Journal of Pediatric Gastroenterology and Nutrition
45:443–450 © 2007 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Liver Stiffness Measurement in Children Using FibroScan: Feasibility Study and Comparison With Fibrotest, Aspartate Transaminase to Platelets Ratio Index, and Liver Biopsy

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ABSTRACT

Objective: Transient elastography (FibroScan) is a novel, noninvasive, rapid bedside method to assess liver fibrosis by measuring liver stiffness in adult patients. The usefulness of FibroScan in children with chronic liver diseases is unknown. The aim of this prospective study was to evaluate the feasibility of liver stiffness measurement and to compare FibroScan, Fibrotest, and aspartate transaminase to platelets ratio index (APRI) with liver biopsy for the diagnosis of cirrhosis in children with chronic liver diseases.

Patients and Methods: Between February 2004 and October 2005, 116 consecutive children with chronic liver diseases were prospectively included. All except 1 child (58 boys, mean age 10.7 years) could have noninvasive tests for fibrosis: FibroScan, Fibrotest, and APRI, and, when necessary, a liver biopsy (n = 33).

Results: FibroScan, Fibrotest, and APRI were correlated with clinical or biological parameters of chronic liver diseases, but the FibroScan marker correlated most with all parameters. By histology, the METAVIR fibrosis category score was F1 in 7 cases, F2 in 8 cases, F3 in 6 cases, and F4 in 12 cases. FibroScan, Fibrotest, and APRI were significantly correlated with the METAVIR fibrosis score. For the diagnosis of cirrhosis, the area under the receiver operating characteristic curve was 0.88, 0.73, and 0.73 for FibroScan, Fibrotest, and APRI, respectively.

Conclusions: These results indicate that liver stiffness measurement is feasible in children and is related to liver fibrosis. A specific probe dedicated to children and slender patients has thus been developed and is currently under evaluation. The FibroScan equipped with this specific probe could become a useful tool for the management of chronic liver diseases in children. ***JPGN 45:443–450, 2007.*** **Key Words:** Cirrhosis—Cystic fibrosis—Fibrosis—Liver stiffness—Portal hypertension. © 2007 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

INTRODUCTION

Liver fibrosis is observed in a large proportion of children with chronic liver disease regardless of its cause. Early treatment of the cause can limit the progression of fibrosis but not always prevent its development until its most advanced stage, known as cirrhosis. Liver transplantation is then the only solution. Biliary atresia (1:14,000 live births worldwide) is the main cause of liver fibrosis in children, followed by viral hepatitis C and B, autoimmune hepatitis, cystic fibrosis, and metabolic diseases such as Wilson disease and α_1-antitrypsin deficiency. In all of the cases follow-up of liver fibrosis appearance and progression is required for the initiation of prophylactic treatment and anticipation of the possible necessity for liver transplantation.

Until recently, liver biopsy followed by conventional histological analysis was the only way to evaluate liver fibrosis; however, liver biopsy can have life-threatening complications in both adults and children (1–3). It is therefore difficult to use as a follow-up tool. Moreover, the accuracy of liver biopsy has also been questioned

Received January 12, 2007; accepted May 23, 2007.

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because of sampling errors and intraobserver and interobserver variability, which lead to an overstaging or understaging of fibrosis (4–7). Thus, there is a need for accurate noninvasive methods of measuring the degree of liver fibrosis (8). Proposed approaches, including physical examination, routine biochemical and hematological tests, and surrogate serum fibrosis markers such as Fibrotest and aspartate transaminase to platelets ratio index (APRI), are not accurate enough, not routinely available, or not validated for children (9–11).

FibroScan (Echosens, Paris, France) is a new medical device based on transient elastography, which measures liver stiffness in a noninvasive, rapid, painless, and reproducible way (12). Several studies have demonstrated that liver stiffness measurement is closely related to fibrosis stage as assessed by liver biopsy in adult patients with chronic hepatitis C and B, alcoholic and nonalcoholic steatohepatitis, hemochromatosis, or biliary diseases (13–21). In all studies accuracy of liver stiffness measurement for the diagnosis of cirrhosis was higher than 90% according to the area under the receiver operating characteristics (AUROC) curve.

