Chapter

2D Shear Wave Elastography for Liver Fibrosis Evaluation

Alina Popescu, Roxana Şirli and Ioan Sporea

Abstract

2D shear wave elastography is a technique embedded in ultrasound machines which allows the interrogation of the tissue by acoustic radiation force impulses induced into the tissues by focused ultrasonic beams and captures the propagation of resulting shear waves in real time. Elasticity is displayed using a color-coded image superimposed on a B-mode image, and at the same time, a quantitative estimation of liver stiffness (LS) can be performed in a certain region of interest (ROI). The published data showed a real value of this method for liver stiffness estimation in patients with chronic hepatitis. It has the following advantages: it is integrated into standard ultrasound systems; it is a real-time elastographic method; and it is also feasible in patients with ascites and with large and adjustable size of the ROI that will be evaluated.

Keywords: 2D shear wave elastography, liver stiffness, liver fibrosis, chronic liver diseases, liver cirrhosis

1. Introduction

Chronic liver diseases of different etiologies are still an important health problem, staging fibrosis being one of the issues that relate to prognosis and treatment decision. Liver biopsy, the gold standard method for liver fibrosis assessment, is an invasive procedure, with possible complications and lower compliance as compared to noninvasive techniques.

Ultrasound-based liver elastography was developed as a noninvasive, easy to perform, and well-accepted tool for liver fibrosis assessment and proved to be a very dynamic research field in the last years, this being demonstrated also by the large number of publications and guidelines published in this field [1–3].

2D shear wave elastography is one of the new developed ultrasound-based techniques [1], embedded in ultrasound machines, that allow the interrogation of the tissue by dynamic acoustic radiation force impulses induced into the tissues by focused ultrasonic beams and capture the propagation of resulting shear waves in real time. The technique has the advantage that the elasticity is displayed using a color-coded image superimposed on a B-mode image, and at the same time, a quantitative estimation of liver stiffness (LS) can be performed in a certain region of interest (ROI), the results being expressed in kPa or m/s.

The measurements are performed, similar to other elastography techniques, with the patient lying in supine position with the right arm in maximal abduction, in the right liver lobe, by placing the probe in between the ribs, in the seventh to ninth intercostal space, perpendicular on the liver surface [1]. The examiner should apply sufficient pressure on the probe to make good contact with the tissue,

