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Noninvasive Assessment of HCV Patients Using Ultrasound Elastography

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Abstract

Among patients with chronic hepatitis C (CHC) infection, extensive research showed that fibrosis progression is a proper surrogate marker for advanced liver disease, eventually leading to dramatic endpoints such as cirrhosis and hepatocellular carcinoma. Therefore, there is growing interest in the use of noninvasive methods for fibrosis assessment in order to replace liver biopsy (LB) in clinical practice and provide optimal risk stratification. Elastographic techniques, such as Vibration Controlled Transient Elastography (VCTE), point-shear wave elastography (p-SWE), and 2D-SWE have shown promising results in this regard, with excellent performance in diagnosing hepatic cirrhosis, and great accuracy for steatosis detection through the Controlled Attenuation Parameter embedded on the VCTE device. In addition, the recent introduction of highly efficient direct-acting antivirals (DAAs) led to viral eradication and a significant decrease in liver damage, lowering the risk of hepatic decompensation, and HCC. Therefore, CHC patients need proper noninvasive and repeatable methods for adequate surveillance, even after treatment, as there still remains a risk of portal hypertension and HCC. However, the usefulness for monitoring fibrosis after the sustained virological response (SVR) needs further research.

Keywords: chronic hepatitis C, fibrosis, Vibration Controlled Transient Elastography, point-shear wave elastography, 2D shear wave elastography

1. Introduction

Hepatitis C virus (HCV) infection is a major causative agent of chronic liver disease (CLD) and liver-related death worldwide. Approximately 4 out of 5 infected individuals develop chronic hepatitis C (CHC) and nearly 20% of them insidiously progress to cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease [1]. It is estimated that 71.1 people were infected in 2015 worldwide, making it a global public health issue due to its substantial prevalence and effect on overall morbidity and mortality [2].

It has been shown that the accumulation of liver fibrosis has a great impact on the evolution of CHC. Fibrosis is the hallmark of progressive disease, eventually leading to cirrhosis and end-stage liver complications [3]. As highlighted by a prospective

study conducted by Yano et al. [4], relatively few patients with absent or low-grade fibrosis develop cirrhosis over the next 20 years (25–30%). However, portal and septal fibrosis were followed by cirrhosis in all cases with a progression rate of 18–20 years for portal fibrosis and 8–10 years for septal fibrosis. Furthermore, the advent of direct-acting antivirals (DAAs) has changed the perspective of CHC therapy, being both well-tolerated and highly efficient in achieving sustained virologic response (SVR) [5]. Therefore, staging liver fibrosis as a triage for starting therapy may no longer be as decisive as before. Rather, prompt diagnosis and management of advanced stages of fibrosis can prevent complications and death through comprehensive preventive and management strategies [6].

Liver biopsy (LB) is traditionally considered the gold standard evaluation for necroinflammatory activity, steatosis, and fibrosis in CHC [7]. However, the method has several drawbacks. Firstly, the result of the histopathological examination is significantly affected by the specimen's quality and the pathologist's experience [8–11]. Secondly, it is an invasive procedure, implies high costs, and might lead to several complications. Noninvasive methods are therefore necessary for optimal risk stratification in order to avoid the use of LB. Even if conventional imaging techniques are noninvasive, they require absolute signs of severe fibrosis or cirrhosis. Therefore, the latest studies focused on noninvasive elastographic techniques, which have shown promising results for the appraisal of liver fibrosis and steatosis in CHC patients.

2. Fibrosis assessment in HCV patients using noninvasive elastographic methods: a classification

Elastography-based imaging techniques quantify tissue stiffness, defined as the resistance of a material in response to an applied mechanical force [12]. Fibrosis modifies the elastic properties of liver tissue so that new techniques have been developed in the past two decades to grade liver fibrosis according to tissue stiffness.

Ultrasonographic (US) and magnetic resonance-based elastographic techniques are available, of which we will focus on US methods. Several guidelines classify elastographic techniques in two main categories: quantitative (“Shear Wave Elastography”, SWE) and qualitative (“Strain Elastography”) [13–15]. Regarding CHC, quantitative methods are most frequently used to evaluate liver stiffness (LS). Currently, three main quantitative techniques showed promising results in this pathology: Vibration Controlled Transient Elastography (VCTE; FibroScan®, Echosens, Paris, France) point-shear wave elastography (pSWE), and 2D-shear wave elastography (2DSWE). For integrative purposes, we decided to summarize the specific advantages and limitations of each technique in HCV patients.

3. Confounders: pathological changes influencing liver stiffness in HCV patients

Several technical and biological factors affect the performance of elastographic techniques due to an increase in LS unrelated to fibrosis. The former includes shear wave frequencies, location and depth of measurements, and device dependencies. The latter include ingestion of food prior to the examination, inflammation, cholestasis, hepatic venous congestion, and amyloid deposits [16, 17]. Inflammation in acute hepatitis might increase LS up to mimicking cirrhosis, returning to normal

simultaneously with the decrease of liver transaminases. A study of 112 CHC patients found a higher value for LS in the case of F3-F4 stages of fibrosis and necroinflammatory activity of at least A2 compared to A0-A1 (14.6 and 6.2 kPa, $p = 0.04$) [18]. Therefore, it is recommended to consider transaminases' value before interpreting LS in order to avoid overestimation [19]. If ALT levels are 3 times the normal value, there is a risk of overestimating the fibrosis stage and this should be mentioned with the results [20].

Concerning cholestasis and heart failure with hepatic congestion, LS decreases after proper treatment, hence the effect on shear wave propagation [21, 22]. Of note, a study suggests FibroScan as a potential tool to reveal heart decompensation [23]. In addition, waist circumference may lead to both technical failure and higher LS, but studies show various results and are mainly referring to body mass index (BMI). This is common because central obesity is associated with low-grade inflammation, insulin resistance, and liver steatosis, increasing LS. Furthermore, male gender, dyslipidemia and statins are debated in this regard, with different results (Table 1) [29].

	Advantages	Disadvantages
Vibration Controlled Transient Elastography (VCTE)	Widely used, less expensive, easy to learn [24] Can be easily repeated overtime Can provide steatosis assessment through CAP measurement Great reproducibility (>90 interclass correlation coefficients) [15] Point-of-care method [6] Good diagnostic accuracy for fibrosis stages and high performance for cirrhosis (AUROC>0.9) [6]	It cannot be performed in subjects with ascites [6] Obesity increases LSM (the use of XL probe reduces the limits among these subjects) [24] Affected by acute hepatitis, food intake, liver congestion, cholestasis, and alcohol consumption [6]
Point-shear Wave Elastography (p-SWE)	Can be easily executed on modified commercial US devices (if the machine is provided with adequate software) [6, 14] Offers the possibility of choosing the ROI in real-time [14, 25] Enables entire liver parenchyma examination under B-mode visualization [26] Avoids masses or large vessels [26] Can evaluate focal liver lesions' stiffness, discriminating between malignant and benign lesions [24] Good applicability: practicable among patients with ascites and obesity [6, 15, 25, 27] Excellent diagnostic accuracy for advanced fibrosis and cirrhosis [6, 25] Enables spleen stiffness measurement [6]	Narrow range (0.5–4.4 m/s), making it difficult to set proper cut-off values [14] Affected by acute hepatitis, food intake, liver congestion, cholestasis, and alcohol consumption [6]
2D-shear Wave Elastography (2D-SW)	Can be easily executed on modified commercial US devices (if the machine is provided with adequate software) [6, 14] Offers the possibility of choosing a large and adjustable ROI in real-time [14, 25, 28] Good applicability: practicable among patients with ascites and obesity [6, 28] Excellent diagnostic accuracy for advanced fibrosis and cirrhosis [6, 28]	Affected by acute hepatitis, food intake, liver congestion, cholestasis, and alcohol consumption [6]

Table 1.
Advantages and disadvantages of noninvasive elastographic techniques.

4. Vibration controlled transient elastography performance for fibrosis staging in HCV-infected patients

As already mentioned, staging fibrosis is beneficial to determine the prognosis and follow-up of patients with chronic HCV infection. VCTE is the most validated elastographic modality in this regard. Several meta-analysis found an excellent diagnostic performance of VCTE in diagnosing hepatic cirrhosis, with an AUROC exceeding 0.90. However, the technique is less accurate in case of significant fibrosis ($\geq F2$), with an AUROC ranging between 0.80 and 0.90 with overlapping cutoff values, so that the method is facing difficulties in distinguishing different stages of fibrosis [30–34]. Concerning CHC, two of these meta-analysis reported AUROC values of 0.83–0.85 and 0.96 for diagnosing significant fibrosis and cirrhosis, respectively [31, 33]. EASL guidelines suggest combining VCTE with serological markers for the assessment of moderate fibrosis (F2-F4) in patients with CHC [6].

