

The Usefulness of Noninvasive Liver Stiffness Assessment Using Shear-Wave Elastography for Predicting Liver Fibrosis in Children

Seunghyun Lee

Seoul National University Hospital

Young Hun Choi (✉ iater@snu.ac.kr)

Seoul National University Hospital

Yeon Jin Cho

Seoul National University Hospital

Seul Bi Lee

Seoul National University Hospital

Jung-Eun Cheon

Seoul National University Hospital

Woo Sun Kim

Seoul National University Hospital

Jae Sung Ko

Seoul National University Hospital

Jaemoon Koh

Seoul National University Hospital

Gyeong Hoon Kang

Seoul National University Hospital

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Abstract

Background: Pediatric patients with liver disease require noninvasive monitoring for the likelihood of fibrosis progression. The purpose of this study is to evaluate the significant factors affecting liver stiffness values from two-dimensional-shear wave elastography (2D-SWE), and whether liver stiffness can predict the fibrosis stage of various childhood liver diseases.

Methods: This study comprised 30 children (22 boys and 8 girls; mean age, 5.1 ± 6.1 years; range, 7 days–17.9 years) who had undergone biochemical evaluation, 2D-SWE examination, and histopathologic analysis with fibrosis grade (F0 to F3), necroinflammatory activity, and steatosis grade between August 2016 and March 2020. The liver stiffness from 2D-SWE were compared between fibrosis stages using the Kruskal-Wallis analysis. The significant affecting factors to liver stiffness were evaluated using univariate and multivariate linear regression analyses. The diagnostic performance was determined from the area under the receiver operating curve (AUC) values of the 2D-SWE liver stiffness.

Results: Liver stiffness at the F0-1, F2, and F3 stages were 7.9, 13.2, and 21.7 kPa ($P < 0.001$). Both of fibrosis stage and necroinflammatory grade were factors significantly associated with liver stiffness ($P < 0.001$ and $P = 0.021$). Liver stiffness value could distinguish significant fibrosis ($\geq F2$) with an AUC of 0.950 (cutoff value, 11.3 kPa) and the severe fibrosis (F3 stage) with an AUC of 0.924 (cutoff value, 18.1 kPa).

Conclusion: The liver stiffness values from 2D-SWE can be effected through both fibrosis and necroinflammatory grade and can provide excellent diagnostic performance in evaluating the fibrosis stage, even in various liver disease.

Background

Pediatric liver diseases have a wide range of etiologies, including congenital, metabolic, toxic, and infectious, as well as a fatty liver.¹ Over time, repeated hepatocellular injury can lead to liver fibrosis, especially in pediatric patients who may exhibit an unpredictable progression.² Therefore, pediatric patients with liver disease require monitoring for the likelihood of liver fibrosis progression similar to adult patients.

Both liver function biochemical assessment and ultrasound (US) examination are used for liver fibrosis monitoring, but liver biopsy, which is performed only if necessary, is considered the gold standard despite its invasiveness and potential for sampling errors.¹ Various noninvasive monitoring methods, such as serum biochemical marker and quantitative liver elastography assessments, are promising alternatives to liver biopsy. Previous studies have shown various serum biochemical indicators such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST to platelet ratio (ARPI), AST and ALT ratio (AAR), or fibrosis index based on the 4 factor (FIB-4) score, could be a candidate marker in adult chronic liver patients.^{3–5} However, further evaluation of their clinical utility for liver fibrosis is needed in pediatric patients because of their different etiologies.^{6,7}

Noninvasive US elastography that measures liver stiffness mainly on the basis of fibrosis could be another option for monitoring fibrosis in pediatric liver diseases.⁸ The two-dimensional-shear wave elastography (2D-SWE) value (expressed in kilopascals [kPa]) offers advantages in quantitative assessment, and several studies have reported the clinical utility of 2D-SWE to assess liver fibrosis in chronic liver disease.^{9,10,11,12} However, only a few studies have used 2D-SWE to evaluate the clinical significance of 2D-SWE liver stiffness in liver diseases in pediatric patients, even though many studies have evaluated the advantages of SWE in adult populations with non-alcoholic fatty liver disease (NAFLD), hepatitis, autoimmune hepatitis, or other liver diseases.^{12–16}

Therefore, this study evaluated the significant factors influencing liver stiffness values in 2D-SWE, and whether liver stiffness can predict the fibrosis stage of various childhood liver diseases.

Methods

Following the Declaration of Helsinki, the study was approved as a retrospective human study by the Institutional Review Board of Seoul National University Hospital (No. 2005-211-1127). The informed consent of patient, parents, or guardians was waived.

Patient Population

Patients with suspected various liver disease were referred for liver biopsies to assess their histopathological conditions between August 2016 and March 2020. We retrospectively reviewed the picture archiving and communication system (Infinitt; Infinitt Healthcare, Korea) database. The patients in our study were included as following conditions: 1) patients under 18 years; 2) patients who had undergone both of 2D-SWE examination and serologic biochemical marker evaluation before the liver biopsy; and 3) patients who had obtained histopathological results through a liver biopsy for various liver diseases.

The fourteen patients were excluded from this study for the following reasons: insufficient quality of SWE as explained 2D-SWE Liver Stiffness Examination section (n = 6), use of different probes such as the high-frequency linear probes (n = 4), and the cases of different US machines due to the retrospective study design (n = 4). The number of excluded patients was 14 patients, with the mean age of 2.1 ± 4.1 years (range: 5 days – 12.1 years). The most common of histopathologic diagnosis in the excluded patients was biliary atresia (BA) (n = 8), and the others including hepatitis (n = 3), Alagille syndrome (n = 1), undiagnosed disease (n = 1), and transient myeloproliferative disorder (n = 1) (Fig. 1).

