Ultrasound Elastography Is Useful for Evaluation of Liver Fibrosis in Children—A Systematic Review

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ABSTRACT

Objectives: Adult studies have proven ultrasound elastography as a validated measure of liver fibrosis. The present study aimed to review the available literature on ultrasound elastography in children to evaluate the ability of the method to distinguish healthy from fibrotic liver tissue and investigate whether cutoff values for liver fibrosis in children have been established.

Methods: A literature search was performed in MEDLINE, EMBASE, the Cochrane Library, and Web of Science to identify studies on ultrasound elastography of the liver in children. Only original research articles in English concerning ultrasound elastography in children with and without liver disease, younger than 18 years, were included. All reference lists of the included articles were hand-searched for further references.

Results: Twenty-seven articles were included. Elastography in children without liver disease was investigated in 14 studies and were comparable to those existing for adults. Twelve studies compared elastography with liver biopsy in children with liver disease and found that cirrhosis was correctly diagnosed, whereas it was more difficult to assess severe fibrosis correctly. For the distinction between no, mild, and moderate fibrosis in children with liver disease the method was less accurate. Ultrasound elastography was able to differentiate between children with and without liver fibrosis. In children without liver disease ultrasound, elastography showed consistent liver stiffness values comparable to those found in adults. No fibrosis-specific cutoffs were proposed.

Conclusions: Ultrasound elastography was able to diagnose cirrhosis, distinguish healthy from fibrotic liver tissue, and showed consistent liver stiffness values in children without liver disease.

Key Words: hepatic disease, pediatric, shear-wave elastography, transient elastography, ultrasound

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What Is Known

- Ultrasound elastography is a well-established method for evaluating liver fibrosis in adults.
- Ultrasound is important in the follow-up of children with chronic liver disease, and elastography could increase its value.
- Different shear-wave elastography methods are used for liver fibrosis, for example, transient, point shear-wave, image shear-wave, and real-time shear-wave elastography.

What Is New

- Ultrasound elastography can successfully evaluate liver stiffness in children with various chronic liver diseases.
- Ultrasound elastography is able to distinguish between children with and without liver fibrosis.
- In children without liver disease, ultrasound elastography shows consistent liver stiffness values.

Ultrasound elastography covers a range of technical approaches, all with the same aim: evaluation of tissue stiffness because pathological activity changes the elastic properties of a tissue (1). For liver fibrosis studies, different shear-wave elastography methods have been investigated, because these methods are quantitative and applicable in nonfocal diseases. Shear-wave speed is proportional to tissue stiffness. Shear waves occur perpendicularly to the direction of the source displacing the tissue. In transient elastography (TE), a piston is incorporated in an ultrasound transducer, and the speed of the mechanically generated shear wave is measured without a B-mode image. In shear-wave elastography, an ultrasound push pulse makes the displacement. Point shear-wave elastography (pSWE) measures shear-wave speed from a region of interest placed on the B-mode image; image shear-wave elastography displays shear-wave speed within an elastogram box on a color scale; real-time shear-wave elastography (rtSWE) displays color images of shear-wave speed in real time. All forms of shear-wave elastography, including TE, give measurements of shear-wave speed in meter per seconds or convert them into kilo Pascal.

For TE guidelines from the manufacturer of FibroScan (Echosens, Paris, France) state that 10 valid measurements should be performed in the right liver lobe with a success rate of at least 60% and with an interquartile range <30% (2,3). Measurements should be obtained through the intercostal space with the patient lying supine and the right arm in maximal

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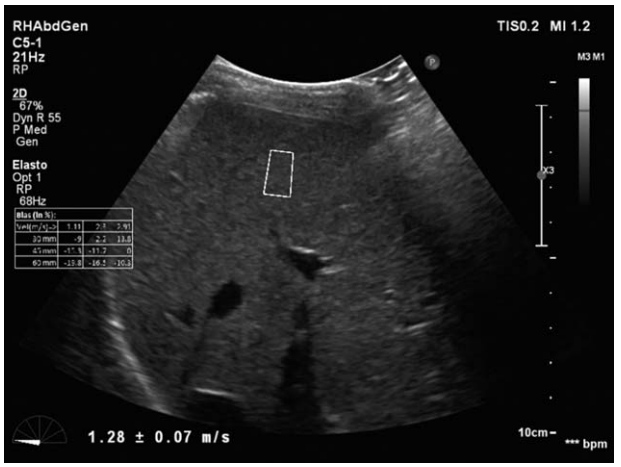

FIGURE 1. Example of ultrasound elastography in a child without liver disease. pSWE in a child without liver disease. The shear-wave speed is 1.28 ± 0.07 meter/second. pSWE = point shear-wave elastography.

abduction. Choice between different-sized probes should rely on chest circumference: S1 probe for <45 cm, S2 probe for 45 to 75 cm, and M probe for >75 cm. Shear-wave elastography is usually performed with the transducer in the right intercostal space with the patient in supine position (4,5). For pSWE and image shear-wave elastography, a region of interest without large vessels is used (examples in Figs. 1 and 2). Multiple measurements in the right liver lobe are recommended. No specific probe is recommended.

