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Liver elastography

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Introduction

In the evolution of chronic viral and non-viral hepatitis, liver fibrosis is an important factor associated with prognosis. A precise evaluation of the severity of fibrosis is necessary in these patients for correct staging and, eventually, to take a decision regarding treatment. Currently, liver biopsy seems to be the optimal method for evaluating changes in fibrosis over time (1). However, liver biopsy has its disadvantages *i.e.* the intra- and interobserver variability (2, 3), the sampling variability (4) and the fact it is an invasive method, with morbidity and mortality greater than zero.

Considering all these factors, non-invasive methods for the evaluation of liver fibrosis have developed in the past few years, to reduce the number of liver biopsies. There has been much debate recently regarding the best method to evaluate these patients. Liver biopsy is still considered the "gold standard" for hepatological evaluation (5), but non-invasive methods of assessment are gaining popularity.

After year 2000, non-invasive test predictors of fibrosis were mainly evaluated in patients with chronic hepatitis C virus (HCV) (6). There have been many articles regarding the usefulness of these methods in other chronic hepatopathies, published in the past few years.

The underlying assumption of using non-invasive methods is that liver disease progression is associated with changes in tissue strain that can be measured by elastography. In general, strain is a measure of tissue deformation owing to an imposed force (stress) (7). It represents the fractional change from the original or unstressed dimension (Lagrangian strain), includes both lengthening or expansion (positive strains) and shortening or compression (negative strains) (8).

Non-invasive methods can be divided into ***biological (serological) tests*** and ***elastographic methods***. Elastographic methods can be subdivided in *MRI elastography* and *ultrasound based elastography*.

Technologies

Ultrasound based elastographic methods can be divided into (9, 10):

- **Strain Elastography**
- **Shear Waves Elastography**
    - **Transient Elastography (TE)**

- **Point Shear Waves Elastography (pSWE): using Acoustic Radiation Force Impulse (ARFI) technique [Virtual Touch Quantification (VTQ)** and **ElastPQ]**
- **Real Time Shear Waves Elastography: 2D-SWE** (available on numerous systems: SuperSonic Imaging Elastography – Aixplorer; General Electric; Toshiba; ElastQ - Philips; Siemens) **and 3D-SWE**

On the other hand, considering how tissue excitation is generated and assessed, elastographic methods can be classified as (11):

1. **Quasi-static strain imaging,** including *Strain Elastography* (SE), *Strain Rate Imaging* (SRI) and *Acoustic Radiation Force Impulse Imaging*. For *SE and SRI*, tissue excitation is performed by manual compression with the transducer or by body physiological movements (heartbeats). They are implemented on most ultrasound machines (Esaote, General Electrics, Philips, Siemens, Hitachi Aloka, Toshiba, Samsung Medison, Ultrasonix, Mindray Zonare), but seldom used for the liver. For *Acoustic Radiation Force Impulse Imaging,* the stimulus is an ultrasound induced focused radiation force impulse at depth, and this technique is implemented on Siemens ultrasound equipment.
2. **Shear Waves Elastography Measurement** including *Transient Elastography* (the stimulus is a mechanical thump on the tissue surface – FibroScan from EchoSens), and *Point Shear Wave Elastography (pSWE),* also known as ARFI quantification (the stimulus is an ultrasound induced focused radiation force impulse at depth). *pSWE* is available on Siemens, Philips and Hitachi Aloka systems.
3. **Shear Waves Elastography Imaging,** including two-dimensional and three-dimensional shear wave elastography (2D-SWE and 3D-SWE) in which a color-coded elastogram is obtained as well. Tissue excitation is performed either by an ultrasound induced focused radiation force at various depths (Toshiba, Philips, Siemens, Mindray Zonare), by multiple parallel ultrasound induced focused radiation force impulses (General Electric) or by an ultrasound induced focused radiation force impulse faster than shear wave speed to create a Mach cone (Supersonic Imagine).

Despite the fact that strain elastography was the first method used for elastographic evaluation, the body of evidence from published papers regarding the accuracy of shear-

waves elastography is much stronger. In these conditions, we will start with the presentation of these methods.

Transient Elastography

Transient Elastography (TE) is an ultrasound-based method, based on the principle of Hooke's law, which characterizes a material's strain response to external stress (12). Transient Elastography is performed with a FibroScan device (EchoSens, Paris, France) by using an ultrasound transducer probe mounted on the axis of a vibrator. The transmission of low-frequency vibrations from the right intercostal space creates an elastic shear wave that propagates into the liver. A pulse-echo ultrasound acquisition is then used to detect the velocity of wave propagation. This velocity is proportional to the tissue stiffness; faster wave progression occurs through stiffer material. Measurement of liver stiffness is then performed and expressed in kilopPascals (kPa) (values between 2.5 kPa and 75 kPa are expected) (13) [Figures 1 and 2]. A new technique for quantification of liver steatosis related to TE and performed with a FibroScan device is ***Controlled Attenuation Parameter (CAP)*** **[**Figure 1].

Figure 1 The screen of FibroScan device (EchoSens, Paris, France), last version which also allows steatosis assessment using the Controlled Attenuation Parameter – CAP.

Figure 2 The FibroScan probe (EchoSens, Paris, France).

Using this method, measurements are performed in the right lobe of the liver, through the intercostal spaces, while the patient lies in a dorsal decubitus position, with the right arm in

maximal abduction. The tip of the transducer is covered with coupling gel and placed on the skin between the ribs, aimed at the right lobe of the liver. The operator, assisted by ultrasound A-mode images provided by the system, locates a portion of the liver at least 6 cm thick and free of large vascular structures. Once the area of measurement had been located, the operator presses the probe button to begin an acquisition. The software automatically rejects acquisitions that do not have a correct vibration shape or a correct follow-up of the vibration propagation.

