applied sciences

MDPI

Review

Current Knowledge in Ultrasound-Based Liver Elastography of Pediatric Patients

Christoph F. Dietrich [1,*], Roxana Sirli [2], Giovanna Ferraioli [3], Alina Popescu [2], Ioan Sporea [2], Corina Pienar [4], Christian Kunze [5], Heike Taut [6], Simone Schrading [7], Simona Bota [8], Dagmar Schreiber-Dietrich [1] and Dong Yi [9]

1 Medizinische Klinik 2, Caritas-Krankenhaus Bad Mergentheim, Uhlandstraße 7, 97980 Bad Mergentheim, Germany; dietrich.dagmar@googlemail.com
2 Department of Gastroenterology and Hepatology, "Victor Babeș" University of Medicine and Pharmacy Timișoara, 300041 Timișoara, Romania; roxanasirli@gmail.com (R.S.); alinamircea.popescu@gmail.com (A.P.); isporea@umft.ro (I.S.)
3 Ultrasound Unit, Clinical Sciences and Infectious Diseases Department, Fondazione IRCCS Policlinico San Matteo, Medical School University of Pavia, 27100 Pavia, Italy; giovanna.ferraioli@unipv.it
4 Pediatrics Department, "Victor Babeș" University of Medicine and Pharmacy Timișoara, 300041 Timișoara, Romania; pienar.corina@umft.ro
5 Klinik für Radiologie, Abteilung Kinderradiologie, Universitätsklinikum Halle (Saale), Martin-Luther-Universität Halle-Wittenberg, 06120 Halle, Germany; christian.kunze@uk-halle.de
6 Klinik und Poliklinik für Kinder-und Jugendmedizin, Universitätsklinikum Carl Gustav Carus an der Technischen Universität Dresden, 01307 Dresden, Germany; Heike.Taut@uniklinikum-dresden.de
7 Klinik für Diagnostische und Interventionelle Radiologie, University of Aachen, 52062 Aachen, Germany; sschrading@ukaachen.de
8 Department of Gastroenterology, Hepatology, Nephrology and Endocrinology, Klinikum Klagenfurt am Wörthersee, 9020 Klagenfurt am Wörthersee, Austria; bota_simona1982@yahoo.com
9 Department of ultrasound, Zhongshan Hospital, Fudan University, Shanghai 200433, China; drdaisydong@hotmail.com
* Correspondence: christoph.dietrich@ckbm.de; Tel.: +49-7931-58-2201

Received: 2 April 2018; Accepted: 28 May 2018; Published: 7 June 2018

Featured Application: In this review we present and discuss the published literature on the use of ultrasound-based liver elastography in children. The published data show that all the available shear wave elastography techniques are feasible and accurate for the assessment of liver fibrosis in children with diffuse liver disease due to several etiologies. For the assessment of focal liver lesions evidences are limited and no conclusion can be drawn so far.

Abstract: Studies performed using transient elastography (TE), point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D-SWE) have shown that these techniques are all feasible and accurate in children for the evaluation of liver fibrosis due to several etiologies. However, for some specific pediatric pathologies, such as biliary atresia, the evidence is still limited. As shown in adults, inflammation is a confounding factor when assessing fibrosis severity and care should be taken when interpreting the results. Due to the scarce comparative data between serological tests and elastography techniques in children, a definite conclusion regarding which is the best cannot be drawn. Neither non-invasive elastographic techniques nor laboratory scores allow determination of the presence and the degree of inflammation, necrosis, iron or copper deposits.

Keywords: ultrasound elastography; pediatric; liver fibrosis; stiffness; shear wave elastography (SWE)

1. Introduction

Ultrasound elastography is a useful non-invasive tool for the diagnosis of liver fibrosis in adults [1–7]. It plays a similar role in children, with some differences in the confounding factors and in the etiological spectrum of the liver disease; however, guidelines and recommendations have not been published yet. Preliminary data using transient elastography (TE), point shear wave elastography (pSWE) and two-dimensional shear wave elastography (2D-SWE) techniques, have shown that they are all feasible and accurate for the evaluation of liver fibrosis due to several etiologies in children [8–29]. Nonetheless, data on the use of ultrasound elastography in children younger than 6 years is still scarce. Assessment of liver stiffness is the most studied application in children. However, there are other applications of ultrasound elastography such as for the evaluation of the thyroid, renal parenchyma, bowel and testis.

Specific considerations relating to pediatric investigations include: (a) feasibility, related also to the differences in anatomy, anthropometrics, metabolic profile and psychology of each age group, the lack of cooperation to stop breathing, and so on; (b) the type of probe that should be used; (c) some differences in etiology and pathology in children; (d) cut-off values (are they the same of the adults?); (e) definition of preventable fibrosis in liver diseases.

2. Possible Indications for Shear Wave Elastography (SWE) Measurement

Currently, some chronic liver diseases can be cured or at least treated; however, follow up examinations are needed for almost all chronic liver disease for screening of complications that include liver cirrhosis, portal hypertension and malignant transformation. Close follow up is required post-liver transplantation, for autoimmune liver diseases, alpha-1 antitrypsin deficiency and cystic fibrosis [30,31]. Patients with biliary atresia, which is the most common cause of neonatal obstructive jaundice, would also benefit from non-invasive follow-up assessment after the Kasai portoenterostomy to determine the best timing for liver transplantation [29,32]. Regarding the indications, contraindications and the technique used, we refer to the published literature [33–41].

Non-alcoholic fatty liver disease (NAFLD) is the most common pediatric chronic liver diseases. It has been shown that elastography could be an excellent non-invasive tool for diagnosing and managing these patients [12,42].

Palliative surgery, such as the Fontan procedure for single ventricle hearts, may lead to longer survival, thus a higher rate of progressive hepatic failure and even hepatocellular carcinoma may be observed in these patients. Hence, the possibility to use a non-invasive tool to follow-up particular pediatric population is of paramount importance [43].

3. Elastographic Methods

According to international guidelines [1,2,4,6], ultrasound-based elastographic methods can be divided into shear wave elastography (SWE) and strain elastography (SE). The SWE techniques measure the speed of the shear waves generated in the tissues by either an external mechanical push or an ultrasound radiation force impulse (ARFI). A greater speed indicates increased tissue stiffness which is known to correlate with the dynamics and severity of fibrosis. SWE techniques can be divided into transient elastography (TE) (FibroScan®) and ARFI-based techniques. These latter are either pSWE, including Virtual Touch Quantification VTQ® from Siemens, ElastPQ® from Philips, SWM® from Hitachi, STQ® from Mindray, S-shearwave® from Samsung, QElaXto® from Esaote or 2D-SWE (first available on the Aixplorer system from SuperSonic Imagine, and later on systems from Siemens, General Electric (GE), Canon, Philips and Mindray) [4,6,44]. The speed of the shear waves is measured in meter/second (m/s); using Young's modulus it can be converted into stiffness measured in kilopascals (kPa), assuming that the tissue is purely elastic and its elastic response is linear, and that the tissue density is always 1000 kg m^{-3} [1].

3.1. Transient Elastography (TE)

Transient elastography is a non-invasive and rapid bedside method used to assess liver fibrosis by measuring liver stiffness. The technique has been described in detail in the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) and World Federation for Ultrasound in Medicine and Biology (WFUMB) guidelines [1,2,4,6,45] and also by others [46]. TE has been used for liver stiffness measurement (LSM) both in children and adults [1,2,47,48]. Figure 1 shows the values obtained with TE in a newborn.

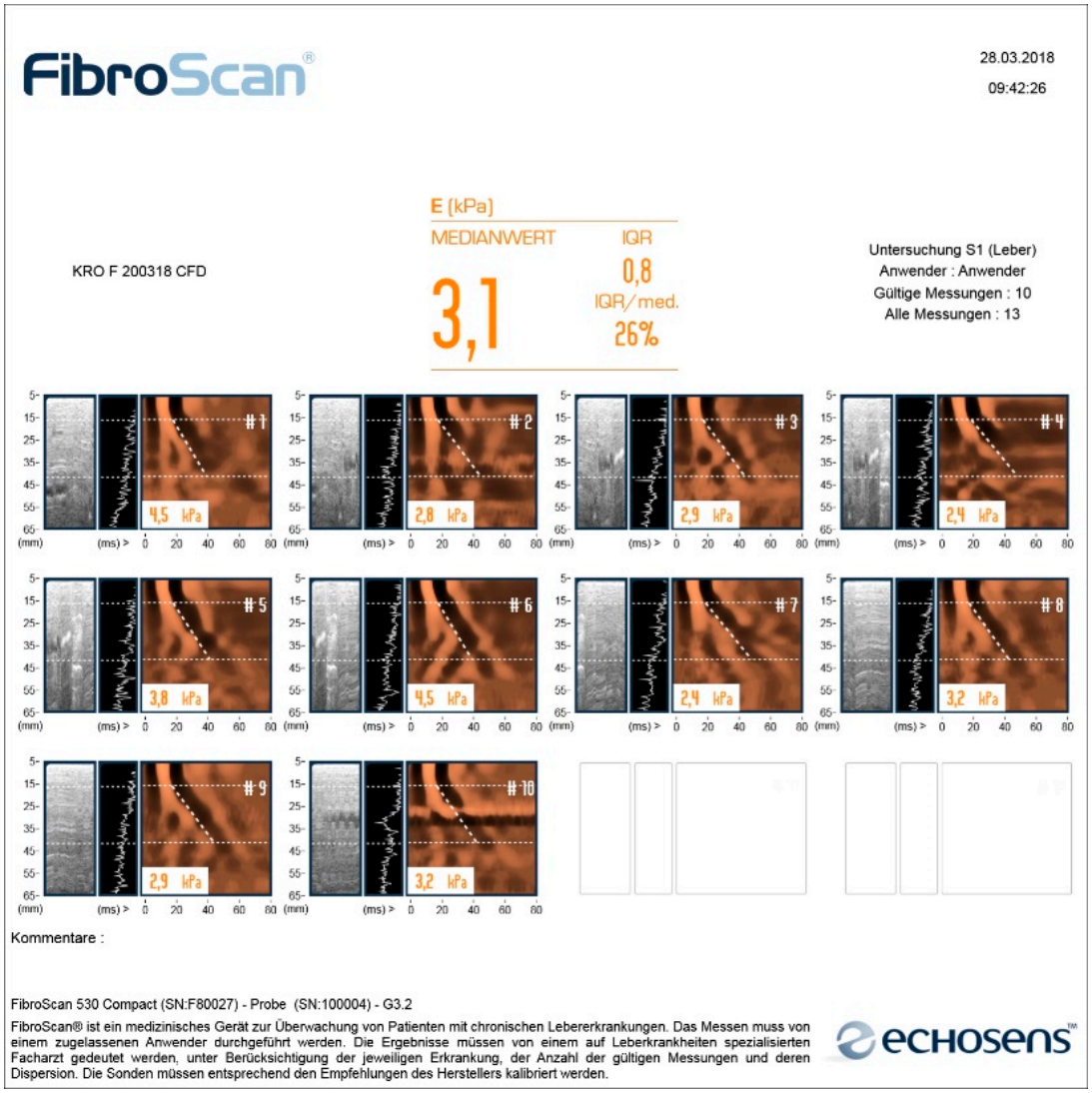

Figure 1. Transient elastography (TE) (S1 probe) in a newborn with alpha-1 antitrypsin deficiency. The individual values of 10 measurements are shown as well the median of the 10 measurements and two quality parameters, the interquartile range and the interquartile range divided by the median.

