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Role of two-dimensional shear wave elastography in chronic liver diseases: A narrative review

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Abstract

Liver biopsy is the gold standard for evaluating the degree of liver fibrosis in patients with chronic liver disease. However, due to the many limitations of liver biopsy, there has been much interest in the use of noninvasive techniques for this purpose. Among these techniques real-time two-dimensional shear wave elastography (2D-SWE) has the advantage of measuring tissue elasticity with the guidance of B-mode images. Recently, many studies have been conducted on the application of 2D-SWE in patients with various liver diseases, and their validity has been confirmed. Here, we briefly discuss the role of 2D-SWE in patients with chronic liver diseases, particularly aspects of the examination techniques and clinical applications.

Key words: Shear wave elastography; Liver disease; Liver fibrosis; Portal hypertension; Hepatocellular carcinoma

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Core tip: Assessing the degree of liver fibrosis in patients with chronic liver disease is clinically important. Real-time two-dimensional shear wave elastography (2D-SWE) has the advantage of measuring tissue elasticity with the guidance of B-mode images. Recently, many studies have shown that 2D-SWE is a useful tool for evaluating not only liver fibrosis in various liver diseases but also portal hypertension, and for predicting the development of hepatocellular carcinoma. Here, we discuss briefly the role of 2D-SWE in patients with chronic liver diseases, particularly aspects of the examination technique and clinical applications.

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INTRODUCTION

Chronic liver diseases are one of the major causes of illness and death worldwide, and a substantial public health issue. Chronic liver diseases can lead to liver fibrosis due to transient or persistent intrahepatic inflammation, and some eventually progress to liver cirrhosis and hepatocellular carcinoma^[1]. Therefore, assessing the degree of fibrosis in patients with chronic liver diseases, especially before the advanced stage, is clinically important to allow early care and prevent fatal liver disease^[1].

To date, the gold standard for evaluating the degree of liver fibrosis is liver biopsy^[2]. However, it has several limitations^[3]. Because it is an invasive method, it may cause pain, bleeding and perforation^[3], and can uncommonly lead to massive bleeding that requires blood transfusion, or to death^[3]. Also, it has limitations for representing the whole liver parenchyma because it evaluates only about 1/50000 of the total liver volume and there is potential for sampling errors and interobserver or intraobserver variability of interpretation^[4,5].

Because of these limitations of liver biopsy, there has been much interest in noninvasive techniques for assessing the degree of liver fibrosis^[6]. In particular, several ultrasonography-based elastographic methods have been developed in the past decade, and evaluation of liver fibrosis by measuring liver stiffness (LS) has been the main type of noninvasive method^[6]. Transient elastography (TE), which was the first method introduced into the market, is a highly reproducible and user-friendly technique for evaluating liver fibrosis, and is also used for assessing portal hypertension and predicting the development of hepatocellular carcinoma (HCC)^[7]. However, it has some limitations, including frequent invalid results especially in patients with ascites or severe obesity^[7]. Also the attempts to ameliorate diagnostic accuracy, adding to TE the calculation realized by software of quantitative measurements of the Glissonian line, have failed^[8].

Real-time two-dimensional shear wave elastography (2D-SWE), which was developed subsequent to TE, can measure tissue elasticity with the real-time guidance of B-mode image. Recently there have been many studies of 2D-SWE, related especially to examination technique and clinical applications. In this article, we review the focusing 2D SWE technique using the Aixplorer ultrasound (US) system (Supersonic Imagine SA, Aix-en-Provence, France).

MEASURING LIVER STIFFNESS

Measurements of liver stiffness (LS) using 2D-SWE are

usually performed through right intercostal scans, with the patient in a supine position. Because the sonographic window gets clearer as the intercostal space enlarges, LS is measured with right arm maximal abduction. Deep inspiration is avoided as it increases the measured LS value, and, if possible, LS is measured with a short breath hold for 4 to 5 s and neutral breathing. A trapezoidal color box (3.5 cm × 2.5 cm) is positioned in the liver parenchyma and acquires the elasticity signals. When the elastogram signals in the color box are judged to reach a plateau, *i.e.*, after about 2 or 3 s, the image is frozen. After call-back, the most homogenous areas of elastogram signals among the sequential frames are identified using a cine loop, and a round ROI (also referred to as the Q-box) is positioned in the region of the color box. The brighter the grayscale image obtained without shadowing in the scan, the more uniform the elastogram signal generated. The ROI is located in a homogenous elastogram signal in the liver parenchyma where there is no large vessel or hepatic nodule. To avoid reverberation artifacts, ROIs are located 1 to 2 cm from the liver capsule. The ROI is as large as possible and up to 2 cm in diameter, but its size is reduced if necessary, depending on the measurable areas of the elastogram signal and the location of large vessels. Also, if the measurement depth is too great, a qualitative elastogram signal is not generated and the signal is less reliable; measurement should preferably be at a depth of less than 6 cm from the capsule. Measured elasticity values are expressed in kilopascal (kPa) and recorded on the image as means and standard deviations (Figure 1).

Technically, measurement of LS using 2D-SWE has several advantages. It is not affected by ascites, because the shear waves are generated by the focused beam inside the liver parenchyma rather than at the surface of the body. Large vessels can be avoided using simultaneous gray scale images, and the sampling volume is larger than in p-SWE. By means of real-time color mapping, an experienced examiner can judge whether measurements are reliable.