Three types of probes are available: S probe – for pediatric use, M probe – for normal weight patients and XL probe – for overweight and obese patients.

According to the manufacturer's recommendations, reliable measurements are defined as median of 10 valid LS measurements with interquartile range interval (IQR) < 30% and success rate (SR) ≥ 60%. Using these quality criteria parameters, reliable measurements using the standard M-probe can be obtained only in 70-85 % of patients, the most important factor associated with unreliable measurements being obesity (14, 15). Using the available XL probe, reliable measurements have been obtained in approximately 75% of obese patients, while using the M probe, LS could be successfully measured only in 45% of cases (16). Liver stiffness values obtained with XL probe are lower than those reported for M-probe, and we suggest to use the cut-offs values proposed by the few published studies which used XL probe for LS assessment, with liver biopsy as "gold-standard" method (17-19). The latest EFSUMB Guidelines were not able to recommend cut-of values to be used for the XL probe (11).

A French group recently proposed new quality criteria for LS measurements by TE (20). Hereby, success rate is no longer considered a quality parameter and the measurements are classified in three categories: very reliable (IQR ≤ 10%), reliable (IQR > 10% and ≤30% or IQR > 30% if LS <7.1kPa), and poorly reliable (IQR > 30% and LS ≥7.1kPa). The new poorly reliable results are similar with the traditional unreliable measurements and should not be used in clinical practice. Using these new criteria, the proportion of reliable measurements increased from 75.7% to 90.9%, without affecting the accuracy of this technique for non-invasive assessment of liver fibrosis. Very recently, these criteria were validated in an independent cohort (21).

According to the latest EFSUMB Guidelines (11) for reliable TE measurements, 10 measurements should be obtained. An IQR/M ≤ 30 % of the 10 measurements is the most important reliability criterion.

The following conditions are associated with falsely elevated LS values by TE: acute hepatitis and aminotransferases flares (22-24), postprandial condition (25, 26), congestive heart failure (27) and extrahepatic cholestasis (28).

The manufacturer specified as contraindication for LS measurement by TE the presence of a cardiac pacemaker or pregnancy. However, no data on side effects related to these conditions have been published.

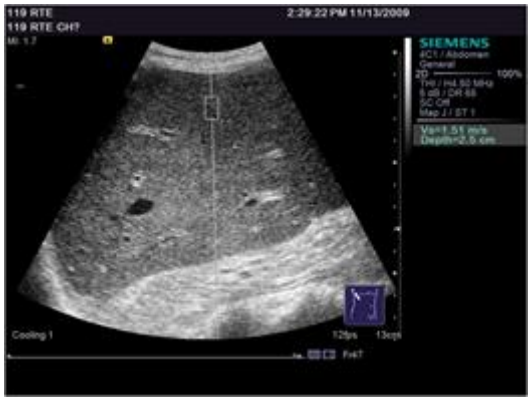
Point Shear Waves Elastography

There are ***two types of point SWE***, using **ARFI technology: VTQ** and **ElastPQ.**

Acoustic Radiation Force Impulse using Virtual Touch Quantification - VTQ (ARFI)

ARFI technology involves targeting an anatomical region to be investigated for elastic properties with the use of a ROI cursor, while performing real-time B-mode imaging. In VTQ (ARFI), the tissue inside the ROI is mechanically excited using short-duration (262µs) acoustic pulses with a fixed transmit frequency of 2.67MHz to generate localized tissue displacement. The displacement results in shear wave propagation away from the region of excitation and is tracked using ultrasound correlation-based methods (29). The shear wave propagation velocity is proportional to the square root of tissue elasticity. Results are expressed in meters per second (m/s) [Figure 3].

Figure 3 VTQ (ARFI) technique in a patient with chronic hepatitis.



It is recommended that the scanning protocol follows the manufacturer's recommendations *e.g.* the right lobe should be scanned by an intercostal approach with normal breathing, this leading to a low measurement variance. Increased variability was observed when the liver is scanned more medially and the patient is asked to take and hold a deep breath, combined with varying the pressure applied with the probe against the liver to get a good image. It is not known why there is increased variability, but one theory is that compressing the liver causes the stiffness to increase. Additionally, a breath-hold raises the venous pressure in a similar way to heart failure, which is known to increase liver stiffness.

The manufacturer recommendations to obtain the best results are: apply minimal scan pressure; exclude data that varies significantly; minimize breathing and avoid cardiac motion; and use the optimal window (intercostal right lobe, segment 8 or 5).

According to the latest EFSUMB Guidelines, measurement of liver stiffness by SWE should be performed through a right intercostal space in supine position, with the right arm in extension, during breath hold, avoiding deep inspiration prior to the breath hold (11). In addition, measurement of liver stiffness by pSWE should be performed at least 10 mm below the liver capsule, by experienced operators, adequate B-mode liver image being a prerequisite (11).

Similar with TE, VTQ (ARFI) reproducibility for liver fibrosis assessment is very good (30-32). Published studies (33, 34) demonstrated that the use of quality criteria parameters similar to those used for TE (IQR <30% and SR ≥ 60%, IQR being especially important) significantly increase the accuracy of VTQ (ARFI) elastography for non-invasive assessment of liver

fibrosis. Unlike TE, the feasibility of VTQ (ARFI) elastography is excellent, reliable liver stiffness measurements using quality criteria parameters being obtained in more than 93% of patients (35).

VTQ (ARFI) elastography can be performed very easy in patients with perihepatic ascites and this technique is safe in pregnant women (36), these representing important advantages in comparison with TE. There are no information available regarding the potential use of this technique in patients with cardiac pacemaker.

