



Two-Dimensional-Shear Wave Elastography with a Propagation Map: Prospective Evaluation of Liver Fibrosis Using Histopathology as the Reference Standard

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Objective: The aim of this study was to prospectively evaluate whether liver stiffness (LS) assessments, obtained by two-dimensional (2D)-shear wave elastography (SWE) with a propagation map, can evaluate liver fibrosis stage using histopathology as the reference standard.

Materials and Methods: We prospectively enrolled 123 patients who had undergone percutaneous liver biopsy from two tertiary referral hospitals. All patients underwent 2D-SWE examination prior to biopsy, and LS values (kilopascal [kPa]) were obtained. On histopathologic examination, fibrosis stage (F0–F4) and necroinflammatory activity grade (A0–A4) were assessed. Multivariate linear regression analysis was performed to determine the significant factors affecting the LS value. The diagnostic performance of the LS value for staging fibrosis was assessed using receiver operating characteristic (ROC) analysis, and the optimal cut-off value was determined by the Youden index.

Results: Reliable measurements of LS values were obtained in 114 patients (92.7%, 114/123). LS values obtained from 2D-SWE with the propagation map positively correlated with the progression of liver fibrosis reported from histopathology ($p < 0.001$). According to the multivariate linear regression analysis, fibrosis stage was the only factor significantly associated with LS ($p < 0.001$). The area under the ROC curve of LS from 2D-SWE with the propagation map was 0.773, 0.865, 0.946, and 0.950 for detecting $F \geq 1$, $F \geq 2$, $F \geq 3$, and $F = 4$, respectively. The optimal cut-off LS values were 5.4, 7.8, 9.4, and 12.2 kPa for $F \geq 1$, $F \geq 2$, $F \geq 3$, and $F = 4$, respectively. The corresponding sensitivity and specificity of the LS value for detecting cirrhosis were 90.9% and 88.4%, respectively.

Conclusion: The LS value obtained from 2D-SWE with a propagation map provides excellent diagnostic performance in evaluating liver fibrosis stage, determined by histopathology.

Keywords: Liver fibrosis; Ultrasonography; Elastography

INTRODUCTION

All chronic liver diseases can progress into liver fibrosis,

and the degree of fibrosis is a well-known prognostic factor in patients with chronic liver disease (1-3). The progression of fibrosis eventually leads to liver cirrhosis as well as

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hepatocellular carcinoma, increasing the rate of morbidities and mortality (4). Indeed, liver fibrosis is an evolving process that can be reversed when appropriately managed, especially in the early stages of the disease; however, liver cirrhosis is usually regarded as an irreversible process (5-7). Therefore, the assessment and early detection of liver fibrosis is an important step in clinical practice for the management of chronic liver disease patients.

To assess fibrosis in the liver, liver biopsy has been the reference standard method for both diagnosis and staging (8). However, due to the invasive nature of biopsies, there has been tremendous effort to develop reliable noninvasive diagnostic methods for evaluating liver fibrosis. After the introduction of transient elastography (TE), shear wave-based ultrasound (US) elastography has been developed as an accurate noninvasive method to evaluate liver fibrosis (9, 10). Among the various shear wave-based elastography techniques, TE has been extensively evaluated and validated (11, 12). Currently, various point shear wave elastography (SWE) methods, including Virtual Touch Quantification (Siemens Healthineers), ElastPQ (Philips Healthcare), and S-Shearwave Elastography (Samsung Medison), have been developed from many vendors with promising results for the evaluation of liver fibrosis (13). In addition to point SWE, two-dimensional (2D)-SWE of supersonic shear imaging (SSI) (Aixplorer; SuperSonic Imagine) has emerged as another noninvasive method to assess liver fibrosis (14-16). In contrast to TE, SWE and 2D-SWE can easily be incorporated into routine B-mode examination transducers and can therefore simultaneously provide grayscale B-mode images of the liver during elastography examinations. In addition to various techniques of SWE, several guiding methods for assisting in the acquisition of reliable liver stiffness measurement results have also been introduced, one of which is the measurement reliability index of point SWE (13, 17). In regard to 2D-SWE, recently, a propagation map that can visualize shear wave generation, as well as propagation, within the liver tissue was developed to assist with reliable liver stiffness measurements (18, 19). As smooth parallel lines on the propagation map indicate stable conditions of shear wave creation and propagation, accurate and reliable liver stiffness measurements are possible when the operator assigns the measurement region of interest (ROI) in the area showing smooth and parallel lines on the propagation map. Lee et al. (18) reported that 2D-SWE with the propagation map was a reliable and accurate method for evaluating liver fibrosis using TE as the reference standard.