Optimal region and number of measurements, and validation

LS was measured in the right lobe in all previous studies. Measurement of LS in the left lobe is inappropriate, because it is affected by cardiac pulsation. Most measurements of LS by 2D-SWE use an intercostal scan, and they are usually made in the right anterior section. When measured in this way, measurement reliability is high and the correlation with histologic hepatic fibrosis staging is good^[9,10].

When LS is measured by TE, it is measured 10 times and validated using a success rate of 60% or more and interquartile range/median (IQR/M) < 0.3, and the median value of the measurements is selected as the LS value. However there is no agreement on the objective number of measurements needed or on the quality criteria for validation of 2D-SWE. Most

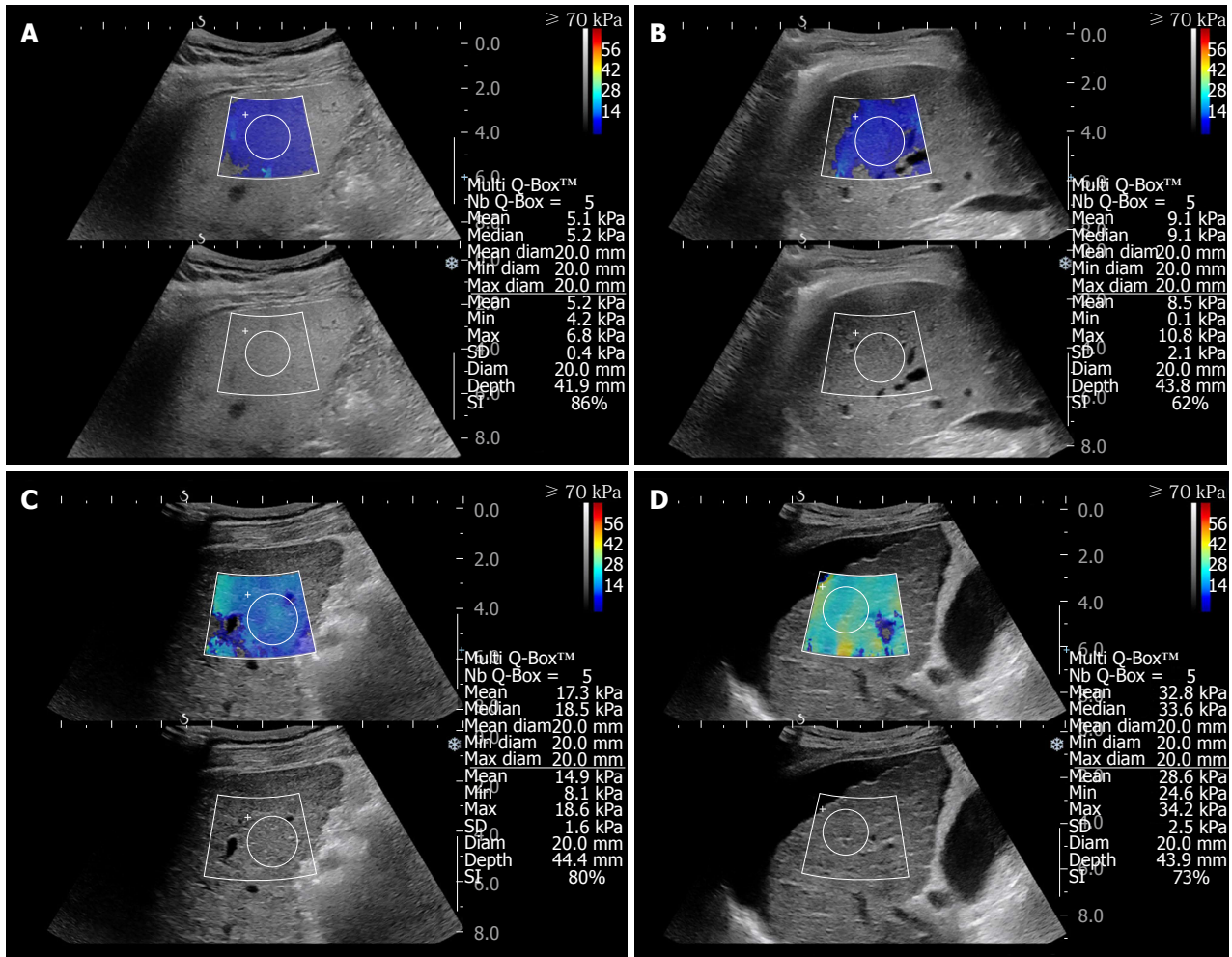


Figure 1 Liver two-dimensional shear wave elastography images. A. 2D-SWE images of a 52-year-old patient without underlying disease with normal range of LS. Ultrasound images show the color-code mapping of 2D-SWE (top) and the corresponding B-mode image (bottom). On the right side of the image, the mean (5.2 kPa) and standard deviation (0.4 kPa) of Young modulus in the ROI have been calculated. And the size and depth of the measured ROI are recorded. The summarized values at the top are the mean and median values of the stiffness values of the previous 4 measurements and the 5th measurement, and the average sizes of the measured ROI. B. A 2D-SWE image of a 58-year-old patient with chronic hepatitis B who was proven as F2 fibrosis in liver biopsy specimen. Increased LS (8.5 kPa) was identified compared to normal patients. C. In 55-year-old patient with chronic hepatitis B and compensated cirrhosis, median LS was 18.5 kPa. D. In 71-year-old patient with chronic hepatitis B and decompensated cirrhosis with ascites, median LS was 33.6 kPa. 2D-SWE: Two-dimensional shear wave elastography; LS: Liver stiffness; ROI: Region of interest.

