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Comparison of Transient Elastography, ShearWave Elastography, Magnetic Resonance Elastography and FibroTest as routine diagnostic markers for assessing liver fibrosis in children with Cystic Fibrosis

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1 **Comparison of Transient Elastography, ShearWave Elastography, Magnetic**
2 **Resonance Elastography and FibroTest as routine diagnostic markers for assessing liver**
3 **fibrosis in children with Cystic Fibrosis**

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1 Abbreviations

2 AUC: Area Under the Receiver Operating Characteristic Curve

3 APRI: AST-to-platelet Ratio Index

4 CF: Cystic Fibrosis

5 CFLD: Cystic Fibrosis Liver Disease

6 GPR: GGT-to-platelet Ratio

7 GRE: Gradient-recalled echo

8 LSM: Liver Stiffness Measurement

9 MRE: Magnetic Resonance Elastography

10 PDFF: Proton Density Fat Fraction

11 SE-EPI: Spin-echo Echo-Planar Imaging

12 SWE: ShearWave Elastography

13 TE: Transient Elastography

14 US: Ultrasound

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1 **Abstract**

2 **Background and Objective:** Reliable markers are needed for early diagnosis and follow-up of liver
3 disease in Cystic Fibrosis (CF).

4 The objective was to evaluate the diagnostic performance of Transient Elastography (TE), Real-
5 Time ShearWave Ultrasound Elastography (SWE), Magnetic Resonance Elastography (MRE) and
6 the FibroTest as markers of Cystic Fibrosis Liver Disease (CFLD).

7 **Methods:** A monocentric prospective cross-modality comparison study was proposed to all children
8 (6 to 18 years of age) attending the CF center. Based on liver ultrasound findings, participants were
9 classified into 3 groups: multinodular liver or portal hypertension (*Nodular US/PH*, advanced
10 CFLD), heterogeneous increased echogenicity (*Heterogeneous US*, CFLD) or neither
11 (*Normal/Homogeneous US*, no CFLD). The 4 tests were performed on the same day. The primary
12 outcome was the FibroTest value and liver stiffness measurements (LSM).

13 **Results:** 55 participants (mean age 12.6 ± 3.3 years; 25 girls) were included between 2015 and 2018:
14 23 in group *Nodular US/PH*, 8 in group *Heterogeneous US* and 24 in group *Normal/Homogeneous*
15 *US* (including 4 with steatosis). LSM on TE, SWE and MRE were higher in participants with CFLD
16 (groups *Nodular US/PH* and *Heterogeneous US*) compared to others (group *Normal/Homogeneous*
17 *US*) ($p < 0.01$), while FibroTest values did not differ ($p = 0.09$). The optimal cut-off values for
18 predicting CFLD on TE, SWE and MRE were 8.7 (AUC=0.83, Se=0.71, Sp=0.96), 7.8 (AUC=0.85,
19 Se=0.73, Sp=0.96) and 4.15 kPa (AUC=0.68, Se=0.73, Sp=0.64), respectively. LSM predicted the
20 occurrence of major liver-related events at 3 years. TE and SWE were highly correlated
21 (Spearman's $\rho = 0.9$) and concordant in identifying advanced CFLD (Cohen's $\kappa = 0.84$) while MRE
22 was moderately correlated and concordant with TE ($\rho = 0.41$; $\kappa = 0.36$) and SWE ($\rho = 0.5$; $\kappa = 0.50$).

23 **Conclusion:** This study demonstrated excellent diagnostic performance of TE, SWE and MRE for
24 the diagnosis of CFLD.

25 **Keywords:** Cystic Fibrosis Liver Disease; Liver Stiffness; Elastography; Children

1 **Introduction**

2 Cystic fibrosis (CF) is the most common autosomal recessive disease in the Caucasian population.
3 It is caused by pathogenic variants in the gene encoding the cystic fibrosis transmembrane
4 conductance regulator (*CFTR*), a chloride channel expressed in epithelial cells. While liver disease,
5 remarkable by its focal nature, is frequently reported during the course of CF, the progression
6 towards cirrhosis is rare (5 to 10% of cases) but unpredictable and usually occurs in childhood [1–
7 4]. Liver disease remains difficult to diagnose at an early stage.

8 European guidelines recommend annual screening for liver disease with ultrasound (US) in addition
9 to physical examination and livers tests [5]. Liver biopsy, considered as the gold standard to
10 diagnose liver diseases, remains debatable in patients with CF because of the focal distribution of
11 lesions leading to a potential risk of sampling error and underestimation of the extent of the disease,
12 and it cannot be used to follow progression of fibrosis overtime [6]. Therefore, most studies have
13 aimed to evaluate the diagnostic performance of ultrasound to identify CFLD. Williams et al
14 initially reported a scoring system based on the coarseness of the parenchyma, nodularity of the
15 liver edge and increased periportal echogenicity, which proved to be reproducible [7]. Sellers et al
16 reported the relatively high prevalence of US abnormalities, such as hyperechogenicity (29%) and
17 nodular (18%) patterns, in patients with no clinical nor biochemical signs of liver involvement. [8].
18 US patterns have been correlated with markers of fibrosis (APRI and Fib-4 scores) [7–9] and with a
19 risk of progression towards cirrhosis [10]. However, while the diagnosis of multinodular liver and
20 portal hypertension is reliable on US, normal US does not rule out extensive fibrosis [11].

21 Liver stiffness assessed by Transient Elastography (TE) or ShearWave Elastography (SWE) has
22 shown promises for the diagnosis of liver fibrosis and monitoring progression of disease severity
23 despite uncertainties regarding confounders such as venous congestion, inflammation, steatosis and
24 non-fasting state [12–17]. TE was demonstrated to be correlated with fibrosis stages in patients with
25 CF [13]. A wide range of cut-off values have been proposed to identify CFLD using TE or SWE,
26 possibly related to inconsistent definitions of CFLD and technical differences between ultrasonic

1 scanners from different manufacturers [13–16,18,19]. For instance, Lewindon et al proposed cut-off
2 values of 5.5 kPa for predicting CFLD and 8.7 kPa for advanced CFLD (F3-F4 stage) on TE. On
3 SWE, Calvopina et al proposed a cut-off value of 6.85 kPa for predicting CFLD. Magnetic
4 Resonance Elastography (MRE), a recent technique allowing full color mapping of liver stiffness,
5 has not yet been largely evaluated in CF children. Only two limited series were reported [20,21].
6 Cross-modality comparison of the different elastography techniques is still missing, although
7 essential for providing relevant guidelines and for future therapeutic studies.
8 Therefore, we aimed to evaluate the diagnostic performance of the FibroTest®, Ultrasonic pulse
9 elastometry or Transient elastography – FibroScan® –, Real-time ShearWave elastography and
10 Magnetic Resonance Elastography as markers of CFLD in children.