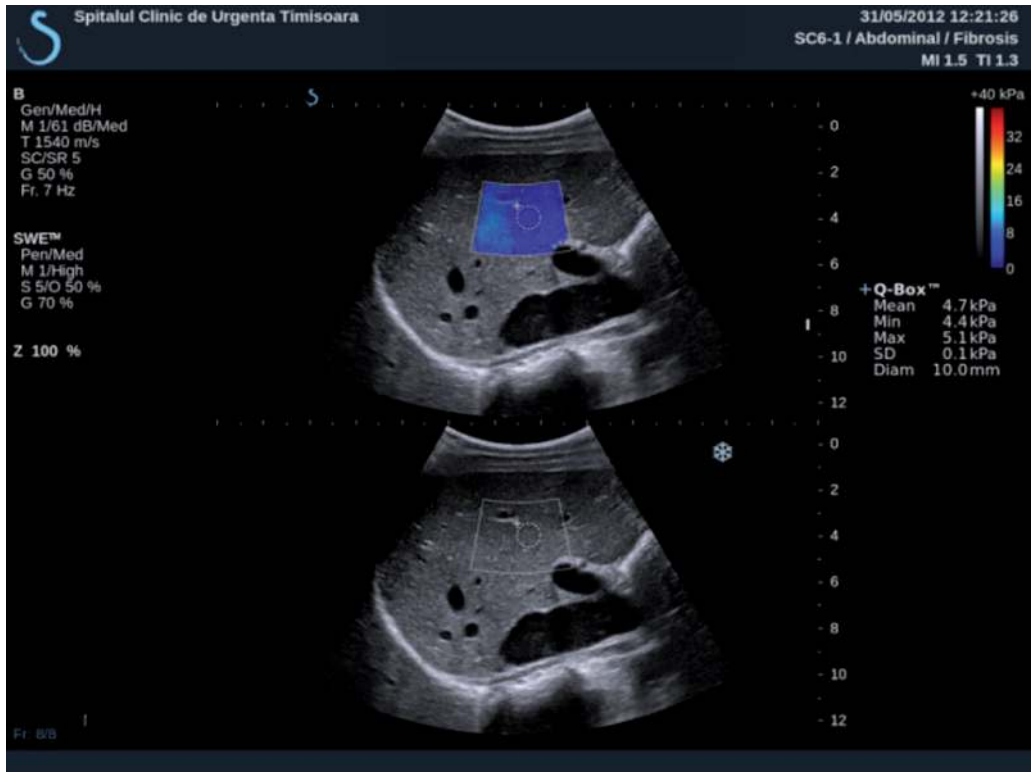

Figure 1.
2D SWE.SSI.

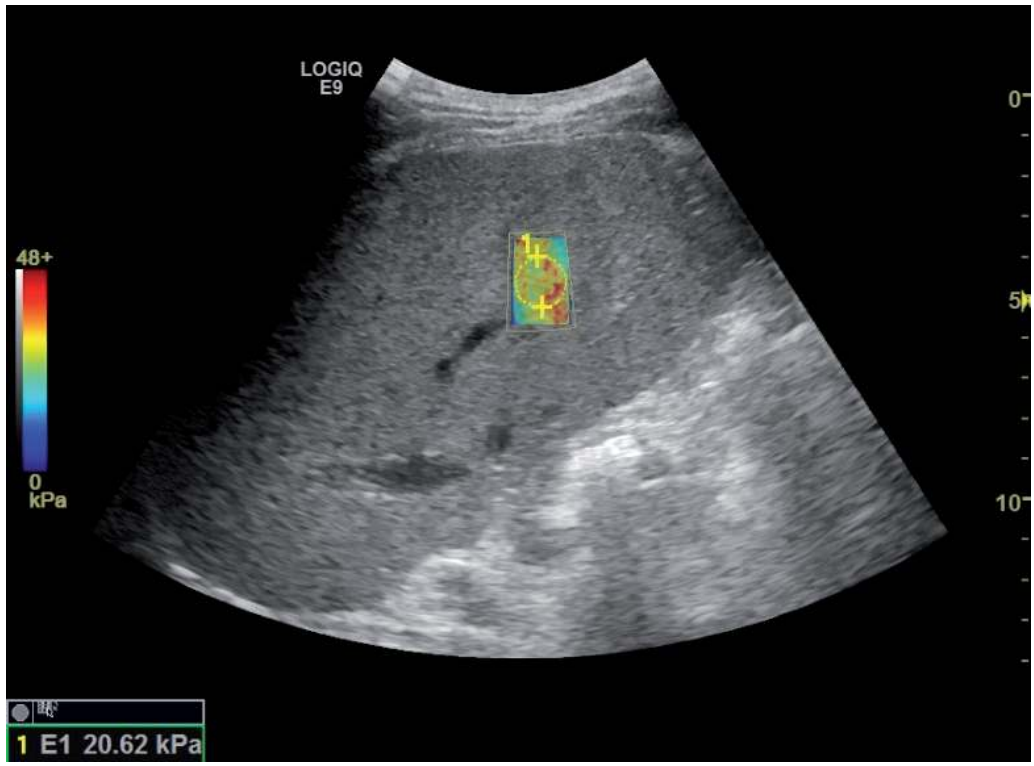

Figure 2.
2D SWE.GE.