studies using 2D-SWE have measured LS with 3 to 5 repetitions. According to previous studies of the number of LS measurements, when LS is measured 6 or more times no further increase in intra-class correlation (ICC) is observed^[11], and the LS from a 10-repetition protocol is not significantly different from that from a 5-repetition protocol^[12]. Another group has concluded that three valid measurements are enough^[13]. There is no evidence about whether the mean or median values of repeated measurements correlate better with liver fibrosis. There are quality criteria for LS measurements by 2D-SWE, such as standard deviation (SD), IQR/M and coefficient of variance (CV, SD/mean), but there is no established standard of validation as there is for TE. Therefore, we suggest that three to five measurements of LS by 2D-SWE are appropriate, and in case of validation by IQR/M, five measurements are required.

In LS measurement using 2D-SWE, it is measured faster and more consistently in a patient with a good sonographic window for B-mode images. In the patients with obese and thick abdominal wall, the shadowing occurs in the liver parenchyma and the elasticity signal is not generated well in the color box. In case of poor sonographic window due to severe shrinkage of liver and interposition of omental fat or bowel, the measurement is not successful. And, if the motion is not restricted because the patient is not coordinated, or the liver is affected by cardiac movement, there is a limitation in the measurement. 2D-SWE has more chance to be affected by technical factors because it has larger sampling volume compared to TE or point shear wave elastography. However, the measurement failure rate of 2D-SWE is lower than that of TE when the experienced examiner measures LS^[14,15].

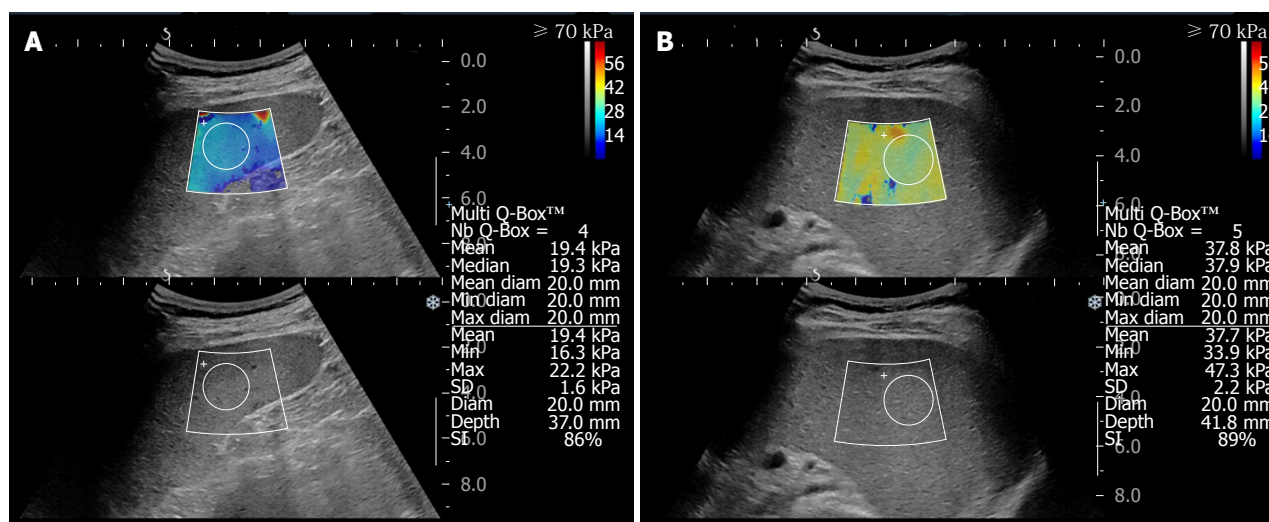


Figure 2 Spleen two-dimensional shear wave elastography images. Spleen 2D-SWE images of a 50-year-old male patient with normal SS (A) and 57-year-old female patient with liver cirrhosis who underwent endoscopic variceal ligation (B). A. The normal patient had a small size and measurable area of spleen. And the SS was measured to 19.4 kPa. B. Patient with liver cirrhosis had relatively large size and measurable area of spleen with good sonographic window. Increased spleen stiffness compared with that of normal patients was identified (37.7 kPa). 2D-SWE: Two-dimensional shear wave elastography; SS: Spleen stiffness.

Reproducibility

The reproducibility of LS measurements by 2D-SWE is high but user-dependent^[16]. The intra-observer reproducibility of 2D-SWE in healthy volunteers is excellent (ICC 0.92 to 0.95)^[16-18]. Inter-observer agreement is good (0.63 to 0.84^[16,18]) and is influenced by operator experience. In the chronic liver disease group, intra-observer reproducibility is excellent, with an ICC of 0.9 to 0.95^[11,19,20], and intra-subject reproducibility at short intervals is excellent, with an ICC of 0.83 to 0.9^[21]. The inter-observer reproducibility of LS measurements using 2D-SWE is excellent, from 0.83 to 0.94^[21,22].

