Article published online: 2021-02-25

Diagnostic Performance of Noninvasive Methods for Liver Biopsy by Fibroscan in Pediatric

Ghobad Heidari[1] Farzaneh Motamed[2,*] Bita Heirati[3] Parisa Rahmani[2,*]

[1] Department of Pediatric, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran
[2] Pediatric Gastroenterology and Hepatology Research Center, Tehran University of Medical Sciences, Tehran, Iran
[3] Department of Pediatric, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

Address for correspondence Parisa Rahmani, Assistant Professor of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran (e-mail: md.p.rahmani@gmail.com).

J Child Sci 2021;11:e55–e59.

Abstract

Liver biopsy is the gold standard for the diagnosis and management of various liver diseases; however, noninvasive diagnostic modalities may help prevent adverse effects of anesthesia, prolonged hospitalization, sampling error, and other serious complications, particularly in pediatric patients. The aim of this study is to compare the results of liver biopsy and fibroscan in children with chronic liver diseases. All patients presenting chronic liver disease admitted in the ward or clinic of Tehran's Children Medical Center were enrolled in the study. Required laboratory tests were performed to diagnose the disease, followed by elastography using fibroscan 402 (M-probe) Echosens machine and liver biopsy using Menghini technique. Samples were scored by using METAVIR scoring system. Thirty-two patients were reported (68.8%, female) with autoimmune hepatitis (18.8%), Wilson disease (12.5%), and glycogen storage disease (12.5%). The most common pathologic stage and fibroscan result was stage III and F0 (46.9%), respectively. Association between pathology and fibroscan results was not significant. Nonetheless, age and diagnosis, age and Fibroscan score, and pathology and liver function test were significantly associated with each other. Fibroscan cannot be used as an alternative to liver biopsy; however, it can be a useful accessory tool.

Keywords
- fibroscan
- liver biopsy
- elastography
- pediatric
- Menghini technique
- METAVIR scoring

Introduction

Despite the development of minimally invasive diagnostic techniques, liver biopsy remains the cornerstone for the diagnosis and management of liver diseases.[1] Examination of liver tissue is an essential tool for the diagnosis of the pathological condition and stage, essentially in pediatric diseases.[2] Alterations in tissue morphology can help differentiate between hepatitis, liver cholestasis disease, steatosis, vascular disorders, and infectious diseases.[3] Liver biopsy is particularly valuable in the cases of overlapping syndromes, atypical clinical signs, or those with unknown diagnosis.[4]

In addition to diagnosis, liver biopsy is now used as a prognostic tool for a variety of liver diseases providing data the cause and etiology of the disease and degree of inflammation and fibrosis, thereby aiding precise clinical decision.[5] Advancements in technology have allowed scientists to develop noninvasive methods, such that the need for liver biopsy can be significantly reduced.[6] Fibroscopy (transient elastography) is a novel noninvasive method used to evaluate the degree of liver fibrosis.[7] The fundamental principle of fibroscopy is a one-dimensional transient elastronic wave,

* The authors contributed equally to this work.

received
September 8, 2020
accepted after revision
January 19, 2021

DOI https://doi.org/10.1055/s-0041-1725079.
ISSN 2474-5871.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

which measures variations in the liver stiffness in kPa (LSM), in response to the changes in the speed of transient elastography.[8] In the past few years, fibroscopy has been more frequently used to evaluate various liver diseases, in comparison with biopsy and other diagnostic modalities. Fibrosopy has been suggested for the diagnosis of cirrhosis in cases where coagulation disorders could preclude biopsy.[9]

The aim of this study was to measure liver hardness measurement (LSM) using fibroscopy and compare these results with liver biopsy to measure the degree of fibrosis/cirrhosis in pediatric patients.

Materials and Methods

In this research, all the pediatric patients referred to the gastroenterology clinic of the Children's Medical Center Hospital in Tehran during 2015 to 2017 were enrolled. After obtaining written consent from parents, patients with chronic liver disease were included in the study. To determine the cause of underlying illness, in cases where there was no definitive diagnosis, further examinations were performed, such as serologic tests for hepatitis B or C virus, sweat test for the evaluation of cystic fibrosis, duodenal duct test for the diagnosis of biliary atresia, assessment of specific antibodies to detect autoimmune hepatitis and ceruloplasmin, and urine copper tests for Wilson's disease. In other cases, the diagnosis was proceeded according to the standard criteria of the case. Cases of thalassemia, cerebrovascular diseases, and neoplasms were not included in the study.