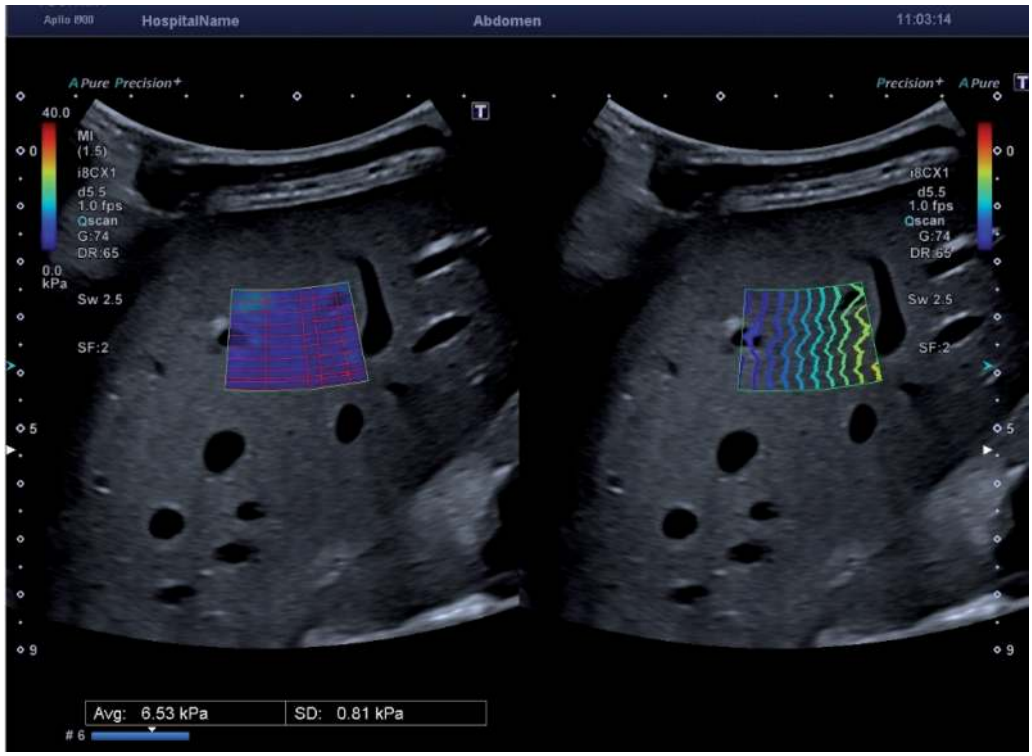

Figure 3.
2D SWE with a propagation map (Canon).

should stabilize the hand and the probe while performing the measurement, and should ask the patient to stop breathing and avoid deep inspiration. The ROI should be placed in an area free of vessels, at least 1–2 cm and at maximum of 6 cm under the liver capsule [1].

The technique has the advantage that can be performed also in patients with ascites, but an adequate B-mode ultrasound live image is necessary for reliable results. On the other hand, published data showed that for a high feasibility of the method, ultrasound experience is needed, especially in difficult cases, for example, obese patients or narrow intercostal spaces [1, 4, 5].

First 2D SWE technique was developed by Supersonic Imagine (France) (2D SWE.SSI) and embedded in Aixplorer® system (**Figure 1**). Other companies followed with similar techniques, for example, General Electric (2D SWE.GE) (**Figure 2**), 2D SWE technique with a propagation map Canon-Toshiba (**Figure 3**), Philips (ElastQ), Samsung, etc.

2. 2D SWE.SSI

Published data showed that 2D SWE.SSI is a feasible and reproducible method [6]. The manufacturer recommends a minimum of three valid measurements to be obtained and rejects any measurement that achieves less than 90% stability index (SI), as a reliability criterion. Other authors [7] used standard deviation/median liver stiffness of ≤0.10 and measurement depth of <5.6 cm as quality parameters for reliable measurements. Most published data showed that reliable LS measurements can be obtained in 90–98.9% of cases [5–10] with a good intra- and interobserver reproducibility [9, 11, 12].

2.1 Healthy volunteers

The values of LS evaluated by 2D SWE.SSI in healthy volunteers varied from 2.6 to 6.2 kPa [13–15], with higher values in male vs. female patients (6.6 ± 1.5 vs. 5.7 ± 1.3 kPa, p = 0.01.) [14].

2.2 Confounding factors

Similar to other ultrasound-based elastographic methods, the liver stiffness results obtained by 2D SWE.SSI may be influenced by food intake; some authors suggest that the values increase significantly in the first hour after food intake and decrease after 60 min after meal [16, 17], while in other studies, these results were not reproduced [18], suggesting that maybe this method is less influenced by food intake. Nevertheless, while more studies are necessary to clarify this issue, the measurements should be performed in fasting condition to avoid any errors.

Other studies are also needed to evaluate the effect of cytolysis, cholestasis, or congestive heart failure on the liver stiffness values obtained through 2D SWE.