A recent meta-analysis counting 24 articles evaluated the performance of VCTE for diagnosing liver cirrhosis in CHC patients. It estimated a sensitivity (Se) of 84% and a specificity (Sp) of 90%, with AUROC 0.95 [35]. Ganne-Carrié suggests in a study with 775 patients that VCTE should be particularly used for ruling out cirrhosis, given its high negative predictive value (NPV) (96%), rather than ruling it in, since the positive predictive value (PPV) was only 74%. Nevertheless, the excellent diagnostic performance for cirrhosis is hereby confirmed [36].

A recent study [37] compares the performance of VCTE with conventional B-mode ultrasound (US). VCTE is clearly superior in diagnosing severe fibrosis and subclinical cirrhosis, with an AUROC of 0.95 for severe fibrosis and 0.96 for cirrhosis versus 0.76 and 0.71, respectively, in the case of US ($p < 0.001$). Furthermore, combining the two methods does not significantly improve diagnostic accuracy compared with VCTE alone. The two would improve Sp (95.7% versus 76.7; $p < 0.001$) and PPV (94.3% versus 77.1%; $p = 0.002$) [37]. Another study by Berzigotti et al. [38] suggests that the two methods work complementary so that US is the preferred technique for ruling in cirrhosis, while VCTE should be used for ruling out the disease. Contrary to the first example, Berzigotti claims a better performance when the two are combined.

The diagnostic performance of VCTE in staging fibrosis is exemplified in **Table 2**, in reliance to our previous research [50]. Cutoff values range from 4.5 to 9.5 kPa for significant fibrosis ($\geq F2$) and from 11.3 to 16.9 kPa for diagnosing cirrhosis (F4). These values vary considerably mainly according to the prevalence of fibrosis in each study group and the expected outcome [51].

5. Liver fibrosis assessment through point-shear wave elastography in HCV patients

Point-shear wave elastography (p-SWE) is incorporated into devices such as Virtual Touch Tissue Quantification (VTTQ®) (Siemens Healthcare, Erlangen, Germany) and Elastography Point Quantification (ElastPQ®) (EPIQ7 ultrasound system, Philips Healthcare, Bothell, WA, USA). Under B-mode visualization, p-SWE enables the precise acquisition of shear wave speed (SWS) in a small ROI (around 1 cm^3). After 10 valid measurements in the right hepatic lobe, the median of SWS is reported and interpreted [15, 52]. Results are expressed in m/s for VTTQ or in m/s and kPa for ElastPQ [13]. However, its narrow range (0.5–4.4 m/s) restricts the

Fibrosis stage		≥ F1			≥ F2			≥ F3			= F4	
Study	Cut-off (kPa)	AUROC	Se/Sp (%)	Cut-off (kPa)	AUROC	Se/Sp (%)	Cut-off (kPa)	AUROC	Se/Sp (%)	Cut-off (m/s)	AUROC	Se/Sp (%)
Njei (n = 756) [39]*	N/S	N/S	N/S	4.5–7.2	N/S	97/64	N/S	N/S	N/S	11.8–14.6	N/S	90/87
Lupsor (n = 1202) [20]	5.3	0.879	84.99/73.21	7.4	0.889	80.32/83.97	9.1	0.941	88.8/88.3	13.2	0.970	93.75/93.31
Castera (n = 183) [40]	N/S	N/S	N/S	7.1	0.83	67/89	9.5	0.90	73/91	12.5	0.95	87/91
Afdhal (n = 560) [41] ¹	N/S	N/S	N/S	8.4	0.73	58/75	9.6	0.83	71.8/80	12.8	0.90	76/85
Degos (n = 913) [42]	N/S	N/S	N/S	5.2	0.75	90/32	N/S	N/S	N/S	12.9	0.90	72/89
Ziol (n = 251) [43]	N/S	N/S	N/S	8.80	0.79/0.81	56/91	9.6	0.91/0.95	86/85	14.6	0.95	87/91
Carrion (n = 169) [44]	8.5	N/S	N/S	N/S	0.90	90/81	N/S	0.93	N/S	12.5	0.95	87/91
Arena (n = 150) [19]	N/S	N/S	N/S	7.8	0.91	83/82	10.8	0.99	91/94	14.8	0.98	94/92
Sporea (n = 191) [45]	N/S	N/S	N/S	6.8	0.733	59.6/93.3	N/S	N/S	NS	N/S	N/S	N/S
Nitta (n = 165) [46]	N/S	N/S	N/S	7.1	0.87	80.8/80.3	9.6	0.91	87.7/82.4	11.6	0.93	62.5–91.7/ 78.9–91.5
Zarski (n = 382) [47]	N/S	N/S	N/S	5.2	0.82	93.6/34.8	N/S	N/S	N/S	12.9	0.93	76.8/89.6
Wang (n = 214) [48]	6.5	0.86	75/78	9.5	0.82	69/81	N/S	0.87	N/S	12	0.93	89/84
Yoneda (n = 102) [49] ²	N/S	N/S	N/S	7.8	0.91	78/90	10.4	0.95	88/91	11.3	0.91	90/84

Abbreviations: N/S – not specified; AUROC – area under ROC curve; Se – sensibility; Sp – specificity
*meta-analysis.
¹HCV 92%, HBV 8%.
²vXL probe.

Table 2.
Performance of VCTE for detecting different stages of fibrosis in HCV-infected patients.

Fibrosis stage	Technology	≥ F1			≥ F2			≥ F3			= F4		
Study		Cut-off (m/s)	ROC	Se/Sp (%)	Cut-off (m/s)	ROC	Se/Sp (%)	Cut-off (m/s)	ROC	Se/Sp (%)	Cut-off (m/s)	ROC	Se/Sp (%)
Lupsor (n = 112) [53]	VTTQ	1.19	0.725	62.07/85.71	1.34	0.869	67.8/92.86	1.61	0.9	79.07/94.83	2.0	0.936	80/95.45
Fierbinteanu-Braticevici (n = 74) [54]	VTTQ	1.185	N/S	89/87	1.215	90.2	100/71	1.54	99.3	97/100	1.94	99.3	100/98.1
Friedrich-Rust (n = 64) [55]	VTTQ	N/S	N/S	N/S	1.35	0.86	72.9/93.8	1.55	0.93	81.5/91.9	1.75	0.95	88.9/89.1
Rizzo (n = 139) [56]	VTTQ	N/S	N/S	N/S	1.3	0.86	81/70	1.7	0.94	91/86	2.0	0.89	83/86
Sporea (n = 274) [57]	VTTQ	1.19	0.880	73/93	1.21	0.893	84/91	1.58	0.908	84/94	1.82	0.937	91/90
Friedrich-Rust (n = 380) [58]*	VTTQ	N/S	N/S	N/S	N/S	0.88	N/S	N/S	0.90	N/S	N/S	0.92	N/S
Sporea (n = 911) [59]	VTTQ	1.19	0.779	69.9/80	1.33	0.792	69.1/79.8	1.43	0.829	74.8/81.5	1.55	0.842	84.3/76.3
Chen (n = 127) [60]	VTTQ	N/S	N/S	N/S	1.55	0.847	74.1/87	1.81	0.902	90.2/89.5	1.98	0.831	88.9/79.8
Zhang (n = 108) [61]	N/S	N/S	N/S	N/S	1.529	0.779	56.9/88.9	1.78	0.863	73.2/92.5	1.797	0.79	78.6/74.5
Nishikawa (n = 108) [62]	VTTQ	1.28	0.810	69.1/85.7	1.28	0.909	81.8/87.1	1.44	0.869	88.9/82.5	1.73	0.885	85.7/86.2
Yamada (n = 124) [63]	VTTQ	N/S	N/S	N/S	1.26	0.890	92.5/76.2	1.46	0.943	84.6/87.8	N/S	N/S	N/S
Li (n = 128) [64]	ElastPQ	N/S	N/S	N/S	1.53	0.775	57.6/89.5	1.79	0.901	76.4/96.5	1.789	0.792	78.9/75.4
Takaki (n = 176) ¹ [65]	VTTQ	N/S	N/S	N/S	1.25 1.205	0.773 0.882	75/78.1 75/90.9	1.595 1.595	0.863 0.858	84.9/81.5 94.3/81.8	1.775 1.775	0.915 1.000	85.6/88.9 100/40

