+Q-Box™
Mean   6.2
Min   5.2
Max   7.6
SD   0.5
Diam   20.0

EFSUMB Course Book

2nd Edition

Editor: Christoph F. Dietrich

Ch03: Liver elastography

Ioan Sporea[1], Mireen Friedrich-Rust[2], Odd Helge Gilja[3], Simona Bota[4], Roxana Șirli[1]

1. Department of Gastroenterology and Hepatology, Victor Babeș University of Medicine and Pharmacy, Timişoara, Romania.
2. Department of Internal Medicine 1, J.-W.-Goethe-University Hospital, Frankfurt, Germany.
3. National Centre for Ultrasound in Gastroenterology, Department of Medicine, Haukeland University Hospital, and Institute of Medicine, University of Bergen, Bergen, Norway. 4Department of Gastroenterology, Hepatology, Nephrology, Rheumatology and Endocrinology, Klinikum Klagenfurt, Klagenfurt, Austria.

Corresponding author: Professor Dr. Ioan Sporea
Department of Gastroenterology and Hepatology, Victor Babeș University of Medicine and Pharmacy, Timişoara, Romania
Tel: +40 256 488003. E-mail: isporea@umft.ro

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)**

o **Point Shear Waves Elastography (pSWE): using Acoustic Radiation Force Impulse (ARFI) technique [Virtual Touch Quantification (VTQ)** and **ElastPQ]**

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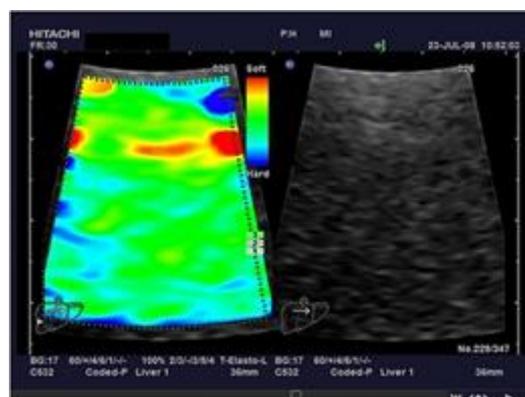
This method has been used in clinical practice for the assessment of focal lesions in the breast, thyroid, prostate and pancreas (61) and, more recently, for the evaluation of hepatic fibrosis (58, 62-64).

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≥2) 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≥3) (p=0.0016), and a significantly higher accuracy than VTQ (ARFI) for the diagnosis of significant fibrosis (F⩾2) (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.

References

1.   McHutchison J, Poynard T, Afdhal N, Participants IFGM. 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.
2.   Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, Feng ZZ, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-2618.
3.   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.
4.   Ratziu V, Charlotte F, Heurtier A, Gombert S, Giral P, Bruckert E, Grimaldi A, et al. Sampling variability of liver biopsy in nonalcoholic fatty liver disease. Gastroenterology 2005;128:1898-1906.
5.   Gebo KA, Herlong HF, Torbenson MS, Jenckes MW, Chander G, Ghanem KG, El-Kamary SS, et al. Role of liver biopsy in management of chronic hepatitis C: a systematic review. Hepatology 2002;36:S161-172.
6.   Rosenberg WM, Voelker M, Thiel R, Becka M, Burt A, Schuppan D, Hubscher S, et al. Serum markers detect the presence of liver fibrosis: a cohort study. Gastroenterology 2004;127:1704-1713.
7.   Gregersen H, Gilja OH, Hausken T, Heimdal A, Gao C, Matre K, Ødegaard S, et al. Mechanical properties in the human gastric antrum using B-mode ultrasonography and antral distension. Am J Physiol Gastrointest Liver Physiol 2002;283:G368-375.
8.   Ahmed AB, Gilja OH, Gregersen H, Ødegaard S, Matre K. In vitro strain measurement in the porcine antrum using ultrasound doppler strain rate imaging. Ultrasound Med Biol 2006;32:513-522.
9.   Bamber J, Cosgrove D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, Cantisani V, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. Ultraschall Med 2013;34:169-184.
10.   Cosgrove D, Piscaglia F, Bamber J, Bojunga J, Correas JM, Gilja OH, Klauser AS, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. Ultraschall Med 2013;34:238-253.
11.   Dietrich CF, Bamber J, Berzigotti A, Bota S, Cantisani V, Castera L, Cosgrove D, et al. EFSUMB Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, Update 2017 (Long Version). Ultraschall Med 2017;38:e16-e47.

12.   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.

13.   Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, Christidis C, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29:1705-1713.