Elastic examination was performed by Fibroscan Fs402 (including probe model M), Echosens, France. The scan was performed on the right lobe of the liver while patients were in the dorsal decubitus position, and the right arm was placed at maximum abduction. At first, liver tissue with a thickness of at least 6 cm and no large vessels was identified by using A-mode sonography. At minimum, 10 images were prepared according to the manufacturer's instructions and 6 images were used for the validation, so that less than 30% of the cases were in the range of 25 to 75th percentile. The samples were divided into five stages of the disease based on the METAVIR scoring system: F0: without fibrosis; F1: port fibrosis without septum; F2: the presence of port fibrosis and few septum; F3: abundant septum without evidence of cirrhosis; and F4 Cirrhosis. Liver biopsy was performed by using the Menghini technique in accordance to the age of the patient, using Hepafix needles of 1.2 to 1.6 mm in diameter (Braun, Melsungen, Germany). The results of liver biopsies were evaluated by a pathologist, who was uninformed regarding the results of the fibroscopy and biomarkers.

For each patient, a questionnaire including demographic characteristics such as age, gender, the underlying cause of liver disease, pathologic findings, and elastogram was recorded. Considering the annual rate of referral to gastrointestinal and liver wards, a sample size of approximately 30 was used to study liver disease by elastography and biopsy. Considering the sensitivity of 90% of the fibroscopy test in 30 patients, the estimated sensitivity of the fibroscopy test was approximately 0.107. If the sensitivity of the test in the study is, for example 80%, the actual test sensitivity was considered between 70 and 90%.

With regard to specificity, 79% of fibroscopy specifications were considered by including 30 healthy individuals in the study, and the estimated fiberscope test specification was 0.145. That is, if the test feature in the study, for example is 80%, the actual test specification would be between 0.945 and 0.655%. This study was approved by the Research Ethics Board of Tehran University of Medical Sciences (REC. TUMS:2017.0912).

Data Analysis Method

Data were analyzed by using SPSSv17 software. Quantitative and qualitative data were reported as standard deviation ± mean and frequency, respectively. Qualitative findings were analyzed by Chi-square test and quantitative findings, using nonparametric Kolmogorov–Smirnov test. The diagnostic accuracy of the fibroscopy for cirrhosis (METAVIR score: F0–F4) was calculated based on the ROC (receiver operating characteristics) curve.

Results

In our study, 32 patients were examined in total, 10 boys (31.3%) and 22 girls (68.8%). The mean age and the age range of the patients were 44.59 ± 70.53 and 5 months to 14 years, respectively. Patients presented the following liver diseases: six cases of autoimmune hepatitis (18.8%), two cases of cholestasis and hepatitis B (6.2%, each), three cases of extracellular portal hypertension and metabolic disease (9.4%, each), and four cases of GSD, steatosis and Wilson disease (12.5%, each), one case of celiac disease, congenital hepatitis, sarcoidosis, and primary sclerosing cholangitis (3.1%, each; ►**Fig. 1**).

Pathological examination of patients showed the following results: four cases of Stage 0 (12.5%), six cases of Stage I (18.8%), eight cases of Stage II (25%), seven cases of Stage III (21.9%), five cases of Stage IV (15.6%), and two cases of Stage V (6.3%) (►**Fig. 2**).

Fibroscopic examination of the patients showed 15 cases of F0 (46.9%), eight cases of F1 (25%), seven cases of F2 (21.9%), and two cases of F3 (6.3%), whereas liver function test revealed that 4 cases (12.5%) were normal, 4 cases (12.5%) were 2 times less than normal, 10 cases (31.3%) were twice as normal, and 14 (43.8%) of them were 2.5 times more than normal. (►**Fig. 3**).

In 29 cases (90.6%), international normalized ratio was lower than 1.5, where in three cases (9.4%), it was above 1.5 statistical

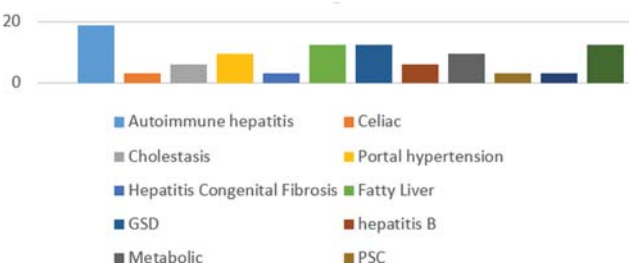

Fig. 1 Illnesses of patients studied.