Considering that histopathology is still regarded as the gold standard for evaluating liver fibrosis, we believed that the diagnostic performance of assessing liver fibrosis with 2D-SWE and a propagation map was required to be determined using histopathology as the reference standard for the accurate evaluation of the clinical usefulness of this novel technique. Therefore, the purpose of this study was to prospectively evaluate whether liver stiffness, calculated from 2D-SWE with a propagation map, could evaluate the stage of fibrosis in the liver using histopathology as the reference standard.

MATERIALS AND METHODS

Patients

The Institutional Review Board of Seoul National University Hospital and Chung-Ang University Hospital approved this prospective study, and written informed consent was obtained from all participants. Patients who were suspected to have diffuse liver disease and who were referred for liver biopsy to evaluate the etiology and disease activity were consecutively enrolled from two university-affiliated hospitals between January 2018 and December 2018, and each center examined each patient. The inclusion criteria for this study were as follows: 1) patients aged between 20 years and 85 years; 2) patients who were planning to undergo liver biopsy for evaluation of the etiology and activity of diffuse liver disease and who provided informed consent to participate in this study; and 3) no bleeding tendency—i.e., platelet count greater than 80000/mm³ and the international normalized ratio of prothrombin activity less than 1.5. Baseline characteristics, including age, sex, and etiology of liver disease, and laboratory test results, such as liver function tests, were also assessed and recorded.

Evaluation of Liver Parenchyma Using 2D-SWE

All patients underwent 2D-SWE evaluation of the liver parenchyma just prior to liver biopsy using an US scanner (Aplio i900; Canon Medical Systems) with a convex probe (PVI-475BX, 1–8 MHz; Canon Medical Systems) by one of three board-certified radiologists (with 11 years of experience in liver US [n = 57], with 10 years of experience [n = 22], and with 5 years of experience [n = 35]). All patients were asked to fast for at least 6 hours prior to 2D-SWE examination, and liver parenchyma was evaluated with the patient in the supine position. To stretch the

intercostal muscles and obtain the proper sonic window, the right arm was extended above the head during the examination. We evaluated the liver parenchyma with B-mode imaging initially to detect any focal liver lesions. Thereafter, the 2D-SWE mode was activated, and we placed a 2 x 2 cm-sized sample box within the liver parenchyma on grayscale imaging. To avoid areas showing reverberation artifacts, the sample box was placed at least 1 cm beneath the Glisson's capsule according to the European Federation of Societies for Ultrasound in Medicine and Biology and the World Federation of Societies for Ultrasound in Medicine and Biology practice guidelines for 2D-SWE (20-22). After placing the sample box within the liver parenchyma, shear wave propagation was created using acoustic radiation force, and patients held their breath for 1 second during data acquisition. The convex probe was also kept still for 1 second during acquisition in the one-shot mode. After acquisition of shear wave propagation data, our US system automatically displayed the twin view of B-mode images and shear wave propagation maps. Using an elasticity map, we measured liver stiffness with the following equation:

$$E = 3\rho V_s^2 \quad (\rho = \text{density of the tissue, } V_s = \text{estimated shear-wave velocity})$$

liver stiffness values were expressed as units of kilopascal (kPa).

We placed three 1 cm-sized circular ROIs on each map within the sample box in the liver parenchyma, avoiding large hepatic vessels. Under the guidance of the propagation map, operators placed ROIs in the area showing smooth and parallel lines on the propagation map, indicating a stable measurement condition (18) (Fig. 1). Activation of shear wave propagation and data filling of the sample box were performed three times for each patient, and one shear wave propagation data had three 1 cm-sized ROIs; therefore, we measured liver stiffness nine times in each patient. The median values of liver stiffness were chosen for further analysis. A reliable measurement was defined as less than 30% of the interquartile range (IQR)/median value (20-22), and patients in whom acquisition of reliable measurement failed were excluded from further analysis.