In adults with chronic liver disease, meta-analyses have shown that the ultrasound elastography is diagnostically accurate for determining varying degrees of fibrosis and cirrhosis (6–8). Severe fibrosis and cirrhosis are the end stages of chronic liver disease and may cause complications such as variceal bleeding, spontaneous bacterial peritonitis, and encephalopathy (9). Liver biopsy is considered the criterion standard for evaluation of liver fibrosis. Nevertheless, biopsy can cause complications, for example, hemorrhage, pain, and anesthesia-related problems (10,11). Conventional ultrasound is therefore an important tool in addition to blood samples in the follow-up of children with chronic liver disease, and ultrasound elastography could be a valuable adjunct.

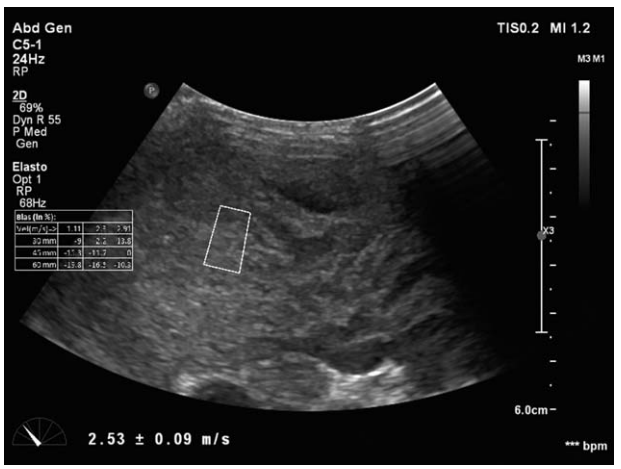

FIGURE 2. Example of ultrasound elastography in a child with liver disease. pSWE in a child with biliary atresia post Kasai portoenterostomy. The shear-wave speed is 2.53 ± 0.09 meter/second, which could indicate fibrotic activity in the liver tissue. pSWE = point shear-wave elastography.

The aim of the present article was to review the available literature on ultrasound elastography in children to evaluate the ability of the method to distinguish healthy liver tissue from liver fibrosis and investigate whether cutoff values for liver fibrosis have been established.

METHODS

The PRISMA 2009 checklist was used as guideline for reporting in this review (12). The content of the review was agreed on before the search process was initiated.

Search Strategy

A literature search was made in MEDLINE, EMBASE, the Cochrane Library, and Web of Science. With MEDLINE as example, the following search terms were applied: MeSH terms ''Elasticity Imaging Technique,'' ''Child,'' ''Child, preschool,'' ''Infant,'' ''Infant, newborn,'' and ''Liver.'' To ensure the inclusion of studies not yet indexed with MeSH terms, a free text search was included using the terms ''Elastography,'' ''Child,'' ''Infant,'' ''Pediatric,'' ''Liver,'' and ''Hepatic.'' All free text terms included an asterisk that permitted inclusion of words with different suffixes. No predetermined limits were incorporated in any of the searches. The searches were performed on February 19, 2015.

Two authors (S.B.A. and C.E.) reviewed all titles and abstracts. Only original research articles in English concerning ultrasound elastography in children with and without liver disease, both groups younger than 18 years, were included. All included articles were subsequently retrieved and read by the same 2 authors. Consensus was obtained through discussion. All reference lists of the included articles were hand-searched for further references. We registered authors, study year and country; study type; number, age, and diagnoses of eligible participants; elastography method; study technique including identity and experience of the investigators and circumstances under which elastography was performed (patient positioning, fast, breathing, anatomical location, and number of measurements); criterion standard; results including mean/median stiffness values, comparison to criterion standard, cutoff values, area under the ROC curve analyses and relation to age, sex, BMI, anatomical measurement site and probe type; any additional relevant information about the studies.

To evaluate risk of bias and applicability of the included studies, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used (13). The tool covers an evaluation of patient selection, the index and reference test used, and the timing of these tests in relation to each other.