14.   Castera L, Foucher J, Bernard PH, Carvalho F, Allaix D, Merrouche W, Couzigou P, et al. Pitfalls of liver stiffness measurement: a 5-year prospective study of 13,369 examinations. Hepatology 2010;51:828-835.

15.   Sirli R, Sporea I, Bota S, Jurchis A. Factors influencing reliability of liver stiffness measurements using transient elastography (M-probe)-monocentric experience. Eur J Radiol 2013;82:e313-316.

16.   de Ledinghen V, Vergniol J, Foucher J, El-Hajbi F, Merrouche W, Rigalleau V. Feasibility of liver transient elastography with FibroScan using a new probe for obese patients. Liver Int 2010;30:1043-1048.

17.   Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Beaton M, Levstik M, Duarte-Rojo A, et al. Discordance in fibrosis staging between liver biopsy and transient elastography using the FibroScan XL probe. J Hepatol 2012;56:564-570.

18.   Wong VW, Vergniol J, Wong GL, Foucher J, Chan AW, Chermak F, Choi PC, et al. Liver stiffness measurement using XL probe in patients with nonalcoholic fatty liver disease. Am J Gastroenterol 2012;107:1862-1871.

19.   Wong GL, Vergniol J, Lo P, Wai-Sun Wong V, Foucher J, Le Bail B, Choi PC, et al. Non-invasive assessment of liver fibrosis with transient elastography (FibroScan(R)): applying the cut-offs of M probe to XL probe. Ann Hepatol 2013;12:570-580.

20.   Boursier J, Zarski JP, de Ledinghen V, Rousselet MC, Sturm N, Lebail B, Fouchard-Hubert I, et al. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology 2013;57:1182-1191.

21.   Schwabl P, Bota S, Salzl P, Mandorfer M, Payer BA, Ferlitsch A, Stift J, et al. New reliability criteria for transient elastography increase the number of accurate measurements for screening of cirrhosis and portal hypertension. Liver Int 2015;35:381-390.

22.   Coco B, Oliveri F, Maina AM, Ciccorossi P, Sacco R, Colombatto P, Bonino F, et al. Transient elastography: a new surrogate marker of liver fibrosis influenced by major changes of transaminases. J Viral Hepat 2007;14:360-369.

23.   Vigano M, Massironi S, Lampertico P, Iavarone M, Paggi S, Pozzi R, Conte D, et al. Transient elastography assessment of the liver stiffness dynamics during acute hepatitis B. Eur J Gastroenterol Hepatol 2010;22:180-184.

24.   Chan HL, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, Chan FK, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009;16:36-44.

25.   Mederacke I, Wursthorn K, Kirschner J, Rifai K, Manns MP, Wedemeyer H, Bahr MJ. Food intake increases liver stiffness in patients with chronic or resolved hepatitis C virus infection. Liver Int 2009;29:1500-1506.

26.   Arena U, Lupsor Platon M, Stasi C, Moscarella S, Assarat A, Bedogni G, Piazzolla V, et al. Liver stiffness is influenced by a standardized meal in patients with chronic hepatitis C virus at different stages of fibrotic evolution. Hepatology 2013;58:65-72.

27.   Millonig G, Friedrich S, Adolf S, Fonouni H, Golriz M, Mehrabi A, Stiefel P, et al. Liver stiffness is directly influenced by central venous pressure. J Hepatol 2010;52:206-210.

28.   Millonig G, Reimann FM, Friedrich S, Fonouni H, Mehrabi A, Buchler MW, Seitz HK, et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. Hepatology 2008;48:1718-1723.

29.   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.

30.   Bota S, Sporea I, Sirli R, Popescu A, Danila M, Costachescu D. Intra- and interoperator reproducibility of acoustic radiation force impulse (ARFI) elastography--preliminary results. Ultrasound Med Biol 2012;38:1103-1108.

31.   Boursier J, Isselin G, Fouchard-Hubert I, Oberti F, Dib N, Lebigot J, Bertrais S, et al. Acoustic radiation force impulse: a new ultrasonographic technology for the widespread noninvasive diagnosis of liver fibrosis. Eur J Gastroenterol Hepatol 2010;22:1074-1084.

32.   D'Onofrio M, Gallotti A, Mucelli RP. Tissue quantification with acoustic radiation force impulse imaging: Measurement repeatability and normal values in the healthy liver. AJR Am J Roentgenol 2010;195:132-136.

