

## Comparison of three ultrasound based elastographic techniques in children and adolescents with chronic diffuse liver diseases.

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### Abstract

Non-invasive techniques for liver fibrosis assessment were developed for adults and recent researches tested their accuracy in children. The only validated elastographic method for non-invasive liver fibrosis evaluation in children is Transient Elastography (TE). The aim of our study was to investigate the feasibility of liver stiffness (LS) measurement in paediatric patients with chronic liver diseases by means of Acoustic Radiation Force Impulse Elastography (ARFI) and 2D-Shear Wave Elastography (2D-SWE), compared to TE as reference method. **Material and methods:** We enrolled 54 consecutive children and adolescents with different chronic liver diseases. All patients were examined by means of TE, ARFI, and 2D-SWE. All measurements were performed in the right liver lobe, in the same session, in fasting condition. We considered reliable LS elastographic measurements as follows: for TE and ARFI – the median value of ten measurements with a success rate  $\geq 60\%$  and an interquartile range  $< 30\%$ , for 2D-SWE – the median value of five measurements. **Results:** The successful measurement rate for TE was 94.4% (51/54). Taking TE as a reference method, sensitivity of ARFI for detecting fibrosis F1 was 71.42%, for F2-77.77%, for F3-62.5% and for F4-71.42%. Sensitivity of 2D-SWE for detecting F1 was 92.85%, for F2-83.33%, for F3-87.5% and for F4-85.71%. We found significant correlations between TE and 2D-SWE on the entire lot (Kappa correlation factor=0.843,  $p=0.001$ ). Analyzing the subgroup with SR=60%-70%, we did not find significant correlation between TE and ARFI (Kappa correlation factor=0.172,  $p=0.452$ ). Assessing the subgroup with SR>70%, we found a significant correlation between TE and ARFI (Kappa correlation factor=0.761,  $p=0.001$ ). **Conclusions:** Overall, 2D-SWE correlate better with TE compared to ARFI in children. Excluding patients with less satisfactory technical parameters, we obtained significant correlations between all three methods. Both SWE and ARFI are non-invasive techniques feasible of performing on paediatric patients along with TE.

**Keywords:** children, liver stiffness, Transient Elastography, Acoustic Radiation Force Impulse Elastography, 2D-Shear Wave Elastography.

### Introduction

Fibrosis is a progressive process that appears as a consequence of liver injuries in the majority of chronic liver diseases, including chronic B and C viral hepatitis, metabolic liver diseases such as Wilson disease or hemochromatosis, billiary atresia, or nonalcoholic stea-

to-hepatitis. Early detecting of liver fibrosis can significantly improve the prognosis of paediatric patients [1]. It is recognised that liver biopsy is the gold standard for diagnosis of fibrosis, but biopsy is an invasive technique and may have a potential risk of complications such as bleeding [2]. Also, the tissue biopsy specimen can be too small to obtain reliable results [3]. Besides sampling error, there can be interobserver variation in staging [4].

Ultrasonography based elastographic methods that are expected to replace liver biopsy have recently been developed, including transient elastography (TE), acoustic radiation force impulse (ARFI), real-time tissue elastography (RTE), and two-dimensional real-time shear wave elastography (2D-SWE) [5]. 2D-SWE is the new-

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est of these methods and has the following advantages compared to TE: real-time 2D imaging, simple operation, qualitative (color coded) and quantitative measurements, expressed in meter/second (m/s) or kiloPascals (KPa) [6].

Non-invasive techniques for liver stiffness (LS) assessment were developed for adult patients, but recent research has tested their accuracy in children. Liver biopsy is not very well accepted by the parents of children with chronic hepatitis and it is difficult to use it during the follow-up in case of paediatric patients. There is a trend towards replacing liver biopsy by elastography for the evaluation of liver fibrosis among children with chronic diffuse liver diseases [7,8].