3.1.1. TE in Healthy Children

Since 2008, following the release of a new probe with a smaller diameter (S-probe 5 mm) compared to the regular probe (M-probe 7 mm), LSM using TE could be obtained in small children and infants. The feasibility of LSM in children was assessed using the S-probe (thorax perimeter < 45 cm (S1) or 45–75 cm (S2)) and the M-probe (thorax perimeter > 75 cm) according to the manufacturer's recommendations [49]. TE was technically achievable in children of all age groups. TE is feasible also in infants, but confounding factors such as the probe choice, sedation, or food intake need to be taken

into account when interpreting the results. The success rate of TE decreased in children younger than 24 months even under ideal conditions. General anesthesia significantly increased LSMs in healthy children (5.4 vs. 4.2 kPa; $p < 0.01$). Probe choice equally influenced results in paired comparisons (S1 5.5 vs. S2 4.8 kPa; $p < 0.01$), as did food intake (5.9 vs. 5.4 kPa; $p = 0.015$). Inter- and intra-observer agreements were good. Normal liver stiffness was 4.5 (2.5–8.9) kPa and did not vary significantly with age or sex [50]. However, another study found that LSMs were significantly age-dependent with values of 4.40, 4.73, and 5.1 kPa in children 0–5, 6–11, and 12–18 years ($p = 0.001$) respectively (Table 1), while the interquartile range decreased with age (0.8, 0.7, and 0.6 kPa). The upper limit of normal (median plus 1.64 times standard deviation) was 5.96, 6.65, and 6.82 kPa, respectively. Girls between 11 and 18 years showed a significantly lower LSM than boys of the same age (4.7 vs. 5.6 kPa; $p < 0.005$) [48]. In younger children, the number of invalid measurements increased significantly due to movement artifacts [48], however, the measurement was reliable from the age of 6 without sedation.

Table 1. Factors that may affect measurement of liver stiffness with shear wave elastography in healthy children.

	Factor		LSM, kPa	*p* Value	No. of Children	Study
Transient elastography	Factor		5.5 vs. 4.8	<0.01	527	Goldschmidt et al., 2013 [1]
	Sedation (with vs. without general anesthesia)		5.4 vs. 4.2	<0.01	527	Goldschmidt et al., 2013 [1]
	Food intake (no vs. yes)		5.4 vs. 5.9	0.01	527	Goldschmidt et al., 2013 [1]
	Age (years)	0–5 vs. 6–11 vs. 12–18	4.40 vs. 4.73 vs. 5.1	0.001	240	Engelmann et al., 2012 [2]
		0–2 vs. 3–5 vs. 6–11 vs. 12–18	3.5 vs. 3.8 vs. 4.1 vs. 4.5	0.0006	173	Lewindon et al., 2016 [3]
		1–5 vs. 6–11 vs. 12–18	3.4 vs. 3.8 vs. 4.1	0.001	139	Tokuhara et al., 2016 [4]
	Gender: boys vs. girls		5.6 vs. 4.7	<0.005	240	Engelmann et al., 2012 [2]
			4.8 vs. 4.1	N.S	173	Lewindon et al., 2016 [3]
Point shear wave elastography			SWV, m/s			
	Probe (linear vs. convex)		1.11 vs. 1.13	0.52	109	Hanquinet et al., 2013
			1.15 vs. 1.19	N.S	60	Fontanilla et al., 2014
	Age (years)	0–1 vs. 2–5 vs. 6–10 vs. 11–18	1.05 vs. 1.00 vs. 1.12 vs. 1.12	<0.05	176	Bailey et al., 2017
		0–1 vs. 1–5 vs. 1–10 vs. 10–17	1.11 vs. 1.15 vs. 1.08 vs. 1.14	N.S	109	Hanquinet et al., 2013
		0–5 vs. 6–11 vs. 12–17	1.11 vs. 1.05 vs. 1.06	0.01	150	Matos et al., 2014
	Gender: boys vs. girls		1.08 vs. 1.08	N.S	176	Bailey et al., 2017
			1.19 vs. 1.13	0.02	132	Eiler et al., 2012
			1.11 vs. 1.14	0.3	109	Hanquinet et al., 2013
			1.07 vs. 1.08	0.47	150	Matos et al., 2014
			1.21 vs. 1.18	0.36	60	Fontanilla et al., 2014
	Left liver lobe vs. right liver lobe		1.19 vs. 1.14	0.03	132	Eiler et al., 2012
			1.21 vs. 1.07	0.000	150	Matos et al., 2014
			1.27 vs. 1.19	N.S	60	Fontanilla et al., 2014

Table 1. *Cont.*

	Factor		LSM, kPa	*p* Value	No. of Children	Study
Two-dimensional shear wave elastography	Probe (linear vs. convex)		LSM, kPa			
			5.96 vs. 6.94	0.006	51	Franchi-Abella et al., 2016
	Age	vs. 1–5 vs. 1–10 vs. 10–17 years	6.00 vs. 6.85 vs. 7.14 vs. 6.97	0.11	51	Franchi-Abella et al., 2016
		0–60 vs. ≥ 60 days	6.61 vs. 5.3	0.02	40	Zhou et al., 2017
	Gender: boys vs. girls		6.61 vs. 6.54	0.41	51	Franchi-Abella et al., 2016
			5.4 vs. 5.6	0.63	40	Zhou et al., 2017

Explanations: LSM: liver stiffness measurement; kPa: kilopascal, SWV: shear wave velocity; N.S non-significant; m/s: meter per second.

As shown in Table 1, in a series of non-sedated control group of children LSM also increased with age; 0–2 years (3.5 ± 0.5 kPa), 3–5 years (3.8 ± 0.3 kPa) and 6–11 years (4.1 ± 0.2 kPa), with healthy older children 12–18 years having values similar to adults (4.5 ± 0.2 kPa). LSM did not vary significantly with gender (female, 4.5 ± 0.2 vs. male, 4.8 ± 0.2 kPa). Children with non-hepatic illnesses had higher LSM (5.2 ± 0.2 kPa) compared to healthy children (4.1 ± 0.1 kPa) [51].

Another study has confirmed that LSM increased with age: it was 3.4 kPa (2.3–4.6 kPa) at ages 1–5 years; 3.8 (2.5–6.1) kPa at ages 6–11; and 4.1 (3.3–7.9) kPa at ages 12–18 ($p = 0.001$). The M-probe was suitable in a wide age range of children from age 1 year onwards. In children without evidence of liver disease, LSM showed an age-dependent increase [23].

Still, when using the M probe in children with a thoracic perimeter below 45 cm, one should consider the "underestimation" phenomenon. It has been shown that LSM decreased with probe size (S1 < S2 < M) and caution is needed when interpreting the results [52].

3.1.2. TE in Non-Alcoholic Fatty Liver Disease (NAFLD)

In children with NAFLD (age range from 5.5 to 11.3 years), the combination of pediatric NAFLD fibrosis index (PNFI) and TE were used to assess the presence of clinically significant liver fibrosis. Both PNFI and TE values were significantly higher in children with significant fibrosis [53]. The combined use of PNFI and TE predicted the presence or absence of clinically significant fibrosis in 98% of children with NAFLD. This could help to identify children who should undergo liver biopsy because the confirmation of advanced fibrosis would lead to closer follow up and screening for cirrhosis-related complications.

In a series of 52 biopsy-proven pediatric non-alcoholic steatohepatitis (NASH), the following cutoffs for staging liver fibrosis were found: 5–7 kPa for F1 (area under the receiver-operating characteristic (AUROC) curve, 97.7%), 7–9 kPa for F2 (AUROC, 99.2%), >9 kPa for F3 (AUROC, 100%) [42].

3.1.3. Correlation with Fibrosis Stage and Different Etiologies

LSM using TE in pediatric patients with chronic liver disease correlated significantly with both fibrosis area fraction [54] and Ishak scores, the correlation appearing better with the latter (r = 0.839 vs. 0.879, $p < 0.0001$ for both). LSM discriminated individual stages of fibrosis with high performance. Sensitivity ranged from 81.4% to 100% and specificity ranged from 75.0 to 97.2%. However, LSMs for the same stage of fibrosis varied according to different etiologies. For example, for F3 Ishak stage, higher values were obtained in children with autoimmune hepatitis (16.15 ± 7.23 kPa) compared to those with Wilson's disease (8.30 ± 0.84 kPa) and hepatitis C virus (HCV) hepatitis (7.43 ± 1.73 kPa).

Multiple regression analysis revealed that Ishak fibrosis stage was the only independent variable associated with higher LSM ($p < 0.0001$) [17].

In a study that prospectively included 116 consecutive children with chronic liver diseases, de Ledinghen et al. reported that the AUROCs for the diagnosis of cirrhosis were 0.88, 0.73, and 0.73 for FibroScan, Fibrotest, and Aspartateaminotransferase-to-Platelet Ratio Index (APRI), respectively. The FibroScan equipped with the specific smaller diameter probe (S-probe 5 mm) could become a useful tool for the management of chronic liver diseases in children [49].

In a pediatric cohort, TE findings were compared with the ability of serum hyaluronic acid (HA) and human cartilage glycoprotein-39 (YKL-40) values in predicting advanced hepatic fibrosis [55]. For the prediction of advanced fibrosis, TE showed an AUROC significantly higher (0.83) than HA (0.72) or YKL-40 (0.52). The optimal TE cut-off value for predicting F3–F4 fibrosis was 8.6 kPa. The combination of TE and HA was not better than TE alone for predicting advanced fibrosis [56].

Studies in adults have shown that inflammation increases liver stiffness, leading to an overestimation of fibrosis. The influence of inflammation to LSMs in children/young adults has been investigated as well. In patients with fibrosis stages F0–F2, the proportion of those with LSM > 8.6 kPa increased with increasing alanine aminotransferase (ALT). In patients with F3–F4, there was no association between ALT and LSM. A weak correlation between a change in ALT and LSM was observed in patients with no/minimal fibrosis and inflammatory liver diseases (r = 0.33). In children with no/minimal hepatic fibrosis and inflammatory liver disease, high ALT values were associated with LSM in the range typical for advanced fibrosis. However, with more advanced fibrosis, inflammation did not appear to contribute to LSM. Caution must be taken when interpreting LSM for assessing fibrosis severity in the setting of inflammation [11].

TE may be useful in follow-up of children following Fontan surgery. The technique is feasible and it has been reported that pediatric Fontan patients have markedly elevated LSMs (18.6 versus 4.7 kPa) [18]. There was no association between TE values and patient age, time since Fontan surgery, or median Fontan circuit pressure. [18].