Fibrosis stage	Technology	≥ F1			≥ F2			≥ F3			= F4		
		Cut-off (m/s)	ROC	Se/Sp (%)	Cut-off (m/s)	ROC	Se/Sp (%)	Cut-off (m/s)	ROC	Se/Sp (%)	Cut-off (m/s)	ROC	Se/Sp (%)
Silva Junior (n = 51) [66]	VTTQ	1.19	0.88	88.4/75	1.31	0.90	89.3/87	1.68	0.97	94.4/90.9	1.95	0.98	100/95.2
Tai (n = 83) [67]	VTTQ	N/S	N/S	N/S	N/S	N/S	N/S	N/S	N/S	N/S	1.41	0.802	70.6/80.3
Chen (n = 137) [68]	VTTQ	N/S	N/S	N/S	1.59	0.8434	72.8/79.4	1.73	0.8997	91.4/77.2	1.96	0.9036	100/68.1
Joo (n = 101) [69]	VTTQ	1.190	0.872	84/85.7	1.335	0.853	83.8/75.8	1.645	0.840	79.5/75.8	1.665	0.828	85/69.1
Mare (n = 168) ^{2,3} [70]	ElastPQ	N/S	N/S	N/S	6.4	0.96	92/100	6.7	0.97	88.4/100	8.9	0.83	90.9
Gani (n = 29) [71]	N/S	N/S	N/S	N/S	1.32	0.802	79/75	1.48	0.802	78/80	1.79	0.802	72/82
Ragazzo (n = 107) [72]	VTTQ	N/S	N/S	N/S	1.22	0.67	64/69	1.41	0.74	57/84	2.37	0.96	100/94
Alem (n = 2103) [73] ³	VTTQ	N/S	N/S	N/S	1.36	0.89	87.5/80.6	1.45	0.94	97.5/90.3	1.7	0.95	90.3/90.9
Hsu (n = 63) [74]	N/S	N/S	N/S	N/S	1.225	0.786	65/70.9	1.370	0.857	73.1/78.4	1.710	0.937	81.8/86.5
Ueda (n = 108) [75]	VTTQ	N/S	N/S	N/S	1.26	0.93	N/S	1.78	0.83	N/S	1.94	0.86	N/S
Baldea (N = 176) [76] ^{2,3}	ElastPQ	N/S	N/S	N/S	6.51	0.92	96.6/76.4	8.73	0.94	88/85.4	11.1	0.95	86.8/96.7

Abbreviations: N/S – not specified; ROC – receiver operating characteristics curve; Se – sensibility; Sp – specificity

*meta-analysis.

¹The Takaki study used two groups: the training set (n = 120) the validation set of VIA index (n = 56); for integrative purposes, we presented in our table only the values of p-SWE measurement (SWV), omitting the VIA index' ones.

²The Mare and Baldea studies used kPa for ElastPQ cut-off values.

³VCTE as reference method.

Table 3.
Performance of p-SWE for detecting different stages of fibrosis in HCV-infected patients.

demarcation of proper cutoff values for discriminating between certain fibrosis stages, making management decisions difficult [14].

We identified several studies that evaluate p-SWE in HCV-infected patients [53–76]. A 2011 pooled meta-analysis by Friedrich-Rust et al. [58] with 380 CHC patients, found AUROC values of 0.88, 0.90, and 0.92 for diagnosing moderate fibrosis ($\geq F2$), severe fibrosis ($\geq F3$), and cirrhosis ($= F4$), respectively. Subsequently, an international multicenter study with 911 HCV-infected patients offered cut-off values of 1.19, 1.33, 1.43, respectively 1.55 m/s for $\geq F1$, $\geq F2$, $\geq F3$ respectively $F4$, with AUROC values of 0.779, 0.792, 0.829 and 0.842, respectively [59]. Of note is the Takaki study [65] which elaborated the VIA index, a formula that increases the diagnostic accuracy of SWV alone, from 0.882, 0.858 and 1.000 to 0.917, 0.906, and 1.000 for moderate fibrosis, severe fibrosis, and cirrhosis, respectively in the validation set. In 2019, Hsu et al. [74] propound different SWV cutoff values in various diseases. For CHC patients, a SWV cut-off value of 1.225, 1.370 and 1.710 m/s predicts fibrosis stages $\geq F2$, $\geq F3$ and $F4$ with AUROC values of 0.786, 0.857 and 0.937, respectively. Overall, in our considered studies presented in **Table 3**, the AUROC ranged from 0.725 to 0.88 for $\geq F1$, 0.67 to 0.93 for $\geq F2$, 0.74 to 0.97 for $\geq F3$ and 0.79 to 1 for $F4$ prediction. Nonetheless, the EFSUMB Clinical Practice Guidelines suggest that pSWE can be the first-line assessment in HCV-infected patients for fibrosis evaluation, performing best at ruling out cirrhosis [15].

6. Appraisal of liver fibrosis by 2D shear wave elastography in HCV-infected patients

2D shear wave elastography, a novel US-based technique, allows the estimation of tissue dynamics using focused ultrasonic beams in a certain ROI. This technique has the advantage of displaying a real-time color-coded map overlaid on a B-mode image. Furthermore, 2D-SWE estimates LS expressed in kPa or m/s [28, 77]. It should be executed in a well-visualized area of the right hepatic lobe, clear of large vessels, ligaments, gallbladder, and the liver capsule, with the patient situated in a supine position with breathing suspension [15].

As exemplified in **Table 4**, several studies reported the diagnostic accuracy of 2D-SWE for fibrosis assessment among HCV-infected patients [76, 78–86, 88]. In 2017, Herrmann et al. [81] performed a meta-analysis including 13 studies, gathering 379 patients with CHC, that evaluated the diagnostic performance of 2D-SWE for the noninvasive staging of liver fibrosis. They found AUROC values of 0.863, 0.915, and 0.929 for diagnosing significant fibrosis, severe fibrosis, and cirrhosis, respectively. In our analysis, the AUROC values range from 0.82 to 0.888 for $\geq F1$, 0.783 to 0.97 for $\geq F2$, 0.877 to 0.97 for $\geq F3$ and 0.893 to 0.98 for $\geq F4$, respectively (**Table 4**).

7. HCV post-sustained virological response/antiviral therapy appraised by liver stiffness

Due to their potency, ease of use, tolerability, and safety, DAA regiments are the recommended choice in subjects with compensated advanced chronic liver disease (cACLD). Their introduction resulted in increasing rates of SVR, reducing LS among these patients. Nonetheless, most of the studies concerning interferon-free treatments are retrospective, with small sample sizes, with short follow-up after SVR, and

Fibrosis stage		≥ F1			≥ F2			≥ F3			= F4	
Study	Cut-off (kPa)	ROC	Se/Sp (%)	Cut-off (kPa)	ROC	Se/Sp (%)	Cut-off (kPa)	ROC	Se/Sp (%)	Cut-off (kPa)	ROC	Se/Sp (%)
Bavu (n=113) [78]	N/S	N/S	N/S	9.12	0.948	72/81	10.08	0.962	0.968	13.3	0.968	87/80
Ferraioli (n = 121) [79]	N/S	N/S	N/S	7.1	0.92	90/87.5	8.7	0.99	97.3/95.1	10.4	0.98	87.5/96.8
Tada (n = 55) [80]	N/S	N/S	N/S	8.8	0.940	88.9/91.9	N/S	N/S	N/S	N/S	N/S	N/S
Herrmann (n = 379) [81]*	N/S	N/S	N/S	7.1	0.864	94.7/52	9.2	0.915	90.3/76.8	13.0	0.929	85.8/87.8
Abe (n = 233) ¹ [82]	1.480	0.888	75.9/88.2	1.560	0.915	85.3/85.5	1.720	0.940	88.8/83.8	1.930	0.949	91.4/90.8
Serra (n = 51) [83]	N/S	N/S	N/S	9.225	0.783	59.1/86.2	10.695	0.877	72.7/90	11.525	0.893	85.7/88.6
Villani (n = 178) [84] ^{2,3}	N/S	N/S	N/S	8.15	0.899	87.1/73	10.31	0.900	77.2/85.4	12.65	0.899	73.3/88.5
Baldea (n = 176) [76]	N/S	N/S	N/S	6.5	0.92	84.1/88.2	8.19	0.93	96.7/77.4	11.3	0.96	95.7/92.7
Baldea (n = 208) [85] ^{3,4}	N/S	N/S	N/S	7.7	0.97	86.3/96.9	8.3	0.97	94.8/90.3	9.7	0.97	92.6/91.6
				8.5	0.96	87.6/100	11.1	0.95	89.7/95.1	12.3	0.96	92.5/94
Aksakal (n = 43) [86]	6.09	0.82	86/70	7.81	0.97	84/96	9.00	0.97	90/97	12.47	0.98	85/98
Numao (n = 141) [87]	N/S	N/S	N/S	N/S	0.86	N/S	N/S	0.97	N/S	N/S	0.91	N/S

Abbreviations: N/S – not specified; ROC – receiver operating characteristics curve; Se – sensibility; Sp – specificity.

