J Surg Med. 2021;5(7):700-704.
DOI: 10.28982/josam.817897

Research article

Journal of Surgery and Medicine
e-ISSN-2602-2079

The role of sonoelastography in the evaluation of hepatic fibrosis in pediatric patients

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Ethics Committee Approval
The study protocol was approved by the Institutional Ethics Committee (Gazi University Ethics Committee, approval study number 27/06/2012-280.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2021 July 28

Abstract

Background/Aim: Hepatic fibrosis is caused by excessive accumulation of collagen-containing extracellular matrix proteins in chronic liver diseases. The gold standard for determining the degree of liver fibrosis is liver biopsy, which is an invasive method with complication risks. This study aimed to evaluate the potential role of ultrasound elastography, a non-invasive method, in the assessment of hepatic fibrosis among pediatric patients.
Methods: Twenty-four pediatric (0-18 years) patients with chronic liver disease and suspected hepatic fibrosis were included in this study. All patients were evaluated with B-mode and sonoelastography using Hitachi EUB 7500 digital ultrasound equipment. The biopsy procedure was performed on all patients a week after sonoelastography. Elastographic scores of liver parenchyma were categorized into four main groups, nonfibrotic, mild, moderate, and severe fibrosis. Strain index values were calculated. The elastographic scores and mean strain index values of the liver parenchyma were correlated with their pathological diagnosis.
Results: Elastographic scores and strain index values were significant for the presence of hepatic fibrosis (P=0.001 and P=0.006 respectively). Elastography has 100% sensitivity and 83.3% specificity to distinguish hepatic fibrosis when the cut-off value of strain index is 1.03.
Conclusion: Our findings support that real-time elastography is a non-invasive method for the diagnosis and staging of hepatic fibrosis with the potential to prevent recurrent biopsy and complications.

Keywords: Liver cirrhosis, Sonoelastography, Hepatic fibrosis

How to cite: Bilgin E, Bilgin EY, Oktar SO. The role of sonoelastography in the evaluation of hepatic fibrosis in pediatric patients. J Surg Med. 2021;5(7):700-704.

Introduction

Hepatic fibrosis is caused by excessive accumulation of collagen-containing extracellular matrix proteins in chronic liver diseases. Advanced liver fibrosis may result in cirrhosis, liver failure, and portal hypertension, all of which may require liver transplantation [1]. The gold standard for determining the degree of liver fibrosis in patients with chronic hepatitis is liver biopsy [2].

The histopathological examination of the tissue sample obtained from the liver by percutaneous, transjugular, laparoscopic methods, or perioperatively determines the etiological factor that causes the pathology and the degree of liver damage. An evaluation of response to treatment is also possible with repeated biopsies. Although the percutaneous method is used most often, biopsies can be performed using transjugular, laparoscopic, and perioperative methods.

The mortality rate of percutaneous liver biopsy is 0.009%, and some minor (13.6%) and major complications (1.0%) may develop afterward. These complications include pain (30%), bleeding, temporary hypotension, perforation of the gallbladder, haemobilia, pneumothorax, pneumoperitoneum, septic shock, subphrenic abscess, intrahepatic arteriovenous fistula, and carcinoid crisis. Also, sampling errors, at least 6 to 12 hours of hospitalization, and high costs are the disadvantages of biopsy [3-5].

Many studies report that ultrasonography can predict liver cirrhosis or advanced fibrosis. In the evaluation of cirrhosis in chronic liver diseases, grayscale ultrasonography reveals findings such as changes in liver surface nodularity, blunted liver edge, and roughened parenchymal structure. It is shown in the studies that the most sensitive sonographic finding of advanced fibrosis is liver surface nodularity. In addition, in ultrasonography, liver capsule thickness, the maximum oblique diameter of the right lobe, the diameters of the main portal vein and the right and left portal veins, the thickness of the gallbladder wall, the size of the spleen, the diameter of the splenic vein and the portal vein blood flow rate are related to the degree of fibrosis [6].