2.3 2D SWE.SSI for predicting liver fibrosis in chronic liver diseases of various etiologies

Several studies showed good accuracy for 2D SWE.SSI for predicting significant fibrosis and liver cirrhosis in chronic liver diseases of different etiologies (**Table 1**). Overall, the method has good accuracy for evaluating both significant and severe fibrosis, slightly better for liver cirrhosis, but with very different cutoff values between etiologies and between different studies.

Ref.	Year	Etiology	Patients (*n*)	Fibrosis stage	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Jeong et al. [20]	2014	Mixt	70	F ≥ 2	0.915	8.60	78.2	93.3	97.7	53.8
				F = 4	0.878	14.00	77.3	85.4	70.8	89.2
Deffieux et al. [21]	2015	Mixt	120	F ≥ 2	0.890	8.90	77.0	79.0	77.0	79.0
				F = 4	0.890	10.20	83.0	76.0	38.0	96.0
Sporea et al. [22]	2014	Mixt	383	F ≥ 2	0.859	7.8	76.8	82.6	77.9	81.5
				F = 4	0.914	11.5	80.6	92.7	60.9	97.1
Sporea et al. [23]	2018	Mixt	82	F ≥ 2	0.853	7.1	96.8	78	73.8	97.5
				F = 4	0.94	13	78.9	97.7	88.2	95.5
Bavu et al. [24]	2011	HCV	113	F ≥ 2	0.950	9.12	81.0	72.0		
				F = 4	0.970	13.30	80.0	87.0		
Ferraioli et al. [5]	2012	HCV	121	F ≥ 2	0.920	7.10	90.0	87.5	91.3	85.7
				F = 4	0.980	10.40	87.5	96.8	87.5	96.8
Tada et al. [25]	2013	HCV	55	F ≥ 2	0.940	8.80	88.9	91.9	84.2	94.4
Leung et al. [8]	2013	HBV	226	F ≥ 2	0.880	7.100	84.70	92.10	85.3	91.7

Ref.	Year	Etiology	Patients (*n*)	Fibrosis stage	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
				F = 4	0.980	10.100	97.40	93.00	60.1	99.6
Zeng et al. [26]	2014	HBV	206	F ≥ 2	0.917	7.200	86.36	86.96	88.8	84.2
				F = 4	0.945	11.700	91.89	89.70	66.7	98.0
Wu et al. [27]	2016	HBV	437	F ≥ 2	0.903	8.200	78.16	85.28	82.6	81.4
				F = 4	0.926	11.256	91.80	84.31	48.7	98.4
Zhuang et al. [28]	2017	HBV	304	F ≥ 2	0.970	7.600	92.00	90.00	98.4	64.3
				F = 4	0.980	10.400	94.60	94.90	95.7	93.5
Zeng et al. [29]	2017	HBV	257	F ≥ 2	0.882	7.100	88.89	76.38	76.2	89.0
				F = 4	0.926	11.300	93.55	87.25	52.7	98.9
Cassinotto et al. [30]	2016	NAFLD	291	F ≥ 2	0.860	8.90	68.0	94.0		
				F = 4	0.880	10.00	95.0	69.0		
Takeuchi et al. [31]	2018	NAFLD	71	F ≥ 2	0.750	11.57	52.0	44.0		
				F = 4	0.900	15.73	100.0	82.0		
Thiele et al. [32]	2016	Alcohol	199	F ≥ 2	0.940	10.20	82.0	93.0	90.0	88.0
				F = 4	0.950	16.40	94.0	91.0	71.0	99.0
Zeng et al. [33]	2017	Autoimmune	114	F ≥ 2	0.850	9.70	81.7	81.3	91.8	63.4
				F = 4	0.860	16.30	87.0	80.2	52.6	96.1
Li et al. [34]	2018	Autoimmune	51	F ≥ 2	0.781	9.15	83.3	72.7		

Table 1.
Diagnostic performance of 2D SWE.SSI for significant fibrosis (F ≥ 2) and cirrhosis (F = 4) in different chronic liver diseases—adapted after Jeong JY et al. [19].