*meta-analysis.

¹The Abe study used SWV, expressed in m/s.

²The Villani study used the novel EPIQ 7 US system (ElastQ).

³These studies used VCTE as reference standard for fibrosis evaluation.

⁴The Baldea study offered result two 2D-SWE techniques: General Electric and SuperSonic Imagine, respectively.

Table 4.

Performance of 2D-SWE for detecting different stages of fibrosis in patients with CHC.

lacking post-SVR LB [6, 89, 90]. A recent prospective longitudinal study by Knop et al. [91] sought to elucidate the dynamics of liver and spleen stiffness in cirrhotic patients through VCTE and p-SWE, 3 years post-treatment. Even if their analysis showed that LS decreases in a significant proportion of patients with CHC, spleen stiffness, a non-invasive marker for portal hypertension, remained unchanged. Similarly, other research found lower LS values by p-SWE (VTTQ) in HCV-infected patients who achieved SVR [92, 93].

In addition, the diagnostic accuracy of VCTE for SVR prediction remains controversial, since the improvement of LS post-DAA treatment may be overrated by elastography in contrast with histological staging [94]. In fact, a recent prospective multicenter study comprising of 746 HCV-infected patients with CHC with SVR evaluated 3 years post-DAA therapy, discovered cirrhosis by LB in more than half of cACLD patients, in spite of normal VCTE values or liver function parameters. Due to its poor diagnostic accuracy (AUROC = 0.75), VCTE turned out to be an unreliable method for the accurate identification of the fibrosis stage in HCV-infected patients who acquired SVR [95].

Latest EASL guidelines conclude that neither noninvasive elastographic techniques are appropriate enough to detect fibrosis regression after SVR in CHC patients. Additionally, cut-off values of LS by VCTE used in untreated HCV patients should not be utilized for liver fibrosis staging after SVR. Therefore, the appraisal of liver disease severity and prognosis remains an unmet need in this field, requiring larger cohort sizes and extended follow-up in order to establish the role of noninvasive techniques in treating HCV-infected patients [6].

8. The prognostic value of elastography for the prediction of clinical outcomes (decompensation; HCC) in patients with HCV-related cACLD who achieved sustained virological response

In HCV-infected patients, the risk of all-cause mortality and the incidence of HCC diminished in subjects who achieved SVR after interferon-based antiviral therapy, regardless of the grade of fibrosis [96, 97]. In addition, the introduction of novel highly efficient DAAs improved the capability of decreasing the HCC risk, even among patients with advanced liver disease [50]. Nonetheless, a relevant risk of 1.5% remains, requiring proper and cost-effective surveillance methods for these patients [98, 99]. Evidence shows that clinically significant portal hypertension (CSPH), defined as hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, is the strongest predictor for hepatic decompensation [6]. For these patients, compensated advanced CLD (cACLD) is the proposed term by the Baveno VI consensus [100]. However, HVPG is an invasive and expensive method, requiring reliable noninvasive alternatives [50].

Being a noninvasive, low-cost, and easy to perform method, VCTE turned out to be an outstanding diagnostic instrument for CSPH, with a hierarchical summary ROC of 0.93 [101]. A recent multicenter study of 5648 patients, found that lowering the dual-threshold to <7 kPa and > 12 kPa, provided excellent Se of 91% for excluding and great Sp of 92% for diagnosing cACLD, respectively [100]. In addition, elastography might enable the dynamic appraisal of the HCC risk, especially before and after antiviral treatment. Several studies aimed to elucidate whether VCTE, p-SWE, and 2D-SWE may facilitate HCC surveillance in HCV-infected patients [102–105]. A recent meta-analysis, comprising 3398 patients, found a pooled HR for HCC development of 3.43 (95% CI, 1.63–7.19) between positive and negative LSM, indicating that

VCTE is a trustworthy procedure for HCC prediction in CHC patients treated with DAAs [106]. In a multicenter cohort study, Alonso et al. [107] provided two easy and broadly applicable models for the estimation of HCC risk after SVR. Their model, including baseline albumin ($\geq$ or $<$ 4.2 g/dl), baseline LS ($>$ or $\leq$ 17.3 KPa), and LS after 1 year ($\geq$ or $<$ 25.5%), increased HCC surveillance efforts (Harrell's C: 0.77). In 2018, Ioannou et al. [108] internally validated models that calculate the HCC risk following antiviral treatment. However, current EASL clinical practice guidelines recommend that patients with cACLD before antiviral therapy should be continuously supervised for HCC and portal hypertension, regardless of measurement values of noninvasive tests post-SVR.

9. Controlled attenuation parameter (CAP) for the noninvasive estimation of steatosis in HCV-infected patients

Steatosis is a common histological feature and has an important role in the evolution of CHC, in particular in HCV genotype 3 infections [109, 110]. According to a meta-analysis counting 25 studies and 6400 patients, the prevalence of steatosis in CHC patients is estimated at 55.54%, in most cases affecting less than 33% of hepatocytes [111, 112].

Steatosis seems to accelerate fibrosis in the early stages of the disease, reduce treatment response and promote oncogenesis [2, 113, 114]. A recent retrospective study with 515 CHC patients undergoing DAA treatment found a significant correlation between the grade of steatosis and mortality of any cause or HCC development. Furthermore, steatosis surpasses advanced fibrosis regarding the prediction of a poor response to treatment [115]. Steatosis is thus a simple and important predictor of progression in chronic HCV patients.

US is the commonest imaging technique used in clinical practice to diagnose steatosis due to its high accessibility and low cost. However, it is operator- and machine-dependent and the performance is questionable [116, 117]. There is an increasing interest in developing novel tools for steatosis evaluation. At present, the non-invasive parameter, called controlled attenuation parameter (CAP), available on the FibroScan system, is the most validated one. Using the postulate that fat content is directly related to US beam attenuation, CAP enables the diagnosis and quantification of steatosis [118]. Results are expressed in decibels per meter (dB/m), with values ranging from 100 to 400 dB/m.

Several meta-analysis assessed the CAP performance for detecting and grading hepatic steatosis using LB as reference standard [119, 120]. One of the most important meta-analysis dates from 2017 and includes 2735 patients (36.5% with HCV infection) [119]. Results are consistent, so that CAP provided an AUROC of 0.823 (Se = 68.8%, Sp = 82.2%) for detecting mild steatosis ($\geq$ S1), 0.865 (Se = 77.3%, Sp = 81.2%) for moderate steatosis ($\geq$ S2) and 0.882 (Se = 88.2%, Sp = 77.6%) for severe steatosis ($\geq$ S3) [119].

Concerning CHC, we cite 3 studies, one with 854 CHC patients, the other with 115 patients with chronic hepatitis, 76% of them being infected with HCV, and the latter with 201 patients with 118 (58.7%) subjects with HCV infection [121–123]. CAP had good diagnostic accuracy for detecting steatosis and for differentiating between different grades at least two grades apart, independently of fibrosis stage or activity grade. Optimal cutoff values were similar and are presented in **Table 5**. Further validation in large cohorts is however needed in order to validate proper cutoff values. CAP could be ideal as a screening test, as the NPV was high, 0.89–0.87 for $\geq$ S1.

		Sasso et al. [121]	Ferraioli [122]	Lupsor-Platon [123]
	Patients number	854	115 (76% HCV pts)	201 (58.7% HCV pts)
≥S1	Optimal cutoff (dB/m)	222	219	260
	AUROC	0.80	0.76	0.813
≥S2	Optimal cutoff (dB/m)	233	296	285
	AUROC	0.86	0.82	0.822
≥S3	Optimal cutoff (dB/m)	290	N/S	294
	AUROC	0.88	N/S	0.838

Table 5.
Diagnostic performance of CAP in HCV-infected patients.

10. Perspectives

Since shear wave propagation spectroscopy can also provide additional mechanical information on soft tissues, such as viscosity, it might be possible to achieve additional data regarding the utility of 2D-SWE (SSI) for viscosity quantification, a potential marker for necroinflammatory activity [124]. Nonetheless, large cohort prospective studies are required in order to assess the performance of such parameters in biopsied HCV-infected patients.

