

Update on the role of elastography in liver disease

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Abstract: The diagnosis of liver fibrosis and the assessment of its severity are important to provide appropriate management, to determine the prognosis or the need for surveillance. Currently, for fibrosis staging, liver stiffness measurement (LSM) with the shear wave elastography (SWE) techniques is considered a reliable substitute for liver biopsy in several clinical scenarios. Nonetheless, it should be emphasized that stiffness value is a biomarker of diffuse liver disease that must be interpreted taking into consideration anamnesis, clinical and laboratory data. In patients with diffuse liver disease, it is more clinically relevant to determine the likelihood of advanced disease rather than to obtain an exact stage of liver fibrosis using a histologic classification. In this regard, a 'rule of five' for LSMs with vibration-controlled transient elastography (VCTE) and a 'rule of four' for LSMs with the acoustic radiation force impulse (ARFI)-based techniques have been proposed. In patients with advanced chronic liver disease (CLD), the risk of liver decompensation increases with increasing liver stiffness value. SWE has been proposed as a tool to predict the risk of death or complications in patients with CLD. LSM by VCTE combined with platelets count is a validated non-invasive method for varices screening, with very good results in terms of invasive procedures being spared. ARFI-based techniques also show some promising results in this setting. LSM, alone or combined in scores or algorithms with other parameters, is used to evaluate the risk of hepatocellular carcinoma occurrence. Due to the high prevalence of CLD, screening the population at risk is of interest but further studies are needed.

Keywords: shear wave elastography, chronic liver disease, liver stiffness, chronic hepatitis, portal hypertension, clinical outcomes, VCTE, ARFI-based techniques, cirrhosis, NAFLD, guidelines

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Introduction

Liver fibrosis, which is the hallmark of chronic liver disease (CLD) due to several etiological agents, may lead to liver cirrhosis with its related complications.¹ Assessment of the presence and severity of liver fibrosis is important in the management of patients with CLD because the amount of fibrosis can predict the prognosis and might influence the treatment choice.

With the availability of effective treatments for viral hepatitis, the rate of virus-induced CLD is decreasing while the rate of non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) is increasing due to the obesity and

diabetes epidemics and sedentary lifestyles. Currently, NAFLD has become the most common cause of liver disease with an estimated prevalence of about 25% in the adult population and an increased risk in patients with obesity, type 2 diabetes, hypertension, or dyslipidemia.^{2,3} It has been reported that the prevalence of NASH among NAFLD patients without an indication for liver biopsy is around 7% in Asia and almost 30% in North America.³

Liver biopsy is considered the reference standard for the assessment of CLD because the analysis of the histologic specimen gives several other information besides fibrosis staging. However, it is an

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invasive procedure with some risks of complications and some limitations including sampling errors and interobserver variability.^{4,5} In the real world, it has been reported that there is also a not negligible variability in reporting and grading NASH and fibrosis staging.⁶

Shear wave elastography (SWE) assesses the biomechanical properties of the liver tissue giving a numerical value of stiffness that is a quantitative surrogate biomarker of liver fibrosis.⁷ It is available since several years and has become an accepted substitute for liver biopsy for fibrosis staging in several clinical scenarios.⁸

SWE can be performed with ultrasound (US) systems or magnetic resonance imaging systems. All SWE techniques assess the velocity of shear waves created by a mechanically induced stress.

US SWE techniques include vibration controlled transient elastography (VCTE) and acoustic radiation force impulse (ARFI)-based techniques. In the former, the shear waves are generated by a body-surface-controlled vibration, whereas in the latter they are generated by the push-pulse of a focused US beam. The ARFI-based techniques include point SWE (pSWE) that measures the stiffness in a small and fixed area and two-dimensional SWE (2D-SWE) that measures the stiffness over a larger area in which a color-coded parametric map of the stiffness is also displayed. The values of the US SWE techniques are given in meter/second (m/s), that is, the velocity of the shear waves, or can be converted to the unit of the Young's modulus in kilopascal (kPa) making some assumptions that are not always correct.⁹

With magnetic resonance elastography (MRE), the shear waves are generated on the body surface by a driver that produces low-frequency vibrations. The stiffness assessment is made in a region of interest that is typically the right lobe of the liver, and thus in a much larger volume of tissue respect to US-based elastography methods. Results are given in the shear modulus unit in kPa. It must be underscored that the shear modulus is about three times smaller than the Young's modulus; therefore, results are not comparable.

