NON-INVASIVE ASSESMENT OF CHRONIC LIVER DISEASE BY TWO DIMENSIONAL SHEAR WAVE ELASTOGRAPHY: AN OVERVIEW

RUNNING TITLE: 2D-SWE in chronic liver disease

[1]Ivica Grgurevic, [1]Tomislav Bokun, [2]Massimo Pinzani

[1]Department of Gastroenterology, Hepatology and Clinical Nutrition, University Hospital Dubrava, University of Zagreb School of Medicine and Faculty of Pharmacy and Biochemistry, Zagreb, Croatia

[2]UCL Institute for Liver and Digestive Health, Sheila Sherlock Liver Centre, Royal Free Hospital, London, UK

AUTHOR CONTRIBUTION:

(1) substantial contributions to conception and design of the study, acquisition of data, or analysis and interpretation of data: Ivica Grgurevic, Tomislav Bokun

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CORRESPONDENCE TO:

Ivica Grgurevic, MD PhD, Assist Prof

Department of Gastroenterology, Hepatology and Clinical Nutrition

Department of Medicine, University Hospital Dubrava, University of Zagreb School of Medicine and Faculty of Pharmacy and Biochemistry

Avenija Gojka Suska 6, Zagreb 10 000, Croatia

Phone +385 1 290 3434, Fax +385 1 290 2550

E-mail: ivica.grgurevic@zg.htnet.hr

ABSTRACT

Liver stiffness (LS) assessed by sonoelastography (SE), has been demonstrated as reliable non-invasive indicator of liver fibrosis stage in patients with chronic liver diseases (CLD). Sonoelastography performs best in ruling-out cirrhosis (F=4) and ruling-in signifficant fibrosis (F≥2). However, it is insufficiently accurate to replace endoscopy for detection of esophageal varices (EV), being able to only ruling-out large EV. LS ≥ 25 kPa by transient elastography (TE) is considered highly suggestive for the presence of clinically significant portal hypertension (CSPH). Higher liver and spleen stiffness have been asociated with adverse clinical outcomes in CLD.

Two-dimensional shear wave elastography (2D-SWE), the latest developed SE method, allows both visualisation and quantification of liver elasticity in real time superimposed over B-mode ultrasound image. Meta-analysis of studies with Supersonic Shear Imaging (SSI) revealed comparable performance of this 2D-SWE to TE in fibrosis staging, with AUROCs 0.85 for F≥2 (LS cut-off 8.04 kPa) and 0.93 for F=4 (LS cut-off 11.12 kPa). Few studies reported very good performance of 2D-SWE (SSI) to rule-in CSPH (AUROCs 0.79-0.95; LS cut-offs 15-25 kPa). While conflicting data exist with respect to its performance in predicting the presence of EV, prognostic utility of 2D-SWE (SSI) was demonstrated in a single study that reported 3.4-fold (*P*=0.026) higher risk of adverse outcome in patients with baseline LS≥21.5 kPa followed over 28 months.

In conclusion, 2D-SWE (SSI) might be used to stage liver fibrosis in CLD, identify patients with compensated cirrhosis under risk of adverse outcomes and potentially stratify risk of having CSPH and EV.

KEYWORDS: Liver Cirrhosis, Fibrosis, Esophageal Varices, Prognosis, Ultrasonography, Elasticity Imaging Techniques

INTRODUCTION

Epidemiology, clinical signifficance and diagnostic challanges in chronic liver disease

In patients with chronic liver disease (CLD) liver fibrosis has been consistently reported as the most important indicator of the disease severity and predictor of the rate and dynamics of development of liver related complications and overall mortality (1,2). Cirrhosis as the distinctive advanced histological stage and clinical entity represents a turning point in the natural history of CLD (3,4). Liver cirrhosis is among the leading causes of death worldwide, with trends of increasing prevalence and mortality. It was ranked the 13th cause of death on the global level in 2013 (5–7). Cirrhosis is no longer considered as a static stage of liver disease, neither histologically nor clinically (8,9). It is indeed increasingly clear that there is a defined chronology in the development of the complications of liver cirrhosis refecting progressive deterioration of liver function and portal hypertension as well as the increased risk of hepatocelular carcinoma (HCC) development (10,11,12). Increased portal pressure is the main driving force for devopment of EV and ascites, and major determinant of prognosis in cirrhotic patients (13). It is important to stress that the measurement of liver stiffness by transient elastography (TE), broadly employed in todays clinical practice, reflects many of the tissue changes typical of an evolving cirrhotic liver.

