

Noninvasive Assessment of Liver Diseases using 2D Shear Wave Elastography

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ABSTRACT

There has been great interest in the development of non-invasive techniques for the diagnosis of liver fibrosis in chronic liver diseases, including ultrasound elastographic methods. Some of these methods have already been adequately studied for the non-invasive assessment of diffuse liver diseases. Others, however, such as two-dimensional Shear Wave Elastography (SWE), of more recent appearance, have yet to be validated and some aspects are for the moment incompletely elucidated. This review discusses some of the aspects related to two-dimensional SWE: the examination technique, the examination performance indicators, intra and interobserver agreement and clinical applications. Recommendations for a high-quality examination technique are formulated.

Key words: fibrosis – liver – noninvasive – Two-dimensional Shear Wave Elastography.

Abbreviations: 2D- SWE: Two-dimensional Shear Wave Elastography; 3D- SWE: Three-dimensional Shear Wave Elastography; AUROC: area under the receiver operating characteristic curves; ARFI Acoustic Radiation Force Impulse Elastography; EFSUMB: European Federation of Societies for Ultrasound in Medicine and Biology; HVPG: hepatic venous pressure gradient; LS: liver stiffness; LR: likelihood ratio; NPV: negative predictive value; PPV: positive predictive value; ROI: region of interest; RT-E: Real Time-Elastography; Se: sensitivity; Sp: specificity; TE: Transient Elastography; US: ultrasound; VM: valid measurement; E: Young's modulus

INTRODUCTION

Chronic liver diseases are an important public health issue. Regardless of the nature of liver injury, the pattern of progression toward inflammation, necrosis, fibrosis and then cirrhosis, dysplasia and possibly hepatocellular carcinoma is observed. An important step in this process is fibrogenesis. As liver necroinflammatory injuries persist, an increase in extracellular matrix produced by fibroblast-like cells is observed, and subsequently the liver becomes stiffer than normal [1]. Therefore, recently scientific interest has focused on the development of non-invasive techniques for the diagnosis of liver fibrosis. An important

category of non-invasive methods for the assessment of liver fibrosis includes ultrasound (US) elastographic methods.

The available US-based elastographic techniques are classified, according to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines [2, 3] in:

1) Shear Wave Elastography (SWE) (quantitative elastography), which includes: a) Transient Elastography (TE) – the only method non-integrated into a standard ultrasound system; b) Point SWE: Acoustic Radiation Force Impulse Elastography (ARFI) and ElastPQ technique; c) Real Time SWE: Two-dimensional SWE (2D-SWE) and Three-dimensional SWE (3D-SWE)

2) Strain Elastography (quasi-static elastography, qualitative elastography): Real Time-Elastography (RT-E).

Some of these methods have already been adequately studied for the non-invasive assessment of diffuse liver diseases. Others, however, such as 2D-SWE, of more recent appearance [4], have yet to be validated and some aspects are for the moment incompletely clarified. This review presents some aspects related to two-dimensional SWE (2D-SWE), starting with the examination technique, the examination performance indicators, intra and inter-observer agreement and some

clinical applications. Last but not least, we propose some recommendations for a high-quality examination technique.

2D-SWE can be performed using several ultrasound systems. We will focus in this review on the 2D-SWE technique available on the Aixplorer® equipment (SuperSonic Imagine S.A., Aix-en-Provence, France).

PRINCIPLE OF 2D-SWE

The principle of 2D-SWE is the combination of a radiation force induced into the tissues by focused ultrasonic beams and a very high frame rate US imaging sequence, able to capture the propagation of resulting shear waves in real time [2, 5]. The US system captures the generated shear waves. To capture them in sufficient detail, frame rates of a few thousand images per second are required. This ultrafast imaging mode acquires raw radiofrequency data at a very high frame rate, up to 5000 frames/s [3]. The shear wave speed is then estimated by a Doppler-like acquisition over a region of interest (ROI). The shear wave speed is used to calculate the tissue stiffness [2, 3, 5, 6]. The relationship between Young's modulus (E) and the shear wave (c) is the following: $E=3\rho c^2$ (ρ = tissue density). In order to calculate Young's modulus, SWE uses for reference the density of water (1000 kg/m^3), assuming on one hand that tissue density is close to that of water and, on the other hand, that it is uniform [7].

