypertension remains the hepatic vein pressure gradient, however the recent development of non-invasive assessment using elastography techniques offers valuable alternatives. In this review, we discuss the diagnostic accuracy and utility of such techniques in patients with portal hypertension due to cirrhosis.

Areas covered: A literature search focused on liver and spleen stiffness measurement with different elastographic techniques for the assessment of the presence and severity of portal hypertension and oesophageal varices in people with chronic liver disease. The combination of elastography with parameters such as platelet count and spleen size is also discussed.

Expert commentary: Non-invasive assessment of liver fibrosis and portal hypertension is a validated tool for the diagnosis and follow-up of patients. Baveno VI recommended the combination of transient elastography and platelet count for ruling out varices needing treatment in patients with compensated advanced chronic liver disease. Assessment of aetiology specific cut-offs for ruling in and ruling out clinically significant portal hypertension is an unmet clinical need. The incorporation of spleen stiffness measurements in non-invasive algorithms using validated software and improved measuring scales might enhance the non-invasive diagnosis of portal hypertension in the next five years.

1) Introduction

Portal hypertension (PH) is a clinical syndrome characterised by a combination of increased resistance to blood flow in the portal venous system and/or its tributaries and endothelial dysfunction. Cirrhosis is the most common cause of intrahepatic sinusoidal PH.PHin cirrhosisdevelops as a consequence of structural changes of liver parenchyma due to inflammation, collagen deposition, nodule formation and vascular occlusion/remodelling. This "static" component causes the initial vascular modifications responsible of increasing portal pressure. Nevertheless about 1/3 is caused by a functional "dynamic" component[1, 2]. Porto-systemic collaterals develop as a consequence of the high pressure in the portal vein. However, even when portal blood flow is entirely diverted through collaterals, PH persists because of a concomitant increase in portal venous inflow, which in turn is caused by splanchnic vasodilatation[3]. This mechanism leads to further and progressive increase in PHthe relevance of which derives from its complications: formation of oesophageal or gastric varices, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, porto-pulmonary hypertension, hepatic encephalopathy, portal hypertensive gastropathy, enteropathy and altered metabolism of endo- and xenobiotics normally metabolised by the liver[4]. The most important collaterals are gastro-esophageal varices since they represent a "marker" of PHon routine endoscopy screening and because they potentially can rupture leading to life threatening bleeding.

The gold standard to assess the presence and severity of PHremains the hepatic venous pressure gradient (HVPG), however the recent development of non-invasive assessment using elastography techniques offers valuable alternatives. In this review, we discuss the diagnostic accuracy and utility of such techniques in patients

with established chronic liver disease. The use of these techniques in non-cirrhotic portal hypertension is outside the scope of this review.

2) Assessment of pH

a) HVPG and endoscopy

Gastroscopy as a screening test for varices is routinely offered once the diagnosis of cirrhosis is confirmed because of its excellent diagnostic accuracy and potential therapeutic approach. Once the presence of gastro-esophageal varices is confirmed, medical or endoscopic treatment and subsequent follow up istailored depending on the size of varices, presence of wale marks and severity of underlying liver disease that determine the risk of bleeding [5, 6]. However, although endoscopy is obviously an important procedure to be carried out because of both diagnostic and therapeutic applications, the most important diagnostic investigation for PH is the HVPG measurement. The relationship between wedge and free hepatic venous pressure is able to provide important clues on the underlying site of resistance and hence allow an appropriate diagnosis of what is causing the increase in portal pressure. Moreover, HVPG is directly proportional to the severity of PHin cirrhosis and therefore, it is considered the most important predictor of clinical outcome in chronic liver disease [7-11]. An HVPG of ≥10 mmHg defines clinically significant PH (CSPH) because is independently associated with an increased risk of decompensation [12] and development of hepatocellular carcinoma (HCC) [13].

b) Elastography

Over the last years, the assessment of liver disease has improved substantiallydue to theintroduction of elastography. The possibility toestimate liver fibrosis and indirectly the severity of PH[14]by measuring liver stiffness (LS) has changed patient management; liver elastography is now routinely used in the clinical evaluation of

patients with chronic liver disease [15, 16].The use of elastography in clinical practice is based on the rationale that an applied force to a certain tissue will induce a parenchymal displacement,the entity of which is related to the tissue characteristics and properties. By measuring the speed of displacement, elastography enables to measure the parenchymal biomechanical properties that in liver disease are modified as a consequence of collagen deposition. Although the presence of fibrosis is the main determinant of increased stiffness, "confounding" factors might contribute or might even drive independently LS by increasing intrahepatic pressure (cholestasis, congestion, inflammation, food intake).