33.   Bota S, Sporea I, Sirli R, Popescu A, Danila M, Sendroiu M. Factors that influence the correlation of acoustic radiation force impulse (ARFI), elastography with liver fibrosis. Med Ultrason 2011;13:135-140.

34.   Bota S, Sporea I, Sirli R, Popescu A, Jurchis 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.

35.   Bota S, Sporea I, Sirli R, Popescu A, Danila M, Jurchis A, Gradinaru-Tascau O. Factors associated with the impossibility to obtain reliable liver stiffness measurements by means of Acoustic Radiation Force Impulse (ARFI) elastography--analysis of a cohort of 1,031 subjects. Eur J Radiol 2014;83:268-272.

36.   Sugitani M, Fujita Y, Yumoto Y, Fukushima K, Takeuchi T, Shimokawa M, Kato K. A new method for measurement of placental elasticity: acoustic radiation force impulse imaging. Placenta 2013;34:1009-1013.

37.   Popescu A, Bota S, Sporea I, Sirli R, Danila M, Racean S, Suseanu D, et al. The influence of food intake on liver stiffness values assessed by acoustic radiation force impulse elastography-preliminary results. Ultrasound Med Biol 2013;39:579-584.

38.   Goertz RS, Egger C, Neurath MF, Strobel D. Impact of food intake, ultrasound transducer, breathing maneuvers and body position on acoustic radiation force impulse (ARFI) elastometry of the liver. Ultraschall Med 2012;33:380-385.

39.   Bota S, Sporea I, Peck-Radosavljevic M, Sirli R, Tanaka H, Iijima H, Saito H, et al. The influence of aminotransferase levels on liver stiffness assessed by Acoustic Radiation Force Impulse Elastography: a retrospective multicentre study. Dig Liver Dis 2013;45:762-768.

40.   Pfeifer L, Strobel D, Neurath MF, Wildner D. Liver stiffness assessed by acoustic radiation force impulse (ARFI) technology is considerably increased in patients with cholestasis. Ultraschall Med 2014;35:364-367.

41.   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.

42.   Sporea I, Bota S, Gradinaru-Tascau O, Sirli 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.

43.   Yoo H, Lee JM, Yoon JH, Lee DH, Chang W, Han JK. Prospective Comparison of Liver Stiffness Measurements between Two Point Shear Wave Elastography Methods: Virtual

Touch Quantification and Elastography Point Quantification. Korean J Radiol 2016;17:750-757.

44.   Ferraioli G, Tinelli C, Lissandrin R, Zicchetti M, Dal Bello B, Filice G, Filice C. Point shear wave elastography method for assessing liver stiffness. World J Gastroenterol 2014;20:4787-4796.

45.   Ling W, Lu Q, Quan J, Ma L, Luo Y. Assessment of impact factors on shear wave based liver stiffness measurement. Eur J Radiol 2013;82:335-341.

46.   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.

47.   Sporea I, Gradinaru-Tascau O, Bota S, Popescu A, Sirli R, Jurchis A, Popescu M, et al. How many measurements are needed for liver stiffness assessment by 2D-Shear Wave Elastography (2D-SWE) and which value should be used: the mean or median? Med Ultrason 2013;15:268-272.

48.   Leung VY, Shen J, Wong VW, Abrigo J, Wong GL, Chim AM, Chu SH, et al. 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.

49.   Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C, Liver Fibrosis Study G. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology 2012;56:2125-2133.

50.   Sporea I, Bota S, Jurchis A, Sirli R, Gradinaru-Tascau O, Popescu A, Ratiu I, et al. Acoustic radiation force impulse and supersonic shear imaging versus transient elastography for liver fibrosis assessment. Ultrasound Med Biol 2013;39:1933-1941.

51.   Procopet B, Berzigotti A, Abraldes JG, Turon F, Hernandez-Gea V, Garcia-Pagan JC, Bosch J. Real-time shear-wave elastography: applicability, reliability and accuracy for clinically significant portal hypertension. J Hepatol 2015;62:1068-1075.

52.   Hudson JM, Milot L, Parry C, Williams R, Burns PN. Inter- and intra-operator reliability and repeatability of shear wave elastography in the liver: a study in healthy volunteers. Ultrasound Med Biol 2013;39:950-955.

53.   Poynard T, Munteanu M, Luckina E, Perazzo H, Ngo Y, Royer L, Fedchuk L, et al. Liver fibrosis evaluation using real-time shear wave elastography: applicability and diagnostic performance using methods without a gold standard. J Hepatol 2013;58:928-935.

