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REVIEWS

Liver stiffness in chronic hepatitis C virus infection

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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 cannot 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 relapsers 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 aspartat- aminotranferase-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

Tsochatzis 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

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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 inter-quartile 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 [8]. 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 cannot 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 it cannot 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 9^{th}, 10^{th} or 11^{th} 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 chronically 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 cannot 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 elastograhpy, according to the meta-analysis made by Tsochatzis 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].

Table 1
Liver fibrosis assessment by transient elastography and ElastPQ

Technique used for assessment (kPa)	**Fibrosis stage**			**References**
	F ≥ 2	F ≥ 3	F = 4	
TE	7.0	9.5	12	[35]
TE	6.6	8.9	12.2	[28]
ElastPQ	7.2	8.5	8.9	[35]

Legend: TE = transient elastography

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 gudeline considers that acoustic radiation force impulses can better detect liver cirrhosis than significant fibrosis and it 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 chronically 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 14.76 times the risk in the total patient population which was analyzed, and 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 – A POSSIBLE MEANS FOR PORTAL HYPERTENSION ASSESSMENT

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 cannot 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 cannot 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 $\geq$ 17 kPa could be an independent predictor for the presence of esophageal varices as well as a spleen with a longitudinal span $\geq$ 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 150×10^9/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 110×10^9 cells/L are new criteria (Expanded-Baveno VI) that safely avoid 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 it is not indicated to be used to determine which patients no longer need hepato-cellular 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 for 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 relapsers 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.

Table 2
The evolution of liver stiffness after the etiological treatment of chronic hepatitis C virus infection

No. of patients	Treatment	Technical means of liver stiffness assessment	LS evolution	References
22	DAA	TE	LS decreased from 20.8 kPa (at baseline) to 11.5 kPa at end of treatment	[39]
33 coinfected with HCV and HIV	DAA (SOF/LDV or 2D/3D) antiretroviral therapy	TE + (FibroScan)	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	[61]
304	DAA	TE	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	[3]
80	DAA	TE	Mean LS decreased from 15.6 ± 10.8 at baseline to 12.1 ± 8.7 kPa when sustained virological response at 24 weeks was obtained	[59]
211	DAA (Viekirax/Exviera + Ribavirin)	TE	Mean LS measurements diminished from 26.4+/-11.7 kPa at baseline to 23.5+/-13.3 kPa at the end of treatment	[62]

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

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 HEPATITS 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 in 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 metallo-proteinase 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 ones (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 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.

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

Conflict of Interest disclosure. The author declares that there are not conflicts of interest.

Introducere. *Severitatea fibrozei hepatice poate fi estimată astăzi măsurând rigiditatea hepatică. Elastografia tranzitorie controlată de vibrații, elastografia prin măsurarea vitezei undelor de forfecare sau elastografia prin rezonanță magnetică nucleară sunt tehnici folosite tot 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, utilitatea 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" și „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 prezența varicelor esofagiene, ca şi o splină cu axul longitudinal de ≥ 15 cm pentru pacienții cu o valoare a rigidității hepatice de < 17 kPa. O scădere progresivă şi persistentă a rigidității hepatice este dependentă de obținerea răspunsului virusologic susținut. Absența scăderii rigidității hepatice s-a asociat cu recidivele şi 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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REFERENCES