The recent Baveno VI consensus conference on portal hypertension has proposed the new term "compensated advanced chronic liver disease" (cACLD) encopassing both severe fibrosis and compensated cirrhosis as a continuum to indetify asymptomatic individuals at risk of developing clinically significant portal hypertension (CSPH, defined as hepatic venous pressure gradient-HVPG>10 mmHg) (14).

For these reasons it is increasingly relevant to correlate the stage of liver fibrosis and its progressive worsening in patients with advanced fibrosis and cirrhosis without overt clinical manifestations. Indeed, information on the stage of liver fibrosis helps to prioritize patients for diagnostic approaches such as measurement of HVPG, upper GI endoscopy to evaluate the presence of EV and for reaching a realistic estimate of the risk of liver decompensation, HCC formation and death

These goals can be achieved by using invasive and noninvasive diagnostic methods. Liver fibrosis may be detected and quantified by histological examination of liver biopsy specimen or by non-invasive methods encompassing serological tests and elastographic assesment of the liver stiffness mostly by ultrasound technology but also with magnetic resonance imaging (MRI) (15). The best method to assess severity of portal hypertension (PH) is HVPG measurement, while endoscopy remains golden standard for EV detection and staging (14).

Ultrasound-based elastography (sonoelastography, *SE*) methods have become important in clinical hepatology due to their non-invasiveness, increasing availability and simplicity of handling, as well as diagnostic reliability especially in terms of fibrosis assessment. At present, different SE methods that have been endorsed by the hepatology community might be divided into following cathegories (16) :

1. Shear wave elastography (SWE):
    1.1. Transient elastography (TE)
    1.2. Point Shear wave elastography (pSWE): Virtual Tissue Quantification (VTQ) and Elasticity Point quantification (ElastPQ),
    1.2. Two dimensional Shear Wave elastography (2D-SWE)
2. Strain elastography

These methods have been used in CLD to assess LS as the physical expression of the amount of liver fibrosis, and some of them to measure spleen stiffness (SS) as this may reflect the increased pressure in the portal vein leading to splenic congestion (17). Both LS and SS have also been investigated for their ability to assess severity of PH, predict the presence of EV and prognosticate long-term clinical outcomes in patients with liver cirrhosis.

Although introduced relatively late 2D-SWE has brought some important technological advances in the arena largely dominated by TE. In this review we aimed to critically adress current clinical use of 2D-SWE especialy Supersonic Shear imaging (SSI) in CLD based on the available scientific evidence. Performance of 2D-SWE (SSI) for non-invasive assessment of liver fibrosis, portal hypertension, EV and prognostic purposes in compensated liver cirrhosis will be discussed making a comparison with the results obtained by employing other SE methods.

DISCUSSION

1. Quantitative ultrasound elastography (sonoelastography): technological aspects

Quantitative elastographic (or elastometric) methods measure the velocity of waves that travel through the organ/tissue of interest following mechanical or acoustic compression from the external source to the investigated structure (16). These vawes travel faster through harder/stiffer tissue, such as fibrotic liver typical of CLD. The final result of the measurement is expressed in m/s or in kPa, with the later calculated by the formula relative to the Young's modulus of elasticity (16). Thanks to this physical approach, elastography provides a non-invasive estimate of liver fibrosis and provides information on the stage of CLD.

The first among ultrasound based methods that used elastography for the assesment of of liver fibrosis was TE (18). This method uses an external mechanical vibrator to induce low-frequency (50Hz) elastic shear waves which are tracked in 4x1 cm large region of interest within the liver by ultrasound transducer coaxially mounted on the vibrator (17). Since introduced, the method has gained large popularity due to its simplicity and was tested on very large number of patients of different ethnicity and with different etiology of CLD (19). The limitation of TE is that it does not provide US image of the investigated liver, it is not able to meassure LS in patients with ascites and has limitted performance in owerveight/obese patients (20).

The second technological approach uses a modified conventional US probe to generate enforced acoustic impulses (Acoustic Radiation Force Impusle Imaging-ARFI) and transmit them into the investigated structure, i.e. liver. On their way these impulses make small displacement of the liver tissue and generate shear waves that travel perpendiculary to the axis of the exciting impulse with their velocity measured by the same US probe and expressed in m/s or kPa (16,21). These technological solutions are integrated within the conventional ultrasound machines and enable 2D US imaging of the investigated structure with the possibility of selecting an area of interest by a measuring box. By this approach it is possible to meassure stiffness in a selected region avoiding anatomical structures that may interrupt or make signal unreliable such as blood vessels, ribs, air, gallbladder, tumors etc. Methods based on ARFI technology using shear waves may be furtherly divided in to point SWE (pSWE: such as VTQ and ElastPQ) and 2D-SWE (22). In pSWE only a small measuring box (6x10 mm) is used with no direct visualisation of elastographic images making these methods similar to TE in terms of stiffness measurement.