The rationale that brought to use LS measurement as an expression of PH is based on the fact that LS depends on the amount of collagen and therefore the mechanical "static"component of portal pressure. With the progression of liver disease, extra-hepatic factors contribute to further increase in portal pressure. These are mainly vasoactive molecules that act by inducing intra-hepatic vasoconstriction and splanchnic vasodilation hence increasing portal pressure independently from the amount of collagen deposition. Therefore, as PH becomes more severe, the correlation between LS and HVPG is lost, as demonstrated by Vizzuti, et al.[17], because the factors which contribute to the further increase in portal pressure go beyond the amount of fibrosis. In such cases, the measurement of spleen stiffness (SS) seems to be a more reliable marker of PH as well as predictor of hepatic decompensation. The portal vein receives blood from the splenic vein, hence any increase in portal pressure is theoretically transmitted to the spleen with a subsequent increase in intrasplenic pressure and related increased stiffness.

The European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) issued guidelines regarding the clinical application of elastography [18-

20]. According to these guidelines, ultrasound based-elastographic techniques are classified in: strain techniques and shear wave elastography techniques. The last category includes transient elastography (TE), point shear wave elastography (pSWE) and shear wave elastography (SWE) imaging (including 2D-SWE and 3D-SWE).

3) Elastography for the assessment of HVPG

a) Liver Stiffness

TEwas the first elastographic method introduced to assess LSwith the objective toestimate liver fibrosis. Published meta-analysis of studies on TE validation compared toliver biopsy demonstratea good diagnostic accuracy for staging fibrosis in chronic liver disease with different cut-off values according to aetiology [15, 16, 21-23].

Many studies, summarized in table 1, have been published so far regarding the correlation between TE measurement and HVPG and 12 of them have been included in a recent meta-analysis aimed to evaluate the diagnostic performance of LS-TE for CSPH[17, 24-35]. Eight studies were prospective and four retrospective with a total sample size of 1491 patients. Among these studies, 10 provided information on both the correlation between TE and HVPG values and the diagnostic performance ofLS-TE in specifically detecting CSPH.

The summary correlation coefficient was 0.783 (95% CI, 0.737-0.823), suggesting a reasonable correlation between liver stiffness and HVPG. However, this correlation seems to become poor for high values of HVPG (HVPG>12 mmHg), probably because of the increasing relevance of extra-hepatic factors influencing the progression of PH[36]. A summary sensitivity and specificity of 87% (95%CI 76-94%) and 85% (95%CI, 77-91%), respectively, indicates a good diagnostic performance of

LS-TE to diagnose CSPH, with a cut-off value widely ranging from 8.74 kPa to 25 kPa and an AUROC of 0.90.

This wide range of cut-offsis partly due to an outlier study that included patients without CSPH [27]. An additional reason could be the heterogeneous aetiology, with a high number of ALD and NASH patients possibly having a significant inflammatory component, and the variable inclusion of patients with advanced/decompensated liver disease.

Abraldes et al. studied a population of 518 patients with compensated advanced chronic liver disease of different aetiology and showed that simple parameters such as LS by TE, platelet count and spleen diameter in different combinations, can identify up to 80% of patients with CSPH. This allows the clinician to reliably predict which patients have a very high risk of CSPH, thus allowing an early, non-invasive identification of patients at higher risk of developing decompensation [37].

Even though these results are encouraging, the heterogeneity of the studied populations, the relatively small number of available data and the lack of prospective studies with predefined cut-offs represent important limitation factors in terms of overall accuracy.

Among pSWE techniques, acoustic radiation force imaging (ARFI) has been widely used. Although ARFI represents a valid tool to diagnose liver cirrhosis in comparison to TE, there is only one study that evaluated the usefulness of ARFI elastography as a predictor of CSPHin 78 patients who underwent HVPG measurement [38]. The LS values were significantly higher in CSPH, with a high diagnostic performance of ARFI (AUC 0.93). However, even in this study the population was very heterogeneous in terms of aetiology, hence raising concerns on its reliability and application in clinical practice on a larger scale.