Liver Biopsy and Histopathologic Examination

Percutaneous liver biopsy was performed immediately after 2D-SWE evaluation of the liver parenchyma using an 18-gauge automatic biopsy gun (ACECUT; TSK Laboratory), by

the same operator who performed the 2D-SWE examination. We performed a biopsy in liver segment V or VIII, close to where the sample box from the SWE examination was placed through the intercostal plane. There were no procedure-related complications after percutaneous liver biopsy in this study. Two approximately 2.2 cm-long liver specimens were obtained and fixed in formalin. After embedding in paraffin, the liver specimens were stained with hematoxylin and eosin. We also used Masson's trichrome staining to evaluate liver fibrosis more accurately. All histopathologic examinations were performed by one of two experienced pathologists (both with 15 years of experience in liver pathology), and both the stage of liver fibrosis and degree of necroinflammatory activity were assessed based on the standardized guidelines proposed by the Korean Study Group for the Pathology of Digestive Disease (23-25). Fibrosis stage was graded using a five-point scale from F0 to F4, similar to the METAVIR scoring system. To evaluate the necroinflammatory activity grade, we considered both porto-periportal activity and lobular activity, with a grading from A0 to A4: A0, no activity; A1, minimal activity; A2, mild activity; A3, moderate activity; and A4, severe activity (23). The degree of hepatic steatosis was also evaluated and classified as follows: S0, < 5% of the fat area; S1, 5-33% of the fat area; S2, 34-66% of the fat area; and S3, > 66% of the fat area.

Statistical Analysis

To compare liver stiffness obtained from 2D-SWE with a propagation map with different fibrosis stages, we used the Kruskal-Wallis test. Univariate and multivariate linear regression analyses were used to determine significant affecting factors for liver stiffness. All variables with a *p* value < 0.05 on univariate analysis were chosen for multivariate analysis to evaluate their value as independent predictors. We also performed receiver operating characteristic (ROC) curve analysis to evaluate the diagnostic performance of liver stiffness values obtained from 2D-SWE with a propagation map to determine each stage of fibrosis diagnosed by histopathologic examination. The optimal cut-off value for each stage of fibrosis was estimated using the Youden index and the corresponding sensitivity, specificity, and area under the ROC curve (AUC) were then calculated. A *p* value < 0.05 was considered to indicate a significant difference. All statistical analyses were performed using commercially available software programs: MedCalc software package, Version 15.2 (MedCalc) and SPSS version 25 (IBM Corp.).