11. Conclusions

Elastography-based imaging methods are of high interest nowadays. HCV patients can greatly benefit from VCTE due to its numerous qualities- rapid, noninvasive, repeatable for longitudinal evaluation, and cost-effectiveness. It has great discriminative power for fibrosis assessment, performing better at ruling out cirrhosis rather than diagnosing it, because of high specificity and negative predictive value. In addition, CAP is a precious tool for the noninvasive quantification of steatosis. Further validation in large cohorts is still needed in order to validate cutoff values in CHC patients. Among other elastographic techniques, pSWE and 2D-SWE proved to have the similar diagnostic performance to VCTE for the prediction of fibrosis severity in HCV-infected patients. One of the main advantages of non-invasive techniques is that they opened a new era in HCV management, since it can be easily executed when deemed necessary before antiviral therapy and after HCV eradication, as a repeatable surveillance method. Since the introduction of DAAs in HCV therapy, many patients achieve SVR, which is associated with a reduction in fibrosis. However, clinical practice guidelines do not currently recommend using elastography for the assessment of fibrosis decrease after treatment. Moreover, patients should continue surveillance for decompensation and HCC after SVR, regardless of the result of noninvasive methods.

It is essential that further studies focus on establishing standardized cutoff values of LS for adequate prediction of HCC risk in HCV patients, which is considered to be of great importance in current clinical practice.

Conflict of interest

The authors declare no conflict of interest.

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References

- [1] Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) infection. *International Journal of Medical Sciences*. 2006;**3**(2):47-52
- [2] Blach S, Zeuzem S, Manns M, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. *The Lancet Gastroenterology & Hepatology*. 2017;**2**(3):161-176
- [3] Sebastiani G, Alberti A. How far is noninvasive assessment of liver fibrosis from replacing liver biopsy in hepatitis C? *Journal of Viral Hepatitis*. 2012;**19**(Suppl 1):18-32
- [4] Yano M, Kumada H, Kage M, Ikeda K, Shimamatsu K, Inoue O, et al. The long-term pathological evolution of chronic hepatitis C. *Hepatology*. 1996;**23**(6):1334-1340
- [5] Banerjee D, Reddy KR. Review article: Safety and tolerability of direct-acting anti-viral agents in the new era of hepatitis C therapy. *Alimentary Pharmacology & Therapeutics*. 2016;**43**(6):674-696
- [6] European Association for the Study of the Liver. Electronic address eee, Clinical Practice Guideline P, Chair, representative EGB, Panel m. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. *Journal of Hepatology*. 2021;**75**(3):659-689
- [7] Bedossa P, Carrat F. Liver biopsy: The best, not the gold standard. *Journal of Hepatology*. 2009;**50**(1):1-3
- [8] Colloredo G, Guido M, Sonzogni A, Leandro G. Impact of liver biopsy size on histological evaluation of chronic viral hepatitis: The smaller the sample, the milder the disease. *Journal of Hepatology*. 2003;**39**(2):239-244
- [9] Pagliaro L, Rinaldi F, Craxi A, Di Piazza S, Filippazzo G, Gatto G, et al. Percutaneous blind biopsy versus laparoscopy with guided biopsy in diagnosis of cirrhosis. A prospective, randomized trial. *Digestive Diseases and Sciences*. 1983;**28**(1):39-43
- [10] Poniachik J, Bernstein DE, Reddy KR, Jeffers LJ, Coelho-Little ME, Civantos F, et al. The role of laparoscopy in the diagnosis of cirrhosis. *Gastrointestinal Endoscopy*. 1996;**43**(6):568-571
- [11] Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pylsopoulos NT, et al. Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. *The American Journal of Gastroenterology*. 2002;**97**(10):2614-2618
- [12] Wells RG. Tissue mechanics and fibrosis. *Biochimica et Biophysica Acta*. 2013;**1832**(7):884-890
- [13] Ferraioli G, Filice C, Castera L, Choi BI, Sporea I, Wilson SR, et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 3: liver. *Ultrasound in Medicine & Biology*. 2015;**41**(5):1161-1179
- [14] European Association for Study of L, Asociacion Latinoamericana para el Estudio del H. EASL-ALEH clinical practice guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *Journal of Hepatology*. 2015;**63**(1):237-264

- [15] Dietrich CF, 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 in der Medizin (Stuttgart, Germany : 1980)*. 2017;**38**(4):e16-e47
- [16] Tang A, Cloutier G, Szeverenyi NM, Sirlin CB. Ultrasound elastography and mr elastography for assessing liver fibrosis: Part 2, diagnostic performance, confounders, and future directions. *AJR. American Journal of Roentgenology*. 2015;**205**(1):33-40
- [17] Mueller S, Sandrin L. Liver stiffness: A novel parameter for the diagnosis of liver disease. *Hepatic Medicine : Evidence And Research*. 2010;**2**:49-67
- [18] Vispo E, Barreiro P, Del Valle J, Maida I, de Ledinghen V, Quereda C, et al. Overestimation of liver fibrosis staging using transient elastography in patients with chronic hepatitis C and significant liver inflammation. *Antiviral Therapy*. 2009;**14**(2):187-193
- [19] Arena U, Vizzutti F, Corti G, Ambu S, Stasi C, Bresci S, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. *Hepatology*. 2008;**47**(2):380-384
- [20] Lupsor Platon M, Stefanescu H, Feier D, Maniu A, Badea R. Performance of unidimensional transient elastography in staging chronic hepatitis C. Results from a cohort of 1,202 biopsied patients from one single center. *Journal of Gastrointestinal and Liver Diseases*. 2013;**22**(2):157-166
- [21] Millonig G, Reimann FM, Friedrich S, Fonouni H, Mehrabi A, Buchler MW, et al. Extrahepatic cholestasis increases liver stiffness (FibroScan) irrespective of fibrosis. *Hepatology*. 2008;**48**(5):1718-1723
- [22] Trifan A, Sfarti C, Cojocariu C, Dimache M, Cretu M, Hutanasu C, et al. Increased liver stiffness in extrahepatic cholestasis caused by choledocholithiasis. *Hepatitis Monthly*. 2011;**11**(5):372-375
- [23] Colli A, Pozzoni P, Berzuini A, Gerosa A, Canovi C, Molteni EE, et al. Decompensated chronic heart failure: Increased liver stiffness measured by means of transient elastography. *Radiology*. 2010;**257**(3):872-878
- [24] Lupsor-Platon M, Serban T, Silion AI, Tirpe A, Florea M. Hepatocellular carcinoma and non-alcoholic fatty liver disease: A step forward for better evaluation using ultrasound elastography. *Cancers (Basel)*. 2020;**12**(10):2778
- [25] Berzigotti A, Ferraioli G, Bota S, Gilja OH, Dietrich CF. Novel ultrasound-based methods to assess liver disease: The game has just begun. *Digestive and Liver Disease*. 2018;**50**(2):107-112
- [26] Barr RG. Shear wave liver elastography. *Abdominal Radiology (NY)*. 2018;**43**(4):800-807
- [27] Ferraioli G, Wong VW, Castera L, Berzigotti A, Sporea I, Dietrich CF, et al. Liver ultrasound elastography: An update to the world federation for ultrasound in medicine and biology guidelines and recommendations. *Ultrasound in Medicine & Biology*. 2018;**44**(12):2419-2440
- [28] Popescu A, Sirli R, Sporea I. 2D shear wave elastography for liver fibrosis evaluation. In: Lupsor-Platon M, editor. *Ultrasound Elastography*. London, United Kingdom: IntechOpen; 2019. pp. 37-48
- [29] Bazerbachi F, Haffar S, Wang Z, Cabezas J, Arias-Loste MT, Crespo J, et al. Range of normal liver stiffness and factors associated with increased

stiffness measurements in apparently healthy individuals. *Clinical Gastroenterology and Hepatology*. 2019;**17**(1):54-64

[30] Stebbing J, Farouk L, Panos G, Anderson M, Jiao LR, Mandalia S, et al. A meta-analysis of transient elastography for the detection of hepatic fibrosis. *Journal of Clinical Gastroenterology* 2010;**44**(3):214-219

[31] Friedrich-Rust M, Ong MF, Martens S, Sarrazin C, Bojunga J, Zeuzem S, et al. Performance of transient elastography for the staging of liver fibrosis: A meta-analysis. *Gastroenterology*. Apr 2008;**134**(4):960-974

