Liver stiffness in chronic hepatitis C virus infection

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RUNNING HEAD: Liver stiffness in CHC
Abstract

Introduction: The severity of liver fibrosis can be assessed noninvasively today by liver stiffness measurements. Vibration-controlled transient elastography, shear wave elastography or magnetic resonance elastography are techniques increasingly used for this purpose.

Methods: This article presents the recent advances in the use of new techniques for liver fibrosis assessment in chronic hepatitis C: the correlation between liver stiffness values and liver fibrosis estimated by liver biopsies, the prognosis role of liver stiffness values, their usefulness in monitoring the treatment response, in assessing the severity of portal hypertension and in estimating the presence of esophageal varices. Scientific articles from January 2017 to January 2018 were searched in PubMed and PubMed Central databases, using the terms "liver stiffness" and "hepatitis C".

Results: The median liver stiffness values measured with different techniques are not identical, so that FibroScan thresholds can not be used on any other elastographic machine. The higher the liver's stiffness measurement, the higher the liver-related events in patients with chronic hepatitis C. A liver stiffness measurement over 17 kPa could be an independent predictor for the presence of esophageal varices as well as a spleen with a longitudinal span ≥15 cm for patients with a value of liver stiffness <17 kPa. A progressive and persistent decrease in liver stiffness is dependent on sustained virological response achievement. The lack of liver stiffness decrease has been associated with relapers and a low value of liver stiffness at baseline.

Conclusion: Liver stiffness provides clues about the severity and evolution of liver disease.

Key words: Chronic hepatitis C; Liver fibrosis; Liver stiffness; Shear wave elastography; Transient elastography

INTRODUCTION

Liver biopsy was the only way to diagnose liver fibrosis during a long period of time. But it is an invasive technique with possible side effects and risk of sampling. Its interpretation depends on the experience of the anatomopathologist and involves a degree of subjectivity. The study of the dynamics of the fibrogenesis process requires its subsequent repetition and is a stressful factor for patients who sometimes refuse it. Some refuse it right from the start. Thus, patients with chronic liver disease have been frequently diagnosed lately in the past, in advanced stages of the disease, due to the lack of non-invasive markers for liver fibrosis [1]. There are different direct and indirect serologic markers of liver fibrosis, but some of them are available only in some centers, more for
research purposes, and there is no consensus on using one of them everywhere, excepting aspartate-aminotransferase-to-platelet ratio index and FIB-4. Instead, the study of liver stiffness tends to expand rapidly throughout the world.

The possibility to explore and quantify the severity of liver fibrosis by liver stiffness measurement is an undeniable progress in hepatology. Only an early detection followed by second preventive strategies can favorably affect patient outcomes [1]. Interferon treatments have demonstrated that liver fibrosis is a reversible process after eradication of hepatitis C virus (HCV), but only in patients with early liver cirrhosis [2]. In addition, despite today's performing direct-acting antiviral therapies that allow the achievement of sustained virological response in most patients, a significant proportion of them continue to have important liver fibrosis 24 weeks after the end of treatment, so only an early etiological treatment is the strategy that can prevent an important residual liver damage [3].

**ATTEMPTS TO ASSESS LIVER FIBROSIS BY IMAGING MEANS**

Tsocatlis pointed out that liver biopsy is more a reference standard than a gold standard for liver fibrosis assessing today [4]. Indeed, exploration of liver fibrosis through hepatic biopsy is increasingly being replaced by noninvasive techniques, as it is an invasive procedure with possible complications and misclassification due to the risk of sampling. Liver fibrosis can be assessed non-invasively by imagistic means using vibration-controlled transient elastography, shear wave elastography [5] (including acoustic radiation force pulse imaging and and ElastPQ) [6], or magnetic resonance elastography [5].

Vibration-controlled transient elastography is the most commonly used technique for assessing liver stiffness nowadays, and it accumulates the most scientific evidences [7]. Transient elastography quantifies the velocity of a low-frequency elastic shear wave penetration through the hepatic parenchyma. A faster shear wave propagation occurs in a stiffer tissue [8]. A session of liver stiffness measurements is valid if the number of valid shots is at least 10; the interquartile range that reflects the variability of the liver stiffness measurements is less than 30% of the median measurements, and the ratio between the valid shots and the total number of shots is above 60% [8, 9]. The results range between 1.5 and 75 kPa. The normal values are considered to be around 5 kPa. The men and subjects with low or high body mass index have higher values [8, 10-13]. Transient elastography requires less than 5 minutes and can be done after a training of about 100 examined patients. The XL probe has a 2.5 MHz transducer, which allows deeper examinations and reduces the number of measurement failures (especially due to obesity) compared to M samples.
Liver stiffness values obtained on the shear wave elastography with the XL probe are generally lower than those provided with the M probe. Therefore, EFSUMB makes no recommendation on cut-offs to be used (broad consensus - 77%) [14].

Liver fibrosis assessed by vibration-controlled transient elastography correlated with that of liver biopsies for all classes and levels of fibrosis, but this noninvasive modality to estimate liver fibrosis is influenced by the accuracy of individual measurements [15] and the examiner's experience [1]. In addition, the elastography technique has other limits, too, as ultrasound can not propagate through any environment: recent meal examination, patient obesity, cholestasis or congestion of the liver veins, necroinflammation, presence of ascites [1].

