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ORIGINAL ARTICLE

Bidimensional shear-wave elastography for assessing liver fibrosis in children: a proposal of reference values that correlate with the histopathological Knodell–Ishak score

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Abstract

Background A limited number of publications correlate bidimensional shear-wave elastography (2-D SWE) and stages of liver fibrosis in children.

Objective To correlate liver elastography values using 2-D SWE and liver biopsy classified by Knodell–Ishak score to evaluate fibrosis in pediatric patients with liver disease, and to propose values of 2-D SWE (kPa) correlating with Knodell–Ishak score, which have not been defined in the literature.

Materials and methods We conducted a prospective cross-sectional observational study on the performance of diagnostic tests. Between June 2016 and June 2018, elastography was performed in 213 children and young adults who had undergone liver biopsy. B mode, Doppler and 2-D SWE were performed using an Aixplorer (SuperSonic Imagine, Aix-en-Provence, France). Histology samples were classified using the Knodell–Ishak score. We evaluated performance by assessing sensitivity, specificity, positive predictive value and negative predictive value. To determine cut-off points for the continuous variables, we used receiver operating characteristic (ROC) curves. All the cutoff values we established apply only to the SuperSonic Aixplorer system.

Results Measurement with 2-D SWE was successful, with a good correlation with fibrosis stage. The area under the curve (AUC) to differentiate between early (Stages 1–2) and moderate (Stages 3–4) fibrosis was 0.91 (95% confidence interval [CI]: 0.87–0.96), with a sensitivity of 92% and specificity of 86%, with a cutoff value 12 kPa (2 m/s). The AUC of severe fibrosis (early stages of cirrhosis; Stage 5) was 0.95 (95% CI: 0.92–0.97), with a sensitivity of 94% and specificity of 90%, with a cutoff value 18.5 kPa (2.48 m/s). In two patients with hematopoietic stem cell transplantation and suspicion of graft versus host disease we found high 2-D SWE values in correlation with the fibrosis stages (Stage 0 with a median of 13 kPa [2.08 m/s] with hemosiderosis Grade 2 in one child and Stage 2 with a median of 46 kPa [3.91 m/s] and hemosiderosis Grade 4 in the other).

Conclusion Our study shows the usefulness and accuracy of 2-D SWE for detecting liver fibrosis in pediatric patients. We propose reference values for Knodell–Ishak Stages 1 and 5. We found hemosiderosis as a possible confounding factor that hasn't been described with 2-D SWE.

Keywords Children · Fibrosis · Knodell–Ishak score · Liver · Shear-wave elastography · Ultrasound

Introduction

Liver fibrosis is a progressive process resulting from liver damage mainly caused by chronic liver disease. In pediatric patients, liver disease comprises a variety of entities, including infections such as Hepatitis B and C, metabolic disorders, congenital diseases such as biliary atresia, and immune diseases such as autoimmune hepatitis. These entities cause liver fibrosis that can evolve to cirrhosis, portal hypertension, liver failure and need for organ transplantation, or in some cases development of hepatocarcinoma [1]. Early diagnosis of the

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stage of fibrosis is useful to establish different therapeutic strategies, which can improve the prognosis depending on the etiology of the disease; for example, significant regression of fibrosis in pediatric patients with autoimmune hepatitis can result with adequate treatment [2, 3].

Different imaging methods, including ultrasonography (US), MRI and CT scan can identify morphological changes caused by advanced fibrosis or cirrhosis. These techniques, particularly MRI and US, can detect some signs of fibrosis in mild and moderate degrees. However, these methods do not allow for the quantification of fibrosis progression, for which liver biopsy with histopathological study is still considered to be the gold standard in children [1, 4–6]. Staging is performed with the histopathological scoring systems METAVIR (meta-analysis of histological data in viral hepatitis) or Knodell–Ishak, the latter of which is the most adequate for pediatric disease [3, 7–9].

Liver biopsy has several limitations, such as the poor acceptance by patients and parents, the need for sedation and general anesthesia, probability of a limited sample if 10 portal spaces are not included, interobserver variability, and potential complications that can be severe, such as hemoperitoneum [10]. Altogether these factors make the repetition of the liver biopsy to monitor fibrosis not the ideal approach. Therefore, different imaging methods for the noninvasive assessment of fibrosis, which currently include the US-based shear-wave elastography [4] and MR elastography techniques, have been developed.

Magnetic resonance elastography is used in children and adults with chronic liver disease, with good results in the quantification of liver stiffness in the presence of fibrosis; however, the technique is limited by its high cost, low availability in many places, need for sedation or anesthesia in some patients, and signal loss in the setting of iron overload. However, spin-echo echoplanar imaging sequences have been developed that allow imaging in the setting of considerable iron deposition because they are less susceptible to T2* effects [11].