The elasticity is displayed using a colour-coded image superimposed on a B-mode image: stiffer tissues in red and softer tissues in blue [2, 3, 5, 6]. At the same time, a quantitative estimation of liver stiffness (LS) is performed; the mean LS value in the region of interest (the size can be modified by the operator) as well as the standard deviation of the measured elasticity are displayed on the screen. FDA has approved the display of the shear wave in m/s; in any case, the equipment allows the visualisation of results both in kPa and in m/s, with a maximum value reaching 300 kPa (10m/s, respectively) [7].

EXAMINATION TECHNIQUE

The examination is performed after an overnight fast, with the patient positioned in a dorsal decubitus position, with the right arm in maximum abduction above his/her head, in order to widen the intercostal spaces. This position ensures the best possible access for the assessment of right lobe parenchyma.

The region of interest (ROI) for the elastography assessment is a trapezoid window; it should be positioned in the center of the screen, in an homogeneous parenchymal area, free from any large tubular structures, at least 2 cm below the liver capsule, in order to prevent the overestimation of results due to the high fibrosis content in the capsule and in the subcapsular area. The patient is requested to hold his/her breath for a few seconds, in order to eliminate the artefacts induced by the breath movements; when a stable and good quality image is obtained, the best screen shot for the quantification is selected and saved. The circular „Q box” area of interest is then located within the trapezoid one, allowing the system to automatically calculate the shear wave velocity (m/s) and tissue stiffness (kPa), according to the examiner's choice, and then to display the minimal, maximal and mean values, as well as the standard deviation.

The colour-coded elastographic information of the region of interest is superimposed on the 2D image; the size can be adjusted up to 3x3 cm, as well as the depth, but a depth of 8 cm maximum is recommended (the measurements may be incorrect beyond 8 cm or when the ROI is placed at the edge of the image instead of the center) [7].

The optimal depth for elastography quantification

The studies performed on a „phantom” showed that all measurements taken between 0 and 8 cm are valid, while all those taken at 8-9 cm in depth are invalid; the smallest variation coefficient between measurements was found between 2 and 6 cm in depth [8]. On the other hand, the deeper the measurement is taken, the higher the value of Young's modulus, and the lower the measurement accuracy are detected [8].

When discussing the distance from the liver capsule, the examination success rate and accuracy were found to be higher when the measurements were taken 3-5 cm in depth from the transducer, as compared to those taken in more superficial (<3 cm) or deeper regions (>5 cm) [8]. The factors responsible for low performance in superficial regions are the liver capsule and the subcutaneous fat. The liver capsule creates reflexion and reverberation of shear waves and furthermore, the fibrosis content is higher in the subcapsular region, explaining the lower accuracy in fibrosis estimation of liver biopsies performed in this area [9]. In more profound regions, the US attenuation is increased and the amplitude of shear waves decreases [10]. In what concerns the subcutaneous fat, a thicker layer may lead to a lower rate of success, even at a similar body mass index, due to the acoustic characteristics and different tissue composition of fat from the liver parenchyma, as well as for the several interfaces present in the fatty tissue, which alter the pattern of the shear waves [8].

In clinical practice, for a high quality assessment, it is recommended that the ROI in 2D-SWE be placed 1-2 cm under the liver capsule and 3-5 cm from the transducer. This way, the effect of the liver capsule is minimised and the success rate, the accuracy [8] and reproducibility in longitudinal examinations are improved [6].

The ideal region for quantification and number of measurements

In the study of Samir et al., the estimates of LS with 2D-SWE showed the highest correlation with the stage of fibrosis when obtained in the upper right lobe of the liver ($r=0.41$, $p<0.001$); the values obtained in the left lobe did not correlate with the fibrosis stage at liver biopsy ($r=0.16$, $p=0.06$) [11].

As for the *number of measurements* to be performed for a high-quality evaluation, the manufacturers of equipments based on 2D-SWE did not specifically recommend a particular protocol. There is no consensus available yet [3], and the number varies in various studies between 3 [12-14], 4 [15] and 5 [16-18]. Some authors found an almost perfect correlation between the median of 3 measurements and the median of 4 or 5 measurements and suggested that 3 measurements would be enough for a high-quality evaluation of portal hypertension, for example [14].

