

2015 Advances in Cirrhosis

Ultrasound-based elastography for the diagnosis of portal hypertension in cirrhotics

Roxana Şirli, Ioan Sporea, Alina Popescu, Mirela Dănilă

Roxana Şirli, Ioan Sporea, Alina Popescu, Mirela Dănilă, Department of Gastroenterology and Hepatology, “Victor Babeş” University of Medicine and Pharmacy, 300736 Timișoara, Romania

Author contributions: Şirli R designed the research regarding the paper and wrote the manuscript; Şirli R, Sporea I, Popescu A and Dănilă M performed research; Sporea I, Popescu A and Dănilă M revised and completed the manuscript; all authors approved the final version of the manuscript.

Conflict-of-interest statement: None of the authors have any conflicts of interest regarding this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Roxana Şirli, MD, PhD, Department of Gastroenterology and Hepatology, “Victor Babeş” University of Medicine and Pharmacy, 10, Iosif Bulbuca Bv., 300736 Timișoara, Romania. roxanasirli@gmail.com
Telephone: +40-723-537039
Fax: +40-256-488003

Received: April 28, 2015

Peer-review started: May 6, 2015

First decision: June 2, 2015

Revised: July 11, 2015

Accepted: August 31, 2015

Article in press: August 31, 2015

Published online: November 7, 2015

Abstract

Progressive fibrosis is encountered in almost all chronic

liver diseases. Its clinical signs are diagnostic in advanced cirrhosis, but compensated liver cirrhosis is harder to diagnose. Liver biopsy is still considered the reference method for staging the severity of fibrosis, but due to its drawbacks (inter and intra-observer variability, sampling errors, unequal distribution of fibrosis in the liver, and risk of complications and even death), non-invasive methods were developed to assess fibrosis (serologic and elastographic). Elastographic methods can be ultrasound-based or magnetic resonance imaging-based. All ultrasound-based elastographic methods are valuable for the early diagnosis of cirrhosis, especially transient elastography (TE) and acoustic radiation force impulse (ARFI) elastography, which have similar sensitivities and specificities, although ARFI has better feasibility. TE is a promising method for predicting portal hypertension in cirrhotic patients, but it cannot replace upper digestive endoscopy. The diagnostic accuracy of using ARFI in the liver to predict portal hypertension in cirrhotic patients is debatable, with controversial results in published studies. The accuracy of ARFI elastography may be significantly increased if spleen stiffness is assessed, either alone or in combination with liver stiffness and other parameters. Two-dimensional shear-wave elastography, the ElastPQ technique and strain elastography all need to be evaluated as predictors of portal hypertension.

Key words: Portal hypertension; Transient elastography; Acoustic radiation force impulse elastography; Two-dimensional shear-wave elastography

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Ultrasound-based elastographic methods are being used more and more for the non-invasive assessment of liver fibrosis, with very good accuracy in diagnosing cirrhosis. Transient elastography is a

promising method for predicting portal hypertension in cirrhotics, but it cannot replace upper digestive endoscopy. The diagnostic accuracy of employing acoustic radiation force impulse elastography in the liver to predict portal hypertension is debatable. It may be significantly increased if spleen stiffness is assessed, whether alone or in combination with liver stiffness and other parameters. Two-dimensional shear-wave elastography, the ElastPQ technique and strain elastography all need to be evaluated as predictors of portal hypertension.

Şirli R, Sporea I, Popescu A, Dănilă M. Ultrasound-based elastography for the diagnosis of portal hypertension in cirrhotics. *World J Gastroenterol* 2015; 21(41): 11542-11551 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i41/11542.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i41.11542>

INTRODUCTION

Almost all chronic liver diseases can evolve to liver cirrhosis, which is characterized by profound changes in liver structure that are caused by pseudo-nodule formation as a consequence of necrosis and fibrosis. The main causes of chronic liver disease are infections with hepatitis B and C viruses (HBV and HCV), but a rising incidence of alcoholic and non-alcoholic steatohepatitis (ASH and NASH, respectively) has been observed in developed countries^[1]. Published data from the World Health Organization (WHO), state that 160 million individuals are infected with HCV, representing 2.35% of the population, with the highest prevalence in Egypt (20%) and the lowest prevalence in northern European countries (< 0.5%)^[2]. It is estimated that up to 30% of HCV patients will develop cirrhosis at least 10 years after diagnosis^[3]. The prevalence of HBV is even higher, with more than 240 million chronically infected patients; the highest prevalence is reported in sub-Saharan Africa and South-East Asia (5%-10% in adults) and the lowest is reported in Western Europe and North America (< 1%)^[4]. It is estimated that 650000 deaths occur each year as a consequence of liver cirrhosis and hepatocellular carcinoma (HCC) secondary to chronic hepatitis B infection^[4]. Alcoholic cirrhosis is also a major cause of disease burden and death. In 2010, 493300 deaths were attributable to alcoholic cirrhosis worldwide (7.2 per 100000 people; 47.9% of all liver cirrhosis deaths)^[5]. In Europe, also in 2010, 43500 deaths were caused by alcoholic cirrhosis^[5]. More than 5500 liver transplants are performed in Europe each year, 59% of them for liver cirrhosis; of these, 33% come from a purely alcoholic etiology, and 5% come from a mixed alcoholic and viral etiology^[6].

It is easy to diagnose decompensated liver cirrhosis in which clinical, biologic and ultrasound signs are

evident. However, the most important aspect of prognosis is the differentiation between compensated cirrhosis and chronic hepatitis. Until a few years ago, liver biopsy (LB) was considered to be the reference method for staging chronic hepatitis^[7]. However, because it has some drawbacks, including sampling variability and intra- and interobserver variability^[8-10], and most importantly because it is an invasive method, noninvasive tests were developed to stage chronic hepatitis, ergo, to diagnose cirrhosis. These noninvasive tests are either serologic, including the FibroTest and ActiTest^[11], or elastographic.

Elastographic methods evaluate a property that is intrinsic in every tissue: elasticity, which is the capacity of a tissue to deform and then return to its initial shape when an extrinsic force is applied. Regarding the liver, more fibrosis means that the tissue is less elastic (stiffer). Liver stiffness (elasticity) can be evaluated by magnetic resonance elastography^[12,13] or by ultrasound-based elastographic methods^[14,15]. According to the guidelines and recommendations published by the European Federation of Societies of Ultrasound in Medicine and Biology (EFSUMB) regarding the clinical use of ultrasound elastography, ultrasound-based elastographic methods can be classified as the following: (1) strain elastography (quasi-static, qualitative elastography), which includes real time-elastography (RT-E); and (2) shear-wave elastography (SWE) (quantitative elastography), which includes a: transient elastography (TE); b: Point SWE [acoustic radiation force impulse elastography (ARFI) and the ElastPQ technique]; and c: real-time SWE [including two-dimensional SWE (2D-SWE) and three-dimensional SWE (3D-SWE)]^[14,16,17].

It is a known fact that patients with advanced cirrhosis have shorter survival rates due to severe complications such as: portal hypertension (development of esophageal varices - EV), HCC, and hepatorenal syndrome. Thus, it would be advantageous to identify the patients who are at risk for these complications and to screen them: for EV by upper endoscopy and for HCC by ultrasound.