11

12 **Methods**

13 **Study design**

14 The main objective of this monocentric prospective study was to evaluate the diagnostic
15 performance of the 4 non-invasive tests (FibroTest, TE, SWE and MRE) as markers of CFLD in
16 children compared to US patterns as proposed by Sellers et al [8].

17 The secondary objectives were to (1) define cut-off values for predicting CFLD, (2) evaluate the
18 correlation between the 4 tests, (3) the concordance of the 4 tests in terms of predicting advanced
19 fibrosis, and (4) the diagnostic performance of the 4 tests to predict the occurrence of severe liver
20 events (liver transplantation, variceal bleeding or prophylactic band ligation of esophageal varices,
21 liver failure, ascites) at 3-year follow-up.

22 Written consent was obtained from both parents, and children above 11 years of age.

23 **Study Participants**

24 From January 2015 to January 2018, we consecutively included all children aged from 6 to 18 years
25 old attending the CF center for their annual follow-up. We excluded children with liver transplants,
26 liver disease not related to CF, peri-hepatic ascites, respiratory insufficiency (FEV1 below 30%,

1 oxygen therapy) or ongoing bronchopulmonary infection. Participants were prospectively classified
2 into 3 groups (blinded to the results of the 4 tests) based on morphological criteria of the liver US
3 performed at inclusion: group *Nodular US/PH* (i.e. advanced CLFD) included those with US signs
4 of multinodular liver (nodular contours of the liver, liver nodules [22]) suggestive of cirrhosis or
5 signs of portal hypertension (slow or reverse flow in portal vein, porto-systemic shunts,
6 splenomegaly [23] and ascites); group *Heterogeneous US* (i.e. CFLD) included the participants with
7 a heterogeneous increased liver echogenicity but without evidence of multinodular liver or portal
8 hypertension; group *Normal/Homogeneous US* (i.e. no CFLD) included the remaining participants
9 with a homogeneous increased liver echogenicity (i.e., suggesting isolated steatosis) or normal liver
10 echogenicity and echostructure.

11 Non-invasive assessment of liver fibrosis

12 All tests were performed on the same day at inclusion in fasting conditions.

13 *FibroTest®*

14 This test, largely used as a marker of fibrosis in chronic viral hepatitis [24], uses the combination
15 of 5 serum markers (GGT, total bilirubin, alpha-2-macroglobulin, apolipoprotein A1 and
16 haptoglobin) with an adjustment according to age and gender of the patient [25].

17 *TE examination*

18 Liver stiffness was assessed using FibroScan® (Echosens, Paris, France). Liver stiffness
19 measurements (LSM) were all performed by one pediatric hepatologist (M.G.) using the S (small)
20 or M (medium) probe, positioned at an intercostal space facing the right liver, according to the
21 thoracic perimeter. The median (kPa) of 10 valid measurements was computed. LSM reliability was
22 defined according to the interquartile range to the median [26].

23 *US and SWE examinations*

24 US and LSM were performed on Aixplorer® (Supersonic Imagine, Aix-en-Provence, France) by
25 one pediatric radiologist with 20 years of experience in abdominal and CF imaging (S.F.). A
26 complete evaluation of the liver through a standardized report was performed by using B-mode and

1 Doppler imaging (Table S1). Real time SWE was acquired with a low frequency abdominal convex
2 probe SC6-1 (1-6 MHz). SWE LSM were obtained during a short apnea by positioning the
3 transducer in the intercostal space (right lobe) and then in the epigastric area (left lobe). At least 5
4 measurements (ROI diameter = 14 mm) in each lobe were performed. Reliability was defined by a
5 stability index greater than 90% [27]. The median of mean values (kPa) of each lobe was computed.

6 *Magnetic resonance imaging (MRI) and MRE examination*

7 A complete-protocol MRI was performed on a 1.5T scanner (Optima MR450, General Electric
8 Healthcare, Milwaukee, USA). The standardized MRI protocol included 3D FSPGR T1-, axial Fat
9 Sat T2-, axial multi-b-value diffusion weighted-imaging, MR cholangiography, quantification of
10 liver proton density fat fraction (PDFF) using IDEAL-IQ sequence and MR Elastography with
11 gradient-recalled echo (Supplemental Material). MRE post-processing was applied to exclude
12 unreliable areas, i.e., absence of correct propagation of the shear waves. Cut-off values for grade 1,
13 2 and 3 steatosis were 4.1, 15.7 and 20.9% as previously published [28]. Eight LSM in the right
14 lobe and 4 in the left lobe (ROI surface = 1 cm²) were randomly performed on a stiffness color
15 mapping of 4 axial slices. The median of mean values (kPa) of each lobe was computed.

16 Statistical analysis

17 We intended to include 100 children, including 40 with advanced liver disease, to allow a correct
18 estimation of sensitivity and specificity. Indeed, assuming a sensitivity/specificity estimate of 85%,
19 these were supposed to be estimated with an accuracy of 10%.