Different studies have been published on the diagnostic performance of LS measured by the 2D-SWE technique of Supersonic imaging (SSI) in the assessment of PH compared to HVPG measurement. According to the published results, SSI represents a very good tool in diagnosing CSPH and severe PH (SPH), with sensitivity, specificity and cut-off values ranging from 81% to 90.5%, 80% to 89.5% and 15.2 kPa to 24.5 kPa, respectively [39-41].

Jansen et al [42] adopted dual cut-offs (rule-in and rule-out) to reach a better performance; one third of patients (48/155) were in the unclassified range and would need to undergo HVPG to be correctly diagnosed. Probably, this is due to the high number of patient with alcoholic liver disease (ALD) and NASH (53% and 17%, respectively) compared to other studies.

No data are available regarding the predictive value of ElastPQ techniques for PH measured by HVPG.

Moreover, LS seems to have a better diagnostic performance for CSPH when used alone than when integrated with spleen size and platelets count (LSPS) (AUC 0.87 and 0.76, respectively) [40, 41]. This may be due to the non-linear relationship between spleen size and PH. Although the pathogenic mechanisms causing spleen enlargement in patients with PH are still not completely understood, splenomegaly is not a simple increase of spleen size due to passive congestion development, but also to lymphoid hyperplasia, angiogenesis and fibrogenesis. For this reason, even if splenomegaly represents a very frequent finding in patients with PH, its clinical utility is controversial and spleen parameters non-invasively assessed as spleen size and area have not been widely developed and pursued.

b) Spleen Stiffness

Fourstudies (Table 2) prospectively evaluated the correlation between SS measured with TE and PH assessed by HVPG [28, 36, 40]. However, in one of them [36] the authors only reported the correlation between the two techniques (r=0.433), without giving data on the performance of SS in predicting CSPH. Moreover, this correlation was not significant for HVPG>19 mmHg, reflecting the fact that SS does not have a linear correlation with HVPG when PH is more severe.

Data regarding the diagnostic performance of TE-SS in predicting CSPH and SPH are quite controversial. TE-SS had a good performance in the studies by Zykus, et al. [43] and Colecchia, et al [28]. However, in the latter the authors had to use rule-in and rule-out cut-off values to get a better sensitivity and specificity, with a widerange of unclassified patients. TE-SS had a poor diagnostic performance in the study of Elkrief, et al.[40]. This discrepancy may be explained by the presence of a high number of patients with decompensated liver disease and more severe PH in the population enrolled in this studywith respect to those of Zykus and Colecchia (Child-Pugh C44%, 0.9% and 0%, respectively; median HVPG 17 mmHg, 14 and 12 mmHg, respectively).

It is important to mention that the number of non-reliable/failed SS assessments with TE is higher compared to those of LS. This is due to technical issuesmainly caused bysmall sizedspleens and represents an important limitation. In addition, a conventional ultrasound device is usually needed to locate the spleen.

There is only one study that evaluated the diagnostic performance of ARFI in patients who underwent an invasive measurement of portal pressure [38].

The performance of SS using ARFI in assessing both SPH and CSPH was better than TE in this study that included a significant proportion of patients with

decompensated liver disease and high HVPG values (Child-Pugh C 18%, median HVPG 18 mmHg). Importantly, no SS assessment failureswere reported. This is due to the fact that ARFI is an elastographic technique integrated in an ultrasound system, which allows scanperformance even in patients with high BMI, ascites or a small spleen.

Data about the diagnostic performance of SSI were controversial in two studies with heterogeneous populations regarding the severity of liver disease[40]. Similarly to ARFI, SSI is better than TE in measuring SS. Although the use of rule-in and rule-out cut-off values results in better diagnostic performance, the number of patients in the unclassified range is high (41%)[42]

No data are available regarding the predictive value of ElastPQ techniques for PH measured by HVPG.

4) Elastography for the assessment of oesophageal varices (EV)

a. Liver Stiffness

Many studies (Table 3) have been published showing the usefulness of TE-LS in predicting the presence of EV and large EV assessed by upper gastrointestinal endoscopy (UGI-endoscopy). Fifteen of thesestudies have been included in a recent meta-analysis which included a total of 2697 patients[44]. The summary sensitivity, specificity and AUROC were 84%, 62% and 0.82, respectively, for the detection of EV. TE-LS diagnosed the presence of large EV with a summary sensitivity, specificity and AUROC of 78%, 76% and 0.82, respectively. The cut-off values range was 12 kPa-29.7 kPa and 19 kPa-48 kPa for EV and large EV, respectively.