The aim of this prospective study was to evaluate the feasibility of liver stiffness measurement in children using FibroScan and to compare FibroScan, Fibrotest, and APRI with liver biopsy for the diagnosis of cirrhosis and with clinical and biological parameters for the severity of the liver disease.

PATIENTS AND METHODS

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by our institutional review board. Enrollment in the study was proposed to all consecutive children with chronic liver diseases but without ascites who were seen at the Pediatric Hepatology Unit of Pellegrin Hospital (University Hospital of Bordeaux, France). Patients were included after written informed consent was obtained from the parents. Children with new diagnoses and children with known chronic liver disease were included. Determination of the cause of chronic liver disease was made as follows: hepatitis C virus (HCV) or hepatitis B virus (HBV) infection by serological detection of HCV antibodies (with positive serum HCV-RNA by polymerase chain reaction) and hepatitis B surface antigen, respectively; cystic fibrosis by sweat test and assessment of CFTR mutations; biliary atresia by surgical exploration and histological examination of the biliary tree; autoimmune hepatitis by detection of antinuclear, antiliver kidney microsome-1 and anti–smooth muscle and anticytosol autoantibodies; and Wilson disease by dosage of ceruloplasmin and copper in urine and in the liver. All other diseases were diagnosed according to standard diagnostic criteria.

Biochemical and Clinical Parameters

For all of the children, the following parameters were determined at the time of the liver stiffness measurement. Biological parameters included aspartate aminotransferase (AST), alanine aminotransferase, γ-glutamyl transpeptidase, total bilirubin, platelet count, prothrombin time, albumin, α_2-macroglobulin, apolipoprotein-A1, and haptoglobin. Clinical parameters included height, weight, presence of esophageal varices (after upper gastrointestinal endoscopy), and presence of splenomegaly and hepatic dysmorphy at ultrasonographic examination.

Liver Histology

Independent of this study, the indication for biopsy was either to find the cause of abnormal liver test results, to confirm the nature of a suspected liver disease, or to assess the evolution of a prediagnosed liver disease. Liver biopsy was performed either percutaneously by a senior operator using the Menghini technique (22) with a 1.2- to 1.6-mm diameter needle (Hepafix; Braun, Melsungen, Germany) according to the child's age, or surgically with deep cuneiform subcapsular specimens. Liver biopsy was performed on the same week as liver stiffness assessment. Liver specimens were fixed in formalin and embedded in paraffin. Sections measuring 4 μm were stained with hematein-eosin-saffron and with Masson trichrome, picrosirius red, and reticulin stains for the evaluation of fibrous tissues. All of the liver specimens were analyzed by an experienced pathologist (B.L.B.) blinded to the results of FibroScan and biochemical fibrosis markers. For needle biopsies, the number of fragments and the total length of the core tissue analyzed on the slide were noted; for surgical biopsies, an evaluation of the total surface was done. Liver fibrosis was evaluated by 2 systems. The METAVIR scoring system (23) consists of 5 stages according to the architectural features of the portal fibrosis: F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis and few septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis. When there was a disparity between 2 adjacent stages, scores were allocated for the more advanced stage in all children. The semiquantitative score (SQS) adapted from Chevallier et al (24) describes both the liver architecture and the quantity of fibrotic deposit in all lobular compartments (portal/periportal, perivenular, and perisinusoidal) and the number and thickness of fibrous septa. This results in a nonlinear score, ranging from 0 to 37. Steatosis was considered significant when the percentage of hepatocytes with fat deposits was higher than 30%.

Biochemical Fibrosis Markers

Serum parameters of the Fibrotest score (Biopredictive, Paris, France) were assessed according to the laboratory preanalytic and analytic recommendations (9). The Fibrotest score was computed on the Biopredictive Web site (*www.biopredictive.com*), and the usual precautions were taken to analyze the results (eg, search for inflammatory syndrome, hemolysis, Gilbert disease). Fibrosis as determined by Fibrotest was staged on a scale of 0 to 4 with respect to METAVIR fibrosis staging. For Fibrotest scores from 0 to 0.21, fibrosis was staged F0; from 0.22 to 0.31, F1; from 0.32 to 0.58, F2; from 0.59 to 0.72, F3; and from 0.73 to 1, F4. The APRI index was calculated as follows: AST (× upper limit of normal) × 100/platelet count (10^9/L) (11).