Elastography point quantification is a new technique that allows estimating the severity of liver fibrosis by measuring liver stiffness. Patients with liver stiffness greater than 6.16 kPa had significant liver fibrosis in liver biopsy (≥S3), and those with a value of over 6.79 kPa had advanced hepatic fibrosis in their biopsy (≥S4). The presence of obesity can create discordance between the histological stage of liver fibrosis and the assessment of liver stiffness through elastography point quantification [16].

Two point shear wave elastographic techniques are currently available: acoustic radiation force impulse elastography and ElastPQ. Both techniques have a very good feasibility for liver fibrosis estimation and can well predict the presence of liver pathology. The values of liver stiffness obtained by Elast PQ technique are lower than those provided by acoustic radiation force impulse elastography [6]. The shear wave velocity can be obtained in a smaller region than in transient elastography, but the region can be selected using the B-mode visualization [8, 17]. An adequate B-mode liver examination is a prerequisite for shear wave elastography measurements (strong consensus - 100%) [14]. Acoustic radiation impulse imaging can be implemented on ultrasound machines and its failure rate is lower than that obtained with transient elastography. An overestimation of hepatic fibrosis degree due to food intake, an increase in serum aminotransferases or necro-inflammatory activity may be produced using either transient elastography or acoustic radiation impulse imaging [8, 17].

Shear wave elastography is used only for liver elasticity measurement and by people who are not imaging specialists. The transient shear deformation propagates into the liver tissue. Its near constant rate for about 4 cm in the liver parenchyma is measured by a straight line automatically [14].

Virtual Touch™ Quantification is a new software which represents an application of acoustic radiation force impulse technology [18] that can be used to diagnose and monitor the evolution of liver fibrosis [19]. It can more accurately estimate liver fibrosis versus aspartate
aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index. Discrepancies between the pathological fibrosis stage and the liver stiffness values estimated by virtual touch quantification may exist when the distance between the skin and the liver capsule is over 17.5 mm [18]. It has slightly higher sensitivity and specificity on significant fibrosis assessment versus transient elastography, according to the results of a meta-analysis that included patients with chronic hepatitis B or C virus infection. The prevalence of cirrhosis was similarly estimated by the two imaging methods, but fibrosis ≥ 2 was less common with Virtual Touch™ Quantification than transient elastography (55 vs. 62%) [19].

Magnetic resonance elastography shear wave velocity may not only assess noninvasively the severity of liver disease, but it also correlates with the hepatic venous pressure gradient, as follows from a study that also included a small group of patients with chronic HCV +/- human immunodeficiency virus (HIV) infection (9 + 9 patients, respectively) [20]. Three-D magnetic resonance elastography can analyze almost all of the liver and can be used well in patients with ascites or obesity. Instead, it is an expensive examination that takes a relatively long time and has no indication for patients with iron overload due to signal-to-noise limitation [8].

GUIDELINES RECOMMENDATIONS

The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America recommended (with a rating of IA) to evaluate HCV-infected patients for advanced fibrosis using liver biopsy, imaging, and / or noninvasive markers, to choose the best decision on HCV treatment strategy and to add additional measures for the management of liver cirrhosis [21].

They also mention in the HCV Guidance that liver stiffness measured using vibration-controlled transient liver elastography correlates well with a substantial degree of fibrosis or cirrhosis in chronic HCV-infected patients. However, there is an overlap between the measurement range and the stages [21-24]. But liver stiffness measurement can reliably distinguish patients with a high probability of having liver cirrhosis [21, 25, 26].

Transient elastography is safe, simple and widely available, but can not offer results in ascites or important obesity and depends on the examiner's experience, according to European Association for the Study of the Liver and Asociación Latinoamericana para el Estudio del Hígado (EASL-ALEH). The protocol can be applied to a patient who has not eaten at least 2 hours, in the supine position, with the right arm in abduction, with the probe placed in the 9th, 10th or 11th intercostal space, on the midaxillary line [8], and after a rest of minimum 10 minutes [14]. EFSUMB
guidelines recommend that the examinations with shear wave elastography is indicated to be made during breath hold, without a deep inspiration prior to the breath hold, and at least 10 mm below the liver capsule [14]. This examination requires at least 10 shots [8].

The following parameters must be met for a correct interpretation of the results: an interquartile range, which reflects the variability of the measurements, below 30%; the serum level of aminotransferases should not exceed 5 times the upper limit of normal values; the XL probe is indicated if the patient is obese or the distance between the skin and the liver capsule is over 25 mm; the patient is without extra-hepatic cholestasis, right heart failure, any cause of congestive liver or excessive ethanol consumption. The quality criteria for correct interpretation of acoustic radiation impulse imaging are not yet well-defined. Magnetic resonance elastography seems more indicated for research purposes, due to its cost and the time it requires [8].

In chronic HCV-infected patients, there are two clinically relevant targets: the detection of significant fibrosis and the diagnosis of liver cirrhosis. However, due to the availability of highly effective novel antiviral interferon-free agents, significant fibrosis may no longer be a relevant target in HCV-infected patients, but the detection of liver cirrhosis is still important to guide the actual treatment (A1) [8].