The liver stiffness score of biliary atresia patients was significantly higher than that of normal controls (27.37 ± 22.48 and 4.69 ± 1.03 kPa; $p < 0.001$). The sensitivity (and specificity) of TE (using a cut-off value of 12.7 kPa) and APRI (using a cut-off value of 1.92) in predicting esophageal/gastric varices were 84% (77%) and 84% (83%), respectively [57].

3.2. Point SWE (pSWE)

The technique has been described in detail in the EFSUMB and WFUMB guidelines [1,2,4,6].

Trout et al. reported that pSWE and magnetic resonance elastography (MRE) values correlated well in patients with a body mass index (BMI) of less than 30 kg/m^2 and minimal US data dispersion; increasing US data dispersion was directly related to a higher BMI [27]. In another study, SWVs differed between normal-weight and obese children (1.08 ± 0.14 versus 1.44 ± 0.39 m/s; $p < 0.001$), but not by gender. Multivariate linear regression demonstrated that the shear wave velocities (SWV)s were primarily associated with age in normal-weight children ($p < 0.05$) and with BMI in obese children ($p < 0.001$). In the obese group, mean SWV was significantly higher in children with abnormal echogenic livers than in those with livers of normal appearance (1.53 ± 0.38 vs. 1.17 ± 0.27), $p < 0.05$. The difference was not significant in the normal-weight group [58].

In the study of Eiler et al., which included 132 patients 0–17 years, the mean value of SWV was 1.16 (0.14) m/s. Neither age ($p = 0.533$) nor depth of measurement ($p = 0.066$) had a significant influence on SWV, whereas a significant effect of gender was found, with lower values in females ($n = 71$, $p = 0.025$); however, there was no significant interaction between age groups (before or after puberty) and gender ($p = 0.276$). There was an inter-lobar difference with lower values in the right liver lobe compared to the left (1.14 ± 0.22 m/s vs. 1.19 ± 0.28 m/s, $p = 0.036$) and with a significantly lower variance in the right lobe ($p < 0.001$). Consistent values were measured by different examiners ($p = 0.108$); however, the inter-examiner variance deviated significantly ($p < 0.001$) [59].

SWV measurement was feasible in children at any age with acceptable reliability. The depth of measurements in the liver seemed to have no influence on the results. There was no statistical difference between measurements taken at different ages, with a mean SWV of 1.12 m/s (range: 0.73 to 1.45 m/s) [60].

In another study, mean SWV in the right liver lobe was 1.07 ± 0.10 m/s. No significant differences were found according to sex or among different probe locations [61]. SWVs were, however, significantly higher in the left liver lobe in comparison to the right lobe (1.07 ± 0.10 m/s, right; 1.21 ± 0.16 m/s, left). The depth of measurements also influenced the SWV values, being slightly lower at deeper locations. Regarding the age, significant differences were found for children <6 years old compared with other age groups. SWV seems to be influenced by age, depth, and measurement location. A mean SWV of 1.07 ± 0.10 m/s for a healthy pediatric population with the possibility of reaching 1.12 m/s in the case of younger children was found. SWV values were more consistently obtained when assessing the right liver lobe and at depths lower than 5 to 6 cm [61].

pSWE and 2D-SWE values were able to detect high-grade histopathological fibrosis and had high success rates when distinguishing high-grade from low-grade fibrosis. In a series of 75 children, SWV cut offs were 1.67 m/s for pSWE and 1.56 m/s for 2D-SWE in detecting fibrosis or inflammation and 2.09 m/s for pSWE and 2.17 m/s for 2D-SWE in discriminating children with low and high histological liver fibrosis scores. However, both techniques had limited success rates when differentiating low-grade fibrosis from normal liver tissue [14]. In another prospective study, pSWE was feasible in children using both the convex and the linear transducers. Mean SWV measured in the right lobe was 1.19 ± 0.04 m/s with the convex transducer and 1.15 ± 0.04 m/s with the linear transducer. Age had a small effect on the measurements. BMI and gender had no significant effects on SWV, whereas site of measurement had a significant effect, with lower SWV values in the right hepatic lobe. The authors suggested that the SWV values obtained in the right lobe may be used as reference values for normal liver stiffness in children [62].

Another prospective study in 235 healthy children (6–17 years) showed also a significant difference between the values of right and left liver lobe and a small influence of age and gender with lower values in older children and significant lower values in females after puberty. It was suggested that best point of examination is the right lobe in the interaxillar line with transverse transducer direction [62].

3.2.1. Liver Fibrosis

Quantification of liver fibrosis correlates with the histological fibrosis stage in children with chronic liver disease [63]. The accuracy of pSWE in determining the extent of liver fibrosis in pediatric patients with short bowel syndrome has been evaluated. The AUROCs to differentiate moderate/severe liver fibrosis from mild disease were 0.83 and 0.86 for the median and mean SWV, respectively [10].

In children without inflammation, SWV was higher when fibrosis was present compared to the absence of fibrosis (average SWV 1.8 vs. 1.4 m/s). A SWV cut-off of 1.7 m/s had 100% positive predictive value and 24% negative predictive value for detecting liver fibrosis or inflammation [15].

Fibrosis related to several causes can be diagnosed in children and adolescents' liver grafts. In a small series (30 subjects), the AUROCs for SWV, APRI, and AST/ALT (aspartate aminotransferase/alanine aminotransferase) ratio index for significant fibrosis were 0.76, 0.74, and 0.69, respectively. Through multivariate logistic regression analysis, the only independent predictor of significant fibrosis was SWV. SWV assessment may serve as a potential method for assessing significant fibrosis in pediatric patients with liver transplants, particularly in combination with AST/ALT ratio [64].

Graft fibrosis is a common finding from biopsies after pediatric liver transplantation. LSMs had good accuracy for diagnosing graft fibrosis after pediatric living donor liver transplantation. SWVs significantly increased with increased portal and pericellular fibrosis grades [65]. For the diagnosis of significant fibrosis, the AUROCs were 0.760 and 0.849 for the midline and intercostal

values, respectively, and the optimal cut-off values were 1.30 and 1.39 m/s for midline and intercostal values. The pericellular pattern of fibrosis was frequently observed in this setting, and moderate pericellular fibrosis was detectable by SWV [65].

3.2.2. Values in Obesity

The mean pSWE value was 1.13 (0.20) m/s for obese children and 1.02 (0.11) m/s for children in the control group, whereas other authors did not find any statistically significant influence of the BMI on pSWE values [66–69]. SWV showed excellent correlation with AST/ALT ratios in obese children and may be used as a non-invasive tool to detect NAFLD and associated hepatic changes, especially in pediatric patients, for whom liver biopsy is not always feasible [9].

3.2.3. Liver Disease Associated with Cystic Fibrosis (CFLD)

Liver disease associated with cystic fibrosis (CFLD) is the second cause of mortality in these patients [31,70]. Comparing the SWV values of CFLD with those of a control healthy group, values in the right lobe were higher in patients with CFLD. A SWV cut-off value to detect CFLD of 1.27 m/s with a sensitivity of 56.5% and a specificity of 90.5% has been reported. Cystic fibrosis patients were found to have higher SWV spleen values than the control group, without any clinical consequence. A study that enrolled children with liver disease, found that a value of 1.16 m/s (±0.14 m/s) allows a differentiation of healthy versus pathological liver tissue [30].

3.3. Two-Dimensional Shear Wave Elastography (2D-SWE)

The technique has been described in detail in the EFSUMB and WFUMB guidelines [1,2,4,6]. A 2D-SWE techinique is exemplified in Figure 2.

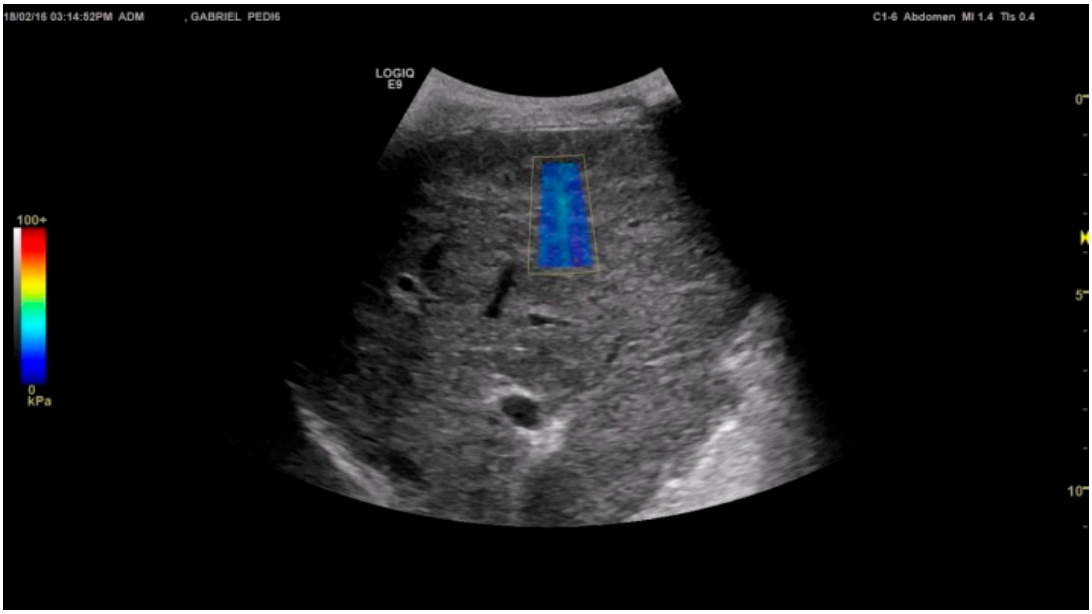

Figure 2. Two-dimensional shear wave elastography (2D-SWE) in a 10 years old boy with cystic fibrosis associated liver disease. The median of liver stiffness measurements using the convex probe was 4.47 kPa, IQR = 1.13. Point SWE results were 1.47 m/s (convex probe).

A recent meta-analysis analyzed 12 studies on 550 patients to assess the diagnostic performance of 2D-SWE for determining the severity of liver fibrosis in children and adolescents. The summary sensitivity was 81% (95% CI: 71–88) and the specificity was 91% (95% CI: 83–96) for the prediction of significant liver fibrosis. Subgroup analysis revealed that 2D-SWE had an excellent diagnostic

performance according to each degree of liver fibrosis. 2D-SWE had a higher sensitivity ($p < 0.01$) and specificity ($p < 0.01$) than VTQ® [71]. In this meta-analysis, the number of LSMs performed was a significant factor influencing study heterogeneity.