Portal hypertension is one of the most feared complications of cirrhosis. It can lead to the development of esophageal and gastric varices (EV and GV, respectively) and upper digestive bleeding due to variceal rupture. The best method to assess bleeding risk is measurement of hepatic venous pressure gradient (HVPG), available only in specialized centers, and an invasive procedure. In clinical practice, the size of EV is used to assess bleeding risk. According to Baveno V and AASLD Consensus, primary prevention of variceal bleeding should be applied to patients with large (grade 2 or 3) EV^[18,19]. To diagnose clinically significant EV (large-grade 2 or 3 EV), a screening program inclusive of periodic upper digestive endoscopy should be implemented. However, repeated endoscopies are often poorly accepted by patients and are also expensive. Thus, it would be very useful to

Table 1 Predictive value of transient elastography in the liver for clinically significant portal hypertension

Study	HPVG \geq 10 mmHg				HPVG \geq 12 mmHg			
	Cut-off (kPa)	AUROC	Se	Sp	Cut-off (kPa)	AUROC	Se	Sp
Vizzutti <i>et al</i> ^[30] , <i>Hepatology</i> 2007	13.6	0.990	97%	92%	17.6	0.92	94.0%	81.0%
Bureau <i>et al</i> ^[31] , <i>Aliment Pharmacol Ther</i> 2008	21	0.945	89.9%	93.2%	-	-	-	-
Reiberger <i>et al</i> ^[34] , <i>Wien Klin Wochenschr</i> 2012	18	0.871	83.4%	82.2%	20.0	0.79	84.2%	80.7%
Salzl <i>et al</i> ^[35] , <i>Ultraschall Med</i> 2014	16.8	0.870	89.7%	75%	-	-	-	-
¹ Shi <i>et al</i> ^[46] , <i>Liver Int</i> 2013	-	0.930	90%	79%	-	-	-	-

¹Meta-analysis: HSROC and summary Se and summary Sp are presented. HPVG: Hepatic venous pressure gradient; Se: Sensitivity; Sp: Specificity; AUROC: Area under the receiver operating characteristics curve.

find a non-invasive, inexpensive technique to predict the occurrence of significant varices and the risk of bleeding. It was logical to evaluate the proficiencies of various elastographic methods in this regard because they have been proven to be very accurate in predicting the presence of cirrhosis.

TE

TE was the first elastographic method that was developed to evaluate LS as a predictor for fibrosis^[20]. It uses a FibroScan device (Echosens, Paris, France) that includes a special ultrasound probe (3.5 MHz for the standard M probe) integrated into a piston that "punches" the body surface. The "punch" generates shear waves that propagate into the liver. Their velocity is measured by pulse-echo ultrasound acquisition and is proportional to LS, increasing in parallel with LS. The FibroScan device displays a Young's modulus, expressed in kilopascals (kPa), which is proportional to the shear-wave velocity^[14,16,17]. Measured values range from 2.5 to 75 kPa.

Liver stiffness is measured in the right liver lobe, in fasting patients. The software automatically rejects measurements with an inconsistent vibration shape or follow-up. For a reliable assessment, ten valid shots should be obtained, and the median value of these measurements should be considered indicative of the LS value. The technical quality parameters that should be considered for correct LS measurements include the success rate (SR) and the interquartile range (IQR). SR is the percentage of valid shots from the total number of shots, while IQR is a measure of variability and is calculated as the difference between the 75th and the 25th percentile of obtained values. Thus, TE measurements are regarded as unreliable if 10 valid shots cannot be obtained or if the IQR is higher than 30% of the median value and/or the SR is lesser than 60%. If no valid shots are obtained, TE measurement is considered failed^[21].

Several published meta-analyses have demonstrated that LS measurement by TE is a reliable method for diagnosing cirrhosis, with a pooled sensitivity ranging from 84.45% to 87% and a pooled specificity ranging from 91% to 94.69%^[13,22]. In the most recent meta-analysis, for a mean optimal cut-off of 15 kPa, the summary sensitivity was 0.83

for diagnosing cirrhosis with summary specificity of 0.89^[23]. However, the cut-off values for diagnosing cirrhosis may vary according to its etiology^[24]. Published studies have found the following cut-offs: in HCV infection - 12.5 kPa^[25], in HBV infection - 13.4 kPa^[26], in NAFLD - 10.3 kPa^[27], in ASH - 22.4 kPa^[28], and in cholestatic chronic diseases - 17.3 kPa (primary sclerosing cholangitis and primary biliary cirrhosis)^[29].

Several studies were published regarding the correlation between TE measurements and HVPG (Table 1). The first studies were performed in rather small numbers of patients. In an Italian study on a small number of patients, the AUROC for predicting HVPG \geq 10 mmHg was 0.99 with 97% sensitivity, while for predicting HVPG \geq 12 mmHg the calculated AUROC was 0.92 with 94% sensitivity. The calculated cut-offs were 13.6 kPa for HVPG \geq 10 mmHg and 17.6 kPa for HVPG \geq 12 mmHg. The cut-off was also 17.6 kPa for predicting any EV (90% sensitivity, AUROC = 0.76)^[30].

In a French study, TE accurately predicted HVPG > 10 mmHg (significant portal hypertension); the AUROC was 0.945. The calculated cut-off was 21 kPa^[31]. In another French study by the same group, which followed up for 2 years 100 patients evaluated by TE and HVPG, similar performances of TE and HVPG for predicting portal hypertension were observed, with AUROCs of 0.830 and 0.845, respectively. During the follow-up, none of the patients with LS values lower than the calculated cut-off (21.1 kPa) had complications of portal hypertension, vs 47.5% of those with values higher than the cut-off^[32].

In an Austrian study including 122 cirrhotics with EV, a stronger correlation was observed between LS measurements by TE and HVPG in patients with HVPG lower than 12 mmHg ($r = 0.951$) vs those with HVPG higher than 12 mmHg ($r = 0.538$) and that the correlation improved in patients who were hemodynamic responders to beta-blocker therapy ($r = 0.864$), while in non-responders it remained the same ($r = 0.535$)^[33]. The calculated cut-off to discriminate between patients with grade 1 EV and those with grade 2 or 3 EV was 47.5 kPa, with good sensitivity (80.6%) but rather poor specificity (47.7%)^[33].

The same Austrian group evaluated 502 patients by TE and HVPG. They observed a strong correlation between LS assessment by TE and HVPG ($r = 0.794$;

Table 2 Predictive value of Transient Elastography in the liver for esophageal varices

Study	At least grade 1 EV				At least grade 2 EV			
	Cut-off (kPa)	AUROC	Se	Sp	Cut-off (kPa)	AUROC	Se	Sp
Nguyen-Khac <i>et al</i> ^[39] <i>Alcohol Clin Exp Res</i> 2010	-	-	-	-	47.2 (alcoholic)	0.770	84.6%	63.6%
Nguyen-Khac <i>et al</i> ^[39] <i>Alcohol Clin Exp Res</i> 2010	-	-	-	-	19.8 (viral)	0.730	88.9%	55.1%
Sporea <i>et al</i> ^[40] <i>Med Ultrason</i> 2013	-	-	-	-	32.5 (alcoholic)	0.836	85%	74.6%
Sporea <i>et al</i> ^[40] <i>Med Ultrason</i> 2013	-	-	-	-	24.8 (viral)	0.867	81%	80.7%
Castéra <i>et al</i> ^[41] <i>J Hepatol</i> 2009	21.5 (HCV)	0.84	76%	78%	30.5 (HCV)	0.870	77%	85%
Sporea <i>et al</i> ^[45] <i>World J Gastroenterol</i> 2011	31	0.78	83%	62%	-	-	-	-
¹ Shi <i>et al</i> ^[46] <i>Liver Int</i> 2013	-	0.84	87%	53%	-	0.780	0.86%	0.59%

¹Meta-analysis: HSROC and summary Se and summary Sp are presented. EV: Esophageal varices; Se: Sensitivity; Sp: Specificity; AUROC: Area under the receiver operating characteristics curve.

$P < 0.0001$). The correlation was stronger in cirrhotics with viral etiology ($r = 0.838$) than in those with alcoholic disease ($r = 0.756$). For a cut-off of 18 kPa, TE had an 86% positive predictive value and an 80% negative predictive value in identifying cirrhotics with clinically significant portal hypertension (CSPH: HPVG ≥ 10 mmHg)^[34].