This review analyses the role played by US SWE in CLD, discussing advantages and limitations.

Liver stiffness for fibrosis staging

The diagnosis of liver fibrosis and the assessment of its severity are important to provide appropriate management, to determine the prognosis or the need for surveillance.

Several guidelines have been released regarding the use of SWE techniques for the staging of liver fibrosis.⁹⁻¹⁵ Currently, liver stiffness measurement (LSM) with the SWE techniques is considered a reliable substitute for liver biopsy in several clinical settings. All SWE techniques perform better in assessing advanced fibrosis/cirrhosis – mainly in ruling out the disease – than in identifying early stages of liver fibrosis.⁹⁻¹⁵

Among the SWE techniques, VCTE is the most validated and most used in the clinical practice, particularly because it is a user-friendly technique giving an LSM without dealing with the quality of the US B-mode image that is instead of utmost importance when using an ARFI-based technique.¹³ VCTE is available since 2003, there is abundant literature regarding its accuracy, and it has become a point-of-care tool for the non-invasive assessment of liver fibrosis. The stiffness value, in kPa, is obtained together with the controlled attenuation parameter (CAP) which is an estimate of the attenuation (given in decibel/meter) of the US beam that traverses the liver tissue and is directly related to the amount of fat in the liver.^{16,17} Currently, an attenuation coefficient to quantify liver fat content is available also on several US systems and early works suggest an accuracy higher than CAP.^{16,17}

The ARFI-based techniques, that is, the techniques integrated into US systems, became commercially availability some years later than VCTE and the published studies are fewer than that performed with VCTE. However, it must be underscored that all studies that have compared the ARFI-based techniques to VCTE using histology as the reference standard have shown that the accuracy in fibrosis staging is similar or better than that of VCTE.⁹⁻¹⁵

It is worth mentioning that all SWE techniques assess stiffness. Even though stiffness is strongly related to liver fibrosis, there are several other conditions that lead to an increase in liver stiffness independently of liver fibrosis, including liver congestion, inflammation, acute hepatitis,

extra-hepatic cholestasis, and infiltrative diseases.^{9–15} Altogether, these are confounding factors when stiffness is used as a surrogate marker of liver fibrosis. Hence, the stiffness value should be interpreted in the clinical context taking into consideration the patient's anamnesis, clinical conditions, and laboratory tests. An increase in transaminases values is an indirect biomarkers of liver inflammation. Transaminases flares lead to overestimation of liver fibrosis.^{9–15} It has been reported that in treatment-naïve chronic hepatitis B patients even a mild to moderate increase in ALT values (one to five times the upper limit of normal) may lead to liver stiffness values higher than that observed in patients with the same etiology of liver disease but with normal ALT levels.¹⁵ As for liver steatosis, there are conflicting results in the literature about its impact on LSM accuracy and the risk of false-positive results.^{11,13,15}

There is also a transient increase in liver stiffness after eating that may last for up to 3 h.¹⁸ Therefore, fasting for 4 h before the stiffness assessment is recommended.¹³

SWE techniques were validated using liver histology as the reference standard. This has allowed to prove the positive relationship between liver stiffness and liver fibrosis and to obtain thresholds for fibrosis staging with SWE. Nonetheless, it is important to underscore that elastography measures the stiffness, which is related not only to fibrosis but also to inflammation and liver congestion among other factors.^{9–15} Therefore, it is inappropriate to report and interpret the stiffness values using a histological classification of liver fibrosis.¹⁹ Moreover, stiffness is a quantitative estimate in a continuous scale, whereas the histological scoring systems for liver fibrosis are generally based on categorical scales. Thus, even in 'ideal' conditions, an overlap between consecutive stages of liver fibrosis is unavoidable when using liver stiffness as a quantitative biomarker of liver fibrosis.

It must be highlighted that the spectrum of advanced fibrosis (F3 stage) and cirrhosis (F4 stage) is a continuum in asymptomatic patients and often it is not possible to clinically differentiate the two stages.²⁰ Therefore, the Baveno VI consensus on portal hypertension (PH) has proposed the term 'compensated advanced chronic liver disease' (cACLD), which includes F3 and F4 stages.²⁰ Clinically, it is more relevant to

rule-in or rule-out significant disease than to provide a precise stage of liver fibrosis.