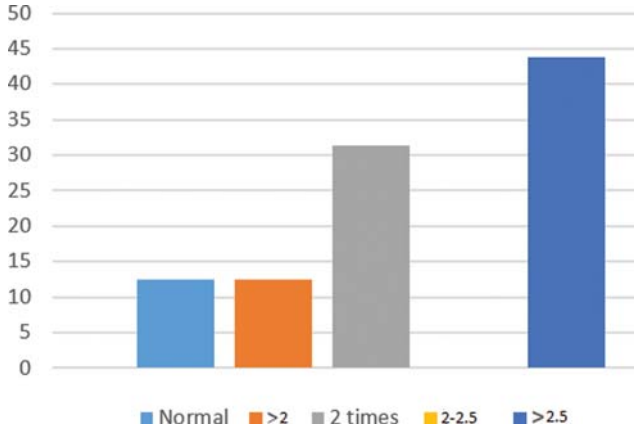

Fig. 2 Different stages of cirrhosis of the patients studied.

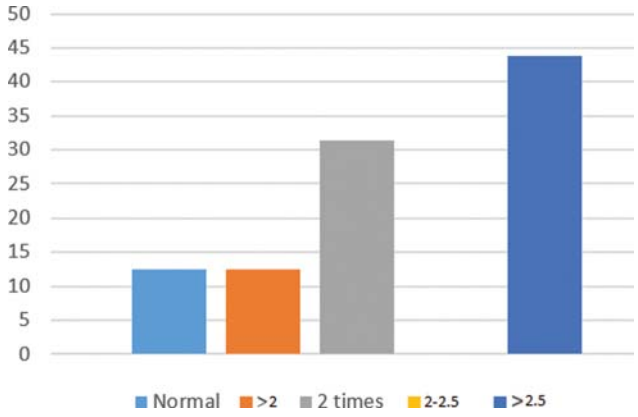

Fig. 3 Distribution of liver function test results in patients under study.

analysis showed that the stage of fibroscan was positively related with the score in relative terms; however, there was no significant relationship between the two parameters ($p = 0.808$). As shown in ►**Tables 1** and **2**, age was significantly related to the outcomes of fibroscopy ($p = 0.038$), whereas pathology was related to LFT status ($p = 0.479$).

Discussion

Assessing the progression of chronic liver disease (or its recurrence upon treatment) holds clinical importance in the field of hepatology. The severity of fibrosis is the most significant predictor of the status of liver disease, regardless of etiology. Patients with advanced-stage fibrosis are likely to develop cirrhosis.[10] Evaluating the effectiveness of the treatment, for example in liver autoimmune disease, is also important. Several gastrointestinal pathologies are associated with cirrhosis, that is, hepatocellular carcinoma, hepatic encephalopathy.[11] Liver biopsy is now used as a gold standard for evaluating fibrosis; however, it requires hospitalization and anesthesia, and sampling error is frequent along with serious risks such as bleeding.[12] Designing accurate and reliable noninvasive method to determine the stage of fibrosis for chronic liver disease is, therefore, of utmost importance.

In adults, several noninvasive methods are recognized for the diagnosis of liver fibrosis, including the simple cohort-derived markers such as APRI,[13] microRNA 122, and Forns,[14]

Table 1 Pearson's correlations among study variables

	1	2	3	4	5
Age					
Pathology	0.336[a]				
Fibroscan	−0.368	0.217			
LFT	0.039	0.479[b]	0.064		
INR	0.304[a]	0.205	0.265	0.178	

Abbreviations: INR, international normalized ratio; LFT, liver function test.
[a]Correlation is significant at the 0.1 level (two-tailed).
[b]Correlation is significant at the 0.05 level (two-tailed).

