



Review Elastography—A Bona Fide Non-Invasive Method for Assessing Non-Alcoholic Fatty Liver Disease in Children

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Abstract: Pediatric obesity has become a major public health problem worldwide, resulting in a wide spectrum of systemic complications. Liver disease associated with obesity, also known as nonalcoholic fatty liver disease (NAFLD), is currently the most common chronic liver condition in children. Therefore, its timely and proper diagnosis is essential for preventing further development of cirrhosis. Multiple studies focused on identifying the most accurate non-invasive diagnostic method for liver fibrosis or cirrhosis. Although liver biopsy remains the gold-standard in terms of this hepatopathy, elastography methods emerged as a relatively reliable alternative to liver biopsy. Thus, recent studies revealed the great importance of these non-invasive methods not only in diagnosing pediatric NAFLD, but also in its staging. MRE is commonly considered to have a greater accuracy than ultrasound-based elastography methods, but with lower availability and higher costs. Ultrasoundbased elastography methods (transient elastography (TE), p-SWE, and 2-dimensional shear wave elastography (2D-SWE)) were proved to have similar accuracy in NAFLD staging. Nevertheless, multiple confounding factors account for potential challenges when using elastography for liver stiffness measurement, such as age, obesity itself (i.e., BMI), transaminase levels, or portal flow. A potential solution for facing these challenges might be represented by a complex approach based on the combination between elastography, clinical and laboratory findings. Although the studies that assessed the role of elastography in pediatric NAFLD staging are scarce, the current knowledge underlines a crucial role of these techniques taking into account their ability to distinguish between fibrosis degrees, their non-invasive patterns, lower costs and side effects when compared to liver biopsy. Therefore, elastography might become a cornerstone in staging pediatric NAFLD.

Keywords: elastography; children; nonalcoholic fatty liver disease

1. Introduction

Childhood obesity is a continuous emerging burden worldwide. According to the World Health Organization reports from 2018, pediatric overweight and obesity represent two major public health problems affecting over 40 million children aged under 5 years [1]. Both conditions consist of excessive fat accumulation and carry a wide-spectrum of associated complications. Although genetic susceptibility was proven to be a mandatory factor in the development of obesity [2], the contribution of environmental factors in this process is a sine qua non condition. Moreover, it was underlined that overweight is not only a preliminary step in the development of obesity, but it might represent an optimal, essential opportunity of self-awareness for further hindering the occurrence of obesity [3]. A wide-spectrum of conditions were defined as obesity-associated complications such as cardiovascular, hepatic, or metabolic disorders [4]. Most of these complications were related to the well-documented systemic inflammatory status encountered in patients with obesity [5,6].



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Liver disease in the setting of obesity is currently acknowledged as one of the most frequent complications of children with this nutritional disorder. Thus, non-alcoholic fatty liver disease (NAFLD) was reported in approximately 50% of children with obesity, being considered the most common pediatric chronic liver disease, with an incidence ranging between 5 and 17% among children from Western countries [7]. NAFLD, defined as accumulation of fat in the liver, is generally a silent, potentially reversible condition, but it might also progress into a more severe form, i.e., non-alcoholic steatohepatitis (NASH) associating steatosis, inflammation and cellular injury with or without fibrosis [8], with an increased the risk for cirrhosis and end-stage liver disease [9,10]. The gold-standard in providing an accurate diagnosis and staging of NAFLD is undoubtedly liver biopsy, which also allows a proper assessment of other hepatic conditions. Nevertheless, this procedure carries multiple risks in children and parents' refusal is a major hindrance for this approach in young ages. Therefore, the early diagnosis and staging of NAFLD might represent a real challenge in children since no free national screening programs similar to other conditions are currently available [11,12]. A complex approach consisting of the assessment of several laboratory parameters combined with different imaging tools represents an alternative for liver biopsy. Most of the studies sustain that elevated liver transaminases represent a common finding associated with liver disease in children with obesity [5]. Taking into account their fluctuations over time and even their normal levels in children with NAFLD, or even NASH, their role as single parameter in diagnosing this hepatic condition is doubtable [13]. The American Association for the Study of Liver Disease (AASLD) recommends the use of two algorithms, FIB-4 and NFS, for the assessment of liver fibrosis based on routine clinical and laboratory parameters, which seem to be useful in predicting advanced hepatic cirrhosis or fibrosis [14]. Thus, FIB-4 takes into account the age, platelets count, aspartate aminotransferase (AST), and alanine aminotransferase, and it was proved to be useful for the stratification of NAFLD patients differentiating between those with advanced fibrosis versus none [15-17]. NFS is an even more complex algorithm including not only the age, the platelets, and AST/ALT ration, but also BMI, albumin levels, and the assessment of glucose tolerance/diabetes, representing a reliable alternative for liver biopsy [8]. Studies performed on children and adolescents with obesity pointed out higher levels of AST/platelets ratio index (APRI) in these patients, but failed in identifying a correlation with liver stiffness [18,19]. In addition to liver transaminases, bilirubin, lipid profile parameters, fasting glucose, and insulin are also useful for diagnosing fatty liver disease in patients with metabolic syndrome [13]. A clear bidirectional interrelation has been stated between NAFLD and metabolic syndrome, whose components (e.g., type 2 diabetes mellitus, obesity, hypertension, dyslipidemia) additionally increase the risk of developing NAFLD [20–23]. Furthermore, NASH carries higher rates of both morbidity and mortality increasing the risk of cirrhosis and hepatocellular carcinoma [24], with a higher mortality as compared to isolated or simple steatosis [25]. Taking into account the current era of pediatric obesity, the early detection and staging of NAFLD based on a more complex non-invasive approach including clinical, laboratory, and elastography parameters might contribute to the effective prevention of further irreversible hepatic lesions and decrease mortality during adulthood.