RESULTS

Study Selection and Overview

A flowchart of the article search and selection is shown in supplementary Fig. 1 (*http://links.lww.com/MPG/A617*). The initial search yielded 307 publications when all duplicates were removed. From the title, 212 articles were excluded and further 45 articles were excluded from the abstract. The articles were excluded because of inadequate or irrelevant content, non-English language, article type (reviews, letters to the editor, conference abstracts), or age of study participants. Of the remaining

TABLE 1. Elastography in healthy children

Author, year and country	Study type	No. of participants	Age, y; mean/median*	Elastography method (TE probe type)	Elastography values†, mean/median*	Comments
Engelmann et al, 2011, Germany (14)	Prospective	240	9.3 (female)* 7.9 (male)*	TE (MG)	4.70*	
Menten et al, 2010, Belgium (15)	Prospective	31	8.5	TE (M)	4.30	
Witters et al, 2009, Belgium (16)	Prospective	59	10.2	TE (−)	<12 y: 5.63‡ >12 y: 6.50‡	
Goldschmidt et al, 2013, Germany (17)	Prospective	270	6.0* (all 547)	TE (MG)	4.50*	
Rubio et al, 2009, France (18)	Prospective	19	12.7	TE (M)	4.34	Also investigates diseased children, see Table 2
Honsawek et al, 2013, Thailand (19)	Prospective	20	9.5	TE (−)	5.00	Also investigates diseased children, see Table 2
Fontanilla et al, 2014, Spain (20)	Prospective	60	Max 14 (only range)	pSWE	4C1 transducer: 1.19 9L4 transducer: 1.15	
Eiler et al, 2012, Germany (21)	Prospective	132	9.2	pSWE	1.16	
Hanquinet et al, 2013, Switzerland (22)	Prospective	103	6.3	pSWE	1.12	
Lee et al, 2013, Republic of Korea (23)	Prospective	202	8.1	pSWE	1.12	
Marginean et al, 2012, Romania (24)	Prospective	32	5.9*	pSWE	1.18*	Also investigates diseased children, see Table 2
Noruegas et al, 2012, Portugal (25)	Prospective	20	7.0	pSWE	1.11	Also investigates diseased children, see Table 2
Matos et al, 2014, Portugal (26)	Prospective	150	8.9§	pSWE	1.07	
Tutar et al, 2014, Turkey (27)	Prospective	50	7.4*	rtSWE	7.41 kPa 1.56 m/s	Also investigates diseased children, see Table 2

pSWE = point shear-wave elastography; rtSWE = real-time shear-wave elastography; TE = transient elastography.
Probe type: −= probe type not mentioned; M = M-size probe; MG = manufacturer's guidelines; S = S-size probe.
* Median.
† TE is measured in kPa, pSWE in m/s, rtSWE in both kPa and m/s.
‡ Only upper limits were presented in the present study.
§ Mean age calculated from mean of the three age groups in the study.

50 articles, 27 were included in this review after reading the full-text articles.

Fourteen of the studies had data from children without liver disease (Table 1). Eighteen studies included data from children with varying degrees of fibrosis (Table 2). Five studies investigated values in both children with and without liver disease and were therefore registered in both tables (18,19,24,25,27). Two articles included data from the same children without liver disease; in one of the articles these children were compared with children with liver disease and in the other only values from the children without liver disease were reported. They are listed in their respective tables (22,35). Fourteen studies used TE, 12 studies used pSWE, and 1 used rtSWE.

The results from QUADAS-2 are listed in Table 3. Most studies were considered to have a low risk of bias. The studies on children without liver disease have uncompleted evaluations because of their lack of a reference standard and a high risk of bias in the index test because of the investigator's knowledge of the children's liver status.

Results From Ultrasound Elastography

Ultrasound Elastography in Children Without Liver Disease

TE values ranged from 4.3 to 5.0 kPa with upper limits reported from 5.63 to 6.5 kPa (14,16,17). pSWE values ranged from 1.07 to 1.19 meter per second. One study investigated rtSWE and reported normal values of 7.41 kPa (1.56 meter/second). Overall liver stiffness values were fairly consistent between studies as displayed in Table 1.