20 The primary outcome was the FibroTest value and LSM by each elastography test. To assess
21 diagnostic performance and compare SWE and MRE with TE, statistical analysis was performed
22 with the right LSM. The optimal cut-off values for predicting CFLD (groups *Normal US/PH* and
23 *Heterogeneous US*) were defined using the Youden's index maximizing sensitivity and specificity.
24 The diagnostic performance of the 4 tests was assessed by the area under the receiver operating
25 characteristic curve (AUC), sensitivity, specificity with their 95% confidence interval according to
26 these cut-off values and the ones previously published: 5.55 kPa [13] and 6.8 kPa [16] for TE and

1 6.85 kPa for SWE (Supersonic Imagine) [14]. None has been published for MRE in CFLD.
2 Concordance of classification between the 4 tests were evaluated using Cohen's Kappa. Results of
3 the 4 tests were compared between groups using the Wilcoxon-Mann-Whitney test. Association
4 between 2 continuous variables was measured using the Spearman's rank correlation coefficient.
5 All statistical tests were performed on R Version 3.5.1 (Copyright© 2018 The R Foundation for
6 Statistical Computing).

7

8 **Results**

9 Population

10 Fifty-six participants were enrolled in the study. One participant was excluded a posteriori after
11 withdrawal of consent. Fifty-five participants were seen at inclusion. The study profile is shown in
12 Figure 1. Main characteristics of the study population are shown in Table 1 (CFTR variants are
13 listed in Table S2).

14 Twenty-three participants were assigned to the group *Nodular US/PH* (22 with multinodular liver at
15 US suggestive of cirrhosis; 1 with non cirrhotic portal hypertension suggestive of porto-sinusoidal
16 vascular disorder), 8 to the group *Heterogeneous US* and 24 to the group *Normal/Homogeneous US*
17 of whom 20 had no sign of liver involvement based on a normal US liver pattern and 4 had a
18 homogeneous increased liver echogenicity.

19

20 Missing data

21 No data was missing for FibroTest. TE failed to obtain valid measurements in one participant due to
22 obesity with a chest circumference greater than 90 cm. One participant didn't undergo SWE
23 because of operational issues. SWE failed to obtain reliable measurements of the left liver in 5
24 participants (stability index < 90% in 4 participants and 1 participant with atrophic left liver).
25 Reliable measurements on MRE were missing for 3 participants (technical failure due to respiratory
26 insufficiency with FEV1 = 32% in 1 participant and technical issues in 2 participants)

1

2 Diagnostic Performance of the 4 tests based on right liver stiffness measurements

3 FibroTest values did not differ between the 3 groups, therefore, no further analysis was performed
4 for this test. Median right LSM assessed by TE, SWE and MRE were significantly higher in the
5 group *Nodular US/PH* compared to the two other groups ($p<0.05$; Figure 2A). Median right LSM
6 assessed by TE and SWE were significantly higher in the group *Heterogeneous US* compared to the
7 group *Normal/Homogeneous US* ($p<0.05$) while there was no difference in LSM measured by MRE
8 ($p=0.8$). The optimal cut-off values for predicting CFLD on TE, SWE and MRE were 8.7, 7.8 and
9 4.15 kPa, respectively (Figure 2A). Diagnostic performances of TE, SWE and MRE for predicting
10 CFLD using these cut-off values are shown in Table 2. Sensitivity was similar for the 3 techniques,
11 but specificity was higher for TE and SWE compared to MRE. Diagnostic performances of TE and
12 SWE using these cut-off values demonstrated higher AUC values and specificity for predicting
13 CFLD than when using the previously published cut-off values, as shown in Table 3.

14 Regarding the 20 participants of the group *Normal/Homogeneous US*, 1 had right LSM above the
15 cut-off value of CFLD on TE, 1 on SWE and 8 on MRE. The increase in LSM, especially on MRE,
16 could be related to focal fibrosis, although not seen on US or MRI, but artifacts cannot be excluded
17 (Figure 3). Of the 4 participants with a homogeneous increased echogenicity pattern, all had diffuse
18 liver steatosis on PDFF-MRI (10, 23, 26 and 31%). Only the participant with a 31% steatosis had
19 right LSM above the cut-off value of CFLD on SWE and MRE (detailed data are provided in Table
20 S3).

21

22 Comparison between the elastography techniques

23 TE and SWE were the best correlated tests with a Spearman's ρ of 0.9 ($p<0.001$). MRE was
24 correlated to a lesser degree with TE, $\rho=0.47$ ($p<0.001$), and SWE, $\rho=0.5$ ($p<0.001$).

1 TE and SWE demonstrated high concordance ($\kappa=0.84$ – 95% CI [0.71-0.96]) in identifying
2 participants with CFLD (groups 1 and 2). However, MRE demonstrated low concordance with TE
3 ($\kappa=0.41$ – 95% CI [0.21-0.62]) and SWE ($\kappa=0.50$ – 95% CI [0.29-0.67]). Figure 4 illustrates the
4 concordance of non-invasive elastography methods respectively in a participant of the group
5 *Nodular US/PH* with cirrhosis and portal hypertension (Figure 4A), and in a participant of the group
6 *Heterogeneous US* with a heterogeneous increased echogenicity liver pattern (Figure 4B).
7 SWE and MRE median LSM in the right and left lobes were correlated with a Spearman coefficient
8 of 0.89 ($p<0.001$) and 0.77 ($p<0.001$), respectively.

9
10 Diagnostic performance of the elastography tests in predicting the occurrence of severe liver related
11 events

12 A 3-year clinical follow-up was available in 47 participants, including 22 participants in group
13 *Nodular US/PH*, 8 in group *Heterogeneous US* and 17 in group *Normal/Homogeneous US*. Among
14 participants of *group Nodular US/PH*, 8/22 (36%) presented with severe liver related events: 2
15 underwent liver transplantation for cirrhosis with portal hypertension, 2 presented with variceal
16 bleeding, 4 underwent prophylactic band ligation of esophageal varices, 1 developed liver failure
17 and 1 presented with ascites decompensation. Patients who developed liver related events at 3 years
18 had significantly higher LSM at inclusion compared to the other 13 participants ($p < 0.01$ for TE,
19 SWE and $p<0.05$ for MRE; Figure 2B). Using the Youden's index, the optimal cut-off values for
20 predicting the occurrence of severe liver related events at 3 years were 21.0, 13.1 and 4.9 kPa on
21 TE, SWE and MRE, respectively (Figure 2B).