A meta-regression and subgroup analysis showed that the aetiology of liver disease represents the reason of this wide heterogeneity only in the EV group, with lower cut-off values in viral aetiology and higher in alcoholic cirrhosis. Similar results have

been shown by two meta-analyses published in 2016[45, 46]. Therefore LS on its own cannot reliably diagnose or rule out varices of any size or varices needing treatment.

In 2010 Kim et al found significant differences in LS, spleen diameter and platelet count between patients with and without EVs. Accordingly, they developed a LS-spleen diameter to platelet count ratio score (LSPS), which showed a good reliability and performance for detection of EVs[47]. In 2013, Berzigotti et al confirmed that the accuracy to non-invasively assess PH improved by combining LS, spleen size and platelet count. LSPS score showed a very good correlation with CSPH evaluatednot only by the presence of EVs at endoscopy but also by HVPG[48].

In 2014 Augustin et al evaluated 250 patients and those with LS > 13.6 kPa underwent endoscopy and portal pressure measurement by HVPG. 90% of EVs detected by endoscopy belonged to the group of patients with platelet count <150.000, LS > 13.5 kPa and abnormal ultrasound (nodular profile and increased spleen size). A LS cut-off of 25 KPa was excellent at ruling-in CSPH[25].

A retrospective study conducted by Ding demonstrated that the combination of LS ≤25 kPa and platelet count ≥ 100.000 could be used in clinical practice to exclude the presence of high-risk GOV in patients with Child-Pugh A cirrhosis [49].

On the basis of these results, during the Baveno VI Consensus Workshop, the combination of TE-LS and platelet count wasproposed as a non-invasive tool to rule out patients with compensated advanced chronic liver disease (cACLD) and Child Pugh A cirrhosis who can safely avoid screening endoscopy. In particular, patients with a liver stiffness<20 kPa and a platelet count >150,000 have a very low risk of having varices requiring treatment, and can avoid screening endoscopy. These patients can be followed up by yearly repetition of TE and platelet count. If the liver

stiffness increases or the platelet count declines, these patients should undergo screening endoscopy [37, 50-52]. Figure 1 is a graphic representation of the Baveno VI criteria. These criteria have been evaluated in multiple studies since 2015, which confirm that less than 5% of patients with varices needing treatment are missed [51](Table 4).However, implementation of the criteria spares just 20% of screening endoscopies.

For this reason, the Baveno VI criteria have recently been expanded with new criteria (Expanded-Baveno VI) in a study with a derivation and two additional validation cohorts from London (309 patients) and Barcelona (117 patients). The best new expanded classification rule was platelet count >110 x10^9 cells/L and LS <25 kPa. The Expanded-Baveno VI criteria would potentially spare 40% of endoscopies vs. only 21% using the original Baveno-VI criteria. These new criteria performed well in patients with compensated advanced chronic liver disease due to HCV, ALD and NASH [53].

b. Spleen Stiffness

TE-SS alone or in combination with TE-LS and/or other parameters (i.e. laboratory, spleen size) represents a promising tool for predicting EV in patients with liver cirrhosis. Moreover, in some studies (Table 5) the diagnostic performance seems to be better than that of TE-LS. However, data regarding the strength of performance and cut-offsvary depending on the underlying aetiology and the Child Pugh stage of the enrolled patients.

Although the data collected so far in this setting showed that TE is promising, the percentage of failures is higher when it is performed on the spleen compared to the liver, as already mentioned. Moreover, the upper limit cut-off value of 75 kPa

represents a further limitation, as SS often is higher than that value[28, 36, 54-58] (Table 5).

SS measured by ARFI represents a more reliable technique to predict EVs and high-risk EVs with a better performance compared to platelet count, spleen size and even LS in most studies[59-61]. Only one study reported no correlation between SSmeasured by ARFI and the presence or severity of EV, as well as the risk of variceal bleeding. However, the authors did not provide information about liver disease aetiology and severity[62].

In a recent published prospective multicentre study, Jansen demonstrated that the diagnostic performance in detecting CSPH improved by combining LS and SS. Using a LS cut-off value of 38 kPa and SS cut-off value of 27.9 kPa, a total of 91.6% of 158 patients were correctly classified with a sensitivity of 98.3% and specificity of 83.9% [42, 63]. This needs to be further validated in independent cohorts.