Liver Stiffness Measurement

Transient elastography relies on the fact that the speed of propagation of an elastic shear wave depends on the stiffness (or elasticity) of the medium. The harder the medium, the faster the shear wave propagates. Liver stiffness measurement consists in creating an elastic shear wave within the liver, measuring its speed of propagation and calculating the corresponding stiffness expressed in kilopascals. To do so, the probe of the FibroScan is equipped with a 3.5-MHz central frequency and a 9-mm external diameter ultrasonic transducer mounted on the axis of a vibrator. The probe is placed between the rib bones in proximity to the right lobe of the liver. The operator, assisted by a time-motion mode ultrasonic image (Fig. 1), locates a 5-cm deep portion of liver parenchyma free of large vascular structures or heterogeneities. When the measurement is triggered, the vibrator gives a painless push to the tissue, creating an elastic shear wave. While this shear wave propagates away from the probe a series of ultrasonic acquisitions is performed. By comparison of successive ultrasonic signals, local deformations of the medium caused by the propagation of the shear wave are mapped according to time and depth (Fig. 1). On the elastogram thus constructed, the diagonal black band represents the shear wave propagating deeper and deeper within the medium with time.

Measurements Reprocessing for Young Children

Once the elastogram has been obtained, the software is set to evaluate the speed of propagation of the shear wave (and the stiffness) from 2.5 to 6.5 cm below the skin surface. This relies on the assumption that for most adults, only liver parenchyma without liver capsule or subcutaneous tissue lies within these depths. Obviously, this assumption is not valid for young children, and the depths of measurement need to be adapted. To do so, elastograms were stored and reprocessed with the same software, but the depths of measurements were adapted. In children from 0 to 7 years old, liver stiffness measurement was assessed from 2.5 to 5.5 cm below the skin surface. These depths of measurements were chosen to both maximize the depth of measurement and remain within the liver parenchyma as shown by the time-motion mode images provided by the FibroScan. In children older than 7 years, the depths of measurement were kept as for adults.

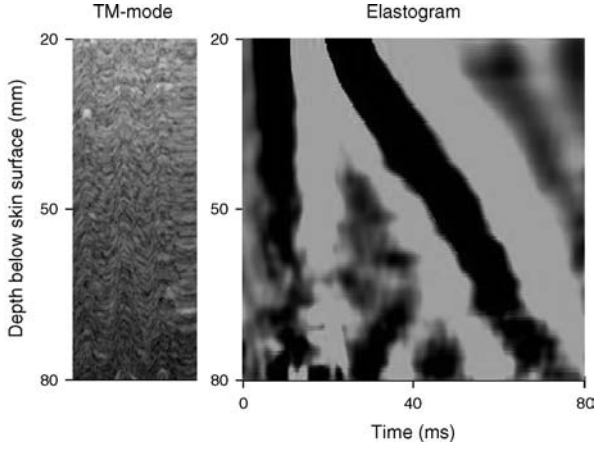

FIG. 1. Time-motion mode image and elastogram displayed on the screen of FibroScan during liver stiffness measurement.

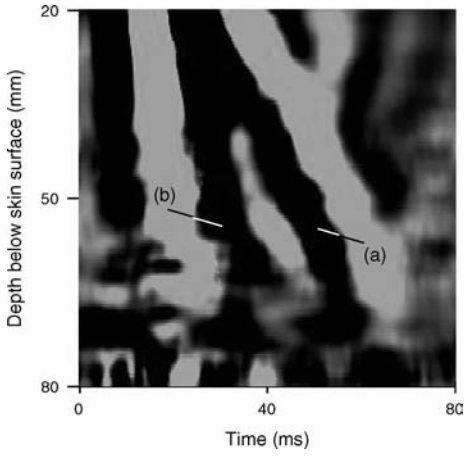

FIG. 2. Example of elastogram with 2 black bands in an A pattern. A, Slow wave; B, fast wave.

Another limitation in children is that the size of the probe must be small enough to fit between the ribs. When the intercostal space is too narrow, the 9-mm external diameter transducer gives a push to both the soft tissues and the rib bones, creating several waves and leading to a specific pattern on the elastogram with 2 diagonal black bands in the shape of an A (Fig. 2) instead of 1. The slower band corresponds to the wave propagating into the liver parenchyma and the faster to the interferences. With this kind of elastogram, the software is unable to recognize the correct wave and alternatively chooses one or the other, which leads to an overestimation of the stiffness. To avoid this bias, incorrect measurements were manually rejected and labeled as invalid. The final liver stiffness result was the median value of the 5 to 10 first valid measurements, depending on the number of valid measurements that had been obtained on each patient.