Since 2D-SWE measurement is user-dependent, it is recommended that at least 50 supervised scans and measurements are performed by a novice operator to ensure consistent measurements^[23].

Normal values of liver stiffness, and confounders

The LS value using 2D-SWE in healthy volunteers was found to be 4.5-5.5 kPa^[17,24]. Food intake increases LS value and IQR^[25-27], and may result in over-staging of liver fibrosis and unreliable measurements. According to Mederacke *et al*^[28], LS value declines to the normal range by 180 min after food intake; hence it is recommended to measure LS at least 4 h after food consumption, or after overnight fasting. Caffeine intake, smoking, and exercise also increase LS value^[29], as do acute hepatic inflammation, obstructive cholestasis, and hepatic congestion^[30-36]. The effect of hepatic steatosis on LS value is not yet clear^[37-40]. These confounding factors should be avoided when measuring LS, and patient co-morbidities must be considered when interpreting LS values so as to prevent over-staging of hepatic fibrosis.

MEASURING SPLEEN STIFFNESS

According to a recent meta-analysis, Spleen Stiffness (SS) values measured by 2D-SWE are useful for predicting clinically significant portal hypertension in chronic liver diseases^[41]. They are significantly correlated with the presence of esophageal varix, and are superior to LS values^[42]. In addition, 2D-SWE can check real-time grayscale images at the time of measurement, so that SS can be measured in the most appropriate region. SS is measured by left intercostal or subcostal scans, and is not fundamentally different from LS measurements (Figure 2). The spleen is smaller than the liver and varies in size, and the measurement success rate is lower than that of LS (over 90%). The success rate of SS in all patient groups according to the meta-analysis was 75.5%^[41], and most of the studies included (many) portal hypertension patients with advanced liver cirrhosis. However in a study by Grgurevic *et al*^[43], which included many non-cirrhotic chronic liver disease patients, the success rate of SS measurements was only 53.7%. As spleen size increases, the measurement success rate of SS by 2D-SWE also increases, so that the LS and SS success rates are not significantly different in patients with advanced liver cirrhosis versus severe portal hypertension.

ROLE OF 2D-SWE IN ASSESSING LIVER FIBROSIS

Various liver diseases

Several studies have evaluated fibrosis in various liver diseases by 2D-SWE (Table 1)^[44,45]. LS measured by 2D-SWE had an excellent diagnostic performance with areas under the curve (AUROCs) of about 0.9 for

Table 1 Diagnostic performance of shear wave elastography for significant fibrosis ($F \geq 2$), advanced fibrosis ($F \geq 3$) and cirrhosis (F4) in patients with various liver diseases

Ref.	Year	Patients (n)	F ≥ 2 (%)	F ≥ 3 (%)	F = 4 (%)	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Jeong <i>et al</i> ^[44]	2014	70	78.6			0.915	8.60	78.2	93.3	97.7	53.8
				50		0.913	10.46	88.6	80.0	81.6	87.6
					31.4	0.878	14.00	77.3	85.4	70.8	89.2
Deffieux <i>et al</i> ^[45]	2015	120	48.0			0.890	8.90	77.0	79.0	77.0	79.0
				33		0.880	9.10	85.0	72.0	60.0	90.0
					15.0	0.890	10.20	83.0	76.0	38.0	96.0

AUROC: Area under ROC curve; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; SWE: Shear wave elastography.

Table 2 Diagnostic performance of shear wave elastography for significant fibrosis ($F \geq 2$), advanced fibrosis ($F \geq 3$) and cirrhosis (F4) in patients with chronic hepatitis C

Ref.	Year	Patients (n)	F ≥ 2 (%)	F ≥ 3 (%)	F = 4 (%)	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Bavu <i>et al</i> ^[46]	2011	113	55.8			0.950	9.12	81.0	72.0		
				34.5		0.960	10.08	75.0	78.0		
					13.3	0.970	13.30	80.0	87.0		
Ferraioli <i>et al</i> ^[47]	2012	121	58.7			0.920	7.10	90.0	87.5	91.3	85.7
				31.4		0.980	8.70	97.3	95.1	90.0	98.7
					19.8	0.980	10.40	87.5	96.8	87.5	96.8
Tada <i>et al</i> ^[48]	2013	55	32.7			0.940	8.80	88.9	91.9	84.2	94.4
Herrmann <i>et al</i> ^[49]	2018	379	58.3			0.863	7.10	94.7	52.0		
				33.5		0.915	9.20	90.3	76.8		
					18.2	0.929	13.00	85.8	87.8		

¹The reference fibrosis level is derived from the algorithm proposed by Sebastiani *et al*^[29]. AUROC: Area under ROC curve; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value.

assessing each stage of fibrosis^[44,45]. However, since the burden of fibrosis depends on the dominant disease, the value of LS for a given stage of fibrosis is also dependent on the dominant disease in the patients that are examined. Therefore, the diagnostic performance of 2D-SWE, which was expected to be superior to other noninvasive fibrosis methods such as TE, did not show a statistically significant dependence on stage of fibrosis.