Transient elastography is a non-invasive standard for liver stiffness measurements (A1), well validated in viral hepatitis (A1). It detects better liver cirrhosis than significant hepatic fibrosis (A1). It can make a reliable diagnosis of liver cirrhosis in patients with chronic liver disease, with a good negative predictive value (higher than 90%) (A1) [8].

According to EFSUMB guidelines, the operator must have the appropriate knowledge and training in ultrasound elastography (this is a strong consensus - 100%) [14].

**COULD LIVER FIBROSIS PRESENCE AND SEVERITY BE ASSESSED BY LIVER STIFFNESS MEASUREMENT?**

Liver stiffness assessed by FibroScan was compared with liver fibrosis of resected liver sections quantified with METAVIR system. A positive correlation ($P \leq 0.0001$) was observed between them in a group of patients with chronic HCV infection and liver tumor, so that FibroScan can be used for non-invasive staging of hepatic fibrosis [27].

An important correlation was found between transient elastographic evaluation of hepatic fibrosis and its serological markers (APRI index and FIB-4) in a study that included 81 consecutive patients chronically infected with the HCV [28]. Indeed, transient elastography correlated also well with the FIB-4 index in another study [29], but the first proved to be superior for the evaluation of
hepatic fibrosis in chronic HCV infected patients. The transient elastography measurements correlated better with clinical and biological markers of significant hepatic fibrosis: the presence of esophageal varices, splenomegaly, low albuminemia, and elongated prothrombine time [29].

Liver and spleen stiffness assessment should be done at more than 3 hours after the last meal to avoid a wrong classification of liver fibrosis stage; otherwise, there is a risk of over-estimating fibrosis in about half of the patients, according to a study that included 60 patients (mostly alcoholic liver disease) examined with real-time two-dimensional shear wave elastography and transient elastography [30].

Estimating liver fibrosis is made more accurately using a combination of two tests (a blood marker and liver stiffness measurement) versus one (having as a reference the fibrosis from the histopathological examination of liver biopsy) in patients with chronic HCV infection, according to a study made by Ducancelle, which included 698 patients with chronic hepatitis C and 628 infected with both HCV and HIV [31].

Liver stiffness measurement, made both with transient elastography and acoustic radiation force impulses, was significantly and moderately correlated with the presence of fibrosis in liver biopsies of same patients chronic infected with HCV, and evaluated with METAVIR score. Transient elastography has been shown to be superior for the evaluation of significant fibrosis and cirrhosis prediction [32].

Whether the thresholds for liver stiffness assessment established using FibroScan are known and can be applied in clinical practice, they are not known for all the other ultrasound elastography machines that are available today. A recent study investigated liver stiffness thresholds measured with FibroScan and 7 different elastographic machines in a group of 16 patients with chronic HCV infection. Both the median stiffness values and the coefficients of both accuracy and precision were different among the different devices used, so that FibroScan thresholds can not be used on any other elastographic machine [33].

Both transient elastography and ElastPQ technique require 10 measurements and the result is their median value and an interquartile range smaller than 30% [34]. The cut-off values for liver stiffness estimated by transient elastography, according to the meta-analysis made by Tschochatzis and the study published by Paranaguá-Vezozzo [28], and those assessed by ElastPQ reported by Mare [35] are presented in Table 1. A strong correlation was found between the values obtained by transient elastography and ElastPQ, so both methods can be used to accurately estimate liver fibrosis [34].
Shear wave elastography correlated with more accuracy with the stage of hepatic fibrosis compared to the right portal vein velocity determined by Doppler ultrasound, especially when fibrosis was in advanced stages (3 and 4) [36].

EASL-ALEH guideline considers that acoustic radiation force impulses can better detect liver cirrhosis than significant fibrosis and is validated in chronic hepatitis C (A1). Acoustic radiation force impulses have equivalent performance to transient elastography for detection of significant liver fibrosis and cirrhosis (A1). Transient elastography is the most accurate non-invasive method that can be used to detect liver cirrhosis in patients with viral hepatitis (A1) and has equivalent performance with serum biomarkers for detecting significant liver fibrosis in patients with viral hepatitis (A1) [8].

According to EFSUMB, a normal value measured using shear wave elastography can rule out significant liver fibrosis when this is in agreement with clinical and laboratory findings (broad consensus - 94%). Transient elastography can be used as the first-line assessment for the severity of liver fibrosis in hepatitis C virus chronic infected patients. Transient elastography can be used as the first-line assessment for the severity of liver fibrosis in chronic hepatitis C virus infected patients. It can be used with greater accuracy to exclude liver cirrhosis (broad consensus - 94%) [14].

**THE PROGNOSIS ROLE OF LIVER STIFFNESS**

The higher the liver's stiffness measurement, the higher the liver-related events in patients with chronic HCV infection. This risk is higher in cirrhotic patients than in those without cirrhosis. A value of liver stiffness measurement equal or greater than 25kPa is associated with a higher risk than lower values. Each increase with one unit in the natural logarithm of liver stiffness measurement increased with 14.76 times the risk in the total patient population which was analyzed, and with 10.56 times in cirrhotic patients [37].

