Section A -Research paper

Assessment of Liver Stiffness by Elastography in Patients with Hepatitis C

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Abstract:

Study of the possible changes in liver stiffness in hepatitis c patients following treatment with new drugs by noninvasive techniques as elsatogram to be assured more about the effect of this drug on liver stiffness and How can we optimize its use to get the best benefits.

Keywords: USE, Stiffness, Liver.

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Introduction:

Ultrasound elastography (USE) is an imaging technology sensitive to tissue stiffness that was first described in the 1990s. It has been further developed and refined in recent years to enable quantitative assessments of tissue stiffness. Elastography methods take advantage of the changed elasticity of soft tissues resulting from specific pathological or physiological processes. For instance, many solid tumors are known to differ mechanically from surrounding healthy tissues(**1).**

Similarly, fibrosis associated with chronic liver diseases causes the liver to become stiffer than normal tissues. Elastography methods can hence be used to differentiate affected from normal tissue for diagnostic applications (**2**).

Conventional ultrasound (US) has the advantage of being an inexpensive, versatile, and widely available modality that can be used at the bedside, which also applies to USE. USE has been explored for several clinical applications in recent years and has been introduced into clinical routine for specific applications such as liver fibrosis assessment or breast lesion characterization(**3).**

Elasticity imaging by USE provides complementary information to conventional US by adding stiffness as another measurable property to current US imaging techniques (**4**).

1.Principles and Techniques of Ultrasound Elastography

The following provides a summary of USE physics and current techniques. (**5).**

Ultrasound elastography physics

Elastography assesses tissue elasticity, which is the tendency of tissue to resist deformation with an applied force, or to resume its original shape after removal of the force. Assuming that a material is entirely elastic and its deformation has no time dependency (i.e. viscosity), elasticity can be described by Hooke's Law **(1)**:

2. Classification & types:

Ultrasound elastography techniques:

The different currently available USE techniques can be classified by the measured physical quantity (Figure 1) **(1)**

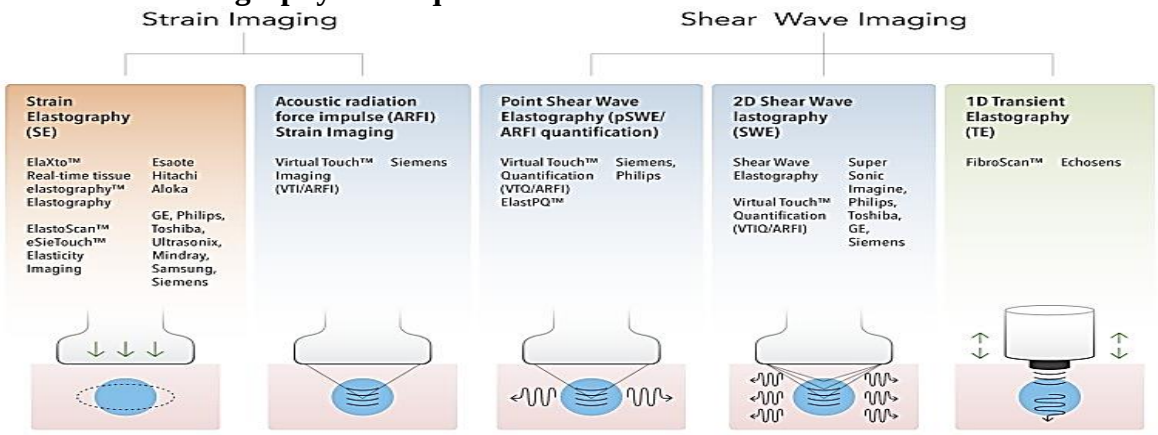

Figure 1: Ultrasound Elastography Techniques. Currently available USE techniques can be categorized by the measured physical quantity: 1) strain imaging (left), and 2) shear wave imaging (right). Excitations methods include quasi-static mechanically induced displacement via active external compression or passively induced physiologic motion (orange), dynamic mechanically induced compression via a "thumping" transducer at the tissue surface to produce shear waves (green), and dynamic ultrasound-induced tissue displacement and shear waves by acoustic radiation force impulse excitation (blue) **(1)**.

1) Strain imaging: In this technique, a normal stress σn is applied to tissue and the normal strain εn is measured (**6**).
2) Shear wave imaging (SWI): In this technique, a dynamic stress is applied to tissue by using a mechanical vibrating device in 1D transient elastography (1D-TE) or acoustic radiation force in point shear wave elastography (pSWE) and 2D shear wave elastography (2D-SWE). Shear waves created by the excitation are measured perpendicular to the acoustic radiation force application or parallel to the 1D transient elastography excitation.

I Strain imaging:

Strain imaging was the first introduced USE technique **(7)** and there are two approaches for strain imaging using ultrasound: Strain elastography (SE) and acoustic radiation force impulse (ARFI) strain imaging.

a) Strain Elastography:

Strain elastography can be further subdivided by the excitation method:

1) In he first method, the operator exerts manual compression on the tissue with the ultrasound transducer. Manual compression works fairly well for superficial organs such as the breast and thyroid but is challenging for assessing elasticity in deeper located organs such as the liver (**8).**
2) In the second excitation method, the ultrasound transducer is held steady, and tissue displacement is generated by internal physiologic motion (e.g. cardiovascular, respiratory). Since this method is not dependent on superficially applied compression, it may be used to assess deeper located organs (**9**).

b) Acoustic radiation force impulse (ARFI) strain imaging:

This is an alternative approach for measuring strain. In this technique a short-duration (0.1-0.5 ms) high-intensity (spatial peak pulse average = 1400 W/cm2, spatial peak temporal average = 0.7 W/cm2) acoustic "pushing pulse" (acoustic radiation force) is used to displace tissue (displacement of ~ 10-20 μm) in the normal direction, i.e. perpendicular to the surface (**10).**

II Shear wave imaging: (SWI)

In contrast to strain imaging, which measures physical tissue displacement parallel to the applied normal stress, SWI employs a dynamic stress to generate shear waves in the parallel or perpendicular dimensions. Measurement of the shear wave speed results in qualitative and quantitative estimates of tissue elasticity. There are currently three technical approaches for SWI: 1) 1 dimensional transient elastography (1D-TE), 2) point shear wave elastography (pSWE), and 3) 2-dimensional shear wave elastography (2D-SWE). The main characteristics of each method are summarized in Table (1) **(1)**.