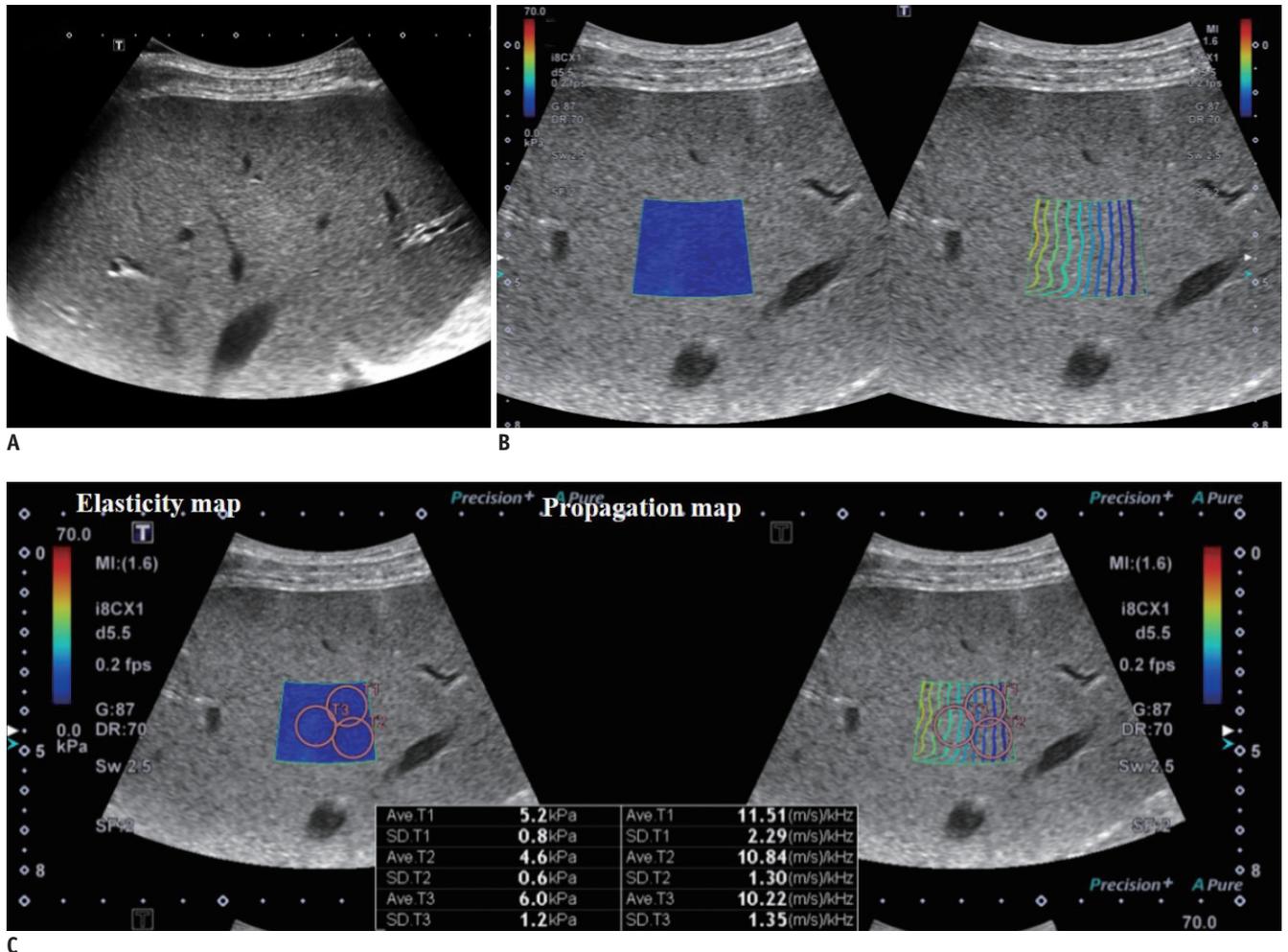


Fig. 1. Evaluation of liver parenchyma using ultrasound-based shear wave elastography in 49-year-old male with elevated liver enzymes.

A. B-mode image shows no focal lesion in liver parenchyma. **B.** 2 × 2 cm-sized sample box was placed within liver parenchyma, avoiding large vessels, more than 1 cm below Glisson’s capsule, and shear wave propagation was activated using acoustic radiation force. Shear wave propagation was seen within sample box as smooth parallel lines, indicating stable measurement condition. **C.** After data acquisition within sample box, three regions of interest, each 1 cm in size, were placed within sample box. In this patient, median liver stiffness value on elasticity map was 5.3 kPa, indicating no fibrosis. On histopathologic examination, F0 stage of fibrosis was diagnosed.

RESULTS

Patients

During the study period, 130 consecutive patients were referred for liver biopsy. Among these, seven patients were excluded from the study due to refusal to participate in the study ($n = 3$) or an age under 20 years old ($n = 4$). 2D-SWE examination prior to liver biopsy was performed on the remaining 123 patients. After 2D-SWE examination, we excluded an additional nine patients (7.3%, 9/123) in whom obtaining reliable measurement failed. Therefore, our final study population comprised a total of 114 patients. The characteristics of the study population are summarized in Table 1.

Liver Stiffness according to the Fibrosis Stage

The median values with IQRs of liver stiffness obtained from 2D-SWE with the propagation map according to the stage of fibrosis are summarized in Table 2 and Figure 2. The liver stiffness values were significantly different among the patients with different stages of liver fibrosis ($p < 0.001$).