1.1. Two-Dimensional Shear Wave Elastography

Two-Dimensional Shear Wave Elastography uses multiple and repeated acoustic impulses focused on the different depths to form a conus-shaped wavefront in the liver maintaining the pressure and

increasing the power and range of the shear waves within the tissue (23). By the SSI these waves are scanned with an ultrafast US probe that, in contrast to conventional US probes, processes 5000 images/second and hence enables immaging of tissue elasticity in real-time, for which reason this technology is also called Real Time 2-Dimensional Shear Wave Elastography (RT-2D-SWE) (24). In 2D-SWE elasticity imaging is displayed in wider region of interest (for SSI round-shaped Q-box with diameter up to 30 mm is used). Due to all these features 2D-SWE (SSI) seems potentialy advantageous as compared to other SE methods. However, the clinical utility of TE and to some lesser extent VTQ, has been strongly founded by scientific evidences in clinical hepatology, yet to be challenged by 2D-SWE. At the same time 2D-SWE shares common limitations with other SE methods in terms of aplicability which is limited in overweight people and still lacks standardized criteria for reliability of measurements (25). Similar 2D-SWE technology has been developed by other manufacturers in the meanwhile (General Electric, Siemens, Toshiba); however only SSI has been sufficiently validated by now. For this reason the further text will focus on the data obtained by SSI as the representative of 2D-SWE methods and the term 2D-SWE (SSI) would be used and may be considered synonymous to RT-2D-SWE.

2. Clinical applications of 2D-SWE in hepatology

2.1. Non-invasive staging of liver fibrosis

All SE methods have been used to differentiate stages of liver fibrosis in different CLD. Most data on this issue have been obtained in patients with chronic viral hepatitis by TE, ARFI, and more recently by 2D-SWE (SSI), with preliminary reports suggesting also a good performance of ElastPQ (26–30). Transient elastography is a more accurate for the diagnosis of cirrhosis (F=4) than significant fibrosis (F≥2), with AUROC values 0.93-0.96 (correct classification 80-98%) and 0.84-0.87 (correct classification 57-90%) respectively (15,31). Transient elastography performs better in ruling out than ruling in cirrhosis as negative and positive predictive values of 96 and 74% were reported (15,26–30,32). Comparable results have been obtained by other SE methods such as ARFI.

Several meta-analyses on the performance of 2D-SWE (SSI) for fibrosis staging have been recently published (Table 1) (33–35). The meta-analysis that included 12 studies with a total of 1635 patients reported cut-off values for stages F≥1, F≥2, F≥3 and F=4 were 7.50 ± 1.51 (range, 6.20–9.51), 8.04 ± 1.24 (range, 6.65–10.72), 9.27 ± 1.03 (range, 7.90–11.12), and 11.12 ± 1.45 (range, 9.59–14.00) kPa with corresponding AUROCs (95% CI) 0.87 (0.84–0.90); 0.85 (0.81–0.88); 0.93 (0.91–0.95) and 0.93

(0.90–0.95) respectively (33). In line with the results obtained by other SE methods 2D-SWE (SSI) seems to perform better to diagnose severe fibrosis/cirrhosis than significant fibrosis.

It should be kept in mind that reported cut-off values of LS by all SE methods largely depend on the prevalence of cirrhotic patients included in the study, a fenomenon known as "spectrum bias". Furthermore, respective positive (PPV) and negative predictive values (NPV) of LS cut-offs by TE are influenced by disease prevalence and therefore not expected to work equally in populations with low (such as general population) or high prevalence of cirrhosis (such as in tertiary hospitals, that produced most of the quoted studies). According to one meta-analysis on TE and taking into account the reported prevalence of F≥2 (roughly 70-75% per study) and F=4 (prevalence 20-30%) stages accurate diagnosis following positive measurement (over the treshold) may be achieved in 92% of F≥2 patients when pre-test probability is 75%, and in 72% of F4 patients when pre-test probability is 25% (such as in studies encompassed by the meta-analysis) (26). At the same time and with the same pre-test probabilities, diagnosis would be missed in 45% of F≥2 cases following negative measurement (below the treshold), but only in 6% of F4 cases. Therefore, TE is reliable method to rule-in significant fibrosis and rule-out cirrhosis, but not reliable enough to rule-out significant fibrosis or rule-in cirrhosis.