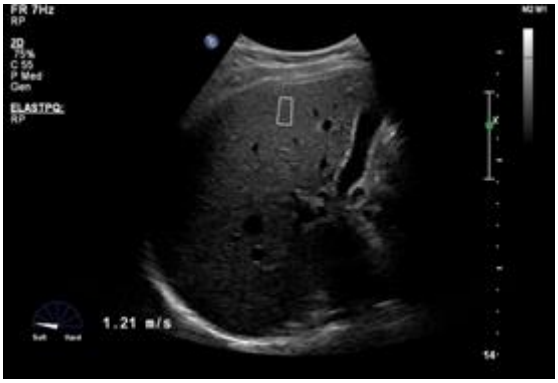
Liver stiffness values assessed by VTQ (ARFI) elastography are falsely elevated in the following situations: postprandial condition (37, 38), elevated aminotransferases level (39), right heart insufficiency (38) and extrahepatic cholestasis (40). Regarding the elevated aminotransferases level, VTQ (ARFI) elastography seems to be less influenced by moderately elevated values (between 2-5 x upper limit of normal) as compared with TE (39).

ElastPQ technique

Liver stiffness measurements by means of ElastPQ technique are performed with Philips ultrasound systems. The examination technique uses ARFI technology and the results can be expressed either in m/s or in kPa **[**Figure 4]. Nor the manufacturer, nor published studies propose any quality criteria parameters that should be applied to LS measurements assessed by means of this technique.

Similar to ARFI (VTQ) elastography, according to the latest EFSUMB Guidelines, measurement of liver stiffness by ElastPQ should be performed through a right intercostal space in supine position, with the right arm in extension, during breath hold, avoiding deep inspiration prior to the breath hold, at least 10mm below the liver capsule, by experienced operators, adequate B-mode liver image being a prerequisite (11). Ten valid LS measurements can be obtained in more than 95% of patients (41-43) and a good inter-operator reproducibility was observed for this technique (41, 44). The lowest variability of LS values assessed by ElastPQ was obtained when the measurements were performed in segment V of the liver (45).

Figure 4 ElastPQ measurement in a patient with chronic hepatitis C and significant fibrosis (F2 METAVIR).



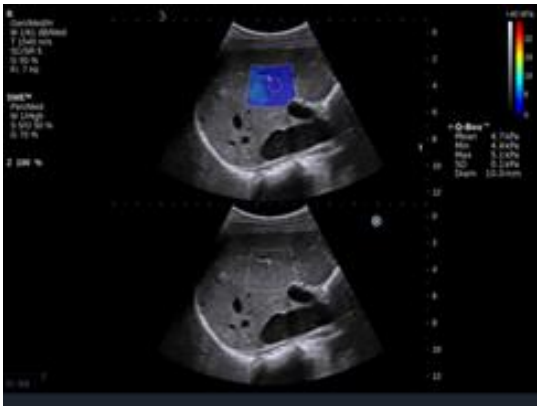
Real Time Shear Waves Elastography (2D-SWE and 3D-SWE)

Real-time SWE is an elastographic technique in which liver stiffness is measured and a color-coded elastogram is obtained as well. Tissue excitation is performed either by an ultrasound induced focused radiation force at various depths (Toshiba, Philips, Siemens, Mindray Zonare), by multiple parallel ultrasound induced focused radiation force impulses (General Electric) or by an ultrasound induced focused radiation force impulse faster than the shear wave speed, to create a Mach cone (Supersonic Imagine).

2D-SWE by Supersonic Imagine (2D-SWE.SSI, Aixplorer system)

The first 2D-SWE technology was developed by Supersonic Imagine (2D-SWE.SSI), and integrated into the Aixplorer^{TM} US system (SuperSonic Imagine S.A., Aix-en-Provence, France). This technique is a combination of a radiation force induced into the tissues by focused ultrasonic beams and a very high frame rate ultrasound imaging sequence. Elasticity is displayed using a color coded image, superimposed on a B-mode image: in red – stiffer tissues and in blue – softer tissues (46). At the same time, a quantitative estimation of LS is performed. LS value in the region of interest (whose size can be modified by the operator), is displayed on the screen, expressed either in kPa, or in m/s **[**Figure 5].

Figure 5 2D-SWE.SSI technique in a patient with mild fibrosis.



For this technique, a SC6-1 convex probe is used. The operator places the region of interest in an area without large vessels, at a depth more than 2 cm, but no deeper than 8 cm. Several studies evaluated the method's accuracy if three, four or five valid 2D-SWE.SSI measurements were taken into consideration to measure LS (47-49), but the latest EFSUMB Guidelines recommend that for 2D-SWE.SSI a minimum of three measurements should be obtained; the result should be expressed as the median together with the interquartile range (11).

Initially no quality criteria were recommended by the manufacturer, but if the same quality criteria as in TE are applied (IQR<30% and SR≥60%), the rate of reliable measurements can decrease to 71.3% (50). Other authors used as quality technical parameters standard deviation/median liver stiffness ≤ 0.10 and measurement depth < 5.6 cm (51). The new software version of the Aixplorer system also shows the stability index (SI) and, according to the manufacturer, a reliable LSM should exclude measurements with an SI < 90 %.

Most published studies showed that three/five LS measurements by means of 2D-SWE.SSI could be obtained in 90-98.9% of cases (52, 53). The intra- and inter-observer reproducibility of 2D-SWE.SSI seem to be very good for non-invasive assessment of liver fibrosis with this technique (52), but previous experience in ultrasound is needed to increase the rate of valid measurements, especially in obese patients (54).