In patients with virus-related chronic hepatitis or with NAFLD, guidelines have suggested to interpret LSMs by referring to the disease risk rather than to an exact stage of fibrosis mimicking histology. For VCTE, the 'rule of five' has been proposed: LSM ≤ 5 kPa has a high probability of being normal; LSM < 10 kPa in the absence of other known clinical signs rules out cACLD; LSM between 10 and 15 kPa is suggestive of cACLD but needs further tests for confirmation; LSM > 15 kPa is highly suggestive of cACLD while LSM ≥ 20 –25 kPa together with platelets count $< 150,000$ rule in clinically significant portal hypertension (CSPH).^{15,20,21} It must be highlighted that, based on recent literature data,^{22,23} the 2021 update of the European Association for the Study of the Liver (EASL) clinical practice guidelines on non-invasive tests for evaluation of liver disease severity and prognosis has recommended that advanced fibrosis is ruled out with an LSM by VCTE < 8 kPa in NAFLD and alcoholic liver disease (ALD).¹¹

In ALD patients, LSM is strongly influenced by liver inflammation, and even a minor increase in aspartate aminotransferase (AST) level affects LSMs and might lead to overestimation of the severity of liver fibrosis.²⁴ Of note, a meta-analysis reported that for concentrations of AST and bilirubin within the normal range the liver stiffness cutoffs were similar to those reported in chronic hepatitis C for all stages of liver fibrosis.²⁵ Active drinking is associated with an increase in liver stiffness that declines rapidly after alcohol withdrawal (0.5–4 weeks of abstinence).^{26–28} The decline is associated with a normalization of transaminases, bilirubin, alkaline phosphatase, and/or gammaglutamyltransferase. Therefore, caution is needed in interpreting the results obtained in individuals with ongoing alcohol abuse or with acute alcoholic hepatitis.¹⁵

A drawback of the ARFI-based techniques is that the thresholds for fibrosis staging are different among different US systems. However, these differences are smaller for LSMs up to 15 kPa which is the most clinically relevant range of values for the staging of liver fibrosis.²⁹

Based on literature data, the update to the Society of Radiologists in Ultrasound (SRU) consensus

has highlighted that the overlap of LSMs between METAVIR stages is as large if not larger than the difference between different techniques.¹³ The SRU consensus recommends using a low cutoff value below which there is a high probability of no or mild fibrosis and a high cutoff value above which there is a high probability of cACLD. It suggests to use a 'rule of four' for fibrosis staging with ARFI-based techniques in patients with chronic viral hepatitis or NAFLD: LSM ≤ 5 kPa has high probability of being normal; LSM < 9 kPa, in the absence of other clinical signs of CLD, rules cACLD out; LSM between 9 kPa and 13 kPa is suggestive of cACLD but may need further test for confirmation; and LSM > 13 kPa is highly suggestive of cACLD. There is high risk of CSPH with LSMs > 17 kPa, but additional tests may be required. In patients with NAFLD, the cutoff values for cACLD may be lower and follow-up or additional testing, even among those with LSMs between 7 and 9 kPa, is recommended.¹³

There is a decline of liver stiffness values in patients with chronic viral hepatitis who achieve sustained virologic response (SVR) with treatment due also to improvement of the inflammation, and this decline is very rapid in patients with chronic hepatitis C successfully treated with direct acting antivirals (DAAs). In these cases, the rule of four for the ARFI techniques or the rule of five for VCTE cannot be applied because the use of LSM cutoffs that were obtained in treatment-naïve patients can underestimate liver fibrosis.^{9,11,13,15} Moreover, SWE is not recommended to detect fibrosis regression after antiviral treatment using liver stiffness cutoffs that were obtained in viremic patients, and screening for hepatocellular carcinoma (HCC) and PH should continue despite the decrease in liver stiffness if the patient had cACLD before starting the treatment.^{9,11,13,15}

Given the NAFLD disease burden, the use of non-invasive tests is cost-saving and can decrease the risk related to performing a liver biopsy. A recent individual patient-data meta-analysis has reported that sequential combinations of non-invasive markers with a lower cutoff to rule-out advanced fibrosis and a higher cutoff to rule-in cirrhosis can reduce the need for liver biopsy in patients with NAFLD.³⁰ The proposed algorithm combined the fibrosis-4 score (FIB-4) with VCTE: FIB-4 < 1.3 followed by LSM by VCTE < 8 kPa to rule-out advanced fibrosis,

and FIB-4 ≥ 2.67 followed by LSM ≥ 10 kPa to rule-in advanced fibrosis (66% sensitivity and 86% specificity). With cutoffs of Fib-4 and LSM, respectively, ≥ 3.48 and ≥ 20 kPa the specificity increased to 90%.