3.3.1. Technical Success Rates of Liver Stiffness Estimates

Five studies on healthy subjects and/or patients with chronic liver diseases have reported results on the technical success rate of 2D-SWE in pediatric patients. In two studies on, respectively, 96 and 88 subjects, no technical failure was observed [72,73]. In another study on NASH pediatric patients, 2D-SWE was feasible in 68/69 (99%) of them [12]. In a large series, the success rates of LSMs in the study group and the control group were 96.4% (244/253) and 100% (40/40), respectively [73]. The main reasons for failure were crying and body movements. No technical failure was observed in a free-breathing status [72]. A more recent study evaluated the stability index (SI) of 2D-SWE acquisitions as a quality indicator of measurements [74]. Using an SI < 90% as an indicator of unreliable measurement, failure to obtain reliable 2D-SWE measurements was observed in five of 29 patients (17%) in the free-breathing group and in two of 29 patients (7%) in the breath-holding group. Comparison of the mean elasticity value revealed no significant difference between free breathing and breath-holding (6.31 ± 3.98 kPa vs. 6.47 ± 4.09 kPa, $p = 0.354$, $n = 29$) [74].

Hepatic 2D-SWE performed with free breathing yielded results similar to the breath-hold condition. With a substantially lower time requirement, which could be further reduced by lowering the number of acquisitions, it was concluded that the free-breathing technique may be suitable for infants and less cooperative children not capable of breath-holding [13].

3.3.2. Reproducibility and Variability of Liver Stiffness Estimates

The intra-operator reproducibility of LSMs was found to be excellent, comparing the average of 3, 5 or 7 measurements to the average of 15 considered as the reference, with intraclass correlation coefficient (ICC) of 0.944 (95% CI: 0.899–0.972), 0.958 (95% CI: 0.923–0.978) and 0.969 (95% CI: 0.945–0.982), respectively, in free-breathing status. Results were very similar in the group of patients studied with breath-hold: ICC = 0.937 (95% CI: 0.887–0.978), ICC = 0.938 (95% CI: 0.876–0.981), and ICC = 0.941 (95% CI: 0.878–0.983) for the average of 3, 5 and 7 measurements, respectively [74]. An excellent correlation of repeated measurements made by each of three operators was also reported in another study, with intra-operator ICCs ranging from 0.93 to 0.96 [73]. This study also investigated inter-observer agreement in 39 randomly selected children (9 controls, 16 patients without biliary atresia (BA) and 14 with BA. Very good reproducibility was found among the three operators (ICC = 0.98; 95% CI: 0.96–0.99), and the Bland–Altman analysis also showed that the interobserver agreements within each pair of operators were good [73].

Another study on NASH patients with various stages of liver fibrosis (F0: $n = 5$; F1: $n = 16$; F2–3: $n = 14$) showed that the inter-observer agreement between two operators was excellent, as indicated by an ICC for absolute agreement of 0.95 (95% CI: 0.90, 0.97) [12]. Using the SI as an indicator of unreliable measurements, it has been found that an intra-operator ICC of 0.87 (95% CI, 0.74 to 0.94) in the free-breathing group increased to 0.99 (95% CI, 0.97 to 0.99) when the SI was used. Similarly, the ICC of 0.95 (95% CI, 0.90 to 0.98) in the breath-holding group increased to 0.99 (95% CI, 0.99 to 0.99) when the SI was used [74].

3.3.3. Liver Stiffness Estimates in Healthy Controls

Liver stiffness estimates in healthy subjects have been assessed in several studies, and most information comes from the control group of case-control studies. The mean 2D-SWE value was 5.5 ± 1.3 kPa in free-breathing status and 5.5 ± 1.1 kPa, with a range of 3.7–7.7 kPa [73]. The breathing method does not seem to have an impact on 2D-SWE values and their variability [72,73]. The gender seems not to significantly affect 2D-SWE values [73], with average values of 5.4 ± 1.1 kPa in males versus 5.6 ± 1.1 kPa in females ($p = 0.637$) [73]. LSMs were found to correlate with children's age

(r = 0.429, p = 0.006), and to be significantly higher (6.1 ± 1.1 kPa) in babies older than 60 days (n = 10) than in babies of 60 days or below (5.3 ± 1.0 kPa) (n = 30) (p = 0.026) [73]. However, another study didn't find any significant difference between different age groups (p = 0.11) [25] and only a trend to an increase of LSMs with age was found when using the linear transducer (p = 0.05). Technical factors may also affect LSMs, including the transducer used: a significant difference was found for mean elasticity between the linear and convex transducers: 5.96 kPa ± 1.31 and 6.94 kPa ± 1.42, respectively (p = 0.006) [25].

3.3.4. Number of Measurements Needed

2D-SWE enables evaluation of the velocity of several shear wave fronts in real-time. There are no specific manufacturer recommendations on how many measurements are sufficient to obtain reliable results. In addition, repeating procedures to obtain 10 measurements is challenging in children. The mean LSMs obtained with three, five and seven acquisitions demonstrated almost perfect agreement with the reference obtained with 15 acquisitions in both free-breathing and breath-holding status. Three acquisitions can be enough for hepatic LSMs in children older than 6 years regardless of breathing status or hepatic pathology. More acquisitions are recommended for children under the age of 5 years during free breathing [72]. To reach an acceptable liver stiffness error range below 5%, the use of the SI to identify unreliable measurements was found to reduce the number of acquisitions required from 8 to 5 in the free-breathing group, and from 6 to 2 in the breath-hold group [74].

3.3.5. Pediatric Patients with NAFLD

2D-SWE is an accurate and reproducible non-invasive technique that efficiently depicts the presence of significant liver fibrosis and, less accurately, mild liver fibrosis in pediatric patients with NAFLD. 2D-SWE showed a very high correlation with liver fibrosis ($p < 0.001$) at univariate and multivariate analyses. The AUROCs for the association of any and significant fibrosis were 0.92 and 0.97, respectively [12].

3.3.6. Liver Fibrosis in Biliary Atresia (BA) Patients

The availability of an effective non-invasive tool for monitoring liver fibrosis in children with BA is important, but evidence is limited. 2D-SWE is a more promising tool to assess liver fibrosis than APRI and fibrosis-4 (FIB-4) in children with BA after the Kasai procedure. The AUROCs of 2D-SWE, APRI and their combination were 0.79, 0.65 and 0.78 for significant fibrosis; 0.81, 0.64 and 0.76 for advanced fibrosis; and 0.82, 0.56 and 0.84 for cirrhosis, respectively [19].

LSM was found to be higher in patients with BA as compared to controls: 12.6 kPa (10.6–18.8) versus 9.6 kPa (7.5–11.7) ($p < 0.001$), without any difference between gender (p = 0.071) [73]. The difference in LSMs between BA patients and controls also applied to the two age groups using the 60-day age cutoff ($p < 0.001$ below age cutoff and p = 0.002 above age cutoff). Using a cutoff value ≥10.2 kPa, the sensitivity, specificity, positive predictive value and negative predictive value for the diagnosis of BA were 81.4%, 66.7%, 76.0%, and 73.5%, respectively. Using the same cutoff value, the sensitivity of the test improved to 92.5% in the >60 days old age group (n = 60), whereas it decreased to 68.2% in younger babies (n = 53). In these patients, age, direct and indirect bilirubin levels significantly correlated with LSM (all $p < 0.001$), whereas both ALT and AST levels did not correlate (both $p > 0.05$) [73]. In 12 patients after the Kasai intervention (M:F = 3:9, mean age 9.3 ± 4.4 years, age range 3–18 years old), without clinical evidence of acute illness including cholangitis, and no incidental mass or cystic lesion in the liver, the mean value from fifteen LSMs was 8.0 ± 2.2 kPa.

3.3.7. Intrahepatic Portal Hypertension

LSM has been significantly correlated with hepatic venous-pressure gradient (HVPG). The AUROC for predicting clinically significant portal hypertension was 0.914, and the best cut-off value of 18.4 kPa showed sensitivity of 87.5% and specificity of 84.0%. 2D-SWE had excellent diagnostic

performance for predicting clinically significant portal hypertension in children with suspected liver diseases. It has been suggested that a coefficient of variation (CV) ≤ 0.2 may possibly be used as a reliability criterion in 2D-SWE measurement [16].

3.3.8. Focal Liver Lesions

Evidences are limited and no conclusion can be drawn. In a case-control study on 20 patients with hepatic tumors, stiffness estimates of malignant tumors by two operators were found to be significantly higher ($p = 0.02$) than that of hepatic hemangiomas: 47 kPa and 58 kPa for malignant lesions versus 22 kPa and 24 kPa, respectively, for both operators. The AUROC of SWE for differentiating hepatic hemangiomas from malignant hepatic tumors was 0.77 with a sensitivity of 72.7% and a specificity of 66.7%, using a cutoff value of 23.62 kPa. IContrast-enhanced ultrasound (CEUS) is used for the improved detection and characterization of focal liver lesions [75–81]. CEUS does not influence the measurement of liver stiffness [82].

3.4. Strain Imaging (Real-Time Elastography (RTE))

Real-time elastography (RTE) has been used mainly for the evaluation of the pancreas [83–86], the thyroid [87–94], the prostate [95], the breast [5,96] but also for the liver [1,2,7,97]. Published evidence in children is scarce and contradictory [98–100].

4. Comparison of TE, pSWE and 2D-SWE

Using TE as a reference method, sensitivity of pSWE was 71.42% for detecting F1 fibrosis, 77.77% for F2, 62.5% for F3, and 71.42% for F4. Sensitivity of 2D-SWE was 92.85% for detecting F1, 83.33% for F2, 87.5 % for F3, and 85.71 % for F4. Significant correlation was found between TE and 2D-SWE overall (Kappa correlation factor = 0.843, $p = 0.001$). Analyzing the subgroup with success rate (SR) = 60–70%, no significant correlation between TE and pSWE was found (Kappa correlation factor = 0.172, $p = 0.452$). Assessing the subgroup with SR > 70%, a significant correlation between TE and pSWE was found (Kappa correlation factor = 0.761, $p = 0.001$). Overall, 2D-SWE correlated with TE better than pSWE [24].

5. What Is the Benefit of SWE in Children?

Invasive methods for the evaluation of the severity of liver diseases in children are more difficult to perform. Sedation is sometimes necessary, the parents and the children are afraid of the procedure and its complications, especially if repeated procedures are needed for follow-up. Thus, in this population the need for non-invasive modalities of evaluation is of great interest. The main advantages of ARFI-based elastography techniques are that they are rapid, repeatable when necessary, not expensive and available in high-end ultrasound machines. Moreover, they are painless, take less than 5 min and little cooperation is needed from the child. In infants, the procedures may take longer time since cooperation from the patient is more difficult, and may require parent support. On the other hand, liver biopsy, which is the reference standard for fibrosis staging, has several limitations, including bleeding and possible surgery, the possible need for sedation, pain, fear and others, so it is not always feasible in the follow-up of patients with chronic parenchymal liver diseases [36,37,40,69].