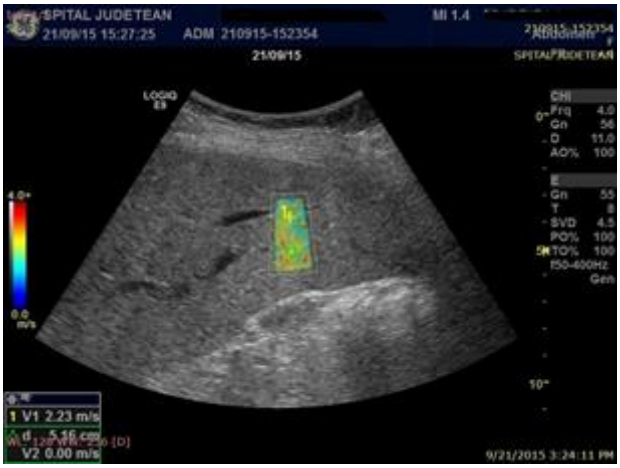
For performing this method, patients must be in fasting condition (like for all ultrasound based elastographic methods), non-fasting condition being associated with falsely elevated LS values (11, 55).

2D-SWE by General Electric

Another technology using 2D-SWE was developed by General Electric, and implemented into the Logic E9 and S8 ultrasound systems (2D-SWE.GE). Tissue excitation is realized by multiple parallel ultrasound induced focused radiation force impulses.

According to EFSUMB recommendations, similar to other 2D-SWE techniques, 2D-SWE.GE is performed with the patient in supine position, in intermediate breathing, through an inter-costal space (11). The right liver lobe is scanned and a region of interest (ROI) is placed at least 10 mm below the liver capsule, in a region free of vessels. Once a suitable image window is found, the shear wave acquisition is initiated. At least 10 Shear Wave frames are acquired. The measurements are then performed by placing a circular measurement ROI over each saved Shear Wave elastographic image **[**Figure 6]. The measurement regions are chosen to exclude obvious artifacts. The average stiffness, expressed in terms of Young's Modulus within each measurement region, is automatically recorded by the system in a worksheet. The system automatically calculates the median value and the interquartile range of the valid measurements.

Figure 6 LS measurement by 2D-SWE.GE in a patient with cirrhosis.



Since it is a very new technique, few studies have been published in extenso. The manufacturer recommends that 10 LS measurements should be performed for a reliable assessment.

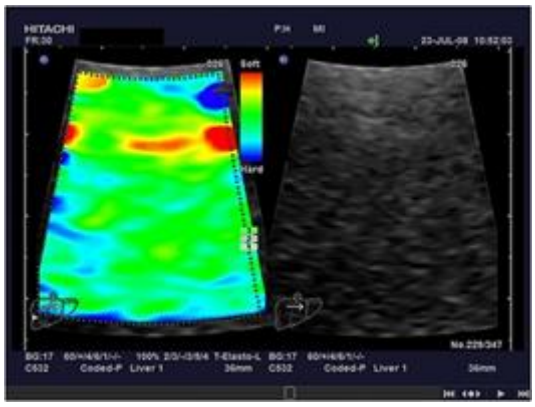
A Romanian study demonstrated that the accuracy of 2D-SWE.GE measurement was not impaired if only 5 measurements were taken into consideration (56). Regarding reproducibility, 2D-SWE.GE showed excellent inter and intra-operator agreement, but with better results in more experienced operators (57).

Strain Elastography (RT-E)

RT-E performed with the Hitachi system (EUB-8500 and EUB-900, Hitachi Medical Systems) was the first to appear on the market (58). It uses a conventional ultrasound probe to compare and analyze echo signals before and under slight compression (59). To perform free-hand RT-E, the examiner must apply stress by moving the transducer (60).

The Hitachi SonoElastography (HiRT-E) module uses an extended combined autocorrelation method to produce a real-time elasticity image by using a freehand approach to compress the tissues with the ultrasound transducer. Newer machines use the internal pressure generated by the heartbeats on the liver parenchyma. The relative elasticity of the tissues is calculated and displayed as a color overlay on the conventional B-mode image. Stiffer tissue is displayed in blue, while the more easily deformed tissues are displayed in red. HiRT-E uses the combined autocorrelation method to rapidly calculate the relative tissue stiffness based on tissue distortion, and displays this information as “real-time” color images **[**Figure 7].

Figure 7 Hitachi SonoElastography assessment in a patient with chronic hepatitis C and significant fibrosis (F2 METAVIR).



This method has been used in clinical practice for the assessment of focal lesions in the breast, thyroid, prostate and pancreas (61) and, more recently, for the evaluation of hepatic fibrosis (58, 62-64).

Normal values for the different technologies

Transient Elastography

Liver stiffness values assessed by TE in subjects without liver pathology range between 4.3-5.3 kPa, higher values being obtained in men as compared to women (65-68).

Point Shear Waves Elastography

Acoustic Radiation Force Impulse using Virtual Touch Quantification - VTQ (ARFI)

The LS values assessed by VTQ (ARFI) in subjects without liver pathology range between 1.07-1.19 m/s, no differences were observed according to gender (69-74).

ElastPQ technique

According to the available data, mean LS values in healthy volunteers are 1.08 m/s, equivalent with 3.5 kPa, higher values being obtained in men as compared with women (42, 45).

Real Time Shear Waves Elastography (2D-SWE and 3D-SWE)

2D-SWE by Supersonic Imagine (Aixplorer system)

The reported LS in healthy volunteers was 6 ± 1.4 kPa (median 5.7 kPa), higher values being obtained in men as compared to women (75).

2D-SWE by General Electric

2D-SWE.GE values in a cohort of healthy liver individuals was 5.1±1.3 kPa, higher in men than in women and in patients older than 40 years (76).