[32] Talwalkar JA, Kurtz DM, Schoenleber SJ, West CP, Montori VM. Ultrasound-based transient elastography for the detection of hepatic fibrosis: Systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*. Oct 2007;**5**(10):1214-1220

[33] Shaheen AA, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: A systematic review of diagnostic test accuracy. *The American Journal of Gastroenterology*. 2007;**102**(11):2589-2600

[34] Abd El Rihim AY, Omar RF, Fathalah W, El Attar I, Hafez HA, Ibrahim W. Role of fibroscan and APRI in detection of liver fibrosis: A systematic review and meta-analysis. *Arab Journal of Gastroenterology*. 2013;**14**(2):44-50

[35] Ying HY, Lu LG, Jing DD, Ni XS. Accuracy of transient elastography in the assessment of chronic hepatitis C-related liver cirrhosis. *Clinical and Investigative Medicine*. 2016;**39**(5):E150-EE60

[36] Ganne-Carrie N, Ziol M, de Ledinghen V, Douvin C, Marcellin P,

Castera L, et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. *Hepatology*. 2006;**44**(6):1511-1517

[37] Zhang GL, Zhao QY, Lin CS, Hu ZX, Zhang T, Gao ZL. Transient elastography and ultrasonography: Optimal evaluation of liver fibrosis and cirrhosis in patients with chronic hepatitis B concurrent with nonalcoholic fatty liver disease. *BioMed Research International*. 2019;**2019**:3951574

[38] Berzigotti A, Abraldes JG, Tandon P, Erice E, Gilabert R, Garcia-Pagan JC, et al. Ultrasonographic evaluation of liver surface and transient elastography in clinically doubtful cirrhosis. *Journal of Hepatology*. 2010;**52**(6):846-853

[39] Njei B, McCarty TR, Luk J, Ewelukwa O, Ditah I, Lim JK. Use of transient elastography in patients with HIV-HCV coinfection: A systematic review and meta-analysis. *Journal of Gastroenterology and Hepatology*. 2016;**31**(10):1684-1693

[40] Castera L, Vergniol J, Foucher J, Le Bail 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**(2):343-350

[41] Afdhal NH, Bacon BR, Patel K, Lawitz EJ, Gordon SC, Nelson DR, 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. *Clinical Gastroenterology and Hepatology*. 2015;**13**(4):772-779

[42] Degos F, Perez P, Roche B, Mahmoudi A, Asselineau J, Voitot H, et al. Diagnostic accuracy of FibroScan

- and comparison to liver fibrosis biomarkers in chronic viral hepatitis: A multicenter prospective study (the FIBROSTIC study). *Journal of Hepatology*. 2010;**53**(6):1013-1021
- [43] Ziol M, Handra-Luca A, Kettaneh A, Christidis 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**(1):48-54
- [44] Carrion JA, Navasa M, Bosch J, Bruguera M, Gilibert R, Forns X. Transient elastography for diagnosis of advanced fibrosis and portal hypertension in patients with hepatitis C recurrence after liver transplantation. *Liver Transplantation*. 2006;**12**(12):1791-1798
- [45] Sporea I, Sirli R, Deleanu A, Tudora A, Curescu M, Cornianu M, et al. Comparison of the liver stiffness measurement by transient elastography with the liver biopsy. *World Journal of Gastroenterology*. 2008;**14**(42):6513-6517
- [46] Nitta Y, Kawabe N, Hashimoto S, Harata M, Komura N, Kobayashi K, et al. Liver stiffness measured by transient elastography correlates with fibrosis area in liver biopsy in patients with chronic hepatitis C. *Hepatology Research*. 2009;**39**(7):675-684
- [47] Zarski JP, Sturm N, Guehot J, Paris A, Zafrani ES, Asselah T, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: The ANRS HCEP-23 study. *Journal of Hepatology*. 2012;**56**(1):55-62
- [48] Wang JH, Changchien CS, Hung CH, Eng HL, Tung WC, Kee KM, et al. FibroScan and ultrasonography in the prediction of hepatic fibrosis in patients with chronic viral hepatitis. *Journal of Gastroenterology*. 2009;**44**(5):439-446
- [49] Yoneda M, Thomas E, Sclair SN, Grant TT, Schiff ER. Supersonic shear imaging and transient elastography with the XL probe accurately detect fibrosis in overweight or obese patients with chronic liver disease. *Clinical Gastroenterology and Hepatology*. 2015;**13**(8):1502-1509
- [50] Florea M, Serban T, Tirpe GR, Tirpe A, Lupsor-Platon M. Noninvasive assessment of hepatitis C virus infected patients using vibration-controlled transient elastography. *Journal of Clinical Medicine*. 2021;**10**(12):2575
- [51] Poynard T, Halfon P, Castera L, Munteanu M, Imbert-Bismut F, Ratziu V, et al. Standardization of ROC curve areas for diagnostic evaluation of liver fibrosis markers based on prevalences of fibrosis stages. *Clinical Chemistry*. 2007;**53**(9):1615-1622
- [52] Karlas T, Pfrepper C, Wiegand J, Wittekind C, Neuschulz M, Mossner J, et al. Acoustic radiation force impulse imaging (ARFI) for non-invasive detection of liver fibrosis: Examination standards and evaluation of interlobe differences in healthy subjects and chronic liver disease. *Scandinavian Journal of Gastroenterology*. 2011;**46**(12):1458-1467
- [53] Lupsor M, Badea R, Stefanescu H, Sparchez Z, Branda H, Serban A, et al. Performance of a new elastographic method (ARFI technology) compared to unidimensional transient elastography in the noninvasive assessment of chronic hepatitis C preliminary results. *Journal of Gastrointestinal and Liver Diseases*. 2009;**18**(3):303-310
- [54] Fierbinteanu-Braticevici C, Andronescu D, Usvat R, Cretoiu D,

- Baicus C, Marinoschi G. Acoustic radiation force imaging sonoelastography for noninvasive staging of liver fibrosis. *World Journal of Gastroenterology*. 2009;**15**(44):5525-5532
- [55] Friedrich-Rust M, Wunder K, Kriener S, Sotoudeh F, Richter S, Bojunga J, et al. Liver fibrosis in viral hepatitis: Noninvasive assessment with acoustic radiation force impulse imaging versus transient elastography. *Radiology*. 2009;**252**(2):595-604
- [56] Rizzo L, Calvaruso V, Cacopardo B, Alessi N, Attanasio M, Petta S, et al. Comparison of transient elastography and acoustic radiation force impulse for non-invasive staging of liver fibrosis in patients with chronic hepatitis C. *The American Journal of Gastroenterology*. 2011;**106**(12):2112-2120
- [57] Sporea I, Sirli R, Bota S, Fierbinteanu-Braticevici C, Petrisor A, Badea R, et al. Is ARFI elastography reliable for predicting fibrosis severity in chronic HCV hepatitis? *World Journal of Radiology*. 2011;**3**(7):188-193
- [58] Friedrich-Rust M, Nierhoff J, Lupsor M, Sporea I, Fierbinteanu-Braticevici C, Strobel D, et al. Performance of acoustic radiation force impulse imaging for the staging of liver fibrosis: A pooled meta-analysis. *Journal of Viral Hepatitis*. 2012;**19**(2):e212-e219
- [59] Sporea I, Bota S, Peck-Radosavljevic M, Sirli R, Tanaka H, Iijima H, et al. Acoustic radiation force impulse elastography for fibrosis evaluation in patients with chronic hepatitis C: An international multicenter study. *European Journal of Radiology*. 2012;**81**(12):4112-4118
- [60] Chen SH, Li YF, Lai HC, Kao JT, Peng CY, Chuang PH, et al. Effects of patient factors on noninvasive liver stiffness measurement using acoustic radiation force impulse elastography in patients with chronic hepatitis C. *BMC Gastroenterology*. 2012;**12**:105
- [61] Zhang DK, Chen M, Liu Y, Wang RF, Dong XY, Li ZY, et al. Clinical value of acoustic radiation force impulse imaging for quantitative evaluation of degree of liver fibrosis in chronic hepatitis C patients. *Zhonghua Gan Zang Bing Za Zhi*. 2013;**21**(8):599-603
- [62] Nishikawa T, Hashimoto S, Kawabe N, Harata M, Nitta Y, Murao M, et al. Factors correlating with acoustic radiation force impulse elastography in chronic hepatitis C. *World Journal of Gastroenterology*. 2014;**20**(5):1289-1297
- [63] Yamada R, Hiramatsu N, Oze T, Morishita N, Harada N, Miyazaki M, et al. Significance of liver stiffness measurement by acoustic radiation force impulse (ARFI) among hepatitis C patients. *Journal of Medical Virology*. 2014;**86**(2):241-247
- [64] Li SM, Li GX, Fu DM, Wang Y, Dang LQ. Liver fibrosis evaluation by ARFI and APRI in chronic hepatitis C. *World Journal of Gastroenterology*. 2014;**20**(28):9528-9533
- [65] Takaki S, Kawakami Y, Miyaki D, Nakahara T, Naeshiro N, Murakami E, et al. Non-invasive liver fibrosis score calculated by combination of virtual touch tissue quantification and serum liver functional tests in chronic hepatitis C patients. *Hepatology Research*. 2014;**44**(3):280-287
- [66] Silva Junior RG, Schmillevitch J, Nascimento Mde F, Miranda ML, Brant PE, Schulz PO, et al. Acoustic radiation force impulse elastography and serum fibrosis markers in chronic hepatitis C. *Scandinavian Journal of Gastroenterology*. 2014;**49**(8):986-992