5.1. What Is Best in Children: TE, pSWE or 2D-SWE and Why?

As for the adult population, maybe it is too early to answer this question. Each method has its strong points, including feasibility, reproducibility, acceptable number of false positive or negative results. TE is quick to perform and very little cooperation is needed. It is also the most studied technique since it was the first available on the market. On the other hand, the cost of the machine and the additional cost for probe calibration in a system that is not embedded in an ultrasound machine should be considered. However, it is a unique device that has also the advantage of steatosis

assessment by controlled attenuation parameter (CAP). pSWE and 2D-SWE techniques are available on conventional high-end ultrasound machines and have the advantage of good feasibility. Moreover, these techniques are accurate in staging liver fibrosis. Future comparative, prospective studies are necessary for the definitive answer to this question.

5.2. Scores in Fatty Liver Disease and Fibrosis: Are They Better than SWE?

Another alternative for the non-invasive assessment of liver fibrosis are the serologic tests such as FibroTest, APRI, Forns Index, Fib-4, NAFLD test, PNFI, pediatric NAFLD fibrosis score (PNFS), and so on. FibroTest-ActiTest has been validated in children with chronic hepatitis C [101,102]. Only a few studies have been published regarding the comparative value of ultrasound-based elastographic techniques and serologic tests. In a pilot study, it was found that, for the diagnosis of cirrhosis, the AUROCs for TE, FibroTest, and APRI were 0.88, 0.73, and 0.73, respectively [49]. In an Egyptian cohort, the AUROCs of TE and APRI score for discriminating significant fibrosis (F2, Metavir score) were 0.883 and 0.746, while the correlations with liver biopsy were 0.58 and 0.53, respectively [21].

The advantages of serological tests are that they do not require any specialized equipment, however patented tests are expensive and not readily available. FibroTest-ActiTest, even though expensive, has the advantage of giving information regarding the severity of inflammation.

Considering the scarce comparative data between serology and elastography tests in children, a definite conclusion regarding which one is the best cannot be drawn.

6. Limits of Liver Elastography

Neither non-invasive elastographic techniques nor laboratory scores allow a determination of the presence and the degree of inflammation, necrosis, fat deposits (micro- or macro-vesicular, mixed) and iron or copper deposits. Elastography does not replace biopsy and histological evaluation in autoimmune hepatitis including treatment control and some other forms of acute and chronic liver disease before and after transplantation. Elastographic techniques cannot discriminate between contiguous stages of fibrosis (F0 vs.F1; F1 vs. F2). Quality parameters are of importance [103].

Some prognostically important markers such as portal inflammation and the exact degree of fibrosis are best determined by liver biopsy [28,104]. It seems clear that SWE cannot replace all information shown in the complex published scores for adult and pediatric patients (e.g., Desmet (CHC), METAVIR and Ishak (CHC, CHB)) to evaluate the necro-inflammatory activity (grading) and stage of fibrosis. The Semiquantitaive Scoring System (SSS) of Chevallier was developed to quantify fibrosis irrespective of the underlying disease. In a series of 430 obese children the association and prognosis of portal inflammation, metabolic syndrome and fibrosis was shown only with histology [28]. This information cannot be obtained with non-invasive measurements.

7. Conclusions

SWE techniques have increasingly been used in children with several etiologies of diffuse liver disease. Each technique has its strong points, including feasibility, reproducibility, acceptable number of false positive or negative results. TE is quick to perform and very little cooperation is needed. It is also the most studied method since it was the first available on the market. Point SWE and 2D-SWE techniques are available on conventional high-end ultrasound machines and have the advantage of allowing the morphological assessment of the liver in B-mode as well.

Studies have shown that all SWE techniques are feasible in children at any age with acceptable reliability. LSMs values seem age-dependent, with children of age 12 or more having values similar to adults. The majority of studies have shown that girls have significantly lower LSMs than boys of the same age; however some studies did not confirm this finding. SWE is feasible also in babies but confounding factors such as the probe choice, sedation, or food intake need to be taken into account when interpreting the results.

As reported in adults, LSMs obtained in the right liver lobe are lower than those obtained in the left lobe, and measurements should be performed in the right lobe whenever possible. The majority of studies have shown that LSMs are not influenced by the BMI.

The intra-operator reproducibility of LSMs by 2D-SWE was found to be excellent and the breathing does not seem to affect the results. Three 2D-SWE acquisitions can be enough for hepatic LSMs in children older than 6 years old regardless of breathing status or hepatic pathology. More acquisitions seem needed for children under the age of five during free breathing.

Ultrasound elastography is a reliable non-invasive method to monitor liver fibrosis in pediatric patients. However, for some pathologies, such as biliary atresia, the evidence is still limited. As shown in adults, inflammation is a confounding factor when assessing fibrosis severity and care should be taken when interpreting the results. Elastographic techniques cannot discriminate between contiguous stages of fibrosis (F0 vs. F1; F1 vs. F2). Moreover, as reported in adults, LSMs for the same stage of fibrosis vary according to different etiologies of liver disease and different values are obtained with different ultrasound systems.

Due to the scarce comparative data between serology and elastography techniques in children, a definite conclusion regarding which is the best cannot be drawn. Neither non-invasive elastographic techniques nor laboratory scores allow a determination of the presence and the degree of inflammation, necrosis, iron or copper deposits.

Acknowledgments: We acknowledge the discussion with Gerhard Alzen, Giessen, Germany. We acknowledge the support of the Bad Mergentheimer Leberzentrum e.V.

Conflicts of Interest: Christoph F Dietrich, speaker for: Hitachi Medical Systems, Siemens Healthineers, Mindray Medical Systems, Supersonic, GE, Bracco, Pentax, Olympus, Fuji, Boston Scientific, AbbVie, Falk, Novartis. Giovanna Ferraioli: Philips Healthcare, Canon Medical Systems, Hitachi Medical Systems, Mindray Medical Systems. Roxana Sirli: I have received financial support (congress travel grant or speaker fees) from Philips, Abbvie, Zentiva. Alina Popescu: I have received financial support (congress travel grants, speaker fees) from: Philips, General Electric, Abbvie, AstraZeneca, Zentiva. Ioan Sporea: I have received financial support (congress travel grant or speaker fees) from Philips, Siemens, General Electric, Abbvie, Zentiva, Bristol Meyers Squibb. Corina Pienar and Christian Kunze declare no conflict of interest.

References

1. Dietrich, C.F.; Bamber, J.; Berzigotti, A.; Bota, S.; Cantisani, V.; Castera, L.; Cosgrove, D.; Ferraioli, G.; Friedrich-Rust, M.; Gilja, O.H.; et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (long version). *Ultraschall Med.* **2017**, *38*, e16–e47. [CrossRef] [PubMed]
2. Dietrich, C.F.; Bamber, J.; Berzigotti, A.; Bota, S.; Cantisani, V.; Castera, L.; Cosgrove, D.; Ferraioli, G.; Friedrich-Rust, M.; Gilja, O.H.; et al. EFSUMB guidelines and recommendations on the clinical use of liver ultrasound elastography, update 2017 (short version). *Ultraschall Med.* **2017**, *38*, 377–394. [CrossRef] [PubMed]
3. Dong, Y.; Sirli, R.; Ferraioli, G.; Sporea, I.; Chiorean, L.; Cui, X.; Fan, M.; Wang, W.P.; Gilja, O.H.; Sidhu, P.S.; et al. Shear wave elastography of the liver—Review on normal values. *Z. Gastroenterol.* **2017**, *55*, 153–166. [CrossRef] [PubMed]
4. Bamber, J.; Cosgrove, D.; Dietrich, C.F.; Fromageau, J.; Bojunga, J.; Calliada, F.; Cantisani, V.; Correas, J.M.; D'Onofrio, M.; Drakonaki, E.E.; et al. Efsumb guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: Basic principles and technology. *Ultraschall Med.* **2013**, *34*, 169–184. [CrossRef] [PubMed]
5. Cosgrove, D.; Piscaglia, F.; Bamber, J.; Bojunga, J.; Correas, J.M.; Gilja, O.H.; Klauser, A.S.; Sporea, I.; Calliada, F.; Cantisani, V.; et al. Efsumb guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: Clinical applications. *Ultraschall Med.* **2013**, *34*, 238–253. [PubMed]
6. Shiina, T.; Nightingale, K.R.; Palmeri, M.L.; Hall, T.J.; Bamber, J.C.; Barr, R.G.; Castera, L.; Choi, B.I.; Chou, Y.H.; Cosgrove, D.; et al. Wfumb guidelines and recommendations for clinical use of ultrasound elastography: Part 1: Basic principles and terminology. *Ultrasound Med. Biol.* **2015**, *41*, 1126–1147. [CrossRef] [PubMed]