22 Among participants of the groups *Heterogeneous US* and *Normal/Homogeneous US*, none
23 developed signs of cirrhosis or portal hypertension. US at 3-year was available in 11 of the 20
24 participants (median age, 14 years) with a normal US liver pattern at inclusion. While US was still
25 normal in 7 participants, changes occurred in 4: homogeneous increased in liver echogenicity in 1

1 and heterogeneous increased in liver echogenicity in 3, who all had LSM above the cut-off value for
2 CFLD on 1 of the 3 tests (TE, SWE or MRE) performed at inclusion (Figure 5).

3

4 **Discussion**

5 This study supports the contribution of liver stiffness as a non-invasive marker for the diagnosis of
6 CFLD in children. The three non-invasive elastography methods showed good-to-excellent
7 diagnostic performance to discriminate study participants with CFLD based on US criteria and thus,
8 reciprocally reinforce US as a reliable tool when performed by experts. TE and SWE were highly
9 correlated and concordant in identifying participants with CFLD [18] while MRE was less
10 correlated and concordant with TE and SWE. On the other hand, FibroTest did not prove
11 contributory in this population as it could not discriminate participants with advanced or non-
12 advanced CFLD from those without CFLD. Increased liver stiffness (TE, SWE and MRE) was
13 associated with the occurrence of severe liver events up to 3 years follow-up, allowing the
14 proposition of cut-off values (21.0, 13.1 and 4.9 kPa on TE, SWE and MRE, respectively), useful
15 for identifying the patients most at risk and adapting therapeutic management.

16 Diagnostic performances (AUC, sensitivity, specificity) of TE and SWE in our study population
17 using other previously published cut-off values (5.55 kPa [13], 6.8 kPa [16], 6.85 kPa [14]) for
18 predicting CFLD are consistent with those respectively reported in CF children by Lewindon et al
19 (70% sensitivity and 82% specificity) [13], Kitson et al. (76% sensitivity and 92% specificity) [16]
20 and Calvopina et al (75% sensitivity and 71% specificity) [14]. The proposed optimal cut-off values
21 for predicting CFLD on TE (8.7 kPa) and on SWE (7.8 kPa) are higher than those previously
22 published [13,14,16] but this can be explained by 1) a more selective definition of CFLD based on
23 US abnormalities while previous studies had used broader criteria including patients with abnormal
24 physical or biochemical liver tests and 2) a balance between participants with advanced CFLD and
25 without CFLD in our study. TE and SWE can be easily performed in young patients. Compared to
26 TE, SWE allows real-time liver stiffness color mapping even in the case of ascites or obesity. SWE

1 can be performed during the B-mode and Doppler ultrasound examination. Technical issues such as
2 intercostal spaces may be resolved using high-frequency linear probe [27]. However, it is important
3 to highlight that, in contrast to TE, SWE may not provide comparable LSM and therefore cut-off
4 values may vary when performed by ultrasonic scanners from different manufacturers [13–
5 16,18,19]. This limitation is overcome by following patients on the same SWE system.

6 MRE demonstrated slightly poorer diagnostic performance than TE and SWE with a greater overlap
7 of LSM and no difference in LSM between groups *Heterogeneous US* and *Normal/Homogeneous*
8 *US*. The cut-off value for predicting CFLD on MRE was found to be 4.15 kPa. The technical failure
9 rate of MRE was low (5%) and comparable to a previously reported rate of 4% in a large pediatric
10 series including 468 gradient-recalled MRE [29]. Discrepancies with TE or SWE and the poorer
11 diagnostic performance (based on US criteria) could be related to a higher sensitivity of MRE for
12 the diagnosis of focal fibrosis. Indeed, MRE is considered as the reference standard of liver stiffness
13 in adults [30], particularly for early stages of fibrosis [31], allowing a complete color mapping of
14 the liver stiffness. Nevertheless, the poorer diagnostic performance in our study could be related to
15 the MR acquisition technique, the age of the study population and the pulmonary involvement in
16 patients with CF. MRE has been conducted with gradient-recalled echo (GRE) instead of spin-echo
17 echo-planar imaging (SE-EPI). If GRE MRE and SE-EPI seem to show a strong agreement on
18 LSM, it has been well established that SE-EPI MRE has a lower technical failure rate, higher image
19 quality and allows measurements across larger areas of the liver [32–35]. GRE MRE requires
20 several apneas, whereas a single breath hold is needed with SE-EPI MRE, and this difference may
21 be even more relevant in CF children with pulmonary involvement. Finally, LSM by ROI-based
22 segmentation compared to volumetric segmentation may be another limitation in heterogeneous and
23 focal fibrosis [36]. The use of a volumetric segmentation and SE-EPI technique may be more
24 appropriate in patients with CF to overcome MRE limitations related to focal fibrosis. In addition to
25 MRE, MRI provides an exhaustive evaluation of the liver, particularly useful to discriminate
26 cirrhotic from non-cirrhotic portal hypertension [2,37].

1 This study has some limitations. Only 55 out of 100 expected participants were included (a few
2 patients could not be included due to severe respiratory involvement) and only 8 (14.5%) patients
3 were found to have a heterogeneous increased liver echogenicity at US while a much higher
4 proportion (about 40%) had advanced CFLD, due to a referral bias related to the presence on site of
5 a pediatric hepatology and liver transplantation center. The higher prevalence of advanced CFLD
6 may result in an overestimation of sensitivity of the elastography tests. A potential confounding bias
7 could be the inclusion of patients with porto-sinusoidal vascular disorder without cirrhosis in the
8 group *advanced CFLD (Nodular US/PH)*, with expected lower LSM than the threshold for cirrhosis
9 with clinically significant portal hypertension. However, in our series only one patient had portal
10 hypertension without abnormalities of liver parenchyma. Although debatable, the study gold
11 standard did not include a pathological evaluation of the liver to allow correlations of LSM with the
12 degree of fibrosis. Liver ultrasound was chosen as the gold standard for the evaluation of liver
13 disease despite intra- and inter-reader variability. To avoid inter reader variability, all US were
14 performed by a single radiologist experienced in liver and CF imaging [27] which minimized the
15 risk of misclassification. This highlights the importance of patient referrals to experienced
16 radiologists in CF liver imaging. However, we acknowledge that liver US is an imperfect gold
17 standard that may underestimate early-stage focal fibrosis. This could explain the poor diagnostic
18 performances of MRE to distinguish patients with a heterogenous liver (i.e., CFLD) from those with
19 a homogenous liver (i.e., no CFLD) on liver US. Other elastography techniques were not evaluated
20 in this study such as point-SWE (ARFI, Siemens Healthcare, Germany) that provides focal
21 measurements of liver stiffness. A limited series of 27 children with CF reported a positive
22 correlation between point-SWE and MRE [21].