Chronic hepatitis C

Studies of the degree of fibrosis according to the disease involved were the first to evaluate patients with chronic hepatitis C (CHC). The results are summarized in Table 2. LS measured by 2D-SWE showed a significant positive correlation with fibrosis stage evaluated by the METAVIR scoring system in patients with CHC^[46-48]. Also, 2D-SWE had a similar or better diagnostic performance than TE for evaluating liver fibrosis^[46-48].

Bavu *et al*^[46] compared 2D-SWE and TE after classifying fibrosis stage on serology without histological examination. In that study, the AUROCs for diagnoses of significant fibrosis ($\geq F2$), advanced fibrosis ($\geq F3$) and cirrhosis (F4) were 0.948, 0.962 and 0.968, respectively^[46]. Ferraioli *et al*^[47] compared 2D-SWE with TE for assessing fibrosis stage using liver biopsy specimens. The AUROCs of 2D-SWE were 0.92 for $\geq F2$, 0.98 for $\geq F3$ and 0.98 for F4, and were similar ($\geq F3$ and F4) or significantly higher ($\geq F2$) than

those of TE^[47]. In several studies the optimal cutoff values for each fibrosis stage were 7.1-9.12 kPa for $\geq F2$, 8.7-10.08 kPa for $\geq F3$, and 10.4-13.30 kPa for F4^[46-48]. In recently published patient data based on a meta-analysis, the AUROCs for $\geq F2$, $\geq F3$ and F4 of 2D SWE were 0.863, 0.915 and 0.929, respectively, and the proposed cut off values were 7.1 kPa, 9.2 kPa and 13.0 kPa, respectively^[49]. However, the diagnostic performance of 2D SWE for each stage of fibrosis was not significantly different from that of TE^[49].

2D-SWE can be used to predict the efficacy of antiviral treatment in CHC as well as the degree of fibrosis. Tada *et al*^[50] reported that patients with CHC who achieved a sustained virologic response showed an early decrease in LS after administration of a direct acting agent (DAA), and this was the case especially in patients with progressive liver fibrosis. Similarly, Korda *et al*^[51] found a significant decrease in LS after DAA treatment in patients with recurrent HCV infection after liver transplantation. Therefore 2D-SWE may be a useful tool in the follow-up after treatment of CHC.

Chronic hepatitis B

So far the disease most studied for assessing degree of fibrosis by 2D-SWE is hepatitis B virus (HBV) infection. Studies of patients with chronic hepatitis B (CHB) have been mainly performed in China, where HBV is endemic. LS measured by 2D-SWE was positively

Table 3 Diagnostic performance of shear wave elastography for significant fibrosis ($F \geq 2$), advanced fibrosis ($F \geq 3$) and cirrhosis ($F4$) in patients with chronic hepatitis B

Ref.	Year	Patients (n)	$F \geq 2$ (%)	$F \geq 3$ (%)	$F = 4$ (%)	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Leung <i>et al.</i> ^[14]	2013	226	60.2	35.4	15.5	0.880	7.100	84.70	92.10	85.3	91.7
						0.930	7.900	89.80	90.30	71.8	97.0
						0.980	10.100	97.40	93.00	60.1	99.6
Zeng <i>et al.</i> ^[54]	2014	206 (104)	45.7 (45.1)	69.0 (70.1)	81.1 (83.7)	0.917 (0.907)	7.200	86.36 (85.19)	86.96 (80.85)	88.8 (83.6)	84.2 (82.6)
						0.945 (0.934)	9.100	91.94 (89.66)	85.71 (80.56)	74.0 (65.0)	96.0 (95.1)
						0.945 (0.967)	11.700	91.89 (88.24)	89.70 (88.10)	66.7 (60.0)	98.0 (97.4)
Wu <i>et al.</i> ^[53]	2016	437	47.2			0.903	8.200	78.16	85.28	82.6	81.4
Zhuang <i>et al.</i> ^[55]	2017	304(155)	86.8 (84.6)	70.4 (67.8)	54.9 (48.4)	0.926	11.256	91.80	84.31	48.7	98.4
						0.970 (0.970)	7.600	92.00 (91.6)	90.00 (87.5)	98.4 (96.0)	64.3 (65.0)
						0.960 (0.970)	9.200	91.60 (88.6)	96.70 (96.0)	98.5 (97.8)	82.9 (80.1)
Zeng <i>et al.</i> ^[52]	2017	257	46.3	24.9	13.2	0.980 (0.980)	10.400	94.60 (92.0)	94.90 (95.0)	95.7 (94.5)	93.5 (92.7)
						0.882	7.100	88.89	76.38	76.2	89.0
						0.917	8.300	89.66	76.84	55.9	95.8
Herrmann <i>et al.</i> ^[49]	2018	379	52.0	29.8	13.0	0.926	11.300	93.55	87.25	52.7	98.9
						0.906	7.100	87.60	73.60		
						0.931	8.100	94.90	73.10		
						0.955	11.500	79.90	93.90		

¹These studies are divided into index cohort and validation cohort and parentheses are index cohort. AUROC: Area under ROC curve; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value.

correlated with liver fibrosis stage evaluated by the METAVIR scoring system in patients with CHB, as it was for those with CHC^[14,52-55].