Shear-wave elastography is based on the property of ultrasound waves that, when traveling longitudinally, generate transversal waves that propagate perpendicular to the original wave with a velocity that is directly related to the value of elasticity of the tissue. In other words, the stiffer the tissue, the greater the velocity of the transversal waves. Currently, the following systems of ultrasonography allow for the quantitative measurement of SWE: transient elastography [12–17], acoustic radiation force impulse (ARFI) imaging with point measurement (point shear-wave elastography [p-SWE]) [18–21], and real-time two-dimensional shear-wave elastography (2-D SWE) [2, 5, 6, 22–26].

This technique has numerous advantages in children because it is a fast, accessible, portable and reproducible method that does not require sedation or anesthesia. Among the SWE techniques, 2-D SWE has additional features that make it a valuable tool in children, such as the possibility of assessing liver stiffness with color maps of quantitative tissue elasticity. The shear waves in this equipment are generated simultaneously at different levels by various acoustic pulses and the velocity of the shear waves is estimated by an ultrafast Doppler-like acquisition of 5,000 frames per second. The measurement of velocity in meters per second (m/s) is automatically converted into a stiffness value in kilopascals (kPa) through Young's modulus. These features allow for the fast acquisition of different simultaneous measures plotted on a color map including a frozen image. The advantage of the color map is that it allows for a larger region of interest (ROI) and retrospective analysis compared to p-SWE and transient elastography, making it especially suitable for use in children (Table 1, [27]).

There are few pediatric studies on the various SWE methods compared to those in adults; the number of studies using 2-D SWE is even lower than those for transient elastography and p-SWE. Studies using transient elastography or p-SWE have shown good accuracy for detecting moderate-to-severe fibrosis, while the few that were performed with 2-D SWE had a high diagnostic precision to differentiate initial as well as moderate-to-severe stages of fibrosis [2, 12, 21].

The aim of this study was to correlate the values of liver 2-D SWE on an Aixplorer system with the results of liver biopsy with histopathological study using the Knodell–Ishak scoring system, which presents certain advantages over the METAVIR scoring system (preferably used in people with chronic Hepatitis C) to evaluate fibrosis in pediatric patients with liver disease [3]. The Knodell–Ishak score establishes two stages, Stage 1, describing an initial grade of fibrosis with fibrous expansion to some portal spaces; and Stage 5, considering a grade of severe fibrosis (early stages of cirrhosis). The accuracy in determining these stages is important and has implications for the treatment because in Stage 1 the changes are often reversible and in Stage 5 progression to complete cirrhosis can be avoided with adequate treatment [3, 7, 9].

A correlation between Knodell–Ishak stage and values of liver elastography in children was previously published using transient elastography [17, 28] and ARFI p-SWE [5] but not, according to our knowledge, using 2-D SWE. The reference values with 2-D SWE in the literature are mainly based on the METAVIR histopathological scoring system [6, 23, 24]. This score considers five stages, from F0 to F4, in which F0 is a normal liver without fibrosis, F1 is portal fibrosis without septa, F2 is portal fibrosis with rare septa, F3 is numerous septa without cirrhosis, and F4 is cirrhosis. In the literature, different tables have been published comparing and converting both scores, in which Stages 1 and 2 of the Knodell–Ishak score correspond to METAVIR F1 and Stages 4 and 5 of the Knodell–Ishak score correspond to METAVIR F3 [3, 4]. Nevertheless, for two stages (1 and 5) no relation has been established using 2-D SWE, leading us to propose values for these reference parameters.

Table 1 Different methods of shear-wave elastography [27]

Method	Applied force	Advantages	Disadvantages
Transient elastography	Mechanically induced	– Use in adults for liver diseases (advanced fibrosis)	– No anatomical information – Limited by obesity, movement and ascites
Point shear wave (p-SWE)	Ultrasound induced Focused radiation force impulse at depth (ARFI)	– Incorporated into ultrasound equipment – Evaluates a focal area	– Limited by movement – No available linear transducers – No measurements are available in frozen images
Two-dimensional shear wave (2-D SWE)	Ultrasound induced Radiation force down at multiple and simultaneous levels	– Simultaneous anatomical information with the color maps of tissue elasticity – Fast acquisition of 5,000 frames per second – Measurements are available in frozen images	– Less limited by movement

ARFI acoustic radiation force impulse

Materials and methods

We conducted a prospective cross-sectional observational study of the performance of a diagnostic test. According to our hospital legislation and procedures, informed consent was not required to use routine data for observational studies. This protocol was approved by the institutional review board and the ethics committee.

Study population

We prospectively included 213 children ages 0–18 years undergoing liver biopsy for the evaluation of their underlying disease or liver failure at our hospital between May 2016 and June 2018. In all children, elastography measurements of the liver were performed.

The maximum time lapse between liver biopsy and elastography measurement was 2 months (pre or post). The measurements that were taken after biopsy were made at least 20 days after the procedure to avoid measurement errors caused by edema or hematoma. In children in whom the biopsy was immediately required, elastography was performed just prior to the procedure.

A sample size of 213 patients was considered for a prevalence of fibrosis of at least 70%, with a power of 80% and an alpha error of 5%. The rate of 70% was based on experience in our hospital, a tertiary care center, where many children with severe disease are referred. The children with a fibrosis stage of 0 according to the Knodell–Ishak score were made control patients for the purposes of this study.