Recent meta-analyses [9,10] have reported that TE is a reliable diagnostic tool for the non-invasive evaluation of liver fibrosis in patients with chronic liver conditions and is a validated method for LS evaluation both in children and adults [11]. The advantage of TE is its non-invasiveness, which makes it possible to perform repeated liver fibrosis assessments on a large number of asymptomatic patients in a cross-sectional and serial fashion [12]. The principle of ARFI is that shearing of the examined tissue induces a strain into the tissues [13,14]. Few recent paediatric studies have set the standard ARFI elastography values for liver in healthy children [15,16] only defining normal liver ARFI values in children, without discriminating between the different degrees of liver fibrosis in paediatric patients. 2D-SWE is based on Supersonic Imaging (SSI), an ultrasound-based technique used for real-time visualization of soft tissue viscoelastic properties [6]. Due to paucity of researches on this topic in the paediatric population, no validated specific cut-off range values for ARFI and 2D-SWE have been established in order to discriminate fibrosis degree among children with different liver diseases.

The aim of this paper was to investigate the feasibility of LS measurement in children and adolescents with chronic diffuse liver diseases by means of ARFI and 2D-SWE, compared to TE as reference method. This study assessed the correlations between three elastographic methods: TE, ARFI and 2D-SWE, with respect to their practical use in paediatric patients, attempting to validate alternative elastographic techniques with similar accuracy to TE in children.

## Material and methods

### Study design

The study was conducted at the "Louis Turcanu" Emergency Hospital for Children in Timisoara and the Gastroenterology Unit of Emergency County Hospital Timisoara, Romania. The study group consisted of 54

consecutive children and adolescents admitted with different chronic liver diseases: 14 with chronic B hepatitis, 10 chronic C hepatitis, 5 autoimmune hepatitis, 19 non-alcoholic steato-hepatitis, 4 Wilson disease, 2 juvenile hemochromatosis. LS was measured for each subject using three elastographic methods in the same session: TE, ARFI and 2D-SWE.

All legal guardians/parents of patients enrolled in this study signed an informed consent form prior to inclusion. Institutional ethical approval was obtained for this work.

Inclusion criteria were: paediatric patients with chronic liver diseases aged between 6 and 18 years old, (mean age  $8.6 \pm 2.5$  years), weighing over 20 kg and with thorax perimeter  $>45$  cm. These somatic parameters were set as inclusion criteria in order to obtain reliable results by FibroScan according to the manufacture's indication for using M probe. All subjects had normal or slightly elevated aminotransferases levels. Exclusion criteria were: patients with elevated aminotransferases level ( $>3$  times upper limit of normal values), significant cholestasis, decompensated cirrhosis and focal liver lesions.

For all patients LS was measured by means of TE using a FibroScan device (EchoSens, Paris, France). For each patient 10 valid TE measurements were performed using M or XL probe according to the body mass index (BMI) and the median value was calculated. Reliable measurements were defined as: median value of 10 valid LS measurements with a success rate (SR)  $\geq 60\%$  and an interquartile range interval (IQR)  $\leq 30\%$ . SR represents the ratio of the number of successful acquisitions over the total number of acquisitions and IQR represents the difference between the 75th and 25th percentile, essentially the range of the middle 50% of the data.

ARFI was performed with a Siemens Acuson S2000 Virtual Touch ultrasound system (Siemens AG, Erlangen, Germany) with a 4CI probe. The measurements were performed at two cm under the liver capsule. Ten valid ARFI measurements were performed and the median value was calculated. Even if the manufacturer did not recommend for ARFI the use of technical parameters IQR and SR well-known in TE, based on a published paper from our group [2], we considered for ARFI those measurements with a SR  $\geq 60\%$  as reliable determinations in this study.

2D-SWE was performed with an Aixplorer<sup>TM</sup> ultrasound (SuperSonic Imagine, Aix-en-Provence, France), using a SC6-1 convex probe. The median value of 5 valid measurements was calculated. The measurement was performed 1-2 cm under the liver capsule. Results were expressed in KPa.

All measurements were performed under fasting conditions, with minimal scanning pressure applied by the operator in the right liver lobe, in supine position

Table I. The cut-off range values for fibrosis staging used in this study for each elastographic technique [11,15,17].