Table 1: Summary of Shear Wave Imaging methods **(1)**.

PswE	2D-SWE	1D-TE
• Excitation method: dynamic stress by ARFI, in the normal direction, in a single focal location. • Shear waves measured perpendicular to plane of excitation. • Shear wave speed (C.) reported or converted in Young's modulus (E) to provide quantitative estimate of tissue elasticity. • Operator can use B-mode US to directly visualize and select ROI. • Does not show an image of stiffness. • Can be performed on conventional US machine using standard ultrasound	• Excitation method: dynamic stress by ARFI, in the normal direction in multiple focal zones • Shear waves measured perpendicular to ARFI application. • Multiple focal zones are interrogated in rapid succession, faster than the shear wave speed, creating a near cylindrical shear wave cone, allowing real-time monitoring of shear waves in 2D for measurement of Cs or E and generation of quantitative elastograms. • Operator is guided by both anatomical and tissue stiffness information, has real-time visualization of a color box; quantitative	• Excitation method: dynamic stress by a mechanical vibrating device. • Shear waves measured parallel to excitation. Stiffness estimated along ultrasonic A-line, in a fixed region, neither user adjustable nor image guided. • Operator selects imaging area using time-motion ultrasound, based on multiple A-mode lines in time at different proximal locations forming low quality image. The same probe uses A-mode US to measure Cs and E is calculated. • First system commercially available. The most widely used and validated technique for assessment of liver

probe.	elastogram superimposed on a B-mode image stiffness information.	fibrosis.

a) 1D Transient Elastography:

The first SWI system commercially available was a 1D-TE system FibroScanTM (Echosens, Paris, France) for assessment of the liver. It is the most widely used and validated technique for assessment of liver fibrosis, and it is often used by clinicians in the office (**11).**

The FibroscanTM probe is a single device that contains both an ultrasound transducer and a mechanical vibrating device. Although 1D-TE is an US-based technique, it is used without direct B-mode image guidance. The operator selects the imaging area using time-motion ultrasound (based on multiple A-mode lines in time at different proximal locations assembled to form a low quality image) to locate a liver portion 2.5 - 6.5 cm below the skin surface and free of large vascular structures. The mechanical vibrating device then exerts a controlled vibrating external “punch” on the body surface to generate shear waves which propagate through the tissue **(12).**

Measurements assess a tissue volume of approximately 1 cm wide x 4 cm long, which is >100 times larger than the average volume of a biopsy sample. (**13)**

The examiner takes repeated measurements with the following criteria for validation: (1) at least 10 valid measurements, (2) ratio of number of valid measurements to the total number of measurements is ≥ 60%, (3) interquartile range (IQR), which reflects the variability of measurements, is less than 30% of the median value of liver stiffness measurements. The entire exam takes approximately 5 minutes (**14).**

Point shear wave elastography:

In this technique, ARFI is used to induce tissue displacement in the normal direction in a single focal location, similar to ARFI strain imaging. Unlike ARFI strain imaging, the tissue displacement itself is not measured. Instead, a portion of the longitudinal waves generated by ARFI is intra-converted to shear waves through the absorption of acoustic energy. The speed of the shear waves perpendicular to the plane of excitation *cs* are measured (**15).**

In liver applications, there are several advantages of pSWE compared to 1D-TE. First, the operator can use B-mode US to directly visualize the liver to select a uniform area of liver parenchyma without large vessels or dilated bile ducts. pSWE produces shear waves which originate locally inside the liver, making pSWE less affected by ascites and obesity (**16).**

b) Two-dimensional (2D) Shear wave elastography:

Two-dimensional (2D) SWE is the currently newest SWI method that uses acoustic radiation force. Instead of a single focal location as in ARFI strain imaging and pSWE, multiple focal zones are interrogated in rapid succession, faster than the shear wave speed. This creates a near cylindrical shear wave cone, allowing real-time monitoring of shear waves in 2D for measurement of shear wave speed or Young's modulus *E* and generation of quantitative elastograms **(17).**

The advantages of this technique include real-time visualization of a color quantitative elastogram superimposed on a B-mode image, enabling the operator to be guided by both anatomical and tissue stiffness information **(18).**

3. Clinical Applications of Ultrasound Elastography as regard to Liver:

1) Diffuse Liver Disease:

The multiple causes of chronic liver disease (CLD) (including hepatitis viral disease, nonalcoholic fatty liver disease, alcoholic liver disease and autoimmune liver disease) follow a common pathway towards liver fibrosis and finally cirrhosis, increasing the risk for the development of portal hypertension (PH), hepatic insufficiency, and hepatocellular carcinoma (HCC) (**19).**

Currently, liver biopsy is the best available reference standard for evaluating and classifying stages of liver fibrosis/cirrhosis, with the METAVIR score being the most widely used histopathologic grading system. According to this system, the fibrosis stages are: F0= normal liver, F1= minimal fibrosis, F2= significant fibrosis, F3= severe fibrosis and F4= cirrhosis (**20).**

However, liver biopsy has several limitations. It is invasive and can cause minor complications including temporary pain in approximately 20% of cases. Major complications, such as bleeding, hemobilia, bile peritonitis, bacteremia, sepsis, pneumothorax, hemothorax and even death, occur in 1.1% of liver biopsies. (**21)**