Liver elastography method

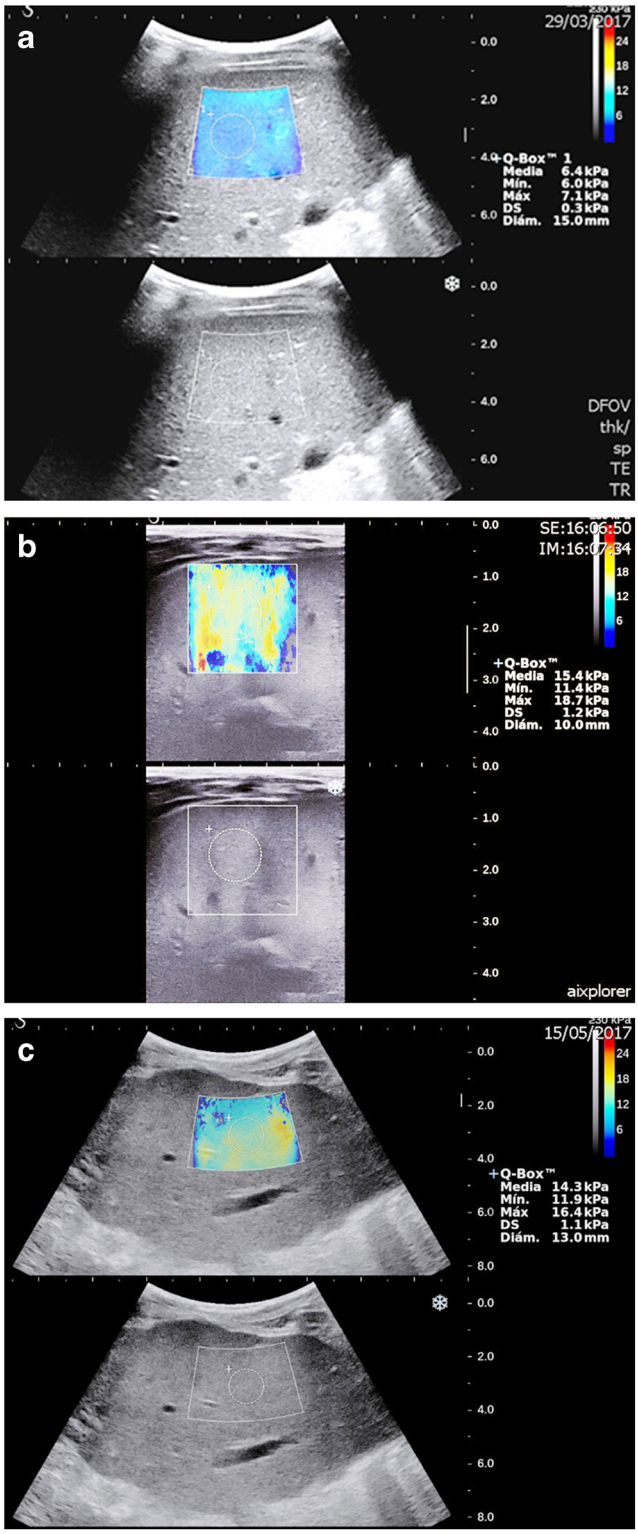
In all cases B mode and Doppler ultrasonography and 2-D SWE were performed using an Aixplorer (SuperSonic Imagine, Aix-en-Provence, France). Each SWE examination was performed by a single radiologist among these five: E.P.D., with 23 years of experience in US imaging and 4 years of experience with elastographic techniques; M.E.O., with 16 years of experience in US imaging and 3 years of experience with elastographic techniques; J.L., with 18 years of experience in US imaging and 3 years of experience with elastographic techniques; C.L., with 5 years of experience in US imaging and 2 years of experience with elastographic techniques; and S.L., with 4 years of experience in US imaging and 2 years of experience with elastographic techniques. All SWE measurements were taken before or after biopsy; sedation or anesthesia was not required.

All children were initially evaluated with a convex (SC6–1) transducer. We used the linear transducer (SL 2–10) in children younger than 1 year in whom no or weak signal was obtained in the stiffness color map with the convex transducer. We performed complete evaluation of the abdomen in liver mode B and Doppler before obtaining elastography measurements. Pre-test fasting ranged from 2 h (in neonates) to 6 h (in adolescents), depending on the age of the child.