Studies for assessing liver fibrosis in primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and autoimmune hepatitis (AIH) are few and performed mostly using VCTE.¹¹ Currently, in the autoimmune cholangiopathies, liver biopsy is needed only if there is the suspicion of coexistence of AIH, NASH, or other comorbidities, or in PBC cases unresponsive to the therapy.^{11,31}

In PSC patients, studies performed using VCTE have shown that LSM has a good accuracy in predicting advanced fibrosis and cirrhosis. In a series of 73 patients, the threshold of liver stiffness by VCTE to identify patients with cACLD was 9.6 kPa with sensitivity, specificity, and accuracy above 80% and an area under the receiver operating characteristic (AUROC) > 0.90 .³²

According to different studies, VCTE seems to be a reliable non-invasive tool for assessing advanced liver fibrosis and disease progression in patients with PBC. The largest is a multicenter study on 167 treatment-naïve PBC patients that identified two cutoff values (LSM by VCTE ≤ 6.5 and > 11.0 kPa) to rule-out or rule-in, respectively, advanced fibrosis and validated them externally.³³

Data regarding the use of ARFI techniques in PBC and PSC are promising but still scarce to translate them in clinical practice.

In patients with AIH, the role of hepatic inflammation as a confounding factor that can lead to overestimation of liver stiffness, independently from fibrosis stage, should be taken into account. For this reason, guidelines have recommended to stage liver fibrosis after at least 6 months of immunosuppressive therapy.¹¹

Portal hypertension

The hepatic venous pressure gradient (HVPG) assessment remains the gold standard procedure to detect not only the presence and the severity of PH, but also the mechanism leading to it since it gives information about the site of the increased resistance to the portal flow. A HVPG value ≥ 10 mmHg defines CSPH and is independently

associated with an increased risk of complications and death. However, HVPG represents an expensive and invasive technique not available in all clinical settings.³⁴ There is an excellent correlation between liver stiffness and HVPG values and it has been shown that the accuracy of LSM in ruling-in and ruling-out CSPH increases when combined with other parameters.³⁵ In the 'ANTICIPATE' study, a score called liver stiffness-spleen size-to-platelet ratio score (LSPS) was able to identify up to 80% of patients with CSPH. Furthermore, LSPS identified also patients with a very low risk (<5%) of varices needing treatment (VNT); therefore, it was proposed as a tool to triage patients needing simple follow-up or further investigation with endoscopy.³⁶

The Baveno VI consensus has proposed the combination of LSM by VCTE and platelet count as a non-invasive approach to screen patients with virus-related cACLD for high-risk varices. In particular, it is highlighted that an LSM < 20 kPa together with a platelet count > 150,000/mm³ is associated with a very low risk of having VNT and these patients can safely avoid screening endoscopy and can be followed up by yearly repetition of VCTE and platelet count. Screening endoscopy should be carried out in case the LSM increases or the platelet count declines.²⁰

Although the application of the Baveno VI rules had a good diagnostic accuracy in predicting the presence of VNT, the total number of spared endoscopies using these rules seems relatively low.³⁷ For this reason, patients from the ANTICIPATE cohort (499 patients with cACLD of different etiologies) were used to evaluate the diagnostic performance of new thresholds of LSM and platelet count for the identification of patients at very low risk (<5%) of having VNT. The new criteria (expanded-Baveno VI) were further validated in two additional cohorts. The new expanded classification rule with platelet count > 150,000/mm³ and LSM < 25 kPa would have potentially spared 40% of endoscopies *versus* 21% with Baveno VI criteria, with a very low risk of missing VNT (1.6%) in patients with cACLD due to hepatitis C virus (HCV), ALD or NASH.³⁷

The Baveno VII consensus has underscored that non-invasive tests are accurate to identify CSPH in clinical practice and has refined the previous criteria, reinforcing the 'rule of 5'. In particular, LSM by VCTE ≤ 15 kPa plus platelet count