Liver stiffness increased during a 5 year follow-up period in the absence of treatment with a median value that progressively varied between different genotypes of interleukin 28B, from 6.7 kPa in TT/CC to 1.7 kPa in the GG/TT genotype, as assessed by FibroScan®. These two genotypes are predictive factors of liver stiffness progression in multivariate analysis [38].

EASL-ALEH guideline considers that there is increasing evidence of the prognosis value of non-invasive liver tests, in particular liver stiffness measurement using transient elastography, in patients with liver cirrhosis (A1). An increase of liver stiffness measures over time could be associated with a poor prognosis in patients with liver fibrosis or cirrhosis (A2) [8].
Liver stiffness measurement can serve for non-invasive staging of liver fibrosis, rule out a possible liver cirrhosis, and estimate the presence of esophageal varices [7]. EASL-ALEH recommends that all HCV-infected patients should be screened to exclude liver cirrhosis by transient elastography if available (A1) [8]. A liver stiffness measurement over 20-25 kPa can serve to diagnose a clinically significant portal hypertension [7]. Most patients with clinically significant portal hypertension still have a risk of decompensation and death after the end of therapy with direct-acting antivirals, due to portal hypertension that remains elevated despite viral eradication [2]. HCV eradication and liver fibrosis regression are necessary conditions for obtaining a decrease of portal blood pressure, but this decrease was observed only in patients found in subclinical stage of portal hypertension at baseline [2]. Indeed, in addition to liver stiffness lowering, the liver portal pressure normalized to 64% of patients who had subclinical portal hypertension at baseline and obtained complete virological response after interferon-free regimens in another study [39].

Liver stiffness measurements made at 6 months after interferon-free therapy in patients with chronic HCV infection that reached the stage of liver cirrhosis decreased significantly compared with those made at baseline, but this lowering did not correlate with hepatic venous pressure gradient, and liver stiffness cut-off values do not allow to exclude a clinically significant portal hypertension (CSPH) after the achievement of sustained virological response. CSPH was still present in 1/3 of patients with sustained virological response who achieved a reduction in liver stiffness below 13.6 kPa [40].

Recent data suggest that spleen stiffness can be included together with liver stiffness measurement in an algorithm for portal hypertension diagnosis, although previous data on its utility were controversial [7].

According to EASL-ALEH guideline, non-invasive tests can not be used to replace hepatic venous pressure gradient for portal hypertension evaluation or upper digestive endoscopy for detecting the presence and degree of varices (A1). Only where the hepatic venous pressure gradient measurement can not be made, transient elastography could be a solution to stratify the risk of clinically significant portal hypertension (A2) [8]. According to EFSUMB guidelines, liver stiffness measurements with transient elastography are useful in identifying patients with a high probability of clinically significant portal hypertension [14].
LIVER STIFFNESS INVOLVEMENT IN THE ASSESSMENT OF ESOPHAGEAL VARICES

A liver stiffness measurement ≥ 17 kPa could be an independent predictor for the presence of esophageal varices as well as a spleen with a longitudinal span ≥15 cm for patients with a value of liver stiffness <17 kPa, according to a study that included 123 chronic hepatitis C Egyptian patients. Liver stiffness measurement obtained with a FibroScan machine can serve to discriminate esophageal varices; in this study mean liver stiffness varied between 9.94 ± 6 kPa in patients with grade 1 varices and 46.1 ± 15 kPa in those with grade 4 varices (detected and classified by esophagogastroduodenoscopy) [41].

A liver stiffness measurement below 20 kPa together with a platelet count of over 150x10^9/L in patients with compensated advanced chronic liver disease may indicate the absence of oesophageal varices requiring treatment, according to Baveno VI consensus [42]. But a liver stiffness measurement of less than 25 kPa together with a platelet count above 110 x 10^9 cells/L are new criteria (Expanded-Baveno VI) that safely avoids superior digestive endoscopy as varices screening in patients with compensated advanced chronic liver disease. The risk of not finding patients who have varices needing treatment and who meet the above criteria is 1.6%. These thresholds were also validated in patients with chronic HCV infection [43].

But a correspondence between the liver stiffness values and the presence of esophageal varices was not found by all authors. Thus, liver stiffness did not correlate with the presence of endoscopic signs of portal hypertension in a study conducted on 70 patients with chronic HCV infection [44]. Growth arrest-specific gene 6 is part of a profibrogenic pathway in the liver. It has the same sensitivity (94%) with Baveno VI criteria for varices detection, and can be used when transient elastography is not available [45].

Liver stiffness values obtained using transient elastography combined with platelet counts are useful to rule out varices requiring treatment. Although the results obtained so far are encouraging, there is no sufficient evidence to recommend shear wave elastography for this purpose (broad consensus - 93%) [14].

LIVER STIFFNESS – A WAY TO MONITOR THE EVOLUTION OF PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION
Etiological treatment of chronic hepatitis C is indicated in all patients with significant or advanced liver fibrosis [46] that can be assessed by liver stiffness measurement. This is the most widespread opinion today. Indeed, nonaccidental mortality was elevated in patients with chronic HCV virus infection and moderate fibrosis (adjusted hazard ratio 1.66), according to a study involving 964 subjects whose liver stiffness was measured twice a year for 9 years. But it should be underlined that neither liver stiffness nor demographic, clinical or behavioral factors could accurately predict the transition from mild to moderate liver fibrosis, so these patients should receive etiological treatment regardless of the stage of liver disease [47].