The same conclusion arises from the meta-analyses of studies by 2D-SWE (SSI) revealing better performance of the method to rule-in significant fibrosis (post-test probability of correct result 93% following over the threshold LS measurement, at 75% pre-test probability of the disease, according to Fagan plot analysis) and rule-out cirrhosis (post-test probability of uncorrect classification only 5% following below the threshold LS measurement, at 25% pre-test probability of cirrhosis). With the same pre-test probability of the disease (fibrosis stage) post-test probability of uncorrect diagnosis following below the threshold measurement for significant fibrosis is 35-41%, whereas post-test probability of cirrhosis following over the threshold measurement is only 68-70% (33,34) . This led authors to conclusion that 2D-SWE (SSI) might still not be ready for fibrosis staging in low-risk population (34).

Although widely available, user-friendly and extensively validated , TE has additional limitations as its performance is hampered in overweight individuals (BMI > 30 kg/m^2), elderly (>52 years of age) and diabetics, with uninterpretable measurements (both complete failure + unreliable measurements) in 10-20% of patients (20,28,36).

In the absence of clear-cut instructions by the manufacturer, different reliability criteria for 2D-SWE (SSI) measurement success have been proposed by investigators including the following: 3-5 measurements should be obtained during apnea in expiration from the same intercostal spot from the right liver lobe (28,37,38), coefficient of variation of measurements less than 30%, lowest value captured by the measuring box not < 0,2 kPa, SD/median of LS <10% and depth of LS measurement<5.6 cm (25,39). This could be one of the reasons explaining the proportion of unreliable measurements

(including complete failure) reported in the range of 6.2-26% (28,29,37,40). Again, the highest drop-out rates were reported in obese and eldery people. SS measurements were unreliable in almost 40% of patients, with significantly higher drop-out rates observed in obese and those with smaller spleen size, the conditions making the spleen less accessible to US examination (29). Liver steatosis or necroinflammation do not significantly affect the results of LS measurement by 2D-SWE (SSI) according to the results published by Samir EA et al. (41). The impact of steatosis on LS measurements remains a controversial issue with some studies showing that moderate to severe steatosis falsely increases LS and overestimates fibrosis and other studies demostrating an underestimation (42,43). Overall, the main problem hampering a reliable clinical utilisation of 2D-SWE (SSI) as well as all other SE methods remains the lack of prospective validation of the proposed cut off values.

2.2. Assessment of portal hypertension and detection of esophageal varices

For the non invasive assessment of PH, most experience derives from studies employing TE and VTQ which have provided data on both liver and spleen stiffness, while preliminary data have been reported with 2D-SWE (SSI). Liver stiffness shows a good correaltion with HVPG, but only up to 10-12 mmHg (10 mmHg representing treshold for CSPH), with a much weaker correlation for higher HVPG values. (44). Along these lines, LS might serve to detect CSPH with 81% probability of correct diagnosis (AUROC 0.93), whereas it is not accurate enough to replace endoscopy for detection and grading of EVs (AUROCs 0.84 and 0.87 for any EV and large EV respectively, primarily due to low specificity of 0.53 and 0.59), with overall accuracy of <70% following over the threshold measurement according to a meta analysis that evaluated studies performed by TE (45). By using 2 cut-offs for >90% sensitivity (13.6 kPa) and >90% specificity (21 kPa) it was possible to avoid invasive HVPG measurements and correctly classify 53% of patients with compensated cirrhosis undergoing liver resection due to HCC. The remaining 47% of patients had either failure to obtain reliable measurements or had LS values in between these cut-offs (46). In an elegant study by Augustin et al. performed in patients with compensated chronic liver disease (mostly hepatitis C) and LS>13.6 kPa with no clinical signs of PH, EV were detected in 20% (10/49) of patients. Of them only 2 had LS<25 kPa, and all others had LS>25 kPa. No EV were detected if liver/spleen ultrasound and platelet count were normal, and 90% of EV were detected in patients with abnormal both ultrasound and platelet count (47). At the cut-off value of 25 kPa, LS by TE might be reliably used to rule-in CSPH (PPV 94%, NPV 59%) and rule-out EV (NPV 93%, PPV 42%). In both cases around 50% of patients would remain in a „grey zone“ with LS below/above these values respectively. Based on the available scientific evidence, the Baveno VI conference endorsed non-invasive methods to rule-in CSPH at least in virus-related etiology of CLD. Accordingly, LS by TE (>20–25 kPa; at least two measurements on different days in fasting condition), alone or