Fibrosis staging	TE (KPa)	ARFI (m/s)	2D-SWE (KPa)
F0	2.5-5.9	0-1.19	0-7.39
F1	6-7.19	1.2-1.39	
F2	7.2-9.59	1.4-1.59	7.4-8.69
F3	9.6-14.49	1.6-1.99	8.7-9.19
F4	>14.5	>2	>9.2

TE – Transient elastography, ARFI – Acoustic Radiation Force Impulse Elastography, 2D-SWE – 2D-Shear Wave Elastography

by intercostal approach, with the right arm in maximum abduction, in the same session. The measurements were performed by two highly skilled operators with experience in adult patients.

The cut-off range values for fibrosis staging used in this study for each elastographic technique according to the most recently published studies are shown in table I [11,15,17].

**Statistical analysis**

The statistical analysis was performed using SPSS17 software. Means and standard deviations (SD) were calculated for numerical variables with a normal distribution, whereas for variables with a non-normal distribution, medians and ranges were calculated. Qualitative variables were expressed as numbers and percentages. Kappa Statistic tests were computed in order to assess correlations between variables. Chi<sup>2</sup> test (with Yates’ correction for continuity) was used to compare proportions expressed as percentages. Ninety-five percent confidence intervals (95% CI) were calculated for each predictive test. A p-value <0.05 was considered as indicating significance for each statistic test.

**Results**

From 54 children assessed by TE using FibroScan, in 51 cases we obtained valid measurements with SR≥60% and IQR≤30%. The proportion of valid measurements by means of TE using FibroScan was 94.4% (51/54 patients). Three cases were obese children with BMI>25 kg/m<sup>2</sup> and although we used XL probe, the results were indeterminate. These cases were excluded from further analyses.

All 51 patients with valid TE measurements had also valid results when performing ARFI and 2D-SWE. For all ARFI measurements we obtained SR=100% and IQR<30%. The feasibility for 2D-SWE was 100%.

According to TE measurements, from 51 paediatric patients examined, 4 patients had no fibrosis (F0), 14 cases had F1, 18 cases had F2, 8 cases had F3 and 7 cases had cirrhosis – F4. The mean values for each elastographic technique are shown in table II.

Table II. The mean values of the elastographic technique obtained in the study group.

Technique	Mean values
TE	9.29 ±3.95 kPa, 95% CI [8.18 – 10.40]
ARFI	1.50 ± 0.40 m/s, 95% CI [1.39 – 1.62]
2D-SWE	7.76 ± 2.46 kPa, 95% CI [7.07 – 8.46]

TE – Transient elastography, ARFI – Acoustic Radiation Force Impulse Elastography, 2D-SWE – 2D-Shear Wave Elastography

Table III. The specificity and sensitivity for ARFI and 2D-SWE in staging hepatic fibrosis.

Method / Fibrosis stage	ARFI		2D-SWE	
	Sp	Sn	Sp	Sn
F1	89%	71.42%	89.18%	92.85%
F2	96.96%	77.77%	96.96%	83.33%
F3	100%	62.5%	100%	87.5%
F4	100%	71.42%	100%	85.71%

Sp – specificity, Sn – sensitivity, ARFI – Acoustic Radiation Force Impulse Elastography, 2D-SWE – 2D-Shear Wave Elastography

Table IV. Kappa correlation factor between TE/ARFI and TE/2D-SWE

Kappa factor TE/ARFI	0.683, p=0.001, 99% CI [0.000-0.001]
Kappa factor TE/2D-SWE	0.843, p=0.001, 99% CI [0.000-0.001]

TE – Transient elastography, ARFI – Acoustic Radiation Force Impulse Elastography, 2D-SWE – 2D-Shear Wave Elastography

The specificity (Sp) and sensitivity (Sn) for detecting each stage of fibrosis for both methods ARFI and 2D-SWE are detailed in table III.

The Sn for detecting F1 and F2 for 2D-SWE elastography were significantly higher than ARFI technique (p<0.05). Also, Sn of 2D-SWE for detecting severe fibrosis F3 and F4 was significantly higher than ARFI (p<0.05). The Sp of both methods ARFI and 2D-SWE were similar, increasing with the severity of fibrosis. Both techniques can discriminate between paediatric patients with mild and severe fibrosis.