1. THIELE M., KJAERGAARD M., THIELSEN P., KRAG A. *Contemporary use of elastography in liver fibrosis and portal hypertension*. Clin Physiol Funct Imaging 2017; **37**:235-42.
2. GRUGUREVIC I., BOZIN T., MADIR A. *Hepatitis C is now curable, but what happens with cirrhosis and portal hypertension afterwards?* Clin Exp Hepatol 2017; **3**:181-6.
3. DOLMAZASHVILI E., ABUTIDZE A., CHKHARTISHVILI N., KARCHAVA M., SHARVADZE L., TSERTSVADZE T. *Regression of liver fibrosis over a 24-week period after completing direct-acting antiviral therapy in patients with chronic hepatitis C receiving care within the national hepatitis C elimination program in Georgia: results of hepatology clinic HEPA experience*. Eur J Gastroenterol Hepatol 2017; **29**:1223-30.
4. TSOCHATZIS E.A., GERMANI G., HALL A., MANUOUSOU P., DHILLON A.P., BURROUGHS A.K. *Noninvasive assessment of liver fibrosis: The need for better validation.* Hepatology 2011; **53**:1781-2.
5. SINGH S.,MUIR A.J., DIETERICH D.T., FALCK-YTTER Y.T. *American gastroenterological association institute technical review on the role of elastography in chronic liver diseases*. Gastroenterology 2017; **152**:1544-77.
6. SPOREA I., BOTA S., GRĂDINARU-TAŞCĂU O., ŞIRLI R., POPESCU A. *Comparative study between two point Shear Wave Elastographic techniques: Acoustic Radiation Force Impulse (ARFI) elastography and ElastPQ.* Med Ultrason 2014; **16**:309-14.
7. GRGUREVIC I., BOKUN T., BOZIN T., MATIC V., HABERLE S., SPOREA I. *Non-invasive diagnosis of portal hypertension in cirrhosis using ultrasound based elastography*. Med Ultrason 2017; **19**:310-7.
8. EUROPEAN ASDSOCIATION FOR THE STUDY OF THE LIVER, ASOCIATIÓN LATINOAMERICANA PARA EL ESTUDIO DEL HIGADO. *EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis*. J Hepatol 2015; **63**:237-64.
9. CASTERA L., FORNS X., ALBERTI A. *Non-invasive evaluation of liver fibrosis using transient elastography*. J Hepatol 2008; **48**:835-47.
10. ROULOT D., CZERNICHOW S., LE CLESIAU H., COSTES J.L., VERGNAUD A.C., BEAUGRAND M. *Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome*. J Hepatol 2008; **48**:606-13.
11. KIM S.U., CHOI G.H., HAN W.K., KIM B.K., PARK J.Y., KIM DO Y., *et al. What are 'true normal' liver stiffness values using FibroScan?: a prospective study in healthy living liver and kidney donors in South Korea*. Liver Int 2010;**30**:268-74.
12. COLOMBO S., BELLOLI L., ZACCANELLI M., BADIA E., JAMOLETTI C., BUONOCORE M., *et al. Normal liver stiffness and its determinants in healthy blood donors*. Dig Liver Dis 2011;**43**:231-36.
13. DAS K., SARKAR R., AHMED S.M., MRIDHA A.R., MUKHERJEE P.S., DHALI G.K., *et al. "Normal" liver stiffness measure (LSM) values are higher in both lean and obese individuals: a population-based study from a developing country*. Hepatology 2012;**55**:584-93.
14. DIETRICH C.F., BAMBER J., BERZIGOTTI A., BOTA S., CANTISANI V., CASTERA L., *et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (long version).* Ultraschall Med 2017;**38**:e16-e47.
15. MENDES L.C., FERREIRA P.A., MIOTTO N., ZANAGA L., GONÇALES E.S.L., PEDRO M.N., *et al. Elastogram quality assessment score in vibration-controlled transient elastography: Diagnostic performance compared to digital morphometric analysis of liver biopsy in chronic hepatitis C*. J Viral Hepat 2018;**25**:335-43.
16. CONTI F., SERRA C., VUKOTIC R., FIORINI E., FELICANI C., MAZZOTTA E., *et al. Accuracy of elastography point quantification and steatosis influence on assessing liver fibrosis in patients with chronic hepatitis C*. Liver Int 2017;**37**:187-95.
17. BOTA S, SPOREA I, PECK-RADOSAVLJEVIC M, SIRLI R, TANAKA H, IIJIMA H, *et al. The influence of aminotransferase levels on liver stiffness assessed by Acoustic Radiation Force Impulse Elastography: a retrospective multicentre study*. Dig Liver Dis 2013;**45**:762– 8.