Serum biochemical analysis was performed on all patients within 1 week before liver biopsy. Serum levels of total bilirubin, alkaline phosphatase, AST, ALT, γ -glutamyl transpeptidase, direct bilirubin, and albumin were measured, as were prothrombin time and platelet counts. We calculated the APRI, the AAR, and the FIB-4 score.^{3,4,17}

2D-SWE Liver Stiffness Examination

All included patients had available results of liver US examination, including 2D-SWE elastography, without any anesthesia performed at least 3 days before or on the day of liver biopsy. The 2D-SWE examinations were performed by two experienced pediatric radiologists who randomly assigned (**BLINDED** and **BLINDED** with 6 and 13 years of pediatric US examination experience, respectively) using the Aixplorer machine (SuperSonic Imagine SA, France) with a convex probe (SC6-1). The 2D-SWE examinations were performed according to the US elastography guideline previously reported.⁸ Patients had maintained fasting state for a minimum of 2 hours before US and 2D-SWE examinations and if suspecting BA, for a minimum of 4 hours to evaluate gallbladder morphology.

The patient was placed in a supine position to visualize the liver's right lobe, and we set a 2.0 × 2.0 cm color-coded box at away 1.0 cm from Glisson's capsule, avoiding large blood vessels. A 10 mm circular region of interest (ROI) was carefully placed over an evenly color-coded area in the SWE box. We obtained the liver stiffness values, standard deviation, and stability index (SI) values in the ROIs. All measurements were performed using SI, and only ROIs with SI values of 90% or higher were considered for evaluation.^{18,19} The information with SI calculation allows the user to rule out low-quality signals before calculating the interquartile range (IQR). In this study, liver stiffness measurements were considered successful when ROIs with SI values of 90% or higher were obtained across the entire series of SWE images. Otherwise, the measurement was considered to have failed and to be insufficient image quality. Also, when the normalized value divided by the IQR / median value from a total of 10 measurements shows a variation of 30% or more, the liver stiffness measurement was regarded to be insufficient image quality because of the high variability of the liver stiffness value.^{18,20} Finally, we selected the median liver stiffness values among sufficient qualified data for further analysis.

Histopathologic Analysis

Within 3 days of the US examination including 2D-SWE, the patients underwent percutaneous liver parenchymal biopsy with an 18-gauge core biopsy device (TSK Ace-cut; Japan) while maintaining mild to moderate sedation using intravenous sedative drugs. We performed the biopsy at the right lobe of the previously measured location for each patient, without any significant adverse event. According to our protocols, biopsy samples were obtained three times with 11 mm of length or two times with 22 mm of length specimens.

Two pediatric pathologists (**BLINDED**, with 6 years of experience in liver histopathologic evaluation and **BLINDED**, over 20 years of experience in pediatric gastrointestinal pathology), who were not aware to the US results for SWE values, reviewed biopsy specimens by the consensus. We retrospectively reviewed the pathologic report and assessed the liver fibrosis stages using the METAVIR staging system. We staged fibrosis on a five-point ordinal scale from 0 to 4 as follows: F0, absent and F4, cirrhosis.¹³ We evaluated the liver necroinflammatory activity grade from 0 to 3: A0, no activity and A3, severe activity.²¹ We also graded the similar steatosis grade from 0 to 3: S0, no steatosis and S3, above the two-third fatty accumulation in the hepatocytes.²²

Statistical Analyses

The descriptive demographic data were expressed as mean \pm standard deviation. The median liver stiffness values were compared among the fibrosis stages using the Kruskal-Wallis analysis. The significant factors affecting liver stiffness values were assessed using linear regression methods by univariate and multivariate analysis.

The areas under the receiver operating characteristic curves (AUCs) were analyzed to assess the diagnostic performance of the 2D-SWE liver stiffness values for the presence of F2 more than and F3, respectively. We also calculated the optimal cutoff values at the highest Youden index and identified sensitivity, specificity, positive predictive values, and negative predictive values.

The statistical analyses were performed using SPSS Statistics, Version 21.0 (IBM Corp., USA).

Results

Clinical Characteristics

A total of 30 patients were included in our study, and the patient's age was 5.1 ± 6.1 years (range: 7 days – 17.9 years). The number of male patients was 22 patients (73.3%) in our study. The histologic diagnoses were as follows: hepatitis (n = 6), BA (n = 6), NAFLD (n = 5), and others (n = 13). Table 1 summarized the etiology of liver disease and the results of the serologic index.

Table 1
Clinical Characteristics

Parameters	Patients (n = 30)
Age (years, mean ± SD) [range]	3.6 ± 5.5 [7 days – 17.9 years]
Sex (n, male:female)	22:8
Etiology of liver disease (%)	
Hepatitis [†]	6 (20.0)
Biliary atresia	6 (20.0)
Non-alcoholic fatty liver disease	5 (16.7)
Others [†]	13 (43.3)
Serologic Index	
ARPI (AST to platelet ratio index) (mean ± SD) [range]	5.0 ± 8.4 [0.3–42.1]
AAR (AST to ALT ratio) (mean ± SD) [range]	1.3 ± 1.2 [0.2–5.0]
FIB-4 (fibrosis-4 score) (mean ± SD) [range]	0.4 ± 0.8 [0.0–3.9]
Grade of fibrosis (%)	
F0-1 (none or mild)	13 (43.3)
F2-3 (moderate or severe)	17 (56.7)
Necroinflammatory activity (%)	
A0-1 (none or minimal)	18 (60.0)
A2-3 (mild or moderate)	12 (40.0)
Degree of steatosis (%)	
S0-1 (none or mild < 33%)	26 (86.7)
S2-3 (moderate or severe, ≥ 33%)	4 (13.3)
Note— [†] progressive familial intrahepatic cholestasis (n = 3), glycogen storage disease (n = 2), hemosiderosis (n = 2), hemophagocytic lymphohistiocytosis (n = 2), autoimmune hepatitis (n = 2), congenital hepatic fibrosis (n = 1), and carnitine palmitoyltransferase I deficiency (n = 1).	