The aim of this review was to assess the role of elastography in pediatric NAFLD staging, as well as identifying its potential limitations and challenges in this age group.

2. Current Elastography Methods

Elastography methods are defined by the non-invasive assessment of tissue elasticity and its mechanical properties resulting from the application of external forces. Two major terms that are commonly confounded in practice must be differentiated: tissue elasticity, i.e., the tissue ability to deform and resume its normal shape in the setting of an applied stress dependently of tissue stiffness, the second term, which indicates tissue composition and structure [26]. Thus, when referring to elastography, the term liver stiffness seems to be more appropriate. Liver elastography has gained a lot of interest in the context of NAFLD, a current global public health problem in all age groups. Thus, liver elastography aims to objectively characterize diffuse liver disease and it might reflect pathologic processes such as fibrosis, inflammation or congestion [27–30]. Taking into account the increased rates of both morbidity and mortality in patients with diffuse liver disease [31], a proper management is essential for the best outcome in these patients. Furthermore, the management depends mostly on the accurate staging of liver fibrosis. Liver elastography seems to be a promising diagnostic tool in the assessment of liver fibrosis irrespectively of the age and type of chronic liver disease.

Current elastography methods for liver assessment encompass magnetic resonance elastography (MRE), and three main ultrasound-based elastography techniques, i.e., transient elastography (TE, Figure 1), acoustic radiation force impulse (ARFI) divided into point shear wave elastography (p-SWE), and 2-dimensional shear wave elastography (2D SWE, Figure 2), and strain elastography. The latter one is not used for liver stiffness measurement and therefore we will not focus on its description since it does not fulfill the aim of this review. Liver fibrosis is a dynamic process consisting of excessive extracellular matrix accumulation as a result to injury and inflammation, followed by degradation of this excessive matrix and consequent remodeling [25]. Fibroblasts and myofibroblasts also contribute to hepatic fibrosis [25]. Independently of its continuous dynamics, at some point hepatic fibrosis exceeds degradation, leading to cirrhosis and related-changes in vascular architecture. Moreover, both excessive extracellular matrix in the setting of liver fibrosis and vascular architecture changes result in increased liver stiffness [25].



Figure 1. Liver transient elastography (TE) in normal weight healthy children.



Figure 2. Liver 2-dimensional shear wave elastography(2D-SWE) in normal weight healthy children.

MRE of liver uses mechanically generated shear waves, which are propagated into the liver and their images are obtained using a modified phase contrast MRI sequence, further converted into tissue stiffness maps or elastograms based on an inversion algorithm [32,33]. It is important to mention that the propagation of these shear waves occurs faster in stiffer tissue than in softer tissue, i.e., in cirrhotic tissue as compared to normal liver. Clinical liver MRE set up usually consists of an active driver, a passive driver positioned in the inferior part of the right chest wall closer to the liver, and a 25-foot-long plastic tube connecting these drivers. The active driver is represented by an acoustic driving system that generates 60 Hz shear waves in tissue from outside the scanner room. The passive driver is activated as a result of varying acoustic pressure triggered from the active driver via the plastic tube. Patients must rest in a supine position during the exam. Tissue displacement caused by the propagation of shear waves is determined by a modified phase contrast imaging sequence, which uses different conventional MR sequences, such as gradient recalled echo, echoplanar imaging, spin echo, or balanced steady state free precision. MRE has the capacity to spatially map and quantify displacement patterns, which are useful for the calculation of certain mechanical characteristics related to wave propagation. Several MRE algorithms are available for the inversion of wave information into stiffness maps such as direct inversion of differential equations of motion, spatial frequency measurement, or iterative method based on the finite element model. These algorithms are used for measuring an important mechanical tissue characteristic, i.e., 'the magnitude of the complex shear modulus' accounting for both elasticity and viscosity, expressed in kilopascals [34-36].

It is well-documented that MRE is more accurate for both detecting and staging of liver fibrosis [32,37] as compared to ultrasound-based elastography methods, but with definitely higher associated costs. MRE technical performance reaches approximately 95% and the most common cause of failure is iron overload [25]. Additionally, a study that assessed 781 liver MREs pointed out other independent factors related to failure, among which were ascites and increased body mass index [38]. Nevertheless, a more recent study performed on 71 healthy pediatric volunteers revealed a mean liver stiffness value of 2.1 kPa, pointing out that sex, age, or BMI had no impact on liver stiffness measurement [34]. Conflicting results might be explained by technical or platform-related differences in terms

of strength, driver frequency used for MRE, MR scanner vendor, or they might reflect the differences between the populations included in the study [34]. Liver thresholds for MRE defined for healthy children differ from those in healthy adults [39]. Thus, Etchell et al. revealed that healthy children present lower liver stiffness values as compared to healthy adults [40]. These findings came in contradiction to those of Sawh et al., who recently found that normal liver stiffness values were higher in children than previously reported for adults [33]. In terms of liver fibrosis, different studies pointed out that the cut-off values range between 2.4–2.93 kPa [41–45]. A strong correlation has been identified between MRE liver stiffness measurements and the amount of fibrosis in the liver biopsy samples suggesting that MRE has the same accuracy as biopsy for liver fibrosis staging [46]. The accuracy of MRE for detecting liver fibrosis increases with the stage of fibrosis, but with an excellent overall performance [37]. Recent studies underlined that MRE has only modest accuracy in distinguish between NASH and simple steatosis [47–49], a large study involving pediatric patients pointing out that liver fat may express a mild softening effect in the setting of MRE assessment [50]. Therefore, a considerably improved alternative method consists of a comprehensive liver MRI study defined by fat quantification, detection of inflammation and staging of liver fibrosis [51], with an obvious higher accuracy, but considerable associated costs. Nevertheless, Chen et al. pointed out that MRE has a 94% sensitivity and a 73% specificity with an accuracy of 0.93 in discriminating between simple steatosis and NASH [45]. In terms of NAFLD, the MRE specificity and sensitivity rates were proven to be 93% and 85% in detecting advanced fibrosis [52]. The most important findings regarding MRE in children are summarized in Table 1. Altogether, ultrasound based elastography methods might be a more available option with lower associated costs and similar result.