18. TSUKANO N., MIYASE S., SAEKI T., MIZOBE K., IWASHITA H., ARIMA N., *et al. Usefulness of Virtual Touch Quantification for staging liver fibrosis in patients with hepatitis C, and the factors affecting liver stiffness measurement failure compared with liver biopsy*. Hepatol Res 2018;**48**:373-82.
19. SUMMERS J.A., RADHAKRISHAN M., MORRIS E., CHALKIDOU A., RUA T., PATEL A., *et al. Virtual Touch™ quantification to diagnose and monitor liver fibrosis in hepatitis B and hepatitis C: A NICE medical technology guidance*. Appl Health Econ Health Policy 2017;**15**:139-54.
20. GHARIB A.M., HAN M.A.T., MEISSNER E.G., KLEINER D.E., ZHAO X., MCLAUGHLIN M., *et al. Magnetic resonance elastography shear wave velocity correlates with liver fibrosis and hepatic venous pressure gradient in adults with advanced liver disease*. Biomed Res Int 2017;**2017**:2067-479.
21. THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES AND THE INFECTIOUS DISEASES SCOCIETY OF AMERICA. HCV *Guidance: recommendations for testing, managing, and treating hepatitis C*. www. HCVGuidance.org on August 13, 2018.
22. ZIOL M., HANDRA-LUCA A., KETTANEH A., CHIRSTIDIS C., MAL F., KAZEMI F., *et al. Noninvasive assessment of liver fibrosis by measurement of stiffness in patients with chronic hepatitis C*. Hepatology 2005;**41**:48-54.
23. AFDAHAL N.H., BACON B.R., PATEL K., LAWITZ E.J., GORDON S.C., NELSON D.R., *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*. Clin Gastroenterol Hepatol 2015;**13**:772-9.
24. CASTERA L., VERGNIOL J., FOUCHER J., LE B.B., CHANTELOUP E., HAASER M., *et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C*. Gastroenterology 2005;**128**:343-50.
25. CASTERA L. *Noninvasive methods to assess liver disease in patients with hepatitis B or C. Gastroenterology* 2012;**142**:1293-302.
26. BONDER A., AFDHAL N.H. *Utilization of FibroScan in clinical practice.* Curr Gastroenterol Rep 2014;**16**:372.
27. NAKAMURA Y., AIKATA H., FUKUHARA T., HONDA F., MORIO K., MORIO R., *et al. Liver fibrosis assessment by FibroScan compared with pathological findings of liver resection specimen in hepatitis C infection*. Hepatol Res 2017;**47**:767-72.
28. PaARANAGUÁ-VEZOZZO D.C., ANDRADE A., MAZO D.F., NUNES V., GUEDES A.L., RAGAZZO T.G., *et al. Concordance of non-invasive mechanical and serum tests for liver fibrosis evaluation in chronic hepatitis C.* World J Hepatol 2017;**9**:436-42.
29. DOLMAZASHVILI E., KARCHAVA M., ABUTIDZE A., SHARVADZE L., TSERTSVADZE T. *Comparative study of FIB-4 index and transient elastography among patients with chronic hepatitis C virus infection in Georgia*. Georgian Med News 2017;**264**:81-6.
30. KJÆRGAARD M., THIELE M., JANSEN C., STÆHR MADSEN B., GÖRTZEN J., STRASSBURG C., *et al. High risk of misinterpreting liver and spleen stiffness using 2D shear-wave and transient elastography after a moderate or high calorie meal*. PLoS One 2017;**12**:e0173992.
31. DUCANCELLE A., LEROY V., VERGNIOL J., STURM N., LE BAIL B., ZARSKI J.P., *et al. A single test combining blood markers and elastography is more accurate than other fibrosis tests in the main causes of chronic liver diseases*. J Clin Gastroenterol 2017;**51**:639-49.
32. GANI R.A., HASAN I., SANITYOSO A., LESMANA C.R.A., URNIAWAN J., JASIRWAN C.O.M., *et al. Evaluation of Acoustic Radiation Force Impulse (ARFI) for fibrosis staging in chronic liver diseases.* Acta Med Indones 2017;**49**:128-35.
33. PISCAGLIA F., SALVATORE V., MULAZZANI L., CANTISANI V., COLECCHIA A.,DI DONATO R., *et al. Differences in liver stiffness values obtained with new ultrasound elastography machines and Fibroscan: A comparative study*. Dig Liver Dis 2017;**49**:802-8.
34. MARE R., SPOREA I., LUPUŞORU R., ŞIRLI R., POPESCU A., DANILA M., *et al. The value of ElastPQ for the evaluation of liver stiffness in patients with B and C chronic hepatopathies*. Ultrasonics 2017;**77**:144-51.
35. TSOCHATZIS E.A., GURUSAMY K.S., NTAOULA S., CHOLONGITAS E., DAVIDSON B.R., BURROUGHS A.K. *Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy*. J Hepatol 2011;**54**:650-9.
36. MOUSTAFA E.F., MAKHLOUF N., HASSANY S.M., HELMY A., NASR A., OTHMAN M., *et al. Non-invasive assessment of liver fibrosis in patients with hepatitis C: Shear wave elastography and colour Doppler velocity profile technique* versus *liver biopsy*. Arab J Gastroenterol 2017;**18**:6-12.
37. GOMEZ-MORENO A.Z., PINEDA-TENOR D., JIMENEZ-SOUSA M.A., SÁNCHEZ-RUANO J.J., ARTAZA-VARASA T., SAURA-MONTALBAN J., *et al. Liver stiffness measurement predicts liver-related events in patients with chronic hepatitis C: A retrospective study.* PLoS One 2017;**12**:e0184404.
38. BOGLIONE L., CUSATO J., CARITI G., DI PERRI G., D'AVOLIO A. *Role of IL28B genotype in the liver stiffness increase in untreated patients with chronic hepatitis C*. Infect Genet Evol 2017;**53**:195-8.
39. SCHWABL P., MANDORFER M., STEINER S., SCHEINER B., CHROMY D., HERAC M., *et al. Interferon-free regimens improve portal hypertension and histological necroinflammation in HIV/HCV patients with advanced liver disease*. Aliment Pharmacol Ther 2017;**45**:139-49.
40. LENS S., ALVARADO E., MARIÑO Z., LONDOÑO M.C., LLOP E., MARTINEZ J., *et al. Effects of all-oral anti-viral therapy on HVPG and systemic hemodynamics in patients with hepatitis C virus-associated cirrhosis*. Gastroenterology 2017;**153**:1273-83.e1.
41. TAG-ADEEN M., ALSENBESY M., GHWEIL A.A., ABD ELRAZEK M.A.H., ELGOHARY E.A., SALLAM M.M., *et al. Liver stiffness measurement and spleen diameter as predictors for the presence of esophageal varices in chronic hepatitis C patients*. Medicine (Baltimore) 2017;**96**:e8621.
42. SILVA M.J., BERNARDES C., PINTO J., LOUREIRO R., DUARTE P., MENDES M., *et al. Baveno VI recommendation on avoidance of screening endoscopy in cirrhotic patients: Are we there yet?* GE Port J Gastroenterol 2017;**24**:79-83.