54.   Gradinaru-Tascau O, Sporea I, Bota S, Jurchis A, Popescu A, Popescu M, Sirli R, et al. Does experience play a role in the ability to perform liver stiffness measurements by means of supersonic shear imaging (SSI)? Med Ultrason 2013;15:180-183.

55.   Vonghia L WW, Pelckmans P, Michielsen P, Francque S. Liver stiffness by shear wave elastography is influenced by meal and meal-related haemodynamic modifications. Ultraschall in Med 2013;34:WS_SL24_09.

56.   Bende F SI, Sirli R, Popescu A, Danila M, Mare R, Lupusoru R. Optimal number of valid measurements for the assessment of liver stiffness using 2D-SWE.GE. . Ultraschall Med 2016;37 (Suppl 1):S41.

57.   Moga TV PC, Stepan AM, Popescu A, Sirli R, Danila M, Sporea I. Inter/intra-observer reproduciibility of a 2DShear Wave Elastography (Logiq E9 system from GE) technique and the impact of ultrasound experience in achieving reliable data. Ultraschall in Med 2016;): SL19_6 2016;37 (Suppl1):S28.

58.   Friedrich-Rust M, Ong MF, Herrmann E, Dries V, Samaras P, Zeuzem S, Sarrazin C. Real-time elastography for noninvasive assessment of liver fibrosis in chronic viral hepatitis. AJR Am J Roentgenol 2007;188:758-764.

59.   Frey H. [Realtime elastography. A new ultrasound procedure for the reconstruction of tissue elasticity]. Radiologe 2003;43:850-855.

60.   Havre RF, Elde E, Gilja OH, Odegaard S, Eide GE, Matre K, Nesje LB. Freehand real-time elastography: impact of scanning parameters on image quality and in vitro intra- and interobserver validations. Ultrasound Med Biol 2008;34:1638-1650.

61.   Shiina T NN, Yamakawa M, Ueno E. Real-time tissue elasticity imaging by the compound autocorrelation method. Medix 2007;suppl:4-7.

62.   Fujimoto K WS, Oshita M, Kato M, Tonomura A, Mitaki T. Non-invasive evaluation of Hepatic Fibrosis in patients with Chronic Hepatitis C using Elastography. Medix 2007;suppl:24-27.

63.   Tatsumi C, Kudo M, Ueshima K, Kitai S, Takahashi S, Inoue T, Minami Y, et al. Noninvasive evaluation of hepatic fibrosis using serum fibrotic markers, transient elastography (FibroScan) and real-time tissue elastography. Intervirology 2008;51 Suppl 1:27-33.

64.   Friedrich-Rust M, Schwarz A, Ong M, Dries V, Schirmacher P, Herrmann E, Samaras P, et al. Real-time tissue elastography versus FibroScan for noninvasive assessment of liver fibrosis in chronic liver disease. Ultraschall Med 2009;30:478-484.

65.   Corpechot C, El Naggar A, Poupon R. Gender and liver: is the liver stiffness weaker in weaker sex? Hepatology 2006;44:513-514.

66.   Roulot D, Czernichow S, Le Clesiau H, Costes JL, Vergnaud AC, Beaugrand M. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. J Hepatol 2008;48:606-613.

67.   Kim SU, Choi GH, Han WK, Kim BK, Park JY, Kim DY, Choi JS, et al. What are 'true normal' liver stiffness values using FibroScan?: a prospective study in healthy living liver and kidney donors in South Korea. Liver Int 2010;30:268-274.

68.   Sirli R, Sporea I, Tudora A, Deleanu A, Popescu A. Transient elastographic evaluation of subjects without known hepatic pathology: does age change the liver stiffness? J Gastrointestin Liver Dis 2009;18:57-60.

69.   Popescu A, Sporea I, Sirli R, Bota S, Focsa M, Danila M, Nicolita D, et al. The mean values of liver stiffness assessed by Acoustic Radiation Force Impulse elastography in normal subjects. Med Ultrason 2011;13:33-37.

70.   Kim JE, Lee JY, Kim YJ, Yoon JH, Kim SH, Lee JM, Han JK, et al. Acoustic radiation force impulse elastography for chronic liver disease: comparison with ultrasound-based scores of experienced radiologists, Child-Pugh scores and liver function tests. Ultrasound Med Biol 2010;36:1637-1643.

71.   Son CY, Kim SU, Han WK, Choi GH, Park H, Yang SC, Choi JS, et al. Normal liver elasticity values using acoustic radiation force impulse imaging: a prospective study in healthy living liver and kidney donors. J Gastroenterol Hepatol 2012;27:130-136.