Statistical Analysis

Results are expressed as mean $\pm$ SD, and significance was set at $P < 0.05$ for all tests. The data did not exhibit normal distribution. Therefore, comparisons of quantitative data were made by use of the nonparametric Kolmogorov-Smirnov test. Qualitative data were compared by use of the χ^2 test. The relationship between noninvasive fibrosis markers and biological or clinical parameters was assessed by the Spearman correlation for quantitative variables and by the Kolmogorov-Smirnov test for binary parameters. Correlations between the histological fibrosis (METAVIR stage or SQS) and esophageal varices sizes versus noninvasive methods were assessed by the Kendall τ_b coefficient. The diagnosis performance of FibroScan and the biochemical markers to detect cirrhosis (METAVIR stages F0 through F3 vs stage F4) was assessed by the receiver operating characteristics (ROC) curve. An assessment of positive or negative was made according to whether the noninvasive marker value was greater than, less than, or equal to a

given cutoff value. Connected with any cutoff value is the probability of a true positive (sensitivity) and the probability of a true negative (specificity). The ROC curve is a plot of sensitivity versus 1 specificity for all possible cutoff values. The most commonly used index of accuracy is the AUROC curve: values go from 0 to 1.0, close to 1.0 indicating maximal diagnostic accuracy, and values above 0.75 having clinical interest. All of the data management and statistical calculations were performed with NCSS 2004 software (Statistical Systems, Kaysville, UT).

RESULTS

Patients

From February 2004 through October 2005, 116 patients were included. Only 1 patient was excluded because fewer than 5 valid measurements had been obtained. Thus, 115 patients were analyzed. The characteristics of the children are summarized in Table 1 (first column). There were 58 boys (50.4%) and 57 girls (49.6%) from 2 months to 20 years in age (mean 10.7 ± 5.6 years). The main chronic liver diseases were cystic fibrosis (n = 42), viral infection (HBV or HCV, n = 22), biliary atresia (n = 13), Wilson disease (n = 9), autoimmune hepatitis (n = 7), congenital hepatic fibrosis (n = 4), and other (n = 18). An endoscopy was performed on 25 children, and 11 children had esophageal varices.

Liver stiffness measurement was possible in all children, even in the 3 children with a body mass index (BMI) above the 97th percentile. The mean number of valid liver stiffness measurements per patient was 9.9 ± 0.6 (range 6–10). The success rate (number of valid measurements over total number of measurements) was $89.5\% \pm 14.9\%$ (range 15%–100%). The median interquartile range (IQR) was 1.1, and median IQR/median of liver stiffness measurement was 23%. Very young children always had hepatomegaly and in this case the liver stiffness measurement was evaluated subcostally. The results of the noninvasive methods to assess fibrosis are presented in Table 1.

Relationship With Biological and Clinical Parameters

The Spearman correlation coefficients of liver stiffness measurements using FibroScan, Fibrotest value, and APRI score with biological and clinical parameters are presented in Table 2. None of the noninvasive fibrosis markers studied was significantly different between boys and girls. The FibroScan, Fibrotest, and APRI values were significantly higher in children with splenomegaly ($P < 0.001$ for each) and hepatic dysmorphy ($P < 0.001$, $P = 0.02$, and $P = 0.002$, respectively). Only FibroScan and Fibrotest values were significantly higher in children with esophageal varices ($P < 0.001$ and $P = 0.01$, respectively). Liver stiffness was the noninvasive marker that correlated most with the numerous biological and