43. AUGUSTIN S., PONS M., MAURICE J.B., BUREAU C., STEFANESCU H., NEY M., *et al. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease*. Hepatology 2017;**66**:1980-8.
44. MARCONI C., BELLAN M., GIARDA P., MINISINI R., FAVRETTO S., BURLONE M.E., *et al. Cardiac dysfunction as an early predictor of portal hypertension in chronic hepatitis C.* Ann Gastroenterol 2017;**30**:675-81.
45. BELLAN M., SAINAGHI P.P., MINH M.T., MINISINI R., MOLINARI L., BALDRIGHI M., *et al. Gas6 as a predictor of esophageal varices in patients affected by hepatitis C virus related-chronic liver disease*. Biomark Med 2018;**12**:27-34.
46. CHROMY D., SCHWABL P., BUCSICS T., SCHEINER B., STRASSI R., MAYER F., *et al. Non-invasive liver fibrosis assessment and HCV treatment initiation within a systematic screening program in HIV/HCV coinfected patients*. Wien Klin Wochenschr 2018;**130**:105-14.
47. CEPEDA J.A., THOMAS D.L., ASTEMBORSKI J., SULKOWSKI M.S., KIRK G.D., MEHTA S.H. *Increased mortality among persons with chronic hepatitis C with moderate or severe liver disease: A cohort study*. Clin Infect Dis 2017;**65**:235-43.
48. FACCIORUSSO A., DEL PRETE V., TURCO A., BUCCINO R.V., NACCHIERO M.C., MUSCATIELLO N. *Long-term liver stiffness assessment in HCV patients undergoing antiviral therapy: Results from a 5-year cohort study.* J Gastroenterol Hepatol 2018;**33**:942-9.
49. CHEN YI MEI S.L.G., THOMPSON A.J., CHRISTENSEN B., CUNNINGHAM G., MCDONALD L., *et al. Sustained virological response halts fibrosis progression: A long-term follow-up study of people with chronic hepatitis C infection*. PLoS One 2017;**12**:e0185609.
50. PONS M., SANTOS B., SIMÓN-TALERO M., VENTURA-COTS M., RIVEIRO-BARCIELA M., ESTEBAN R., *et al. Rapid liver and spleen stiffness improvement in compensated advanced chronic liver disease patients treated with oral antivirals*. Therap Adv Gastroenterol 2017;**10**:619-29.
51. TACHI Y., HIRAI T., KOJIMA Y., ISHIZU Y., HONDA T., KUZUYA T., *et al. Liver stiffness reduction correlates with histological characteristics of hepatitis C patients with sustained virological response*. Liver Int 2017;**38**:59-67.
52. CHAN J., GOELA N., ZHENG H., LAMMERT S., AJAYI T., FRICKER Z., *et al. Direct-acting antiviral therapy for chronic HCV infection results in liver stiffness regression over 12 months post-treatment*. Dig Dis Sci 2018;**63**:486-92.
53. RAMOS H., LINARES P., BADIA E., MARTIN I., GÓMEZ J., ALMOHALLA C., *et al.* Asociación Castellano Y Leonesa de Hepatología ACyLHE. *Interferon-free treatments in patients with hepatitis C genotype 1-4 infections in a real-world setting.* World J Gastrointest Pharmacol Ther 2017;**8**:137-46.
54. ELSHARKAWY A., ALEM S.A., FOUARD R., EL RAZIKY M., EL AKEL W., ABDO M., *et al. Changes in liver stiffness measurements and fibrosis scores following sofosbuvir based treatment regimens without interferon*. J Gastroenterol Hepatol 2017;**32**:1624-30.