Furthermore, the study performed on 112 patients with hepatitis B [19] proved that LS values obtained from 1 valid measurement (VM), 2 VMs, 3 VMs, 5 VMs and all 10 VMs

are similar, and there are no significant differences between these groups. The mean elasticity values accurately distinguish fibrosis stages with no significant differences observed in the five groups. The authors concluded that only one VM might be sufficient to assess the stage of liver fibrosis using LS measurement by SWE without any significant loss of diagnostic accuracy in patients with chronic HBV hepatitis [19]. However, this needs to be verified by other researchers in further practice.

Other authors, however, consider that the optimal minimum number of SWE measurements should be 6, and that SWE using 6 measurements show excellent intraobserver reproducibility [20].

It is obvious that some issues are not yet clearly established in this field and that supplementary data is necessary in order to define the optimal number of SWE measurements required for a correct estimation of liver tissue stiffness.

Some studies used as a final value the mean of all performed measurements [12, 15], while others used the median [18]. Certain preliminary studies [21] showed that the results are similar regardless of which value is chosen – the mean of 3 measurements, respectively the mean or median of 5 measurements. However, the authors urge that this data be further confirmed on large groups of biopsied patients where the etiology as well as the anthropometric and biochemical parameters are taken into consideration, since all may theoretically interfere with the result of an elastography examination.

The examination performance indicators

So far, the producers of the Aixplorer® equipment have not defined the performance parameters of this technique.

Sometimes, the colour-coded elastographic image contains pixels that cannot be quantified through colour (Young's modulus = 0), in which case the image is considered unquantifiable. This phenomenon may occur when the measurements do not fit the range tolerated by the system, the tissues within the ROI are heterogeneous or when there is excessive tissue mobility [8]. The larger the number of pixels not quantified by colour, the less certain the possibility of obtaining a correct quantification [8]. In practice, however, if only a small part of the ROI remains unquantified, the assessment of LS may not be severely impaired, since the Aixplorer system automatically excludes these uncoloured pixels when calculating Young's modulus [8]. In addition, the colour-coded image should be homogeneous.

In a study analysing the performance of 2D-SWE for the assessment of clinically significant portal hypertension, the following performance criteria of the quantitative examination were proposed [14]:

- highly reliable – the ratio between standard deviation/median LS ≤ 0.10 and measurement depth < 5.6 cm;
- reliable – standard deviation/median LS > 0.10 or measurement depth ≥ 5.6 cm;
- unreliable - standard deviation/median LS > 0.10 and measurement depth ≥ 5.6 cm.

The “highly reliable” and “reliable” measurements are considered acceptable; only the „unreliable” ones are considered unacceptable for evaluation and should be rejected [14].

Inter and intraobserver reproducibility of the 2D-SWE technique are good. The intraobserver agreement between measurements performed on the same day on the same subject is 0.95 (95% confidence interval 0.93-0.98) for an experienced examiner and 0.93 (95% confidence interval 0.90-0.96) for a beginner one; on different days, the agreement drops to 0.84 (95% confidence interval 0.69-0.98) for the experienced examiner and 0.65 (95% confidence interval 0.39-0.91) for beginners. Interobserver agreement is 0.88 (95% confidence interval 0.82-0.94) [6]. The highest inter and intraobserver agreement is recorded in the 6th segment, followed by the 8th segment, while the lowest is in segments 2/3 [22].

For high quality examinations, it is advisable that beginner examiners perform at least 50 measurements using this technique beforehand [6]. It has been proven that previous experience in ultrasound examination increases the number of valid measurements, especially in obese patients. In these patients (BMI ≥ 30 kg/m²), the rate of reliable LS measurements is significantly higher for the more experienced examiner as compared with the novice (73.4% vs. 45.9%, $p=0.03$) [23].