5) Changes in elastography under non-selective betablockers and after tips

Few papers have been published so far regarding the influence of non-selective beta-blockers (NSBBs) treatment on LS and SS.

Reiberger et al investigated the correlation between LS and portal pressure in a cohort of 122 patients, with different aetiologies and Child-Pugh class stages (A:88, B:25, C:9). They showed that the correlation between LS measured by TE and HVPG was stronger in patients with HVPG<12 mmHg. The association of HVPG with LS in HVPG>12 mmHg became stronger under treatment with NSBBs, as this restored the linear correlation of HVPG and LS. The improvement in the correlation of LS and HVPG under NSBBs was predominantly in hemodynamic responders [32].

Similar results were obtained by Wong et al in a population of 144 patients (29 receiving NSBBs and 35 with varices). They showed that the diagnostic performance of LS and SS assessed by TE in predicting varices was better in patients on NSBB treatment [58].

These results confirm the increasing contribution of non-structural factors in severe PH and that LS and SS are not reliable in assessing the dynamic components of PH. Only two papers have been published about the influence of transjugular intra-hepatic porto-systemic shunt (TIPS) placement on LS and SS measured by ARFI but in both the population size was very small. Gao et al investigated LS and SS modification after TIPS in 20 patients (10 healthy controls and 10 chronic hepatitis B patients with CSPH). There is no mention of the disease severity stage but all patients had a history of variceal bleeding and they underwent TIPS placement for CSPH treatment. In the results only SS seems to change after TIPS insertion and the authors conclude that it could be used as a marker in monitoring the TIPS function [64]. The study De Santis et al included 38 patients with different aetiologies and severity of disease stages. The indication for TIPS was variceal bleeding or refractory ascites. The results showed that although LS and SS were significantly modified by TIPS, SS decreased significantly more than LS and therefore seems to be superior in detecting the reduction of portal pressure induced by TIPS [65].

7) Expert commentary

Tissue stiffness is a biomechanical measurement that has become crucial for the clinical management of patients with chronic liver disease by providing predictive information not only on the severity of fibrosis, but also on PHand the risk of clinical

decompensation. The 2017 EFSUMB guidelines and recommendation for the clinical application of elastography highlighted recently the wide consensus on the use of different techniques for the diagnosis and staging of fibrosis, however existing data on PHis less extensive and there are still gaps to be filled. The most important change in clinical practice was provided by the latest Baveno VI recommendations, that suggested the combination of LS measurement (performed by TE) of <20 kPa with a platelet count >150,000 to rule out the presence of varices needing treatment in patients with cACLD, thus reducing unnecessary endoscopic screening. Although this is an important step in the management of patients with compensated cirrhosis, the current algorithm spares just 20% of the total number of endoscopies, with many procedure still carried out unnecessarily. Application of the recently published expanded Baveno VI criteria spares 40% of the total number of endoscopies and represents an important step forward. These criteria need validation in patients with cholestatic liver disease and to a lesser extent in patients with NASH and alcohol-related cirrhosis. Moreover, to date varices of any size cannot be diagnosed or ruled out non-invasively with reasonable diagnostic accuracy.

As a principle, there are different aspects that need to be taken into account in the non-invasive assessment of chronic liver disease and the appraisal of existing data. Firstly,LS is relative to the result of the forces that interact within the hepatic parenchyma, while instead fibrosis is a histological diagnosis. Therefore, factors such as inflammation, congestion, obstructive jaundice and hepatic blood inflow influence stiffness potentially "simulating" fibrosis, overestimating its severity and hence the stiffness cut-off values for evaluating the presence of CSPH.

Moreover different patterns of fibrosis and nodular formation that are aetiology-specific in chronic liver disease have a different impact on the development of PH

and hence on the natural history of liver disease. Along these lines, a retrospective study evaluating the amount of fibrosis on explanted livers revealed that the amount of fibrosis measured by collagen proportional area was significantly different amongst different aetiologies of liver disease[66]. Therefore, it is likely that PH has a different onset according to the aetiology of liver disease and LS cut-off values are likely to follow these parenchymal modifications, which should be born in mind when performing a non-invasive assessment. For instance, patients with NASH are likely to develop PH even in pre-cirrhotic stages as shown in the study by Francque [67]. Therefore, specific disease characteristics, such as the large regenerative nodules particularly present in advanced hepatitis B, the inflammatory component of alcoholic liver disease, the pre-sinusoidal characteristics of PH in primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) and the technical issues to accurately measure LS in NASH represent a challenge for the standardisation of elastography measurements for the assessment of PH. Therefore, aetiology specific cut-offs for the assessment of PH need to be prospectively validated.