Factors Affecting the Liver Stiffness Value

The factors affecting the liver stiffness value obtained from 2D-SWE with the propagation map are summarized in Table 3. According to the univariate analysis, the stage of fibrosis, degree of necroinflammatory activity, age, serum alanine transaminase level, and platelet count were associated with the liver stiffness value. However, the

stage of fibrosis was the only significant factor determining the liver stiffness value obtained from 2D-SWE with the propagation map according to the multivariate linear regression analysis ($p < 0.001$) (Table 3).

Diagnostic Performance of Liver Stiffness in the Grading of Liver Fibrosis

The AUC and optimal cut-off values with the corresponding sensitivities and specificities of the liver stiffness value obtained from 2D-SWE with the propagation map for

Table 1. Patient Characteristics

Parameters	Patients (n = 114)
Age (years, mean ± SD) [range]	51.8 ± 16.0 [20–81]
Sex (n, male:female)	39:75
BMI (kg/m ² , mean ± SD) [range]	24.7 ± 4.5 [16.1–42.2]
AST (IU/L, mean ± SD) [range]	67.4 ± 71.1 [8–532]
ALT (IU/L, mean ± SD) [range]	96.8 ± 119.8 [6–854]
Platelets (10 ³ /mm ³ , mean ± SD) [range]	231 ± 65 [82–523]
Etiology of liver disease (%)	
Viral hepatitis	13 (11.4)
Fatty liver disease	41 (36.0)
Primary biliary cirrhosis	9 (7.9)
Autoimmune hepatitis	37 (32.4)
Drug-induced liver disease	8 (7.0)
Alcoholic liver disease	6 (5.3)
Grade of fibrosis (%)	
F0	29 (25.4)
F1	47 (41.2)
F2	14 (12.3)
F3	13 (11.4)
F4	11 (9.7)
Necroinflammatory activity (%)	
A0 (none)	9 (7.9)
A1 (minimal)	26 (22.8)
A2 (mild)	40 (35.1)
A3 (moderate)	33 (28.9)
A4 (severe)	6 (5.3)
Degree of steatosis (%)	
S0 (none, < 5%)	59 (51.7)
S1 (mild, 5–33%)	31 (27.2)
S2 (moderate, 33–66%)	18 (15.8)
S3 (severe, > 66%)	6 (5.3)

ALT = alanine transaminase, AST = aspartate transaminase, BMI = body mass index, SD = standard deviation

Table 2. Median Liver Stiffness Values according to Stage of Fibrosis

	F0 (n = 29)	F1 (n = 47)	F2 (n = 14)	F3 (n = 13)	F4 (n = 11)	P
Liver stiffness value, kPa (IQR)	5.3 (3.8–7.3)	6.6 (5.6–7.8)	8.1 (6.8–10.9)	13.2 (9.9–19.7)	22.2 (13.2–39.0)	< 0.001

IQR is presented within parentheses. IQR = interquartile range

detecting each stage of liver fibrosis are summarized in Table 4. The AUC of the liver stiffness value was 0.773, 0.865, 0.946, and 0.950 for detecting F ≥ 1, F ≥ 2, F ≥ 3, and F = 4, respectively (Fig. 3). The optimal cut-off liver stiffness values were 5.4, 7.8, 9.4, and 12.2 kPa for F ≥ 1, F ≥ 2, F ≥ 3, and F = 4, respectively.

DISCUSSION

In our study, the liver stiffness value determined by 2D-SWE with the propagation map provided good diagnostic performance in terms of grading each stage of liver fibrosis. The AUC of the ROC curve analysis of liver stiffness was 0.950, with a cut-off value of 12.2 kPa, and a corresponding sensitivity of 90.9% and specificity of 88.4% for detecting liver cirrhosis, and was 0.946, with a cut-off value of 9.4 kPa and a corresponding sensitivity of 91.7% and specificity of 87.8% for detecting F ≥ 3 stage.