Recently published studies have also demonstrated a good correlation between TE and HVP. In a study from 2014, the calculated cut-off to predict CSPH was 16.8 kPa, with 89.7% sensitivity and 75% specificity (AUROC = 0.870)^[35]. The same group demonstrated that if new reliability criteria for TE were used [very reliable measurements (IQR/M < 0.1), reliable (IQR/M < 0.3, or > 0.3 if TE < 7.1 kPa) and poorly reliable (IQR/M > 0.3, if TE > 7.1 kPa), where M = the median value], the number of patients who could be evaluated increased (83.2% vs 71.6%) without affecting the accuracy of identifying those with CSPH [88.9% (AUC = 0.957) vs 89.8% (AUC = 0.962) for a cut-off of 16.1 kPa]^[36].

As mentioned above, HPVG measurement is an invasive procedure and is not available at many centers; therefore, in clinical practice, upper digestive endoscopy is used to diagnose EV as a sign of portal hypertension. The first published studies demonstrated that LS values lower than 19 kPa had a high negative predictive value for significant EV (grade 2 and 3)^[37], with cut-offs varying from 27.5 to 47.2 kPa^[38,39]. Additionally, for predicting esophageal bleeding, the calculated cut-off was 62.7 kPa^[38].

Predictive LS values for grade 2 and 3 EV were assessed according to cirrhosis etiology (Table 2). The cut-offs were higher alcoholic cirrhosis (47.2 kPa, AUROC = 0.77, 63.6% specificity, 84.6% sensitivity, 92.5% negative predictive value and 44% positive predictive value) than in patients with viral etiology (19.8 kPa, AUROC = 0.73, 55.1% specificity, 88.9% sensitivity, 96.4% negative predictive value and 26.7% positive predictive value)^[39]. A similar phenomenon was observed in a study from our group that was conducted on almost 700 patients. In our study, the best LS cut-off for significant EV was 32.5 kPa (AUROC = 0.836) in patients with alcoholic cirrhosis compared

with 24.8 kPa (AUROC = 0.867) in those with viral cirrhosis^[40].

In a study from 2009 on HCV cirrhosis, Castéra *et al*^[41] calculated a cut-off of 21.5 kPa to predict the occurrence of EV, but it had only 76% sensitivity and 78% specificity, thus it was concluded that TE cannot be a replacement for upper endoscopy for the diagnosis of EV. In a smaller, more recent study that compared TE with Forns Index, FIB-4 and Lok score for the prediction of grade 2 and 3 EV in patients with HCV cirrhosis, for a 22.4 kPa cut-off, TE showed the highest accuracy (80%) (AUROC = 0.801)^[42].

Chen *et al*^[43] evaluated 238 patients with HBV cirrhosis by TE and upper digestive endoscopy. In patients with significant cytolysis ($\geq 5 \times$ upper limit of normal), for a 36.1 kPa cut-off, TE had 100% negative predictive value with 72.7% positive predictive value for predicting grade 2 and 3 EV, with an AUROC of 0.93^[43].

In 2012 Castera published a review article that evaluated only small studies (47-211 patients) with contradicting results: cut-offs for predicting significant EV 19.8-48 kPa; with AUROCs 0.73-0.87. Castera *et al*^[44] concluded that "diagnostic performances of TE are acceptable for the prediction of clinically significant portal hypertension but far from satisfactory to confidently predict the presence of EV in clinical practice and to screen cirrhotic patients without endoscopy".

This review did not include a Romanian study conducted on 1000 consecutive cirrhotics^[45]. For an optimal cut-off of 31 kPa, we calculated a 76.2% negative predictive value for at least grade 2 EV and a positive predictive value of 71.3%. If the cut-off for at least grade 2 EV was chosen so that the positive predictive value was higher than 85% (> 40 kPa), we calculated 77.8% sensitivity, 68.3% specificity, 86% positive predictive value, with 55% negative predictive value. If the cut-off was chosen so that the negative predictive value was close to 90% (17.1 kPa), we calculated the negative predictive value to be 89.3%, with 43.2% positive predictive value, 92.6% sensitivity and 33.5% specificity for at least grade 2 EV^[45]. Thus, according to our calculations, patients

with LS values higher than 40 kPa will have significant portal hypertension in at least 8/10 cases and should receive prophylactic beta-blocker treatment without undergoing endoscopy. Considering that for the 40 kPa cut-off the negative predictive value was 54.9%, 5/10 cases will have significant (grade 2 and 3) EV, thus we recommend endoscopic evaluation. For the 17.1 kPa criterion the negative predictive value for significant EV was 89.3% (1 in 10 patients), thus we do not recommend endoscopic assessment^[45].

Finally, a method's value is demonstrated by meta-analyses. Regarding TE and portal hypertension, a meta-analysis that included 18 studies with more than 3,500 patients was published in 2013^[46]. It showed that TE had a 0.90 summary sensitivity and a 0.79 summary specificity (AUROC = 0.93) for predicting CSPH (HVPG \geq 10 mmHg), a 0.87 summary sensitivity and a 0.53 summary specificity (AUROC = 0.84) for predicting the occurrence of any EV, and a 0.86 summary sensitivity and a 0.59 summary specificity (AUROC = 0.78) for predicting significant (grade 2 and 3) EV. The conclusion was that, due to the low specificity of this method, TE cannot replace upper gastrointestinal endoscopy for EV screening^[46].

Spleen stiffness (SS) measurement by TE was also assessed as predictor of portal hypertension based on the idea that splenomegaly is one of the clinical signs of cirrhosis. Several studies found a good correlation between SS and LS by TE in patients with cirrhosis and also between SS and the presence of EV^[47,48] or HVPG^[49].

In a cohort of 200 cirrhotics, SS values higher than 40.8 kPa had 94% sensitivity, 76% specificity, 91% positive predictive value and 84% negative predictive value for the presence of any EV. Also, SS by TE was significantly correlated with HVPG ($r = 0.433$, $P = 0.001$). When combining LS (cut-off 27.3 kPa) and SS (cut-off 40.8 kPa), the accuracy of TE in predicting EV was 90%^[50].

Because in many cases a maximum value of 75 kPa is obtained when assessing SS in patients with cirrhosis, the idea of using a modified software version for SS assessment by TE was explored. Using this modified software, which is not commercially available, mSS values of up to 150 kPa could be obtained by TE. In a series of 80 HCV cirrhotics, mSS accurately predicted grade 3 EV: the cut-off was 75 kPa, with 100% sensitivity, 69.01% specificity, 100% negative predictive value and 29% positive predictive value, with an AUROC of 0.903^[51]. Similar results were obtained in another study in which multivariate analysis demonstrated that mSS was the only independent factor associated with grade 2 and 3 EV. The cut-off was 54 kPa, with 80% sensitivity, 70% specificity, and an AUROC of 0.82^[52].

Finally, the EFSUMB guidelines on the use of elastography state that: "TE has some value for predicting the occurrence of complications of liver

cirrhosis, portal hypertension, HCC and liver-associated mortality. It cannot replace upper gastrointestinal endoscopy for identifying patients with varices"^[15].

ARFI

ARFI is a point shear-wave elastographic technique that measures LS as a predictor of fibrosis. ARFI was first developed by Siemens and was integrated into a standard ultrasound machine (Acuson S2000TM, Siemens, Erlangen, Germany); it is also available in newer models. It evaluates LS in a 10/5 mm region of interest (ROI), placed by the operator in a region free of large vessels, while performing B-mode real-time examination. The probe automatically produces a 262 μ s, 2.67 MHz acoustic "push" pulse that induces shear-waves into the liver, which are tracked using ultrasound correlation-based methods^[53]. Shear-waves speed is quantified using a patented application of ARFI technology [Virtual Touch Tissue Quantification (VTQ)]. The measurement result is displayed on the screen (expressed in m/s), together with the measurement depth.

Scanning is performed with minimal scanning pressure, *via* an intercostal approach on the right liver lobe, approximately where a LB would be performed, in fasting patients in a dorsal decubitus position to avoid cardiac motion. Measurements should be performed 1-2 cm under the capsule^[17,54-56]. No recommendations were made by the manufacturer regarding the quality criteria that should be used, but published papers showed a better correlation with histological fibrosis if quality criteria similar to those from TE were used (SR > 60% and especially IQR \leq 30%)^[17,57,58].