Two comparative studies between transient elastography, point SWE (VTQ) and 2D SWE.SSI, were proposed by Cassinotto et al. in chronic liver diseases [35] and NAFLD patients [30]. The first study enrolled 349 consecutive patients with chronic liver diseases who underwent liver biopsy. For each patient, LS was assessed by 2D SWE.SSI, pSWE (VTQ), and transient elastography (FibroScan, M and XL probes). 2D SWE.SSI, transient elastography and VTQ, correlated significantly with histological fibrosis score ($r = 0.79$, $p < .00001$; $r = 0.70$, $p < .00001$; $r = 0.64$, $p < .00001$, respectively) with no significant differences between methods for the diagnosis of mild fibrosis and cirrhosis.

The second study [30] included 291 NAFLD patients in whom liver stiffness was assessed by 2D SWE.SSI, transient elastography (M probe), and VTQ within 2 weeks prior to liver biopsy. The AUROC for 2D SWE.SSI, transient elastography, and VTQ were 0.86, 0.82, and 0.77 for diagnoses of ≥F2; 0.89, 0.86, and 0.84 for ≥F3; and 0.88, 0.87, and 0.84 for F4, respectively. The cutoff values for 2D SWE.SSI and transient elastography for predicting fibrosis with a sensitivity ≥90% were very close: 6.3/6.2 kPa for ≥F2, 8.3/8.2 kPa for ≥F3, and 10.5/9.5 kPa for F4.

In an individual patient data based on meta-analysis [36] that included 1340 patients and compared 2D SWE.SSI with liver biopsy as reference method, 2D SWE.SSI showed a good to excellent performance in LS assessment in patients with HCV, HBV, and NAFLD, with AUROCs of 86.3, 91.6, and 85.9% for diagnosing significant fibrosis ($F \geq 2$) and 96.1, 97.1, and 95.5% for diagnosing cirrhosis ($F = 4$), respectively. The optimal cutoff for diagnosing significant fibrosis in all patients was 7.1 kPa, while for diagnosing liver cirrhosis was 13.5 kPa in HCV and NAFLD and 11.5 kPa in HBV patients.

Other three meta-analyses published that included more than 900 patients each [37–39] confirmed these results, with pooled sensitivities between 0.84 and 0.85, pooled specificities between 0.81 and 0.83 and AUROC between 0.85 and 0.87 for significant fibrosis and with pooled sensitivities between 0.87 and 0.89, and pooled specificities between 0.86 and 0.88 and AUROC between 0.93 and 0.94 for liver cirrhosis.

2.4 2D SWE.SSI for predicting liver cirrhosis complications

The method was studied also as a predictor for the presence of clinically significant portal hypertension. Thus, while Kim et al. showed that for a cutoff value of 15.2 kPa, the sensitivity and specificity of 2D SWE.SSI for predicting clinically significant portal hypertension were 85.7 and 80%, respectively, (AUROC 0.819) (HVPG >10 mmHg) [40], Procopet et al. [7], by using standard deviation/median liver stiffness ≤0.10 and measurement depth < 5.6 cm as quality criteria, had better results for the optimal cutoff value of 15.4 kPa (AUROC =0.948, with sensitivity and specificity both higher than 90%).

Another study that included 79 patients with liver cirrhosis [41] evaluated LS and spleen stiffness (SS) by 2D SWE.SSI, TE, and HVPG measurements; 2D SWE.SSI LS of more than 24.6 kPa had a sensitivity, specificity, and accuracy for clinically significant portal hypertension of 81, 88, and 82%, respectively, with better performance than SS (AUROC of 0.87 vs. 0.64, $P = 0.003$).

In a larger study that enrolled 401 consecutive cirrhotic patients [42], the LS cutoff values for a NPV ≥90% for high-risk esophageal varices, history of ascites, Child-Pugh B/C, variceal bleeding, and clinical decompensation were 12.8, 19, 21.4, 30.5, and 39.4 kPa, respectively, with AUROC of 0.77 for detection of esophageal varices.

Jeong et al. [43] looked on the role of 2D SWE in predicting the development of hepatocellular carcinoma, showing that patients with LS ≥10 kPa by 2D SWE had a fourfold higher risk of presenting hepatocellular carcinoma than those with LS <10 kPa.

More studies are needed to address these issues and conclude for the clinical practice.