- [67] Tai DI, Tsay PK, Jeng WJ, Weng CC, Huang SF, Huang CH, et al. Differences in liver fibrosis between patients with chronic hepatitis B and C: Evaluation by acoustic radiation force impulse measurements at 2 locations. *Journal of Ultrasound in Medicine*. 2015;**34**(5):813-821
- [68] Chen SH, Peng CY, Lai HC, Chang IP, Lee CJ, Su WP, et al. Head-to-head comparison between collagen proportionate area and acoustic radiation force impulse elastography in liver fibrosis quantification in chronic hepatitis C. *PLoS One*. 2015;**10**(10): e0140554
- [69] Joo SK, Kim JH, Oh S, Kim BG, Lee KL, Kim HY, et al. Prospective comparison of noninvasive fibrosis assessment to predict advanced fibrosis or cirrhosis in asian patients with hepatitis C. *Journal of Clinical Gastroenterology*. 2015;**49**(8):697-704
- [70] Mare R, Sporea I, Lupusoru R, Sirli 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**:144-151
- [71] Gani RA, Hasan I, Sanityoso A, Lesmana CRA, Kurniawan J, Jasirwan COM, et al. Evaluation of acoustic radiation force impulse (ARFI) for fibrosis staging in chronic liver diseases. *Acta Medica Indonesiana*. 2017;**49**(2):128-135
- [72] Ragazzo TG, Paranagua-Vezozzo D, Lima FR, de Campos Mazo DF, Pessoa MG, Oliveira CP, et al. Accuracy of transient elastography-FibroScan(R), acoustic radiation force impulse (ARFI) imaging, the enhanced liver fibrosis (ELF) test, APRI, and the FIB-4 index compared with liver biopsy in patients with chronic hepatitis C. *Clinics (São Paulo, Brazil)*. 2017;**72**(9):516-525
- [73] Alem SA, Abdellatif Z, Mabrouk M, Zayed N, Elsharkawy A, Khairy M, et al. Diagnostic accuracy of acoustic radiation force impulse elastography (ARFI) in comparison to other non-invasive modalities in staging of liver fibrosis in chronic HCV patients: Single-center experience. *Abdominal Radiology (NY)*. 2019;**44**(8):2751-2758
- [74] Hsu TH, Tsui PH, Yu WT, Huang SF, Tai J, Wan YL, et al. Cutoff values of acoustic radiation force impulse two-location measurements in different etiologies of liver fibrosis. *Journal of Medical Ultrasound*. 2019;**27**(3):130-134
- [75] Ueda N, Kawaoka T, Imamura M, Aikata H, Nakahara T, Murakami E, et al. Liver fibrosis assessments using FibroScan, virtual-touch tissue quantification, the FIB-4 index, and mac-2 binding protein glycosylation isomer levels compared with pathological findings of liver resection specimens in patients with hepatitis C infection. *BMC Gastroenterology*. 2020;**20**(1):314
- [76] Baldea V, Sporea I, Lupusoru R, Bende F, Mare R, Popescu A, et al. Comparative study between the diagnostic performance of point and 2-D shear-wave elastography for the non-invasive assessment of liver fibrosis in patients with chronic hepatitis C using transient elastography as reference. *Ultrasound in Medicine & Biology*. 2020;**46**(11):2979-2988
- [77] Lupsor-Platon M, Badea R, Gersak M, Maniu A, Rusu I, Suci A, et al. Noninvasive assessment of liver diseases using 2D shear wave elastography. *Journal of Gastrointestinal and Liver Diseases*. 2016;**25**(4):525-532
- [78] Bavu E, Gennisson JL, Couade M, Bercoff J, Mallet V, Fink M, et al. Noninvasive in vivo liver fibrosis evaluation using supersonic shear

imaging: A clinical study on 113 hepatitis C virus patients. *Ultrasound in Medicine & Biology*. 2011;**37**(9):1361-1373

[79] Ferraioli G, Tinelli C, Dal Bello B, Zicchetti M, Filice G, Filice C, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: A pilot study. *Hepatology*. 2012;**56**(6):2125-2133

[80] Tada T, Kumada T, Toyoda H, Ito T, Sone Y, Okuda S, et al. Utility of real-time shear wave elastography for assessing liver fibrosis in patients with chronic hepatitis C infection without cirrhosis: Comparison of liver fibrosis indices. *Hepatology Research*. 2015;**45**(10):E122-E129

[81] Herrmann E, de Ledinghen V, Cassinotto C, Chu WC, Leung VY, Ferraioli G, et al. Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: An individual patient data-based meta-analysis. *Hepatology*. 2018;**67**(1):260-272

[82] Abe T, Kuroda H, Fujiwara Y, Yoshida Y, Miyasaka A, Kamiyama N, et al. Accuracy of 2D shear wave elastography in the diagnosis of liver fibrosis in patients with chronic hepatitis C. *Journal of Clinical Ultrasound*. 2018;**46**(5):319-327

[83] Serra C, Grasso V, Conti F, Felicani C, Mazzotta E, Lenzi M, et al. A new two-dimensional shear wave elastography for noninvasive assessment of liver fibrosis in healthy subjects and in patients with chronic liver disease. *Ultraschall in der Medizin (Stuttgart, Germany: 1980)*. 2018;**39**(4):432-439

[84] Villani R, Cavallone F, Romano AD, Bellanti F, Serviddio G. Two-dimensional shear wave elastography versus transient elastography: A non-invasive comparison for the assessment of liver fibrosis

in patients with chronic hepatitis C. *Diagnostics (Basel)*. 2020;**10**(5)

[85] Baldea V, Bende F, Popescu A, Sirli R, Sporea I. Comparative study between two 2D-shear waves elastography techniques for the non-invasive assessment of liver fibrosis in patients with chronic hepatitis C virus (HCV) infection. *Medical Ultrasonography*. 2021;**23**(3):257-264

[86] Aksakal M, Oktar SO, Sendur HN, Esendagli G, Ozenirler S, Cindoruk M, et al. Diagnostic performance of 2D shear wave elastography in predicting liver fibrosis in patients with chronic hepatitis B and C: a histopathological correlation study. *Abdominal Radiology (NY)*. 2021;**46**(7):3238-3244

[87] Numao H, Shimaya K, Kakuta A, Shibutani K, Igarashi S, Hasui K, et al. The utility of two-dimensional real-time shear wave elastography for assessing liver fibrosis in patients with chronic hepatitis C virus infection. *European Journal of Gastroenterology & Hepatology*. 2021;**33**(11):1400-1407

[88] Matos J, Paparo F, Bacigalupo L, Cenderello G, Mussetto I, De Cesari M, et al. Noninvasive liver fibrosis assessment in chronic viral hepatitis C: Agreement among 1D transient elastography, 2D shear wave elastography, and magnetic resonance elastography. *Abdominal Radiology (NY)*. 2019;**44**(12):4011-4021

[89] Persico M, Rosato V, Aglitti A, Precone D, Corrado M, De Luna A, et al. Sustained virological response by direct antiviral agents in HCV leads to an early and significant improvement of liver fibrosis. *Antiviral Therapy*. 2018;**23**(2):129-138

[90] Singh S, Facciorusso A, Loomba R, Falck-Ytter YT. Magnitude and kinetics of decrease in liver stiffness after antiviral therapy in patients with chronic hepatitis

C: A systematic review and meta-analysis. *Clinical Gastroenterology and Hepatology*. 2018;**16**(1):27-38