7. Ferraioli, G.; Filice, C.; Castera, L.; Choi, B.I.; Sporea, I.; Wilson, S.R.; Cosgrove, D.; Dietrich, C.F.; Amy, D.; Bamber, J.C.; et al. Wfumb guidelines and recommendations for clinical use of ultrasound elastography: Part 3: Liver. *Ultrasound Med. Biol.* **2015**, *41*, 1161–1179. [CrossRef] [PubMed]
8. Ferraioli, G.; Calcaterra, V.; Lissandrin, R.; Guazzotti, M.; Maiocchi, L.; Tinelli, C.; De Silvestri, A.; Regalbuto, C.; Pelizzo, G.; Larizza, D.; et al. Noninvasive assessment of liver steatosis in children: The clinical value of controlled attenuation parameter. *BMC Gastroenterol.* **2017**, *17*, 61. [CrossRef] [PubMed]
9. Kamble, R.; Sodhi, K.S.; Thapa, B.R.; Saxena, A.K.; Bhatia, A.; Dayal, D.; Khandelwal, N. Liver acoustic radiation force impulse (ARFI) in childhood obesity: Comparison and correlation with biochemical markers. *J. Ultrasound* **2017**, *20*, 33–42. [CrossRef] [PubMed]
10. Lodwick, D.; Dienhart, M.; Cooper, J.N.; Fung, B.; Lopez, J.; Smith, S.; Warren, P.; Balint, J.; Minneci, P.C. A pilot study of ultrasound elastography as a non-invasive method to monitor liver disease in children with short bowel syndrome. *J. Pediatr. Surg.* **2017**, *52*, 962–965. [CrossRef] [PubMed]
11. Raizner, A.; Shillingford, N.; Mitchell, P.D.; Harney, S.; Raza, R.; Serino, J.; Jonas, M.M.; Lee, C.K. Hepatic inflammation may influence liver stiffness measurements by transient elastography in children and young adults. *J. Pediatr. Gastroenterol. Nutr.* **2017**, *64*, 512–517. [CrossRef] [PubMed]
12. Garcovich, M.; Veraldi, S.; Di Stasio, E.; Zocco, M.A.; Monti, L.; Toma, P.; Pompili, M.; Gasbarrini, A.; Nobili, V. Liver stiffness in pediatric patients with fatty liver disease: Diagnostic accuracy and reproducibility of shear-wave elastography. *Radiology* **2017**, *283*, 820–827. [CrossRef] [PubMed]
13. Jung, C.; Groth, M.; Petersen, K.U.; Hammel, A.; Brinkert, F.; Grabhorn, E.; Weidemann, S.A.; Busch, J.; Adam, G.; Herrmann, J. Hepatic shear wave elastography in children under free-breathing and breath-hold conditions. *Eur. Radiol.* **2017**, *27*, 5337–5343. [CrossRef] [PubMed]
14. Ozkan, M.B.; Bilgici, M.C.; Eren, E.; Caltepe, G.; Yilmaz, G.; Kara, C.; Gun, S. Role of point shear wave elastography in the determination of the severity of fibrosis in pediatric liver diseases with pathologic correlations. *J. Ultrasound Med.* **2017**, *36*, 2337–2344. [CrossRef] [PubMed]
15. Phelps, A.; Ramachandran, R.; Courtier, J.; Perito, E.; Rosenthal, P.; MacKenzie, J.D. Ultrasound elastography: Is there a shear wave speed cutoff for pediatric liver fibrosis and inflammation? *Clin. Imaging* **2017**, *41*, 95–100. [CrossRef] [PubMed]
16. Yoon, H.M.; Kim, S.Y.; Kim, K.M.; Oh, S.H.; Ko, G.Y.; Park, Y.; Lee, J.S.; Jung, A.Y.; Cho, Y.A. Liver stiffness measured by shear-wave elastography for evaluating intrahepatic portal hypertension in children. *J. Pediatr. Gastroenterol. Nutr.* **2017**, *64*, 892–897. [CrossRef] [PubMed]
17. Behairy, B.S.; Sira, M.M.; Zalata, K.R.; Salama, E.S.E.; Abd-Allah, M.A. Transient elastography compared to liver biopsy and morphometry for predicting fibrosis in pediatric chronic liver disease: Does etiology matter? *World J. Gastroenterol.* **2016**, *22*, 4238–4249. [CrossRef] [PubMed]
18. Chen, B.; Schreiber, R.A.; Human, D.G.; Potts, J.E.; Guttman, O.R. Assessment of liver stiffness in pediatric fontan patients using transient elastography. *Can. J. Gastroenterol. Hepatol.* **2016**, *2016*. [CrossRef] [PubMed]
19. Chen, S.; Liao, B.; Zhong, Z.; Zheng, Y.; Liu, B.; Shan, Q.; Xie, X.; Zhou, L. Supersonic shearwave elastography in the assessment of liver fibrosis for postoperative patients with biliary atresia. *Sci. Rep.* **2016**, *6*, 31057. [CrossRef] [PubMed]
20. Desai, N.K.; Harney, S.; Raza, R.; Al-Ibraheemi, A.; Shillingford, N.; Mitchell, P.D.; Jonas, M.M. Comparison of controlled attenuation parameter and liver biopsy to assess hepatic steatosis in pediatric patients. *J. Pediatr.* **2016**, *173*, 160–164. [CrossRef] [PubMed]
21. Ghaffar, T.A.; Youssef, A.; Zalata, K.; ElSharkawy, A.; Mowafy, M.; Wanis, A.A.A.; Esmat, G. Noninvasive assessment of liver fibrosis in egyptian children with chronic liver diseases. *Curr. Pediatr. Res.* **2016**, *20*, 57–63.
22. Hattapoglu, S.; Goya, C.; Arslan, S.; Alan, B.; Ekici, F.; Tekbas, G.; Yildiz, I.; Hamidi, C. Evaluation of postoperative undescended testicles using point shear wave elastography in children. *Ultrasonics* **2016**, *72*, 191–194. [CrossRef] [PubMed]
23. Tokuhara, D.; Cho, Y.; Shintaku, H. Transient elastography-based liver stiffness age-dependently increases in children. *PLoS ONE* **2016**, *11*, e0166683. [CrossRef] [PubMed]
24. Belei, O.; Sporea, I.; Gradinaru-Tascau, O.; Olariu, L.; Popescu, A.; Simedrea, I.; Marginean, O. Comparison of three ultrasound based elastographic techniques in children and adolescents with chronic diffuse liver diseases. *Med. Ultrason.* **2016**, *18*, 145–150. [CrossRef] [PubMed]

25. Franchi-Abella, S.; Corno, L.; Gonzales, E.; Antoni, G.; Fabre, M.; Ducot, B.; Pariente, D.; Gennisson, J.L.; Tanter, M.; Correas, J.M. Feasibility and diagnostic accuracy of supersonic shear-wave elastography for the assessment of liver stiffness and liver fibrosis in children: A pilot study of 96 patients. *Radiology* **2016**, *278*, 554–562. [CrossRef] [PubMed]
26. Gersak, M.M.; Sorantin, E.; Windhaber, J.; Dudea, S.M.; Riccabona, M. The influence of acute physical effort on liver stiffness estimation using virtual touch quantification (VTQ). Preliminary results. *Med. Ultrason.* **2016**, *18*, 151–156. [CrossRef] [PubMed]
27. Trout, A.T.; Dillman, J.R.; Xanthakos, S.; Kohli, R.; Sprague, G.; Serai, S.; Mahley, A.D.; Podberesky, D.J. Prospective assessment of correlation between US acoustic radiation force impulse and MR elastography in a pediatric population: Dispersion of US shear-wave speed measurement matters. *Radiology* **2016**, *281*, 544–552. [CrossRef] [PubMed]
28. Mann, J.P.; De Vito, R.; Mosca, A.; Alisi, A.; Armstrong, M.J.; Raponi, M.; Baumann, U.; Nobili, V. Portal inflammation is independently associated with fibrosis and metabolic syndrome in pediatric nonalcoholic fatty liver disease. *Hepatology* **2016**, *63*, 745–753. [CrossRef] [PubMed]
29. Hanquinet, S.; Courvoisier, D.S.; Rougemont, A.L.; Wildhaber, B.E.; Merlini, L.; McLin, V.A.; Anooshiravani, M. Acoustic radiation force impulse sonography in assessing children with biliary atresia for liver transplantation. *Pediatr. Radiol.* **2016**, *46*, 1011–1016. [CrossRef] [PubMed]
30. Canas, T.; Macia, A.; Munoz-Codoceo, R.A.; Fontanilla, T.; Gonzalez-Rios, P.; Miralles, M.; Gomez-Mardones, G. Hepatic and splenic acoustic radiation force impulse shear wave velocity elastography in children with liver disease associated with cystic fibrosis. *BioMed Res. Int.* **2015**, *2015*. [CrossRef] [PubMed]
31. Dietrich, C.F.; Chichakli, M.; Hirche, T.O.; Bargon, J.; Leitzmann, P.; Wagner, T.O.; Lembcke, B. Sonographic findings of the hepatobiliary-pancreatic system in adult patients with cystic fibrosis. *J. Ultrasound Med.* **2002**, *21*, 409–416. [CrossRef] [PubMed]
32. Hanquinet, S.; Courvoisier, D.S.; Rougemont, A.L.; Dhouib, A.; Rubbia-Brandt, L.; Wildhaber, B.E.; Merlini, L.; McLin, V.A.; Anooshiravani, M. Contribution of acoustic radiation force impulse (ARFI) elastography to the ultrasound diagnosis of biliary atresia. *Pediatr. Radiol.* **2015**, *45*, 1489–1495. [CrossRef] [PubMed]
33. Dietrich, C.F.; Lorentzen, T.; Sidhu, P.S.; Jenssen, C.; Gilja, O.H.; Piscaglia, F. An introduction to the EFSUMB guidelines on interventional ultrasound (INVUS). *Ultraschall Med.* **2015**, *36*, 460–463. [CrossRef] [PubMed]
34. Lorentzen, T.; Nolsoe, C.P.; Ewertsen, C.; Nielsen, M.B.; Leen, E.; Havre, R.F.; Gritzmann, N.; Brkljacic, B.; Nurnberg, D.; Kabaalioglu, A.; et al. EFSUMB guidelines on interventional ultrasound (INVUS), part I. General aspects (long version). *Ultraschall Med.* **2015**, *36*, E1–E14. [PubMed]
35. Lorentzen, T.; Nolsoe, C.P.; Ewertsen, C.; Nielsen, M.B.; Leen, E.; Havre, R.F.; Gritzmann, N.; Brkljacic, B.; Nurnberg, D.; Kabaalioglu, A.; et al. EFSUMB guidelines on interventional ultrasound (INVUS), part I. General aspects (short version). *Ultraschall Med.* **2015**, *36*, 464–472. [PubMed]
36. Sidhu, P.S.; Brabrand, K.; Cantisani, V.; Correas, J.M.; Cui, X.W.; D'Onofrio, M.; Essig, M.; Freeman, S.; Gilja, O.H.; Gritzmann, N.; et al. EFSUMB guidelines on interventional ultrasound (INVUS), part II. Diagnostic ultrasound-guided interventional procedures (long version). *Ultraschall Med.* **2015**, *36*, E15–E35. [PubMed]
37. Sidhu, P.S.; Brabrand, K.; Cantisani, V.; Correas, J.M.; Cui, X.W.; D'Onofrio, M.; Essig, M.; Freeman, S.; Gilja, O.H.; Gritzmann, N.; et al. EFSUMB guidelines on interventional ultrasound (INVUS), part II. Diagnostic ultrasound-guided interventional procedures (short version). *Ultraschall Med.* **2015**, *36*, 566–580. [PubMed]
38. Dietrich, C.F.; Lorentzen, T.; Appelbaum, L.; Buscarini, E.; Cantisani, V.; Correas, J.M.; Cui, X.W.; D'Onofrio, M.; Gilja, O.H.; Hocke, M.; et al. EFSUMB guidelines on interventional ultrasound (INVUS), part III—abdominal treatment procedures (short version). *Ultraschall Med.* **2016**, *37*, 27–45. [CrossRef] [PubMed]
39. Dietrich, C.F.; Lorentzen, T.; Appelbaum, L.; Buscarini, E.; Cantisani, V.; Correas, J.M.; Cui, X.W.; D'Onofrio, M.; Gilja, O.H.; Hocke, M.; et al. EFSUMB guidelines on interventional ultrasound (INVUS), part III—abdominal treatment procedures (long version). *Ultraschall Med.* **2016**, *37*, E1–E32. [CrossRef] [PubMed]
40. Dietrich, C.F.; Nuernberg, D. *Interventional Ultrasound*; Thieme: Stuttgart, Germany, 2014.
41. Dietrich, C.F.; Nuernberg, D. *Interventioneller Ultraschall. Lehrbuch und Atlas für die Interventionelle Sonographie*; Thieme Verlag: Stuttgart, Germany, 2011.