Liver biopsy is also limited by under-sampling, with a typical biopsy core only representing roughly 1/50,000 of the entire liver volume. Inter-observer agreement among pathologists in grading liver fibrosis/cirrhosis is also not perfect, with kappa statistic ranging from 0.5 to 0.9, depending on the pathologist's expertise **(22).**

Accurate staging of liver fibrosis/cirrhosis is important since treatment recommendations vary by the type of CLD. Evidence supports treatment for all patients infected with Hepatitis C virus (HCV). However, in places where resources are limited, the stage of liver fibrosis is used to prioritize treatment (**23).**

For example, patients with F3 or F4 fibrosis are at the highest priority for treatment due to the risk of severe complications, whereas those with F2 fibrosis are at high but lesser priority for treatment owing to relatively lower risk of complications (**24).**

For Hepatitis B virus (HBV), patients with a minimum F2 fibrosis and HBV DNA > 2000 IU/ml are being considered for

antiviral therapy even if their alanine aminotransferase (ALT) levels are below two times the upper limits of normal (**25).**

A quantitative non-invasive test such as USE that allows accurate longitudinal monitoring of liver stiffness would be clinically helpful with these therapeutic decisions (**26)**.

Since the liver becomes stiffer as fibrosis progresses due to collagen deposition and microstructural changes, USE has the potential to monitor these histopathologic changes through noninvasive quantitative measures of liver stiffness, using different stiffness cut-off values to simulate the METAVIR score (**27).**

Assessment of Liver Fibrosis with Different Liver Elastography Techniques:

A standardized liver elastography technique is critical to obtain reliable and accurate results. The patient is imaged in supine or slight (30º) left lateral decubitus position, with the right arm elevated above the head to open the intercostal spaces and improve the acoustic window to the liver. Since cardiac motion can confound elastography measurements, it is recommended to sample measurements in the right liver lobe, which has shown the most reliable results (**28).**

Transducer pressure on the skin should be similar to regular anatomical B-mode imaging. When using SWE techniques, the acoustic radiation force push pulse should be applied perpendicular to the liver capsule, with measurements obtained 4-5 cm deep to the skin and within a minimum 1-2 cm of liver parenchyma to limit refraction of the pulse **(29).**

Since the assessed tissue extends 1.0 cm above and below the user-designated region of intensity (ROI), the operator should verify that these areas are free of vascular and biliary structures and rib shadows. Furthermore, the patient needs to be coached in breathing (to stop breathing at the end of normal expiration or inspiration) so measurements are taken in a neutral position, as Valsalva maneuver or deep expiration can falsely increase stiffness measurements **(30).**

A) Liver 1D Transient Elastography:

One dimensional TE studies have found that liver stiffness values correlated with histopathologic fibrosis stages in CLD patients. A recent large multicenter 2-phase study in the United States in patients with HCV (n = 700) or HBV (n = 53) compared 1D-TE with liver biopsy. In phase 1 of the study optimal stiffness cut-off values for identification of F2 to F4 fibrosis were identified, and in phase 2 the cut-off values were tested in a second and different patient cohort (**1).**

The presence of hepatic fibrosis in people with alcoholic liver disease. Based on the METAVIR histopathological score for interpreting liver biopsy, there are five stages of hepatic fibrosis **(31).**

The used cut-off values were correlated to METAVIR fibrosis scoring system as follows: F0-F1: 2-7 kpa (fibrosis exists with expansion of portal zones), F2: 7- 9.5 kpa (fibrosis exists with expansion of most portal zones and occasional bridging), F3: 9.5-12.5 kpa

(fibrosis exists with expansion of most portal zones and marked bridging), and F4 >12.5 kpa (presence of cirrhosis) **(32)**.

F0 indicates no fibrosis, F1 indicates portal fibrous expansion, F2 indicates thin fibrous septa emanating from portal triads, F3 indicates fibrous septa bridging portal triads and central veins, and F4 indicates cirrhosis **(31).**

1D-TE showed reasonably high area under the receiver operating characteristic curves (AUROCs) in the HCV group, confirming previous results indicating that 1D-TE allows staging of significant fibrosis (**1).**

A meta-analysis comprised of mostly Asian studies using 1D-TE with 2772 chronic HBV patients found similar results (AUROC F≥2 0.86, F≥3 0.89, F4 0.93) (**33).**

Another meta-analysis of 50 studies in patients with various etiologies of CLD (n=518) using liver biopsy as the reference standard highlighted that 1D-TE was more accurate in diagnosing F4 fibrosis than F2 or F3 fibrosis (AUROC F4 0.93 vs. F≥2 0.87, F≥3 0.91), regardless of the underlying cause of liver disease (**34**).

Overall, 1D-TE is considered useful to diagnose cirrhosis (F4 fibrosis) and for distinguishing significant (≥ F2) from non-significant (F0 and F1) fibrosis. However, distinguishing between individual fibrosis stages is still not well validated (**35)**.

B) Liver Point Shear Wave Elastography:

1D-TE (FibroScanTM) was slightly more accurate than pSWE in diagnosing significant fibrosis (AUROC of 0.92 vs. 0.87) and cirrhosis (0.97 vs. 0.93). In contrast, another meta-analysis which included 1163 patients with CLD found that pSWE (VTQ/ARFI) showed similar predictive value to that of 1D-TE for significant fibrosis (AUROC 0.74 vs. 0.78) and cirrhosis (0.87 vs. 0.89) (**36).**

C) Liver 2D Shear Wave Elastography:

Among the four US systems that have 2D-SWE (as described above), Shear WaveTM Elastography by SuperSonic Imagine (SSI) is currently the most validated system for assessing liver fibrosis. The first study comparing 2D-SWE (SSI) and 1D-TE was performed in 121 patients with chronic HCV using liver biopsy as a reference standard. 2D-SWE was more accurate than 1D-TE in assessing significant fibrosis (F≥2) (AUROC of 0.92 vs. 0.84; p=0.002) (**37**).