How to compare technologies

A meta-analysis published by Bota et al. (77) compared TE and VTQ (ARFI) elastography, considering liver biopsy as „gold-standard" method. This meta-analysis showed that the inability to obtain reliable measurements was more than thrice as high for TE as for VTQ (ARFI) elastography (6.6% vs. 2.1%, $p<0.0001$) and for predicting the presence of significant fibrosis ($F\geq2$) and liver cirrhosis ($F=4$), both elastographic techniques had similar values.
In a recent paper, in a cohort of 349 patients with chronic liver diseases who underwent liver biopsy, stiffness was assessed by 2D-SWE.SSI, VTQ (ARFI) and TE (M probe for patients with BMI < 30 kg/m² and XL probe for patients with BMI ≥ 30 kg/m²) (78). In this study, 2D-SWE.SSI, TE, and VTQ (ARFI) correlated significantly with histological fibrosis ($r=0.79$, $p<.00001$; $r=0.70$, $p<.00001$ and $r=0.64$, $p<.00001$, respectively). The AUROCs of 2D-SWE.SSI, TE, and VTQ (ARFI) were 0.88, 0.84 and 0.81 for significant fibrosis; 0.93, 0.87, and 0.89, for severe fibrosis, and 0.93, 0.90, and 0.90 for the diagnosis of cirrhosis, respectively. 2D-SWE.SSI had a significantly higher accuracy than TE for the diagnosis of severe fibrosis ($F\geq3$) ($p=0.0016$), and a significantly higher accuracy than VTQ (ARFI) for the diagnosis of significant fibrosis ($F\geqslant2$) ($p=0.0003$). No significant difference between all methods was observed for the diagnosis of mild fibrosis and liver cirrhosis. The conclusion of this study was that 2D-SWE.SSI is an efficient method for the assessment of liver fibrosis in chronic liver diseases, and seems to be better than TE or VTQ (ARFI).

Indications

Hepatitis C

Transient Elastography

In chronic hepatitis C patients, according to the results of several studies and meta-analyses (12, 79-83) if the liver stiffness is greater than 6.8–7.6 kPa there is a great probability of finding significant fibrosis on liver biopsy (F2−F4 Metavir score), and the patient rapidly needs antiviral therapy.

In a multicenter French study (83) of 494 chronic hepatitis C patients who were evaluated by percutaneous liver biopsy and TE, a significant correlation was found (p<0.001) between the severity of fibrosis and the values of liver stiffness measured by TE (r=0.57). This study attempted to establish cut-off values for liver stiffness that could differentiate between various stages of fibrosis. Thus, the cut-off value of 7.5 kPa differentiates F0–1 from F2–4 with 67% sensitivity, 87% specificity, 86% positive predictive value (PPV) and 68% negative predictive value (NPV), with a diagnostic accuracy of 76%. Other studies established cut-off values that differentiate F0–1 from F2–4 ranging from 6.8–7.3kPa (79, 81-83).

Point Shear Waves Elastography

Acoustic Radiation Force Impulse using Virtual Touch Quantification - VTQ (ARFI)

VTQ (ARFI) elastography was used initially for liver fibrosis evaluation in chronic hepatitis C patients. Published studies (84-88) showed that the LS cut-off ranges for patients with chronic hepatitis C are: for F≥1 – 1.18-1.19 m/s (AUROC =0.70-0.88), F≥2 – 1.21-1.34 m/s (AUROC = 0.85-0.90), F≥3 – 1.54-1.70 m/s (AUROC = 0.87-0.99) and F=4 – 1.75-2 m/s (AUROC = 0.91-0.99). An international multicenter study (89), which included 914 chronic hepatitis C patients from Europe and Asia assessed by VTQ (ARFI) elastography and liver biopsy, showed that the best cut-offs for predicting significant fibrosis (F≥2) and liver cirrhosis are different for European vs. Asian subjects: 1.21 m/s and 1.74 m/s for European patients and 1.32 m/s and 1.55 m/s for Asian patients, respectively. Similarly, both TE and VTQ (ARFI) could not discriminate well between patients with mild fibrosis and those with significant fibrosis (89).

ElastPQ technique

In patients with chronic hepatitis C, ElastPQ proved to be reliable to predict the severity of fibrosis, considering TE as the reference method. The optimal cutoffs of ElastPQ measurements to predict significant fibrosis, advanced fibrosis and cirrhosis were 6.43, 9.54 and 11.34 kPa (90).

Real Time Shear Waves Elastography (2D-SWE and 3D-SWE)

2D-SWE by Supersonic Imagine (Aixplorer system)

2D-SWE.SSI is a good, reliable method for assessing LS in chronic hepatitis C patients (49). The best cut-off values for different liver fibrosis stages are: for F≥2 - 7.1 kPa (AUROC= 0.92);

for F≥3 - 8.7 kPa (AUROC=0.98) and for F4 - 10.4 kPa (AUROC=0.98). In another study, the AUROCs for elasticity values assessed by 2D-SWE.SSI were 0.948 for F≥2, 0.962 for F≥3 and 0.968 for F=4 (91).