Ultrasound Elastography in Children With Chronic Liver Disease: Liver Stiffness Compared With Histology

Twelve studies compared elastography with the result of liver biopsies and found increasing stiffness with increasing stage of fibrosis (Table 2). Overall cirrhosis was correctly diagnosed with elastography, whereas it was more difficult to assess severe fibrosis

TABLE 2. Elastography in children with liver disease

Author, year, and country	Study type	No of ptt	Age, y; mean/median*	Diagnoses	Criterion standard†	Elastography method (TE probe type)	Elastography values‡, mean/median*	Relation to criterion standard	Cutoff (AUROC)	Comments
Elastography compared with histological findings										
Shin et al, 2014, Korea (28)	Retrospective	47	0.2*	BA	Biopsy, METAVIR	TE (M until 2009, S after)	F1: 10.3* F2: 6.5* F3: 12.0* F4: 34.9*	Positively correlated with METAVIR stages ($\rho = 0.63$; $P < 0.001$)	≥F3: 9.6 (0.86) F4: 18.1 (0.96)	Uses 5 valid TE measurements eventhought the manufacturer recommends 10
Hamidieh et al, 2014, Iran (29)	Prospective	83	8.0*	MT	Biopsy, METAVIR	TE (MG)	Overall: 4.3*	TE increased with METAVIR stages ($r = 0.4$, $P < 0.001$)	≥F0: 3.2 (0.73)	TE values at each fibrosis stage presented in Figure 1 in the article, but not in the text
Alkhouri et al, 2013, USA (30)	Prospective	58	Max 11.3 (only range)	NAFLD	Biopsy, Kleiner	TE (S)	F0–F1: 5.7 F2–F3: 10.9	Significant difference between TE at F0–F1 and F2–F3 ($P < 0.001$)	≥F2: 8.6 (1.00)	Diagnostic accuracy of TE better in combination with other noninvasive marker
Nobili et al, 2008, Italy (31)	Prospective	50	13.6	NASH	Biopsy, Brunt	TE (M)	F0: 4.4 F1: 6.1 F2: 8.6 F3–F4: 20.4	—	≥F1: 5.1 (0.97) ≥F2: 7.4 (0.99) ≥F3: 10.2 (1.00)	
Awad et al, 2013, Egypt (32)	Prospective	30	10.1	Chronic HCV	Biopsy, METAVIR	TE (−)	F0: 3.33 F1: 5.46 F2: 8.13 F3: 11.50 F4: 40.28	TE increased with METAVIR stages ($P < 0.0001$)	≥F1: 4.9 (0.03) ≥F2: 7.4 (0.65) ≥F3: 9.5 (0.82) F4: 12.5 (1.00)	
Fitzpatrick et al, 2013, United Kingdom (33)	Prospective	94	13.6*	Various chronic LD	Biopsy, METAVIR or Kleiner	TE (M)	F0: 5.1* F1: 5.8* F2: 6.2* F3: 8.9* F4: 20.0*	TE values correlated to stage of fibrosis ($r = 0.58$, $P < 0.001$)	≥F1: 6.1 (0.81) ≥F2: 6.8 (0.78) ≥F3: 7.5 (0.79) F4: 14.1 (0.96)	
Marginean et al, 2012, Romania (24)	Prospective	71	Chronic LD: 6* NAFLD: 7.9* Malignancies§: 9.2*	Chronic LD, NAFLD, Malignancies	Chronic LD: biopsy, histological scoring system not mentioned	pSWE	Portal fibrosis: 1.59* Grade 3: 1.74* Grade 4: 2.78*	—	—	Also compared with healthy children. A significant difference was only observed between NAFLD and healthy controls ($P < 0.05$)

TABLE 2. (*Continued*)

Author, year, and country	Study type	No of ptt	Age, y; mean/median*	Diagnoses	Criterion standard†	Elastography method (TE probe type)	Elastography values‡, mean/median*	Relation to criterion standard	Cutoff (AUROC)	Comments
Pinto et al, 2014, Portugal (34)	Prospective	30	11.0	Liver transplant	Biopsy, Batts and Ludwig	pSWE	F0–F1: 1.43 ≥F2: 1.91	pSWE was an independent predictor of ≥F2 ($P < 0.05$)	≥F2: 1.57 (0.76)	Diagnostic accuracy of pSWE better in combination with other noninvasive marker
Hanquinet et al, 2013, Switzerland (35)	Prospective	39	5.6	Various chronic LD	Biopsy, METAVIR	pSWE	Overall: 1.99 F0: 1.47 F1: 1.65 F2: 2.30 F3: 2.61 F4: 2.89	An increase in pSWE values is evident with ≥F3 stages	≥F1: 1.34 (S: 0.82, Sp: 0.45) ≥ F3: 2.00 (S: 1.00, Sp:—)	Also compared with healthy children with a significant difference in liver stiffness (≥F0 vs controls, $P < 0.001$)
Noruegas et al, 2-012, Portugal (25)	Prospective	32	8.0	Various chronic LD	Biopsy, Batts and Ludwig	pSWE	Overall: 1.42 F0: 1.19 F1: 1.48 F2: 1.66 F4: 2.93	Increasing mean stiffness with increasing fibrosis stage, but with a considerable overlap	≥F1: 1.31 (0.83) ≥F2: 1.39 (0.82) F4: 2.25 (0.98)	Also compared with healthy children with a significant difference in liver stiffness (≥F0 vs controls, $P = 0.001$)
Leschied et al, 2015, USA (36)	Prospective	11	0.3	BA and non-BA LD (2 groups)	Biopsy, Ishak	pSWE	VTQ: Non-BA (F0–F1): 1.28 BA (F3–F6): 2.08 VTIQ: Non-BA: 1.61 BA: 3.14	Significant difference between groups VTQ: $P < 0.0001$ VTIQ: $P = 0.003$	—	
Tutar et al, 2014, Turkey (27)	Prospective	76	7.7*	Various chronic LD	Biopsy, Brunt	rtSWE	kPa, m/s F0: 9.9, 1.75 F1: 18.5, 2.37 F2: 18.2, 2.12 F3: 20.2, 2.57 F4: 25.3, 2.88	F0 vs ≥F1: NS NASH > other	≥F1: *kPa* 10.6 (0.95) *m/s* 1.85 (0.96)	Also compared with healthy children with a significant difference in liver stiffness (≥F1 vs controls, $P < 0.001$)