TABLE 1. *Characteristics of 115 patients in the study*

	All children (N = 115)	Children without biopsy (n = 82)	Children with biopsy (n = 33)	P^*
Mean age, y	10.7 ± 5.6	11.1 ± 5.0	9.5 ± 6.8	0.03
Boys/girls	58/57	42/40	15/17	NS
Mean weight, kg	35.7 ± 19.4	36.1 ± 17.3	34.7 ± 24.4	NS
Height, m	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.4	NS
Median BMI percentile (range)	44.68 (3–98)	42.62 (3–98)	50.29 (3–98)	NS
Median AST, IU/L	40	34	103	<0.001
Median alalanine aminotransferase, IU/L	43	31	124	<0.001
Median alkaline phosphatases, IU/L	247	252	220	NS
Median total bilirubin, μmol/L	10	9	19	<0.001
Median γ-glutamyl-transpeptidase, IU/L	21	18	93	<0.001
Platelet count, $10^3/mm^3$	268 ± 120	278 ± 113	244 ± 135	0.013
Prothrombin time, %	89.2 ± 10.5	88.8 ± 8.9	90.1 ± 13.8	0.01
Serum albumin, g/L	40.2 ± 5.2	41.0 ± 5.5	38.4 ± 3.8	NS
Cystic fibrosis, n	42	42	0	
Viral hepatitis B or C, n	22	20	2	
Biliary atresia, n	13	4	9	
Autoimmune hepatitis, n	7	2	5	
Wilson disease, n	9	6	3	
Congenital hepatic fibrosis, n	4	2	2	
Others, n	18	6	12	
FibroScan, kPa	9.5 ± 11.5	6.1 ± 5.5	18.0 ± 17.1	<0.001
Fibrotest	0.33 ± 0.26	0.26 ± 0.21	0.50 ± 0.30	0.002
APRI	1.24 ± 3.04	0.72 ± 1.49	2.60 ± 5.06	<0.001

NS = not significant.
* Patient with liver biopsy vs patient without liver biopsy.

TABLE 2. *Spearman correlations of FibroScan, Fibrotest, and APRI values vs biological and clinical parameters*

r (*P*)	FibroScan	Fibrotest	APRI
Age	NS	NS	−0.22 ($P = 0.02$)
Height	NS	NS	NS
Weight	NS	NS	NS
Platelet count	−0.44 (<0.001)	−0.31 (0.003)	−0.61 (<0.001)
Prothrombin time	NS	NS	NS
Albumin	−0.34 (0.003)	NS	−0.24 (0.04)
Total bilirubin	0.34 (<0.001)	—	0.43 (<0.001)
Alkaline phosphatases	0.25 (0.05)	0.47 (<0.001)	0.36 (<0.001)
γ-Glutamyl-transpeptidase	0.65 (<0.001)	—	0.66 (<0.001)
Aspartate aminotransferase	0.51 (<0.001)	0.51 (<0.001)	—
Alanine aminotransferase	0.50 (<0.001)	0.49 (<0.001)	0.79 (<0.001)

NS = not significant.

clinical parameters, and none of them was significantly related to sex, height, weight, or prothrombin time.

Histology and Diagnosis of Cirrhosis

Thirty-three patients (28%) underwent liver biopsy. No patient was excluded because of unsuccessful interpretation of the liver biopsy specimen. The main causes of liver disease in children who underwent liver biopsy were biliary atresia (n = 9), autoimmune hepatitis (n = 5), Wilson disease (n = 3), chronic hepatitis B (n = 2), and congenital fibrosis (n = 2).

The median length of the 24 liver needle biopsies was 17 mm (range 10–35 mm). The mean surface analyzed in the 8 surgical biopsy specimens was 111 mm^2 (range 63–185 mm^2), and depth under the capsule was 5.7 mm (4–7 mm). Thirteen biopsies were <15 mm but all had more than 4 portal tracts.

The characteristics of patients who did or did not undergo liver biopsy are indicated and compared in Table 1 (second and third columns). All children who underwent liver biopsy had higher values of noninvasive fibrosis markers than did children who did not undergo biopsy, and the distribution of causes differed between both groups. In the 33 patients who underwent liver biopsy, distribution according to the METAVIR fibrosis stage was as follows: F1 in 7 cases (21%), F2 in 8 cases (24%), F3 in 6 cases (18%), and F4 in 12 cases (36%). No patient had F0 fibrosis. The SQS ranged from 1 to 23 (median = 10), with 11 cases having a score above 15. No patient had significant steatosis.