In an intra-individual prospective comparison study comparing 2D-SWE (SSI), pSWE (VTQ/ARFI) and 1D-TE (FibroscanTM) in 349 consecutive patients and using liver biopsy as gold standard, 2D-SWE was shown to have higher diagnostic accuracy than 1D-TE in the diagnosis of severe fibrosis (F≥3) (AUROC of 0.93 vs. 0.87; p=0.0016, respectively) and higher than pSWE in the diagnosis of significant fibrosis (F≥2) (AUROCs of 0.88 vs. 0.81; p = 0.0003, respectively). **(38).**

In another study there was no significant difference in AUROCs for 2D-SWE, pSWE, and 1D-TE in the diagnosis of significant fibrosis (F≥2: 0.87, 0.92, 0.91), advanced fibrosis (F≥3: 0.91, 0.93, 0.94) and liver cirrhosis (F=4: 0.88, 0.90, 0.89), respectively between the three methods (**39)**.

2) Severity of Portal Hypertension:

Portal hypertension (PH) is one of the most important complications of CLD and cirrhosis. When portal pressures and hepatic venous pressure gradient (HVPG) rise to a level the body cannot compensate for, complications such as ascites, variceal bleeding, and hepatic encephalopathy may develop. At an HVPG ≥ 10 mmHg, patients have clinically significant PH and are at high risk of developing varices **(40).**

At an HVPG ≥ 12 mmHg, PH is defined to be severe with an increased risk for acute variceal bleeding, which bears a mortality rate of approximately 15%. The gold standards to assess PH in cirrhotic patients are the direct measurement of HVPG using angiographic techniques as well as upper gastrointestinal endoscopy to assess for the presence and grade of esophageal varices; both are invasive tests (**41)**.

Ultrasound elastography may become a non-invasive alternative by measuring liver stiffness (LS) and/or spleen stiffness (SS). In SS, the same techniques are applied in the spleen as described above for the liver. (**1).**

Recent studies using 1D-TE found that LS was more accurate than SS for the diagnosis of clinically significant PH (AUROCs of 0.95 vs. 0.85; 0.78 vs. 0.63) (**42).**

In contrast, another study in 60 cirrhotic patients examined with pSWE and using HVPG as a reference standard found that SS was the most accurate test in diagnosing both clinically significant (AUROC: 0.943) and severe PH (AUROC: 0.963). In that study, SS cut-off values of 3.36 m/s and 3.51 m/s identified patients with esophageal varices and high-risk esophageal varices, respectively, with a negative predictive value of 96.6% and 97.4% respectively (**43)**.

Several additional studies have found SS to be predictive of esophageal varices. For example, a study using pSWE of the spleen in 340 cirrhotic patients and 16 healthy volunteers with invasive endoscopy as the reference standard found that a shear wave velocity cut-off value of 3.30 m/s identified high risk esophageal varices with a negative predictive value, sensitivity and accuracy of 0.994, 0.989 and 0.721 respectively. (**1)**.

Overall results suggest that both SS and LS are promising parameters that may allow non-invasive screening for PH and the presence of esophageal varices. Additional studies are needed to further validate current results and to assess whether LS, SS, or the combination of the two result in the most accurate assessment (**42)**.

3)Characterization of Focal Liver Lesions:

Currently, the use of ultrasound elastography for characterization of focal liver lesions (FLLs) is still investigational but a few studies have shown promising results (**1)**.

A meta-analysis of 6 studies (4 using pSWE, 2 SE) with histology as the gold standard showed that the pooled sensitivity, specificity, positive likelihood ratio (LR), and negative LR of elastography for the differentiation of malignant from benign lesions were 85%, 84%, 5.69 and 0.17, respectively, with a summary AUROC of 0.93. In another recent study, a cut-off value of 2.52 m/s using virtual touch tissue quantification (VTQ) of acoustic radiation

force impulse (ARFI) VTQ/ARFI allowed differentiation of malignant from benign FLLs with a sensitivity and specificity of 97% and 66%, respectively (**44).**

Since FLLs may occur on different background liver parenchyma, it was reasoned that reporting the ratios (SWV ratio or stiffness ratio) between values obtained in the FLL and the surrounding liver tissue could be more accurate. However, a recent study with VTQ/ARFI in 134 patients with FLLs found that a cut-off values of 2.13 m/s for SWV showed superior performance (sensitivity and specificity of 83.3% and 77.9%, respectively) compared to a cut-off value of 1.37 for SWV ratio (59.6% and 77.3%, respectively) in differentiating malignant from benign FLLs. This was also shown in a larger-scale study in 373 patients using pSWE (by Philips) with an AUROC of 0.87 vs. 0.67, sensitivity of 74% vs. 82% and specificity of 84% vs. 28% (**45).**

To date, the evaluation of USE for FLL characterization appears limited and large ranges of stiffness values for both benign and malignant lesions have been reported, with HCC SWV values ranging from 1.15 m/s (soft) to > 4.0 m/s (stiff) in one study (**46).**

This variability could reflect tumor heterogeneity since inclusion of internal hemorrhage or necrosis in malignant tumors decreases stiffness (**1)**.

Although benign lesions are in general softer than malignant lesions, some benign lesions such as focal nodular hyperplasia (FNH), which is mainly composed of hyperplastic hepatic cells and vessels, also have fibrous septa and a central scar which can increase its stiffness. More research is warranted before USE can be recommended for characterization of focal liver lesions (**1)**.