42. Nobili, V.; Vizzutti, F.; Arena, U.; Abraldes, J.G.; Marra, F.; Pietrobattista, A.; Fruhwirth, R.; Marcellini, M.; Pinzani, M. Accuracy and reproducibility of transient elastography for the diagnosis of fibrosis in pediatric nonalcoholic steatohepatitis. *Hepatology* **2008**, *48*, 442–448. [CrossRef] [PubMed]
43. Kutty, S.S.; Zhang, M.; Danford, D.A.; Hasan, R.; Duncan, K.F.; Kugler, J.D.; Quiros-Tejeira, R.E.; Kutty, S. Hepatic stiffness in the bidirectional cavopulmonary circulation: The liver adult-pediatric-congenital-heart-disease dysfunction study group. *J. Thorac. Cardiovasc. Surg.* **2016**, *151*, 678–684. [CrossRef] [PubMed]
44. Berzigotti, A.; Ferraioli, G.; Bota, S.; Gilja, O.H.; Dietrich, C.F. Novel ultrasound-based methods to assess liver disease: The game has just begun. *Dig. Liver Dis.* **2018**, *50*, 107–112. [CrossRef] [PubMed]
45. Sandrin, L.; Fourquet, B.; Hasquenoph, J.M.; Yon, S.; Fournier, C.; Mal, F.; Christidis, C.; Ziol, M.; Poulet, B.; Kazemi, F.; et al. Transient elastography: A new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med. Biol.* **2003**, *29*, 1705–1713. [CrossRef] [PubMed]
46. Sigrist, R.M.S.; Liau, J.; Kaffas, A.E.; Chammas, M.C.; Willmann, J.K. Ultrasound elastography: Review of techniques and clinical applications. *Theranostics* **2017**, *7*, 1303–1329. [CrossRef] [PubMed]
47. Tsochatzis, E.A.; Gurusamy, K.S.; Ntaoula, S.; Cholongitas, E.; Davidson, B.R.; Burroughs, A.K. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: A meta-analysis of diagnostic accuracy. *J. Hepatol.* **2011**, *54*, 650–659. [CrossRef] [PubMed]
48. Engelmann, G.; Gebhardt, C.; Wenning, D.; Wuhl, E.; Hoffmann, G.F.; Selmi, B.; Grulich-Henn, J.; Schenk, J.P.; Teufel, U. Feasibility study and control values of transient elastography in healthy children. *Eur. J. Pediatr.* **2012**, *171*, 353–360. [CrossRef] [PubMed]
49. De Ledinghen, V.; Le Bail, B.; Rebouissoux, L.; Fournier, C.; Foucher, J.; Miette, V.; Castera, L.; Sandrin, L.; Merrouche, W.; Lavrand, F.; et al. Liver stiffness measurement in children using fibroscan: Feasibility study and comparison with fibrotest, aspartate transaminase to platelets ratio index, and liver biopsy. *J. Pediatr. Gastroenterol. Nutr.* **2007**, *45*, 443–450. [CrossRef] [PubMed]
50. Goldschmidt, I.; Streckenbach, C.; Dingemann, C.; Pfister, E.D.; di Nanni, A.; Zapf, A.; Baumann, U. Application and limitations of transient liver elastography in children. *J. Pediatr. Gastroenterol. Nutr.* **2013**, *57*, 109–113. [CrossRef] [PubMed]
51. Lewindon, P.J.; Balouch, F.; Pereira, T.N.; Puertolas-Lopez, M.V.; Noble, C.; Wixey, J.A.; Ramm, G.A. Transient liver elastography in unsedated control children: Impact of age and intercurrent illness. *J. Paediatr. Child Health* **2016**, *52*, 637–642. [CrossRef] [PubMed]
52. Kim, S.; Kang, Y.; Lee, M.J.; Kim, M.J.; Han, S.J.; Koh, H. Points to be considered when applying fibroscan s probe in children with biliary atresia. *J. Pediatr. Gastroenterol. Nutr.* **2014**, *59*, 624–628. [CrossRef] [PubMed]
53. Alkhouri, N.; Sedki, E.; Alisi, A.; Lopez, R.; Pinzani, M.; Feldstein, A.E.; Nobili, V. Combined paediatric nafld fibrosis index and transient elastography to predict clinically significant fibrosis in children with fatty liver disease. *Liver Int.* **2013**, *33*, 79–85. [CrossRef] [PubMed]
54. Behrens, A.; Labenz, J.; Schuler, A.; Schroder, W.; Runzi, M.; Steinmann, R.U.; de Mas, C.R.; Kreuzmayr, A.; Barth, K.; Bahr, M.J.; et al. [how safe is sedation in gastrointestinal endoscopy? A multicentre analysis of 388,404 endoscopies and analysis of data from prospective registries of complications managed by members of the working group of leading hospital gastroenterologists (ALGK)]. *Z. Gastroenterol.* **2013**, *51*, 432–436. [PubMed]
55. Bernatik, T.; Schuler, A.; Kunze, G.; Mauch, M.; Dietrich, C.F.; Dirks, K.; Pachmann, C.; Borner, N.; Fellermann, K.; Menzel, J.; et al. Benefit of contrast-enhanced ultrasound (CEUS) in the follow-up care of patients with colon cancer: A prospective multicenter study. *Ultraschall Med.* **2015**, *36*, 590–593. [CrossRef] [PubMed]
56. Lee, C.K.; Perez-Atayde, A.R.; Mitchell, P.D.; Raza, R.; Afdhal, N.H.; Jonas, M.M. Serum biomarkers and transient elastography as predictors of advanced liver fibrosis in a united states cohort: The Boston children's hospital experience. *J. Pediatr.* **2013**, *163*, 1058–1064. [CrossRef] [PubMed]
57. Chongsrisawat, V.; Vejapipat, P.; Siripon, N.; Poovorawan, Y. Transient elastography for predicting esophageal/gastric varices in children with biliary atresia. *BMC Gastroenterol.* **2011**, *11*, 41. [CrossRef] [PubMed]
58. Bailey, S.S.; Youssfi, M.; Patel, M.; Hu, H.H.; Shaibi, G.Q.; Towbin, R.B. Shear-wave ultrasound elastography of the liver in normal-weight and obese children. *Acta Radiol.* **2017**, *58*, 1511–1518. [CrossRef] [PubMed]

59. Eiler, J.; Kleinholdermann, U.; Albers, D.; Dahms, J.; Hermann, F.; Behrens, C.; Luedemann, M.; Klingmueller, V.; Alzen, G.F. Standard value of ultrasound elastography using acoustic radiation force impulse imaging (ARFI) in healthy liver tissue of children and adolescents. *Ultraschall Med.* **2012**, *33*, 474–479. [CrossRef] [PubMed]
60. Hanquinet, S.; Courvoisier, D.; Kanavaki, A.; Dhouib, A.; Anooshiravani, M. Acoustic radiation force impulse imaging-normal values of liver stiffness in healthy children. *Pediatr. Radiol.* **2013**, *43*, 539–544. [CrossRef] [PubMed]
61. Matos, H.; Trindade, A.; Noruegas, M.J. Acoustic radiation force impulse imaging in paediatric patients: Normal liver values. *J. Pediatr. Gastroenterol. Nutr.* **2014**, *59*, 684–688. [CrossRef] [PubMed]
62. Fontanilla, T.; Canas, T.; Macia, A.; Alfageme, M.; Gutierrez Junquera, C.; Malalana, A.; Luz Cilleruelo, M.; Roman, E.; Miralles, M. Normal values of liver shear wave velocity in healthy children assessed by acoustic radiation force impulse imaging using a convex probe and a linear probe. *Ultrasound Med. Biol.* **2014**, *40*, 470–477. [CrossRef] [PubMed]
63. Marginean, C.O.; Marginean, C. Elastographic assessment of liver fibrosis in children: A prospective single center experience. *Eur. J. Radiol.* **2012**, *81*, e870–e874. [CrossRef] [PubMed]
64. Pinto, J.; Matos, H.; Nobre, S.; Cipriano, M.A.; Marques, M.; Pereira, J.M.; Goncalves, I.; Noruegas, M.J. Comparison of acoustic radiation force impulse/serum noninvasive markers for fibrosis prediction in liver transplant. *J. Pediatr. Gastroenterol. Nutr.* **2014**, *58*, 382–386. [CrossRef] [PubMed]
65. Tomita, H.; Hoshino, K.; Fuchimoto, Y.; Ebinuma, H.; Ohkuma, K.; Tanami, Y.; Du, W.; Masugi, Y.; Shimojima, N.; Fujino, A.; et al. Acoustic radiation force impulse imaging for assessing graft fibrosis after pediatric living donor liver transplantation: A pilot study. *Liver Transplant.* **2013**, *19*, 1202–1213. [CrossRef] [PubMed]
66. Dhyani, M.; Gee, M.S.; Misdraji, J.; Israel, E.J.; Shah, U.; Samir, A.E. Feasibility study for assessing liver fibrosis in paediatric and adolescent patients using real-time shear wave elastography. *J. Med. Imaging Radiat. Oncol.* **2015**, *59*, 687–694. [CrossRef] [PubMed]
67. Roensch, M. Lebergewebecharakterisierung Mittels Acoustic Radiation Force Impulse-Elastographie und Zone Speed Index im Kindes- und Jugendalter. Ph.D. Thesis, Martin-Luther-Universität Halle-Wittenberg, Halle, Germany, 2017.
68. Weinitschke, K. Vergleichswerterstellung für die Acoustic-Radiation-Force-Impulse-Elastographie der Leber im Kindes- und Jugendalter. Ph.D. Thesis, Martin-Luther-Universität Halle-Wittenberg, Halle, Germany, 2015.
69. Dietrich, C.F.; Nuernberg, D. *Interventional Ultrasound. A Practical Guide and Atlas*; Thieme: Stuttgart, Germany, 2014.
70. Bargon, J.; Stein, J.; Dietrich, C.F.; Muller, U.; Caspary, W.F.; Wagner, T.O. [Gastrointestinal complications of adult patients with cystic fibrosis]. *Z. Gastroenterol.* **1999**, *37*, 739–749. [PubMed]
71. Kim, J.R.; Suh, C.H.; Yoon, H.M.; Lee, J.S.; Cho, Y.A.; Jung, A.Y. The diagnostic performance of shear-wave elastography for liver fibrosis in children and adolescents: A systematic review and diagnostic meta-analysis. *Eur. Radiol.* **2018**, *28*, 1175–1186. [CrossRef] [PubMed]
72. Shin, H.J.; Kim, M.J.; Kim, H.Y.; Roh, Y.H.; Lee, M.J. Optimal acquisition number for hepatic shear wave velocity measurements in children. *PLoS ONE* **2016**, *11*, e0168758. [CrossRef] [PubMed]
73. Zhou, L.Y.; Jiang, H.; Shan, Q.Y.; Chen, D.; Lin, X.N.; Liu, B.X.; Xie, X.Y. Liver stiffness measurements with supersonic shear wave elastography in the diagnosis of biliary atresia: A comparative study with grey-scale us. *Eur. Radiol.* **2017**, *27*, 3474–3484. [CrossRef] [PubMed]
74. Hong, E.K.; Choi, Y.H.; Cheon, J.E.; Kim, W.S.; Kim, I.O.; Kang, S.Y. Accurate measurements of liver stiffness using shear wave elastography in children and young adults and the role of the stability index. *Ultrasonography* **2017**. [CrossRef] [PubMed]
75. Dong, Y.; Wang, W.P.; Xu, Y.; Cao, J.; Mao, F.; Dietrich, C.F. Point shear wave speed measurement in differentiating benign and malignant focal liver lesions. *Med. Ultrason.* **2017**, *19*, 259–264. [CrossRef] [PubMed]
76. Dietrich, C.F.; Averkiou, M.; Nielsen, M.B.; Barr, R.G.; Burns, P.N.; Calliada, F.; Cantisani, V.; Choi, B.; Chammas, M.C.; Clevert, D.A.; et al. How to perform contrast-enhanced ultrasound (CEUS). *Ultrasound Int. Open* **2018**, *4*, E2–E15. [CrossRef] [PubMed]