≥ 150,000/mm³ rules out CSPH. In patients with virus- and/or alcohol-related cACLD and non-obese [body mass index (BMI) < 30 kg/m²] NASH-related cACLD, an LSM value by VCTE ≥ 25 kPa, is sufficient to rule in CSPH. In patients with virus- and/or alcohol-related and non-obese NASH-related cACLD with LSM values < 25 kPa, the ANTICIPATE model can be used to predict the risk of CSPH. Based on this model, patients with LSM values between 20 and 25 kPa and platelet count < 150,000/mm³ or LSM values between 15 and 20 kPa and platelet count < 110,000/mm³ have a CSPH risk of at least 60%. In patients with NASH-related cACLD, the ANTICIPATE NASH model (including LSM, platelet count, and BMI) may be used to predict the risk of CSPH but further validation is needed.²¹

The performance of the ARFI-based techniques has also been assessed in this setting with some promising results; however, more studies are needed before implementing their use in the diagnostic work-up of patients with cACLD.^{13,21}

In case of severe PH, the correlation between liver stiffness and portal pressure is partially lost due to the contribute of dynamic components such as intra-hepatic vasoconstriction and splanchnic vasodilatation. Since the increased portal pressure is transmitted to the spleen through the splenic vein, spleen stiffness measurement (SSM) seems to play a role as a reliable marker of PH in more severe stages.³⁸

Several studies using VCTE have shown the superiority of SSM compared with LSM to assess the risk of CSPH and the presence of esophageal varices (EVs).³⁹ The diagnostic performance obtained from these studies was reasonably good, and specificity and sensitivity were greater than 70% in most of the cases.⁴⁰ However, the range of cutoff values is wide, ranging from 47.6 to 56.3 kPa for CSPH and from 40.8 to 65 kPa for detecting any EVs. For large varices, cutoffs are narrow, ranging from 54 to 54.5 kPa but only few studies have been published.⁴⁰ This wide range of cutoff values was probably due to different grade of severity of the underlying liver disease included in the studies.

In all these studies, the standard VCTE – which has a frequency pressure of 50 hertz (Hz) with a ceiling stiffness threshold of 75 kPa – was used. A

new spleen-dedicated 100 Hz VCTE provided a better correlation with HVPG and a higher accuracy for the detection of EVs and VNT than the standard 50 Hz in patients with cACLD.^{41,42} Furthermore, the combination of Baveno VI criteria and an SSM cutoff value of 38.3 kPa significantly increased the spared endoscopy rate compared with Baveno VI criteria alone or combined with SSM measured by the standard 50 Hz setting of the FibroScan.⁴¹

Based on the literature data, the Baveno VII consensus highlights that SSM by VCTE can be used in cACLD due to viral hepatitis (untreated HCV; untreated and treated HBV) to rule-out and rule-in CSPH with cutoff values of <21 kPa and >50 kPa, respectively. However, validation of the best cutoff using a 100 Hz specific VCTE software as well as using pSWE and 2D-SWE is still needed.²¹

Prediction of clinical outcomes

LSM by VCTE combined with platelets count is a validated non-invasive method for varices screening, with very good results in terms of invasive procedures being spared.

In a recent large-sized retrospective cohort study (5849 patients), the combination of LSM by VCTE and Fib-4 score into a single Fib-5 score demonstrated a superior discrimination (AUROC 0.87) over LSM (AUROC 0.69) and FIB-4 (AUROC 0.67) taken singularly for identifying patients with cACLD at risk of developing complications of PH.⁴³

In patients with cACLD, the risk of liver decompensation increases with increasing liver stiffness value. A study, which evaluated liver-related events (LREs) in a cohort of more than 3000 patients with cACLD due to mixed etiologies, found that the incidence of decompensation at 5 years was 3.7% for LSM <15 kPa, 8.6% for LSM 15–25 kPa, and 19.0% for LSM >25 kPa. Likewise, there was also an association between LSM and the rate of HCC at 5 years: 1.7% for LSM <15 kPa, 2.4% for LSM 15–25 kPa, and 4.1% for LSM >25 kPa.⁴⁴ In a large NAFLD cohort, it was found that a stepwise algorithm with FIB-4 followed by VCTE accurately stratified the LREs risk: in patients with FIB-4 \geq 1.30 and then VCTE >12.0 kPa, the adjusted hazard ratio for LREs was 12.4.⁴⁵