23

24 This study suggests that LSM assessed by TE, SWE and MRE will prove helpful in the diagnosis of
25 liver fibrosis in children with Cystic Fibrosis and for the prediction of severe liver related events.
26 TE and SWE offer some advantages over MRE: simple to perform, available, and less costly. We

1 suggest that elastography assessment in association with multiparametric US be routinely and
2 annually performed to detect the occurrence of CFLD and monitor the progression of liver fibrosis,
3 and could be implemented in therapeutic studies, as liver stiffness is a quantitative and accurate
4 marker. Specific cases of suspected liver involvement with normal ultrasound and elastography
5 assessment or non-cirrhotic portal hypertension may benefit from MRI and MRE. Proposed cut-off
6 values for predicting CFLD and the occurrence of severe liver related events need to be confirmed
7 in a larger independent population.

8

9

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Groups		<i>Nodular US/PH</i>	<i>Heterogeneous US</i>	<i>Normal / Homogeneous US</i>	<i>p</i>
Number of participants		23	8	24	
Sex – n (%)					
<i>Girl</i>		12 (52.2)	0 (0)	13 (54.2)	
<i>Boy</i>		11 (47.8)	8 (100)	11 (45.8)	
Age (years)					
<i>Median (Q1-Q3)</i>		10.0 (9.0-13.5)	12.0 (9.3-14.5)	14.0 (10.0-16.0)	
Age at diagnosis of liver involvement (years)					
<i>Median (Q1-Q3)</i>		5.0 (3.0-8.0)	6.0 (0.5-7.5)	NA	
BMI (kg/cm ²)					
<i>Median (Q1-Q3)</i>		16.0 (15.0-18.0)	18.5 (17.0-20.0)	18.0 (16.0-19.5)	0.08
Biology	ALAT (UI/L)				
	<i>Missing data</i>	0	0	0	< 0.01
	<i>Median (Q1-Q3)</i>	37.0 (30.0-47.5)	60.5 (48.5-75.8)	30.0 (23.0-45.8)	
	GGT (UI/L)				
	<i>Missing data</i>	0	0	0	< 0.01
	<i>Median (Q1-Q3)</i>	43.0 (25.5-62.5)	34.0 (21.5-72.3)	15.0 (11.8-21.3)	
	Total bilirubin (µmol/L)				
	<i>Missing data</i>	1	0	0	0.3
	<i>Median (Q1-Q3)</i>	10.0 (8.0-12.8)	7.5 (6.8-10)	7.0 (5.8-9.3)	
Platelets (G/mm ³)					
<i>Missing data</i>	0	0	0	< 0.01	
<i>Median (Q1-Q3)</i>	172 (86.0)	258 (89.6)	260 (72.6)		
Albumin (g/L)					
<i>Missing data</i>	0	1	1	0.03	
<i>Median (Q1-Q3)</i>	41.6 (39.9-44.2)	44.0 (42.7-45.4)	44.4 (42.1-46.1)		
APRI					
<i>Missing data</i>	0	1	0	< 0.01	
<i>Median (Q1-Q3)</i>	0.63 (0.56-1.12)	0.57 (0.45-0.61)	0.36 (0.29-0.43)		
FIB-4					
<i>Missing data</i>	0	1	0	0.01	
<i>Median (Q1-Q3)</i>	0.43 (0.32-0.74)	0.41 (0.30-0.45)	0.34 (0.23-0.38)		
GPR					
<i>Missing data</i>	0	1	0	< 0.01	
<i>Median (Q1-Q3)</i>	0.31 (0.15-0.44)	0.16 (0.11-0.27)	0.05 (0.04-0.09)		
Ultrasound (n=53)	Normal liver parenchyma – n (%)	1 (4)*	0 (0)	20 (83)	
	Hyperechogenicity – n (%)	22 (96)	8 (100)	4 (17)	
	Homogeneous – n (%)	0 (0)	0 (0)	4 (17)	
	Heterogeneous – n (%)	22 (100)	8 (100)	0 (0)	
	Irregular contours – n (%)	21 (91)	0 (0)	0 (0)	
	Nodules – n (%)	19 (83)	0 (0)	0 (0)	
	Splenomegaly – n (%)	17 (74)	1 (12.5)	0 (0)	
Porto-systemic shunts – n (%)	10 (44)	0 (0)	0 (0)		
MRI-PDFF (n=49)	Steatosis – n (%)				
	<i>Missing data</i>	5	0	1	
	<i>S0 (<4.1%)</i>	7 (39)	2 (25)	5 (22)	
	<i>S1 (4.1–15.7%)</i>	9 (50)	4 (50)	14 (61)	
	<i>S2 (15.7–20.9%)</i>	2 (11)	1 (12.5)	0 (0)	
	<i>S3 (≥20.9%)</i>	0 (0)	1 (12.5)	4 (17)	0.36

Tables

Table 1 - Main Characteristics of the 55 study participants. (note: *Participant with non-cirrhotic portal hypertension; PDFF = Proton Density Fat Fraction; APRI = AST-to-platelet ratio index (AST upper limit of normal = 42 and 37 UI/L for male and female patients, respectively; FIB-4 = fibrosis-4; GPR = GGT-to-platelet ratio)