Regarding the diagnostic performance for assessing the stage of liver fibrosis using 2D-SWE, Herrmann et al. (26) recently reported that the estimated AUC of 2D-SWE was 0.917–0.955 for detecting liver cirrhosis and 0.915–0.931 for detecting F ≥ 3 stage according to the

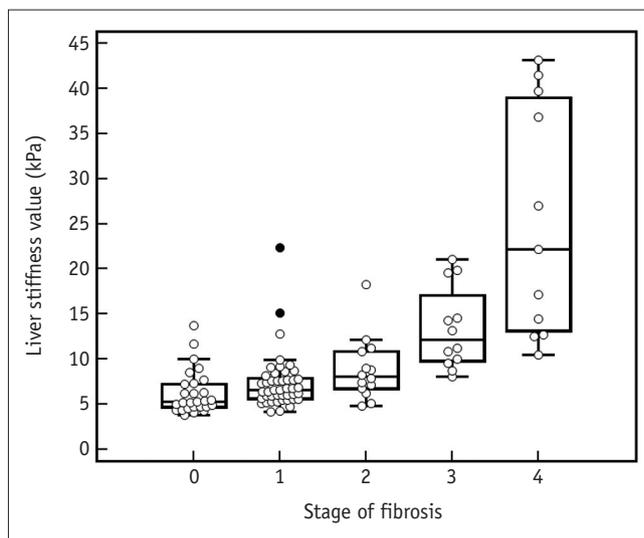


Fig. 2. Box-and-whisker plots of liver stiffness values according to fibrosis stage. Liver stiffness value obtained from two dimensional-shear wave elastography with propagation map increases along with progression of fibrosis stage.

Table 3. Factors Affecting Liver Stiffness Value Determined by 2D-SWE with Propagation Map

Characteristic	Univariate			Multivariate		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Stage of fibrosis	4.02	3.21 to 4.83	< 0.001	4.84	3.72 to 5.96	< 0.001
Necroinflammatory activity	2.88	1.64 to 4.12	< 0.001	0.05	-1.26 to 1.35	0.942
Degree of steatosis	-0.03	-1.55 to 1.50	0.972	-	-	-
Age (years)	0.09	0.02 to 0.17	0.044	-0.02	-0.09 to 0.06	0.647
Sex	1.46	-1.27 to 4.52	0.269	-	-	-
BMI (kg/m ²)	0.03	-0.29 to 0.41	0.735	-	-	-
ALT (IU/L)	0.03	0.01 to 0.05	0.009	0.01	-0.01 to 0.03	0.099
AST (IU/L)	0.01	-0.01 to 0.02	0.822	-	-	-
Platelet count (K/mm ³)	-0.03	-0.05 to -0.01	0.002	0.01	-0.01 to 0.02	0.989

CI = confidence interval, SWE = shear wave elastography, 2D = two-dimensional

Table 4. ROC Analysis for Diagnostic Performance of Liver Stiffness from 2D-SWE with Propagation Map for Detecting Each Stage of Fibrosis

Aim	Cut-Off (kPa)	AUC (95% CI)	Sensitivity (%)	Specificity (%)
≥ F1	5.4	0.773 (0.685–0.846)	89.4 (76/85)	55.2 (16/29)
≥ F2	7.8	0.865 (0.789–0.922)	84.2 (32/38)	78.9 (60/76)
≥ F3	9.4	0.946 (0.888–0.980)	91.7 (22/24)	87.8 (79/90)
≥ F4	12.2	0.950 (0.892–0.982)	90.9 (10/11)	88.4 (91/103)

AUC = area under ROC curve, ROC = receiver operating characteristic

different etiologies of liver disease in their meta-analysis. Our study results were well correlated with the results of this previous meta-analysis using 2D-SWE for staging liver fibrosis, although there was a difference in the US equipment between our study and previous studies (i.e., SSI in previous studies vs. 2D-SWE with a propagation map from the Canon medical systems in our study) (26). Indeed, the AUC of 2D-SWE with a propagation map to detect liver cirrhosis was 0.935 in the previous study performed by Lee et al. (18), using the result of TE as the reference standard, and our study result was also in concordance with that of this study. Considering the results of our study and previous studies, we conclude that 2D-SWE with a propagation map is an accurate noninvasive method for evaluating liver fibrosis, providing comparable diagnostic performance to 2D-SWE with SSI.