Non-invasive assessment in NASH is particularly difficult. The majority of these patients have a high BMI and increased subcutaneous tissue thickness making the acquisition of reliable measurements technically challenging and this is only partially resolved with the XL probe.pSWE and 2D-SWE have the benefit of propagating a shear wave transversally within the hepatic parenchyma and in theory are less affected by the presence of thick subcutaneous tissue. Nevertheless in the presence of a severely steatotic/fibrotic liver in which there is a thick layer of subcutaneous adipose tissue and high posterior attenuation of the ultrasound beam, the region of interest is positioned deeper in the hepatic parenchyma, therefore there is a risk that the measurements acquired might be affected by these factors leading to reduced

accuracy. Another limitation of acquiring LS measurements in such patients is presence of intrahepatic artefacts as a consequence of reverberation from the abundant subcutaneous adipose tissue.

Finally, with worsening PH, there is reduced correlation of LS with HVPG due to the increasing contribution of non-structural factors. This particular limitation can be partially overcome with the use of dual cut-offs for ruling in and ruling out CSPH, even though with this method there will be more than 30% of patients who does fit neither in the rule-in nor in the rule-out group.

SS is an extremely promising extension of the use of elastography for the non-invasive assessment of PH. Although there is limited data compared to LS, SS seems able to overcome the limitations of confounding factors that affect liver parenchyma and also to be a more objective marker of PH regardless of the underlying cause. In fact, if PH is typically characterised by increased resistance to portal flow and this reflects in increased intra-splenic pressure, targeting the latter should provide more accurate information for higher values of portal pressure. The available data is very encouraging in this respect, also because by measuring SS it is potentially possible to predict the presence of CSPH in patients with pre-hepatic PH, idiopathic PH and pre-sinusoidal PH where HVPG is misleading.

8) Five-year view

Although the recent EFSUMB recommendations for non-invasive assessment of PH provide some guidance, this cannot be applied indiscriminately. Currently, the target of elastography evaluation is the exclusion of large varices rather than the diagnosis ofthe severity of PH. Large cohort studies including populations differentiated by aetiology and sub-grouped according to severity of liver disease are warranted to establish reliable LS cut-off values for the prediction of CSPH, its severity, as well as

the risk of clinical decompensation. NASH related cirrhosis represents a true technical challenge and in consideration of its epidemiological burden the efforts of the hepatology community will need to concentrate in order to overcome the current limitations of the available techniques. PBC and PSC are both characterised by pre-sinusoidal PH and LS is thought to underestimate the severity of fibrosis and PH. Moreover in PSC the increased LS might be due to cholestasis rather than fibrosis and there is no predictor of PH in these two conditions. SS measurements are likely to provide these answers and overcome the limitations of LS by information on intra-splenic pressure. Nevertheless further standardisation of the technique is required and we expect over the next few years dedicated software that will improve its performance. Moreover the liver structural modifications accompanied by the splanchnic vascular changes that occur in liver disease suggest that the most accurate information on the diagnosis and severity of PH is provided by the coupled assessment of liver and spleen stiffness. Such algorithms are still awaited, but hopefully will be standardized in the next five years.

9) Key issues

- Portal hypertension represents a common complication of liver cirrhosis and it is the main driver of hepatic decompensation.

- HVPG and upper-endoscopy represent the gold standard techniques to assess the presence of clinical significant portal hypertension and gastro-oesophageal varices, respectively.

- Liver and spleen stiffness measured with different elastography techniques show a good correlation with portal pressure assessed by HVPG and presence of oesophageal varices even though data are controversial about

sensitivity, specificity and cut-off values, probably due to the variability of the studied populations.

- The Baveno VI and expanded Baveno VI criteria can be used to save unnecessary endoscopies for varices detection in patients with compensated advanced chronic liver disease since they have a very high negative predictive value for varices needing treatment.

- Algorithms including both liver and spleen stiffness have a better diagnostic performance in ruling-in and out clinically significant portal hypertension, minimizing the number of misclassified patients.

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* of interest

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Table 1. Diagnostic performance of different elastography techniques for detecting clinically significant PH.