Hepatitis B

Transient Elastography

Three meta-analyses recently confirmed the good performance of TE in chronic hepatitis B staging (92-94). Despite the fact that liver stiffness values showed a substantial overlap among adjacent stages of fibrosis (particularly at lower fibrosis stages), LS may identify patients with F≥2 and F4 with very good performance. Recent publications confirmed previous evidence, suggesting that the AUROCs for F≥2 varies between 0.80 and 0.90 with cut-off values between 6.6 kPa and 8.8 kPa (95-97). Regarding the identification of cirrhosis (F4), again recent data confirm previous evidence, with AUROCs ranging between 0.81 and 0.97 and cut-off values between 9.4 and 13.4 kPa (24, 98). A new published meta-analysis showed that a value > 11.7 kPa should raise suspicion of cirrhosis (92, 93). Since transaminase levels tend to vaguely reflect the degree of intrahepatic inflammation and were shown to influence LS in chronic hepatitis C, and hepatitis flares are often observed in chronic hepatitis B, it has been suggested that LS cut-offs should be adapted to transaminases levels (24).
Other studies showed that ALT-adapted cut-offs do not influence the TE diagnostic performance (99) and that the only variable associated with overestimation of cirrhosis diagnosis in chronic hepatitis B patients is moderate/severe necro-inflammatory activity without any direct correlation with transaminases level (100).

Point Shear Waves Elastography

Acoustic Radiation Force Impulse using Virtual Touch Quantification - VTQ (ARFI)
In a study in which patients with chronic hepatitis B were evaluated by liver biopsy, VTQ (ARFI) and a subgroup of patients also by TE (101), the diagnostic accuracies expressed as AUROC for VTQ (ARFI) and TE were 0.75 and 0.83 for the diagnosis of F≥2, 0.93 and 0.94 for the diagnosis of F≥3, and 0.97 and 0.93 for the diagnosis of liver cirrhosis, respectively. No

significant difference was found between VTQ (ARFI) and TE. There are 2 meta-analyses that confirm these findings, the AUROC for significant fibrosis being 0.88 and the best cut-off 1.35m/s, while for cirrhosis the AUROC was 0.93 and the best cut-off 1.87m/s (102).

ElastPQ technique

In patients with HBV chronic infection, published data (41) showed good value for predicting the presence of significant fibrosis (F≥2) and cirrhosis (F=4), the best LS cut-off values being 6.99 kPa (AUROC=0.94) and 9 kPa (AUROC=0.89), respectively. Liver fibrosis and necro-inflammatory activity were significantly correlated with ElastPQ measurements.

Real Time Shear Waves Elastography (2D-SWE and 3D-SWE)

2D-SWE by Supersonic Imagine (Aixplorer system)

In chronic hepatitis B patients the results of 2D-SWE.SSI are quite similar to those in chronic hepatitis C patients: F≥1: 6.5 kPa (AUROC=0.86), F≥2: 7.1 kPa (AUROC=0.88), F≥3: 7.9 kPa (AUROC=0.93) and F4: 10.1 kPa (AUROC=0.98) (48).

Nonalcoholic fatty liver disease (NAFLD)

Transient Elastography

Transient Elastography performance is better for cirrhosis than for significant fibrosis in patients with NAFLD (103, 104). This elastographic technique has a higher rate of false positive than false-negative results, hence the ability to diagnose bridging fibrosis or cirrhosis is insufficient for clinical decision making (105, 106).

Kwok et al. completed a systematic review of TE in patients with NAFLD involving nine studies and 1,047 patients (107). TE was excellent in diagnosing F3 fibrosis (75% sensitivity, 82% specificity) and cirrhosis (92% sensitivity, 92% specificity), but had only moderate accuracy for F2 fibrosis (79% sensitivity, 75% specificity).

With the M Probe, patients with steatosis > 66% at liver biopsy had higher LS values, which led to higher false-positive LSM results (103). Thus, in obese patients with a high degree of steatosis, TE using the M Probe may be less accurate in diagnosing severe fibrosis in NAFLD; however additional studies on the effects of steatosis on LSM measured with XL probe are needed since XL probe produces lower stiffness values than the M probe.

Cut-offs values (M-Probe) of 7.9 kPa and 9.3 kPa have 90% sensitivity and specificity to rule out and to rule in F3 fibrosis in NAFLD patients, respectively (108).

A new technique for quantification of liver steatosis related to TE and performed with a FibroScan device is ***Controlled Attenuation Parameter (CAP)*** **[**Figure 1]. In a cohort of 115 patients, considering the histological grade of steatosis as reference, CAP was significantly correlated to steatosis (r=0.81, p<0.00001). AUROCs for the detection of >10% and >33% steatosis were 0.91 and 0.95 respectively (109). A meta-analysis (110) which included 11 studies calculated the following AUROCs for predicting the presence of S≥1, S≥2 and S≥3: 0.85, 0.88, and 0.87, respectively. The following cut-offs values were proposed for diagnosing S≥1, S≥2 and S≥3: 232.5 dB/m, 255 dB/m and 290 dB/m, respectively.

Point Shear Waves Elastography

Acoustic Radiation Force Impulse using Virtual Touch Quantification - VTQ (ARFI)

VTQ (ARFI) elastography was also evaluated in NAFLD patients. At a cut-off value of > 1.10 m/s (AUROC = 0.86) (111), VTQ (ARFI) can discriminate between patients with simple steatosis and those with non-alcoholic steatohepatitis. For predicting the presence of severe fibrosis (F≥3) and liver cirrhosis (F=4) in patients with NAFLD, the best cut-off values were 1.77 m/s and 1.9 m/s, respectively (111).

A meta-analysis in NAFLD patients (7 studies with 723 patients) showed that VTQ (ARFI) had 80.2% summary Se, 85.2% summary Sp, with 30.1 pooled diagnostics odds ratio for diagnosing significant fibrosis (112).

ElastPQ technique

No available data.

Real Time Shear Waves Elastography (2D-SWE and 3D-SWE)

2D-SWE by Supersonic Imagine (Aixplorer system)

There are only few studies that evaluated the performance of 2D-SWE.SSI for liver fibrosis assessment in NAFLD patients. The results are contradictory (113, 114).