The shear wave-based methods, i.e., TE and ARFI, assess the speed of these waves in tissue depending on tissue stiffness, the waves being triggered by an external mechanical force in case of TE and the push pulse of a focused ultrasound beam in case of ARFI [53]. TE is a 1D technique provided by the FibroScan system (Echosens, Paris, France) and its latest version uses the controlled attenuation parameter (CAP) tool in order to measure the decrease in amplitude of ultrasound signal in the liver. The results range between 100–400 dB/m depending on the amount of fat tissue within the liver. Three types of probes are available for this system: the S probe, designed for children since their thoracic diameters is <75 cm, for measurements between 1.5–5 cm, with a frequency of 5.0 MHz; the M probe designed for measurements up to 6.5 cm from the skin, with a frequency of 3.5 MHz; and the XL probe designed for a distance >2.5 cm between the skin and liver capsule, with a frequency of 2.5 MHz, for measurements ranging between 3.5–7.5 cm. As of today, CAP has the ability to display only valid measurements, being computed as a result of the ultrasound signals used for acquiring liver stiffness measurements [35].

Xanthakos et al., 2014, USA [58]

Etchell et al., 2017, Australia [40] Prospective/24

Prospective/35

Table 1. Magnetic resonance elastography (MRE) values in normal weight and obese children.									
			MRE	(KPa)					
Author, Year, and Country	Study Type/No of Patients	Age (Years) Mean/Median *	Normal Weight Children Mean/Median *	NAFLD/NASH Children Mean/Median *	Observations				
Sawh et al., 2020, USA [33]	Prospective/81	12.6 ± 2.6	2.45 ± 0.35	-	The values are significant higher than in adults (2.10 \pm 0.23 kPa) (p < 0.001)				
Trout et al., 2020, USA [34]	Prospective/71	12 *	2.1 ± 1.96	-	P95 for normal liver stiffness was 2.8 kPa. Liver stiffness was independent of sex, age, or BMI				
Krishnamurthy et al., 2020, USA [54]	Retrospective/122	14.7 ± 3.5	-	2.6 ± 0.7 kPa for boys 2.8 ± 0.8 kPa for girls	There are stiffness variations within the 8 Couinaud segments of the liver in children				
Joshi et al., 2018, USA [50]	Prospective/202	13.4 ± 2.9	-	2.6 ± 0.6	Relationships between stiffness, and organ volume and some patient-specific factors, including sex, age, BMI, serum ALT, and diabetic status				
Trout et al., 2018, USA [55]	Prospective/86	14.2 *	F0: 2.90 ± 0.87 ; F1: $2.41 \pm$ 0.51; F2: 3.64 ± 1.12 ; F3: 4.55 ± 1.68 ; F4: 4.68 ± 1.32	F0: 2.68 \pm 0.31; F1: 3.04 \pm 0.63; F2: 2.71 \pm 0.59; F3: 7.43 \pm 2.68; F4 not aplicable	MR elastography performs significantly better for distinguishing stage 0–1 versus stage 2 or higher fibrosis in patients without steatosis than in those with steatosis.				
Joshi et al., 2017, USA [56]	Retrospective/372	12.6 ± 3.7	-	$2.94\pm1.11~\mathrm{kPa}$	Mean patient BMI was $29.4 \pm 10.1 \text{ kg/m}^2$				
Schwimmer et al., 2017, USA [57]	Prospective/90	13.1 ± 2.4	-	2.35 kPa	Correlation with fibrosis (by biopsy) was 72.2%				

Children: At 28 Hz: 1.2 \pm $0.2/At\,56$ Hz: $2.2\pm0.3/At\,84$

Hz: At 5.6 ± 0.8

Adolescents: At 28 Hz: 1.3 \pm

 $0.3/At\,56\,Hz$: $2.2\pm0.2/At\,84$ Hz: 6.5 ± 1.2

F1: 2.2 kPa; F3: 3.6 kPa; F4:

4.9 kPa

Legend: MRE—magnetic resonance elastography, y—years; * Mean age calculated from mean of the three age groups in the study.

5-18

13 *

Liver stiffness values are lower and vary less

with frequency in children and adolescents

Cut-off = 2.71 kPa—8% sensitivity, 85%

(95% CI, 0.79-1.00; p = 0.02)

specificity for F2 with an AUROC of 0.92

than in adults.

ARFI techniques are available on both linear and curvilinear transducers and as aforementioned, they rely on the generation of shear waves from the push pulse of the ultrasound beam [59]. In practice, an initial push pulse is applied to the tissue, inducing shear waves perpendicular to the ultrasound beam. The speed of the shear waves propagating through the tissue are estimated using B-mode imaging tracking, and it is proportional to tissue stiffness. Using these methods, liver stiffness can be expressed in m/s displaying the speed of the shear wave through the tissue, or in kPa, based on the Young's modulus. 2-dimensional shear wave elastography (2D-SWE) uses a large field of view with pixel color coding of the stiffness values, while p-SWE is based on the assessment of a fixed region of interest (ROI) of approximately 1 mL. Regarding the actual technique, several specifics are important, such as the transducer's position parallel to the liver capsule, the ROI parallel to the transducer and perpendicular to the ARFI pulse, as well as the observer's focus on avoiding artefactual liver stiffening by taking the measurements 1.5–2 cm under the liver capsule. In order to obtain a value as accurate as possible, ten measurements are recommended in case of p-SWE and 5 for 2D-SWE [60]. Nevertheless, the quality criteria depends on the recommendation of each vendor [61]. The variability of measurements performed with p-SWE and 2D SWE was found to increase with liver stiffness [47]. It is worth mentioning that most of the data available in the literature focused on TE and several studies consider FibroScan as a reference for shear wave-based techniques [62,63]. Cut-off values for ultrasound-based elastography in children identified in the literature were summarized in Table 2.