55. NEUKAM K., MORANO-AMADO L.E., RIVERO-JUÁREZ A., MACÍAS J., GRANADOS R., ROMERO-PALACIOS A., *et al.* Grupo de Estudio de Hepatitis Vírica, of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica: GEHEP- SEIMC and Grupo de Estudio de Hepatitis Vírica, of the Sociedad Andaluza de Enfermedades Infecciosas y Microbiología Clínica: HEPAVIR/Red de Investigación en SIDA (RIS-HEP07). *Liver stiffness predicts the response to direct-acting antiviral-based therapy against chronic hepatitis C in cirrhotic patients.* Eur J Clin Microbiol Infect Dis 2017;**36**:853-61.
56. AKUTA N., SEZAKI H., SUZUKI F., KAWAMURA Y., HASAKA T., KOBAYASHI M., *et al. Favorable efficacy of daclatasvir plus asunaprevir in treatment of elderly Japanese patients infected with HCV genotype 1b aged 70 and older*. J Med Virol 2017;**89**:91-8.
57. OGASAWARA N., KOBAYASHI M., AKUTA N., KOMINAMI Y., FUJIYAMA S., KAWAMURA Y., *et al. Serial changes in liver stiffness and controlled attenuation parameter following direct-acting antiviral therapy against hepatitis C virus genotype 1b*. J Med Virol 2017;**90**:313-9.
58. SINGH S., FACCIORUSSO A., LOOMBA R., FALCK-YTTER Y.T. *Magnitude and kinetics of decrease in liver stiffness after antiviral therapy in patients with chronic hepatitis C: A systematic review and meta-analysis*. Clin Gastroenterol Hepatol 2017;**16**:27-38.e4.
59. TAG-ADEEN M., SABRA A.M., AKAZAWA Y., OHNITA K., NAKAO K. *Impact ofhepatitis C virus genotype-4 eradication following direct acting antivirals on liver stiffness measurement.* Hepat Med 2017;**9**:45-53.
60. JIMÉNEZ-SOUSA M.Á., GÓMEZ-MORENO A.Z., PINEDA-TENOR D., MEDRANO L.M., SÁNCHEZ-RUANO J.J., FERNÁNDEZ-RODRÍGUEZ A., *et al. CXCL9-11polymorphisms are associated with liver fibrosis in patients with chronic hepatitis C: a cross-sectional study.* Clin Transl Med 2017;**6**:26.
61. STEINER S., BUCSICS T., SCHWABL P., MANDORFER M., SCHEINER B., AICHELBURG M.C., *et al. Progress in eradication of HCV in HIV positive patients with significant liver fibrosis in Vienna.* Wien Klin Wochenschr 2017;**129**:517-26.
62. SPOREA I., LUPUŞORU R., MARE R., POPESCU A., GHEORGHE L., IACOB S., *et al. Dynamics of liver stiffness values by means of transient elastography in patients with HCV liver cirrhosis undergoing interferon free treatment*. J Gastrointestin Liver Dis 2017;**26**:145-50.
63. FERRAIOLI G., MAIOCCHI L., LISSANDRIN R., TINELLI C., DE SILVESTRI A., FILICE C. on behalf of the Liver Fibrosis Study Group. *Ruling-in and ruling-out significant fibrosis and cirrhosis in patients with chronic hepatitis C using a shear wave measurement method.* J Gastrointestin Liver Dis 2017;**26**:139-43.
64. TADA T., KUMADA T., TOYODA H., MIZUNO K., SONE Y., KATAOKA S., *et al. Improvement of liver stiffness in patients with hepatitis C virus infection who received direct-acting antiviral therapy and achieved sustained virological response*. J Gastroenterol Hepatol 2017;**32**:1982-8.
65. SUDA T., OKAWA O., MASAOKA R., GYOTOKU Y., TOKUTOMI N., KATAYAMA Y., *et al. Shear wave elastography in hepatitis C patients before and after antiviral therapy*. World J Hepatol 2017;**9**:64-8.
66. DELLA-GUARDIA B., EVANGELISTA A.S., FELGA G.E., MARINS L.V., SALVALAGGIO P.R., ALMEIDA M.D. *Diagnostic accuracy of transient elastography for detecting liver fibrosis after liver transplantation: A specific cut-off value is really needed?* Dig Dis Sci 2017;**62**:264-72.