For the elastography (SWE) study, we placed the child in the decubitus position with the right arm elevated above the head while placing the transducer on the intercostal space perpendicular to the liver surface. We took three independent measurements in the same spot in the hepatic right lobe in each child. Each consisted of a measurement of a 10- to 15-mm diameter ROI, obtained at the center of a stiffness color map with a fixed size (2×1.5 cm with an SL 2–10 transducer and 2.5×2 cm with a SC6–1 transducer) with a depth of 1–5 cm from the capsule, without including vascular structures under neutral or sustained breathing. The ROI was carefully placed in the center of the stiffness color map where the filling was complete and homogeneous, to avoid the inclusion of any artifacts related to motion or pulsation. We obtained mean, minimum and maximum elasticity values in kilopascals and standard derivation within the ROI, as well the information about the depth and diameter of the ROI. An interquartile range/median (IQR/M) less than 0.3 was considered to

validate the measurements [27, 29, 30]. An elastogram color presetting was used with a scale between 0 kPa (0 m/s; blue) and 30 kPa (3.16 m/s; red) (Fig. 1).

In liver-transplant patients with a reduced liver size or a left-lobe graft, measurements were performed in the epigastric region through the intercostal or sternocostal space.



Liver biopsy and histological analysis

All liver biopsies were ordered clinically and performed percutaneously with a 16- to 18-gauge needle in 173 patients, in an explanted liver after transplantation in 31 patients and surgically in 9 patients. Percutaneous biopsies were performed by interventional radiologists under US guidance at the same site where SWE measurements were performed, in hepatic right lobe, except for the liver-transplant patients who had a reduced liver size or a left-lobe graft; surgical and explanted liver biopsies were performed by surgeons and pathologists, respectively.

Liver biopsy specimens received at the department of pathology were fixed in a 10% formalin buffer, processed using routine methods, paraffin embedded, sliced and stained with hematoxylin-eosin (H&E). Special stains were performed according to protocol: periodic acid-Schiff (PAS), digested PAS, Masson trichrome for the evaluation of fibrosis, reticulin silver stain, and Perl's iron stain for iron pigment stores. At least five serial sections were performed with H&E and the special stains. Specimens were analyzed by a single pathologist (A.P.B., a pathologist specializing in gastrointestinal and hepatic pathology with 15 years of experience), who was blinded to SWE results. The liver biopsies were assessed according to a protocol for pathology study considering architecture, portal spaces, inflammation (location, distribution, cell types), histological activity index when applicable (Knodell–Ishak score), and fibrosis stage according to the reference grading system (Knodell–Ishak score) [7, 8], considering the stages listed in Table 2 [8].

Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Hospital Garrahan [1, 2]. For continuous variables, we used summary and dispersion

Fig. 1 Elastography color maps. **a** Two-dimensional shear-wave elastography (2-D SWE) measurements obtained with an SC6–1 transducer in an 8-year-old boy with bone marrow transplant and suspected graft-versus-host disease. Knodell–Ishak score was 0 at liver biopsy. US images show a stiffness color map (*top*) that is homogeneous, with blue areas that correspond with lower values of liver stiffness in the region of interest (*bottom*), in this case a median of 6.4 kPa (1.46 m/s), which confirms that liver elasticity is normal. **b** Two-dimensional SWE measurements obtained with an SL2–10 transducer in a 1-month-old boy with biliary atresia and a Knodell–Ishak score of 4 at liver biopsy. US images show a stiffness color map (*top*) that is heterogeneous, with yellow areas that correspond with high values of liver stiffness in the region of interest (*bottom*), in this case a median of 15.4 kPa (2.26 m/s). **c** Two-dimensional SWE measurements obtained with an SC6–1 transducer in a 12-year-old girl with liver transplant, left-lobe graft and chronic rejection with a Knodell–Ishak score of 3 at liver biopsy. US images show a stiffness color map (*top*) that is heterogeneous, with yellow areas that correspond with high values of liver stiffness in the region of interest (*bottom*), in this case a median of 14.3 kPa (2.18 m/s). Measurements were performed in the epigastric region through the sternocostal space

Table 2 Stages of fibrosis according to the Knodell–Ishak score [8]

Stage 0	No fibrosis
Stage 1	Fibrous expansion of some portal areas, with or without short fibrous septa
Stage 2	Fibrous expansion of all portal areas, with or without short fibrous septa
Stage 3	Fibrous expansion of most portal areas with occasional portal-to-portal (P–P) bridging
Stage 4	Fibrous expansion of portal areas with marked bridging, portal to portal (P–P) as well as portal to central (P–C)
Stage 5	Marked bridging (P–P or P–C) with occasional nodules (incomplete cirrhosis)
Stage 6	Cirrhosis, probable or definite

measures according to their distribution. Categorical variables were summarized as proportions or percentages. Measurements of performance were evaluated assessing sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). To determine cut-off points for the continuous variables, we used receiver-operating characteristic (ROC) curves.

Results

Patients

Between May 2016 and June 2018, we prospectively enrolled 213 children and young adults in the study. Of these, 128 were female (60%). Mean age was 6.9 years (range: 2.0 months to 18.4 years). The mean body mass index for the population included in the analysis was 16.8 kg/m^2 (range: 8.5–25.3 kg/m^2).

The most common indications for liver biopsy were post-liver transplantation control or suspicion of T cell-mediated acute or chronic rejection in 92/213 (43.2%), biliary atresia in 33/213 (15.5%), and autoimmune hepatitis in 26/213 (12.2%) patients; the other indication for liver biopsy are given in Fig. 2. In the liver transplant cohort, there were 52 left lateral lobe transplants, 3 split and 37 whole-organ transplants. Table 3 shows a summary of the demographic characteristics of the study population.