Technique failure

LS cannot be assessed by 2D-SWE in around 10.4% of cases, more frequently in obese patients and in those with a chest wall thicker than 25 mm in the area where the method is performed [24]. These percentages depend, however, on the prevalence of obesity in the studied groups. Generally speaking, the following factors are possibly associated with a higher rate of invalid measurements: narrow intercostal spaces [15], high BMI, chest wall thickness over 25 mm [24] and older age [18].

Recommendations for a high quality examination (“tips and tricks”) [7, 8]

- Accurate SWE images can be obtained by scanning the right hepatic lobe through the right intercostal spaces. When compared to right lobe measurements, those taken on the left lobe are more difficult to obtain due to pulsations transmitted from the heart. In addition, right intercostal scanning is also recommended in order to prevent an excessive compression of the liver with the transducer;
- Before initiating the SWE module the best possible 2D images should be obtained, with the least artefacts possible;
- When activating the SWE module, the transducer must be fixed firmly and the patient be required to hold his/her breath for a few seconds, preferably after breathing out;
- In case of excessive attenuation (for instance in overweight patients), it is possible that lower frequencies of the transducer need to be employed for the examination;
- The ROI in 2D-SWE should be placed 1-2 cm below the liver capsule and at 3-5 cm from the transducer.

Normal LS as assessed by 2D-SWE

A study using the 2D-SWE technique performed on 196 subjects with a normal liver, all potential donors with pathology confirmation, found a normal LS value with a mean of 4.4 ± 0.9 kPa (between 2.2-6.2 kPa); the values followed a Gaussian distribution, with no significant correlation to age, BMI or the presence of steatosis [13]. These values were in agreement

with other results of studies on healthy subjects, but without pathology confirmation (4.6-4.9 kPa) [5, 6].

Error factors when interpreting the results

The influence of food intake on LS values as measured by SWE with an Aixplorer ultrasound system

Similarly to other ultrasound elastographic techniques, the examination after food intake is correlated with a false increase in LS values, as quantified by 2D-SWE [25].

Gersak et al. [26], analysed the variation of LS after a standardized meal using 2-D shear wave elastography in 31 apparently healthy subjects. In most of the cases, LS values increased between 20 and 40 min after the meal ($p < 0.005$) and then significantly decreased between 60 and 80 min ($p < 0.05$). When measured 120 min after food intake, LS values were significantly lower compared with those recorded under fasting conditions ($p < 0.05$). Gender, but not body mass index, had an important role in LS variation after food intake ($p < 0.01$), with a mean peak value increase of 12% in males. However, it must be stressed that before drawing any conclusions on this aspect, more studies on larger numbers of subjects are required. In conclusion, to avoid the influence of food intake on LS estimation, 2D shear wave elastography should be performed only under fasting conditions.

There have been no sufficiently documented data on the effect of cytolysis, cholestasis or congestive heart failure on the values obtained through 2D-SWE.

CLINICAL APPLICATIONS OF THE 2D-SWE TECHNIQUE

Assessment of fibrosis in chronic hepatitis C

In the preliminary studies performed so far on patients with HCV infection, the cut-off values proposed for the assessment of fibrosis stages are slightly different, but with a very good performance. In the study by Ferraioli et al. [15], the cut-off values (chosen for the highest sum between sensibility and specificity) in a group of 121 patients were the following: 7.1 kPa (for the prediction of stages $F \geq 2$), 8.7 kPa (for $F \geq 3$), and 10.4 kPa (for the prediction of cirrhosis). The performance of these values is displayed in Table I. In the study by Bavu et al. [15], the following cut-off values were obtained: 9.12 kPa for $F \geq 2$, 10.08 kPa for $F \geq 3$, and 13.3 kPa for F4.

Table I. Cut-off values proposed by Ferraioli for the prediction of fibrosis stages in patients with chronic HCV hepatitis [15]

Chronic HCV hepatitis	$\geq F2$ (Metavir)	$\geq F3$ (Metavir)	F4 (Metavir)
Cut-off (kPa)	7.1	8.7	10.4
Se (%)	90	97.3	87.5
Sp (%)	87.5	95.1	96.8
PPV (%)	91.3	90	87.5
NPV (%)	85.7	98.7	96.8
+LR	7.2	19.7	27.4
-LR	0.11	0.03	0.13
AUC	0.92	0.98	0.98

Se: sensibility; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: likelihood ratio; AUC: area under curve.