The fibrosis grades, necroinflammatory activity and steatosis grades are also summarized in Table 1. In all analyses, we considered the F0 and F1 stages as identical. Only two patients showed no signs of fibrosis (F0) on histopathologic analysis. One of these patients had hemosiderosis, and the other had a very rare metabolic liver disease, namely, carnitine palmitoyltransferase I deficiency. Therefore, we

included these patients with F0 stage fibrosis in the F1 stage fibrosis group for statistical analysis, and the total number of patients in this combined F0-1 stage fibrosis group was 13. Subsequently, fibrosis stages were divided into two subgroups: no or mild hepatic fibrosis (F0 and F1; n = 13) and significant hepatic fibrosis (F2 and F3; n = 17). The significant necroinflammatory activity (A2 and A3; n = 12) and steatosis grade (S2 and S3; n = 4) were also found as histopathologic abnormality (Table 1).

Significant Affecting Factors to Liver Stiffness Values

On 2D-SWE liver stiffness measurements, Table 2 summarized the median liver stiffness values according to the fibrosis stage. There was a significant difference in liver stiffness values among the F0-1, F2, and F3 stages ($P < 0.001$). Table 3 showed the histologic, demographic, and serologic factors influencing the 2D-SWE liver stiffness value. In the univariate analysis, fibrosis grade (odds ratio [OR] = 4.064; 95% confidence interval [CI] = 2.010–6.117; $P < 0.001$) and necroinflammatory grade (OR = 2.189; 95% CI = 0.099–4.280; $P = 0.041$) were associated with the 2D-SWE liver stiffness value. In the multivariate linear regression analysis, fibrosis grade (OR = 4.356, 95% CI = 2.618–6.095; $P < 0.001$) and necroinflammatory grade (OR = 2.207, 95% CI = 0.365–4.050; $P = 0.021$) were significant associated with the liver stiffness value.

Table 2
Median Liver Stiffness Values in Fibrosis Stages

Variable	Fibrosis Stages			P value*
	F0-1 (n = 13)	F2 (n = 11)	F3 (n = 6)	
Liver Stiffness, kPa (IQR)	8.2 (7.3–10.9)	13.2 (12.6–15.8)	21.7 (17.4–23.7)	< 0.001

Note—IQR is presented within parentheses. IQR = interquartile range. *P value is determined using the Kruskal-Wallis analysis.

Table 3
Factors Affecting Liver Stiffness Value Determined by 2D-SWE

Characteristics	Univariate			Multivariate		
	Coefficient	95% CI	<i>P</i> value	Coefficient	95% CI	<i>P</i> value
Fibrosis Stage	4.064	2.010 to 6.117	< 0.001	4.356	2.618 to 6.095	< 0.001
Necro-inflammatory activity	2.189	0.099 to 4.280	0.041	2.207	0.365 to 4.050	0.021
Steatosis grade	1.316	-1.496 to 4.129	0.341	-		
Age (years)	-0.209	-0.600 to 0.182	0.280	-		
Sex	-0.740	-3.732 to 2.252	0.612	-		
ARPI	-0.043	-0.207 to 0.121	0.593	-		
AAR	0.235	-0.990 to 1.460	0.694	-		
FIB-4	0.959	-1.268 to 3.187	0.381	-		

Note—2D-SWE = two-dimensional shear-wave elastography, CI = confidence interval, APRI = AST to platelet ratio index; AAR = AST to ALT ratio; FIB-4 = fibrosis-4 score.

Diagnostic Performance of Liver Stiffness Predicting Fibrosis

The 2D-SWE liver stiffness values above 11.3 kPa showed 94.1% sensitivity and 84.6% specificity in distinguishing significant fibrosis (\geq F2) from no or mild fibrosis (AUC = 0.950; 95% CI = 0.803–0.996; $P < 0.001$). At the advanced fibrosis stage F3, a liver stiffness value greater than 18.1 kPa showed 83.3% sensitivity and 100.0% specificity for differentiating fibrosis stages (AUC = 0.924; 95% CI = 0.766–0.989; $P < 0.001$) (Table 4). Representative 2D-SWE and histopathologic specimen of the F1 case are shown in Fig. 2A and 2B. Each 2D-SWE and histopathologic sample of the F2 and F3 are shown in Fig. 3A and 3B and Fig. 4A and 4B, respectively.

Table 4
Diagnostic Performance of 2D-SWE for Liver Fibrosis

Stage	Cutoff	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	P value*
F ≥ 2	> 11.3	0.950 (0.803–0.996)	94.1	84.6	84.2	90.9	< 0.001
F ≥ 3	> 18.1	0.924 (0.766–0.989)	83.3	100.0	100.0	96.0	< 0.001

Note—2D-SWE = two-dimensional shear-wave elastography. Diagnostic accuracy of each variable in association with any fibrosis stage. Performance of the selected best cutoff values is indicated. PPV = positive predictive value. NPV = Negative predictive value; *Determined using the receiver operating characteristic curve analysis.