Table 2 The average age of patients based on pathologic prognosis

	n	Mean	Standard deviation	Minimum	Maximum
GSD	5	38.40	39.25	12	108
Cholestasis	2	6.5	2.12	5	8
Hepatitis B	1	120		120	120
Metabolic disease	3	28	27.71	12	60
Hepatitis autoimmune	6	84	28.39	48	120
Wilson	4	72	21.90	48	96
Sarcoidosis	1	120		120	120
Fatty liver	4	90	39.79	60	144
Sclerosing cholangitis	1	96		96	96
Extra-liver problems	3	88	54.11	36	144
Congenital diseases	1	48		48	48
Celiac	1	168		168	168
Total	32	70.53	44.59	5	168

Abbreviation: GSD, glycogen storage disease.

and algorithms including extracellular matrix turnover factors, such as fibrometer,[5] fibrotest,[15] and hepa-score.[16]

Serum markers often cannot differentiate sufficiently between the degrees of fibrosis. Over the past 5 to 6 years, the use of transient elastography (TE) has been accepted more, as a noninvasive method to evaluate liver disease.[17] TE is performed by the transmission of the vibration through the chest wall to the liver, using an ultrasound probe with a vibration transducer. An elastic shear wave is induced in the liver, and using the Young modulus (E) index, liver elasticity is determined from the wave velocity. Liver stiffness is expressed in kilopascals. Accuracy of this method is extensively reported in adult patients;[18] however, fewer studies have been conducted in children.[19,20]

In our study, 32 patients were studied, of which 68.8% were females. A study conducted by Fitterpatrick et al,[21] similar to our study, showed that the majority of subjects (60%) were boys. Engelmann's[22] study found that in girls between 11 and 18 years of age, liver stiffness was

significantly lower than that in boys (4.71 vs. 5.6 kPa). The average age of patients in our study was 70.53 months (~6 years), while in Fitzpatrick study, it was 13.6 years. Fibroscopy has been associated with radical variations in the outcomes due to the diversification of the age in the different studies. Engelmann reported that liver firmness was significantly dependent on age; hence among the children between 0 and 5 years, the mean liver rigidity score was 4.7 kPa. While in 6 to 11 years old children, it was 4.73 kPa and in children 12 to 18 years of the age, it was 5.1 kPa, thereby suggesting the implication of fibroscopy in children of different age groups. The study also reported that from 6 years of the age, efficient fibroscopy without anesthesia is reliable. Goldsmith's study[23] reports that data regarding children under the age of 6 years is scarce and the effects of technical aspects of fibroscopy such as probe selection and the location of measurement on the results are unknown. This study reports an overall success rate of 90%, where 83% of the patients were under the age of 24 months. In our study, age had a significant effect on the results of fibroscopy.

The diagnosed disease was not significantly related with the score of fibroscopy or pathology, but was statistically related with age. In the study by Fitzpatrick et al, out of 104 patients, 27 presented autoimmune diseases, 37 had nonalcoholic liver, 16 post-transplant, 8 hepatitis B and C, and 5 had Wilson's disease. Fibroscopy was most effective in autoimmune and post-transplant patients. Nonetheless, our study does not report similar data perhaps due to small sample size and the dispersion of diagnoses, reducing the validity of the results for the comparison between the groups.

The study by Shen et al[24] provided comparison between fibroscan and liver biopsy in BA. In that study, LSM was statistically different between the two stages F2 and F4. This difference was also found between F3 and F4, while no such differences were seen in our study and the relationship between degrees of fibrosis and pathology was not significant. Fewer samples with great variations in the type of pathology can explain such discrepancies.

Similarly, the type of the pathology and the LFT were significantly related in our study. Higher hepatic fibrosis, approaching to cirrhosis stage, was associated with impaired liver function.[25,26]

Our findings are based on a small sample size and data regarding biochemical findings are not presented. Further studies are therefore required in this regard comparing other imaging modalities for the diagnosis of liver fibrosis in children.

Conclusion

In our study, no significant correlation was found between the scores of fibroscopy and the pathologic stage. Therefore, according to our findings, fibroscan cannot be used as an alternate to biopsy to determine the stage of the disease. In our study, the relationship between age and fibroscopy and the type of disease and pathology with LFT status was marked statistically significant.

Note

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Authors' Contributions

P.R. and G.H. conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. F.M. designed the data collection instruments, collected data, performed the initial analyses, and reviewed and revised the manuscript. B.H. coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Funding

None.

Conflict of Interest

None declared.