[91] Knop V, Hoppe D, Vermehren J, Troetschler S, Herrmann E, Vermehren A, et al. Non-invasive assessment of fibrosis regression and portal hypertension in patients with advanced chronic hepatitis C virus (HCV)-associated liver disease and sustained virologic response (SVR): 3 years follow-up of a prospective longitudinal study. *Journal of Viral Hepatitis*. 2021;**28**(11):1604-1613

[92] Tachi Y, Hirai T, Kojima Y, Miyata A, Ohara K, Ishizu Y, et al. Liver stiffness measurement using acoustic radiation force impulse elastography in hepatitis C virus-infected patients with a sustained virological response. *Alimentary Pharmacology & Therapeutics*. 2016;**44**(4):346-355

[93] Chen SH, Lai HC, Chiang IP, Su WP, Lin CH, Kao JT, et al. Performance of acoustic radiation force impulse elastography for staging liver fibrosis in patients with chronic hepatitis C after viral eradication. *Clinical Infectious Diseases*. 2020;**70**(1):114-122

[94] Pan JJ, Bao F, Du E, Skillin C, Frenette CT, Waalen J, et al. Morphometry confirms fibrosis regression from sustained virologic response to direct-acting antivirals for hepatitis C. *Hepatology Communications*. 2018;**2**(11):1320-1330

[95] Broquetas T, Herruzo-Pino P, Marino Z, Naranjo D, Vergara M, Morillas RM, et al. Elastography is unable to exclude cirrhosis after sustained virological response in HCV-infected patients with advanced chronic liver disease. *Liver International*. 2021;**41**(11):2733-2746

[96] van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;**308**(24):2584-2593

[97] Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: A meta-analysis of observational studies. *Annals of Internal Medicine*. 2013;**158**(5 Pt 1):329-337

[98] European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology*. 2018;**69**(1):182-236

[99] Kanwal F, Kramer JR, Asch SM, Cao Y, Li L, El-Serag HB. Long-term risk of hepatocellular carcinoma in HCV patients treated with direct acting antiviral agents. *Hepatology*. 2020;**71**(1):44-55

[100] Papatheodoridi M, Hiriart JB, Lupsor-Platon M, Bronte F, Boursier J, Elshaarawy O, et al. Refining the Baveno VI elastography criteria for the definition of compensated advanced chronic liver disease. *Journal of Hepatology*. 2021;**74**(5):1109-1116

[101] Shi KQ, Fan YC, Pan ZZ, Lin XF, Liu WY, Chen YP, et al. Transient elastography: A meta-analysis of diagnostic accuracy in evaluation of portal hypertension in chronic liver disease. *Liver International*. 2013;**33**(1):62-71

[102] Lee HW, Chon YE, Kim SU, Kim BK, Park JY, Kim DY, et al. Predicting liver-related events using transient elastography in chronic hepatitis c

patients with sustained virological response. *Gut Liver*. 2016;**10**(3):429-436

[103] Hamada K, Saitoh S, Nishino N, Fukushima D, Horikawa Y, Nishida S, et al. Shear wave elastography predicts hepatocellular carcinoma risk in hepatitis C patients after sustained virological response. *PLoS One*. 2018;**13**(4):e0195173

[104] Fernandes FF, Piedade J, Guimaraes L, Nunes EP, Chaves U, Goldenzon RV, et al. Effectiveness of direct-acting agents for hepatitis C and liver stiffness changing after sustained virological response. *Journal of Gastroenterology and Hepatology*. 2019;**34**(12):2187-2195

[105] Tachi Y, Hirai T, Kojima Y, Tachino H, Hosokawa C, Ohya T, et al. Diagnostic performance of real-time tissue elastography in chronic hepatitis C patients with sustained virological response. *European Journal of Gastroenterology & Hepatology*. 2020;**32**(5):609-615

[106] You MW, Kim KW, Shim JJ, Pyo J. Impact of liver-stiffness measurement on hepatocellular carcinoma development in chronic hepatitis C patients treated with direct-acting antivirals: A systematic review and time-to-event meta-analysis. *Journal of Gastroenterology and Hepatology*. 2021;**36**(3):601-608

[107] Alonso Lopez S, Manzano ML, Gea F, Gutierrez ML, Ahumada AM, Devesa MJ, et al. A model based on noninvasive markers predicts very low hepatocellular carcinoma risk after viral response in hepatitis C virus-advanced fibrosis. *Hepatology*. 2020;**72**(6):1924-1934

[108] Ioannou GN, Green PK, Beste LA, Mun EJ, Kerr KF, Berry K. Development of models estimating the risk of hepatocellular carcinoma after antiviral treatment for hepatitis C. *Journal of Hepatology*. 2018;**69**(5):1088-1098

[109] Modaresi Esfeh J, Ansari-Gilani K. Steatosis and hepatitis C. *Gastroenterology Report (Oxford)*. 2016;**4**(1):24-29

[110] Mazhar SM, Shieh Morteza M, Sirlin CB. Noninvasive assessment of hepatic steatosis. *Clinical Gastroenterology and Hepatology*. 2009;**7**(2):135-140

[111] El-Zayadi AR. Hepatic steatosis: a benign disease or a silent killer. *World Journal of Gastroenterology*. 2008;**14**(26):4120-4126

[112] Lonardo A, Loria P, Adinolfi LE, Carulli N, Ruggiero G. Hepatitis C and steatosis: A reappraisal. *Journal of Viral Hepatitis*. 2006;**13**(2):73-80

[113] Kurosaki M, Hosokawa T, Matsunaga K, Hirayama I, Tanaka T, Sato M, et al. Hepatic steatosis in chronic hepatitis C is a significant risk factor for developing hepatocellular carcinoma independent of age, sex, obesity, fibrosis stage and response to interferon therapy. *Hepatology Research*. 2010;**40**(9):870-877

[114] Castera L, Hezode C, Roudot-Thoraval F, Bastie A, Zafrani ES, Pawlotsky JM, et al. Worsening of steatosis is an independent factor of fibrosis progression in untreated patients with chronic hepatitis C and paired liver biopsies. *Gut*. 2003;**52**(2):288-292

[115] Peleg N, Issachar A, Sneh Arbib O, Cohen-Naftaly M, Harif Y, Oxtrud E, et al. Liver steatosis is a major predictor of poor outcomes in chronic hepatitis C patients with sustained virological response. *Journal of Viral Hepatitis*. 2019;**26**(11):1257-1265

[116] Stauber RE, Lackner C. Noninvasive diagnosis of hepatic fibrosis in chronic hepatitis C. *World Journal of Gastroenterology*. 2007;**13**(32):4287-4294

- [117] Hepburn MJ, Vos JA, Fillman EP, Lawitz EJ. The accuracy of the report of hepatic steatosis on ultrasonography in patients infected with hepatitis C in a clinical setting: A retrospective observational study. *BMC Gastroenterology*. 2005;**5**:14
- [118] Sasso M, Beaugrand M, de Ledinghen V, Douvin C, Marcellin P, Poupon R, et al. Controlled attenuation parameter (CAP): A novel VCTE guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. *Ultrasound in Medicine & Biology*. 2010;**36**(11):1825-1835
- [119] Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Ledinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. *Journal of Hepatology*. 2017;**66**(5):1022-1030
- [120] Wang Y, Fan Q, Wang T, Wen J, Wang H, Zhang T. Controlled attenuation parameter for assessment of hepatic steatosis grades: A diagnostic meta-analysis. *International Journal of Clinical and Experimental Medicine*. 2015;**8**(10):17654-17663
- [121] Sasso M, Tengher-Barna I, Ziol M, Miette V, Fournier C, Sandrin L, et al. Novel controlled attenuation parameter for noninvasive assessment of steatosis using Fibroscan((R)): Validation in chronic hepatitis C. *Journal of Viral Hepatitis*. 2012;**19**(4):244-253
- [122] Ferraioli G, Tinelli C, Lissandrin R, Zicchetti M, Dal Bello B, Filice G, et al. Controlled attenuation parameter for evaluating liver steatosis in chronic viral hepatitis. *World Journal of Gastroenterology*. 2014;**20**(21):6626-6631
- [123] Lupşor-Platon M, Feier D, Stănescu H, Tamas A, Botan E, Sparchez Z, et al. Diagnostic accuracy of controlled attenuation parameter measured by transient elastography for the non-invasive assessment of liver steatosis: A prospective study. *Journal of Gastrointestinal and Liver Diseases*. 2015;**24**(1):35-42
- [124] Deffieux T, Gennisson JL, Bousquet L, Corouge M, Coscinea S, Amroun D, et al. Investigating liver stiffness and viscosity for fibrosis, steatosis and activity staging using shear wave elastography. *Journal of Hepatology*. 2015;**62**(2):317-324