Other etiologies of chronic liver disease

Few data are available regarding other etiologies of liver disease. Most of them are available regarding Transient Elastography.

Transient Elastography in patients with prior or current ***chronic alcohol overuse*** can distinguish absence and mild fibrosis (F0-1) from severe fibrosis and cirrhosis, but cannot differentiate between mild fibrosis and absence of liver fibrosis (115). Additionally, in the published studies which included only patients with alcoholic liver disease, there is no consensus regarding optimal cut-off values for significant fibrosis, severe fibrosis or liver cirrhosis (116-120). Optimal cut-off values range from 7.8 to 9.6 kPa (121, 122) for significant fibrosis, from 8 to 17.0 kPa for severe fibrosis (116, 123) and from 12.5 to 22.7 kPa for cirrhosis (116, 123). Transient Elastography is more suited to rule out rather than rule in cirrhosis. At a cut-off of 12.5 kPa, TE may rule out cirrhosis with a negative likelihood ratio of 0.07 (115). In patients submitted for alcohol detoxification, 0.5 to 4 weeks of abstinence causes a significant decrease in TE (123-125). However, the decrease is associated with a normalisation of transaminases, bilirubin, alkaline phosphatase and/or gamma-glutamyltransferase.

Transient elastography is currently considered one of the best surrogates to assess fibrosis in ***primary sclerosing cholangitis*** (PSC). High baseline or increasing values over time indicated a worse outcome in this population (126). Liver stiffness was investigated by transient elastography in 73 patients with PSC, regularly undergoing clinical and elastographic follow-up (126). Transient elastography measurements were able to differentiate severe vs. non-severe fibrosis with a high discriminative accuracy for cirrhosis (AUROC 0.88). There was a high reproducibility between two operators. Higher baseline liver stiffness and increase of liver stiffness over time were associated with adverse outcome such as death, liver transplantation, ascites, hepatic encephalopathy and gastrointestinal bleeding or hepatocellular carcinoma (126). Dilatation of the intrahepatic biliary system due to a dominant stricture should be ruled out in PSC before interpreting the value of liver stiffness measurement, since as previously stated, cholestasis increases liver stiffness independent of liver fibrosis.

No indications for SWE

Shear wave elastography should not be performed in case of acute hepatitis, transaminases flares (ALT > 5 ULN), extra-hepatic cholestasis, and congestive heart failure (11).

Rules for SWE

The most important EFSUMB recommendations regarding SWE elastography are (11):

- Measurement of liver stiffness by SWE should be performed through a right intercostal space in supine position, with the right arm in extension, during breath hold, avoiding deep inspiration prior to the breath hold (LoE 2b, GoR B). Strong consensus (18/0/0, 100%).
- Experienced operators (LoE 2b, GoR B) should perform measurement of liver stiffness by SWE. Strong consensus (18/0/0, 100%).
- Measurement of liver stiffness by pSWE and 2D-SWE should be performed at least 10 mm below the liver capsule (LoE 1b, GoR A). Strong consensus (18/0/0, 100%).
- The major potential confounding factors (liver inflammation indicated by AST and/or ALT elevation > 5 times the normal limits, obstructive cholestasis, liver congestion, acute hepatitis and infiltrative liver diseases) should be excluded before performing LSM with SWE, in order to avoid overestimation of liver fibrosis (LoE 2b, GoR B), and/or should be considered when interpreting the SWE results (LoE 1b, GoR B). Broad consensus (15/0/1, 94%).
- Patients should fast for a minimum of 2 hours and rest for a minimum of 10 minutes before undergoing liver stiffness measurement with SWE (LoE 2b, GoR B). Majority consensus (13/2/3, 72%).
- SWE within the normal range can rule out significant liver fibrosis when in agreement with the clinical and laboratory background (LoE 2A, GoR B). Broad consensus (17/0/1, 94%)
- Adequate B-mode liver image is a prerequisite for pSWE and 2D-SWE measurements (LoE 5, GoR D). Strong consensus (18/0/0, 100%).
- The results with the lowest variability in comparing different pSWE or 2D-SWE systems were obtained at a depth of 4–5 cm from the transducers (with convex transducers)

(LoE 4, GoR C). Accordingly, this location is recommended if it is technically suitable. Broad consensus (17/0/1, 94%).

- TE can be used as the first-line assessment for the severity of liver fibrosis in patients with chronic viral hepatitis C. It performs best with regard to the ruling out of cirrhosis (LoE 1b, GoR A). Broad consensus (17/0/1, 94%).
- pSWE as demonstrated with VTQ® can be used as the first-line assessment for the severity of liver fibrosis in patients with chronic hepatitis C. It performs best with regard to the ruling out of cirrhosis (LoE 2a, GoR B). Broad consensus (17/0/1, 94%).
- 2D-SWE as demonstrated with SSI can be used as a first-line assessment for the severity of liver fibrosis in patients with chronic hepatitis C. It performs best with regard to the ruling out of cirrhosis (LoE 1b, GoR A). Broad consensus (17/0/1, 94%).
- TE is useful in patients with CHB to identify those with cirrhosis. Concomitant assessment of transaminases is required to exclude flare up (elevation >5 times upper limit of normal). (LoE 1b, GoR A). Broad consensus (17/1/0, 94%).
- pSWE as demonstrated with VTQ® is useful in patients with CHB to identify those with cirrhosis (LoE 2a, GoR B). Strong consensus (18/0/0, 100%).
- 2D-SWE as demonstrated with SSI is useful in patients with CHB to identify those with cirrhosis (LoE 3a, GoR C). Broad consensus (17/0/1, 94%).