Elastography is a relative tissue stiffness mapping technique. Ultrasonographic elastography (sonoelastography) is a noninvasive imaging technique that is based on the determination of the stiffness and flexibility properties of the tissues by applying repetitive pressure effect on the tissue to figure out their spatial displacement (strain). Hard tissues or tissues that differ from their surroundings in terms of elasticity (tissues formed by cancer cells in breast and prostate cancer) respond with less displacement to the change of the pressure applied than the surrounding tissues [7,8]. Displacements at each point of the texture are encoded in different colors by real-time scanners superimposed on the B-mode review. The image that appears after coding is the elastogram of the tissue. Color coding can be done in grayscale or color. For example, in color coding, colors traced from yellow to red represent soft tissues, while green and blue indicate hard tissues. The colors may differ with devices.

Materials and methods

Twenty-four patients in the pediatric age group with a pre-diagnosis of chronic liver disease who were referred to the radiology department with a biopsy request between October 2011 and October 2012 were included in this prospective cohort study. The study protocol was approved by Gazi University, Institutional Ethics Committee with the number 27/06/2012-280. The procedure was explained to all the patients and their relatives, and informed consent forms were obtained. The biopsies were performed one week after the sonoelastographic examination.

The d-value method, developed by Cohen, was used in the calculation of the effect size. According to similar academic studies that reported the d value and based on the ANOVA test, the total sample size was calculated as 24 patients with d=0.91, α=0.05 (type-1 error), 1-β =0.90 (power) using G-power version 3.1) package program.

Sonographic examinations were conducted by two radiologists in the semi-bright ultrasonography room. The imaging was performed with a digital ultrasonography device that had real-time elastography software (Hitachi EUB 7500) using a 13–8 MHz linear transducer. In all cases, after B-mode examination, elastography mode was switched and real-time elastography images were obtained through the 13–8 MHz linear transducer.

After the elastograms were obtained, the liver parenchyma and the strain of the intercostal muscles were measured and proportioned with the help of ROI. The first measurement that was adjusted to include the liver parenchyma observed on the elastogram was determined as A, and the strain value of intercostal muscles on the same elastogram was determined as B. The ratio of these two values (B/A) was considered the strain index (SI). In 16 of the 24 patients participating in the study, this value was measured and recorded at least 3 times. In the other 8 cases, the measurements could not be performed due to patient-related causes. For the evaluation of elastograms, elastography scoring was made using the information from the literature (Table 1) [9].

Table 1: Elastography scores

Score	Comment	Elastographic view of liver parenchyma
1	Soft	Uniform light green area; in favor of no fibrotic activity
2	Substantially soft	Partially blue regions in the light green area
3	Substantially hard	Light green and blue colors are mixed.
4	Hard	Mostly blue areas

Nowadays, the most widely used histopathological evaluation methods are Knodell, Modified Ishak, and Metavir staging methods [10]. Modified Ishak classification was used in our study [11]. In the evaluation made by an experienced pathologist from our hospital, cases without fibrosis were evaluated as F0. Patients with fibrous enlargement and/or short fibrous septae in the portal area were evaluated as slightly fibrotic (F1), cases with fibrous enlargement in most portal areas and cases with rare or prominent porto-portal, porto-central bridging necrosis were evaluated as moderately fibrotic (F2), and patients with the presence of rare nodules or with a diagnosis of cirrhosis in addition to prominent bridging were considered highly fibrotic (F3).

Statistical analysis

SPSS (Statistical Package for the Social Sciences) version 25.0 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis of the data. Descriptive statistical methods (number, percentage, mean, median, standard deviation, etc.), the Kruskal-Wallis-H test, and the Mann-Whitney U test were used to assess the quantitative difference between the groups.

Multiple comparisons were made using Bonferroni correction subgroup analysis in groups where the difference was significant in the Kruskal-Wallis analysis. ROC analysis was used to determine the most appropriate strain index positive cut margin for hepatic fibrosis. The results were evaluated at a 95% confidence interval and *P*-value <0.05 significance level.

Results

The ages of 24 patients in this study ranged between 0 and 18 years. There were 8 females and 16 males. In histopathological analyses, 8 had no fibrotic activity (F0), 5 had mild fibrosis (F1), 9 had moderate fibrosis (F2), and 2 had advanced fibrosis (F3).