Evaluation of liver fibrosis using 2-D shear-wave elastography

Measurements were feasible in all the patients, showing a strong correlation with the histological fibrosis stages. Table 4 shows median values and the median of minimum and maximum values of 2-D SWE obtained for each stage of fibrosis according to the Knodell–Ishak scoring system, including and the number of patients categorized to each level of fibrosis.

In our study, diagnostic accuracy to determine any stage of fibrosis (≥ Stage 1) showed an AUC of 0.81 (95% CI: 0.73–0.9) and a cut-off value of 7.8 kPa (1.61 m/s), sensitivity of 85% and specificity of 72%. Cut-off points to differentiate stages of mild (≤ Stage 2; 9.6 kPa; 1.78 m/s) and moderate to severe (≥ Stage 3; 12 kPa; 2 m/s) fibrosis showed a strong correlation in the ROC curve analysis, with an AUC for median values of 0.91 (95% CI: 0.87–0.96) and a sensitivity of 92% and specificity of 86% (Fig. 3). Analysis of ROC curves for minimum and maximum values showed a similar sensitivity and specificity.

Differentiation between moderate stages of fibrosis and severe fibrosis (early stages of cirrhosis; Stage 5), revealed a cut-off value of 18.5 kPa (2.48 m/s) with a sensitivity of 94%, specificity of 90% and an AUC of 0.95 (95% CI: 0.92–0.97) (Fig. 4). Minimum and maximum cut-off values for Stage 5 showed a similar sensitivity, specificity and AUC. Sensitivity, specificity, AUC, PPV, NPV and optimal cut-off values for each stage of liver fibrosis according to the Knodell–Ishak score are listed in Table 5.

Discussion

Few pediatric studies have considered the correlation between different methods of elastography and liver biopsy for assessing liver fibrosis on the various SWE methods compared to studies in adults. The number of studies using 2-D SWE is even fewer than those using transient elastography and p-SWE. Those that used transient elastography or ARFI p-SWE showed good accuracy for detecting significant fibrosis (≥F2 on the METAVIR or ≥ Stage 3 on the Knodell–Ishak scale), whereas studies performed with 2-D SWE had a high diagnostic accuracy differentiating both the initial and moderate-to-severe stages of fibrosis [2, 6, 12, 21, 24, 25] (Table 6).

In the analysis of our series, the most common indications for liver biopsy were control of possible rejection in liver-transplant patients (43.1%), biliary atresia (15.6%), and control of possible autoimmune hepatitis (11.8%), similar to reports in the literature [5, 15, 22, 24].

Valid measurements of liver elasticity could be obtained in all 213 patients, with a strong correlation with the grades of fibrosis even in the initial stages, similar to other studies on the use of 2D-SWE in children [6, 24], with an AUC of 0.91 (95% CI: 0.87–0.96) in the differentiation between stages of mild fibrosis (Knodell–Ishak Stages 1–2) and moderate fibrosis (≥ Stage 3).

Among the patients included in our study, 32 were classified as Stage 0 (absence of fibrosis) and had median 2-D SWE values of 6.9 kPa (range 6.2–7.5) or 1.51 m/s (range 1.43–1.58 m/s). Those patients with a fibrosis score of 0 were deemed to be control patients for the purposes of this study.

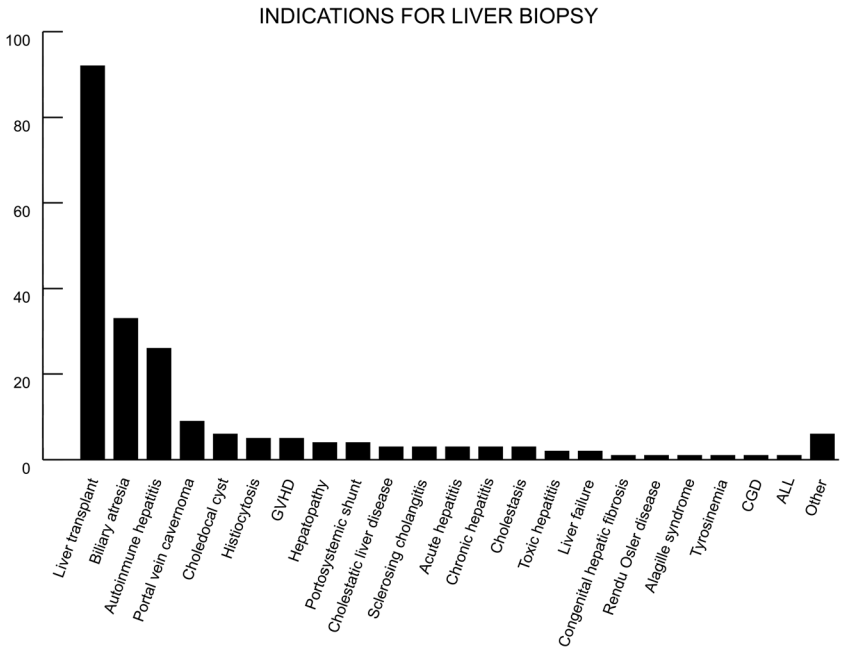


Fig. 2 Graph shows indications for liver biopsy in the study population. *ALL* acute lymphoblastic leukemia, *CGD* chronic granulomatous disease, *GVHD* graft-versus-host disease

The values were comparable to other studies performed with a similar equipment (SuperSonic) but higher than those performed with other commercial brands.