Leung *et al.*^[14] reported that the AUROCs for $\geq F2$, $\geq F3$, and $F4$ of 2D-SWE were 0.88, 0.93, and 0.98, respectively, and 2D-SWE performed better than TE for predicting all fibrosis stages. In particular, the cutoff value of 7.1 kPa for $F2$ by SWE had a relatively high specificity of 92.1%, indicating that 2D-SWE is an excellent screening tool for diagnosing significant fibrosis, which is an important starting point for the treatment of chronic viral hepatitis^[14]. In addition, as fibrosis progressed, the optimal cut off value had a high negative predictive value, indicating that 2D-SWE is a very reliable tool for excluding cirrhosis^[14]. Similar trends were seen in other studies.

Zeng *et al.*^[54] and Zhuang *et al.*^[55] analyzed hepatitis B patients using an index cohort and a validation cohort, and showed that SWE had good diagnostic accuracy in predicting each fibrosis stage. Diagnostic performances in patients with CHB are summarized in Table 3. AUROCs for $\geq F2$, $\geq F3$ and $F4$ were 0.88-0.97, 0.917-0.96 and 0.926-0.98, respectively^[14,52-55]. The optimal cutoff values for each fibrosis stage were 7.1-8.2 kPa for $\geq F2$, 7.9-9.1 kPa for $\geq F3$, and 10.1-11.3 kPa for $F4$ ^[14,52-55]. In addition, the diagnostic performance of 2D-SWE was equivalent or superior to use of non-invasive fibrosis markers including TE in most fibrosis stages^[14,52,53,55].

In a recently published patient data-based meta-analysis, the AUROCs for $\geq F2$, $\geq F3$ and $F4$ of 2D-SWE were 0.906, 0.931, and 0.955, respectively, and the proposed cut off values were 7.1 kPa, 8.1 kPa, and 11.5 kPa, respectively^[49]. In addition, 2D-SWE in patients with CHB had a better diagnostic performance than TE in predicting $\geq F2$ and $F4$, but not $\geq F3$, unlike in

patients with CHC^[49].

Non-viral liver diseases

One of the most common causes of advanced liver disease worldwide is nonalcoholic fatty liver disease (NAFLD)^[56]. It is important to diagnose the fibrosis stage in patients with NAFLD because the degree of fibrosis is the most important prognostic factor in these patients^[57]. Three studies on the degrees of fibrosis in NAFLD have recently been published (Table 4)^[20,49,58]. LS measurements by 2D-SWE in these patients had a relatively high failure rate (2.7%-13%) because of the higher BMIs in these patients^[20,58]. Diagnostic performance in predicting each fibrosis stage was relatively low, and the cut-off values of the fibrosis stages differed between the studies^[20,49,58]. This suggests that steatosis may have an effect on liver stiffness measurements, and further studies are needed^[58].

The only study of patients with alcoholic liver disease was one performed by Thiele *et al.*^[19]. In that study, SWE had high diagnostic performances with AUCs of 0.94 and 0.95, respectively, for detecting significant fibrosis (Ishak fibrosis stage ≥ 3) and cirrhosis (Ishak fibrosis stage ≥ 5)^[19]. In addition, the cutoff values for predicting the fibrosis stages there were higher than in other diseases, particularly in chronic viral hepatitis; liver injury in alcoholic liver disease is associated with relatively high levels of perivenular and pericellular fibrosis with central extension, and this may have resulted in a higher fibrosis burden^[19].

There are two recent studies of autoimmune liver disease^[59,60]. Because of the low prevalence of this disease, these studies included patients with autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and overlap syndrome, all of

Table 4 Diagnostic performance of shear wave elastography for significant fibrosis ($F \geq 2$), advanced fibrosis ($F \geq 3$) and cirrhosis ($F4$) in patients with non-viral liver diseases

Ref.	Year	Etiology	Patients (n)	F ≥ 2 (%)	F ≥ 3 (%)	F = 4 (%)	AUROC	Cutoffs (kPa)	Se (%)	Sp (%)	PPV (%)	NPV (%)
Cassinotto <i>et al.</i> ^[20]	2016	NAFLD	291	70.8	43.3	16.8	0.860	8.90	68.0	94.0		
							0.890	9.30	84.0	83.0		
							0.880	10.00	95.0	69.0		
Takeuchi <i>et al.</i> ^[58]	2018	NAFLD	71	64.8	45.1	7.0	0.750	11.57	52.0	44.0		
							0.820	13.07	63.0	57.0		
							0.900	15.73	100.0	82.0		
Herrmann <i>et al.</i> ^[49]	2018	NAFLD	156	58.3	32.1	12.2	0.855	7.10	93.8	52.0		
							0.928	9.20	93.1	80.9		
							0.917	13.00	75.3	87.8		
Thiele <i>et al.</i> ^[19]	2016	Alcohol	199	42.0	18.0	18.0	0.940	10.20	82.0	93.0	90.0	88.0
							0.950	16.40	94.0	91.0	71.0	99.0
							0.850	9.70	81.7	81.3	91.8	63.4
Zeng <i>et al.</i> ^[59]	2017	Autoimmune	114	71.9	41.3	20.2	0.850	13.20	83.0	74.6	69.6	86.2
							0.860	16.30	87.0	80.2	52.6	96.1
							0.781	9.15	83.3	72.7		
Li <i>et al.</i> ^[60]	2018	Autoimmune	51	35.2								

AUROC: Area under ROC curve; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; NAFLD: Non-alcoholic fatty liver disease

which have different liver damage patterns^[59,60]. For this reason, the AUROCs of autoimmune liver disease according to fibrosis stage were lower than those of chronic viral hepatitis^[59,60]. Further studies should be performed separately for each disease.