	<i>Group Nodular US/PH (n=23)</i>	<i>Group Heterogeneous US (n=8)</i>	<i>Group Normal/Homogeneous US (n=24)</i>	CF Liver Disease		
				<i>AUC (95% CI)</i>	<i>Se (%) (95% CI)</i>	<i>Sp (%) (95% CI)</i>
<i>FibroTest Missing Median [Q1-Q3]</i>	0 0.25 [0.18-0.40]	0 0.29 [0.20-0.40]	0 0.20 [0.13-0.29]	-	-	-
<i>Transient Elastography Missing Median [Q1-Q3]</i>	0 17.60 [10.65-28.80]	0 6.20 [4.90-9.85]	1 4.90 [4.33-5.43]	<i>Cut-off value = 8.7 kPa</i>		
<i>Patients with LSM > Cut-off values</i>	<i>n = 19</i>	<i>n = 3</i>	<i>n = 1</i>	0.83 (0.75-0.91)	71.0 (57.1-84.4)	95.7 (87.0-100)
<i>ShearWave Elastography Missing Median [Q1-Q3]</i>	0 12.30 [8.00-23.00]	0 7.80 [6.65-9.05]	1 5.40 [4.85-6.55]	<i>Cut-off value = 7.8 kPa</i>		
<i>Patients with LSM > Cut-off values</i>	<i>n = 19</i>	<i>n = 4</i>	<i>n = 1</i>	0.85 (0.76-0.92)	73.3 (59.1-87.0)	95.7 (87.0-100)
<i>MR Elastography Missing Median [Q1-Q3]</i>	1 5.28 [4.54-7.23]	1 4.20 [3.18-4.58]	1 3.73 [2.81-4.95]	<i>Cut-off value = 4.15 kPa</i>		
<i>Patients with LSM > Cut-off values</i>	<i>n = 17</i>	<i>n = 4</i>	<i>n = 8</i>	0.68 (0.57-0.79)	73.1 (58.6-86.7)	63.6 (45.8-81.0)

Table 2 - Diagnostic performance of FibroTest®, Transient Elastography, ShearWave Elastography and Magnetic Resonance Elastography (right liver measurements) in the diagnosis of liver fibrosis in children with cystic fibrosis. (note: AUC = Area Under the Curve; Se = Sensitivity; Sp = Specificity; LSM = Liver Stiffness Measurement)

	Cut-off values	AUC (95% CI)	Se (%) (95% CI)	Sp (%) (95% CI)
Transient Elastography	Reported in [13] 5.55 kPa	0.79 (0.69-0.89)	83.9 (73.1-93.9)	73.9 (57.1-89.5)
	Reported in [16] 6.8 kPa	0.79 (0.70-0.88)	71.0 (57.1-84.4)	87.0 (73.9-96.4)
	Present Study 8.7 kPa	0.83 (0.75-0.91)	71.0 (57.1-84.4)	95.7 (87.0-100)
ShearWave Elastography	Reported in [14] 6.85 kPa	0.83 (0.75-0.92)	76.7 (63.0-88.6)	87.0 (74.2-96.4)
	Present Study 7.8 kPa	0.85 (0.76-0.92)	73.3 (59.1-87.0)	95.7 (87.0-100)

Table 3 - Comparison of the diagnostic performances of Transient Elastography, ShearWave Elastography and Magnetic Resonance Elastography according to different cut-off values ([13,14,16]). (note: AUC = Area Under the Curve; Se = Sensitivity; Sp = Specificity)

Figures legends

Figure 1. Flow Diagram

Figure 2. Right liver stiffness median values [Q1-Q3] assessed by Transient Elastography, ShearWave Elastography and Magnetic Resonance Elastography (A) in groups *Nodular US/PH, Heterogeneous US, and Normal/Homogeneous US* and (B) according to the occurrence of severe liver events in a 3-year follow-up.

(Note: $p < 0.05$ by Wilcoxon-Mann-Whitney test. Values are expressed in kPa. Dashed lines represent the cut-off values for Cystic Fibrosis Liver Disease)

Figure 3. Areas of focal increase of liver stiffness on MR Elastography. (A) Liver ultrasound and (B) axial FS-T2 weighted MRI do not show any abnormalities of liver parenchyma. (C) MR elastography highlights focal increases in liver stiffness (ROI = 9.8 kPa – arrow). Median liver stiffness on MR elastography is increased above the threshold for advanced fibrosis (cut-off value = 4.15 kPa) unlike Transient Elastography (5.3 kPa) and ShearWave Elastography (6 kPa).

Figure 4. Concordance of the elastography tests in participants of groups *Nodular US/PH* and *Heterogeneous US*. (A) Multinodular liver with portal hypertension in a 15-year-old participant on liver ultrasound. Gastroscopy demonstrated grade III esophageal varices and portal hypertensive gastropathy. Transient Elastography, ShearWave Elastography (SWE) and Magnetic Resonance Elastography (MRE) were concordant with each other. Respective median values of right liver stiffness measurements were 51.4, 39 and 8.8 kPa. MR Elastography color mapping illustrates advanced fibrosis. (B) Liver involvement in a 15-year-old participant assigned to the *group Heterogeneous US* with a heterogeneous increased echogenicity pattern of the liver without associated signs of portal hypertension. Median liver stiffness measurement is high on SWE (8.4 kPa) in concordance with Transient Elastography (8 kPa). (F) MRE (6.35 kPa) clearly shows the heterogenous pattern of fibrosis according to the color mapping.

Figure 5. Ultrasound follow-up at 3-year in 11 participants with normal liver pattern at inclusion.