4)Elastography: Fatty Liver Assessment:

Controlled Attenuation Parameter (CAP)

Vibration-controlled transient elastography (VCTE) (FibroScan®, EchoSens, Paris, France) is an ultrasound-based elastography technique developed more than 15 years ago, firstly used for fibrosis assessment in chronic liver diseases. It is the most validated elastography technique, accepted by international guidelines as a reliable tool to quantify liver fibrosis (**47).**

VCTE measures the velocity of shear waves generated inside the liver by a mechanical impulse. In CLD, liver stiffness increases with the progression of fibrosis. The stiffer the liver is, the higher the shear waves' velocity (**48).**

Several years later, CAP feature was added to the FibroScan® device. It measures the attenuation of the US beam as it passes through the liver. CAP correlates with the viscoelastic characteristics of the liver, dependent in their turn on the quantity of fat droplets in the hepatocytes. CAP measurements can be performed by either the M or XL probes (chosen according to the skin to liver capsule distance), and the results are expressed in decibels per meter (dB/m), ranging from 100 to 400 dB/m (**49).**

At the beginning, CAP was available only on the M probe of the FibroScan®.

Later, it was implemented also on the XL probe developed for obese subjects (**48).**

The initial studies regarding CAP showed excellent feasibility-92.3% of cases with only the M probe, improved to 96.8% when both M and XL probes have been used, also with excellent reproducibility, inter-rater agreement 0.82–0.84 with the M probe, but lower with the XL probe, 0.75 and 0.65, respectively (**50).**

No quality technical parameters have been recommended by the producers to ensure reliable measurements. Therefore, most authors used the quality criteria recommended for VCTE: 10 valid measurements with an IQR/M < 30% (**51).**

A study published in 2017 recommended as a quality criterion for CAP measurements an IQR < 40 dB/m (**52**).

When this quality criterion was used, the AUROC of CAP to assess steatosis as compared to liver biopsy increased from 0.77 to 0.9. Another study has set the IQR upper limit at 30 dB/m, while another study found no difference in CAP performance when the IQR was ≥30 dB/m or ≥40 dB/m (**53).**

A recently published study demonstrated that CAP-IQR/M < 0.3 as a quality criterion improves accuracy and feasibility of CAP measurements, performing better than the IQR < 40 dB/m criterion (**54).**

Several studies demonstrated that CAP measurements are not influenced by the severity of liver fibrosis, nor by the presence of cirrhosis (**55**).

However, several factors have been proven to influence CAP values, among them BMI, the presence of diabetes and etiology, especially NAFLD, while CAP values higher than 300 dB/m may lead to an overestimation of fibrosis severity by VCTE in patients with lower stages of fibrosis (**56).**

The controlled attenuation parameter (CAP) measured by transient elastography (TE) is an easy and rapid noninvasive examination method for the detection of hepatic steatosis. It is based on the physical phenomenon that the amplitude of ultrasound waves is attenuated more quickly when they traverse across a steatotic liver (**57**).

TE can also quantify the speed of a mechanically induced shear wave in liver tissue and hence generate a parameter called liver stiffness measurement (LSM) to estimate liver fibrosis (**58).**

CAP is measured simultaneously with LSM, making it possible to assess hepatic steatosis and fibrosis at the same time. Studies with CAP have been performed in NAFLD, alcoholic liver disease, and viral hepatitis, but very few data are available on AILDs (**53).**

It has been showed that in patients with chronic viral hepatitis and advanced liver fibrosis, CAP performed better than ultrasound for assessing liver steatosis. Besides, a recent meta-analysis showed that CAP diagnosed moderate and severe hepatic steatosis with diagnostic accuracies above 0.85 in patients with liver disease of mixed etiology. However, the analysis did not include patients with AILDs (**59).**

CAP cut-off values indicating liver steatosis (S) were adapted from the study by Kamali et al. as follows: (1) <237 dB/m (S0, no steatosis), (2) 237.0-259.0 dB/m (S1,

mild steatosis), (3) 259.0-291.0 dB/m (S2, moderate steatosis), and (4) 291.0-400.0 dB/m (S3, severe steatosis) **(60).**

Limitations of Liver Ultrasound Elastography:

Liver USE measurements can be confounded by both pathologic and normal physiologic processes. Notably, since the liver is surrounded by a stiff minimally distensible capsule (Glisson's capsule), any increase in liver volume also increases its stiffness and elevates elasticity measurements (**61).**

Besides physiologic differences such as the patient's level of inspiration and expiration and postprandial state, several disease processes including liver inflammation, passive hepatic congestion for example in cardiac insufficiency, cholestasis and hepatic steatosis, have been reported to influence USE measurements **(5).**

Presence of hepatic steatosis as a possible confounder warrants further discussion since inconsistent results have been reported in the literature on the effects of hepatic steatosis on shear wave measurements **(62).**

Using 1D-TE in 253 biopsy-proven patients with non-alcoholic fat liver disease (NAFLD), Petta et al found that steatosis grade was an independent predictor of higher liver stiffness measurement (p=0.03), leading to a false-positive rate of 23.6% in the diagnosis of significant liver fibrosis (**63).**

A multi-center 1D-TE study including 650 patients with chronic HCV assessed the influence of steatosis on liver stiffness USE measurements with comparison to quantitative and precise morphometric measurements of liver histology obtained by biopsy. The liver biopsy histology slides were scanned to obtain high quality images to be evaluated by morphometry. They found that 12.6% of F0/1 were misclassified as F2 when the steatosis area of the liver specimen (area of steatosis vesicles over complete liver surface estimated by morphometry) was < 4.0 %. When the steatosis area was ≥ 4%, the rate of misclassification rose to 32.4% **(63).**

However, other studies suggested that presence of steatosis did not influence fibrosis estimation. Samir et al used 2D-SWE (SSI) to evaluate 136 patients with CLD, and found that steatosis did not correlate with SWE measurements obtained in the upper right liver lobe (r=0.45, p=0.06), lower right liver lobe (r=0.26, p=0.09), and biopsy site (r=0.04, p=0.62)**. (30).**

Similarly, **Wong et al (64**) found no influence of the presence of steatosis on liver stiffness measurements (p=0.31)

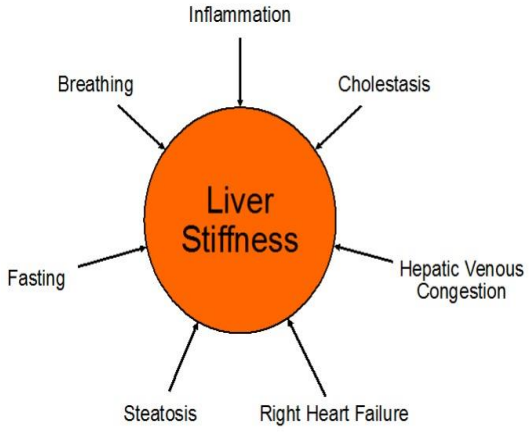

Figure 2: Pathologic and normal physiologic processes which can be confounders of liver stiffness measurements. Among other causes, right heart failure can lead to hepatic venous congestion with consecutive elevation of liver stiffness due to the increased venous pressure.