Initial comparative statistical analysis included the entire lot of 51 children with valid measurements. Kappa correlation factor was computed in order to assess the concordance between TE/ARFI and TE/2D-SWE. The results are depicted in table IV.

Further, the study group was divided in two subgroups based on SR values from TE measurements. The first subgroup included 11 children with valid measurements, but less satisfactory technical parameters: SR=60%-70% and/or IQR=30%. The second subgroup consisted of 40 subjects with SR between 70% and 100%

Table V. Kappa correlation factor between TE/ARFI and TE/2D-SWE in the first and second subgroup.

1 <sup>st</sup> Subgroup (SR=60%-70% and/or IQR=30%)	Kappa factor TE/ARFI	0.172, p=0.452 99% CI [0.439 – 0.465]
	Kappa factor TE/2D-SWE	0.758, p=0.001 99% CI [0.000 – 0.001]
2 <sup>nd</sup> Subgroup (SR>70% and IQR<30%)	Kappa factor TE/ARFI	0.761, p=0.001 99% CI [0.000 – 0.001]
	Kappa factor for TE/2D-SWE	0.860, p=0.001, 99% CI [0.000 – 0.001]

TE – Transient elastography, ARFI – Acoustic Radiation Force Impulse Elastography, 2D-SWE – 2D-Shear Wave Elastography, SR – success rate, IQ – interquartile range

and IQR<30%. Advanced comparative statistical analysis was performed. Kappa Statistics was applied in order to assess the concordance between TE/ARFI and TE/2D-SWE in both subgroups (table V).

### Discussions

Most of the studies that have compared liver biopsies with different elastographic methods were performed on an adult population; there are only few studies performed on children [18]. A recent paediatric study compared TE with liver biopsies in a cohort of children with chronic C hepatitis, in order to elaborate the specific cut off values for this technique in paediatric patients [19], and another paediatric study focused on the performance of TE for evaluating liver fibrosis in infants with biliary atresia [20]. Recently, 2D-SWE accuracy was evaluated in children post liver transplantation [21]. Other studies analyzed the influence of some technical parameters on measurement reliability such as: type of probe used, place and depth of measurement [15,22]. Tutar et al [23] showed that although liver fibrosis can be assessed using 2D-SWE in children, differentiation of mild to moderate fibrosis stages (F1, F2) could not be achieved. The presence of steatosis significantly increased the mean 2D-SWE values on elastography and care should be taken when assessing children with nonalcoholic steatohepatitis [23].

Further paediatric studies should define different cut-off range values for discriminating between different fibrosis stages for each available elastographic method according to the underlying condition [24].

To our knowledge, this is the first direct comparison of TE, ARFI, and 2D-SWE among paediatric patients. Our study tried to validate alternative elastographic techniques with similar accuracy to TE in children and adolescents. The advantage of ARFI and 2D-SWE is highlighted by the fact that these ultrasound based elastographic methods are integrated in an ultrasound machine, that can be used for others examinations, such as gray scale ultrasound, Doppler, Contrast Enhanced Ul-

trasonography (CEUS) [25]. FibroScan is an expensive machine that can be used only for LS evaluation and more recent for steatosis assessment in the liver using Controlled Attenuation Parameter (CAP) [26].

Children with narrow intercostal spaces may have high failure rates when performing TE with a standard M probe. The paediatric S probes can improve reliability in this regard. A recent study [22] aimed at addressing points of consideration in the probe choice and interpretation of measured LS by comparing FibroScan S1, S2 and M probes in children with biliary atresia. The authors concluded that the S1 probe is more appropriate for use in small children, especially those with a thorax perimeter of <45 cm, but if no S probe is available, the M probe may be acceptable in children whose thorax perimeter is >45 cm [22].