3. The Opportunities and Challenges of Ultrasound-Based Elastography in Children NAFLD

Liver fibrosis in pediatric patients is commonly seen in the setting of fatty liver disease, hepatitis, primary sclerosing cholangitis, autoimmune hepatitis, congestive hepatopathy, cystic fibrosis, biliary atresia, Alagille syndrome, Fontan-associated liver disease, a-1 antitrypsin deficiency, storage disorders, and Wilson's disease [36,60]. Nevertheless, as we already mentioned, NAFLD has become one of the most common causes of chronic liver disease in pediatric populations due to the alarmingly persistent increasing incidence of obesity worldwide. Liver fibrosis is a common pathogenic feature of the above mentioned conditions and its assessment is extremely important in order to provide risk stratification, to guide therapeutic decision, and most important to monitor disease severity [26]. Taking into account the relatively low cost, the lack of invasive approach, no need for sedation, elastography might be a reliable alternative for the assessment of liver fibrosis. The importance of elastography methods for assessing liver fibrosis in adult patients is definitely incontestable, but in pediatric populations several challenges are related especially to their age-specific low compliance, resulting in possible invalid elastography measurement (Figures 3 and 4). Multiple confounding factors identified in pediatric populations were reported to influence liver stiffness on elastography, such as age, sedation, hepatic steatosis, or inflammation [64,65]. Hepatic congestion and inflammation, commonly seen in patients with congenital heart diseases and inflammatory liver disorders, might also result in increased liver stiffness unassociated with fibrosis [36,66].



Figure 3. TE—liver invalid measurement (children).



Figure 4. 2D-SWE—liver invalid measurement (children).

Multiple studies revealed an increase in liver stiffness with age, but the results remain controversial since the association was found to be weak [64,67–70]. Thus, Li et al. proved a strong association between increasing age and liver stiffness measurements in children \geq 3 years [64]. It is most likely that these findings might be related to microstructure, vascular, and metabolic changes that occur during maturation as it was proved on animal models [71,72]. Similar trends were noticed by Tokuhara et al. in a study performed on 123 children using TE, who found a liver stiffness value of 3.4 kPa between 1–5 years of age, 3.8 kPa in children aged 6 to 11 years, and 4.1 kPa in those aged 12 to 18 [73]. In addition, a study performed on 206 normal weight healthy children assessing liver stiffness using both 2D SWE and TE identified an increase in elastography values on both methods directly related to the individual's age. This study pointed out that the cutoff values on 2D SWE ranged between 4.13 kPa in children aged between 3-5 years and 4.88 in those between 12 to 15; while on TE these values varied from 4.40 kPa between 3–5 years of age and 5.1 kPa in adolescents aged 15–18 years [74]. It is also worth mentioning that according to Goldschmidt et al., liver stiffness values are not affected by either age or gender in children, who found a normal median liver stiffness value of 4.5 kPa in healthy children with no comorbidities, without assessing other laboratory parameters, such as serum liver enzymes or APRI [75]. Therefore, age represents a potential limitation as well as a challenge in the assessment of liver stiffness on elastography and it should be taken into account as a potential confounder in order to increase the accuracy of these methods.

	Study Type/No of Patients	Age (Years) Mean/Median *				
Author, Year, and Country			TE (KPa) Mean/Median *	p-SWE/ARFI (m/s) Mean/Median *	2D-SWE/rSWE (Stiffness—kPa and Velocity—m/s) Mean/Median *	Observations
Trout et al., 2020, USA [67]	Prospective/128	5.04 *	-	-	$1.29\pm0.13~\textrm{m/s}$	-
Ferraiolii et al., 2020, Italy [60]	Prospective/31— Siemens and 238—Samsung	7 *	-	Siemens: 1.24 m/s (4.61 kPa) Samsung: 1.17 m/s (4.1 KPa)	-	-
Mărginean et al., 2020, Romania [74]	Prospective/206	3–18	3.797 ± 0.4859	-	$3.72\pm0.48~\mathrm{kPa}$	Stiffness cutoff: 4.13 for 3–5 y and 4.88 for 12–15 y Velocity cutoff: 1.18 m/s for 6–8 y and 1.35 m/s for 12–15 y
Mjelle et al., 2019, Norway [76]	Prospective/ TE and pSWE—87; rSWE—243	4–17	4.1 kPa (1.17 m/s; range 2.4–11.2 kPa)	4.1 kPa (1.17 m/s; range 2.8–7.1 kPa	3.3 kPa (1.05 m/s; range 2.0–7.7 kPa)	lower values using 2D-SWE versus pSWE/TE (p < 0.001); liver stiffness increases with the age
Galina et al., 2018, Greece [77]	Prospective/202	0–16	-	-	$4.29\pm0.59~\mathrm{KPa}$	Higher values in neonates, infants and adolescents versus preschoolers children (p < 0.001)
Bailey et al., 2017, USA [68]	Prospective/176	8.6 ± 5.6	-	-	1.08 ± 0.14 m/s	Comparation between normal-weight and obese groups (p < 0.001)

Table 2. Stiffness values by different type of elastography in healthy children.