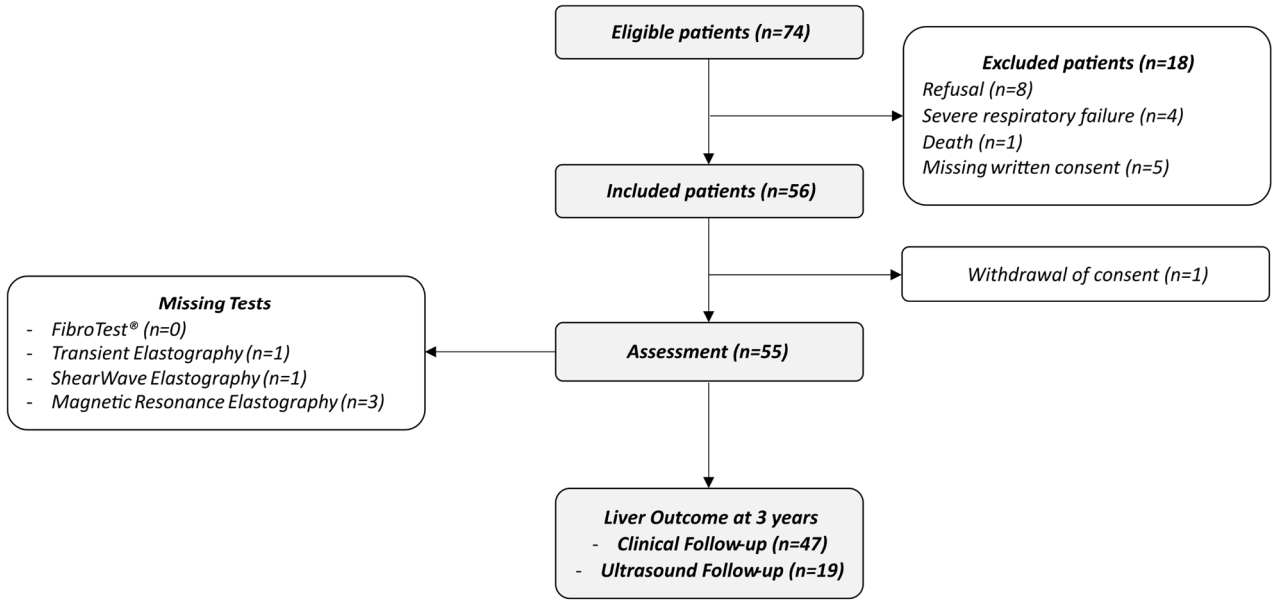


Figure 1

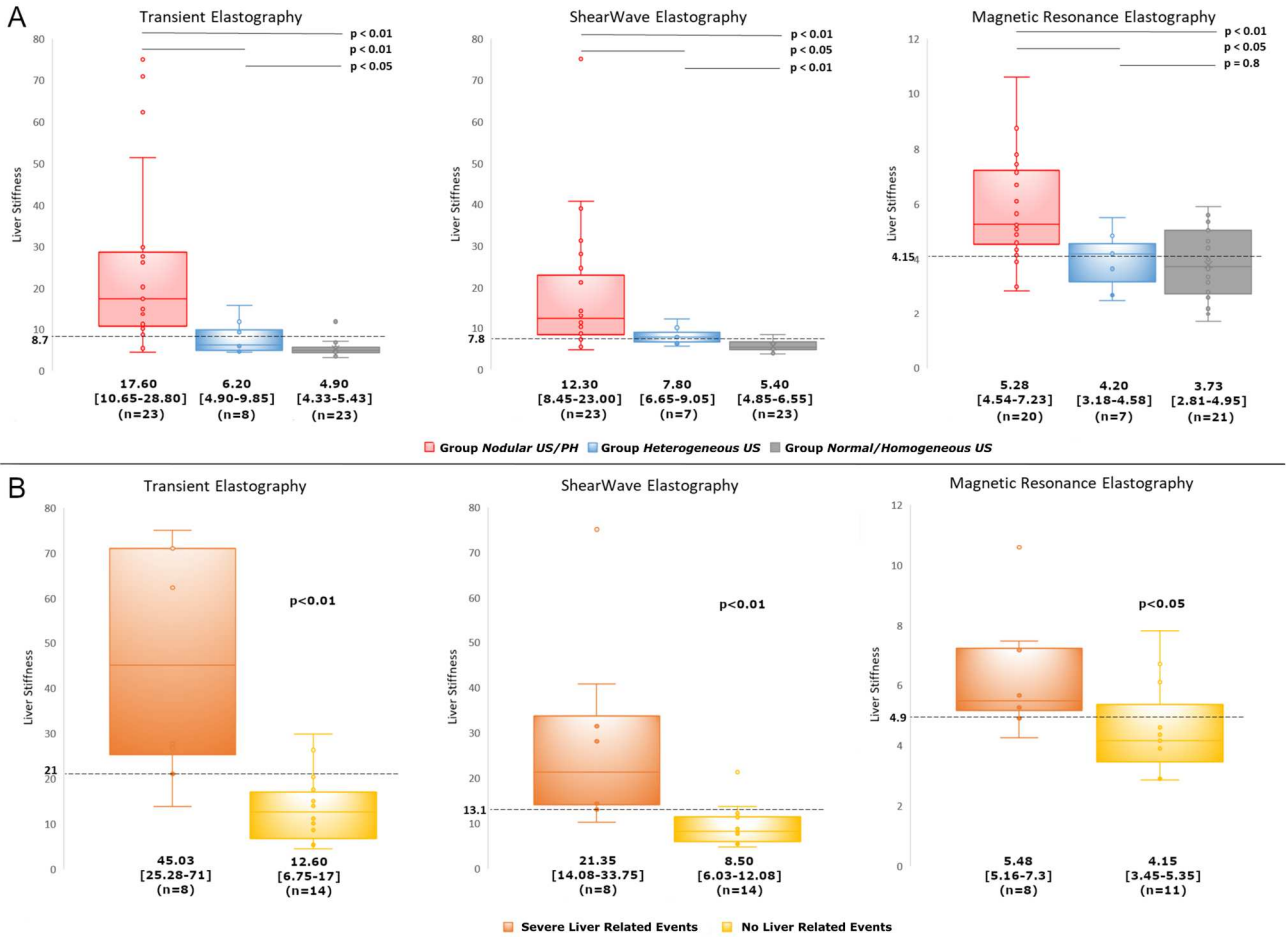


Figure 2

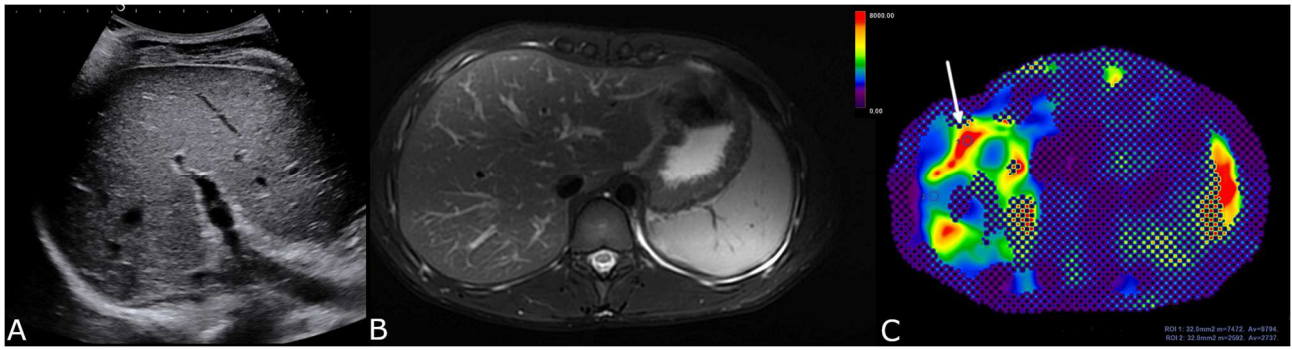