Among the reports using the same type of equipment (SuperSonic), Franchi-Abella et al. [24] found similar normal values with a mean of 5.96±1.31 kPa (1.40±0.66 m/s) for tests performed with a linear transducer and 6.94±1.42 kPa (1.51 ±0.68 m/s) for those performed with a convex transducer. These measurements were performed in a control group of 51 healthy patients without a liver biopsy. In the other group of 45 patients who had undergone a liver biopsy for different reasons, similar to our study, four patients who had a Stage 0 biopsy result had a mean of 6.3 kPa (1.44 m/s).

In another study, Tutar et al. [22] found mean values of 7.41 ±4.2 kPa (1.57±1.18 m/s) in 50 patients in the healthy control group and 9.9±6.1 kPa (3.3±1.42 m/s) in 19 patients in whom the biopsy results were Stage F0. Shin et al. [23] found values of 5.5 ±1.3 kPa (1.35±0.65 m/s) in a healthy population without biopsy.

A study conducted by Galina et al. [26] using different equipment (Logiq E9 US system; GE Healthcare, Waukesha, WI) in 202 healthy children revealed lower values with a mean of 4.29±0.59 kPa (1.19±0.44 m/s), suggesting that the reference values vary according to the equipment used. Therefore, it is necessary for studies comparing similar populations but using different types of equipment, to draw careful conclusions.

The Knodell–Ishak histopathological scoring system with seven stages, from 0 to 6 (Table 2) is a wider and more sensitive scale, and clearly separates early or developing fibrosis from established cirrhosis. Additionally, it has shown a higher sensitivity than the METAVIR scale for assessing fibrosis regression after the treatment of entities such as autoimmune hepatitis in children [3, 31]. The Knodell–Ishak score establishes two stages, Stage 1, describing an initial grade of fibrosis with fibrous expansion to some portal spaces; and Stage 5, considering a grade of severe fibrosis (early stages of

Table 3 Demographic characteristic of the study population

Characteristics	Liver transplant group	Biliary atresia group	Autoimmune hepatitis group	Others
n patients (% of 213)	92 (43.2%)	33 (15.5%)	26 (12.2%)	62 (29.1%)
Age				
≤1 y	16.3%	50%	12.6%	25%
>1 y	83.7%	50%	87.4%	75%
Gender	39.9%	53.3%	52.2%	40.0%
Male	60.1%	46.7%	47.8%	60.0%
Female				
Interquartile range/median (IQR/M)	0.3	0.25	0.29	0.28

y years

Table 4 Reference values of two-dimensional shear-wave elastography (2-D SWE) for each stage of liver fibrosis according to the Knodell–Ishak scoring system

Knodell–Ishak scale		0	1	2	3	4	5	6
2-D SWE kPa (m/s)	*n*	32	41	38	39	13	21	29
	Median	6.9 (1.5)	7.6 (1.6)	10.7 (1.9)	14.0 (2.2)	14.5 (2.2)	22.5 (2.7)	37.5 (3.5)
	Minimum	6.2 (1.4)	7.0 (1.5)	10.0 (1.8)	13.1 (2.09)	13.3 (2.1)	22.0 (2.7)	35.5 (3.4)
	Maximum	7.5 (1.6)	8.0 (1.6)	11.8 (2.0)	15.0 (2.2)	15.6 (2.3)	23.0 (2.8)	40.0 (3.7)

cirrhosis). The accuracy in determining these stages is important and has implications for treatment because in Stage 1 the changes are often reversible and in Stage 5 progression to complete cirrhosis can be avoided with adequate treatment.

Compared to the literature [24], we found in our study median values of 7.60 kPa (1.59 m/s) for Knodell–Ishak Stage 1, between the values for the Knodell–Ishak Stage 0 of 6.90 kPa (1.51 m/s) and Knodell–Ishak Stage 2 of 10.65 kPa (1.88 m/s). The median value corresponding to Knodell–Ishak Stage 5 was 22.50 kPa (2.73 m/s), between the Knodell–Ishak Stage 4 value of 14.50 kPa (2.19 m/s) and Knodell–Ishak Stage 6 value of 37.50 kPa (3.53 m/s). We found an overlap of median values for Stage 3 (14 kPa and 2.16 m/s) and Stage 4 (14.5 kPa and 2.19 m/s), which is probably related to the small difference between the stages of the histopathological classification and the small number of patients in the group with Knodell–Ishak Stage 4.