combined to platelets and spleen size is sufficient to rule-in CSPH. On the other hand, patients with LS<20 kPa and with a platelet count >150,000 have a very low risk of having varices requiring treatment, and can safely avoid screening endoscopy (14). These reccomendations were validated recently in a study that included 310 patients with a diagnosis of compensated chronic liver disease who had LSM≥10kPa and an upper gastrointestinal endoscopy performed within 12 months (48). Among patients (102/310 (33%)) who met combined LS and platelets criteria 11% had EV and 2% had high risk EV. Therefore, by applying Baveno VI criteria it was possible to correctly identifiy 98% of patients who could safely avoid endoscopy.

Spleen has been well recognized as one of the organs highly influenced by the hemodynamic changes in the portal circulation that develop during the evolution of CLD. This leads to splenic congestion, splenomegaly, but also to other structural changes within the splenic parenchyma including tissue hyperplasia and fibrosis development resulting finally in an increased splenic stiffness (49,50). Furthermore, as LS correlates well with HVPG only up to 10 mmHg (treshold for CSPH), SS has attracted attention since it might hypothetically better reflect changes beyond this level of PH and therefore might be used to non-invasivelly predict the size of EV, the goal not met by LS measurements. Several studies with different SE methods reported on the high accuracy of SS measurements for non-invasive detection of CSPH and EV. In patients with HCV-related cirrhosis performance of SS (by TE) was similar to that of LS with AUROCs of 0.941 vs 0.899 (p=0.133) for EV and 0.966 vs 0.920 (p=0.099) for CSPH respectively (51). A 54.0 kPa SS cut-off obtained by TE predicted grade 2/3 EV with 80% sensitivity and 70% specificity (AUROC 0.82) (52). In a study performed on 200 patients with cirrhosis of mixed etiology, HVPG (n=52) showed significant correlation with SS (r=0.433, P=0.001) as assessed by TE, but not with LS (r=0.178, p=0.20) (53). LS was significantly different between patients with and without EV (51.4 vs. 23.9 kPa, *P* = 0.001), but not between the large vs small or bleeding vs non-bleeding, whereas SS values were different between all the respective groups. LS at the cut-off value of ≥27.3 kPa and SS ≥40.8 kPa had the same diagnostic accuracy of 86% for predicting EV. At the cutoff value of 54.5 kPa, SS could predict bleeding EV with 76 % sensitivity, 73 % specificity and AUROC of 0.819. These studies proposed different but close cut-off values of SS for the prediction of EV in different causes of PH ranging from 41.3 kPa by Colecchia A *et al. (HCV), to 46.4 kPa by* Stefanescu *et al.* (HCV and alcohol related cirrhosis) (51,54). In a Japaneese study performed on 340 patients with cirrhosis of mixed etiology, mailnly HCV, a SS valee of 3.18 m/s, measured by ARFI, identified patients with EVs with 98.4% negative predictive value, 75.0% accuracy, and SS cutoff value of 3.30 m/s identified patients with high-risk EVs with a 99.4% negative predictive value, 72.1% accuracy. On the other hand, several studies reported significant number of wrongly classified patients with respect to the presence and the size of EV based on SS measurements both with TE and ARFI (52,55,56).

Finaly, meta analysis of the 12 studies that reported results obtained by TE, VTQ and RTE revealed suboptimal performance of SS for detecting the presence and size of EV with overal sensitivity and specificity below 80% (57).