Several studies have proven that ARFI elastography is a reliable technique to predict cirrhosis when compared to LB, with cut-offs ranging from 1.55 to 2 m/s and AUROCs ranging from 0.89 to 0.937^[54,59-62]. Additionally, when ARFI elastography was compared to TE with LB as the reference method, it had similar performance to TE in diagnosing cirrhosis^[61,62].

Several meta-analyses have confirmed that ARFI is a valuable method for diagnosing cirrhosis, with mean diagnostic accuracies reported as AUROCs of 0.93^[63] and 0.91^[64], which are comparable to TE^[63,65].

Published studies showed controversial results regarding liver assessment by ARFI elastography as a predictor of portal hypertension (Table 3). A study from our group showed no significant differences between mean LS by ARFI in patients with no or grade 1 EV (2.73 \pm 0.71 m/s) vs those with grade 2 and 3 EV (2.8 \pm 0.71 m/s, $P = 0.49$), nor between those that had a history of variceal bleeding (2.78 \pm 0.81) vs those with no bleeding history (2.77 \pm 0.7 m/s, $P = 0.99$)^[66]. Additionally, another study from Romania showed a rather poor performance of ARFI elastography in predicting large EV, with an AUROC of only 0.596^[67], which is a similar result to that from another European study in which the AUROC for predicting large EV was

Table 3 Predictive value of acoustic radiation force impulse elastography in the liver for esophageal varices

Study	At least grade 1 EV				At least grade 2 EV			
	Cut-off (m/s)	AUROC	Se	Sp	Cut-off (m/s)	AUROC	Se	Sp
Bota <i>et al</i> ^[67] , <i>Ann Hepatol</i> 2012	-	-	-	-	2.25	0.596	93.4%	28.9%
Morishita <i>et al</i> ^[69] , <i>J Gastroenterol</i> 2014	2.05	0.89	83%	76%	2.39	0.868	81.0%	82.0%

EV: Esophageal varices; Se: Sensitivity; Sp: Specificity; AUROC: Area under the receiver operating characteristics curve.

0.58^[68].

Much better results were obtained in Asian studies (Table 3). In a Japanese study, the LS cut-off by ARFI for predicting any EV was 2.05 m/s (83% sensitivity, 76% specificity, AUROC = 0.89), while for high-risk EV the cut-off was 2.39 m/s (81% sensitivity, 82% specificity, AUROC = 0.868)^[69].

An European study showed a good correlation ($r = 0.646$; $P < 0.001$) between LS measurements by ARFI elastography and HVPG. The calculated cut-off to predict CSPH was 2.58 m/s (71.4% sensitivity, 87.5% specificity, AUROC = 0.855)^[35].

Similar to TE, SS assessment by ARFI elastography was evaluated as a predictor of portal hypertension, also with controversial results.

In a study by Rifai *et al*^[70], SS performed significantly worse than LS in predicting CSPH (AUROC 0.68 vs 0.90), but it must be considered that the LS cut-off calculated to predict CSPH was only 1.67 m/s, which is much lower than that proposed for diagnosing liver cirrhosis^[59-62]. The optimal SS cut-off for predicting CSPH was 3.29 m/s, but with rather poor specificity and sensitivity: 73% and 47%, respectively^[70]. In a smaller study on only 33 cirrhotic HCV patients, in which only 12 had EV, it was found that evaluating SS by ARFI correlates with the presence of ascites but not with the presence of EV^[71].

In a study by Vermehren *et al*^[68], the situation was reversed. It was demonstrated by multiple logistic regression analysis that SS by ARFI performed better than LS by ARFI for predicting the presence of large EV, even if the AUROCs of ARFI of the liver and ARFI of the spleen were similar (0.58 for both)^[68].

Another study measured liver and SS by ARFI before and after placement of a transjugular intrahepatic portosystemic shunt (TIPS). The mean LS determined by ARFI did not differ before and after TIPS placement, while SS significantly decreased after TIPS placement, at 3.65 ± 0.32 m/s before vs 3.27 ± 0.30 m/s after TIPS ($P < 0.001$)^[72].

In a study from our group, we combined several parameters to improve the accuracy of ARFI elastography for predicting grade 2 and 3 EV. LS and SS values by ARFI as well as the presence of ascites were associated with significant EV by univariate analysis. Using multiple regression analysis, the following formula to predict at least grade 2 EV was calculated: Prediction of significant EV (Pred EV₂₋₃) score = $-0.572 + 0.041 \times \text{LS (m/s)} + 0.122 \times \text{SS (m/s)}$

+ $0.325 \times \text{ascites (1-absent, 2-present)}$. The optimal Pred EV(2-3) cut-off for predicting grade 2 and 3 EV was 0.395, with 69.6% accuracy (AUROC = 0.721)^[67].

Considering these conflicting results, further studies and meta-analysis are necessary to assess the real value of LS and SS by ARFI elastography as predictors of portal hypertension in cirrhotics, either alone or in combination.

Published studies have not explained why TE can predict portal hypertension while ARFI cannot. One explanation may be that there is a wider range for TE above the cut-off for cirrhosis (approximately 12.5-13.5 kPa up to 75 kPa) than for ARFI (approximately 1.8-2 m/s up to 5 m/s).

2D-SWE

2D-SWE is an elastographic method integrated into an AixplorerTM ultrasound machine (SuperSonic Imagine S.A., Aix-en-Provence, France). To obtain a stiffness measurement, tissue is stimulated by an acoustic "push" pulse generated by the transducer, which generates shear-waves in the tissue. Ultrafast imaging technology allows the acquisition of raw radiofrequency data with a very high frame rate, of up to 5000 frames/s, which enables shear-wave speed estimation by a Doppler-like acquisition over a ROI, which is used for tissue stiffness assessment. Elasticity is displayed as a color-coded image superimposed on a standard, grey-scale B-mode image: red denotes stiffer tissues and blue denotes softer tissues. Additionally, a numerical value is displayed together with the standard deviation of the measured elasticity, either in kPa or in m/s^[14,16,17,73,74].

2D-SWE measurements are performed under fasting conditions *via* an intercostal approach using 3-5 acquisitions, after which a mean value is calculated^[15]. Starting from the first published studies regarding 2D-SWE, this method has proven to be accurate for diagnosing cirrhosis. In hepatitis C patients, the reported AUROCs were 0.94^[75] and 0.98^[76]. The cut-off value was 10.4 kPa^[76]. In hepatitis B patients, the cut-off for cirrhosis was 10.1 kPa (AUROC = 0.98)^[77]. In a recently published study in hepatitis B patients, the AUROC for predicting cirrhosis was 0.945 in the index cohort and 0.967 in the validation cohort for a cut-off of 11.7 kPa^[78]. In mixed etiology patients, the cut-off for 2D-SWE in predicting cirrhosis was 11.5 kPa (AUROC = 0.914)^[79]. In a very recent study, the AUROC of 2D-SWE in predicting cirrhosis was also very

good at 0.926^[80].

Regarding 2D-SWE as a tool to predict portal hypertension, we found only two published studies, both in 2015. In the one performed by Kim *et al.*^[80], LS measurement by 2D-SWE was used to predict portal hypertension assessed by HVPG measurement. For a cut-off value of 15.2 kPa, 2D-SWE accurately predicted CSPH (HVPG > 10 mmHg), with 85.7% sensitivity and 80% specificity (AUROC = 0.819). In a study by Procopet *et al.*^[81], a very good accuracy of LS by 2D-SWE was observed when quality technical parameters were taken into consideration (SD/median LS ≤ 0.10 for depth of measurement < 5.6 cm and SD/median LS > 0.10 for depth of measurement ≥ 5.6 cm). In this category of patients, the best cut-off to predict CSPH was 15.4 kPa (AUROC = 0.948, with sensitivity and specificity both higher than 90%).