We retrospectively reviewed the picture archiving and communication system database for the period between August 2016 and March 2020. Of the 44 potential candidates who underwent two-dimensional shear-wave elastography (SWE) prior to liver biopsy, 14 were excluded for the following reasons: insufficient quality of SWE (n = 6), use of different probes (n = 4), and use of different US machines (n = 4).

The serum biochemical marker levels are as follows: AST to platelet ratio index (APRI), 1.5; AST to alanine aminotransferase ratio (AAR), 0.9; and fibrosis-4 (FIB-4) score, 0.1. A, Two-dimensional shear-wave elastography (2D-SWE) showing diffuse hyperechoic parenchyma with 9.4 kPa liver stiffness value. B, Histopathologic specimen showing diffuse enlargement of hepatocytes with clear cytoplasm and enlargement of the fibrotic portal tract with METAVIR score, F1.

The serum biochemical marker levels are as follows: AST to platelet ratio index (APRI), 14.5; AST to alanine aminotransferase ratio (AAR), 0.8; and fibrosis-4 (FIB-4) score, 0.4. A, Two-dimensional shear-wave elastography (2D-SWE) showing diffuse hyperechoic parenchyma with 14.7 kPa liver stiffness value. B, Histopathologic specimen showing moderate lobular necroinflammatory activity and few portal fibrosis with METAVIR score, F2.

The serum biochemical marker levels are as follows: AST to platelet ratio index (APRI), 1.3; AST to alanine aminotransferase ratio (AAR), 0.4; and fibrosis-4 (FIB-4) score, 0.4. A, Two-dimensional shear-wave elastography (2D-SWE) showing diffuse hyperechoic parenchyma with 21.2 kPa liver stiffness value. B, Histopathologic specimen showing mild necroinflammatory activity, severe macrovesicular steatosis, and much septal fibrosis with architectural distortion with METAVIR score, F3.

Discussion

Our study demonstrated that the liver stiffness measurement performed using 2D-SWE showed a stronger potential for noninvasively monitoring patients with liver fibrosis than did the assessments of biochemical or histopathologic confounding factors. The 2D-SWE liver stiffness values in pediatric liver diseases showed significant differences in histopathologic liver fibrosis stages. The liver stiffness values could distinguish significant fibrosis (≥ F2) with an AUC of 0.950 (cutoff value, 11.3 kPa). Additionally, the presence of severe fibrosis (F3 stage) could be identified with an AUC of 0.924 (cutoff value, 18.1 kPa).

Liver fibrosis involves the progressive deposition of collagen material in the liver, and this is a recovery response after chronic liver injury from various causes.²³ Noninvasive monitoring of mild to moderate liver fibrosis is important because cirrhosis—the end result of fibrosis—is irreversible. Previous studies have reported the performance of noninvasive diagnostic methods of liver fibrosis staging in adult patients.^{24–26} A previous systematic review on the 2D-SWE in liver fibrosis reported that the median cutoff value for presenting significant liver fibrosis (\geq F2) was 8.0 kPa (range, 7.1–10.5) in adult patients.²⁵ Although liver elastography had been widely reported to have excellent diagnostic performance in adult patients, only a few studies have applied it in pediatric patients because of the difficulty to control and coordinate breathing in these patients despite the advantage offered by US evaluation. Recently, Kim et al.¹⁵ had reported that liver stiffness value might be an excellent diagnostic value for evaluating liver fibrosis regards children and adolescents in the meta-analysis about five studies, with a cutoff value of 9.4 kPa, a similar value in adult patients.

Our study showed similar or slightly higher cutoff values for each fibrosis stage than did a previous study on pediatric patients. However, our cutoff values should be compared to those of previously reported pediatric studies on a similar disease etiology.¹⁰ Dhyanani et al. reported that the cutoff value for the F2 stage would be 8.8 kPa in children and adolescents with diverse liver diseases.²⁷ Tutar et al.²⁸ and Franchi-Abella et al.¹⁶ also reported that the cutoff values would be 10.4 kPa and 12.1 kPa in patients with NAFLD and early stage fibrosis, respectively. Therefore, in each study, the cutoff value may differ because of various causes and patient age groups. Our study could not demonstrate the cutoff value in any specific disease because of the diverse etiologies of pediatric liver diseases. Nevertheless, an advantage of our study is that it included various pediatric liver diseases unlike other studies that specifically included only NAFLD or hepatitis. Another advantage was that this study yielded meaningful results similar to existing data without sedation even in neonates.

We also evaluated a variety of biochemical markers that can affect liver fibrosis. Previous studies on adult patients with viral hepatitis reported that the fibrosis stage and gamma-glutamyl transpeptidase levels could influence the liver stiffness value measured using 2D-SWE.^{24,26} Previous studies also reported that the APRI might be a diagnostic value in predicting the fibrosis stage in pediatric liver diseases.^{6,29} However, there was a controversy in the APRI diagnostic accuracy as a predictive indicator of liver fibrosis in children.^{6,30} In adults, these scoring systems could provide good diagnostic performance in not only NAFLD but also viral hepatitis.³¹ Yang et al.³² reported that the APRI and FIB-4 scores might be significant markers for predicting fibrosis in children with NAFLD. However, Mansoor et al.⁶ reported that the APRI, AAR, and FIB-4 scores had a poor diagnostic performance in identifying significant fibrosis in NAFLD pediatric patients. Even recently developed fibrosis prediction systems, such as the improved liver fibrosis (ELF) scoring system, require unique serum markers, making their general use difficult.³³ Our study showed that serum biochemical markers such as the APRI, AAR, and FIB-4 scores have not yet become reliable markers for fibrosis. This might also explain their performance in various hepatic diseases resulting in histopathologic changes in our study population.