It has been reported that, after adjusting for age, sex, model for end-stage liver disease (MELD), cohort source, and etiology of liver disease, the risk of LREs increased by 6% for each unit increase in the LSM above 20 kPa.⁴⁶ Similar results were obtained in a meta-analysis that included studies performed with VCTE or MRE: each kPa unit increase in LSM was associated with a 7% higher risk of developing decompensated cirrhosis and with an 11% higher risk of HCC.⁴⁷

In a cohort of patients with liver transplantation, it has been reported that LSM by a 2D-SWE technique \geq 11 kPa was independently associated with mortality (hazard ratio: 2.45).⁴⁸

A multicenter study has shown that a combination of the MELD score with LSMs is useful for predicting clinical outcomes in patients with ACLD.^{49,50} A MELD score of 10 points and an LSM of 20 kPa by 2D-SWE ('M10LS20' algorithm) were the optimal cutoffs for stratifying the 2-year risk of mortality. Using the M10LS20 algorithm, the patients were stratified into three different risk groups: good prognosis (patients with both MELD score and LSM below the cutoffs), intermediate prognosis (patients with one parameter above and the other one below the cutoff), and poor prognosis (patients with both parameters above the cutoffs). The three groups had significantly different survival rates both at short-term and long-term follow-up and different risk of decompensation or further decompensation. Of note, the M10LS20 algorithm showed a similar performance also using pSWE or VCTE for LSMs.

In patients with chronic viral hepatitis, the risk of developing LREs cannot be completely eliminated even in those who achieve SVR; this risk is mainly related to the stage of liver fibrosis before starting the treatment.

It has been reported that successful treatment with DAAs in HCV patients with compensated or decompensated cirrhosis is associated with reduced risk for HCC.⁵¹ The relative risk reduction is similar in patients with and without cirrhosis.⁵² However, another study has demonstrated that patients with cirrhosis before SVR to treatment for HCV infection continue to have a high risk for HCC (>2%/year) for several years and should continue surveillance.⁵³

A recent multicenter prospective study, including more than 1000 patients who achieved SVR after treatment with DAAs, has reported that patients with VCTE values >10 kPa or with cirrhosis assessed by US before the treatment had a higher risk for HCC if the FIB-4 was >3.25 with respect to patients with FIB-4 <3.25 .⁵⁴ The rate of HCC occurrence was 8.8% in the former group and 2.4% in the latter group. Of note, patients who maintained FIB-4 >3.25 and VCTE values >10 kPa after SVR had the highest risk of HCC occurrence (13.7%).

A study in a large series of US veterans with hepatitis C treated with DAAs has reported that post-treatment liver stiffness >20 kPa by VCTE, but not pre-treatment liver stiffness, was independently associated with the development of decompensated cirrhosis and the composite outcome of death, liver transplant, decompensated cirrhosis, or HCC.⁵⁵

A study that included HCV patients who achieved SVR after DAAs treatment reported that the main predictors of HCC risk were the values, at the follow-up, of albumin and LSM by VCTE. In patients with LSM <10 kPa or with LSM between 10 and 20 kPa and with albumin ≥ 4.4 g/dl the incidence of HCC was 0.6/100 patients-year, whereas in patients with LSM ≥ 20 kPa or those with LSM between 10 and 20 kPa but albumin <4.4 g/dl the incidence was 2.9/100 patients-year.⁵⁶ Of note, in contrast to what reported in other studies, when patients were stratified for the risk of HCC according to LSM at baseline, there was not any differences in HCC incidence among patients with LSM ≥ 20 kPa and those with LSM <20 kPa. Another study reported that a 30% decrease in LSM after DAAs was one of the predictors inversely associated with the risk of HCC.⁵⁷

Several models have been proposed in patient with chronic hepatitis B treated with antivirals for predicting the risk of HCC. They are based on different combinations of LSM and several other parameters, such as age, gender, albumin, ALT, HBV-DNA, HBsAg, and they all show a good performance.^{58–62}

In an international retrospective study on almost 4000 patients with PBC, it was found that LSM improved the prognostic ability of established blood-based biomarkers of response to treatment:

VCTE LSM cutoffs of 8 kPa and 15 kPa were optimal in separating low, medium, and high-risk groups.⁶³

For ALD, the EASL clinical practice guidelines have highlighted that MELD score is still the recommended prognostic tool for predicting the outcome in patients with decompensated cirrhosis, and none of the non-invasive tests is currently useful in this setting.¹¹

Screening for liver fibrosis in the general population

The global burden of diseases study has reported that cirrhosis accounts for 2.2 million deaths worldwide.⁶⁴ The global prevalence of cirrhosis is probably underestimated because most patients develop symptoms only at a late stage when decompensation of cirrhosis or development of HCC occur.⁶⁵ A recent study based on the National Health and Nutrition Examination Survey (NHANES) data source estimated that the prevalence of cirrhosis was 0.27% of the general US population, with hepatitis C, alcohol, and diabetes mellitus playing a significant role.⁶⁶ Of note, 70% of the participants with cirrhosis were unaware of their liver disease.