In the sonoelastography examination performed blinded to the histopathological diagnoses, the elastography scores of patients with (n=16) and without fibrosis (16) ranged between 1-3 (Figure 1) and 2-4 (Figure 2), respectively. The mean elastography scores of the non-fibrotic and fibrotic patients were 1.75 (0.707) and 2.94 (0.772), respectively. Elastography scores were significant (*P*=0.001) in showing the presence of hepatic fibrosis.

Figure 1: Liver parenchyma elastography score 1 in a nonfibrotic patient (F0)

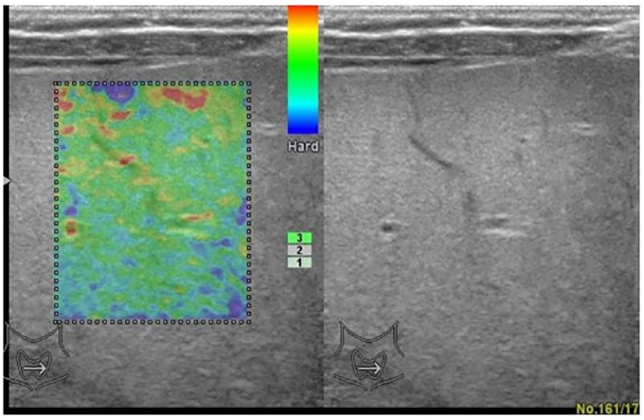
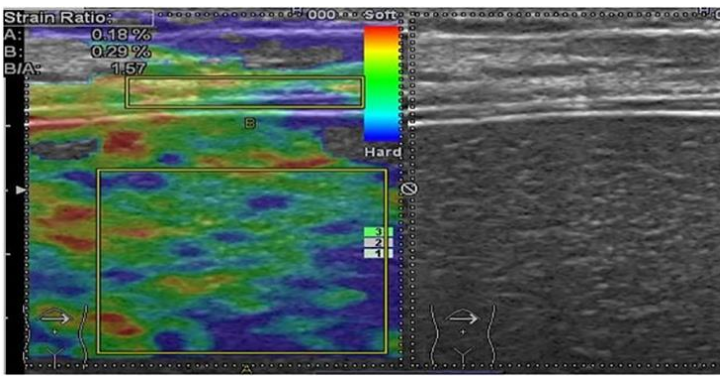


Figure 2: Liver parenchyma elastography score 3 with moderate fibrotic activity (F2)



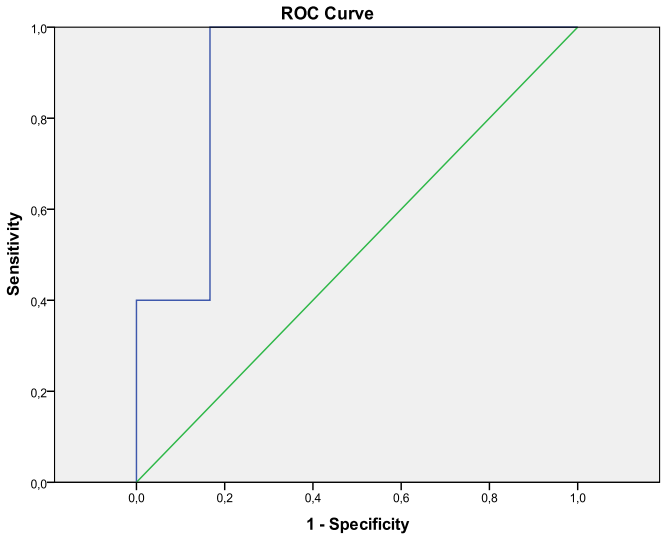
The elastography scores of patients with mild (F1), and moderate fibrosis (F2) ranged between 2-3, and 2-4, respectively, while those of all patients with advanced fibrosis (F4) were 4. When patients with moderate to advanced fibrosis were grouped, a significant difference was found between the cases with mild and moderate-advanced fibrosis (*P*=0.037). Mean strain index values of the non-fibrotic and fibrotic patients were 0.69 (0.56) and 1.76 (0.56), respectively. The mean strain index was 1.45 (0.21) in patients with mild fibrosis, and 1.88 (0.58) in patients with moderate to advanced fibrosis (Table 2). The ROC curve is presented in Figure 3. The area under the curve (AUC) was 0.92 and accordingly, the strain index had a significant diagnostic value (*P*=0.006). ROC analysis was performed with the available data, and the optimal strain index score cut-off point for hepatic fibrosis was 1.03, with 100% sensitivity, 83.3% specificity, a positive predictive value of 93.8%, and a negative predictive value of 100%.