Assessment of fibrosis in chronic hepatitis B

The cut-off values proposed for the prediction of various stages of fibrosis (according to the Metavir staging system) for chronic hepatitis B were: 7.2 kPa for $F \geq 2$, 9.1 kPa for $F \geq 3$, and 11.7 kPa for the prediction of cirrhosis, with areas under the ROC curve above 0.90 (Table II). This method staged correctly 71.3% of patients, the highest proportion of correctly staged patients being in stages F0-F1, while the lowest in stage F3 [27].

Table II. The cut-off values proposed by Zeng et al. and their performance in the prediction of fibrosis stages in patients with HBV infection [27].

HBV	$\geq F2$ (Metavir)	$\geq F3$ (Metavir)	F4 (Metavir)
Cut-off (kPa)	7.2	9.1	11.7
Se (%)	86.36	91.94	91.89
Sp (%)	86.96	85.71	89.70
PPV (%)	88.8	74.0	66.7
NPV (%)	84.2	96.0	98.0
+LR	6.62	6.44	8.92
-LR	6.62	6.44	8.92
AUC	0.917	0.945	0.945

For abbreviations see Table I.

Assessment of fibrosis in various diffuse liver diseases, regardless of etiology

2D-SWE performance for the prediction of each fibrosis stage seems to be similar when including all patients, regardless of etiology, as well as when including only viral hepatic diseases [24, 28, 29] (Table III).

In two recent meta-analyses [30, 31], with a total of 2303 and 934, respectively, included patients, the summary area under the curve (AUC) was 0.85 for $\geq F1$, 0.87-0.88 for $\geq F2$, 0.93-0.94 for $\geq F3$ and 0.92-0.94 for F4 (Table IV).

Until now, the optimal cut-off values for predicting each fibrosis stage have not been established. In the studies published so far, these values vary between 6.2-7.8 kPa for $\geq F1$, 7.1-10.49 kPa for $\geq F2$, 8.7-11.5 kPa for $\geq F3$, and 9.59-18.1 kPa for F4 (Table V). Further studies, on larger groups of biopsied patients with various etiologies of the diffuse liver disease, are required in order to establish the most appropriate cut-off values, taking into account also the prevalence of fibrosis stages in each particular population.

Assessment of portal hypertension

The LS measured by 2D-SWE is correlated with the hepatic venous pressure gradient (HVPG) when the pressure is below 10 mmHg, but not above this threshold. When the measurements are acceptable (according to the criteria proposed by Procopet et al. [14]), a cut-off value of 15.4 kPa predicted clinically significant portal hypertension with sensibility and specificity above 90%.

Choi et al. [37] showed a moderate relationship between HVPG in patients with liver cirrhosis and LS measured at SWE ($r = 0.593$). In addition, the LS variation is strongly correlated with the HVPG variation. Patients with a decrease in LS of more than 2% tended to show improvement of portal hypertension, while an increase of more than 1% in LS suggested aggravation of portal hypertension. Consequently,

Table III. The performance of 2D-SWE for the prediction of fibrosis stages in patients with various diffuse liver diseases [24, 28, 29].

	≥F1				≥F2				≥F3				F4			
	Various DLDs	Various DLDs			Viral infection	Various DLDs			Viral infection	Various DLDs			Viral infection			
	Cassimotto [24]	Deffieux [28]	Cassimotto [24]	Jeong [29]	Deffieux [28]	Deffieux [28]	Cassimotto [24]	Jeong [29]	Deffieux [28]	Deffieux [28]	Cassimotto [24]	Jeong [29]	Deffieux [28]			
Cut-off (kPa)	7.8	8.9	8	8.60	7.9	9.1	8.9	10.46	9.1	10.2	10.7	14	10.2			
Se (%)	68	77	83	78.2	87	85	90	88.6	86	83	85	77.3	100			
Sp (%)	100	79	82	93.3	76	77	81	80	74	76	83	85.40	79			
PPV (%)	100	77	88	-	83	60	77	-	61	38	65	-	45			
NPV (%)	33	79	75	-	81	90	92	-	92	96	93	-	100			
+LR	-	3.6	-	11.73	3.6	3	-	4.43	3.3	3.5	-	5.3	4.8			
-LR	-	0.3	-	0.23	0.2	0.2	-	0.14	0.2	0.2	-	0.27	0			
AUC	0.89	0.81	0.89	0.908	0.85	0.80	0.92	0.893	0.82	0.85	0.92	0.877	0.90			

DLD: diffuse liver disease; F: fibrosis. For other abbreviations see Table I.