72.   Goertz RS, Amann K, Heide R, Bernatik T, Neurath MF, Strobel D. An abdominal and thyroid status with Acoustic Radiation Force Impulse Elastometry--a feasibility study: Acoustic Radiation Force Impulse Elastometry of human organs. Eur J Radiol 2011;80:e226-230.

73.   Karlas T, Pfrepper C, Wiegand J, Wittekind C, Neuschulz M, Mossner J, Berg T, et al. Acoustic radiation force impulse imaging (ARFI) for non-invasive detection of liver fibrosis:

examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease. Scand J Gastroenterol 2011;46:1458-1467.

74.   Madhok R, Tapasvi C, Prasad U, Gupta AK, Aggarwal A. Acoustic radiation force impulse imaging of the liver: measurement of the normal mean values of the shearing wave velocity in a healthy liver. J Clin Diagn Res 2013;7:39-42.

75.   Sirli R, Bota S, Sporea I, Jurchis A, Popescu A, Gradinaru-Tascau O, Szilaski M. Liver stiffness measurements by means of supersonic shear imaging in patients without known liver pathology. Ultrasound Med Biol 2013;39:1362-1367.

76.   Bende F, Mulabecirovic A, Sporea I, Popescu A, Sirli R, Gilja OH, Vesterhus M, et al. Assessing Liver Stiffness by 2-D Shear Wave Elastography in a Healthy Cohort. Ultrasound Med Biol 2018;44:332-341.

77.   Bota S, Herkner H, Sporea I, Salzl P, Sirli 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.

78.   Cassinotto C, Lapuyade B, Mouries A, Hiriart JB, Vergniol J, Gaye D, Castain C, et al. Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan(R). J Hepatol 2014;61:550-557.

79.   Castera L, Vergniol J, Foucher J, Le Bail B, Chanteloup E, Haaser M, Darriet M, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. Gastroenterology 2005;128:343-350.

80.   Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, Herrmann E. Performance of transient elastography for the staging of liver fibrosis: a meta-analysis. Gastroenterology 2008;134:960-974.

81.   Sporea I, Sirli R, Deleanu A, Tudora A, Curescu M, Cornianu M, Lazar D. Comparison of the liver stiffness measurement by transient elastography with the liver biopsy. World J Gastroenterol 2008;14:6513-6517.

82.   Ziol M, Handra-Luca A, Kettaneh A, Christidis C, Mal F, Kazemi F, de Ledinghen V, et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C. Hepatology 2005;41:48-54.

83.   Nahon P, Thabut G, Ziol M, Htar MT, Cesaro F, Barget N, Grando-Lemaire V, et al. Liver stiffness measurement versus clinicians' prediction or both for the assessment of liver fibrosis in patients with chronic hepatitis C. Am J Gastroenterol 2006;101:2744-2751.

84.   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 Gastrointestin Liver Dis 2009;18:303-310.

85.   Friedrich-Rust M, Wunder K, Kriener S, Sotoudeh F, Richter S, Bojunga J, Herrmann E, et al. Liver fibrosis in viral hepatitis: noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. Radiology 2009;252:595-604.

86.   Sporea I, Sirli R, Bota S, Fierbinteanu-Braticevici C, Petrisor A, Badea R, Lupsor M, et al. Is ARFI elastography reliable for predicting fibrosis severity in chronic HCV hepatitis? World J Radiol 2011;3:188-193.

87.   Fierbinteanu-Braticevici C, Andronescu D, Usvat R, Cretoiu D, Baicus C, Marinoschi G. Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis. World J Gastroenterol 2009;15:5525-5532.

88.   Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S, Fatuzzo F, et al. 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.

89.   Sporea I, Bota S, Peck-Radosavljevic M, Sirli R, Tanaka H, Iijima H, Badea R, et al. Acoustic Radiation Force Impulse elastography for fibrosis evaluation in patients with chronic hepatitis C: an international multicenter study. Eur J Radiol 2012;81:4112-4118.

90.   Ferraioli G, Maiocchi L, Lissandrin R, Tinelli C, De Silvestri A, Filice C, Liver Fibrosis Study G. Accuracy of the ElastPQ Technique for the Assessment of Liver Fibrosis in Patients with Chronic Hepatitis C: a "Real Life" Single Center Study. J Gastrointestin Liver Dis 2016;25:331-335.

91.   Bavu E, Gennisson JL, Couade M, Bercoff J, Mallet V, Fink M, Badel A, et al. 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.