References

1 Cassinotto C, Boursier J, de Lédinghen V, et al. Liver stiffness in nonalcoholic fatty liver disease: a comparison of supersonic shear imaging, FibroScan, and ARFI with liver biopsy. Hepatology 2016; 63(06):1817–1827
2 Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017;64(02):319–334
3 Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith ADAmerican Association for the Study of Liver Diseases. Liver biopsy. Hepatology 2009;49(03):1017–1044
4 Lefkowitch JH. Scheuer's Liver Biopsy Interpretation E-Book. Elsevier Health Sciences 2015
5 Boursier J, Vergniol J, Guillet A, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol 2016;65(03):570–578
6 Malekzadeh R, Poustchi H. Fibroscan for assessing liver fibrosis: an acceptable alternative for liver biopsy: fibroscan: an acceptable alternative for liver biopsy. Hepat Mon 2011;11(03):157–158
7 Honar N, Jooya P, Haghighat M, et al. Complications of blind versus ultrasound-guided percutaneous liver biopsy in children. Arab J Gastroenterol 2015;16(3-4):90–93
8 Foucher J, Chanteloup E, Vergniol J, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. Gut 2006;55(03):403–408
9 Abdelaal UM, Morita E, Nouda S, et al. Evaluation of portal hypertensive enteropathy by scoring with capsule endoscopy: is transient elastography of clinical impact? J Clin Biochem Nutr 2010;47(01):37–44
10 Trout AT, Sheridan RM, Serai SD, et al. Diagnostic performance of MR elastography for liver fibrosis in children and young adults with a spectrum of liver diseases. Radiology 2018;287(03): 824–832
11 Kalaitzakis E. Gastrointestinal dysfunction in liver cirrhosis. World J Gastroenterol 2014;20(40):14686–14695
12 Potretzke TA, Saling LJ, Middleton WD, Robinson KA. Bleeding complications after percutaneous liver biopsy: do subcapsular

lesions pose a higher risk? AJR Am J Roentgenol 2018;211(01): 204–210
13 Gamil M, Alboraie M, El-Sayed M, et al. Novel scores combining AFP with non-invasive markers for prediction of liver fibrosis in chronic hepatitis C patients. J Med Virol 2018;90(06):1080–1086
14 Omran AA, Osman KS, Kamel HM, Abdel-Naem EA, Hasan DE. MicroRNA-122 as a novel non-invasive marker of liver fibrosis in hepatitis C virus patients. Clin Lab 2016;62(07):1329–1337
15 Huang Y, Adams LA, Joseph J, Bulsara MK, Jeffrey GP. The ability of hepascore to predict liver fibrosis in chronic liver disease: a meta-analysis. Liver Int 2017;37(01):121–131
16 Adams LA, Bulsara M, Rossi E, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. Clin Chem 2005;51(10):1867–1873
17 Siddiqui MS, Vuppalanchi R, Van Natta ML, et al; NASH Clinical Research Network. Vibration-controlled transient elastography to assess fibrosis and steatosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2019;17(01):156–163.e2
18 Zhang X, Wong GL-H, Wong VW-S. Application of transient elastography in nonalcoholic fatty liver disease. Clin Mol Hepatol 2020;26(02):128–141
19 Aqul A, Jonas MM, Harney S, et al. Correlation of transient elastography with severity of cystic fibrosis-related liver disease. J Pediatr Gastroenterol Nutr 2017;64(04):505–511
20 Lewindon PJ, Puertolas-Lopez MV, Ramm LE, et al. Accuracy of transient elastography data combined with APRI in detection and staging of liver disease in pediatric patients with cystic fibrosis. Clin Gastroenterol Hepatol 2019;17(12):2561–2569.e5
21 Fitzpatrick E, Quaglia A, Vimalesvaran S, Basso MS, Dhawan A. Transient elastography is a useful noninvasive tool for the evaluation of fibrosis in paediatric chronic liver disease. J Pediatr Gastroenterol Nutr 2013;56(01):72–76
22 Engelmann G, Gebhardt C, Wenning D, et al. Feasibility study and control values of transient elastography in healthy children. Eur J Pediatr 2012;171(02):353–360
23 Goldschmidt I, Streckenbach C, Dingemann C, et al. Application and limitations of transient liver elastography in children. J Pediatr Gastroenterol Nutr 2013;57(01):109–113
24 Shen Q-L, Chen YJ, Wang ZM, et al. Assessment of liver fibrosis by Fibroscan as compared to liver biopsy in biliary atresia. World J Gastroenterol 2015;21(22):6931–6936
25 Binkovitz LA, El-Youssef M, Glaser KJ, Yin M, Binkovitz AK, Ehman RL. Pediatric MR elastography of hepatic fibrosis: principles, technique and early clinical experience. Pediatr Radiol 2012;42 (04):402–409
26 Cho Y, Tokuhara D, Morikawa H, et al. Transient elastography-based liver profiles in a hospital-based pediatric population in Japan. PLoS One 2015;10(09):e0137239