Due to high prevalence of CLD and the fact that the affected individuals are often asymptomatic, screening the general population for liver fibrosis could be of interest. A diagnosis of liver fibrosis before cirrhosis develops or at an early stage of cirrhosis would lead to an appropriate treatment that might stop or reverse the process.⁶⁷

Studies reported that 5.7%–7.5% of individuals older than 45 years without a known CLD had LSM by VCTE >8 kPa, which was the level used for defining significant fibrosis, and the probability of having significant fibrosis increased by age decade.^{68,69} Participants with both diabetes and steatosis had the highest probabilities of significant fibrosis.⁶⁹ A study in a large Asian population, randomly selected from the government census database and invited for a check-up, reported that 28.6% subjects had fatty liver detected by magnetic resonance spectroscopy, and 3.7% of them had LSM by VCTE ≥ 9.6 kPa, a value suggestive of advanced fibrosis. Of note, fatty liver was found in 14.3% of subjects with normal ALT according to the updated lower cutoffs.⁷⁰ In all these studies, the diagnosis of CLD

would have been missed if patients had been evaluated only with the standard laboratory tests.

What is worrisome is that a study based on the NHANES 2017–2018 database has shown that a significant percentage of adolescents and young adults are at risk for ALD and NAFLD and a subset of these subjects is at risk for significant fibrosis.⁷¹

Individuals with metabolic risk factors, type 2 diabetes, or excessive alcohol consumption are at higher risk of advanced fibrosis. In a large UK cohort, using a serial biomarker algorithm based on blood biomarkers and subsequently LSMs with VCTE, it has been shown that 26.8% of participants with risk factors for developing CLD – defined as hazardous alcohol use, type 2 diabetes, or persistently elevated ALT with negative serology – had clinically significant liver disease (defined as LSM \geq 8 kPa).⁷² In another large Asian cohort of diabetic patients, 17.7% had LSMs in the range of advanced fibrosis.⁷³ Indeed, the recent update to EASL guidelines has suggested to apply non-invasive tests to populations with risk factors for liver disease rather than unselected populations. This would minimize the spectrum effect due to the prevalence of the disease that leads to a low sensitivity in an unselected population.¹¹

Considering the healthcare costs for treating patients with advanced liver disease, screening programs for liver fibrosis with non-invasive tests in categories of subjects at risk could be cost-saving. Large international studies are needed for understanding the benefits and limitations for liver fibrosis screening before applying it to populations at risk for CLD.⁷⁴

Combining cohorts of seven previous independent prospective studies from six countries in which VCTE was used as a screening method for liver fibrosis detection in individuals with and without risk factors for CLD, it has been reported that a cutoff of 9.1 kPa had the best accuracy for the diagnosis of significant fibrosis (\geq F2) in the general population, whereas a cutoff of 9.5 kPa was optimal for individuals at risk of ALD.⁷⁵ Overall, the VCTE screening had a 12% chance of being cost-saving.

A study has been designed for assessing whether LSM by VCTE in the general population is useful to identify subjects with asymptomatic, advanced

CLD.⁷⁶ It will include 30,000 subjects from eight European countries. Results are awaited.

Conclusions

Over the years, SWE techniques have increasingly been used for the staging of fibrosis in patients with diffuse liver disease and their availability has led to a substantial reduction of the number of liver biopsy being performed. SWE techniques, alone or combined with other parameters in scores or algorithms, have shown to be of great value also for assessing the clinical outcome of patients with CLD. LSM by VCTE is a validated non-invasive method for varices screening, with very good results in terms of invasive procedures being spared. ARFI-based techniques also show some promising results in this setting. Due to the high prevalence of CLD, screening the population at risk is of interest but further studies are needed.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contribution(s)

Giovanna Ferraioli: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing.

Davide Roccarina: Data curation; Methodology; Writing – original draft; Writing – review & editing.

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Davide Roccarina: Nothing to disclose.

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