Liver stiffness measurement allows to monitor patient progress during and after treatment through repeated measurements at varying intervals. The results can be used for risk stratification and for possible complications monitoring. Thus, the liver stiffness assessment is a useful tool for a personalized medicine practice [1].

The highest reduction of liver stiffness value in patients with chronic HCV infection who responded to the treatment with interferon or direct antiviral agents was observed at the end of treatment (-2.5 kPa) and six months later (-3.7 kPa). From a value of 12.3 kPa at baseline, it decreased by almost 50% in those with sustained virological response at five years, but the rate of decline progressively declined after one year since the end of therapy. The results were spectacular with respect to the presence of liver cirrhosis: it disappeared in half of the patients after 6 months and it was still present in just under 5% of them after 4 years of the end of therapy. Instead, if patients did not respond to treatment, the liver stiffness value declined slightly at its end (from 19.2 kPa to 18.1 kPa), after which it returned to the baseline value after half a year and then increased along time to 23.7 kPa at 5 years [48].

The non-invasive assessment of liver fibrosis with transient elastography is indicated to be used to monitor its decrease during antiviral therapy. But the correlation of liver fibrosis improvement, assessed using non-invasive measurement, with liver histology has yet to be determined (B2) [8].

According to EASL-ALEH, the management of non-cirrhotic patients does not include a routine use of non-invasive tests during treatment or after obtaining the SVR (A1). In addition, it should be noted that EASL-ALEH guideline supports that the routine use of non-invasive tests after obtaining the SVR in patients with HCV liver cirrhosis has a high false rate and is not indicate to be used to determine which patients no longer need hepatocellular carcinoma screening or for the diagnosis of liver cirrhosis reversal (A2) [8].

Neither shear wave elastography is recommended to monitor liver fibrosis evolution during anti-HCV treatment (strong consensus - 100%) and liver stiffness measurements after successful
HCV treatment should not serve to change the management strategy (broad consensus - 94%), according to EFSUMB guidelines [14].

Indeed, recent data showed that it is unclear if the improvement of the transient elastography values after interferon-free treatment indicates a true regression of fibrosis or merely resolution of chronic liver inflammation. Up to date, non-invasive tests to stage liver fibrosis (including also transient elastography) have not been validated in patients after SVR that is why the physician needs to know that the management of patients must be based on pre-treatment fibrosis staging and that elastography evaluation post-SVR is more useful to assess for progression than regression of fibrosis.

THE FOLLOW-UP OF PATIENTS USING VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY DURING AND AFTER INTERFERON-BASED ANTIVIRAL REGIMENS

The results of a long-term follow-up of patients with chronic HCV infection and treated mostly with interferon-based antiviral regimens (83% of them) have recently been published. Liver fibrosis was assessed at baseline by liver biopsy and at the end of the follow-up period by liver stiffness measurement (with FibroScan) in 86% of patients and by liver biopsy for the others. After a median follow-up of 14 years, advanced fibrosis was found in 25% of patients who obtained sustained virological response, compared with 30% at baseline, but this difference was not statistically significant. In contrast, advanced fibrosis was present in 31% of those with persistent viraemia, compared to 10% at baseline. It appears that eradication of HCV is a necessary condition for the stagnation or regression of hepatic fibrosis [49].

THE FOLLOW-UP OF PATIENTS USING VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY DURING AND AFTER DIRECT ANTIVIRAL AGENTS-BASED REGIMENS

THE LIVER STIFFNESS DURING TREATMENT

A rapid improvement of liver stiffness from a baseline value of 20.8 kPa to one of 17.5 kPa after 4 weeks of treatment with direct acting antivirals observed in a group of patients with hepatitis C in a compensated advanced stage reflects a decrease in inflammation and not a reduction in liver fibrosis [2, 50], as the last requires a longer period of time [2]. A severe liver fibrosis can still be present in these patients, despite this decrease of liver stiffness. Furthermore, liver stiffness did not
vary significantly from week 4 to end of treatment and from this moment to week 48 of follow-up. A reduction in liver stiffness of over 10% during treatment was present in patients with a lower spleen stiffness and bilirubin levels and higher platelet counts [50].

THE LIVER STIFFNESS AFTER TREATMENT

A higher improvement in liver stiffness at the end of treatment correlates with a higher baseline inflammatory activity, and a higher reduction in liver stiffness at 24 weeks after the end of antiviral treatment can be achieved in patients with higher baseline fibrosis [51].

Reducing the liver stiffness one year after the end of treatment of chronic HCV infection with direct-acting antiviral drugs would be due to the decrease of liver fibrosis in parallel with those of inflammation [52].

Lower liver stiffness (assessed during treatment at week 4, and after treatment at week 12) was associated with the achievement of sustained virological response in a large observational study (that included 462 patients treated with interferon-free regimen for chronic hepatitis C with viral genotype 1-4) [53].