STUDY, year	Elastography	Patients, n	CP-C, n	NAFLD/ALD, n	CSPH Cut-off value, kPa	Sensitivity,%	Specificity,%
Augustin, 2014[25]	TE	40	0	-/-	25	65	93
Bureau, 2008[26]	TE	150	21	11/51	21	90	93
Carrion, 2006[27]	TE	129	-	0/0	8.74 *	0	61
Colecchia, 2012[28]	TE	100	0	0/0	24.2	52	97
Hong, 2013[29]	TE	59	-	0/36	21.95	83	74
Llop, 2012[31]	TE	79	0	3/8	21	53	92
Reiberger, 2012[32]	TE	122	9	0/66	18	82	83
Salzl, 2014[33]	TE	59	-	-/-	16.8	91	77
Sanchez-Conde, 2011[34]	TE	38	11	0/0	14	93	50
Schwabl, 2014[35]	TE	226	-	-/31	16.1	95	87
Vizzutti, 2008[17]	TE	61	5	0/0	13.6	98	93
Attia, 2015[38]	ARFI	78	14	-/40	2.17**	97	89
Jansen, 2016[42]	SSI	158	14	27/89	24.2	68	80

Elkrief, 2015[40]	SSI	79	35	6/33	24.5	81	88
Procopet, 2015[39]	SSI	88	-	-/23	15.4	91	90
Kim, 2015[41]	SSI	92	11	-/56	15.2	86	80

Abbreviations: CP-C=Child-Pugh C; TE=transient elastography; ARFI=acoustic radiation force imaging; SSI=supersonic imaging;

NAFLD=non-alcoholic fatty liver disease; ALD=alcoholic fatty liver disease; CSPH=clinical significant PH.

* no patients with CSPH

** m/sec

Table 2. Diagnostic performance of splenic stiffness measured by elastography techniques for detecting clinically significant PH.

								CSPH					
STUDY, year	Patients, n	Elastography	CP-C, n	NAFLD /ALD, n	COV, kPa	Se, %	Sp, %	Rule-in, kPa	Se, %	Sp, %	Rule-out, kPa	Se, %	Sp,%
Colecchia, 2012[28]	100	TE	0	0/0				52.8	77	97	40	99	74
Elkrief, 2015[40]	79	TE	35	6/33	56.3	73	67						
Zykus, 2015[43]	107	TE	1	-/19	47.6	77	79						
Elkrief, 2015[40]	79	SSI	35	6/33	34.7	40	100						
Jansen, 2016[42]	158	SSI	14	27/89	26.3	80	84	35.6	51	92	21.7	92	50
Attia, 2015[38]	78	ARFI	14	-/40	2.32*	96	89						

Abbreviations: CP-C=Child-Pugh C; TE=transient elastography; ARFI=acoustic radiation force imaging; NAFLD=non-alcoholic fatty liver disease; ALD=alcoholic fatty liver disease; Se=sensitivity; Sp=specificity; CSPH=clinical significant PH.

* m/sec

Table 3. Diagnostic performance of liver stiffness measured by elastography techniques for detecting oesophageal varices and large oesophageal varices.

STUDY, year	Patients, n	Elastography	CP-C, n	NAFLD/ALD, n	Presence of EVs (grade 0,1)			Large EVs (grade 2,3)		
					COV, kPa	Se,%	Sp,%	COV, kPa	Se,%	Sp,%
Sporea, 2013[68]	697	TE	-	184				29.5	78	87
Sharma, 2013[36]	174	TE	20	-/77	27.3	91	72			
Saad, 2013[69]	32	TE	0	0/0	29.7	95	67	38.2	100	77
Nguyen-Khac, 2010[70]	183	TE	20	6/103				48	73	73
Kazemi, 2006[71]	165	TE	0	-/9	13.9	95	43	19	91	60
Jung, 2008[72]	112	TE	-	-	19.7	87	70			
Hu, 2015[73]	200	TE	-	0/0	20.25	86	72	25.55	84	72
Castera, 2009[74]	70	TE	0	0/0	21.5	76	78	30.5	77	85
Calvaruso, 2013[54]	96	TE	0	0/0	17	71	57	19	72	55
Bintintan, 2015[75]	60	TE	8	-/33	15	95	100	28.8	87	83
Stefanescu, 2011[56]	137	TE	9	-/-	28	74	64			
Stefanescu, 2011[76]	231	TE	13	-/116	19	84	32	38	56	75

| Wang, 2012[77] | 126 | TE | 0 | 0 | 12 | 67 | 77 | 21 | 77 | 87 |
| Augustin, 2014 [25] | 49 | TE | 0 | -/- | 25 | 80 | 72 | | | |

Abbreviations: NAFLD=non-alcoholic fatty liver disease; ALD=alcoholic liver disease;Se= sensitivity; Sp=specificity; COV=cut-off

value; CP-C=Child-Pugh C; EVs=esophageal varices

Table 4. Summary of studies evaluating performance of Baveno VI criteria for screening endoscopy in patients with compensated advanced chronic liver disease.