(*continued overleaf*)

TABLE 2. (*Continued*)

Author, year, and country	Study type	No of ptt	Age, y; mean/ median*	Diagnoses	Criterion standard†	Elastography method (TE probe type)	Elastography values‡, mean/ median*	Relation to criterion standard	Cutoff (AUROC)	Comments
Elastography compared with other noninvasive methods										
Hahn et al, 2013, Korea (37)	Retrospective	69	0.2	BA	LRE at follow-up¶	TE (−)	Baseline:	Multivariate analysis: TE is a predictor of the development of LRE ($P = 0.018$)	19.9 (0.94)	
							LRE: 21.7 No LRE: 6.7 3-mo surgery: LRE: 34.8 No LRE: 13.1			
Honsawek et al, 2013, Thailand (19)	Prospective	40	9.5	BA	Jaundice (n=18) vs nonjaundice group (n = 22)	TE (−)	Overall: 29.7	Positively correlated to other markers:	—	Also compared with healthy children with a significant difference in liver stiffness ($P < 0.001$)
					Biochemical markers		Jaundice: 47.3	sRAGE: $r = 0.65$		
							No jaundice: 15.2	ALAT: $r = 0.61$ ($P < 0.001$) Bilirubin: $r = 0.48$ ($P = 0.002$)		
Rubio et al, 2009, France (18)	Prospective	19	13.7	HIV-1	FibroTest.	TE (M)	Overall: 5.91	Patients with abnormal FibroTest had higher TE values ($P = 0.01$)	—	Also compared with healthy children with a significant difference in liver stiffness ($P = 0.014$)
					CDC-classification stages.		Asymptomatic: 7.46	Asymptomatic vs symtomatic ($P = 0.013$)		
							Symptomatic: 5.36			
Rath et al, 2012, Germany (38)	Prospective	45 without CFLD	No CFLD: 10.9	CF	Liver disease guidelines and conventional US of the liver	TE (<15 kg = S)	CFLD: 9.6	Significant difference between CFLD and no CFLD ($P = 0.01$)	CFLD: 5.5 (0.68)	S and NPV improved when combined with the respective biomarker for the diagnosis of CFLD, Sp was lowered
		30 with CFLD	CFLD: 10.6				No CFLD: 4.7			
Monti et al, 2012, Italy (39)	Prospective	75	14.4	CF	Compared with US score of CFLD ranging from 0 (no US evidence of CFLD) to 4 (all of the parameters were present)	pSWE	US scores	Significantly correlated ($P < 0.05$) to US score	—	Also correlated to other signs of severe liver disease: pancreatic insufficiency, splenomegaly, portal hypertension, and oesophageal varices

TABLE 2. (*Continued*)

Author, year, and country	Study type	No of ptt	Age, y; mean/median*	Diagnoses	Criterion standard†	Elastography method (TE probe type)	Elastography values‡, mean/median*	Relation to criterion standard	Cutoff (AUROC)	Comments
							0: 0.97[a] 1: 1.07[a] 2: 1.17[a] 3: 1.33[a] 4: 1.68[a]			
Behrens et al, 2013, Germany (40)	Prospective	36	Max 18 (only range)	CF	Grey-scale US findings (groups): 1: normal 2: discrete findings 3: severe findings	pSWE	1: 1.22 2: 1.28 3: 2.29	Group 3 differed significantly from groups 1 and 2	—	Values on healthy children in discussion (and in Fig. 1) but not in the results text

BA = biliary atresia; CF = cystic fibrosis; CFLD = cystic fibrosis liver disease; LD = liver disease; LRE = liver-related events; M = M-size probe; MT = major thalassemia; NAFLD = nonalcoholic fatty liver disease; NASH = nonalcoholic steato-hepatitis; NPV = negative predictive value; pSWE = point shear-wave elastography; rtSWE = real-time shear-wave elastography; TE = transient elastography.