The addition of interferon to direct-acting antiviral did not result in an additional decrease in liver stiffness values [3].

A significant proportion of patients who achieved a sustained virological response has important liver fibrosis 24 weeks after the end of treatment, probably because the antiviral treatment in these cases started in patients with METAVIR fibrosis stage of F3/F4, that spans a very wide range of fibrosis deposition.

THE RISK OF RELAPSE

A large retrospective study included 337 Egyptian patients infected with chronic HCV, especially with genotype 4, who were treated with sofosbuvir-based regimen. Those who achieved a sustained virological response at 12 weeks had significant decreases in liver stiffness (P = 0.000). The lack of liver stiffness decrease has been associated with relapers and a low value of liver stiffness at baseline [54]. HCV infection has a higher probability of relapse after a direct-acting antiviral treatment also in cirrhotic patients with a baseline liver stiffness of more than 12.5 kPa. This value can serve to choose the duration and scheme of direct-acting antiviral drugs to avoid a possible relapse [55].
IS SUSTAINED VIROLOGICAL RESPONSE A CONDITION FOR LIVER FIBROSIS REGRESSION?

A study that included 844 patients with chronic HCV genotype 1b and treated with asunaprevir and daclatasvir for 24 weeks established that liver stiffness significantly decreased after the end of treatment compared to baseline in both groups of patients - who have and who have not achieved sustained virological response. So, the authors of this study concluded that diminishing of liver stiffness is independent of the efficacy of the treatment [56]. A decrease in the liver stiffness value was observed in other studies both in patients who achieved or not sustained virological response, but the decrease was more important in responders. Thus, a 24-week treatment with asunaprevir and daclatasvir given in a group of 214 elderly patients with chronic HCV genotype 1b resulted in a significant reduction in liver stiffness at the end of treatment and at 24, 48, and 72 weeks later. Compared to its baseline value, the decrease was higher in cirrhotic patients than in those with chronic hepatitis. Patients who achieved sustained virological response had a higher liver stiffness measurement reduction, but the others also showed a significant decrease of liver stiffness value at the end of treatment and 24 and 72 weeks later [57].

But a meta-analysis that included 24 randomized controlled trials or observational studies with patients with chronic HCV infection in the cirrhotic stage found that only those who obtained sustained virological response had a decrease in liver stiffness assessed with vibration-controlled transient elastography. This reduction was of 2.4 kPa at the end of the treatment and of 4.1 kPa over 1 year after its completion. The decrease was significantly higher in those with higher baseline serum levels of alanine aminotransferases, baseline diagnosis of cirrhosis (compared to non-cirrhotics) and after a treatment with direct-acting antiviral drugs (versus interferon-based regimens) [58].

OTHER FACTORS THAT CORRELATE WITH THE REDUCTION OF LIVER STIFFNESS VALUES

The decrease of liver stiffness was more important in a group of patients with higher baseline levels of bilirubin (≥1 mg/dl), alanine aminotransferase, aspartate aminotransferase, and liver stiffness (≥9 kPa). The regression to non-cirrhotic stage of liver fibrosis was obtained in 39% of 80 Egyptian patients (where genotype-4 has the highest prevalence) [59].

Genotypes CXCL9 rs10336 AG, CXCL11 rs4619915 AG, and CXCL10 rs3921 CG were often associated with lower liver stiffness values in codominant or overdominant models of
inheritance transmission. In contrast, the same genotypes transmitted in the recessive model (CXCL9 rs10336 AA, CXCL11 rs4619915 AA, and CXCL10 rs3921 CC) correlated with higher values of liver stiffness [60].

Some recent studies on liver stiffness decrease after antiviral treatment are presented in Table 2.

THE FOLLOW-UP OF PATIENTS USING SHEAR WAVE ELASTOGRAPHY

The cut-off values of liver stiffness assessed by point shear wave measurement were 6.78 kPa for a significant fibrosis (F≥2) and 9.15 kPa for cirrhosis (F=4) in a study made on consecutive patients with chronic HCV infection [63].

The median decrease in liver stiffness values evaluated by shear wave elastography began even during the treatment with daclatasvir and asunaprevir (8.8 kPa at the end of the treatment versus 10.2 kPa at baseline) (p<0.001) in a group of 210 patients who achieved sustained virological response. It continued to diminish and attained a median value of 7.6 kPa at 24 weeks after the end of the treatment (the difference between it and that from the end of the treatment is significant - p<0.001). This early decrease of liver stiffness is more important in patients who have progressive liver fibrosis [64].

Shear wave propagation velocity correlates with the α-feto protein value and the Mac-2 binding protein glycosylation isomer in patients with chronic HCV infection who achieve sustained virological response, so that shear wave propagation velocity could predict hepatocarcinogenesis in these patients [65].

THE FOLLOW-UP OF PATIENTS WITH RECURRENT HEPATITIS C AFTER A LIVER TRANSPLANT

Transient elastography could represent an alternative to liver biopsy for assessing liver fibrosis post-liver transplantation in chronic HCV infected patients. The optimal cut-off value of liver stiffness ranged from 8.1 kPa for liver fibrosis stage ≥1 to 17.6 for stage 4 [66].