Figure 3

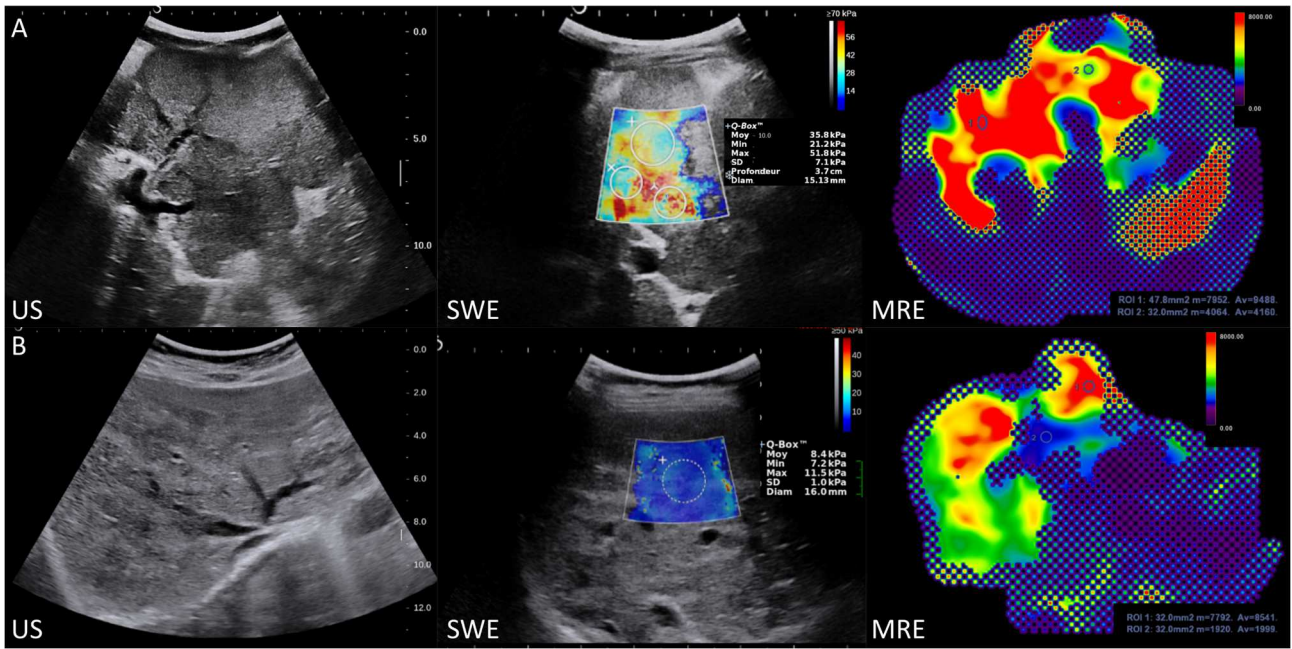


Figure 4

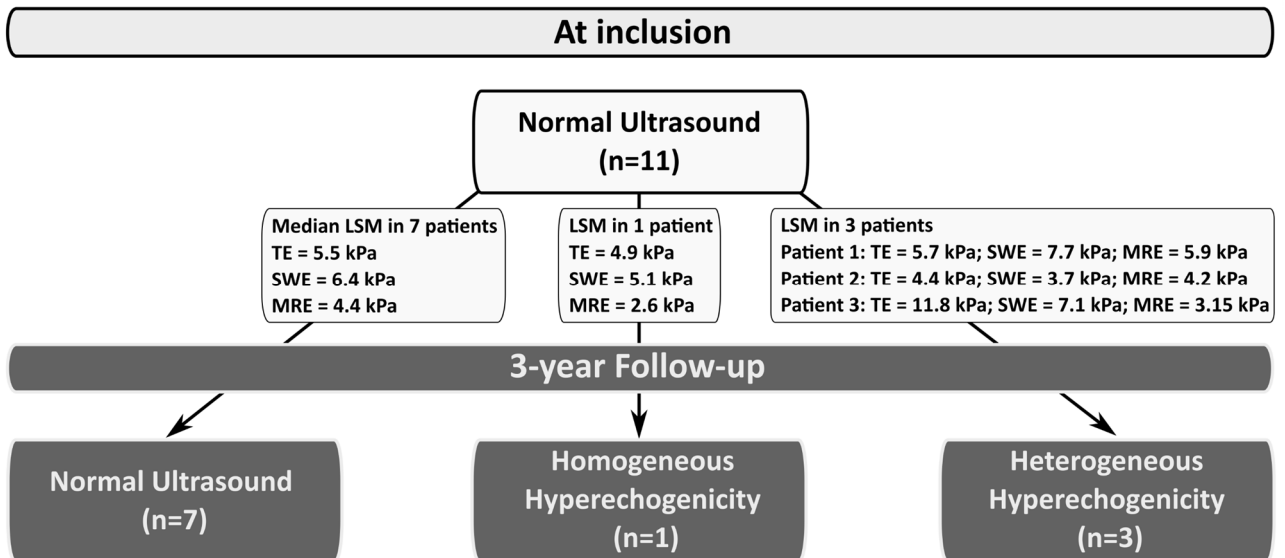


Figure 5