Increased levels of inspiration and expiration (Valsalva maneuver) can also increase liver stiffness and, therefore, patients need to be coached regarding breathing instructions when obtaining liver stiffness measurements **(1).**

Other limitations relate to the specific USE methods. Since in 1D-TE excitations are applied at the skin surface, it is limited by patient obesity, narrow intercostal spaces and the presence of perihepatic ascites **(65).**

Also, 1D-TE requires specialized equipment and annual or biannual probe recalibration. The equipment does not provide B-mode images, which can limit selection of an appropriate sampling area. These factors contribute to a high rate of unreliable results (approximately 16%) with 1D-TE **(1).**

The newer methods including pSWE and 2D-SWE are available on conventional US systems and do not require specialized equipment. However, greater technical and anatomical expertise is needed with these methods, which are therefore usually performed by a radiologist or sonographer. Finally, since both pSWE and 2D-SWE are newer technologies compared to 1D-TE, more validation studies are needed to assess their diagnostic accuracy in grading liver fibrosis, prediction of esophageal varices, or characterization of FLLs **(66).**

References:

1. **Sigrist RMS, Liau J, Kaffas AE, Chammas MC, Willmann JK.** Ultrasound Elastography: Review of Techniques and Clinical Applications. Theranostics. 2017;7(5):1303-1329.
2. **Kennedy, P., Wagner, M., Castéra, L., Hong, C. W., Johnson, C. L., Sirlin, C. B., & Taouli, B. (2018).** Quantitative elastography methods in liver disease: current evidence and future directions. *Radiology*, *286*(3), 738-763.
3. **Qian X, Wodnicki R, Kang H, Zhang J, Tchelepi H, Zhou Q.** Current ultrasound technologies and instrumentation in the assessment and monitoring of COVID-19 positive patients. IEEE transactions on ultrasonics, ferroelectrics, and frequency control. 2020 Aug 28;67(11):2230-40.
4. **Elbeblawy YM, Eshaq Amer Mohamed M.** Strain and shear wave ultrasound elastography in evaluation of chronic inflammatory disorders of major salivary glands. Dentomaxillofacial Radiology. 2020 Mar;49(3):20190225.
5. **Tang A, Cloutier G, Szeverenyi NM, Sirlin CB**. Ultrasound Elastography and MR Elastography for Assessing Liver Fibrosis: Part 1, Principles and Techniques. American journal of roentgenology. 2015;205:22–32.
6. **Smiseth OA, Torp H, Opdahl A, Haugaa KH, Urheim S.** Myocardial strain imaging: how useful is it in clinical decision making?. European heart journal. 2016 Apr 14;37(15):1196-207.
7. **Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X.** Elastography: a quantitative method for imaging the elasticity of biological tissues. Ultrasonic imaging. 1991;13:111–34.
8. **Morikawa H, Fukuda K, Kobayashi S, Fujii H, Iwai S, Enomoto M. et al.** Real-time tissue elastography as a tool for the noninvasive assessment of liver stiffness in patients with chronic hepatitis C. Journal of gastroenterology. 2011;46:350–8.

9. **Gennisson JL, Deffieux T, Fink M, Tanter M.** Ultrasound elastography: principles and techniques. Diagnostic and interventional imaging. 2013;94:487–95.
10. **Faruk, T., Islam, M. K., Arefin, S., & Haq, M. Z. (2015).** The journey of elastography: background, current status, and future possibilities in breast cancer diagnosis. *Clinical breast cancer*, *15*(5), 313-324.
11. **Garra BS.** Elastography: history, principles, and technique comparison. Abdominal imaging. 2015;40:680–97.
12. **Dhyani M, Anvari A, Samir AE.** Ultrasound elastography: liver. Abdominal imaging. 2015;40:698–708.
13. **Konyalioglu E, Tarhan H, Cakmak O, Pala EE, Zorlu F.** Prostate cancer volume estimations based on transrectal ultrasonography-guided biopsy in order to predict clinically significant prostate cancer. International braz j urol. 2015 May;41:442-8.
14. **Mulabecirovic A, Mjelle AB, Gilja OH, Vesterhus M, Havre RF.** Repeatability of shear wave elastography in liver fibrosis phantoms—Evaluation of five different systems. PLoS One. 2018 Jan 2;13(1):e0189671.
15. **Nightingale K**. Acoustic Radiation Force Impulse (ARFI) Imaging: a Review. Current medical imaging reviews. 2011;7:328–39.
16. **Ferraioli G, Filice C, Castera L, Choi BI, Sporea I, Wilson SR. et al.** WFUMB Guidelines and Recommendations for Clinical Use of Ultrasound Elastography: Part 3: Liver. Ultrasound in medicine & biology. 2015;41:1161–79.
17. **Shiina T, Nightingale KR, Palmeri ML, Hall TJ, Bamber JC, Barr RG. et al.** WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 1: basic principles and terminology. Ultrasound in medicine & biology. 2015;41:1126–47.
18. **Cosgrove D, Piscaglia F, Bamber J, Bojunga J, Correas JM, Gilja OH. et al**. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. Ultraschall in der Medizin. 2013;34:238–53.
19. **Udompap P, Kim D, Kim WR**. Current and Future Burden of Chronic Nonmalignant Liver Disease. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2015;13:2031–41.
20. **Teufel-Schäfer U, Flechtenmacher C, Fichtner A, Hoffmann GF, Schenk JP, Engelmann G.** Transient elastography correlated to four different histological fibrosis scores in children with liver disease. European Journal of Pediatrics. 2021 Jul;180(7):2237-44.
21. **Thomaides-Brears HB, Alkhouri N, Allende D, Harisinghani M, Noureddin M, Reau NS, French M, Pantoja C, Mouchti S, Cryer DR.** Incidence of complications from percutaneous biopsy in chronic liver disease: a systematic review and meta-analysis. Digestive Diseases and Sciences. 2021 Jun 15:1-29.
22. **Kose S, Ersan G, Tatar B, Adar P, Sengel BE**. Evaluation of Percutaneous Liver Biopsy Complications in Patients with Chronic Viral Hepatitis. The Eurasian journal of medicine. 2015;47:161–4.
23. **Ehsan N, Sweed D, Elsabaawy M.** Evaluation of HCV-related liver fibrosis