67. KORDA D., LENARD Z.M., GERLEI Z., JAKAB Z., HABOUB-SANDIL A., WAGNER L., *et al. Shear-wave elastography for the assessment of liver fibrosis in liver transplant recipients treated for hepatitis C virus recurrence*. Eur J Gastroenterol Hepatol 2017;**30**:27-32.
68. MARTINI S., SACCO M., STRONA S., ARESE D., TANDOI F., DELL OLIO D., *et al. Impact of viral eradication with sofosbuvir-based therapy on the outcome of post-transplant hepatitis C with severe fibrosis.* Liver Int 2017;**37**:62-70.
69. MAURO E., CRESPO G., MONTIRONI C., LONDOÑO M.C., HERNÁNDEZ-GEA V., RUIZ P., *et al. Portal pressure and liver stiffness measurements in the prediction of fibrosis regression after SVR in recurrent hepatitis C*. Hepatology 2018;**67**:1683-94.
70. BREGENZER A., CONEN A., KNUCKEL J., FRIEDL A., EIGENMANN .F, NÄF M., *et al. Management of hepatitis C in decentralised* versus *centralised drug substitution programmes and minimally invasive point-of-care tests to close gaps in the HCV cascade*. Swiss Med Wkly 2017;**147**:w14544.
71. PARISI S.G., BASSO M., MENGOLI C., SCAGGIANTE R., ANDREIS S., FRANZETTI M.M., *et al. Liver stiffness is not associated with short- and long-term plasma HIV RNA replication in immunocompetent patients with HIV infection and with HIV/HCV coinfection*. Ann Gastroenterol 2017;**30**:534-1.
72. ERMAN A., SATHYA A., NAM A., BIELOECKI J.M., FELD J.J., THEIN H.H., *et al. Estimating chronic hepatitis C prognosis using transient elastography-based liver stiffness: A systematic review and meta-analysis*. J Viral Hepat 2018;**25**:502-13.
73. BRUNO G., SARACINO A., SCUDELLER L., FABRIZIO C., DELL'ACQUA R., MILANO E., *et al. HCV mono-infected and HIV/HCV co-infected individuals treated with direct-acting antivirals: to what extent do they differ?* Int J Infect Dis 2017;**62**:64-71.
74. MERCHANTE N., RIVERO-JUÁREZ A., TÉLLEZ F., MERINO D., RÍOS-VILLEGAS M.J., OJEDA-BURGOS G., *et al.*; Grupo Andaluz para el Estudio de las Hepatitis Víricas (HEPAVIR) de la Sociedad Andaluza de Enfermedades Infecciosas (SAEI). *Liver stiffness predicts variceal bleeding in HIV/HCV-coinfected patients with compensated cirrhosis.* AIDS 2017;**31**:493-500.
75. XU H., KONG W., LIU L., CHI X., WANG X., WU R., *et al. Accuracy of M2BPGi, compared with Fibro Scan®, in analysis of liver fibrosis in patients with hepatitis C.* BMC Gastroenterol 2017;**17**:62.
76. SOTO M., SAMPIETRO-COLOM L., LASALVIA L., MIRA A., JIMÉNEZ W., NAVASA M. *Cost-effectiveness of enhanced liver fibrosis test to assess liver fibrosis in chronic hepatitis C virus and alcoholic liver disease patients*. World J Gastroenterol 2017;**23**:3163-73.
77. BACHOFNER J.A., VALLI P.V., KRÓGER A., BERGAMIN I., KÜNZLER P., BASERGA A., *et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index*. Liver Int 2017;**37**:369-76.

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