LS could play a major role in the non-invasive monitoring of the portal hypertension degree. If these results are confirmed in larger prospective studies, it may be possible to monitor patients with portal hypertension by using US elastography rather than HVPG measurement.

In the past few years, the assessment of portal hypertension through the analysis of splenic stiffness has attracted increasing interest. Unfortunately, the results obtained with 2D-SWE are rather poor; spleen stiffness may be measured in only about 60% of cases, and the method cannot be applied to small spleens. Even when the spleen stiffness can be measured, this parameter has a low discriminative ability, when compared with unidimensional transient elastography [14]. In any case, further studies are required to clarify this issue.

Assessing rejection after liver transplantation

Four weeks after liver transplantation, LS values were significantly higher in patients with acute cellular rejection than in those without rejection [17]. In contrast, in less than 4 weeks, LS values rose even without significant pathological changes, because transplanted liver goes through some degree of injury, either ischemic or due to reperfusion, which induces hepatocyte ballooning and cholestasis in the biliary canaliculi, with non-specific portal and lobular inflammation. The recovery after this type of tissular injury usually lasts more than 2-3 weeks [17].

2D-SWE is useful in post-transplantation assessment, and a cut-off value of 10.82 kPa appear to have a much higher

specificity (>80%) for the detection of acute cellular rejections than functional hepatic tests [17].

Assessment of focal liver lesions

2D-SWE can visualise the changes in elasticity of focal liver lesions and in the surrounding parenchyma, but at the present time few studies have been published on the subject, meaning that the efficacy of the method in the differential diagnosis of focal liver lesions cannot yet be established [7].

One study evaluating 139 focal liver lesions [35] showed that the method may be useful in differentiating adenomas (having a mean stiffness of 9.4 ± 4.3 kPa) from focal nodular hyperplasia (33 ± 14.7 kPa), as well as hepatocarcinomas (14.86 ± 10 kPa) from cholangiocarcinomas (56.9 ± 25.6 kPa). Ronot et al. [38] stressed the fact that the method cannot differentiate between benign and malignant lesions. It could be useful in discriminating between focal nodular hyperplasia and other benign lesions, which usually had a significantly lower stiffness, as well as in discriminating the various adenoma types (telangiectatic or inflammatory adenomas are significantly stiffer than steatotic ones) [38]

In the assessment of focal liver lesions, 2D-SWE holds certain limitations [7]:

- accurate assessment of lesions located in the left lobe can be difficult due to transmitted cardiac pulsations;
- deep focal lesions cannot always be evaluated (because of the limitation of deep measurements, linked to the acoustic power);

Table IV. 2D-SWE performance for the diagnosis of liver fibrosis in some meta-analysis [30, 31]

	≥F1		≥F2		≥F3		F4	
	Jiang et al. [30]	Li et al. [31]	Jiang et al. [30]	Li et al. [31]	Jiang et al. [30]	Li et al. [31]	Jiang et al. [30]	Li et al. [31]
Se	0.76	-	0.84	0.85	0.89	0.90	0.89	0.87
(95% CI)	(0.71–0.81)		(0.81–0.86)	(0.82–0.88)	(0.86–0.92)	(0.83–0.95)	(0.84–0.92)	(0.80–0.92)
Sp	0.92	-	0.83	0.81	0.86	0.81	0.88	0.88
(95% CI)	(0.80–0.97)		(0.77–0.88)	(0.71–0.88)	(0.82–0.90)	(0.75–0.86)	(0.84–0.92)	(0.80–0.93)
AUC	0.85	-	0.87	0.88	0.93	0.94	0.94	0.92
	(0.81–0.88)		(0.84–0.90)	(0.85–0.91)	(0.91–0.95)	(0.92–0.96)	(0.92–0.96)	(0.89–0.94)

F: fibrosis; Se: sensitivity; Sp: specificity; AUC: area under curve.