post-successful DAA therapy. Egyptian Liver Journal. 2021 Dec;11(1):1-7.

24. **Axley P, Mudumbi S, Sarker S, Kuo YF, Singal A.** Patients with stage 3 compared to stage 4 liver fibrosis have lower frequency of and longer time to liver disease complications. PloS one. 2018 May 10;13(5):e0197117.
25. **Kawanaka M, Nishino K, Kawamoto H, Haruma K.** Hepatitis B: Who should be treated?-managing patients with chronic hepatitis B during the immune-tolerant and immunoactive phases. World Journal of Gastroenterology. 2021 Nov 11;27(43):7497.
26. **Panel AIHG.** Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015;62:932–54.
27. **Cheng JY, Wong GL.** Advances in the diagnosis and treatment of liver fibrosis. Hepatoma Research. 2017 Aug 8;3:156-69.
28. **Zhang YN, Fowler KJ, Ozturk A, Potu CK, Louie AL, Montes V, Henderson WC, Wang K, Andre MP, Samir AE, Sirlin CB.** Liver fibrosis imaging: A clinical review of ultrasound and magnetic resonance elastography. Journal of Magnetic Resonance Imaging. 2020 Jan;51(1):25-42.
29. **Ferraioli G, Barr RG, Farrokh A, Radzina M, Cui XW, Dong Y, Rocher L, Cantisani V, Polito E, D'Onofrio M, Roccarina D.** How to perform shear wave elastography. Part I. Medical Ultrasonography. 2022 Feb 16;24(1):95-106.
30. **Samir AE, Dhyani M, Vij A, Bhan AK, Halpern EF, Mendez-Navarro J. et al**. Shear-wave elastography for the estimation of liver fibrosis in chronic liver disease: determining accuracy and ideal site for measurement. Radiology. 2015;274:888–96.
31. **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 Jan 22;1(1):CD010542 .
32. **Castera L, Forns X, Alberti A**. Non-invasive evaluation of liver fibrosis using transient elastography. Journal of hepatology. 2008 May 1;48(5):835-47.
33. **Scarponi CF, Silva RD, Souza Filho JA, Guerra MR, Pedrosa MA, Mol MP.** Hepatitis delta prevalence in South America: a systematic review and meta-analysis. Revista da Sociedade Brasileira de Medicina Tropical. 2019 Jan 24;52
34. **Friedrich-Rust, M., Romen, D., Vermehren, J., Kriener, S., Sadet, D., Herrmann, E., ... & Bojunga, J. (2012).** Acoustic radiation force impulse-imaging and transient elastography for non-invasive assessment of liver fibrosis and steatosis in NAFLD. *European journal of radiology*, *81*(3), e325-e331.
35. **Afdhal NH, Bacon BR, Patel K, Lawitz EJ, Gordon SC, Nelson DR. et al.** Accuracy of fibroscan, compared with histology, in analysis of liver fibrosis in patients with hepatitis B or C: a United States multicenter study. Clinical gastroenterology and hepatology. 2015;13:772–9. e1-3.
36. **Bota S, Sporea I, Sirli R, Popescu A, Danila M, Jurchis A. et al.** 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. European journal of radiology. 2014;83:268–72.

37. **Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C. et al.** Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology. 2012;56:2125–33.
38. **Cassinotto C, Lapuyade B, Mouries A, Hiriart JB, Vergniol J, Gaye D. et al.** Non-invasive assessment of liver fibrosis with impulse elastography: comparison of Supersonic Shear Imaging with ARFI and FibroScan(R) Journal of hepatology. 2014;61:550–7.
39. **Gerber L, Kasper D, Fitting D, Knop V, Vermehren A, Sprinzl K. et al.** Assessment of liver fibrosis with 2-D shear wave elastography in comparison to transient elastography and acoustic radiation force impulse imaging in patients with chronic liver disease. Ultrasound in medicine & biology. 2015;41:2350–9.
40. **Castera L, Pinzani M, Bosch J.** Non invasive evaluation of portal hypertension using transient elastography. Journal of hepatology. 2012;56:696–703.
41. **Cabrera L, Tandon P, Abraldes JG**. An update on the management of acute esophageal variceal bleeding. Gastroenterologia y hepatologia; 2016.
42. **Zykus R, Jonaitis L, Petrenkiene V, Pranculis A, Kupcinskas L.** Liver and spleen transient elastography predicts portal hypertension in patients with chronic liver disease: a prospective cohort study. BMC gastroenterology. 2015;15:183.
43. **Elkrief L, Rautou PE, Ronot M, Lambert S, Dioguardi Burgio M, Francoz C. et al**. Prospective comparison of spleen and liver stiffness by using shear-wave and transient elastography for detection of portal hypertension in cirrhosis. Radiology. 2015;275:589–98.
44. **Goya C, Hamidi C, Yavuz A, Hattapoglu S, Uslukaya O, Cetincakmak MG**, The Role of Acoustic Radiation Force Impulse Elastography in the Differentiation of Infectious and Neoplastic Liver Lesions. Ultrasonic imaging; 2015.
45. **Lu Q, Ling W, Lu C, Li J, Ma L, Quan J. et al.** Hepatocellular carcinoma: stiffness value and ratio to discriminate malignant from benign focal liver lesions. Radiology. 2015;275:880–8.
46. **Simon V, Dudea SM, Crisan N, Stanca VD, Dudea-Simon M, Andras I, Mihaly ZA, Coman I.** Elastography in the Urological Practice: Urinary and Male Genital Tract, Prostate Excluded. Diagnostics. 2022 Jul 16;12(7):1727.
47. **Lim J. K., Flamm S. L., Singh S., et al.** American gastroenterological association institute guideline on the role of elastography in the evaluation of liver fibrosis. Gastroenterology. 2017;152(6):1536–1543.
48. **Sirli R, Sporea I.** Controlled Attenuation Parameter for Quantification of Steatosis: Which Cut-Offs to Use? Can J Gastroenterol Hepatol. 2021 Mar 26;2021:6662760.
49. **de Lédinghen V., Vergniol J., Capdepont M., et al.** Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study