92.   Chon YE, Choi EH, Song KJ, Park JY, Kim DY, Han KH, Chon CY, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. PLoS One 2012;7:e44930.

93.   Xu X, Su Y, Song R, Sheng Y, Ai W, Wu X, Liu H. Performance of transient elastography assessing fibrosis of single hepatitis B virus infection: a systematic review and meta-analysis of a diagnostic test. Hepatol Int 2015;9:558-566.

94.   Li Y, Huang YS, Wang ZZ, Yang ZR, Sun F, Zhan SY, Liu XE, et al. Systematic review with meta-analysis: the diagnostic accuracy of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B. Aliment Pharmacol Ther 2016;43:458-469.

95.   Seo YS, Kim MN, Kim SU, Kim SG, Um SH, Han KH, Kim YS. Risk Assessment of Hepatocellular Carcinoma Using Transient Elastography Vs. Liver Biopsy in Chronic Hepatitis B Patients Receiving Antiviral Therapy. Medicine (Baltimore) 2016;95:e2985.

96.   Meng F, Zheng Y, Zhang Q, Mu X, Xu X, Zhang H, Ding L. Noninvasive evaluation of liver fibrosis using real-time tissue elastography and transient elastography (FibroScan). J Ultrasound Med 2015;34:403-410.

97.   Liu Y, Dong CF, Yang G, Liu J, Yao S, Li HY, Yuan J, et al. Optimal linear combination of ARFI, transient elastography and APRI for the assessment of fibrosis in chronic hepatitis B. Liver Int 2015;35:816-825.

98.   Dong DR, Hao MN, Li C, Peng Z, Liu X, Wang GP, Ma AL. Acoustic radiation force impulse elastography, FibroScan(R), Forns' index and their combination in the assessment of liver fibrosis in patients with chronic hepatitis B, and the impact of inflammatory activity and steatosis on these diagnostic methods. Mol Med Rep 2015;11:4174-4182.

99.   Cardoso AC, Carvalho-Filho RJ, Stern C, Dipumpo A, Giuily N, Ripault MP, Asselah T, et al. Direct comparison of diagnostic performance of transient elastography in patients with chronic hepatitis B and chronic hepatitis C. Liver Int 2012;32:612-621.

100.   Fraquelli M, Rigamonti C, Casazza G, Donato MF, Ronchi G, Conte D, Rumi M, et al. Etiology-related determinants of liver stiffness values in chronic viral hepatitis B or C. J Hepatol 2011;54:621-628.

101.   Friedrich-Rust M, Buggisch P, de Knegt RJ, Dries V, Shi Y, Matschenz K, Schneider MD, et al. Acoustic radiation force impulse imaging for non-invasive assessment of liver fibrosis in chronic hepatitis B. J Viral Hepat 2013;20:240-247.

102.   Nierhoff J, Chavez 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.

103.   Petta S, Vanni E, Bugianesi E, Di Marco V, Camma C, Cabibi D, Mezzabotta L, et al. The combination of liver stiffness measurement and NAFLD fibrosis score improves the noninvasive diagnostic accuracy for severe liver fibrosis in patients with nonalcoholic fatty liver disease. Liver Int 2015;35:1566-1573.

104.   Naveau S, Lamouri K, Pourcher G, Njike-Nakseu M, Ferretti S, Courie R, Tranchart H, et al. The diagnostic accuracy of transient elastography for the diagnosis of liver fibrosis in bariatric surgery candidates with suspected NAFLD. Obes Surg 2014;24:1693-1701.

105.   Tapper EB, Challies T, Nasser I, Afdhal NH, Lai M. The Performance of Vibration Controlled Transient Elastography in a US Cohort of Patients With Nonalcoholic Fatty Liver Disease. Am J Gastroenterol 2016;111:677-684.

106.   Kumar R, Rastogi A, Sharma MK, Bhatia V, Tyagi P, Sharma P, Garg H, et al. Liver stiffness measurements in patients with different stages of nonalcoholic fatty liver disease: diagnostic performance and clinicopathological correlation. Dig Dis Sci 2013;58:265-274.

107.   Kwok R, Tse YK, Wong GL, Ha Y, Lee AU, Ngu MC, Chan HL, et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease--the role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther 2014;39:254-269.

108.   Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454-462.

109.   Sasso M, Beaugrand M, de Ledinghen V, Douvin C, Marcellin P, Poupon R, Sandrin L, et al. Controlled attenuation parameter (CAP): a novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol 2010;36:1825-1835.