But how respond the patients with recurrent hepatitis C after a liver transplant to the treatment? All 23 patients with hepatitis C recurrence after liver transplantation obtained the blood disappearance of HCV RNA at the end of 24-week therapy with directly-acting antiviral agents, when they had a significant decrease in median liver stiffness values from 8.72±3.77 (at baseline) to 7.19±2.4 kPa, measured by shear-wave elastography [67]. In another study, all patients with chronic
HCV infection who received a sustained virological response after the end of sofosbuvir + ribavirin +/- simeprevir treatment, made after a median time of 4.3 years of liver transplantation, also had a decrease in liver stiffness assessed by elastography and FIB-4 and APRI index. About half of the responders (with F3 or even F4 stage of fibrosis) exhibited also a reduction in fibrosis stage [68].

And how did they evolve to follow up? Two-thirds of patients with recurrent hepatitis C after a liver transplant achieved a reduction in the severity of liver fibrosis, according to their serial liver biopsies, one year after sustained virological response achievement. Liver stiffness measurement also diminished after the achievement of sustained virological response. The baseline level of liver stiffness measurement was one of the independent predictor factors of fibrosis regression. Liver stiffness measurement can rule out the suspicion of severe liver fibrosis or a portal hypertension with clinical significance at 12 months after the achievement of sustained virological response [69].

**THE FOLLOW-UP OF PATIENTS CO-INFECTED WITH HEPATITIS C AND HUMAN IMMUNODEFICIENCY VIRUS**

Patients with chronic HCV infection and HIV coinfection or with alcohol overconsumption have a double risk of severe fibrosis/cirrhosis, assessed using FibroScan® [70]. HIV can directly cause liver damage. The mean liver stiffness measurement was higher in patients coinfected with HIV and HCV (P<0.0001) than in those infected with HIV alone. But liver stiffness did not correlate with HIV replication at the immunocompetent patients coinfected with both viruses at the 12- or 36-month study period [71].

Patients with FIB-4 <1.45 may also have significant or advanced liver fibrosis assessed by transient elastography, so that estimating fibrosis using FIB-4 is not useful to exclude these cases of fibrosis in double-infected patients: with HCV and HIV, according to the study published by Chromy [46].

The time until cirrhosis constitution estimated by liver stiffness progression rates (assessed by transient elastography technique) was close to that estimated by fibrosis progression rates (an estimation based on histological stages of liver fibrosis) (39 versus 38 years) in a meta-analysis made on 27 studies in which 58% of patients were double infected: with HCV and HIV. Liver stiffness progression rates were positively associated with HIV and male gender, and negatively with age [72].
A liver stiffness value of over 20 kPa was associated with lower sustained virological response rates after direct-acting antiviral schedules in patients with chronic HCV +/- HIV infection [73].

Gastrointestinal bleeding due to portal hypertension can be excluded in patients co-infected with HCV and HIV if the liver stiffness is below 21 kPa (the negative predictive value was 100% in a study involving 446 such patients) [74].

According to EASL-ALEH guideline, transient elastography is adequate for the diagnosis of severe liver fibrosis / cirrhosis in HCV infected and HIV-HCV coinfected patients and is useful in prioritizing patients for HCV therapy based on disease stage (A1) [8].

THE ROLE OF LIVER STIFFNESS MEASUREMENT IN THE ASSESSMENT OF OTHER FIBROSIS BIOMARKERS AND TOGETHER WITH THEM

The Mac-2 Binding Protein Glycosylation isomer, a new liver fibrosis glyco-biomarker, was significantly associated with liver stiffness measurement estimated using a Fibro Scan® in a study involving 680 patients with chronic HCV infection and 164 healthy controls. The optimum cut-off values of this serum biomarker were 0.945 for F2 and 1.355 for F4 [75].

Enhanced liver fibrosis blood test consists in the determination of the following liver fibrosis biomarkers: hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of metalloproteinase 1. The annual performing of this blood test with or without liver stiffness measurement is a cost-effective options versus liver biopsy to estimate liver fibrosis, according to a study made in Spain [76].

Liver stiffness assessed by transient elastography decreased by 32.4% at 18 months after the end of direct antiviral drug therapy for chronic HCV infection compared to its pre-treatment value, according to a study on 392 patients. This rapid decline in liver stiffness assessed with transient elastography is consistent with the drop in FIB-4 and APRI scores, which also assess non-invasively the severity of liver fibrosis [77].

Among the different available strategies used for the detection of liver fibrosis, algorithms that use both transient elastography and serum biomarkers are the most attractive and validated one (A2). Serum biomarkers can be used for the detection of liver cirrhosis in the absence of transient elastography (A1). The diagnosis of liver fibrosis (but not of cirrhosis) has a higher accuracy in viral hepatitis C patients when transient elastography and serum biomarkers results are in agreement. A liver biopsy should be performed in cases of unexplained discordance between these results, if the conclusion of this invasive method could modify the patient management (A1) [8].
CONCLUSION

The severity of liver fibrosis can be assessed noninvasively today by liver stiffness measurements, as it can correctly assess the presence and stage of liver fibrosis. It can also estimate the presence of a possible portal hypertension or the existence of esophageal varices.