The distributions of FibroScan, Fibrotest, and APRI values according to METAVIR fibrosis stages are shown by box plots in Figure 3, and the corresponding median values are presented in Table 3. FibroScan values significantly correlated with METAVIR fibrosis stages ($\tau_b = 0.53$; $P < 0.001$) and SQS ($\tau_b = 0.49$; $P < 0.001$). Fibrotest values also correlated with fibrosis according to both scoring systems: $\tau_b = 0.34$ ($P = 0.02$) for METAVIR fibrosis stages and $\tau_b = 0.38$ ($P = 0.005$) for SQS. APRI values correlated significantly with METAVIR stages ($\tau_b = 0.32$; $P = 0.03$) but not with SQS ($\tau_b = 0.24$; $P = 0.08$).

Figure 4 shows the diagnostic value (ROC curves) of FibroScan, Fibrotest, and APRI for the diagnosis of cirrhosis. The corresponding AUROC curves (95% CI) were 0.88 (0.68–0.95), 0.73 (0.47–0.87), and 0.73 (0.49–0.87), respectively.

DISCUSSION

Liver stiffness measurement has been shown to be closely related to liver fibrosis in patients with chronic liver diseases, but its use so far has been evaluated only in patients older than 18 years (13–21). This study presents the first results, as far as we are aware, of the use of FibroScan in children from 2 months to 20 years.

The first aim of this work was to evaluate the feasibility of liver stiffness measurement in children using the FibroScan. The results suggest that the method can be applied to children but that the probe size and depths of measurement are not adapted to the structure of small children. The use of FibroScan with its standard probe on small children requires reprocessing of all data to adapt measurement depth and to exclude elastograms presenting double wave propagation (A-shape waves). Indeed, without these precautions, FibroScan may give a final result with enough valid measurements, but the values could be biased and lead to wrong evaluation of liver stiffness and therefore of liver fibrosis.

Once measurements are reprocessed, liver stiffness measurements can be obtained in almost all of the patients with chronic liver diseases and no ascites. Of the 116 patients included in this study, only 1 patient was excluded because only 4 valid measurements were obtained. This patient was a 5.9-year-old girl with biliary atresia and a BMI of 15 kg/m^2, which is normal for this age. In the 115 remaining patients, liver stiffness measurements were performed, and the main difficulty was their relative restlessness compared with adults, especially in children 1 to 3 years old. As with adults, liver stiffness measurements with the FibroScan remain