Further larger studies and meta-analyses are needed to assess 2D-SWE as a predictor of portal hypertension.

Strain elastography

Although strain elastography was the original elastographic method used to assess tissue stiffness and is currently available in most high-end ultrasound machines, its value in assessing liver stiffness as a predictor of fibrosis severity is not yet defined due to unstandardized methodology. Initially, hand compression was used for tissue deformation, but in newer systems heartbeats are used to stress the tissue. Elasticity is displayed as a color-coded image superimposed on a standard, gray-scale, B-mode image: red denotes softer tissues and blue denotes stiffer tissues. In newer systems, a histogram and 11 parameters are also displayed^[17]. Recent studies showed promising results when using strain elastography to predict cirrhosis using both elastic ratios^[82,83] and average strain histograms^[84]. No data are available regarding the use of elastic ratios and average strain histograms obtained by strain elastography for the assessment of portal hypertension.

ElastPQ technique

The ElastPQ technique is the newest elastographic method to appear on the market. It is also a point-SWE technique, which was developed by Philips, and is integrated into the iU22 ultrasound system (Philips Medical Systems, Bothell, WA, United States). An ultrasonic pressure wave generated by the transducer induces shear-waves in liver tissue, whose speed is measured by the Doppler functions of the system within an ROI that is placed by the operator in a desired location using B-mode standard ultrasound. A numeric value indicative of liver stiffness, which is expressed either in m/s or kPa, is displayed on the screen^[17]. Promising results following the use of the ElastPQ technique to predict cirrhosis were obtained in both HCV and HBV patients^[85-87]. No data are available

regarding the predictive value of the ElastPQ technique for portal hypertension.

CONCLUSION

In conclusion, we suggest that all elastographic methods are reliable for the early diagnosis of cirrhosis, especially TE and ARFI, whose value has been proven by meta-analyses. While TE is a promising method to predict portal hypertension in cirrhotics, it cannot replace upper digestive endoscopy. The diagnostic accuracy of LS assessment by ARFI in predicting portal hypertension in cirrhotics is debatable. The accuracy of ARFI elastography may be significantly improved if SS is also assessed, either alone or in combination with liver stiffness and other parameters. 2D-SWE, the ElastPQ technique and strain elastography all need to be evaluated as predictors of portal hypertension.

REFERENCES

- 1 **Portincasa P.** Non-alcoholic steatohepatitis (NASH): approaching more tailored and effective therapies. *J Gastrointest Liver Dis* 2007; **16**: 167-169 [PMID: 17592564]
- 2 **Lavanchy D.** Evolving epidemiology of hepatitis C virus. *Clin Microbiol Infect* 2011; **17**: 107-115 [PMID: 21091831 DOI: 10.1111/j.1469-0691.2010.03432.x]
- 3 **Benvegnù L,** Gios M, Boccato S, Alberti A. Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications. *Gut* 2004; **53**: 744-749 [PMID: 15082595 DOI: 10.1136/gut.2003.020263]
- 4 **World Health Organization.** Hepatitis B. World Health Organization Fact Sheet 204 (Revised August 2008). Available from: URL: <http://www.who.int/mediacentre/factsheets/fs204/en/index.html>. Accessed April 20 2015
- 5 **Rehm J,** Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol* 2013; **59**: 160-168 [PMID: 23511777 DOI: 10.1016/j.jhep.2013.03.007]
- 6 **Blachier M,** Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013; **58**: 593-608 [PMID: 23419824 DOI: 10.1016/j.jhep.2012]
- 7 **McHutchison J,** Poynard T, Afdhal N. Fibrosis as an end point for clinical trials in liver disease: a report of the international fibrosis group. *Clin Gastroenterol Hepatol* 2006; **4**: 1214-1220 [PMID: 16979947 DOI: 10.1016/j.cgh.2006.07.006]
- 8 **Ratziu V,** Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, Capron F, Poynard T. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. *Gastroenterology* 2005; **128**: 1898-1906 [PMID: 15940625 DOI: 10.1053/j.gastro.2005.03.084]
- 9 **Regev A,** Berho M, Jeffers LJ, Milikowski C, Molina EG, Pylsopoulos NT, Feng ZZ, Reddy KR, Schiff ER. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *Am J Gastroenterol* 2002; **97**: 2614-2618 [PMID: 12385448]
- 10 **Persico M,** Palmentieri B, Vecchione R, Torella R, de SI. Diagnosis of chronic liver disease: reproducibility and validation of liver biopsy. *Am J Gastroenterol* 2002; **97**: 491-492 [PMID: 11866299]
- 11 **Munteanu M.** Non-invasive biomarkers FibroTest-ActiTest for replacing invasive liver biopsy: the need for change and action. *J Gastrointest Liver Dis* 2007; **16**: 173-174 [PMID: 17592566]
- 12 **Yin M,** Talwalkar JA, Glaser KJ, Manduca A, Grimm RC, Rossman PJ, Fidler JL, Ehman RL. Assessment of hepatic fibrosis with magnetic resonance elastography. *Clin Gastroenterol*