2.5 2D SWE.SSI in pediatric population

The field of elastography, as noninvasive evaluation tool, became of interest also in pediatric population [44]. Thus a study that enrolled 54 consecutive children and adolescents with different chronic liver diseases that were examined by means of TE, ARFI, and 2D SWE.SSI showed a sensitivity of 2D SWE.SSI for detecting F1, F2, F3, and liver cirrhosis of 92.85, 83.33, 87.5, and 85.71%, respectively [45], better than a point SWE technique.

3. 2D SWE.GE

Another system that implemented the 2D SWE technique comes from General Electrics, embedded first in **LOGIQ E9/LOGIQ E10** ultrasound systems.

This new technique showed also good intra- and interobserver reproducibility. In a study that included 60 patients evaluated by 2D SWE.GE by three examiners with different levels of experience in ultrasound-based elastography and ultrasound, the overall agreement between examiners was excellent: 0.915 (95% confidence interval [CI]: 0.870-0.946). The intra-observer reproducibility for each of the examiners was excellent; however, the inter-class correlation coefficients were higher for the examiners more experienced in elastography: 0.936 (95% CI: 0.896-0.963) vs. 0.966 (95% CI: 0.943-0.980) vs. 0.984 (95% CI: 0. 973-0.991) [46].

The method showed also very good feasibility and reproducibility also in pediatric population. In a study that enrolled 243 healthy participants aged 4–17 years, valid measurements were obtained in 242 of 243 (99.6%) subjects for 2D SWE. GE, with an intraclass correlation coefficients between observers of 0.84 [47].

The mean LS measurement by 2D SWE.GE in healthy subjects was 5.1 ± 1.3 kPa, significantly higher than the LS measurement assessed by transient elastography (4.3 ± 0.9 kPa, $p < 0.0001$) and significantly higher for male vs. female, 5.9 ± 1.2 vs. 4.7 ± 1.2 kPa ($p = 0.0005$) [48].

There are few data available in the literature regarding the performance of this method in evaluating liver fibrosis in chronic liver diseases, but the results are promising.

Thus in a study that enrolled 331 consecutive subjects with or without chronic hepatopathies [49] in whom LS was evaluated in the same session by means of two elastographic techniques, transient elastography and 2D SWE.GE, reliable LS measurements were obtained in 95.8% subjects by 2D SWE.GE and 94.2% by TE ($p = 0.44$), with a strong correlation between the LS values obtained by the two methods: $r = 0.83$, $p < 0.0001$. The best cutoff value for $F \geq 2$, $F \geq 3$, and for $F = 4$ were 6.7, 8.2, and 9.3 kPa.

Similar results were obtained in an Italian study [50] that enrolled 54 healthy subjects and 174 patients with chronic liver diseases and compared 2D SWE.GE with liver biopsy as reference method and obtained reliable LS measurements in all subjects, with a strong correlation the LS measurements and liver fibrosis ($r = 0.628$). The AUROC values were better also for severe fibrosis: for $F \geq 2$: 0.857, for $F \geq 3$: 0.946, and for $F = 4$: 0.935.

4. 2D SWE with propagation map

2D SWE with propagation map (**Figure 3**), technique developed by Canon-Toshiba, is a more recent technology that appeared on the market but also with good perspectives in the field of liver elastography. Thus, in a study [51] on 115 consecutive patients that underwent 2D SWE by two different operators and transient elastography by sonographers during the same day, the correlation coefficient of the intraclass correlation test between an experienced radiologist and a third-year radiology resident was 0.878, and there was a moderate correlation between 2D SWE and transient elastography ($r = 0.511$) in the diagnosis of liver fibrosis. The best cutoff values for predicting significant fibrosis and liver cirrhosis by 2D SWE were > 1.78 (AUROC = 0.777) and > 2.24 m/s (AUROC = 0.935), respectively.

5. Conclusion

Even if 2D SWE techniques are quite newer on the market, they proved to be reliable methods for liver fibrosis evaluation, and several advantages can be

highlighted: they are integrated into standard ultrasound systems, are real-time elastographic methods, and are feasible also in patients with ascites and with large and adjustable size of the ROI that will be evaluated. These techniques have better accuracy for predicting liver cirrhosis, with accuracy more than 95%, and they also have good accuracy (more than 85%) for predicting significant fibrosis (F2).

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