Because BMI is both age-and sex-specific for children, we used the BMI-for-age percentile charts. All obese children with BMI above 95th percentile were assessed by FibroScan using XL probe. Compared with the M probe, the XL probe reduces TE failure and facilitates reliable LS measurements in obese patients [27]. There are no studies regarding the use of the XL probe in obese paediatric subjects, but according to recent studies performed on the adult population [27], we used the XL probe for obese children in this study.

Bota et al [28] published a meta-analysis on an adult population that compared the diagnostic performance of ARFI elastography and TE for the assessment of liver fibrosis using liver biopsy as the „gold standard“. The results showed that for detection of significant fibrosis (F  $\geq$ 2), the summary sensitivity was 0.74 and specificity was 0.83 for ARFI, while for TE the sensitivity was 0.78 and specificity was 0.84. For the diagnosis of cirrhosis, the summary sensitivity was 0.87 and specificity was 0.87 for ARFI elastography and respectively 0.89 and 0.87 for TE. Inability to obtain reliable measurements was higher for TE compared to ARFI [28].

Another study published by Sporea et al [29] compared three elastographic methods TE, ARFI and 2D-SWE on

332 adult patients with respect to the feasibility of their use for liver fibrosis evaluation. In this study, a significantly higher percentage of reliable measurements were obtained for ARFI than for TE and 2D-SWE (92.1% versus 72.2% ,  $p < 0.0001$  and 92.1% versus 71.3%,  $p < 0.0001$ ) [29].

It seems that among adult patients, ARFI showed a higher rate of reliable measurements compared to TE or 2D-SWE. In our study, the proportion of valid measurements by means of TE using FibroScan was 94.4% and all paediatric patients with valid TE measurements had also valid results when performing ARFI and 2D-SWE elastography, with SR of 100% for all ARFI determinations. ARFI measurements correlated significantly with TE values only in those cases with SR  $>70\%$  by FibroScan. In contrast with the adult studies cited above, 2D-SWE showed better correlation with TE measurements compared to ARFI in this paediatric population. Although valid, TE measurements with SR between 60% and 70% might be less reliable in paediatric subjects, regarding the fact that they did not correlate with ARFI, only with 2D-SWE measurements. ARFI imaging and 2D-SWE had similar accuracy with TE in the majority of adult population based studies. The main technical requirement when performing ARFI is to hold breathing for several seconds and usually the adult patients cooperate better than children. Frequent body movements and the inability for young children to perform and keep apnea could decrease the accuracy of this elastographic method, explaining why ARFI values did not correlate with TE and had a lower sensitivity for detecting severe fibrosis compared to 2D-SWE. 2D-SWE can assess LS even without apnea and through very small intercostal spaces, or from the epigastrium, making the paediatric diagnostic process easier and more manageable.

The availability of liver biopsies (the main limitation of the study) in less than half of the cases enrolled in this study has made the comparison between different elastographic methods and the gold standard assessment of liver fibrosis-liver histology not feasible. Therefore, we considered TE by FibroScan the standard reference method. Another limitation of this study was the fact that we used the M probe due to a practical issue: – the lack of a S probe. In order to avoid the use of the M probe as a bias factor, we enrolled in this study children with a mean age of 8.6 years ( $\pm 2.5$ ), weighing more than 20 kg and with thorax perimeter  $> 45$  cm.

Another limitation is related to the heterogeneous etiology of liver injuries in children and adolescents enrolled in this study. We used the cut-off range values for fibrosis staging for each elastographic technique according to the most recently published studies on an adult population, because there are no studies in children

regarding the differences of staging fibrosis in different liver conditions.

### Conclusions

2D-SWE based on SSI is a new technique designed to overcome some of the disadvantages of other elastographic techniques in children. Overall, 2D-SWE seems to correlate better with TE compared to ARFI in children and adolescents. The specificity of 2D-SWE and ARFI increases with the severity of fibrosis. Excluding patients with less satisfactory technical parameters for TE (SR=60%-70% and/or IQR=30%), we obtained significant correlations between all three elastographic techniques. Both 2D-SWE and ARFI are non-invasive techniques feasible to perform on children and adolescents along with TE by FibroScan.

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**Conflict of interest:** none

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