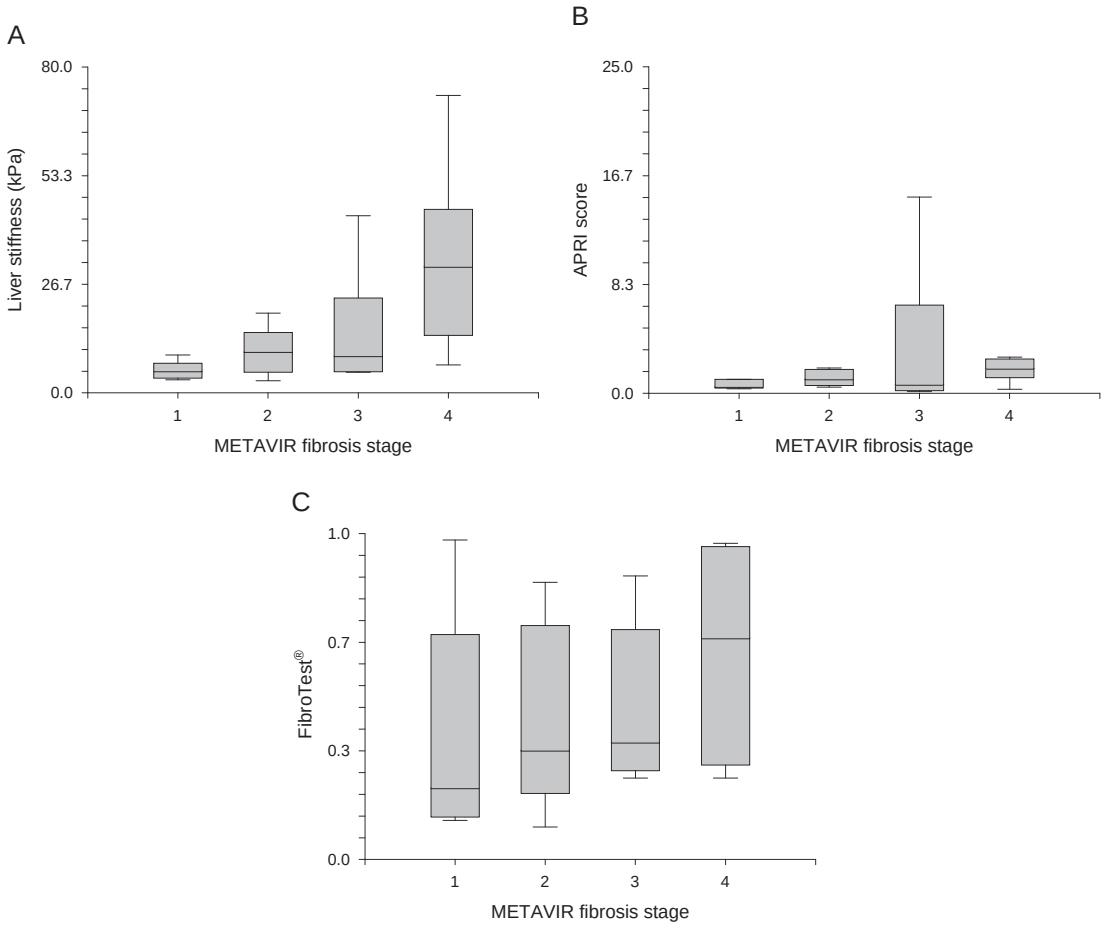

FIG. 3. Box plots of FibroScan (A), Fibrotest (B), and APRI (C) values for each fibrosis stage. Top and bottom of boxes are first and second quartiles, respectively. Length of box thus represents the IQR within which 50% of the values are located. Line through the middle of each box represents the median. Error bars show minimum and maximum values (range).

impossible in children with ascites because elastic shear waves do not propagate through liquid. Obesity can also cause difficulties in measuring liver stiffness. Three children were obese (BMI >97th percentile), but liver stiffness values were obtained easily.

The second aim of this study was to evaluate the relationship between liver stiffness measurements obtained in children and their biological, clinical, and histological parameters and to compare its accuracy with those of 2 blood markers of liver fibrosis. Fibrotest was

TABLE 3. *Median values of noninvasive tests for different stages of fibrosis as defined by METAVIR score in the 33 children with biopsy*

	F1 (n = 7)	F2 (n = 8)	F3 (n = 6)	F4 (n = 12)
FibroScan, kPa	5.4	10.2	9.1	31.1
Fibrotest	0.22	0.34	0.36	0.68
APRI	0.52	1.10	0.69	1.92

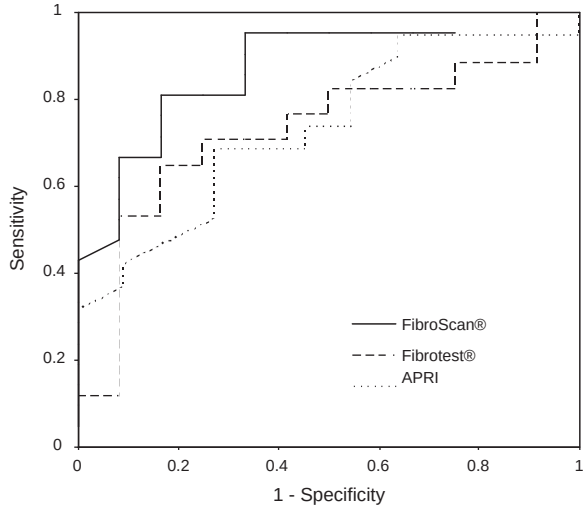

FIG. 4. ROC curves for FibroScan, Fibrotest, and APRI, for diagnosis of cirrhosis (METAVIR F1-2-3 vs F4).

chosen because it is one of the most validated biochemical scores of fibrosis and APRI because it is a simple and free test based on the standard blood parameters included in standard biological liver assessment (9,11). However, to our knowledge, none of these tests had been evaluated in children so far. In the comparison of FibroScan, Fibrotest, and APRI with clinical and biological parameters, liver stiffness measurement was significantly related to the highest number of parameters, including platelet count, albumin, total bilirubin, alkaline phosphatases, γ-glutamyl transpeptidase, AST, alanine aminotransferase, splenomegaly and hepatic dysmorphy assessed by ultrasonography, and esophageal varices. These results are in agreement with those obtained in adults with chronic liver diseases of various causes (19) and suggest that liver stiffness measurements in children are also related to biological parameters and the occurrence of complications of cirrhosis.