Among all the parameters explored in our study, the fibrosis stage was the most relevant factor affecting the 2D-SWE liver stiffness value. This could be because SWE can be applied to liver tissues to reflect the severity of liver fibrosis, even in various pediatric liver diseases. Another histopathologic factor, the necroinflammatory grade, was relevant to the liver stiffness values in pediatric liver diseases. All of these histologic factors might be related to the liver fibrosis stage. We have shown that both necroinflammatory and fibrotic stages based on the histopathologic analysis can influence 2D-SWE liver stiffness values despite various liver diseases. Therefore, the 2D-SWE liver stiffness value is a noninvasive marker suitable for clinical settings because of its correlation with the histologic fibrosis stage in various pediatric liver diseases.

Also, magnetic resonance elastography (MRE) might be another alternative diagnostic tool for the liver fibrosis stage. The diagnostic performance and reproducibility of MRE are generally higher than SWE examination.^{34–36} However, MRE takes a longer time, has a higher cost, and needs sedation, especially for uncooperative pediatric patients compared to ultrasound-based elastography examination.

The present study has several limitations. We included only a small number of patients with a wide age range from neonates to adolescents performing the 2D-SWE evaluation. A small number of patients in each fibrosis stage, in different etiologies, and broad age ranges could limit the results and clinical implications. However, the clinical usefulness of 2D-SWE technology should be established to suspected patients with liver disease even in undiagnosed situations. Therefore, if liver stiffness obtained from 2D-SWE data on these various causes can be collected and estimated, this technique could be applied not only to NFALD or hepatitis but also to fibrosis monitoring in various diffuse liver diseases. Our study's advantage is that even these various liver diseases showed statistically significant higher in the diagnostic accuracy of SWE values along the fibrosis stages. Nevertheless, further research is warranted on the clinical application of 2D-SWE in influencing the prognosis of suspected patients with liver diseases.

Conclusion

In conclusion, the liver stiffness values from 2D-SWE can be affected through both fibrosis and necroinflammatory grades and be an excellent diagnostic tool for the fibrosis stage evaluation, even in various liver disease types.

Abbreviations

AAR: the aspartate aminotransferase to alanine aminotransferase ratio

ALT: alanine aminotransferase

APRI: the aspartate aminotransferase to platelet ratio index

AST: aspartate aminotransferase

AUC: areas under the ROC curve

BA: biliary atresia

FIB-4: fibrosis-4 score

NAFLD: non-alcoholic fatty liver disease

ROC: receiver operating characteristic

SWE: shear-wave elastography

US: ultrasound

Declarations

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Following the Declaration of Helsinki, the study was approved as a retrospective human study by the Institutional Review Board of Seoul National University Hospital (No. 2005-211-1127). The informed consent of patient, parents, or guardians was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors have no competing interest to declare.

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Authors' contributions

SL and YHC: study concept and design, data acquisition, data analysis and interpretation, and writing of manuscript. SBL, JK, GHK: data analysis and interpretation. YJC, JEC, WSK, JSK: data acquisition and revision of manuscript for important intellectual content. All authors reviewed the manuscript.

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Authors' information (optional)

Department of Radiology, Seoul National University Hospital, Seoul, Republic of Korea: Seunghyun Lee, Young Hun Choi, Yeon Jin Cho, Seul Bi Lee, Jung-Eun Cheon, Woo Sun Kim

Department of Radiology, Seoul National University College of Medicine, Seoul, Republic of Korea: Young Hun Choi, Jung-Eun Cheon, Woo Sun Kim

Institute of Radiation Medicine, Seoul National University Medical Research Center, Seoul, Republic of Korea: Jung-Eun Cheon, Woo Sun Kim

Department of Pediatrics, Seoul National University Hospital, Seoul, Republic of Korea: Jae Sung Ko

Department of Pathology, Seoul National University Hospital, Seoul, Republic of Korea: Jaemoon Koh, Gyeong Hoon Kang