On the other hand, we identified non-fibrotic causes that might increase the values of liver elastography, i.e. confounding factors: in the group with Stage 0 we found two patients with acute liver failure who had very high median values, outside the observed range, with median values of 37.5 (3.53 m/s) and 30 kPa (3.16 m/s), respectively. In both cases, liver transplantation was indicated. Histopathology study of the explanted livers showed massive necrosis and absence of fibrosis. Congestion and edema might explain the high values on 2-D SWE measurements.

In two other patients, both of whom had hematopoietic stem cell transplantation and underwent liver biopsy because of graft versus host disease, we found Stage 0 with a median of 13 kPa (2.08 m/s), but with hemosiderosis Grade 2 in one, and Stage 2 with a median of 46 kPa (3.91 m/s) with hemosiderosis Grade 4 in the other. Iron overload has been reported as a limitation to perform MRI elastography and a cause for erroneous measurements using that method, but not as a confounding factor in the use of US elastography [4, 11]. We consider that in both cases the iron deposits led to the overestimation of fibrosis.

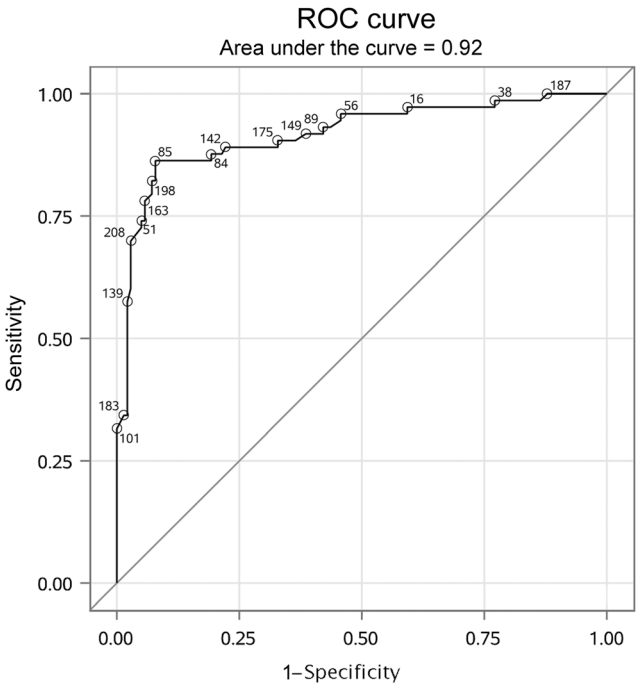


Fig. 3 Receiver operating characteristic (ROC) curve of median 2-D shear-wave elastography (SWE) values for Knodell–Ishak Stage 2. The small numbers along the ROC curve are the ID numbers of the patients

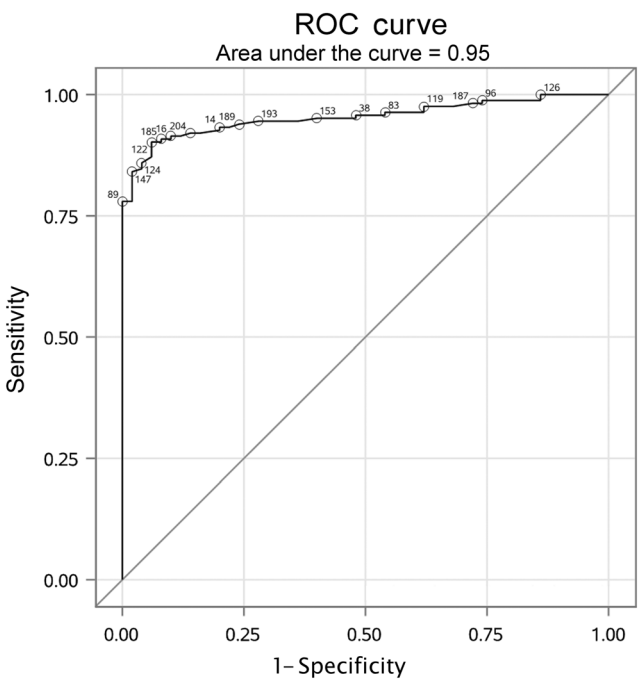


Fig. 4 Receiver operating characteristic (ROC) curve of median 2-D shear-wave elastography (SWE) values for Knodell–Ishak Stage 5. The small numbers along the ROC curve are the ID numbers of the patients

Table 5 Cutoff values in kilopascals (kPa) and meters per second (m/s) for each stage of fibrosis