- Hepatol* 2007; **5**: 1207-1213.e2 [PMID: 17916548 DOI: 10.1016/j.cgh.2007.06.012]
- 13 **Talwalkar JA**, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2007; **5**: 1214-1220 [PMID: 17916549 DOI: 10.1016/j.cgh.2007.07.020]
 - 14 **Bamber J**, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, Cantisani V, Correias JM, D'Onofrio M, Drakonaki EE, Fink M, Friedrich-Rust M, Gilja OH, Havre RF, Janssen C, Klauser AS, Ohlinger R, Saftoiu A, Schaefer F, Sporea I, Piscaglia F. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. *Ultraschall Med* 2013; **34**: 169-184 [PMID: 23558397 DOI: 10.1055/s-0033-1335205]
 - 15 **Cosgrove D**, Piscaglia F, Bamber J, Bojunga J, Correias JM, Gilja OH, Klauser AS, Sporea I, Calliada F, Cantisani V, D'Onofrio M, Drakonaki EE, Fink M, Friedrich-Rust M, Fromageau J, Havre RF, Janssen C, Ohlinger R, Săftoiu A, Schaefer F, Dietrich CF. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. *Ultraschall Med* 2013; **34**: 238-253 [PMID: 23605169 DOI: 10.1055/s-0033-1335375]
 - 16 **Shiina T**, Nightingale KR, Palmeri ML, Hall TJ, Bamber JC, Barr RG, Castera L, Choi BI, Chou YH, Cosgrove D, Dietrich CF, Ding H, Amy D, Farrokhi A, Ferraioli G, Filice C, Friedrich-Rust M, Nakashima K, Schafer F, Sporea I, Suzuki S, Wilson S, Kudo M. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. *Ultrasound Med Biol* 2015; **41**: 1126-1147 [PMID: 25805059 DOI: 10.1016/j.ultrasmedbio.2015.03.009]
 - 17 **Sporea I**, Bota S, Săftoiu A, Şirli R, Gradinăru-Taşcău O, Popescu A, Luşor Platon M, Fierbinteanu-Braticevici C, Gheonea DI, Săndulescu L, Badea R. Romanian national guidelines and practical recommendations on liver elastography. *Med Ultrason* 2014; **16**: 123-138 [PMID: 24791844 DOI: 10.11152/mu.201.3.2066.162.is1sb2]
 - 18 **de Franchis R**. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010; **53**: 762-768 [PMID: 20638742 DOI: 10.1016/j.jhep.2010.06.004]
 - 19 **Garcia-Tsao G**, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatol* 2007; **46**: 922-938 [PMID: 17879356 DOI: 10.1002/hep.21907]
 - 20 **Sandrin L**, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poulet B, Kazemi F, Beaugrand M, Palau R. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol* 2003; **29**: 1705-1713 [PMID: 14698338 DOI: 10.1016/j.ultrasmedbio.2003.07.001]
 - 21 **Castéra L**, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, Couzigou P, de Lédinghen V. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. *Hepatology* 2010; **51**: 828-835 [PMID: 20063276 DOI: 10.1002/hep.23425]
 - 22 **Stebbing J**, Farouk L, Panos G, Anderson M, Jiao LR, Mandalia S, Bower M, Gazzard B, Nelson M. A meta-analysis of transient elastography for the detection of hepatic fibrosis. *J Clin Gastroenterol* 2010; **44**: 214-219 [PMID: 19745758 DOI: 10.1097/MCG.0b013e3181b4af1f]
 - 23 **Tsochatzis EA**, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol* 2011; **54**: 650-659 [PMID: 21146892 DOI: 10.1016/j.jhep.2010.07.033]
 - 24 **Abenavoli L**, Corpechot C, Poupon R. Elastography in hepatology. *Can J Gastroenterol* 2007; **21**: 839-842 [PMID: 18080057]
 - 25 **Castéra L**, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, Couzigou P, De Lédinghen V. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* 2005; **128**: 343-350 [PMID: 15685546 DOI: 10.1053/j.gastro.2004.11.018]
 - 26 **Marcellin P**, Ziol M, Bedossa P, Douvin C, Poupon R, de Lédinghen V, Beaugrand M. Non-invasive assessment of liver fibrosis by stiffness measurement in patients with chronic hepatitis B. *Liver Int* 2009; **29**: 242-247 [PMID: 18637064 DOI: 10.1111/j.1478-3231.2008.01802.x]
 - 27 **Wong VW**, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Lédinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 454-462 [PMID: 20101745 DOI: 10.1002/hep.23312]
 - 28 **Nahon P**, Kettaneh A, Tengher-Barna I, Ziol M, de Lédinghen V, Douvin C, Marcellin P, Ganne-Carrié N, Trinchet JC, Beaugrand M. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. *J Hepatol* 2008; **49**: 1062-1068 [PMID: 18930329 DOI: 10.1016/j.jhep.2008.08.011]
 - 29 **Corpechot C**, El Naggar A, Poujol-Robert A, Ziol M, Wendum D, Chazouillères O, de Lédinghen V, Dhumeaux D, Marcellin P, Beaugrand M, Poupon R. Assessment of biliary fibrosis by transient elastography in patients with PBC and PSC. *Hepatology* 2006; **43**: 1118-1124 [PMID: 16628644 DOI: 10.1002/hep.21151]
 - 30 **Vizzutti F**, Arena U, Romanelli RG, Rega L, Foschi M, Colagrande S, Petrarca A, Moscarella S, Belli G, Zignego AL, Marra F, Laffi G, Pinzani M. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. *Hepatology* 2007; **45**: 1290-1297 [PMID: 17464971 DOI: 10.1002/hep.21665]
 - 31 **Bureau C**, Metivier S, Peron JM, Selves J, Robic MA, Gourraud PA, Rouquet O, Dupuis E, Alric L, Vinel JP. Transient elastography accurately predicts presence of significant portal hypertension in patients with chronic liver disease. *Aliment Pharmacol Ther* 2008; **27**: 1261-1268 [PMID: 18397389 DOI: 10.1111/j.1365-2036.2008.03701.x]
 - 32 **Robic MA**, Procopet B, Métivier S, Péron JM, Selves J, Vinel JP, Bureau C. Liver stiffness accurately predicts portal hypertension related complications in patients with chronic liver disease: a prospective study. *J Hepatol* 2011; **55**: 1017-1024 [PMID: 21354450 DOI: 10.1016/j.jhep.2011.01.051]
 - 33 **Reiberger T**, Ferlitsch A, Payer BA, Pinter M, Homoncik M, Peck-Radosavljevic M. Non-selective β -blockers improve the correlation of liver stiffness and portal pressure in advanced cirrhosis. *J Gastroenterol* 2012; **47**: 561-568 [PMID: 22170417 DOI: 10.1007/s00535-011-0517-4]
 - 34 **Reiberger T**, Ferlitsch A, Payer BA, Pinter M, Schwabl P, Stift J, Trauner M, Peck-Radosavljevic M. Noninvasive screening for liver fibrosis and portal hypertension by transient elastography--a large single center experience. *Wien Klin Wochenschr* 2012; **124**: 395-402 [PMID: 22699260 DOI: 10.1007/s00508-012-0190-5]
 - 35 **Salzl P**, Reiberger T, Ferlitsch M, Payer BA, Schwengerer B, Trauner M, Peck-Radosavljevic M, Ferlitsch A. 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**: 528-533 [PMID: 24871695 DOI: 10.1055/s-0034-1366506]
 - 36 **Schwabl P**, Bota S, Salzl P, Mandorfer M, Payer BA, Ferlitsch A, Stift J, Wrba F, Trauner M, Peck-Radosavljevic M, Reiberger T. New reliability criteria for transient elastography increase the number of accurate measurements for screening of cirrhosis and portal hypertension. *Liver Int* 2015; **35**: 381-390 [PMID: 24953516 DOI: 10.1111/liv.12623]
 - 37 **Kazemi F**, Kettaneh A, N'kontchou G, Pinto E, Ganne-Carrié N, Trinchet JC, Beaugrand M. Liver stiffness measurement selects patients with cirrhosis at risk of bearing large oesophageal varices. *J Hepatol* 2006; **45**: 230-235 [PMID: 16797100 DOI: 10.1016/j.jhep.2006.04.006]
 - 38 **Foucher J**, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, Bertet J, Couzigou P, de Lédinghen V. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006; **55**: 403-408 [PMID: 16020491 DOI: 10.1136/