Pediatric indications

Shear wave elastography can be used also in pediatric population. Transient Elastography has a special probe (S-Probe) for this population. The main indications of elastography in this population are: evaluation of liver fibrosis in children with viral hepatitis, NAFLD, cystic fibrosis, biliary atresia or post-transplant liver graft fibrosis.

The mean LS value assessed by TE obtained in healthy children was 4.7 kPa. Median values of stiffness were significantly age dependent with 4.40, 4.73, and 5.1 kPa in children 0-5, 6-11, and 12-18 years ($p = 0.001$) (127).

Transient Elastography was used to predict different stages of liver fibrosis in a cohort of 90 children with different etiologies of liver disease, using liver biopsy as gold-standard method

(128). Liver stiffness correlated significantly with histological Ishak score (r = 0.879, p < 0.0001). Transient Elastography discriminated individual stages of fibrosis with high performance. Higher values of LS were obtained in autoimmune hepatitis (16.15 ± 7.23 kPa) as compared to Wilson disease (8.30 ± 0.84 kPa) and HCV groups (7.43 ± 1.73 kPa).

A study including 350 pediatric patients (129) evaluated the clinical value of controlled attenuation parameter (CAP) for non-invasive assessment of liver steatosis. This study concluded that, for the evaluation of liver steatosis, CAP performs better than ultrasound and a cut-off value of 249 dB/m rules-in liver steatosis with a very high specificity.

A study (130) including 54 consecutive children and adolescents with different chronic liver diseases used 3 elastographic methods (TE, ARFI-VTQ, and 2D-SWE.SSI) for assessing liver fibrosis. Considering TE as a reference method, sensitivity of VTQ (ARFI) for detecting fibrosis F1 was 71.4%, for F2-77.7%, for F3-62.5% and for F4-71.4%. Sensitivity of 2D-SWE.SSI for detecting F1 was 92.8%, for F2-83.3%, for F3-87.5% and for F4-85.7%.

The normal shear wave values assessed by VTQ (ARFI) in healthy children was 1.07 ± 0.10 m/s. No significant differences were found according to gender or among different probe locations (131).

A study including healthy children and patients with chronic liver diseases with different etiologies showed that a VTQ (ARFI) cut-off of 1.34 m/s is predictive for liver fibrosis (F≥1) (AUROC=0.85) and a cut-off of 2 m/s yielded a sensitivity of 100% for detecting F>2 (132).

The usefulness of 2D-SWE.SSI for non-invasive assessment of liver fibrosis was also studied. In a study (133) which included healthy children and pediatric population with chronic liver disease, the liver stiffness values were significantly higher when a SC6-1 probe was used as compared with values obtained with the SL15-4 probe (6.94 kPa ± 1.42 vs 5.96 kPa ± 1.31; p =0.006). According to the severity of liver fibrosis at liver biopsy, 88.5%-96.8% of patients were correctly classified, with AUROCs of 0.90-0.98.

SWE in other organs

Shear wave elastography, especially the elastographic methods integrated in ultrasound systems, can be performed in other organs such as the spleen, thyroid, kidney, breast or prostate. Elastography was used also for characterization of liver tumors.

Spleen stiffness is currently under evaluation, especially for the non-invasive prediction of portal hypertension. Since splenomegaly and spleen congestion mostly depend upon portal hypertension in cirrhosis, it has been suggested that spleen stiffness might reflect portal pressure better than liver stiffness.

Overall, the spleen is stiffer than the liver even in normal subjects. TE and 2D-SWE.SSI are successful in about 70% of cases in whom measurement is attempted, while spleen stiffness measurement (SSM) by VTQ (ARFI) seems to be possible in most cases, even with a normal sized spleen; however, SSM by VTQ was less reproducible than LSM by VTQ (ARFI) (134).

Overall, spleen stiffness by TE correlates with HVPG slightly better than liver stiffness, and it seems to improve prediction of the presence of varices and varices needing treatment as compared to liver stiffness (both by TE and pSWE). Interestingly, spleen stiffness is increased in patients with non-cirrhotic portal hypertension (extrahepatic portal vein obstruction and idiopathic portal hypertension) in whom liver stiffness is normal or only mildly elevated (135, 136). This suggests that spleen stiffness and the ratio between liver and spleen stiffness could be used in patients with portal hypertension of unknown origin to help differentiating between cirrhotic and non-cirrhotic causes. In one study performed in patients with cirrhosis caused by hepatitis C, spleen stiffness predicted a first episode of clinical decompensation of cirrhosis better than liver stiffness (137).

Currently, the use of shear wave elastography for characterization of **focal liver masses** remains investigational. Elastography has been studied to characterize focal liver lesions, to differentiate between benign and malignant masses. The results of the published studies are contradictory (138-141).

The performance of VTQ (ARFI) for identification of malignant liver lesions was assessed in a meta-analysis that included eight studies with a total of 590 liver lesions (38% of them benign) in 490 patients (138). The major drawback was that the cut-off value of shear wave speed was different across studies, ranging from 1.5 to 2.7 m/s. The summary sensitivity and specificity were 0.86 and 0.89, respectively (138).

VTQ (ARFI) was used in combination with conventional ultrasound for characterization of thyroid nodules. A meta-analysis (142) including 13 studies with 1854 thyroid nodules (72% benign) from 1641 patients showed a summary sensitivity and specificity for differential diagnosis between benign and malignant thyroid nodules of 0.81 and 0.84, respectively.

Conclusion

Shear wave ultrasound based elastographic methods have a good performance for the non-invasive assessment of liver fibrosis, especially to exclude the presence of cirrhosis. All shear wave elastographic methods have a very good reproducibility. Several factors can influence the accuracy of shear wave ultrasound based elastographic methods: transaminases flares, extra-hepatic cholestasis, congestive heart failure or non-fasting condition.

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