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Figures

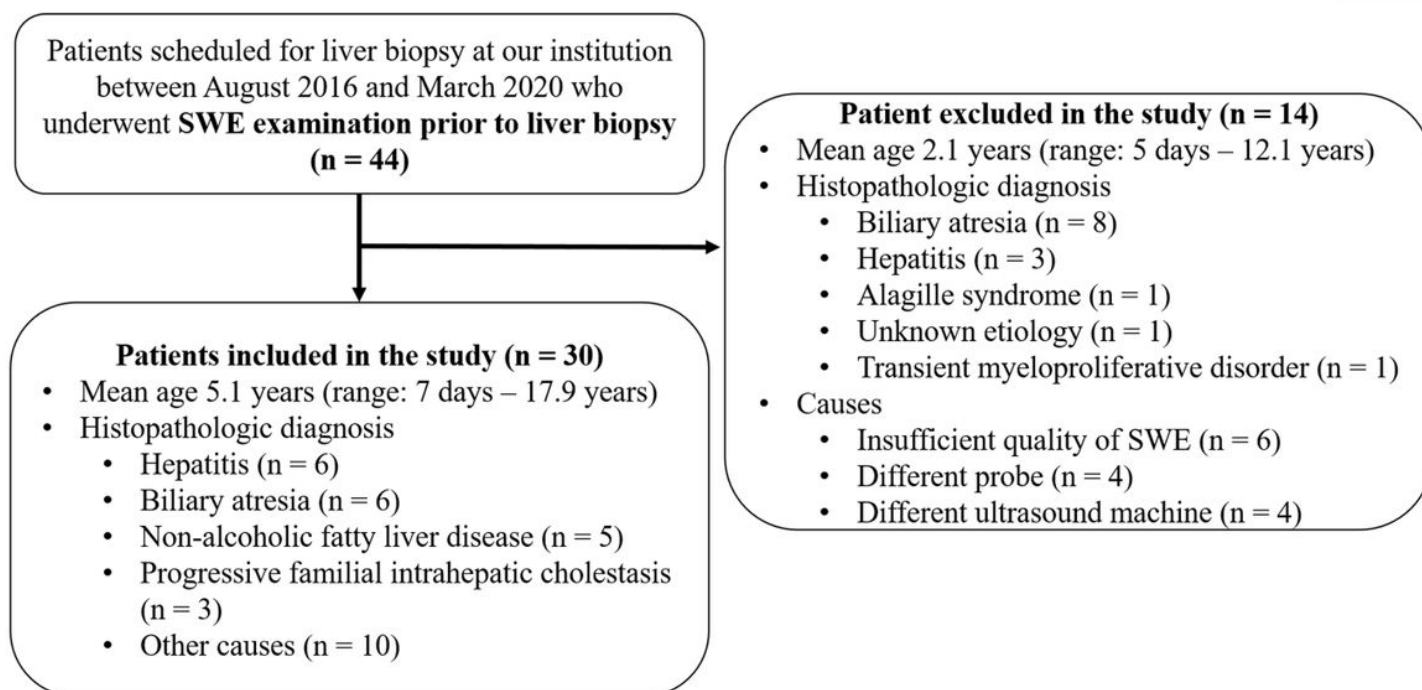


Figure 1

Flowchart Illustrating the Selection of the Study Population. We retrospectively reviewed the picture archiving and communication system database for the period between August 2016 and March 2020. Of the 44 potential candidates who underwent two-dimensional shear-wave elastography (SWE) prior to liver biopsy, 14 were excluded for the following reasons: insufficient quality of SWE (n = 6), use of different probes (n = 4), and use of different US machines (n = 4).

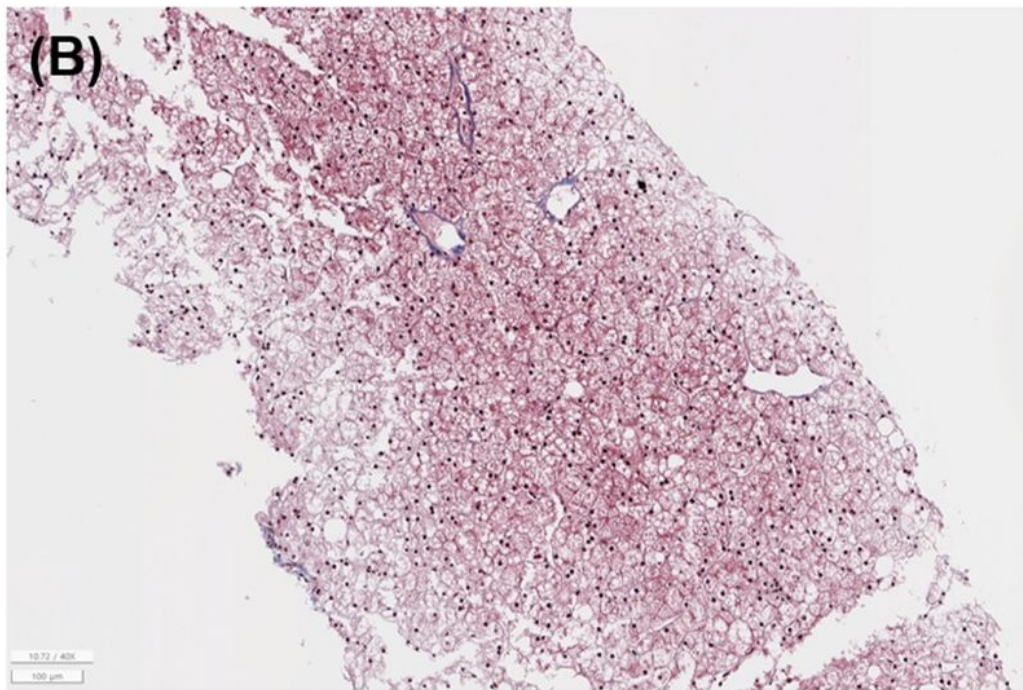
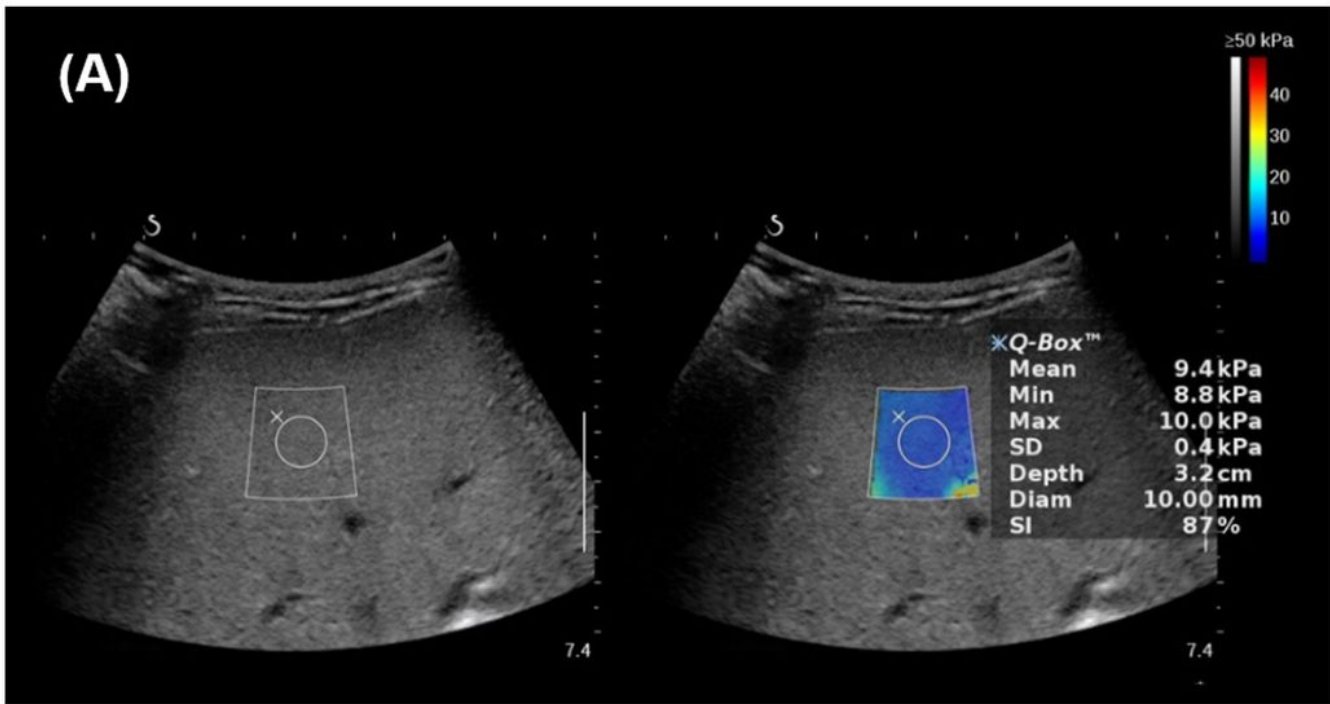