Each device used for liver stiffness measurement must have its own values to quantify the stage of liver fibrosis.

Up to date, non-invasive tests to stage liver fibrosis (including also transient elastography) have not been validated in patients after SVR that is why the physician needs to now that the management of patients must be based on pre-treatment fibrosis staging and that elastography evaluation post-SVR is more useful to assess for progression than regression of fibrosis.

Future clarifications on method limitations and quantification of liver stiffness for each indications will appear in the next years.

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**Introducere:** Severitatea fibrozei hepatice poate fi estimată astăzi măsurând rigiditatea hepatică. Elastografia tranzitorie controlată de vibratii, elastografia prin măsurarea vitezei undelor de forfecare sau elastografia prin rezonanţă magnetică nucleară sunt tehnici folosite to mai mult în acest scop.

**Metode:** Acest articol prezintă progresele recente privind folosirea noilor tehnici pentru estimarea fibrozei hepatice în hepatita cronică C: corelarea dintre valorile rigidității hepatice și fibroza hepatică estimată studiind biopsiile hepatice, rolul prognostic al valorilor rigidității hepatice, utilizaiea ei în monitorizarea răspunsului terapeutic, în aprecierea severității hipertensiunii portale și în estimarea prezenței varicelor esofagiene. Articolele științifice din Ianuarie 2017 până în Ianuarie 2018 au fost căutate în bazele de date PubMed and PubMed Central, folosind termenii de căutare: "rigiditate hepatică" and "hepatită C".

**Rezultate:** Valorile mediane ale rigidității hepatice măsurate prin tehnici diferite nu sunt identice, așa încât pragurile stabilite prin FibroScan nu pot fi folosite de orice aparat elastografic. Cu cât măsura rigidității hepatice este mai mare, cu atât sunt mai frecvente evenimentele hepatice la pacienții cu hepatită cronică C. O valoare a rigidității hepatice de peste 17 kPa poate fi un predictor independent pentru rănirea răspunsului terapeutic, ca și o splină cu axul longitudinal de ≥15 cm pentru pacienții cu o valoare a rigidității hepatice de <17 kPa. O scădere progresivă și persistentă a rigidității hepatice este dependentă de obținerea răspunsului virusologic susținut. Absența scăderii rigidității hepatice s-a asociat cu receivile și cu o valoare scăzută a rigidității hepatice bazale.

**Concluzie:** Estimarea rigidității heaptice este o modalitate utilă pentru practicarea unei medicini personalizate.

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Based Liver

Table 1: Liver fibrosis assessment by transient elastography and ElastPQ.

<table>
<thead>
<tr>
<th>Technique used for assessment (kPa)</th>
<th>Fibrosis stage</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F ≥ 2</td>
<td>F ≥ 3</td>
</tr>
<tr>
<td>TE</td>
<td>7.0</td>
<td>9.5</td>
</tr>
<tr>
<td>TE</td>
<td>6.6</td>
<td>8.9</td>
</tr>
<tr>
<td>ElastPQ</td>
<td>7.2</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Legend: TE = transient elastography
Table 2: The evolution of liver stiffness after the etiological treatment of chronic hepatitis C virus infection.

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Treatment</th>
<th>Technical means of liver stiffness assessment</th>
<th>LS evolution</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>DAA</td>
<td>TE</td>
<td>LS decreased from 20.8 kPa (at baseline) to 11.5 kPa at end of treatment.</td>
<td>[39]</td>
</tr>
<tr>
<td>33</td>
<td>DAA (SOF/LDV or 2D/3D) + antiretroviral therapy</td>
<td>TE (FibroScan)</td>
<td>LS reduced from 11.4 to 8.3 kPa after SOF/LDV schedule, and from 8.1 to 5.7 kPa after 2D/3D schedule at six months after the end of treatment.</td>
<td>[61]</td>
</tr>
<tr>
<td>304</td>
<td>DAA</td>
<td>TE</td>
<td>LS diminished from a median value of 16.9 at baseline to 11.9 kPa at 24 weeks after end of treatment. A LS decrease of at least 20% was found in 65.1% of patients. But more than half of the patients remained with grade 4 fibrosis 24 weeks after the end of therapy.</td>
<td>[3]</td>
</tr>
<tr>
<td>80</td>
<td>DAA</td>
<td>TE</td>
<td>Mean LS decreased from 15.6 ± 10.8 at baseline to 12.1 ± 8.7 kPa</td>
<td>[59]</td>
</tr>
</tbody>
</table>
when sustained virological response at 24 weeks was obtained.

<table>
<thead>
<tr>
<th></th>
<th>DAA</th>
<th>TE</th>
<th>Mean LS measurements [62]</th>
</tr>
</thead>
<tbody>
<tr>
<td>211</td>
<td>DAA (Viekirax/Exviera + Ribavirin)</td>
<td>TE</td>
<td>diminished from 26.4+/−11.7kPa at baseline to 23.5+/−13.3 kPa at the end of treatment</td>
</tr>
</tbody>
</table>

**Legend:** 2D/3D = paritaprevir/ombitasvir +/- dasabuvir; DAA = direct-acting agents; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LS = liver stiffness; SOF = sofosbuvir/ledipasvir; TE = transient elastography.