Regarding the significant affecting factors, the stage of liver fibrosis was the only significant factor determining the liver stiffness value according to the multivariate analysis, and this result was in accordance with the results of previous studies reporting that the stage of liver fibrosis was significantly associated with the liver stiffness value determined by elastography (27, 28).

Currently, TE has been regarded as a good noninvasive method for grading the stage of liver fibrosis, and the utility of TE in the evaluation of liver fibrosis has been

extensively validated. However, TE has limitations in terms of its application in patients with severe obesity, thick subcutaneous fat, or ascites (18). The small sample volume of TE and lack of grayscale liver imaging, which can guide the placement of ROIs for accurate and reliable measurement of liver stiffness, may be another limitation of TE. In contrast to TE, as 2D-SWE with SSI could provide real-time liver grayscale images, similar to 2D-SWE with a propagation map, this can overcome the current limitations of TE. However, the measurement reliability of 2D-SWE with SSI in previous studies has been somewhat disappointing. Yoon et al. (29) reported that the rate of unreliable measurement, defined as greater than 30% of the IQR/median, was 23.0% (29/126) for 2D-SWE with SSI in their prospective cohort. In our study, the rate of unreliable measurement was 7.3% and seemed to be lower than that of SSI. Indeed, the unreliable measurement rate of 2D-SWE with a propagation map was 5.2% (6/115) in a previous study carried out by Lee et al. (18), and our result was well correlated with that of this previous study. The propagation map can show the real-time shear wave creation, as well as propagation within the liver tissue, and smooth and parallel lines on propagation maps indicate that the generation and propagation of shear waves is stable without reverberation or motion artifacts. Therefore, with the use of a propagation map, operators can confidently place ROIs in the area

showing smooth and parallel lines within the sample box, and a more reliable measurement of the liver stiffness value becomes possible. Considering the results of ours and previous studies, we believe that 2D-SWE with propagation maps is an excellent and reliable noninvasive method for evaluating liver fibrosis, although further studies with prospective designs comparing various 2D-SWE techniques,

including 2D-SWE with propagation maps and SSI, are required to validate our study results.

In addition to shear wave-based US elastography, magnetic resonance elastography (MRE) has emerged as another noninvasive method to evaluate liver fibrosis (30-33), and the reported diagnostic performance of MRE in evaluating liver fibrosis is generally higher than that