			Table 2. Cont.			
				Elastography Method (TE/p-SWE/2D-SWE/SE)		
Author, Year, and Country	Study Type/No of Patients	Age (Years) Mean/Median *	TE (KPa) Mean/Median *	p-SWE/ARFI (m/s) Mean/Median *	2D-SWE/rSWE (Stiffness—kPa and Velocity—m/s) Mean/Median *	Observations
Oskan et al., 2017, Turkey [78]	Prospective/31	7*	-	1.24 m/s	-	pSWE in normal weight compared cu obese children
Franchi-Abella et al., 2016, France [79]	Prospective/51	0–17.2	-	-	$6.58\pm1.46~\mathrm{KPa}$	elasticity value incresed with age
Tokuhara et al., 2016, Japan [73]	Prospective/123	11.7 *	3.4 (2.3 \pm 4.6) at 1–5 y 3.8 (2.5 \pm 6.1) at 6–11 y 4.1 (3.3 \pm 7.9) at 12–18 y	-	-	Median LSM increased with age (<i>p</i> < 0.001)
Lewindon et al., 2016, Australia [80]	Prospective/64	9.3 ± 0.5	4.1 ± 0.1	-	-	Comparation between normal weight and intercurrent illness groups (p < 0.001)
Cho et al., 2015, Japan [18]	Prospective/107	11.5 *	3.9 ± 0.9	-	-	significant differences between normal-weight and obese children (p < 0.001)
Fontanilla et al., 2014, Spain [69]	Prospective/60	Max 14 (only range)	-	4C1 transducer: 1.19 * 9L4 transducer: 1.15 *		-
Matos et al., 2014, Portugal [70]	Prospective/150	8.9 **	-	1.07 *	-	-
Tutar et al., 2014, Turkey [81]	Prospective/50	7.4 *	-	-	7.41 kPa; 1.56 m/s	-

			Table 2. Cont.			
Author, Year, and Country	Study Type/No of Patients	Age (Years) Mean/Median *	TE (KPa) Mean/Median *	p-SWE/ARFI (m/s) Mean/Median *	2D-SWE/rSWE (Stiffness—kPa and Velocity—m/s) Mean/Median *	Observations
Honsawek et al., 2013, Thailand [82]	Prospective/20	9.5	5.00 *	-	-	-
Goldschmidt et al., 2013, Germany [75]	Prospective/270	6.0 * (all 547)	4.50 * (MG)	-	-	-
Hanquinet et al., 2013, Switzerland [83]	Prospective/103	6.3 *	-	1.12 *	-	-
Lee et al., 2013, Republic of Korea [84]	Prospective/202	8.1 *	-	1.12 *	-	-
Marginean et al., 2012, Romania [85]	Prospective/32	5.9 *	-	1.18 *	-	-
Noruegas et al., 2012, Portugal [86]	Prospective/20	7.0 *	-	1.11 *	-	-
Engelmann et al., 2012, Germany [87]	Prospective/240	9.3 (female) * 7.9 (male) *	4.70 *	-	-	-
Eiler et al., 2012, Germany [88]	Prospective/132	9.2 *	-	1.16 ± 0.14	-	-
Menten et al., 2010, Belgium [89]	Prospective/31	8.5 *	4.30 (M)	-	-	-
Witters et al., 2009, Belgium [90]	Prospective/59	10.2 *	<12 y > 5.63; >12 y > 6.50	-	-	-
Rubio et al., 2009, France [91]	Prospective/19	12.7 *	4.34 * (M)	_	-	
Francavilla et al., 2008, Italy [92]	Prospective/175	8 ± 3.6	3–7	-	_	4.5 ± 1.4 with M probe; 4.8 ± 1.9 with P probe

Legend: TE = transient elastography, pSWE = point shear-wave elastography, rtSWE = real-time shear-wave elastography; TE is measured in kPa, pSWE in m/s, rtSWE in both kPa and m/s. Probe type: M = M-size probe, P = P-size probe, y—years; *Mean age calculated from mean of the three age groups in the study.

The most recent confounding factor identified in a study performed on patients with Hepatitis C virus (HCV) is represented by serum transaminases hypothesized to increase liver stiffness measurements. Thus, Giuffrè et al. proved as a result of a study on 110 patients with HCV that the probability of liver fibrosis overestimation of two or more grades equals 50% for AST of 99 IU/L and ALT of 90.5 IU/L; 80% for AST of 123.5 IU/L and ALT of 101.5 IU/L; and up to 100% for AST of 211 IU/L and ALT of 140 IU/L [93]. Nevertheless, no data is available to date in pediatric patients regarding the impact of serum transaminases on liver stiffness measurements. Blood flow is another potential confounding factor of liver stiffness since previous studies underlined that increased blood flow as a result of food intake leads to an increased liver stiffness [94]. Thus, a period of at least 4 h of fasting is recommended before the examination in order to avoid this confounding factor [95]. It is well-documented that elastography is of major importance in assessing portal hypertension, but it was proved that severe portal hypertension impairs the correlations between liver stiffness and hepatic venous pressure gradient, emphasizing that the assessment of spleen stiffness could be more reliable in these cases [96]. In terms of spleen stiffness assessment, a recent study performed on HCV patients proved that spleen stiffness increased by 3.220 kPa for each mm of portal vein diameters and by 0.7 kPa for each cm/s of portal vein velocity, underlining that it might be an accurate parameter for portal hypertension stratification [97].