We also compared FibroScan, Fibrotest, and APRI with liver fibrosis assessed from liver biopsy specimens. There is no consensus on a histological scoring system of fibrosis adapted to the various types of liver pathological conditions found in children. The METAVIR score was chosen here because it is widely accepted and used; however, it is a category score based on architectural modifications, which evaluates mostly portal/periportal fibrosis in a nonquantitative way. This score has been validated for hepatitis C infection, and it seems reasonable to use it also for HBV hepatitis and autoimmune hepatitis, wherein the progressive deposition of fibrosis follows a similar distribution from the portal/periportal area. Its adequacy in the evaluation of precirrhotic stages in other pathological conditions, where perivenular and perisinusoidal fibrosis are prominent, can be questioned. For this reason, we also applied a semiquantitative score developed by Chevallier et al (24) that can be applied to any type of chronic liver disease and that takes into account the quantity of fibrous deposits in all of the compartments of the liver. This system has been shown to give good reproducibility and is a good alternative to morphometric analysis of collagen surface, because it correlates well with the morphometric values (24), which, in turn, correlate well with biochemical quantitative determination of hydroxyproline hepatic content (25). The topography of fibrosis deposit is different in children with viral hepatitis or autoimmune disease from that in children with cystic fibrosis or biliary atresia. Indeed, children with viral hepatitis or autoimmune hepatitis have quite homogenous fibrosis across the liver, whereas children with cystic fibrosis or biliary atresia have heterogenous fibrosis. Therefore, there is a need for other studies of FibroScan performance in children according to each cause of disease.

The first part of this analysis was the relation between the noninvasive markers of fibrosis and the histological fibrosis scores. FibroScan, Fibrotest, and APRI were significantly correlated to both fibrosis scores. However, the Kendall τ_b correlation coefficients suggest that liver stiffness measurement was the noninvasive fibrosis marker most closely related to histological fibrosis scores (τ_b from 0.49 to 0.53 for FibroScan and from 0.24 to 0.38 for Fibrotest and APRI). The second part of this analysis was to evaluate the diagnosis accuracy of the 3 noninvasive fibrosis markers for the detection of cirrhosis. In adult studies, AUROC curves were between 0.79 and 0.88 for $F \geq 2$ and between 0.95 and 0.97 for $F = 4$ (13,14,17), indicating a good performance of the test. In our study, owing to the small number of children, only the ROC curve for the diagnosis of cirrhosis was evaluated. As in adult patients, the performance of FibroScan for the diagnosis of cirrhosis was good (0.88), and it was better than the other noninvasive tests tested.

Noninvasive fibrosis markers have been developed recently that use a combination of different biochemical parameters (9–11); however, none of these noninvasive methods have been assessed in children, to our knowledge. In our population of children with various liver diseases, including cholestatic disorders, Fibrotest and APRI values had lower AUROC curves for the diagnosis of cirrhosis and smaller coefficients of correlation with morphological parameters of cirrhosis (ultrasound splenomegaly, ultrasound hepatic dysmorphy, size of esophageal varices). Inasmuch as these biochemical tests include parameters such as bilirubin, AST, or γ-glutamyl transpeptidase, which are increased because of cholestasis itself or liver disease, their use for the diagnosis of cirrhosis and its complications is limited.

In conclusion, these results indicate that liver stiffness measurement is feasible in children (even small children) and is related to liver fibrosis as well as clinical and biological parameters. This preliminary work needs to be confirmed in a larger population but suggests that FibroScan would be able to detect cirrhosis in children with chronic liver diseases of causes not studied before, such as cystic fibrosis and biliary atresia. In this work, measurement depths were adjusted according to the age of the patient; however, age may not be the most representative parameter of patient corpulence; liver size and depth below the skin surface could be other parameters. Moreover, to avoid the propagation of the A-shape wave, the size of the tip of the probe should be reduced. A specific probe dedicated to children and slender patients has been developed and is under evaluation. FibroScan equipped with this specific probe could become a useful tool for the management of chronic liver diseases in pediatric patients.

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