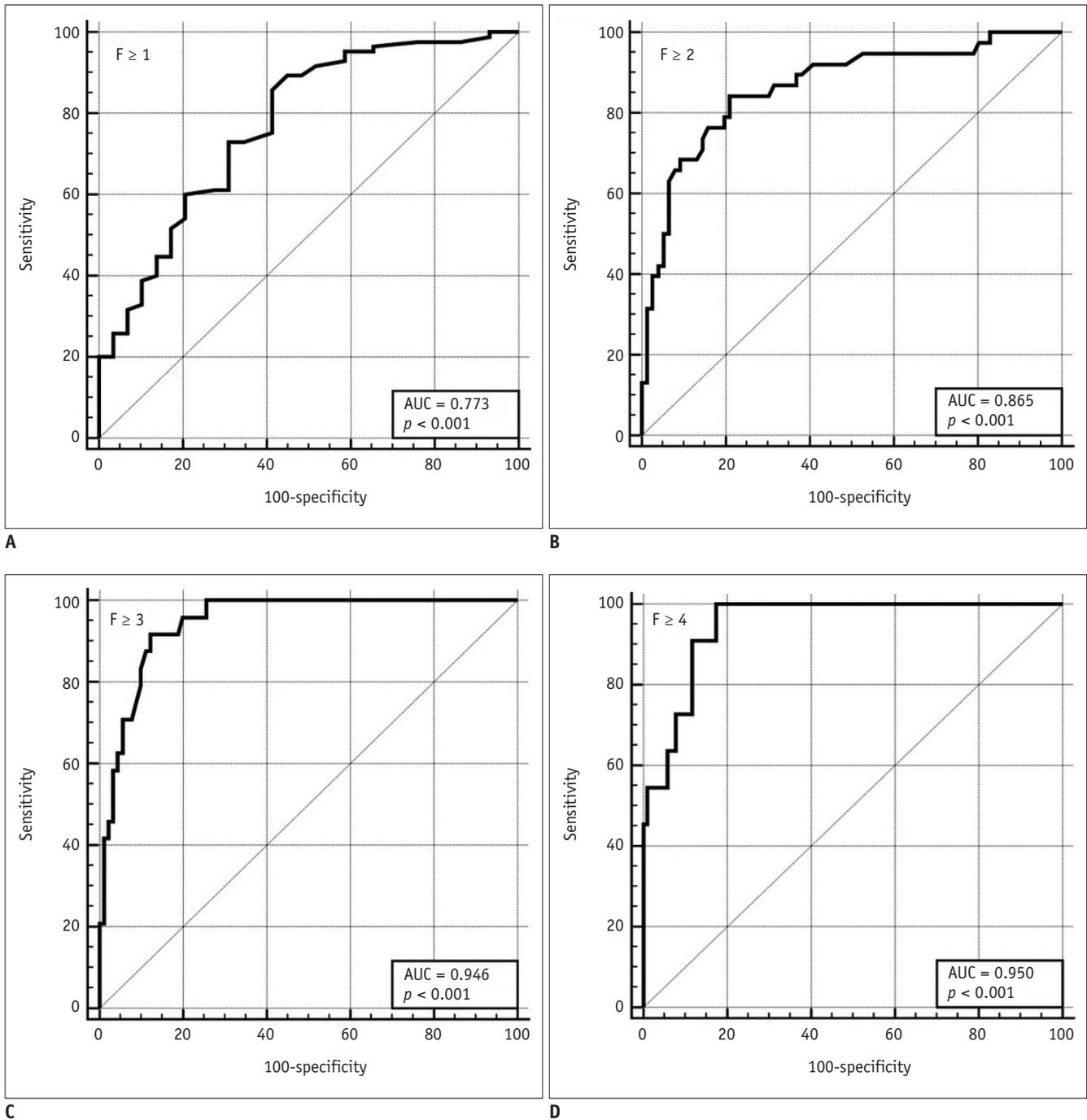


Fig. 3. ROC curve of liver stiffness values for differentiation of liver fibrosis stage.

A. F0 vs. F1–F4. **B.** F0–F1 vs. F2–F4. **C.** F0–F2 vs. F3–F4. **D.** F0–F3 vs. F4. All AUC value was statistically significant. AUC = area under ROC curve, ROC = receiver operating characteristic

of US-based elastography. MRE also provides excellent reproducibility and repeatability of liver stiffness measurements (7). In addition, MRE can be easily acquired as a part of liver MR examinations and can provide additional prognostic information for patients with liver tumors (30). Therefore, MRE may outperform US-based SWE for the evaluation of liver fibrosis. However, the limited availability and high cost compared to US-based elastography are the main limitations of MRE.

There are several limitations in this study. Firstly, regarding the etiology of liver disease, our study population was heterogeneous and included various causes of liver disease. Therefore, the cut-off value in this study should be interpreted with some caution, and further studies with a large number of patients focusing on a specific etiology are warranted to validate our study results. Second, all SWE examinations were performed by one of three board-certified radiologists; thus, the interobserver agreement of the liver stiffness value and shear wave dispersion slope could not be evaluated in this study. Therefore, to evaluate the reproducibility of the measurement, further studies with two or more operators are required. Third, the distribution of liver fibrosis stage was somewhat deviated, and the number of patients with $F \geq 3$ stage was relatively small (21.1%, 24/114). With this uneven distribution of liver fibrosis stages, the accurate assessment of diagnostic performance in evaluating liver fibrosis was limited. Finally, the lack of comparison with current elastography techniques, including TE, is another limitation of this study. To establish the clinical usefulness of 2D-SWE with propagation maps, further prospective studies with head-to-head comparisons with current elastography techniques are warranted.

In conclusion, 2D-SWE with a propagation map is a good noninvasive diagnostic method for evaluating the stage of liver fibrosis by obtaining liver stiffness values.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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