- gut.2005.069153]
- 39 **Nguyen-Khac E**, Saint-Leger P, Tramier B, Coevoet H, Capron D, Dupas JL. Noninvasive diagnosis of large esophageal varices by Fibroscan: strong influence of the cirrhosis etiology. *Alcohol Clin Exp Res* 2010; **34**: 1146-1153 [PMID: 20477777 DOI: 10.1111/j.1530-0277.2010.01191.x]
 - 40 **Sporea I**, Raţiu I, Bota S, Şirli R, Jurchiş A. Are different cut-off values of liver stiffness assessed by transient elastography according to the etiology of liver cirrhosis for predicting significant esophageal varices? *Med Ultrason* 2013; **15**: 111-115 [PMID: 23702500 DOI: 10.11152/mu.2013.2066.152.is1r2]
 - 41 **Castéra L**, Le Bail B, Roudot-Thoraval F, Bernard PH, Foucher J, Merrouche W, Couzigou P, de Lédinghen V. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. *J Hepatol* 2009; **50**: 59-68 [PMID: 19013661 DOI: 10.1016/j.jhep.2008.08.018]
 - 42 **Hassan EM**, Omran DA, El Beshlawey ML, Abdo M, El Askary A. Can transient elastography, Fib-4, Forns Index, and Lok Score predict esophageal varices in HCV-related cirrhotic patients? *Gastroenterol Hepatol* 2014; **37**: 58-65 [PMID: 24365388 DOI: 10.1016/j.gastrohep.2013.09.008]
 - 43 **Chen YP**, Zhang Q, Dai L, Liang XE, Peng J, Hou JL. Is transient elastography valuable for high-risk esophageal varices prediction in patients with hepatitis-B-related cirrhosis? *J Gastroenterol Hepatol* 2012; **27**: 533-539 [PMID: 21871027 DOI: 10.1111/j.1440-1746.2011.06889.x]
 - 44 **Castera L**, Pinzani M, Bosch J. Non invasive evaluation of portal hypertension using transient elastography. *J Hepatol* 2012; **56**: 696-703 [PMID: 21767510 DOI: 10.1016/j.jhep.2011.07.005]
 - 45 **Sporea I**, Raţiu I, Şirli R, Popescu A, Bota S. Value of transient elastography for the prediction of variceal bleeding. *World J Gastroenterol* 2011; **17**: 2206-2210 [PMID: 21633530 DOI: 10.3748/wjg.v17.i17.2206]
 - 46 **Shi KQ**, Fan YC, Pan ZZ, Lin XF, Liu WY, Chen YP, Zheng MH. Transient elastography: a meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. *Liver Int* 2013; **33**: 62-71 [PMID: 22973991 DOI: 10.1111/liv.12003]
 - 47 **Stefanescu H**, Grigorescu M, Lupsor M, Procopet B, Maniu A, Badea R. Spleen stiffness measurement using Fibroscan for the noninvasive assessment of esophageal varices in liver cirrhosis patients. *J Gastroenterol Hepatol* 2011; **26**: 164-170 [PMID: 21175810 DOI: 10.1111/j.1440-1746.2010.06325.x]
 - 48 **Di Marco V**, Bronte F, Calvaruso V, Camma C, Cabibi D, Licata G, Simone F, Craxi A. Fibrospleen: measuring spleen stiffness by transient elastography increases accuracy of staging of liver fibrosis and of portal hypertension in chronic viral hepatitis (abstr). *J Hepatol* 2009; **50**: S148 [DOI: 10.1016/S0168-8278(09)60393-7]
 - 49 **Colecchia A**, Montrone L, Scaiola E, Bacchi-Reggiani ML, Colli A, Casazza G, Schiumerini R, Turco L, Di Biase AR, Mazzella G, Marzi L, Arena U, Pinzani M, Festi D. Measurement of spleen stiffness to evaluate portal hypertension and the presence of esophageal varices in patients with HCV-related cirrhosis. *Gastroenterology* 2012; **143**: 646-654 [PMID: 22643348 DOI: 10.1053/j.gastro.2012.05.035]
 - 50 **Sharma P**, Kirnake V, Tyagi P, Bansal N, Singla V, Kumar A, Arora A. Spleen stiffness in patients with cirrhosis in predicting esophageal varices. *Am J Gastroenterol* 2013; **108**: 1101-1107 [PMID: 23629600 DOI: 10.1038/ajg.2013.119]
 - 51 **Stefanescu H**, Bastard C, Lupsor M, Feier D, Miette V, Sandrin L, Badea R. Spleen stiffness measurement using Fibroscan and a modified calculation algorithm increases the diagnosis performance of large esophageal varices in cirrhotic patients. *J Hepatol* 2011; **54** (Suppl 1): S545 [DOI: 10.1016/S0168-8278(11)61377-9]
 - 52 **Calvaruso V**, Bronte F, Conte E, Simone F, Craxi A, Di Marco V. 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**: 867-874 [PMID: 24304456 DOI: 10.1111/jvh.12114]
 - 53 **Nightingale K**, Soo MS, Nightingale R, Trahey G. Acoustic radiation force impulse imaging: in vivo demonstration of clinical feasibility. *Ultrasound Med Biol* 2002; **28**: 227-235 [PMID: 11937286 DOI: 10.1016/S0301-5629(01)00499-9]
 - 54 **Friedrich-Rust M**, Wunder K, Kriener S, Sotoudeh F, Richter S, Bojunga J, Herrmann E, Poynard T, Dietrich CF, Vermehren J, Zeuzem S, Sarrazin C. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. *Radiology* 2009; **252**: 595-604 [PMID: 19703889 DOI: 10.1148/radiol.2523081928]
 - 55 **Goertz RS**, Zopf Y, Jugl V, Heide R, Janson C, Strobel D, Bernatik T, Haendl T. Measurement of liver elasticity with acoustic radiation force impulse (ARFI) technology: an alternative noninvasive method for staging liver fibrosis in viral hepatitis. *Ultraschall Med* 2010; **31**: 151-155 [PMID: 20306380 DOI: 10.1055/s-0029-1245244]
 - 56 **Sporea I**, Şirli RL, Deleanu A, Popescu A, Focsa M, Danila M, Tudora A. Acoustic radiation force impulse elastography as compared to transient elastography and liver biopsy in patients with chronic hepatopathies. *Ultraschall Med* 2011; **32** Suppl 1: S46-S52 [PMID: 20603783 DOI: 10.1055/s-0029-1245360]
 - 57 **Bota S**, Sporea I, Şirli R, Popescu A, Dănilă M, Sendroiu M. Factors that influence the correlation of acoustic radiation force impulse (ARFI), elastography with liver fibrosis. *Med Ultrason* 2011; **13**: 135-140 [PMID: 21655540]
 - 58 **Bota S**, Sporea I, Şirli R, Popescu A, Jurchiş A. Factors which influence the accuracy of acoustic radiation force impulse (ARFI) elastography for the diagnosis of liver fibrosis in patients with chronic hepatitis C. *Ultrasound Med Biol* 2013; **39**: 407-412 [PMID: 23245820 DOI: 10.1016/j.ultrasmedbio.2012.09.017]
 - 59 **Lupsor M**, Badea R, Stefanescu H, Sparchez Z, Branda H, Serban A, Maniu A. Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C. Preliminary results. *J Gastrointest Liver Dis* 2009; **18**: 303-310 [PMID: 19795024]
 - 60 **Sporea I**, Şirli R, Bota S, Fierbinţeanu-Braticevici C, Petrişor A, Badea R, Lupsor M, Popescu A, Dănilă M. Is ARFI elastography reliable for predicting fibrosis severity in chronic HCV hepatitis? *World J Radiol* 2011; **3**: 188-193 [PMID: 21860715 DOI: 10.4329/wjr.v3.i7.188]
 - 61 **Sporea I**, Badea R, Şirli R, Lupsor M, Popescu A, Danila M, Focsa M, Deleanu A. How efficient is acoustic radiation force impulse elastography for the evaluation of liver stiffness? *Hepat Mon* 2011; **11**: 532-538 [PMID: 22087190]
 - 62 **Rizzo L**, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S, Fatuzzo F, Montineri A, Mazzola A, L'abbate L, Nunnari G, Bronte F, Di Marco V, Craxi A, Cammà C. Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. *Am J Gastroenterol* 2011; **106**: 2112-2120 [PMID: 21971536 DOI: 10.1038/ajg.2011.341]
 - 63 **Friedrich-Rust M**, Nierhoff J, Lupsor M, Sporea I, Fierbinţeanu-Braticevici C, Strobel D, Takahashi H, Yoneda M, Suda T, Zeuzem S, Herrmann E. Performance of Acoustic Radiation Force Impulse imaging for the staging of liver fibrosis: a pooled meta-analysis. *J Viral Hepat* 2012; **19**: e212-e219 [PMID: 22239521 DOI: 10.1111/j.1365-2893.2011.01537.x]
 - 64 **Nierhoff J**, Chávez Ortiz AA, Herrmann E, Zeuzem S, Friedrich-Rust M. The efficiency of acoustic radiation force impulse imaging for the staging of liver fibrosis: a meta-analysis. *Eur Radiol* 2013; **23**: 3040-3053 [PMID: 23801420 DOI: 10.1007/s00330-013-2927-6]
 - 65 **Bota S**, Herkner H, Sporea I, Salzl P, Şirli R, Neghina AM, Peck-Radosavljevic M. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. *Liver Int* 2013; **33**: 1138-1147 [PMID: 23859217 DOI: 10.1111/liv.12240]
 - 66 **Şirli R**, Sporea I, Bota S, Ciof O, Popescu A, Dănilă M. Can Acoustic Radiation Force Impulse Elastography (ARFI) predict the complications of liver cirrhosis? *Medicina Interna* 2010; **7**: 15-20