Taking into account the wide-spectrum of confounding factors identified in children with obesity, among which are obesity itself, fatty liver infiltration, a possible mild heart failure, and the incapacity to hold their breath, it is unsurprising that the reliability of elastography methods is closely related to body mass index [98], requiring the combination of these methods with other clinical and laboratory findings. In compliance to the abovementioned facts, the study of Nobili et al. noticed that a body mass index greater than 35 in children might result in failure to obtain valid TE measurements [99]. This limitation is defined by the impact of skin-to-liver distance on the feasibility and accuracy of liver elastography. In terms of elastography, it was hypothesized that skin-to-liver distance < 34 mm is optimal for discriminating between fibrosis stages [100]. This hypothesis is in line with other studies which concluded that in patients with a BMI \geq 30 kg/m², elastography has a relatively low accuracy in differentiating between the first two fibrosis stages [101,102]. It was also underlined that the success rate in obese patients depends on the technique being proved that TE has a higher failure rate in this group when compared to p-SWE [101]. Moreover, a recent study performed on obese adults emphasized that p-SWE is able to discriminate between fibrosis stages independently of its severity if skin-to-liver distance is taken into account following two rules: a thicker abdominal wall results in a lesser accuracy for a proper histological staging and the impact of skin-to-liver distance on accurate fibrosis staging is machine-dependent [103]. In terms of ARFI, it was showed that interoperator concordance increases when skin-to-liver distance is <2.5 cm [104], being previously documented that a higher concordance is reflected on the correlation between fibrosis stages assessed on ARFI and histology [105]. Using TE, another recent study proved that a skin capsular distance \geq 25 mm results in overestimation of fibrosis affecting the detection of severe fibrosis in patients with NAFLD [106]. Thus, this is an important challenge that should be addressed also in children with NAFLD since to date we found no study on this topic in pediatric patients with NAFLD.

The accuracy of elastography methods might be improved if combined with other clinical or laboratory parameters in order to face the aforementioned challenges/limitations. A recent review which included 27 articles underlined that elastography is a reliable method in diagnosing liver fibrosis and cirrhosis in pediatric patients, whose accuracy is improved when used in combination with other clinical tools, such as serum markers [107]. Previous studies revealed positive associations between ultrasound-based elastography methods and several laboratory parameters such as ALT, APRI, or AST/ALT ratio (AAR), which are well-known to be increased in children with obesity [18,19,108]. The study of Kamble et al. used ARFI in combination with serum liver enzymes and triglyceride values and

proved that liver stiffness is significantly correlated with liver enzymes and most children identified with a value above 1.19 m/s associated AAR > 0.8, defined also as a potential indicator of steatohepatitis [109]. Therefore, the combination between these laboratory parameters and elastography values might increase the accuracy in detecting and staging liver fibrosis in children with obesity.

Multiple studies aimed to compare the performance of ultrasound-based elastography methods in NAFLD patients. Kim et al. stated after reviewing 12 articles that fibrosis in children can be predicted with a higher sensitivity and specificity using supersonic shear imaging in comparison with ARFI, with an increasing accuracy in the setting of advanced fibrosis. The authors pointed out that the reference values according to ARFI are 1.34 m/s in case of stage 1 fibrosis, 1.57 m/s in stage 2, 1.85 m/s for stage 3, and 2.13 m/s for stage 4. Contrarily, in terms of supersonic shear imaging, the authors found a median cutoff value of 7.9 kPa in case of stage 1, 9.4 kPa in stage 2, 14.2 kPa for stage 3, and 23.94 kPa for stage 4 [110], although for ARFI the results are provided in m/s. For supersonic shear imaging such as Young's modulus in kPa, both elastography methods reveal increasing values as liver fibrosis advances. Similar trends were provided by Mărginean et al., who reported the results of 2D-SWE as both m/s and Young's modulus in kPa [19]. Based on these findings we might assume that the values liver stiffness assessed in m/s or in kPa are directly related since an increase in both in noticed in stiffer livers. Another study which assessed the differences between ARFI and TE on children with chronic liver disease in the setting of metabolic disorders, as well as those with normal liver, suggested that ARFI might be more accurate differentiating between the stages of fibrosis [111]. Similar findings were reported by Garcovich et al., concluding that 2D-SWE might be considered reliable in detecting advanced liver fibrosis in children with NASH [112]. Contrarily, Mărginean et al., who assessed liver stiffness in children with obesity using both TE and 2D-SWE, pointed out that TE and velocity measured on 2D-SWE might represent useful tools for detecting NAFLD [19]. Overall, Lee et al. concluded in a comparative study which assessed the diagnostic performance of supersonic shear imaging, TE and ARFI in NAFLD staging that all these methods have similar diagnostic performance for staging fibrosis in the setting of NAFLD [113].

A major limitation of elastography methods is represented by a proper differentiation between mild fibrosis and normal liver tissue. Thus, pSWE was found to have a good accuracy in distinguishing severe from mild fibrosis, but not between normal liver tissue and low-grade fibrosis in children with NAFLD [78]. The increased risk of mortality in patients with NAFLD is mostly related to liver fibrosis itself [114] and its proper diagnosis, as well as its early staging are crucial for improving the long-term prognosis in children with overweight and obesity. A very recent study that compared liver stiffness values on 2D SWE and TE proved higher values in children with obesity as compared to normal ones, suggesting that these methods might be extremely useful in clinical practice for detecting early stages of fibrosis associated to NAFLD [19]. Furthermore, in order to increase the reliability of TE, Alkhouri et al. combined this technique with pediatric NAFLD index and showed that this combination might identify patients that require liver biopsy for advanced fibrosis confirmation and closer follow-up for a timely diagnosis of cirrhosisrelated complications [115]. The most relevant studies that compared the results between liver elastography and biopsy findings in children NAFLD were summarized in Table 3.