USE OF 2D-SWE FOR ASSESSING PORTAL HYPERTENSION AND ESOPHAGEAL VARICES

Measurement of hepatic venous pressure gradient (HVPG) is considered the reference standard for assessing portal hypertension in liver cirrhosis, which is one of the most powerful prognostic factors in advanced chronic liver disease^[61]. However, the use of HVPG is limited because it is unavailable in some centers and because of its invasiveness^[62]. Hence, TE was introduced as a noninvasive tool and is known to be strongly correlated with HVPG and excellent for predicting clinically significant portal hypertension (CSPH, HVPG ≥ 10 mmHg)^[61].

There have been many studies aimed at establishing whether LS measured by 2D-SWE can identify portal hypertension. First, Choi *et al.*^[63] analyzed the association of HVPG with LS by 2D-SWE. They showed that HVPG and LS measured by 2D-SWE were moderately correlated ($r = 0.593$), and that change in LS and change in HVPG were strongly related ($r = 0.863$)^[63]. As a result of that study, 2D-SWE unlike TE, can be considered a useful method for monitoring hemodynamic responses to drug therapy. Since then, several studies have examined whether LS measured by 2D-SWE can predict CSPH, and they are summarized in Table 5^[64-67]. The AUROCs for predicting CSPH ranged from 0.81 to 0.87, which are relatively high diagnostic performances, and optimal cut-off values ranged from 15.2 to 24.6 kPa^[64-67]. The different optimal cut-

off values in the different studies were probably due to differences between the major forms of disease examined in the studies^[64-67]. Therefore, as in the case of degree of fibrosis, studies on the prediction of portal hypertension may need to be carried out separately for each disease.

Efforts have been made to improve the reliability of LS measurements by 2D-SWE for predicting portal hypertension. Procopet *et al.*^[64] obtained a diagnostic performance with an AUC of 0.939 for predicting CSPH using an SD/median ≤ 0.10 and/or depth < 5.6 cm. In addition, Elkrief *et al.*^[65] and Jansen *et al.*^[67] observed a strong correlation between HVPG and LS by 2D-SWE and an excellent AUROC in predicting CSPH, when the variation coefficient (SD/mean) was $< 10\%$.

There have been attempts to complement LS in predicting CSPH by measuring SS, but the results were unsatisfactory. Procopet *et al.*^[64] found a 66% success rate for SS measurements and an AUROC of 0.725 for predicting CSPH. In addition, they obtained a high mismatch rate (25%) and indeterminate outcomes (60%) with a method employing a rule-out CSPH cutoff of $> 90\%$ sensitivity and a rule-in CSPH cutoff of $> 90\%$ specificity^[64]. In that study, a small spleen was the most common reason for the inability to measure SS^[64]. Elkrief *et al.*^[65] achieved a success rate of 97% for SS measurements but the AUC of SS in predicting CSPH was only 0.64, a moderate diagnostic performance. Unlike other studies, Jansen *et al.*^[67] had a success rate of 81.2% for SS measurements and a relatively good diagnostic performance with an AUROC of 0.84 in predicting CSPH. Based on this finding, they proposed a combined algorithm consisting of a rule-in algorithm and a rule-out algorithm, and the diagnostic accuracy of the algorithm was 91.6%^[67]. Therefore they suggested that only those patients who were indeterminate in this algorithm would need to undergo invasive HVPG measurements^[67]. Recently, Elkrief *et al.*^[68] performed

Table 5 Diagnostic performance of shear wave elastography for detecting clinically significant portal hypertension (HVPG \geq 10 mmHg)

Ref.	Year	Patients (n)	Study design	Prevalence (%)	Site	Success rate (%)	Cutoffs (kPa)	AUROC	Se (%)	Sp (%)	PPV (%)	NPV (%)
Procopet <i>et al.</i> ^[64]	2015	88	Restrospective	55.0	LS	99.0	17.0	0.859	80.8	82.1		
							15.4 ¹	0.948	91.3	90.9		
Elkrief <i>et al.</i> ^[65]	2015	79	Prospective	90.9	LS	97.0	24.5	0.870	81.0	88.0	98.0	35.0
					SS	97.0	34.7	0.640	40.0	100.0	100.0	18.0
Kim <i>et al.</i> ^[66]	2015	92	Prospective	83.7	LS	98.3	15.2	0.819	85.7	80.0	95.7	52.2
							21.6 ²	0.867	83.3	80.8	91.7	65.6
Jansen <i>et al.</i> ^[67]	2017	109	Prospective multicenter	67.9	LS	100.0	24.6	0.860	68.3	80.4	87.7	55.4
					SS	81.2	26.3	0.840	79.7	84.2	90.8	68.0

¹Highly reliable and reliable measurements ($n = 45$): SD/median > 0.10 or depth ≥ 5.6 cm; ²Severe portal hypertension (HVPG ≥ 12 mmHg). AUROC: Area under ROC curve; Se: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; LS: Liver stiffness; SS: Spleen stiffness.

an external validation of the algorithm. When it was used in 191 patients with liver cirrhosis, the negative predictive value for rule-out was estimated to be 60% and the positive predictive value for rule-in was 87% for predicting CSPH^[68]. Thus the algorithm was not good enough to diagnose CSPH^[68].