- 67 **Bota S**, Sporea I, Şirli R, Focsa M, Popescu A, Danila M, Strain M. Can ARFI elastography predict the presence of significant esophageal varices in newly diagnosed cirrhotic patients? *Ann Hepatol* 2012; **11**: 519-525 [PMID: 22700634]
- 68 **Vermehren J**, Polta A, Zimmermann O, Herrmann E, Poynard T, Hofmann WP, Bojunga J, Sarrazin C, Zeuzem S, Friedrich-Rust M. Comparison of acoustic radiation force impulse imaging with transient elastography for the detection of complications in patients with cirrhosis. *Liver Int* 2012; **32**: 852-858 [PMID: 22222050 DOI: 10.1111/j.1478-3231.2011.02736.x]
- 69 **Morishita N**, Hiramatsu N, Oze T, Harada N, Yamada R, Miyazaki M, Yakushijin T, Miyagi T, Yoshida Y, Tatsumi T, Kanto T, Takehara T. Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or high-risk esophageal varices among patients with HCV-related cirrhosis. *J Gastroenterol* 2014; **49**: 1175-1182 [PMID: 24005957 DOI: 10.1007/s00535-013-0877-z]
- 70 **Rifai K**, Cornberg J, Bahr M, Mederacke I, Potthoff A, Wedemeyer H, Manns M, Gebel M. ARFI elastography of the spleen is inferior to liver elastography for the detection of portal hypertension. *Ultraschall Med* 2011; **32** Suppl 2: E24-E30 [PMID: 22194051 DOI: 10.1055/s-0031-1281771]
- 71 **Mori K**, Arai H, Abe T, Takayama H, Toyoda M, Ueno T, Sato K. Spleen stiffness correlates with the presence of ascites but not esophageal varices in chronic hepatitis C patients. *Biomed Res Int* 2013; **2013**: 857862 [PMID: 23984413 DOI: 10.1155/2013/857862]
- 72 **Gao J**, Ran HT, Ye XP, Zheng YY, Zhang DZ, Wang ZG. The stiffness of the liver and spleen on ARFI Imaging pre and post TIPS placement: a preliminary observation. *Clin Imaging* 2012; **36**: 135-141 [PMID: 22370134 DOI: 10.1016/j.clinimag.2011.11.014]
- 73 **Bercoff J**, Tanter M, Muller M, Fink M. The role of viscosity in the impulse diffraction field of elastic waves induced by the acoustic radiation force. *IEEE Trans Ultrason Ferroelectr Freq Control* 2004; **51**: 1523-1536 [PMID: 15600098 DOI: 10.1109/TUFFC.2004.1367494]
- 74 **Muller M**, Gennisson JL, Deffieux T, Tanter M, Fink M. Quantitative viscoelasticity mapping of human liver using supersonic shear imaging: preliminary in vivo feasibility study. *Ultrasound Med Biol* 2009; **35**: 219-229 [PMID: 19081665 DOI: 10.1016/j.ultrasmedbio.2008.08.018]
- 75 **Bavu E**, Gennisson JL, Couade M, Bercoff J, Mallet V, Fink M, Badel A, Vallet-Pichard A, Nalpas B, Tanter M, Pol S. Noninvasive in vivo liver fibrosis evaluation using supersonic shear imaging: a clinical study on 113 hepatitis C virus patients. *Ultrasound Med Biol* 2011; **37**: 1361-1373 [PMID: 21775051 DOI: 10.1016/j.ultrasmedbio.2011.05.016]
- 76 **Ferraioli G**, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C; Liver Fibrosis Study Group. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. *Hepatology* 2012; **56**: 2125-2133 [PMID: 22767302 DOI: 10.1002/hep.25936]
- 77 **Leung VY**, Shen J, Wong VW, Abrigo J, Wong GL, Chim AM, Chu SH, Chan AW, Choi PC, Ahuja AT, Chan HL, Chu WC. Quantitative elastography of liver fibrosis and spleen stiffness in chronic hepatitis B carriers: comparison of shear-wave elastography and transient elastography with liver biopsy correlation. *Radiology* 2013; **269**: 910-918 [PMID: 23912619 DOI: 10.1148/radiol.13130128]
- 78 **Zeng J**, Liu GJ, Huang ZP, Zheng J, Wu T, Zheng RQ, Lu MD. Diagnostic accuracy of two-dimensional shear wave elastography for the non-invasive staging of hepatic fibrosis in chronic hepatitis B: a cohort study with internal validation. *Eur Radiol* 2014; **24**: 2572-2581 [PMID: 25027837 DOI: 10.1007/s00330-014-3292-9]
- 79 **Sporea I**, Bota S, Gradinaru-Taşcău O, Şirli R, Popescu A, Jurchiş A. Which are the cut-off values of 2D-Shear Wave Elastography (2D-SWE) liver stiffness measurements predicting different stages of liver fibrosis, considering Transient Elastography (TE) as the reference method? *Eur J Radiol* 2014; **83**: e118-e122 [PMID: 24380640 DOI: 10.1016/j.ejrad.2013.12.011]
- 80 **Kim TY**, Jeong WK, Sohn JH, Kim J, Kim MY, Kim Y. Evaluation of portal hypertension by real-time shear wave elastography in cirrhotic patients. *Liver Int* 2015; Epub ahead of print [PMID: 25875718 DOI: 10.1111/liv.12846]
- 81 **Procopet B**, Berzigotti A, Abrandes JG, Turon F, Hernandez-Gea V, García-Pagán JC, Bosch J. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. *J Hepatol* 2015; **62**: 1068-1075 [PMID: 25514554 DOI: 10.1016/j.jhep.2014.12.007]
- 82 **Koizumi Y**, Hirooka M, Kisaka Y, Konishi I, Abe M, Murakami H, Matsuura B, Hiasa Y, Onji M. Liver fibrosis in patients with chronic hepatitis C: noninvasive diagnosis by means of real-time tissue elastography--establishment of the method for measurement. *Radiology* 2011; **258**: 610-617 [PMID: 21273523 DOI: 10.1148/radiol.10100319]
- 83 **Kanamoto M**, Shimada M, Ikegami T, Uchiyama H, Imura S, Morine Y, Kanemura H, Arakawa Y, Nii A. Real time elastography for noninvasive diagnosis of liver fibrosis. *J Hepatobiliary Pancreat Surg* 2009; **16**: 463-467 [PMID: 19322509 DOI: 10.1007/s00534-009-0075-9]
- 84 **Morikawa H**, Fukuda K, Kobayashi S, Fujii H, Iwai S, Enomoto M, Tamori A, Sakaguchi H, Kawada N. Real-time tissue elastography as a tool for the noninvasive assessment of liver stiffness in patients with chronic hepatitis C. *J Gastroenterol* 2011; **46**: 350-358 [PMID: 20697747 DOI: 10.1007/s00535-010-0301-x]
- 85 **Ferraioli G**, Tinelli C, Lissandrini R, Zicchetti M, Dal Bello B, Filice C. Performance of ElastPQ® Shear Wave Elastography Technique for Assessing Fibrosis in Chronic Viral Hepatitis. *J Hepatol* 2013; **58** (Suppl 1): S7 [DOI: 10.1016/S0168-8278(13)60018-5]
- 86 **Ma JJ**, Ding H, Mao F, Sun HC, Xu C, Wang WP. Assessment of liver fibrosis with elastography point quantification technique in chronic hepatitis B virus patients: a comparison with liver pathological results. *J Gastroenterol Hepatol* 2014; **29**: 814-819 [PMID: 24325607 DOI: 10.1111/jgh.12479]
- 87 **Sporea I**, Bota S, Grădinaru-Taşcău O, Şirli R, Popescu A. Comparative study between two point Shear Wave Elastographic techniques: Acoustic Radiation Force Impulse (ARFI) elastography and ElastPQ. *Med Ultrason* 2014; **16**: 309-314 [PMID: 25463883 DOI: 10.1016/s0168-8278(14)61176-4]

P- Reviewer: Abenavoli L, Tai DI S- Editor: Ma YJ L- Editor: A
E- Editor: Ma S





Published by **Baishideng Publishing Group Inc**

8226 Regency Drive, Pleasanton, CA 94588, USA

Telephone: +1-925-223-8242

Fax: +1-925-223-8243

E-mail: bpgooffice@wjgnet.com

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>



ISSN 1007-9327