Probe type: – = probe type not mentioned; MG = manufacturer's guidelines; ptt = patients; S = sensitivity; S = S-size probe; Sp = specificity; US = ultrasound.

*Median.

†Fibrosis scoring system is mentioned for studies that compare ultrasound elastography with histological results.

‡TE is measured in kPa, pSWE in m/s, rtSWE in both kPa and m/s.

§Malignancies cover acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphomas, nephroblastoma, rhabdomyosarcoma, and retinoblastoma.

•Follow-up time from Kasai surgery ranged from 75 weeks to 445 weeks.

correctly. For the distinction between no, mild, and moderate fibrosis in children with liver disease, the method was less accurate. No fibrosis-specific cutoffs were proposed. Histologically verified necroinflammation was investigated in 2 studies, and the grade of inflammation was also correlated with increasing liver stiffness (32,34).

Ultrasound Elastography in Children With Chronic Liver Disease: Liver Stiffness Compared With Other Noninvasive Markers

Six studies compared ultrasound elastography to other noninvasive markers. These studies were heterogeneous, but all found an association between liver stiffness and the investigated markers (Table 2). Three studies found increasing liver stiffness with increasing fibrosis stages defined by B-mode ultrasound images (38–40). In 2 studies, different serum biomarkers (Fibrotest, sRAGE, ALAT, bilirubin) were correlated to liver stiffness (18,19). Lastly, 1 study found liver stiffness usable as a predictor of the development of liver-related events such as ascites, variceal bleeding, and death (37).

Comparison of Children With and Without Liver Disease

Six studies compared children with and without liver disease. All studies found a statistically significant difference of the liver stiffness between the 2 groups (Table 2, see comments). Four of the studies compared liver stiffness measurements and histological fibrosis stages with measurements in children without liver disease; 1 of the studies was able to distinguish stages F1 or more from healthy liver (27), and 2 studies were able to differentiate F0 from healthy liver (25,35). In the last study, only children with nonalcoholic fatty liver disease (NAFLD) were significantly different from controls (24).

Patient Diagnoses

Eleven of the studies had homogenous patient populations (Table 2). The remaining studies had populations with various diseases. These included NAFLD, biliary atresia, cystic fibrosis, major thalassemia, posttransplant liver fibrosis, viral hepatitis, HIV, autoimmune liver diseases, liver disease following solid and hematologic malignancies, metabolic liver diseases, congenital/hereditary liver diseases, and rare and idiopathic diseases.

Histological Scoring Systems

The Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) fibrosis-scoring system (41) originally made for hepatitis C was used in 4 studies (28,29,32,35). Two studies used the Brunt system (42) specific for NAFLD (27,31), 1 study used the Kleiner system (43) also specific for NAFLD (30), and 1 study used both METAVIR and Kleiner systems (33). Two studies used Batts and Ludwig system (25,34,44), the Ishak system (45) was used in 1 study (36), and 1 study did not mention the scoring system used (24).

Parameters Influencing Liver Stiffness Measurements

Age, Sex, Body Mass Index, and Necroinflammatory Grade

Six studies found a tendency of increasing liver stiffness with age (14,16,18,20,26,28). In 1 of the 6 studies, age only had influence in patients and not in children without liver disease (18). In another study, liver stiffness was only lower in children younger than 1 month compared with the rest of the children (20). Eight studies did not find any effect of age (15,17,21–23,29,32,33). Success rates were lower in younger children (14,15,17,18,22,23). Boys had higher liver stiffness values compared with girls in 2 studies (14,21), but in 6 studies sex had no effect on measurements (16,17,20,22,26,33). Body mass index (BMI) did not influence liver stiffness in 4 studies (16,20,29,32), although a high BMI lead to unsuccessful measurement in other studies (17,31,33). Increasing necroinflammatory grade was correlated to increasing liver stiffness in 2 studies (32,34). Another study found 1 child with high liver stiffness and low fibrosis grade but moderate necroinflammatory activity (29).