110.   Shi KQ, Tang JZ, Zhu XL, Ying L, Li DW, Gao J, Fang YX, et al. Controlled attenuation parameter for the detection of steatosis severity in chronic liver disease: a meta-analysis of diagnostic accuracy. J Gastroenterol Hepatol 2014;29:1149-1158.

111.   Fierbinteanu Braticevici C, Sporea I, Panaitescu E, Tribus L. Value of acoustic radiation force impulse imaging elastography for non-invasive evaluation of patients with nonalcoholic fatty liver disease. Ultrasound Med Biol 2013;39:1942-1950.

112.   Liu H, Fu J, Hong R, Liu L, Li F. Acoustic Radiation Force Impulse Elastography for the Non-Invasive Evaluation of Hepatic Fibrosis in Non-Alcoholic Fatty Liver Disease Patients: A Systematic Review & Meta-Analysis. PLoS One 2015;10:e0127782.

113.   Cassinotto C, Boursier J, de Ledinghen V, Lebigot J, Lapuyade B, Cales P, Hiriart JB, et al. Liver stiffness in nonalcoholic fatty liver disease: A comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 2016;63:1817-1827.

114.   Zheng J, Guo H, Zeng J, Huang Z, Zheng B, Ren J, Xu E, et al. Two-dimensional shear-wave elastography and conventional US: the optimal evaluation of liver fibrosis and cirrhosis. Radiology 2015;275:290-300.

115.   Pavlov CS, Casazza G, Nikolova D, Tsochatzis E, Burroughs AK, Ivashkin VT, Gluud C. Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. Cochrane Database Syst Rev 2015;1:CD010542.

116.   Nahon P, Kettaneh A, Tengher-Barna I, Ziol M, de Ledinghen V, Douvin C, Marcellin P, et al. Assessment of liver fibrosis using transient elastography in patients with alcoholic liver disease. J Hepatol 2008;49:1062-1068.

117.   Kim SG, Kim YS, Jung SW, Kim HK, Jang JY, Moon JH, Kim HS, et al. [The usefulness of transient elastography to diagnose cirrhosis in patients with alcoholic liver disease]. Korean J Hepatol 2009;15:42-51.

118.   Janssens F, de Suray N, Piessevaux H, Horsmans Y, de Timary P, Starkel P. Can transient elastography replace liver histology for determination of advanced fibrosis in alcoholic patients: a real-life study. J Clin Gastroenterol 2010;44:575-582.

119.   Fernandez M, Trepo E, Degre D, Gustot T, Verset L, Demetter P, Deviere J, et al. Transient elastography using Fibroscan is the most reliable noninvasive method for the diagnosis of advanced fibrosis and cirrhosis in alcoholic liver disease. Eur J Gastroenterol Hepatol 2015;27:1074-1079.

120.   Mueller S, Englert S, Seitz HK, Badea RI, Erhardt A, Bozaari B, Beaugrand M, et al. Inflammation-adapted liver stiffness values for improved fibrosis staging in patients with hepatitis C virus and alcoholic liver disease. Liver Int 2015;35:2514-2521.

121.   Thiele M, Detlefsen S, Sevelsted Moller L, Madsen BS, Fuglsang Hansen J, Fialla AD, Trebicka J, et al. Transient and 2-Dimensional Shear-Wave Elastography Provide Comparable Assessment of Alcoholic Liver Fibrosis and Cirrhosis. Gastroenterology 2016;150:123-133.

122.   Nguyen-Khac E, Chatelain D, Tramier B, Decrombecque C, Robert B, Joly JP, Brevet M, et al. Assessment of asymptomatic liver fibrosis in alcoholic patients using fibroscan: prospective comparison with seven non-invasive laboratory tests. Aliment Pharmacol Ther 2008;28:1188-1198.

123.   Mueller S, Millonig G, Sarovska L, Friedrich S, Reimann FM, Pritsch M, Eisele S, et al. Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. World J Gastroenterol 2010;16:966-972.

124.   Trabut JB, Thepot V, Nalpas B, Lavielle B, Cosconea S, Corouge M, Vallet-Pichard A, et al. Rapid decline of liver stiffness following alcohol withdrawal in heavy drinkers. Alcohol Clin Exp Res 2012;36:1407-1411.

125.   Bardou-Jacquet E, Legros L, Soro D, Latournerie M, Guillygomarc'h A, Le Lan C, Brissot P, et al. Effect of alcohol consumption on liver stiffness measured by transient elastography. World J Gastroenterol 2013;19:516-522.