Table V. Cut-off values of liver stiffness (LS) assessed with 2D-SWE in various studies (modified after Jiang et al. 2016) [30]

Author	Population characteristics/Etiology of liver disease	Cutoff value (kPa)			
		≥F1	≥F2	≥F3	F4
Ferraioli et al., 2012 [15]	HCV	-	7.1	8.7	10.4
Leung et al., [12]	HBV	6.5	7.1	7.9	10.1
Cassimotto et al., 2014 [24]	8 HCV, 33 HBV, 145 non-alcoholic steatohepatitis; 8 viral reactivation post-liver transplantation; 5 sclerosing cholangitis; 16 autoimmune diseases; 7 hepatitis E; 7 primary biliary cirrhosis; 13 drug related hepatitis; 3 hemochromatosis; 2 overlap syndrome; 31 unexplained chronic cytolysis	7.8	8	8.9	10.7
Zeng et al., 2014 [27]	HBV	-	7.2	9.1	11.7
Beland et al., 2014 [31]	21 HVC; 15 elevated liver function tests; 5 nonalcoholic steatohepatitis; 3 cirrhosis; 3 autoimmune hepatitis; 2 HBV hepatitis; 1 methotrexate therapy	-	10.49	-	-
Suh et al., 2014 [13]	123 nonsteatotic liver; 73 hepatic steatosis	6.2	-	-	-
Deffieux et al., 2015 [28]	44 HCV, 24 HBV; 11 healthy liver; 11 nonalcoholic steatohepatitis; 10 alcoholic liver; 10 autoimmune diseases; 2 hepatitis E; 2 primary biliary cirrhosis; 2 cryptogenic cirrhosis; 2 steatosis; 1 drug-related hepatitis; 1 hepatocellular carcinoma	-	8.9	9.1	10.2
Tada T et al., 2015 [33]	HCV	-	8.8	-	-
Samir AE et al., 2015 [11]	43 HCV; 8 HBV; 1 alcoholic liver; 18 autoimmune diseases; 1 hemochromatosis; 1 HIV and HCV coinfection; 60 elevated liver function test; 4 elevated liver function test after transplantation;	-	7.29	8.90	9.59
Yoneda M et al., 2015 [34]	117 HCV; 15 HBV; 7 alcoholic liver; 13 non-alcoholic steatohepatitis; 4 autoimmune diseases; 6 primary biliary cirrhosis; 9 primary sclerosing cholangitis; 5 others	6.2	7.9	9.3	11.4
Guibal et al., 2016 [35]	30 nonalcoholic steatohepatitis; 22 HBV or HCV; 17 alcoholic liver; 4 autoimmune hepatitis; 4 chronic cholelithiasis; 14 others	-	8.8	11.5	18.1
Verlinden et al., 2016 [36]	80 HCV, including 26 coinfecting with HIV	-	8.5	10.4	11.3

HCV: chronic hepatitis C; HBV: chronic hepatitis B; HIV: human immunodeficiency virus.

- lesions larger than 3x3 cm cannot be completely evaluated with just one scan, since the maximal size of the colour box is 3x3 cm;

- due to the relatively short time since this technique has been introduced in practice, the number of studies published so far is insufficient to establish clear diagnostic criteria.

CONCLUSIONS

The studies performed so far indicate that SWE could be a promising tool to differentiate the severity of liver fibrosis. In addition, the method may prove useful in monitoring patients with portal hypertension by using US elastography rather than HVPG measurement, as well as for post-transplantation assessment. In any case, large-scale, well-designed, and multi-center studies are required to validate the results obtained so far, in order to explore the possible confounding factors and to further evaluate the potential of SWE.

Conflicts of interest: No conflict to declare.

Authors' contribution: M.L.P. designed the study, contributed to the selection of studies, data extraction with database searching and wrote the manuscript; R.B. and N.H. contributed with suggestions, reviewed and corrected the manuscript; M.G., A.M., I.R., A.S., C.V., H.S. and R.U. contributed to the design of the study, selection of studies and revision of the manuscript. All authors approved the final draft submitted.

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