There have been three studies on the use of 2D-SWE for predicting esophageal varices (EV). Elkrief *et al.*^[65] compared the diagnostic performance of LS and SS in predicting high risk EV. They detected no difference in LS and SS between patients with high risk EV and without high risk EV, and the AUROCs of the LS and SS values for predicting high risk EV were 0.54 and 0.64, respectively^[65]. This outcome was probably due to the small number of patients tested ($n = 35$) most of whom had high HVPG and/or decompensated cirrhosis^[65]. On the other hand, Stefanescu *et al.*^[69] studied the use of LS and SS in predicting EV in 73 patients with compensated liver cirrhosis. The AUROCs of LS, SS and platelet count (PLT) were 0.753, 0.747, and 0.773, respectively, and the best cut-off values of LS, SS and PLT gave moderate diagnostic performances of 19 kPa, 38 kPa, and $100 \times 10^3/\text{mL}$, respectively^[69]. When this result was used to apply the Baveno IV recommendations and stepwise approaches (LS < 19 kPa and PLT $< 100 \times 10^3/\text{mL}$ = no EV, LS > 19 kPa and PLT $> 100 \times 10^3/\text{mL}$ = probable EV; in the Grey zone, SS < 38 kPa = no EV, SS ≥ 38 kPa = probable EV), it had an accuracy of 83.07% for ruling out EV^[69]. However, when the algorithm was used with the platelet counts to predict EV it did not improve the diagnostic accuracy of the rule out algorithm proposed by Jansen *et al.*^[70]. Similarly, Kim *et al.*^[71] evaluated the predictive performance of LS for presence of EV and high risk EV in 103 patients with compensated liver cirrhosis. The AUROCs of LS for presence of EV and high risk EV were 0.887 and 0.880, respectively, and the best cut-off values were 13.9 kPa and 16.1 kPa, respectively^[71].

ROLE OF 2D-SWE IN PREDICTING THE DEVELOPMENT OF HCC

TE is a useful predictor of HCC development in patients

with CHB^[72]. In particular, it is known to identify patients with CHB who do not have clinical cirrhosis but who rather have so-called subclinical cirrhosis with a high risk of developing HCC^[73]. There have been two studies on the role of 2D-SWE in predicting the development of HCC. Jeong *et al.*^[74] followed up 291 compensated hepatitis B patients for 35.8 months and examined the use of measurements of LS by 2D-SWE for predicting HCC development. Patients with LS ≥ 10 kPa by 2D-SWE had a 4-fold higher risk of developing HCC than those with LS < 10 kPa. Lee *et al.*^[75] investigated the role of SWE in the prognosis of HCC after radiofrequency ablation (RFA). In 134 patients who underwent RFA as a curative treatment for HCC, LS by 2D-SWE was a significant predictor of overall survival and recurrence-free survival, and the optimal cutoff value was 13.3 kPa^[75].

ROLE OF 2D-SWE IN ASSESSING FOCAL LIVER LESIONS

Focal lesions are often seen in US examinations, but benign focal lesions and malignant focal lesions are difficult to distinguish by conventional US. In such cases additional Doppler or contrast US has been used. Unlike TE, 2D-SWE can measure the stiffness of focal liver lesions (FLLs) under B-mode guidance. Several groups have reported that stiffness measured by 2D-SWE helps distinguish intrahepatic focal lesions^[76-78]. The stiffness value of malignant lesions was significantly higher than that of benign lesions^[76,78]. In benign lesions, the stiffness of focal nodular hyperplasia was significantly higher than that of hepatocellular adenoma^[77]. In malignant lesions, the stiffness of metastatic tumors was significantly higher than that of HCC^[76].

Recently, Grgurevic *et al.*^[78] analyzed 196 patients with 259 FLLs and found that the best performing cut-off value for malignancy was 22.3 kPa (sensitivity 83%, specificity 86%, positive predictive value 91.5%, negative predictive value 73%). In addition, a Liver Elastography Malignancy Prediction (LEMP) score was constructed by combining lesion stiffness, lesion/liver stiffness ratio and lesion stiffness variability^[78]. The

accuracy of this score was 96.1% for distinguishing between benign and malignant FLL^[78].

CONCLUSION

Assessing liver fibrosis by noninvasive methods is always an important issue in the management of chronic liver diseases. In this article, we have summarized evidence that 2D-SWE is a promising tool for evaluating liver fibrosis in various liver diseases. It is also a useful method for evaluating portal hypertension and predicting HCC development. However, it cannot completely replace invasive methods for managing these patients because of the complexity of liver diseases and the variety of factors that affect liver stiffness. In addition, the data on some aspects of chronic liver diseases based on studies of LS by 2D-SWE are still inadequate. In that context, larger, prospective and multicenter studies of 2D-SWE are needed.

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