Figure 2

Glycogen storage disease of the liver in a 42-month-old boy. The serum biochemical marker levels are as follows: AST to platelet ratio index (APRI), 1.5; AST to alanine aminotransferase ratio (AAR), 0.9; and fibrosis-4 (FIB-4) score, 0.1. A, Two-dimensional shear-wave elastography (2D-SWE) showing diffuse hyperechoic parenchyma with 9.4 kPa liver stiffness value. B, Histopathologic specimen showing diffuse

enlargement of hepatocytes with clear cytoplasm and enlargement of the fibrotic portal tract with METAVIR score, F1.

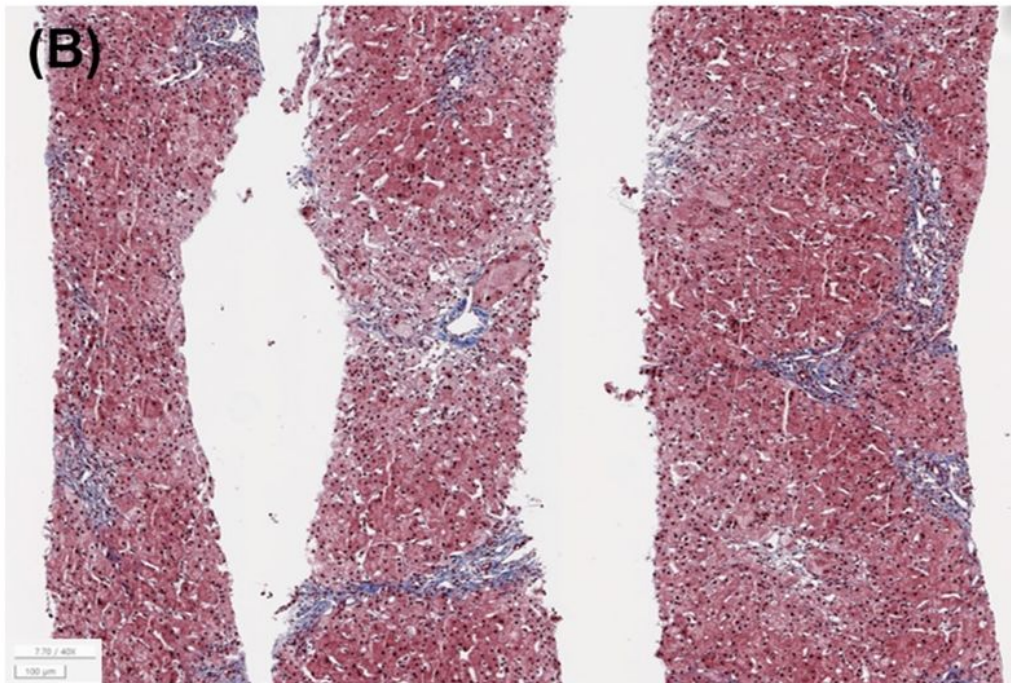
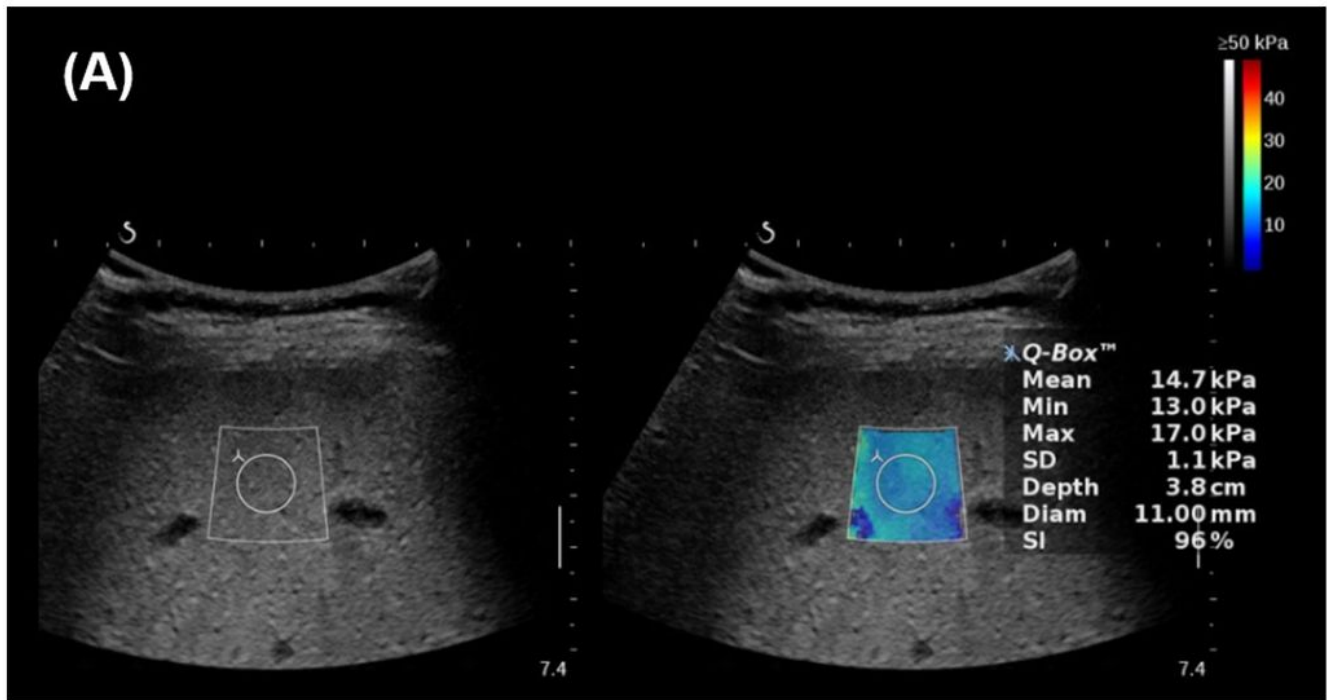