Measurement Site, Probe Size, and Fasting State

Higher liver stiffness values were found in the left liver lobe compared with the right in 3 studies using pSWE (20,21,26). Another study found that children with no liver disease and children with NAFLD had lower liver stiffness values in segment 1 (left lobe) compared with segment 8 (right lobe), but this tendency was not found in children with various chronic liver diseases or malignancies (24). With TE, liver stiffness increased with decrease in probe size (17). Also, success rates were higher with the S-probe compared with the M-probe (28). In pSWE, no statistically significant difference was observed between a linear and a convex array probe (20,22). Lastly, 1 study found that liver stiffness increased after food intake in 75% of children (17).

Practical Performance of Ultrasound Elastography

Overall, studies using TE were in accordance with the manufacturers' guidelines regarding number of valid measurements, except for 1 study in which only 5 valid measurements were collected (28). The number of valid measurements with pSWE ranged from 2 to 18. The failure rate when using TE was reported in 3 studies and ranged from 4% to 15% and reported in 2 studies using pSWE ranging from 0% to 5.5% (14,15,17,20,22). Most studies measured in the right liver lobe, 1 study did not mention the site (25) and 1 measured at the biopsy site (36). The specific probe of choice for TE varied among the studies. Some studies did not specify which probe was used (16,19,32,37), 1 changed from M- to S-probe (28), 1 only used the S-probe (30), 4 only used the M-probe (15,18,31,33), and 1 study chose the S-probe in children with a weight <15 kg (38). The remaining studies used the probes for specific chest circumferences (14,17,29). For pSWE, the probe of choice also varied among studies. Most studies used either a 4-MHz convex probe, a 9-MHz linear probe, or both. Most studies did not mention a fasting protocol, but in 5 studies children fasted between 3 and 6 hours before examination (22,27,28,36,39). Breathing was only mentioned in few studies: in 6 studies, measurements were obtained during breath hold if possible (21–23,26,39,40), 1 study used slow breathing (25), and in 2 studies breathing was normal (20,36).

DISCUSSION

Ultrasound elastography was accurate for the diagnosis of cirrhosis. For the distinction between no, mild, and moderate fibrosis the method was less accurate. The method was able to distinguish healthy from fibrotic liver tissue. In children without liver disease, elastography showed consistent liver stiffness values

TABLE 3. QUADAS-2

	Risk of bias				Applicability concerns		
Study	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Engelmann et al, 2012, Germany (14)	☺	?	—	?	☺	☺	—
Menten et al, 2010, Belgium (15)	☺	☹	?	☺	☺	☺	☺
Witters et al, 2009, Belgium (16)	☺	☺	—	?	☺	☺	—
Goldschmidt et al, 2013, Germany (17)	☺	☹	—	?	☺	☺	—
Rubio et al, 2009, France (18)	☺	☺	?	?	☺	☺	☹
Honsawek et al, 2013, Thailand (19)	☺	?	☹	?	☺	☺	☹
Fontanilla et al, 2014, Spain (20)	☺	☹	—	?	☺	☺	—
Eiler et al, 2012, Germany (21)	☺	☹	—	☺	☺	☺	—
Hanquinet et al, 2013, Switzerland (22)	☺	☹	—	?	☺	☺	—
Lee et al, 2013, Republic of Korea (23)	☺	☹	—	?	☺	☺	—
Marginean et al, 2012, Romania (24)	☺	?	?	☹	☺	?	?
Noruegas et al, 2012, Portugal (25)	?	?	☺	☹	☺	☺	☺
Matos et al, 2014, Portugal (26)	☺	☹	—	?	☺	☺	—
Tutar et al, 2014, Turkey (27)	☺	☺	☺	☺	☺	☺	☺
Shin et al, 2014, Korea (28)	☺	☺	☺	☺	☺	☺	☺
Hamidieh et al, 2014, Iran (29)	☺	☺	☺	☺	?	☺	☺
Alkhouri et al, 2013, USA (30)	☺	☹	☺	☺	☺	☺	☺
Nobili et al, 2008, Italy (31)	☺	☺	☺	☺	☺	☺	☺
Awad et al, 2013, Egypt (32)	☹	☺	☺	☺	?	☺	☺
Fitzpatrick et al, 2013, United Kingdom (33)	☺	☺	☺	☺	☺	☺	☺
Pinto et al, 2014, Portugal (34)	☺	☺	☺	☺	☺	☺	☺
Hanquinet et al, 2013, Switzerland (35)	☺	☺	☺	☺	☺	☺	☺
Leschied et al, 2015, USA (36)	☹	☺	☺	☺	☺	☺	☺
Hahn et al, 2013, Korea (37)	☺	?	?	☺	☺	☺	☹
Rath et al, 2012, Germany (38)	☺	?	—	?	☺	☺	—
Monti et al, 2012, Italy (39)	☺	☹	☹	☺	?	☺	☹
Behrens et al, 2013, Germany (40)	☺	☹	☹	☺	☺	☺	☹