Recently 2D-SWE (SSI) has been evaluated as a tool for non-invasive assessment of PH showing a fair correlation between LS and HVPG (R=0.61-0.65; p<0.001). Cut-off values of LS for CSPH were calculated at 15.4 kPa (sensitivity and specificity both 91%; AUROC 0.95) and 15.2 kPa (sensitivity 85.7%; specificity 80.0%)(Table 2) (25,58). The former study reported acceptable LS measurements by RT-2D-SWE in 83% of patients with compensated chronic liver disease (most of them having cirrhosis) appliying at least 1 of 2 reliability criteria: SD/median of LS <10% and depth of LS measurement <5.6 cm. Using this approach 91% of patients were correctly classified with regard to the presence of CSPH. Confirming what already observed with TE this study showed that the best correlation between LS and HVPG occurs for values of HVPG up to 10 mmHg. In addition, this study reported correlation between SS and HVPG (R=0.51; p<0.001), revealing however a poor performance of SS for the prediction of CSPH with less than 40% of patients correctly classified even after using 2 cut-off points optimised for the best sensitivity (14.1 kPa) and specificity (25.8 kPa). In a French study of patients with advanced cirrhosis most of whom were evaluated for liver transplantation, 2D-SWE (SSI) had success rate of LS and SS measurements of 97%, as compared to 44% and 42% respectively by TE (56). However, after restricting the analysis to patients with SD/mean (variation coefficient) <10% and <20% succes rate of 2D-SWE (SSI) decreased to 48% and 72% for LS measurements and to 46% and 73% for SS respectively. At the cut-off value of 24.5 kPa, LS by 2D-SWE (SSI) had 81% sensitivity, 88% specificity, 98% PPV, 35% NPV and 82% accuracy for CSPH, and it signifficantly outperformed SS measurements (AUROCs 0.87 vs 0.64, *P* = 0.003). The corresponding cut-off value of LS by TE was 65.3 kPa (52% sensitivity, 100% specificity, 100% PPV, 21% NPV and 57% accuracy). Diagnostic Accuracy (AUCs) for CSPH was not significantly different between TE and 2D-SWE (SSI) for both LS (AUROC 0.78 and 0.79) and SS measurements (AUROCs 0.63 and 0.72). However, only 9 out of 79 patients had HVPG<10 mmHg and post-hoc power analysis revealed that statistical power was low for LS assessed by TE (40%) and by SWE (30%). This might be a reason why the obtained cut-off values by TE were much higher as compared to results from previously cited studies. Performance of both methods (TE and 2D-SWE (SSI)) and both sites of measurements (LS and SS) were insufficient to detect the presence of high-risk EV.
In a study on 401 consecutive cirrhotic patients (305 with upper GI endoscopy: of them 43.9% had high-risk EV) the performance of both LS and SS measurements by 2D-SWE (SSI) for detecting EV was reported with AUROCs of 0.74 and 0.75 respectivelly in patients with compensated cirrhosis. At cut-off value of 12.8 kPa, LS had ≥90% negative predictive value for high-risk EV. While promising results for diagnosing EV were obtained by SS measurement (cut-off 25.6 kPa, sens. 94%, spec. 36%, PPV 50%,

NPV 90%), the authors concluded it was not yet sufficiently robust for clinical practice owing to high failure rates of 29.2% (40). Another study on 103 patients with compensated liver cirrhosis of mixed etiology (mostly viral and alcoholic) revealed very good performance of LS by RT-2D-SWE in attempt to predict the presence of any grade (cut-off 13.9 kPa, sens. 75%, spec. 88.9%, AUROC 0.887) or high-risk EV (cut-off 16.1 kPa, sens. 84.6%, spec. 85.6 %, AUROC 0.88) (59) .

Group from Zagreb reported on the performance of 2D-SWE (SSI) to detect EV in patients with cirrhosis (N=87, mixed etiology). Higher LS and SS were associated with higher odds of having EV (by 8% for each 1 kPa of LS (p=0.037) and 13% for 1 kPa of SS (p=0.009)) after adjustment for age, sex, and de-compensation (60). Area under the ROC curve for both LS (0.796) and SS (0.79) had "good discriminative properties". At cut-off values 19.7 kPa for LS and 30.3 kPa for SS, with a 62% prevalence rate of EV (including both patients with compensated (N=44) and decompensated (N=43) cirrhosis), performance of RT-2D-SWE for detection of EV showed modest positive (80.4%) and, in particular, negative predictive values (NPV=71%). However, since predictive values largely depend on the event prevalence, and assuming EV prevalence of 35% (as in compensated cohort in this study, which is indeed target for EV screening), NPV of LS (cut-off 19.7 kPa) would have been 90%, whereas for SS (cut-off 30.3 kPa) it would fell slightly below 90% (87,6%).