In terms of pediatric NAFLD staging, studies that assessed the role of elastography are promising although its precision is not perhaps optimal. Multiple studies aimed to identify if elastography is able to replace liver biopsy in order to diagnose this condition, an emerging concern worldwide. Two histology scoring systems were used for assessing liver fibrosis: Brunt classification [116] defined as grade 0 for no fibrosis, grade 1 for zone 3 perisinusoidal and/or pericellular fibrosis, grade 2—the changes identified in grade 1 plus focal or extensive periportal fibrosis, grade 3 as in grade 2 plus focal or extensive bridging fibrosis and grade 4 defining cirrhosis; and Kleiner activity scoring system with 0 for no fibrosis, 1 for periportal or perisinusoidal fibrosis, 2 for perisinusoidal and portal or

periportal fibrosis, 3 for bridging fibrosis, and 4 when cirrhosis occurs [117]. Garcovich et al. performed a study on 68 pediatric patients with histologically proven NASH according to the Brunt scoring system, and found that SWE established correctly the fibrosis stage in 57 of 68 patients (84%), with higher accuracy in patients with advanced fibrosis. The authors encountered that 6.7 kPa might be a reliable cutoff value for delineating fibrosis stages [112]. Similar findings were reported by Alkhouri et al. on 67 children with histologically proven NAFLD according to the Kleiner's system, who stated that TE is a useful non-invasive indicator of clinically significant liver fibrosis guiding the proper selection of patients that require liver biopsy [115]. Another recent meta-analysis involving 723 patients underlined that TE represents is a highly accurate method for the diagnosis of liver fibrosis in children with a sensitivity of 95% and a specificity of 90% in the setting of significant liver fibrosis, above stage 2 [118]. The most relevant studies that assessed NAFLD in children using ultrasound-elastography based methods are described in Table 4.

Conventional ultrasound might also reveal certain liver abnormalities indicative of liver steatosis or fibrosis, such as abnormal echogenicity or focal lesions, but its capacity is definitely overpassed by elastography. Therefore, a study that compared SWE and conventional ultrasound findings in children with obesity and normal weight ones pointed out that mean SWE velocity values were significantly higher in the obese group with abnormal liver echogenicity at conventional ultrasound that in those with apparently normal aspect of liver, but the authors failed in identifying a significant difference in normal weight children [68]. In terms of conventional ultrasound, similar findings were identified by Mărginean et al., who showed that children with overweight/obesity are more frequently identified with abnormal liver aspects, such as hepatomegaly and hyperchogenicity as compared to normal weight ones [5]. Thus, conventional ultrasound might represent the first step in assessing children with obesity and diagnosing NAFLD [119] in order to guide them for elastography staging, which is definitely associated with greater costs. Contrarily, a study performed on 148 school-aged children concluded as a result of ARFI examination that significant liver fibrosis might be present even in the setting of normal laboratory parameters or normal ultrasound liver aspect [120].

Table 3. Elastography in children with nonalcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)
compared to histological findings obtained by liver biopsy (gold standard).

Author, Year, and Country	Study Type and No Patients	Age (Years) Mean/Median *	Diagnosis	Gold Standard and Score Type	Elastography Method (TE/p- SWE/2D- SWE (pSWE)	Elastography Values Mean/Median	Correlation to Gold Standard/Cut- off AUROC
Hudert et al., 2018, Germany [121]	Prospective/47	14.1 ± 2.2	NAFLD/NASH	Biopsy, Kleiner	Harmonic SWE	F0: $1.45 \pm 0.05 \text{ m/s}$ F1: $1.49 \pm 0.07 \text{ m/s}$ F2: $1.78 \pm 0.13 \text{ m/s}$ F3: $1.81 \pm 0.11 \text{ m/s}$	Usefull for detection of moderate fibrosis in extreme obese children Cutoffs: F1: 1.52 m/s; F2: 1.62 m/s; F3: 1.64 m/s

Author, Year, and Country	Study Type and No Patients	Age (Years) Mean/Median *	Diagnosis	Gold Standard and Score Type	Elastography Method (TE/p- SWE/2D- SWE (pSWE)	Elastography Values Mean/Median	Correlation to Gold Standard/Cut- off AUROC
Oskan et al., 2017, Turkey [78]	Prospective/11	9*	NAFLD	Biopsy, Knodell	pSWE	1.56 m/s (range, 1.32–2.03 m/s)	pSWE— increased in fibrosis; Cutoff: 2.09 m/s VTQ; pSWE cutoff: 1.67m/s
Cho et al., 2015, Japan [18]	Prospective/52	11.5 *	NAFLD	Biopsy only in 8 children, Kleiner	TE	5.5 ± 2.3 kPa	highly correlated with fibrosis stage (Spearman's
Garcovich et al., 2016, Italy [112]	Prospective/68	12.6 ± 2.48	NASH	Biopsy, Brunt	rSWE	F0: 4.4 ± 0.6 KPa F1: 5.6 ± 0.6 KPa F2: 7.1 ± 0.7 KPa	p = 0.320) Significant correlation with liver fibrosis (r = 0.84, p < 0.001)
Alkhouri et al., 2013, USA [115]	Prospective/67	Min 5.5; Max 11.3 (only range)	NAFLD	Biopsy, Kleiner	TE (S)	F0-F1: 5.7 ± 1.2 kPa F2-F3: 10.9 ± 3.3 kPa	Significant difference between TE at F0–1 and F2–3 (p < 0.001) \geq F2: 8.6 (1.00)
Marginean et al., 2012, Romania [85]	Prospective/13	7.9 *	NAFLD	Biopsy, (-)	pSWE	1.65 ± 0.49 m/s	significant difference between NAFLD and healthy controls (p < 0.05)
Nobili et al., 2008, Italy [99]	Prospective/50	13.6 *	NASH	Biopsy, Brunt	TE (M)	F0: 4.4 kPa; F1: 6.1 kPa; F2: 8.6 kPa; F3-4: 20.4 kPa	Cut-off: \geq F1: 5.1 (0.97); \geq F2: 7.4 (0.99); \geq F3: 10.2 (1.00)

 Table 3. Cont.