Study	N	Viral	ALD	Varices	VNT	Varices missed[§]	VNT missed[§]	EGD spared[&]	EGD unneeded[#]
Maurice[78]	310	55%	13%	23%	5%	3.5%	0.6%	33%	48%
Perazzo[79]	97	-	-	54%	0	6%	0	22%	29%
Llop[80]	161	85%	-	16%	1.9%	1.9%	0	33.5%	53%
Tossetti[81]	146	100%	-	45%	8%	6%	0	27%	34%
Jangouk[82]	262	71%	13%	41%	11.8%	-	0	22%	-
Chang [83]	173	55%	-	31%	8%	-	1.7%	20%	-
Thabut [84]	790	100%	-	-	-	10%	0	20%	-
Paternostro [85]	135	47%	30	65%	24%	3%	0	7%	30%

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	N	Viral	ALD %	Varices	VNT				
Silva [86]	112	80%	7%	48%	15%	1.8%	0	11%	43%
Cales[87]	287	26%	64%	44%	17%	2%	0	16.5%	41.5%
Ahmed [88]	478	33%	36%	-	11%	-	0.5%	23%	-
Molina [89]	237	60%	18%	35%	5%	-	0	17%	-
Calvaruso[90]	1381	100%	0	-	9%	5.5%	0.4%	15.6%	-
TOTAL	4569	68%	-	40.2%	9.6%	4.4%	0.2%	20.6%	39.8%

N: Total number of patients in the cohort; Viral: viral etiology; ALD: Alcoholic liver disease; Varices: Percentage of patients with any type of varices; VNT: varices needing treatment (large varices); EGD: Esophagogastroduodenoscopy.

§ Percentage of varices and VNT missed by applying the Baveno VI criteria: n varices/total n patients

& Percentage of patients within the Baveno VI criteria in which endoscopy could be spared.

[#] Percentage of patients out of the Baveno VI criteria without varices in which endoscopy was unneeded.

Table 5. Diagnostic performance of splenic stiffness measurement by elastography techniques for detecting oesophageal varices and large oesophageal varices.

STUDY, year	Patient, n	Elastography	CP-C (n)	NAFLD/ALD, n	Presence of EVs			High-risk EVs		
					COV, kPa	Se, %	Sp, %	COV, kPa	Se, %	Sp, %
Calvaruso, 2013[54]	96	TE	0	0/0	50	65	61	54	80	70
Colecchia, 2012[28]	100	TE	0	0/0	41.3*	98	66			
					55**	72	96			
Fraquelli, 2014[55]	198	TE	-	0/0	65	91	80			
Sharma, 2013[36]	174	TE	20	-/77	40.8	94	76	54.5	76	73
Stefanescu, 2011[56]	191	TE	13	-/-	46.4	84	71			
Wong, 2016[58]	144	TE	-	0/0	21.4*	90	47			
					50.5**	45	91			
Kim, 2015[59]	125	ARFI	8	-/41	3.16~	87	60	3.40~	79	63

Rizzo, 2014[60]	54	ARFI	0	0/0	3.1~	96	88			
Takuma, 2013[61]	340	ARFI	21	3/45	3.18	99	60	3.30	99	63

Abbreviations: NAFLD=non-alcoholic fatty liver disease; ALD=alcoholic liver disease; Se= sensitivity; Sp=specificity; COV=cut-off

value; CP-C=Child-Pugh C; EVs=esophageal varices

*Rule-out cut-off value

**Rule-in cut-off value

~ m/sec

Figure 1. The Baveno VI criteria using a combination of liver stiffness and platelet count to spare screening endoscopies in patients with compensated advanced chronic liver disease. Patients with a liver stiffness <20 kPa and a platelet count >150,000 have a very low risk of having varices requiring treatment and can avoid screening endoscopy. These patients can be followed up by yearly repetition of TE and platelet count. If the liver stiffness increases or the platelet count declines, these patients should undergo screening endoscopy.