Figure 3

Hemophagocytic lymphohistiocytosis combined with the hepatitis in a 2.2-year-old boy. The serum biochemical marker levels are as follows: AST to platelet ratio index (APRI), 14.5; AST to alanine aminotransferase ratio (AAR), 0.8; and fibrosis-4 (FIB-4) score, 0.4. A, Two-dimensional shear-wave

elastography (2D-SWE) showing diffuse hyperechoic parenchyma with 14.7 kPa liver stiffness value. B, Histopathologic specimen showing moderate lobular necroinflammatory activity and few portal fibrosis with METAVIR score, F2.

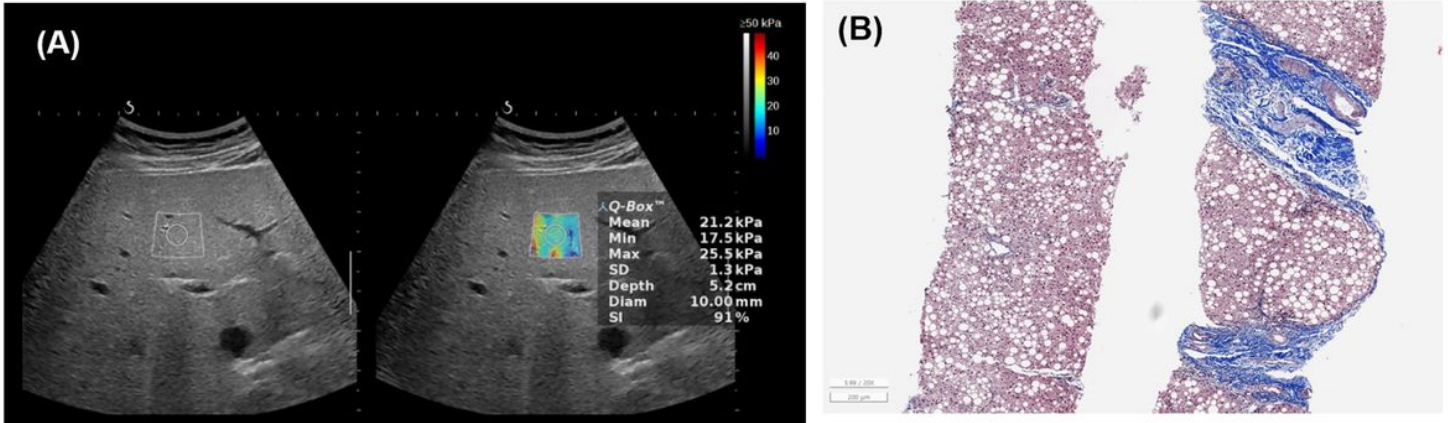


Figure 4

Non-alcoholic fatty liver disease in a 13.9-year-old boy. The serum biochemical marker levels are as follows: AST to platelet ratio index (APRI), 1.3; AST to alanine aminotransferase ratio (AAR), 0.4; and fibrosis-4 (FIB-4) score, 0.4. A, Two-dimensional shear-wave elastography (2D-SWE) showing diffuse hyperechoic parenchyma with 21.2 kPa liver stiffness value. B, Histopathologic specimen showing mild necroinflammatory activity, severe macrovesicular steatosis, and much septal fibrosis with architectural distortion with METAVIR score, F3.