Taken together results on the diagnostic performance of LS by 2D-SWE (SSI) for CSPH and EV are in keeping with the results obtained by other SE methods. They suggest that LS measurement by 2D-SWE (SSI) has good diagnostic performance for ruling-in CSPH. Along these lines it might be considered promising alternative to TE. However, a wide range of cut-off values as proposed by different studies requires prospective validation in the independent cohorts of patients with compensated cirrhosis/cACLD as they represent target population for such an non-invasive approach. On the other hand, LS does not correlate well with PH beyond 10-12 mmHg, and is therefore limited in predicting the presence and size of EV. From the biological point of view this seems logical. Indeed, PH develops as a consequence of progressive tissue fibrosis associated with chronic hepatocellular damage/inflammation and neo-angiogenesis. It is conceivable that up to a certain limit, roughly corresponsing to HVPG values of 10-12 mm Hg, LS is largely reflecting these changes occurring in the liver tissue. It is also understandable how extrahepatic factors responsible for the progression of PH and liver endothelial dysfunction cannot be captured by LS measurements. It should be stressed that all sonoelastographic methods have invariably failed in accurately diagnosing EV, and the only indication for elastography at the moment is for ruling out large varices in Child A patients as indicated in the last Baveno VI criteria (14). Conflicting results exist on the clinical performance of SS measurements for the detection of both CSPH and EV. Its clinical use by 2D-SWE (SSI) is limited by low apllicability (unreliable SS measurements range from 29.2%-36.7% (29,40)) and SS seems not to

consistently reflect the degree of PH at least in patients with advanced cirrhosis. For these reasons SS might not be reccommended for diagnosing CSPH or EV yet.

2.3. Performance of 2D-SWE for prognostic purposes

Another important issue in patients with CLD is assessment of prognosis. LS as assessed by TE has been shown as the most important risk factor for adverse clinical outcomes even independently of the treatment history and treatment success as revealed in large cohort of patients with chronic hepatitis C (61). In a study on 100 patients with compensated CLD (mixed etiology, mostly alcohol-related and chronic viral hepatitis B or C, 65% cirrhosis) 85.4% of those with LS <21.1 kPa by TE did not present liver-related complications at 2-years follow up (62). In a meta-analysis of studies reporting on 7058 patients with CLD, higher degree of baseline LS (by TE or MRE) was associated with significantly increased risk of hepatic decompensation, HCC, death, or a composite of these outcomes (RR 1.32; 95% CI 1.16–1.51) (63). Moreover, SS as assessed by TE has been reported to independently predicted clinical outcomes including decompensation, HCC development and death with OR 1.11 (CI 1.05-1.17) in a cohort of 92 patients with compensated HCV cirrhosis followed for 2 years (64). At the cut-off of 54 kPa, SS had 97% NPV for these adverse clinical outcomes in patients with compensated HCV cirrhosis (64). Beside the influence of baseline LS or SS values, several longitudinal studies demonstrated important impact of dynamic changes of LS over time as the reflection of the evolution of CLD. Among patients with cACLD, LSM≥10 kPa and Child-Pugh score 5 at baseline who were subjects to repeated LSM at 12-24 months, those with baseline LSM≥21 kPa, or increase in LSM (delta-LSM) by 10% had significantly higher risk of death and worsening liver function (decompensation or impairment in at least 1 point in Child–Pugh score) in the follow-up period of median 43.6 months (65). In cohorts of patients with primary sclerosing cholangitis and HCV infection annual increase of LS by >1,5 kPa and >1 kPa respectivelly were associated with worse prognosis in terms of liver related complications and survival (66,67).

Untill recently no study has evaluated the role of 2D-SWE (SSI) as a potential prognostic tool based on assesment of LS and/or SS. The first study to evaluate 2D-SWE (SSI) in this regard has reported on a retrospective analysis of the clinical outcomes of patients with compensated liver cirrhosis (N=44; mixed etiology (45,5% alcoholic liver disease, 31,8% chronic viral hepatitis, 22,7% other)) particularly focusing on survival or occurence of liver decompensation or HCC („event“) during the median period of 28 months following the index measurement of LS and SS (60). The main finding was that patients with baseline LS≥21.5 kPa, with adjustment for age and MELD score, had 3.4-fold (95% confidence interval [CI] 1.16-10.4, *P*=0.026) higher risk of liver-related events. Although significant in univariate