Risk of bias and applicability of the included studies.
☺ Low Risk; ☹ High Risk; ? Unclear risk; Not applicable (no reference standard).

comparable with those in adults (5,46,47). No fibrosis-specific cutoffs were proposed. The results indicate that elastography can be used as a supplement to B-mode ultrasound, blood samples, and clinical examination in the follow-up of children with chronic liver disease. To our knowledge this is the first systematic review to evaluate the available ultrasound elastography studies in children with chronic liver disease.

Factors influencing liver stiffness were also investigated. In adults, age did not influence liver stiffness (46–51) as in the majority of the studies in children. Some studies in adults have found lower liver stiffness values in girls (50,51) whereas other studies have not (46–48), resembling the mixed results in children. As in children, liver stiffness values were also higher in the left liver lobe compared with the right in adults (5,52). Liver stiffness increased significantly with a decrease in probe size (S1 > S2 > M) (17), which has been confirmed in other studies in children not included in this review (53,54). As in adults (55,56), food intake increased liver stiffness (17). Necroinflammatory grade seemed to correlate with liver stiffness, which has also been shown in adults (57).

Fibrosis specific cutoffs for children have not yet been made as in adults (59), but could be a way to avoid unnecessary biopsies. One of the problems in liver elastography is the overlap between measurements and the range in measures in low levels of fibrosis (F0–F1) and in significant fibrosis (F2, by METAVIR). This may lead to pathological values in healthy livers and cause unnecessary worrying. Improved diagnostic accuracy was observed in 3 of the included studies using a combination of elastography and other noninvasive markers (34,29,30). Repeated measurements in the same children over time would probably also improve the accuracy. Studies in adults have shown that ultrasound elastography can be used as a tool to observe disease progression (60,61). Because the studies in this review show similar results regarding implementation and accuracy as those in adults, the use of elastography as a monitoring tool in children seems feasible and should be evaluated in future studies. A comparison of the diagnostic performance of TE and pSWE was not possible because of the heterogeneity of the studies. A meta-analysis on adults with liver fibrosis showed a lower failure rate with pSWE compared with TE (58). pSWE is advantageous because it is performed with a B-mode image, allowing simultaneous sonographic evaluation, but TE may be more effective in a busy clinical setting. More homogenous prospective studies in children are needed to compare the 2 methods further.

Magnetic Resonance elastography (MRE) is an alternative method to determine liver stiffness. The method is safe (62), and high accuracy for the detection of significant fibrosis in children has

been found (63). MRE is user-independent and may be advantageous in children with severe obesity and ascites where ultrasound is not always applicable. MRE investigates a larger volume of liver tissue, which diminishes the risk of sampling errors and gives the opportunity to create a visual map of fibrosis in the whole liver. Disadvantages are the lack of accessibility, price, time spent, and the need of general anesthesia in young children.

LIMITATIONS

Different issues limit the comparability of the studies, beside the ones mentioned earlier. The number and experience of the investigators varied. One study found good interobserver agreement for TE (31), whereas another found that if 2 examiners did their measurements at the same point, interobserver agreement was good, but if examination point was chosen independently, variation increased (17). Studies in adults have shown interobserver variability and inexperience as limitations of ultrasound elastography (63–65). Time from biopsy to ultrasound elastography examination varied from 24 hours to 1 year (25), and some studies did not mention any time interval (24,28–30) causing uncertainty regarding the histological stage at the time of elastography. Also, 5 different histological scoring systems were used (41–45). The children had many different diagnoses and it is not clear whether the liver fibrosis stages are comparable among different liver diseases, and whether the chosen staging system is appropriate; the METAVIR system is validated for hepatitis C in adults (41), but it is used for many diagnoses in the children (28,29,33,35). Finally, a limitation concerns the use of QUADAS-2. No reference standard is applied for the children without liver disease, and the risk of bias evaluation does not apply well. The results in the table are therefore prone to some uncertainty.

In conclusion, ultrasound elastography is able to diagnose cirrhosis and distinguish healthy from fibrotic liver tissue, but for the differentiation between no, mild, and moderate fibrosis in children with liver disease, the method in itself is not yet sufficient. Large prospective studies in homogeneous patients are needed to assess the full usefulness of ultrasound elastography in monitoring the progression of liver disease and in predicting relevant clinical events in children.

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