126.   Corpechot C, Gaouar F, El Naggar A, Kemgang A, Wendum D, Poupon R, Carrat F, et al. Baseline values and changes in liver stiffness measured by transient elastography are associated with severity of fibrosis and outcomes of patients with primary sclerosing cholangitis. Gastroenterology 2014;146:970-979; quiz e915-976.

127.   Engelmann G, Gebhardt C, Wenning D, Wuhl E, Hoffmann GF, Selmi B, Grulich-Henn J, et al. Feasibility study and control values of transient elastography in healthy children. Eur J Pediatr 2012;171:353-360.

128.   Behairy Bel S, Sira MM, Zalata KR, Salama el SE, Abd-Allah MA. Transient elastography compared to liver biopsy and morphometry for predicting fibrosis in pediatric chronic liver disease: Does etiology matter? World J Gastroenterol 2016;22:4238-4249.

129.   Ferraioli G, Calcaterra V, Lissandrin R, Guazzotti M, Maiocchi L, Tinelli C, De Silvestri A, et al. Noninvasive assessment of liver steatosis in children: the clinical value of controlled attenuation parameter. BMC Gastroenterol 2017;17:61.

130.   Belei O, Sporea I, Gradinaru-Tascau O, Olariu L, Popescu A, Simedrea I, Marginean O. Comparison of three ultrasound based elastographic techniques in children and adolescents with chronic diffuse liver diseases. Med Ultrason 2016;18:145-150.

131.   Matos H, Trindade A, Noruegas MJ. Acoustic radiation force impulse imaging in paediatric patients: normal liver values. J Pediatr Gastroenterol Nutr 2014;59:684-688.

132.   Hanquinet S, Rougemont AL, Courvoisier D, Rubbia-Brandt L, McLin V, Tempia M, Anooshiravani M. Acoustic radiation force impulse (ARFI) elastography for the noninvasive diagnosis of liver fibrosis in children. Pediatr Radiol 2013;43:545-551.

133.   Franchi-Abella S, Corno L, Gonzales E, Antoni G, Fabre M, Ducot B, Pariente D, et al. Feasibility and Diagnostic Accuracy of Supersonic Shear-Wave Elastography for the Assessment of Liver Stiffness and Liver Fibrosis in Children: A Pilot Study of 96 Patients. Radiology 2016;278:554-562.

134.   Ferraioli G, Tinelli C, Lissandrin R, Zicchetti M, Bernuzzi S, Salvaneschi L, Filice C, et al. Ultrasound point shear wave elastography assessment of liver and spleen stiffness: effect of training on repeatability of measurements. Eur Radiol 2014;24:1283-1289.

135.   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.

136.   Seijo S, Reverter E, Miquel R, Berzigotti A, Abraldes JG, Bosch J, Garcia-Pagan JC. Role of hepatic vein catheterisation and transient elastography in the diagnosis of idiopathic portal hypertension. Dig Liver Dis 2012;44:855-860.

137.   Colecchia A, Colli A, Casazza G, Mandolesi D, Schiumerini R, Reggiani LB, Marasco G, et al. Spleen stiffness measurement can predict clinical complications in compensated HCV-related cirrhosis: a prospective study. J Hepatol 2014;60:1158-1164.

138.   Ying L, Lin X, Xie ZL, Tang FY, Hu YP, Shi KQ. Clinical utility of acoustic radiation force impulse imaging for identification of malignant liver lesions: a meta-analysis. Eur Radiol 2012;22:2798-2805.

139.   Yu H, Wilson SR. Differentiation of benign from malignant liver masses with Acoustic Radiation Force Impulse technique. Ultrasound Q 2011;27:217-223.

140.   Onur MR, Poyraz AK, Ucak EE, Bozgeyik Z, Ozercan IH, Ogur E. Semiquantitative strain elastography of liver masses. J Ultrasound Med 2012;31:1061-1067.

141.   Guibal A, Boularan C, Bruce M, Vallin M, Pilleul F, Walter T, Scoazec JY, et al. Evaluation of shearwave elastography for the characterisation of focal liver lesions on ultrasound. Eur Radiol 2013;23:1138-1149.

142.   Liu BJ, Li DD, Xu HX, Guo LH, Zhang YF, Xu JM, Liu C, et al. Quantitative Shear Wave Velocity Measurement on Acoustic Radiation Force Impulse Elastography for Differential Diagnosis between Benign and Malignant Thyroid Nodules: A Meta-analysis. Ultrasound Med Biol 2015;41:3035-3043.