analysis (HR 3.9, p=0,013), the association between high SS (≥31.7 kPa) and outcomes was of of borderline significance (HR 2.7; *P*=0.056) after adjustment for age and MELD score. It is interesting to note that LS values around 20 kPa as measured by 2D-SWE (SSI), in line to corresponding results by other SE methods, have been confirmed as important turning point in terms of presence of PH, its complications and long term prognosis. Namely, at LS values <19.7 kPa (as mentioned before) patients with compensated cirrhosis have low risk of EV, whereas values of >21.5 kPa (above which increasing incidence of EV might be expected) increase the rik of adverse clinical outcomes. Moreover, mediation analysis revealed that the association of higher LS with a higher risk of an "event" was largely mediated through its association with the presence of EV at baseline in this study. Hence, LS as assessed by 2D-SWE (SSI) might be valuable non-invasive predictor of clinical outcomes, most likely through its association with the presence of CSPH and EV with respective cut-off points of high accuracy yet to be defined. With respect to the borderline effect of SS on clinical outcomes observed in cohort of patients with mixed etiology of CLD (60), it should be noticed that spleen size, structure and stiffness might differ due to the etiology of liver disease, and maybe the presence of collaterals that bypass the spleen (49,50,68).

The correlation between LS and SS, i.e. the Stiffness Ratio Index (SRI=LSx10/SS), has been proposed but was not shown to be predictive to rule-in or rule-out EV, at least when measured at a single time point (29). Nevertheless, significant differences in SRI were noted between patients with compensated and decompensated cirrhosis pointing to the fact that this ratio diminishes as liver cirrhosis deteriorates. Hence, SRI could possibly be analysed longitudinally to identify patients under higher risk of adverse clinical outcome, similar to what has been already observed with repeated LS measurements. This possibility should be tested prospectively and the overall performance of SRI compared to that of isolated LS or SS measurements.

CONCLUSION

In conclusion, the results of the recent studies suggest that 2D-SWE (SSI), a sophisticated new sonoelastographic method, is a reliable non-invasive tool that might be used over the entire spectrum of CLD with the comparable performance to other already established sonoelastographic methods to stage liver fibrosis, recognize cirrhotic patients under increased risk of adverse clinical outcomes, with promising role in stratifying patients according to the risk of having CSPH and EV.

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Table 1. Results of Meta-analyses on the performance of Real-time 2-dimensional Shear Wave Elastography for staging of liver fibrosis (METAVIR classification: F≥2 (signifficant fibrosis); F=4 (cirrhosis)) in patients with chronic liver disease. All meta-analyses included mixed etiology of liver disease. Sens=sensitivity; Spec=specificity; AUC=area under Receiver operating characteristic curve; Pre-test probability= probability of disease (fibrosis stage) in tested population; Post-test probability (+)=probability of accurate result following over the treshold measurement; Post-test probability (-)=probability of having the disease (fibrosis stage) following below the treshold measurement. NA=not assesed.

		Authors (reference)	**Year**	**Number of patients**	**Cut-off** Mean±SD (kPa) (Range)	**Sens (%)**	**Spec (%)**	**AUC**
F≥2		Feng JC (33)	2016	1635	8.04 ± 1.24 (6.65–10.72)	84	81	0.85
		Li C (34)	2016	934	NA	85	81	0.88
		Jiang T (35)	2016	2303	NA	84	83	0.87
F=4		Feng JC (33)	2016	1635	11.12 ± 1.45 (9.59–14.00)	88	86	0.93
		Li C (34)	2016	934	NA	87	88	0.92
		Jiang T (35)	2016	2303	NA	89	88	0.94

Table 2. Results of the studies on the performance of Real-time 2-dimensional Shear Wave Elastography for detecting clinically signifficant portal hypertension (CSPH) and esophageal varices (EV) in patients with chronic liver disease. All studies included mixed etiology of liver disease. Sens=sensitivity; Spec=specificity; AUC=area under Receiver operating characteristic curve, NA=not assesed.

Author (reference)	**Year**	**Number of patients**	**Clinically significant portal hypertension**					**Eso**	
			Condition prevalence (%)	**Cut-off** (kPa)	**Sens (%)**	**Spec (%)**	**AUC**	**Condition prevalence (%)**	**Cut-o** (kPa)

Procopet B (24)	2015	88	49	15.4	91.3	90.9	0.94	54	NA
Kim TY (58)	2015	92	83.7	15.2	85.7	80	0.82	77.8	NA
Elkrief L (56)	2015	79	88.6	24.5	81	83	0.87	65 (high risk EV)	24.7
Cassinotto C (40)	2015	305	NA	NA	NA	NA	NA	43.9 (high risk EV)	12.8
Kim TY (59)	2016	103	NA	NA	NA	NA	NA	38.8 (any grade) 12.6 (high risk EV)	13.9 16.1