Table 2: Distribution of mean strain ratios according to stages of hepatic fibrosis

	Elastographic score					
	n	Mean	(SD)	Range	K-W	*P*-value
Modified ISHAK Classification					14.443	0.001*
F(0) No hepatic fibrosis[a]	8	1.75	(0.71)	1-3	a vs b	0.289
F(1) Mild hepatic fibrosis[b]	5	2.20	(0.45)	2-3	a vs c	<0.001*
F(2&3) Moderate&severe fibrosis[c]	11(9+2)	3.27	(0.65)	2-4	b vs c	0.037*
	Strain index					
	n	Mean	(SD)	Range	Z	*P*-value
Hepatic fibrosis					-2.770	0.006*
No	6	0.69	(0.56)	0.2-1.7		
Yes	10	1.76	(0.56)	1.1-3.1		

* *P*<0.05, K-W: Kruskal Wallis-H Test, Z: Mann Whitney-U Test, SD: Standard Deviation

Figure 3: ROC curve for strain index values



Discussion

Hepatic fibrosis is caused by excessive accumulation of collagen-containing extracellular matrix proteins in chronic liver diseases. Advanced liver fibrosis may result in cirrhosis, liver failure, and portal hypertension, and require liver transplantation. Staging of hepatic fibrosis is important in terms of prognosis, follow-up, and treatment [12, 13].

Liver biopsy has been used for over a hundred years. Although it is the gold standard for staging hepatic fibrosis, some difficulties may arise due to the invasiveness of the procedure. The mortality rate of percutaneous liver biopsy is 0.009%, and studies are showing that some minor (13.6%) and major complications (1.0%) may develop after the liver biopsy, including pain, bleeding, temporary hypotension, perforation of the gallbladder, haemobilia, pneumothorax, pneumoperitoneum, septic shock, subphrenic abscess and intrahepatic arteriovenous fistulae. The heterogeneity of the amount of fibrosis in the right and left lobes leads to an evaluation error in approximately 10-30% of the cases. In addition, the difference in assessment among pathologists is reported as approximately 20% in studies.

Also, sampling error, at least 6 to 12 hours of hospitalization, and high costs are among its disadvantages; therefore, evaluation of fibrosis by noninvasive methods has gained importance [3, 5, 14, 15].

In the evaluation of chronic liver diseases, findings such as nodularity, blunted liver edge and roughened parenchymal structure are detected on B-mode ultrasonography. In their study with 103 chronic liver disease patients, Nishiura et al. [16] showed that these findings can be used to differentiate nonfibrotic and mildly fibrotic livers from those with moderate to advanced fibrosis. In their study with 156 chronic viral hepatitis patients, Chih-Ching Choong et al. [6] showed that the sonographically most sensitive finding of advanced fibrosis is liver surface nodularity, but these parameters are not sufficient in the diagnosis of early-stage fibrosis. Caudate lobe hypertrophy was compatible with advanced fibrosis in ultrasonography. Liver surface irregularity is an objective sign indicating cirrhosis [17, 18].

Many imaging methods are used to evaluate hepatic fibrosis and new methods continue to be developed. Sonoelastography is one of them. Elastography is a non-invasive relative tissue stiffness mapping technique that began to be used experimentally by Ophir et al. [19] in the late 1980s. It is based on the repetitive compression effect applied on the tissue to determine the spatial displacement (strain) of the tissues according to their stiffness and flexibility. Under the same force, hard tissues are less deformed and respond with less strain than soft tissues [7,8]. If there is a different hardness in the tissue during compression (stress), it can be separated from the surrounding tissue according to the strain index.