Legend: TE = transient elastography, pSWE = point shear-wave elastography, rtSWE = real-time shear-wave elastography. TE is measured in kPa, pSWE in m/s, rtSWE in both kPa and m/s; NAFLD = non-alcoholic fatty liver disease, NASH = non-alcoholic steato-hepatitis, VTQ = Virtual Touch quantification; *Mean age calculated.

Author, Year, and Country	Study Type and No Patients (Normal Weight/Obese Children)	Age (Years) Mean/Median *	Elastography Method (TE/p- SWE/2D-SWE (rSWE)	Elastogpraphy in Healty Children (Mean/Median)	Elastography Values in NAFLD/NASH (Mean/Median)	Correlations/ Observations
Mjelle et al., 2019, Norway [76]	Prospective 243/27	4–17	2D-SWE pSWE TE	8–11 y: 3.35 kPa 15–17 y: 3.78 kPa 4.1 kPa 15–17 y: 4.52 kPa	8–11 y: 4.45 kPa 15–17 y: 4.64 kPa 8–11 y: 4.1 kPa 15–17 y: 3.4 kPa	Significant corellation (p < 0.001/p < 0.008) Significant corellation, p = 0.003 TE lower LSM values in the overweight
Mărginean et al., 2019, Romania [19]	Prospective 210/77	11.29 ± 3.83 y—normal weigh 10.44 ± 3.38 y—obese	TE 2D-SWE	3.80 ± 0.48 kPa 3.73 ± 0.48 kPa 1.09 ± 0.09 m/s	4.23 ± 0.53 kPa 3.84 ± 0.35 kPa 1.18 ± 0.09 m/s	p < 0.0001 p = 0.0314/p < 0.0001 AUC: V median: 0.817 ± 0.028 (p = 0.0001); TE: 0.730± 0.033 (p = 0.0001)
Bailey et al., 2017, USA [68]	Prospective 176/124	9.9 ± 5.3	2D-SWE	$1.08\pm0.14~\mathrm{m/s}$	1.44 ± 0.39 m/s	significant differences between normal-weight and obese children (p < 0.001); Kappa coefficient = 0.64
Berna'-Serna et al., 2017, Spain [120]	Prospective -/148	8.02 ± 1.64	pSWE (ARFI)	-	F0: 1.03 ± 0.13 ; F1: 1.24 ± 0.04 ; F2: 1.40 ± 0.07 ; F3: 1.75 ± 0.08 ; F4: 2.21 ± 0.28	Significant difference between boys and girls (p = 0.0003)
Oskan et al., 2017, Turkey [78]	Prospective 31/11	7 * 9 *	pSWE	1.24 m/s	1.56 m/s (range, 1.32–2.03 m/s)	pSWE significant higher in obese versus normal weight (p < 0.001)
Cho et al., 2015, Japan [18]	Prospective 107/52	11.5 *	TE	3.9 ± 0.9 kPa	5.5 ± 2.3 kPa	significant differences between normal-weight and obese children (p < 0.001)

 Table 4. Elastography in healthy versus NAFLD/NASH children.

Table 4. Cont.

Author, Year, and Country	Study Type and No Patients (Normal Weight/Obese Children)	Age (Years) Mean/Median *	Elastography Method (TE/p- SWE/2D-SWE (rSWE)	Elastogpraphy in Healty Children (Mean/Median)	Elastography Values in NAFLD/NASH (Mean/Median)	Correlations/ Observations
Fitzpatrick et al., 2013, Italy [122]	Prospective/ -/37	13.5 *	TE	_	F0: 6.1 kPa; F1: 5.1 kPa; F2: 5.8 kPa; F3: 7.4 kPa	For severe fibrosis, the AUROC was 0.8 (p = 0.003); a cutoff of 6.9 kPa had a 72% sensitivity and a 85% specificity

Legend: TE = transient elastography, pSWE = point shear-wave elastography, rtSWE = real-time shear-wave elastography; TE is measured in kPa, pSWE in m/s, rtSWE in both kPa and m/s. ARFI = acoustic radiation force impulse measured in m/s, NAFLD = non alcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, AUC—area under curve, y—years; V = velocity; *Mean age calculated.

4. Conclusions

NAFLD is most likely a real challenge for pediatricians and its proper diagnosis and close follow-up are essential for preventing further life-threatening complications, such as cirrhosis, end-stage liver disease, or hepatocarcinoma. Taking into account the expressed need for non-invasive approach in pediatric patients as compared to adults, elastography methods represent promising diagnostic tools with a relatively good accuracy for NAFLD staging. Nevertheless, multiple confounding factors should be closely monitored when assessing NAFLD children on elastography, such as age, BMI, transaminase levels, or portal blood flow. A complex approach combining elastography parameters with clinical and laboratory findings might increase the accuracy of ultrasound-based elastography in terms of NAFLD staging. Albeit elastography is limited in differentiating between mild fibrosis and normal liver, it is extremely useful for diagnosing liver fibrosis in children with obesity. Moreover, elastography is crucial for NAFLD monitoring and for guiding liver biopsy in selected cases. Still, multiple controversies arose due to their relatively novel use for young ages, and further studies are required in order to define their role in delineating the stages of liver fibrosis in children with obesity.

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