of 5323 examinations. Journal of Hepatology. 2014;60(5):1026–1031.

50. **Vuppalanchi R., Siddiqui M. S., Van Natta M. L., et al.** Performance characteristics of vibration-controlled transient elastography for evaluation of nonalcoholic fatty liver disease. Hepatology. 2018;67(1):134–144.
51. **Ferraioli G., Wong V. W.-S., Castera L., et al.** Liver ultrasound elastography: an update to the world federation for ultrasound in medicine and biology guidelines and recommendations. Ultrasound in Medicine & Biology. 2018;44(12):2419–2440.
52. **Wong V. W.-S., Petta S., Hiriart J.-B., et al.** Validity criteria for the diagnosis of fatty liver by M probe-based controlled attenuation parameter. Journal of Hepatology. 2017;67(3):577–584.
53. **Eddowes P. J., Sasso M., Allison M., et al.** Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology. 2019;156(6):1717–1730.
54. **Semmler G., Wöran K., Scheiner B., et al.** Novel reliability criteria for controlled attenuation parameter assessments for non-invasive evaluation of hepatic steatosis. United European Gastroenterology Journal. 2020;8(3):321–331.
55. **Shalimar K. R., Kumar R., Rout G., et al.** Body mass index-based controlled attenuation parameter cut-offs for assessment of hepatic steatosis in non-alcoholic fatty liver disease. Indian Journal of Gastroenterology. 2020;39(1):32–41.
56. **Petta S., Wong V. W.-S., Cammà C., et al.** Improved noninvasive prediction of liver fibrosis by liver stiffness measurement in patients with nonalcoholic fatty liver disease accounting for controlled attenuation parameter values. Hepatology. 2017;65(4):1145–1155.
57. **Sasso M, Audière S, Kemgang A, Gaouar F, Corpechot C, Chazouillères O, Fournier C, Golsztejn O, Prince S, Menu Y, Sandrin L, Miette V.** Liver Steatosis Assessed by Controlled Attenuation Parameter (CAP) Measured with the XL Probe of the FibroScan: A Pilot Study Assessing Diagnostic Accuracy. Ultrasound Med Biol. 2016;42:92–103.
58. **Ni XX, Lian M, Wu HM, Li XY, Sheng L, Bao H, Miao Q, Xiao X, Guo CJ, Li H, Ma X, Hua J.** Evaluation of controlled attenuation parameter in assessing hepatic steatosis in patients with autoimmune liver diseases. World J Gastroenterol. 2021 Jan 7;27(1):80-91.
59. **Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, Kumar M, Lupsor-Platon M, Han KH, Cardoso AC, Ferraioli G, Chan WK, Wong VW, Myers RP, Chayama K, Friedrich-Rust M, Beaugrand M, Shen F, Hiriart JB, Sarin SK, Badea R, Jung KS, Marcellin P, Filice C, Mahadeva S, Wong GL, Crotty P, Masaki K, Bojunga J, Bedossa P, Keim V, Wiegand J.** Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol. 2017;66:1022–1030.
60. **Kamali, L., Adibi, A., Ebrahimian, S., Jafari, F., & Sharifi, M. (2019).**

Diagnostic performance of ultrasonography in detecting fatty liver disease in comparison with fibroscan in people suspected of fatty liver. Advanced biomedical research, 8.

61. **Mowla A, Belford R, Köhn-Gaone J, Main N, Tirnitz-Parker JE, Yeoh GC, Kennedy BF.** Biomechanical assessment of chronic liver injury using quantitative micro-elastography. Biomedical Optics Express. 2022 Sep 1;13(9):5050-66.
62. **Pirmoazen AM, Khurana A, El Kaffas A, Kamaya A.** Quantitative ultrasound approaches for diagnosis and monitoring hepatic steatosis in nonalcoholic fatty liver disease. Theranostics. 2020; 0(9):4277.
63. **Petta S, Maida M, Macaluso FS, Di Marco V, Camma C, Cabibi D. et al.** The severity of steatosis influences liver stiffness measurement in patients with nonalcoholic fatty liver disease. Hepatology. 2015;62:1101–10.
64. **Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B. et al**. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology. 2010;51:454–62.
65. **Suh SW.** Influence of Obesity and Fluid Balance on Operative Outcomes in Hepatic Resection. Journal of Personalized Medicine. 2022 Nov 13;12(11):1897.
66. **Barr RG, Ferraioli G, Palmeri ML, Goodman ZD, Garcia-Tsao G, Rubin J. et al.** Elastography Assessment of Liver Fibrosis: Society of Radiologists in Ultrasound Consensus Conference Statement. Radiology. 2015;276:845–61.