Sonoelastography methods are classified as semi-static (compression elastography) and dynamic (shear wave elastography). In compression elastography, tissue elasticity measurements can be obtained qualitatively (with color-coding) or semi-quantitatively (with strain index measurement). Shear wave elastography uses the acoustic radiation force of the ultrasound wave to push the tissue, and no manual compression is required.

The first study on the diagnosis and staging of hepatic fibrosis was published in 2007 by Friedrich-Rust et al. [20]. This study included 79 patients with chronic hepatitis and 20 healthy participants. Elastography scores were obtained by a computer program with the images obtained in this study. When these scores were combined with laboratory results, the area under the curve for the diagnosis of prominent fibrosis was 0.93 according to the ROC analysis.

In the study of Morikawa et al. [21] including 101 patients diagnosed with hepatitis C and 10 healthy participants, the sensitivity and specificity of sonoelastography in the diagnosis of hepatic fibrosis were 84.1% and 82.7%, respectively. Fujimoto et al. [7] performed a sonoelastography study with 43 chronic hepatitis C patients and showed that the degree of fibrosis increased with the elastography score.

In a study conducted on 111 patients who underwent biopsy for rejection after liver transplantation, the patients were evaluated by shear wave elastography and in patients with significant fibrosis (F2, F3, or F4 according to METAVIR classification), the average elastography value was above 1.76. The specificity and sensitivity of elastography in fibrosis classification were 79% and 77%, respectively. The authors concluded that in the elastography examination performed after liver transplantation, patients with an elastography value<1.76 do not have significant fibrosis and the biopsy procedure can be postponed [22].

A meta-analysis assessed 528 studies about shear wave elastography (SWE) and showed that SWE has high sensitivity and specificity for detecting and staging hepatic fibrosis in patients with ≥F2 Metavir-score. As a non-invasive procedure, elastography is highly suitable for detecting significant fibrosis, and therapeutic outcomes after surgery, e.g., transplantation [23].

In addition, MR elastography, which can be used to demonstrate diffuse liver diseases, investigate fibrosis, differentiate malignant and benign liver masses, and evaluate the response to treatment, has begun to be included in routine workup as a non-invasive diagnostic method [24].

We referred to the literature in elastography scoring. Elastography scores of 1, 2, 3, and 4 define normal liver parenchyma, mild, moderate, and advanced fibrosis, respectively. The elastography score was not 1 in any of the cases with fibrosis and ranged between 1-3 in 8 cases without fibrosis. In only one non-fibrotic case, the elastography score was 3. Elastography score was significant in detecting hepatic fibrosis.

Due to the small number of cases in our study, cases with moderate and advanced fibrosis were evaluated in the same group. In the statistical study, although significant results were obtained in the separation of mild and moderate-advanced fibrosis in sonoelastography, no significant results were found in the distinction of nonfibrotic cases and mild fibrosis.

In our study, strain index values, which we consider to be more objective than the elastography score, were also used. When minimum strain index cut-off was 1.03, its sensitivity and specificity in distinguishing hepatic fibrosis were 100% and 83.3%, respectively, with positive and negative predictive values of 90.9%, and 100%, respectively, and an area under the curve of 0.9.

Limitations

Our study has some limitations, the most prominent ones including its single-center nature, and the low number of cases. We had to group patients with moderate and severe fibrosis. Long-term follow-up, which could not be performed in this study, should provide more information about the effectiveness of sonoelastography in hepatic fibrosis staging.

Conclusion

Although biopsy is the gold standard in the diagnosis and staging of hepatic fibrosis, we have the impression that sonoelastography is a noninvasive method that can contribute to the diagnosis and staging of hepatic fibrosis in the pediatric age group. Therefore, real-time sonoelastography can reduce biopsy repetitions and related possible complications. We think that this will help clinicians in the diagnosis and follow-up of hepatic fibrosis.

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