Fibrosis stage	Cutoff kPa (m/s)	AUC [CI]	Sensitivity (%) [CI]	Specificity (%) [CI]	PPV (%) [CI]	NPV (%) [CI]
1	7.6 (1.59)	0.81 [0.73–0.9]	85 [79–90]	72 [55–84]	94 [88–96]	46 [36–67]
2	9.6 (1.78)	0.91 [0.87–0.96]	92 [85–96]	86 [76–92]	92 [87–96]	85 [76–93]
3	12 (2)	0.89 [0.84–0.94]	89 [82–94]	80 [72–86]	80 [72–90]	89 [81–94]
4	18.5 (2.48)	0.91 [0.86–0.95]	80 [70–89]	92 [87–96]	80 [70–90]	92 [86–96]
5	18.5 (2.48)	0.95 [0.92–0.97]	94 [84–90]	90 [85–94]	74 [64–94]	98 [94–99]
6	21.5 (2.67)	0.96 [0.94–0.98]	100 [88–100]	85 [80–90]	52 [52–NA]	10 [98–100]

AUC area under the curve, *CI* confidence interval, *NA* not applicable because CI not available (there were no subjects over the cutoff point and with Knodell–Ishak score less than 6), *NPV* negative predictive value, *PPV* positive predictive value

In the remaining groups, 2-D SWE allowed for accurate assessment of the degree of fibrosis previously classified according to histopathological stage, even in stages of mild or moderate fibrosis. This finding is essential in children because early diagnosis of the degree of fibrosis helps in the planning of different treatment strategies, to prevent disease progression, and to improve their quality of life [1, 4, 5, 20, 24].

Table 6 Correlation between elastography and liver biopsy for the assessment of fibrosis

Author	Elastography technique	*n* patients	Results
Hwang et al. (2018) [12]	Transient elastography Meta-analysis	723 children and adolescents	For significant liver fibrosis diagnosis (≥F2 METAVIR, ≥F3 Knodell–Ishak) Sensitivity 90% (CI 74–99%) Specificity 90% (CI 81–95%)
Belei at al. (2016) [2]	p-SWE vs. transient elastography vs. 2-D SWE Meta-analysis	54 children and adolescents	Sensitivity for liver fibrosis using p-SWE (METAVIR scoring system) F1 71.4% F2 77.7% F3 62.5% F4 71.4% Using 2-D SWE F1 92.9% F2 83.3% F3 87.5% F4 85.7%
Kim et al. (2017) [21]	ARFI p-SWE vs. 2-D SWE Meta-analysis	550 children and adolescents	For significant liver fibrosis diagnosis ARFI Sensitivity 74% (CI 59–85%) Specificity 85% (CI 75–93%) 2-D SWE Sensitivity 87% (CI 75–93%) Specificity 96% (CI 91–98%)
Dhyani et al. (2015) [6]	2-D SWE SuperSonic Aixplorer	24 children and adolescents	Strong correlation between SWE values and fibrosis grade (r=0.58, P=0.003) Area under the ROC curve differentiating ≥F2 fibrosis was 0.62 (95% CI: 0.26–0.98)
Franchi-Abella et al. (2016) [24]	2-D SWE SuperSonic Aixplorer	89 children and adolescents	For differentiating lower stages of fibrosis (F0–F1 METAVIR) from significant liver fibrosis (F2–F4) AUC 0.98 (CI 0.95–1.00) For differentiating no fibrosis from mild and moderate fibrosis (F1–F2 METAVIR) AUC O.93 (CI 0.87–0.99)
Garcovich et al. (2016) [25]	2-D SWE SuperSonic Aixplorer	68 children and adolescents	For differentiating any fibrosis (stage F1, Brunt score) from absence of fibrosis (stage F0) AUC 0.92 (95% CI 0.86–0.98), AUC for differentiating significant fibrosis (stage≥F2, Brunt score) from fibrosis of less than stage F2 was 0.97 (95% CI 0.95–0.99)

2-D SWE two-dimensional shear-wave elastography, *ARFI* acoustic radiation force impulse, *AUC* area under the curve, *CI* confidence interval, *METAVIR* meta-analysis of histological data in viral hepatitis, *p-SWE* point shear-wave elastography, *ROC* receiver operating characteristic

Some limitations of our study should be recognized. Many operators (five) participated in the research work, but only one per patient. We couldn't consider the interoperator variability. Further, we did not assess value differences between measurements performed with the convex transducer and those performed with the linear transducer.

Because we are a tertiary care hospital, we deal with many liver patients in our daily practice, most of whom were included in the study. The main strength of this study is its large number of patients, in all of whom a correlation with histopathological diagnosis could be made, even in those with Stage 0 fibrosis. The large sample size additionally allowed us to both propose reference values for the 2-D SWE measurements with the Aixplorer system for Knodell–Ishak Stages 1 and 5.

Conclusion

Our study shows the usefulness and accuracy of 2-D SWE on the Aixplorer system for the detection of liver fibrosis in children, even in the initial stages. We propose reference values for Knodell–Ishak Stage 1 (7.6 kPa and 1.59 m/s) and Stage 5 (22.5 kPa and 2.73 m/s). Further studies with large numbers of patients correlating 2-D SWE with this histopathology score are needed to confirm these values. In the analysis of non-fibrotic causes that can increase liver elastography values, we found hemosiderosis as a possible confounding factor that has not been previously described in the literature.

Compliance with ethical standards

Conflicts of interest None

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