77. Sidhu, P.S.; Cantisani, V.; Deganello, A.; Dietrich, C.F.; Duran, C.; Franke, D.; Harkanyi, Z.; Kosiak, W.; Miele, V.; Ntoulia, A.; et al. Role of contrast-enhanced ultrasound (CEUS) in paediatric practice: An EFSUMB position statement. *Ultraschall Med.* **2017**, *38*, 33–43. [CrossRef] [PubMed]
78. Dong, Y.; Wang, W.P.; Mao, F.; Fan, M.; Ignee, A.; Serra, C.; Sparchez, Z.; Sporea, I.; Braden, B.; Dietrich, C.F. Contrast enhanced ultrasound features of hepatic cystadenoma and hepatic cystadenocarcinoma. *Scand. J. Gastroenterol.* **2017**, *52*, 365–372. [CrossRef] [PubMed]
79. Dietrich, C.F.; Dong, Y.; Froehlich, E.; Hocke, M. Dynamic contrast-enhanced endoscopic ultrasound: A quantification method. *Endosc. Ultrasound* **2017**, *6*, 12–20. [CrossRef] [PubMed]
80. Dong, Y.; Wang, W.P.; Cantisani, V.; D'Onofrio, M.; Ignee, A.; Mulazzani, L.; Saftoiu, A.; Sparchez, Z.; Sporea, I.; Dietrich, C.F. Contrast-enhanced ultrasound of histologically proven hepatic epithelioid hemangioendothelioma. *World J. Gastroenterol.* **2016**, *22*, 4741–4749. [CrossRef] [PubMed]
81. Chiorean, L.; Cui, X.W.; Tannapfel, A.; Franke, D.; Stenzel, M.; Kosiak, W.; Schreiber-Dietrich, D.; Jungert, J.; Chang, J.M.; Dietrich, C.F. Benign liver tumors in pediatric patients—Review with emphasis on imaging features. *World J. Gastroenterol.* **2015**, *21*, 8541–8561. [CrossRef] [PubMed]
82. Cui, X.W.; Pirri, C.; Ignee, A.; De Molo, C.; Hirche, T.O.; Schreiber-Dietrich, D.G.; Dietrich, C.F. Measurement of shear wave velocity using acoustic radiation force impulse imaging is not hampered by previous use of ultrasound contrast agents. *Z. Gastroenterol.* **2014**, *52*, 649–653. [CrossRef] [PubMed]
83. Piscaglia, F.; Nolsoe, C.; Dietrich, C.F.; Cosgrove, D.O.; Gilja, O.H.; Bachmann, N.M.; Albrecht, T.; Barozzi, L.; Bertolotto, M.; Catalano, O.; et al. The EFSUMB guidelines and recommendations on the clinical practice of contrast enhanced ultrasound (CEUS): Update 2011 on non-hepatic applications. *Ultraschall Med.* **2012**, *33*, 33–59. [CrossRef] [PubMed]
84. Dietrich, C.F.; Dong, Y.; Jenssen, C.; Ciaravino, V.; Hocke, M.; Wang, W.P.; Burmester, E.; Moeller, K.; Atkinson, N.S.; Capelli, P.; et al. Serous pancreatic neoplasia, data and review. *World J. Gastroenterol.* **2017**, *23*, 5567–5578. [CrossRef] [PubMed]
85. Dietrich, C.F.; Sahai, A.V.; D'Onofrio, M.; Will, U.; Arcidiacono, P.G.; Petrone, M.C.; Hocke, M.; Braden, B.; Burmester, E.; Moller, K.; et al. Differential diagnosis of small solid pancreatic lesions. *Gastrointest. Endosc.* **2016**, *84*, 933–940. [CrossRef] [PubMed]
86. Cui, X.W.; Chang, J.M.; Kan, Q.C.; Chiorean, L.; Ignee, A.; Dietrich, C.F. Endoscopic ultrasound elastography: Current status and future perspectives. *World J. Gastroenterol.* **2015**, *21*, 13212–13224. [CrossRef] [PubMed]
87. Cosgrove, D.; Barr, R.; Bojunga, J.; Cantisani, V.; Chammas, M.C.; Dighe, M.; Vinayak, S.; Xu, J.M.; Dietrich, C.F. WFUMB guidelines and recommendations on the clinical use of ultrasound elastography: Part 4. Thyroid. *Ultrasound Med. Biol.* **2017**, *43*, 4–26. [CrossRef] [PubMed]
88. Dighe, M.; Barr, R.; Bojunga, J.; Cantisani, V.; Chammas, M.C.; Cosgrove, D.; Cui, X.W.; Dong, Y.; Fenner, F.; Radzina, M.; et al. Thyroid ultrasound: State of the art. Part 2—Focal thyroid lesions. *Med. Ultrason.* **2017**, *19*, 195–210. [CrossRef] [PubMed]
89. Dighe, M.; Barr, R.; Bojunga, J.; Cantisani, V.; Chammas, M.C.; Cosgrove, D.; Cui, X.W.; Dong, Y.; Fenner, F.; Radzina, M.; et al. Thyroid ultrasound: State of the art part 1—Thyroid ultrasound reporting and diffuse thyroid diseases. *Med. Ultrason.* **2017**, *19*, 79–93. [CrossRef] [PubMed]
90. Ceyhan Bilgici, M.; Saglam, D.; Delibalta, S.; Yucel, S.; Tomak, L.; Elmali, M. Shear wave velocity of the healthy thyroid gland in children with acoustic radiation force impulse elastography. *J. Med. Ultrason.* **2018**, *45*, 75–80. [CrossRef] [PubMed]
91. Ozturk, M.; Yildirim, R. The usefulness of strain wave elastography in the diagnosis and grading of hashimoto's thyroiditis in children. *Radiol. Med.* **2017**, *122*, 960–966. [CrossRef] [PubMed]
92. Saglam, D.; Ceyhan Bilgici, M.; Kara, C.; Can Yilmaz, G.; Tanrivermis Sayit, A. Does type 1 diabetes mellitus affect the shear wave velocity of the thyroid gland of children without autoimmune thyroiditis? *Ultrasound Q.* **2017**, *33*, 225–228. [CrossRef] [PubMed]
93. Dietrich, C.F.; Bojunga, J. [Ultrasound of the thyroid]. *Laryngorhinootologie* **2016**, *95*, 87–104. [PubMed]
94. Friedrich-Rust, M.; Vorlaender, C.; Dietrich, C.F.; Kratzer, W.; Blank, W.; Schuler, A.; Broja, N.; Cui, X.W.; Herrmann, E.; Bojunga, J. Evaluation of strain elastography for differentiation of thyroid nodules: Results of a prospective degum multicenter study. *Ultraschall Med.* **2016**, *37*, 262–270. [CrossRef] [PubMed]
95. Barr, R.G.; Cosgrove, D.; Brock, M.; Cantisani, V.; Correas, J.M.; Postema, A.W.; Salomon, G.; Tsutsumi, M.; Xu, H.X.; Dietrich, C.F. WFUMB guidelines and recommendations on the clinical use of ultrasound elastography: Part 5. Prostate. *Ultrasound Med. Biol.* **2017**, *43*, 27–48. [CrossRef] [PubMed]

96. Barr, R.G.; Nakashima, K.; Amy, D.; Cosgrove, D.; Farrokh, A.; Schafer, F.; Bamber, J.C.; Castera, L.; Choi, B.I.; Chou, Y.H.; et al. WFUMB guidelines and recommendations for clinical use of ultrasound elastography: Part 2: Breast. *Ultrasound Med. Biol.* **2015**, *41*, 1148–1160. [CrossRef] [PubMed]
97. Friedrich-Rust, M.; Schwarz, A.; Ong, M.; Dries, V.; Schirmacher, P.; Herrmann, E.; Samaras, P.; Bojunga, J.; Bohle, R.M.; Zeuzem, S.; et al. Real-time tissue elastography versus fibroscan for noninvasive assessment of liver fibrosis in chronic liver disease. *Ultraschall Med.* **2009**, *30*, 478–484. [CrossRef] [PubMed]
98. Schenk, J.P.; Alzen, G.; Klingmuller, V.; Teufel, U.; El Sakka, S.; Engelmann, G.; Selmi, B. Measurement of real-time tissue elastography in a phantom model and comparison with transient elastography in pediatric patients with liver diseases. *Diagn. Interv. Radiol.* **2014**, *20*, 90–99. [PubMed]
99. Schenk, J.P.; Selmi, B.; Flechtenmacher, C.; Sakka, S.E.; Teufel, U.; Engelmann, G. Real-time tissue elastography (RTE) for noninvasive evaluation of fibrosis in liver diseases in children in comparison to liver biopsy. *J. Med. Ultrason.* **2014**, *41*, 455–462. [CrossRef] [PubMed]
100. Selmi, B.; Engelmann, G.; Teufel, U.; El Sakka, S.; Dadrich, M.; Schenk, J.P. Normal values of liver elasticity measured by real-time tissue elastography (RTE) in healthy infants and children. *J. Med. Ultrason.* **2014**, *41*, 31–38. [CrossRef] [PubMed]
101. Hermeziu, B.; Messous, D.; Fabre, M.; Munteanu, M.; Baussan, C.; Bernard, O.; Poynard, T.; Jacquemin, E. Evaluation of fibrotest-actitest in children with chronic hepatitis c virus infection. *Gastroenterol. Clin. Biol.* **2010**, *34*, 16–22. [CrossRef] [PubMed]
102. El-Shabrawi, M.H.; Mohsen, N.A.; Sherif, M.M.; El-Karaksy, H.M.; Abou-Yosef, H.; El-Sayed, H.M.; Riad, H.; Bahaa, N.; Isa, M.; El-Hennawy, A. Noninvasive assessment of hepatic fibrosis and necroinflammatory activity in egyptian children with chronic hepatitis c virus infection using fibrotest and actitest. *Eur. J. Gastroenterol. Hepatol.* **2010**, *22*, 946–951. [CrossRef] [PubMed]
103. Dietrich, C.F.; Dong, Y. Shear wave elastography with a new reliability indicator. *J. Ultrason.* **2016**, *16*, 281–287. [CrossRef] [PubMed]
104. Angulo, P.; Kleiner, D.E.; Dam-Larsen, S.; Adams, L.A.; Bjornsson, E.S.; Charatcharoenwitthaya, P.; Mills, P.R.; Keach, J.C.; Lafferty, H.D.; Stahler, A.; et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* **2015**, *149*, 389–397. [CrossRef] [PubMed]