

REVIEW PAPER

Application of bidimensional shear wave liver elastography in the pediatric population

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ABSTRACT

Chronic liver diseases are a notable worldwide problem among adults and children. Pediatric chronic liver diseases have a wide range of etiologies, including congenital, metabolic, toxic, and infectious backgrounds, as well as fatty liver disease. Patients with more advanced stages of fibrosis are more likely to develop cirrhosis with all of its complications. Severity of liver fibrosis and its progression are among the most important factors for the prognosis and treatment policy. Liver biopsy is still considered as a reference standard to quantify liver fibrosis, but it is not a good tool for regular monitoring of disease progression. For these reasons, nowadays huge development of noninvasive methods for the assessment of liver fibrosis can be observed. Ultrasound elastography methods are widely accessible and easily performed in children. Bi-dimensional shear-wave elastography is one of the newest elastography techniques.

KEY WORDS:

children, liver diseases, shear wave elastography.

LIVER BIOPSY

Currently liver biopsy is still considered as a reference standard to quantify liver fibrosis. In addition, it allows grading of steatosis, necrosis, and inflammatory activity, which is a great advantage. However, it is an invasive procedure with potential serious complications that can be severe in up to 1% of cases (hemorrhage, infections, even mortality). Furthermore, there is a possibility of discordance in fibrosis stage given the heterogenous nature of fibrosis distribution and small area sampled by liver biopsy. Its accuracy is limited due to intraobserver and interobserver variability. For these reasons nowadays we can observe huge development of noninvasive methods for the assessment of liver fibrosis, including elastographic methods involving ultrasonography and magnetic resonance imaging. In fact, ultrasound elastography is more

often used than liver biopsy especially in monitoring disease progression.

ULTRASOUND ELASTOGRAPHY

Quantitative ultrasound elastography methods include transient elastography (TE) and acoustic radiation force impulse (ARFI) techniques – such as point shear-wave elastography (pSWE) and bi-dimensional shear-wave elastography (2D-SWE). Transient elastography is a non-imaging elastographic technique that uses a mechanical external push to generate shear waves in the liver, and single line ultrasound is used to estimate the shear wave speed. It was the first commercially available method to measure liver stiffness and is the most widely used and validated technique to assess liver fibrosis – including in the pediatric population. Acoustic radiation force

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impulse techniques are based on the generation of shear waves by the push pulse of the ultrasound beam. In pSWE a single ARFI pulse is used and a small region of interest is placed at the site where the measurement is to be taken, while in 2D-SWE multiple ARFI pulses are applied to generate shear waves in a larger field of view. Both techniques are performed using real-time imaging, so masses and large vessels can be avoided.

Liver fibrosis leads to increased stiffness of its tissue. As generated shear waves travel through it, the speed of the wave depends on the tissue stiffness. In stiffer tissues, the shear-wave speed is greater. Thus, it enables to estimate the degree of liver fibrosis from measuring the speed of a shear wave.

Elastographic measurements of stiffness of examined liver tissue are mainly determined by the degree of fibrosis. But there are several variables that will affect the liver stiffness measurement (Figure 1).

Therefore, elastography results should be carefully interpreted in conjunction with clinical profile, laboratory test results for liver function, and other imaging studies.

ASSESSING LIVER FIBROSIS IN ADULTS AND CHILDREN

Strict and up-to-date recommendations for performing liver elastography with the ARFI techniques are available in an Update to the Consensus Statement of Ultrasound Liver Elastography created by the Society of Radiologists [1]. According to experts, they should be adopted in children as well as adults. In the pediatric population, one of the most important problems during liver stiffness measurement is patients' breath control. In children who are unable to hold their breath, the consensus panel suggests recording a 2D-SWE cine loop for up to 30 seconds, reviewing it and choosing the image demonstrating the most stable pattern for the stiffness measurement.

The most important issue in clinical management with chronic liver disease is to rule in or rule out significant liver fibrosis. Providing an exact stage of fibrosis like in histopathological assessment is not crucial. What matters, especially in monitoring of disease, is the possibility of comparing the patient's results during follow-up examinations.

For these reasons, recommendations for interpretation of liver stiffness values obtained with ARFI techniques in patients with viral hepatitis and nonalcoholic fatty liver disease (NAFLD) were recently published [1]. The consensus panel proposed a vendor-neutral "rule of four" (5, 9, 13, 17 kPa). Liver stiffness of 5 kPa (1.3 m/s) or less has high probability of being normal; liver stiffness less than 9 kPa (1.7 m/s), in the absence of other known clinical signs, rules out compensated advanced chronic liver disease (cACLD); values between 9 kPa (1.7 m/s) and 13 kPa (2.1 m/s) are suggestive of cACLD but may need a further test for confirmation; and values greater than 13 kPa (2.1 m/s) are highly suggestive of cACLD.

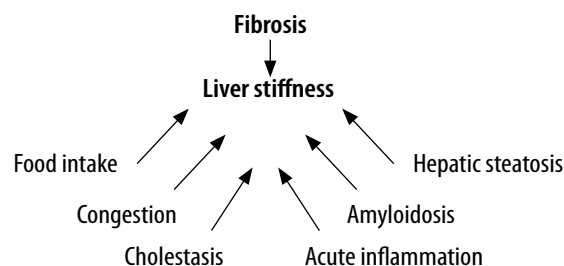


FIGURE 1. Confounding factors for liver stiffness

There is a probability of clinically significant portal hypertension with liver stiffness values greater than 17 kPa (2.4 m/s), but additional patient testing may be required.

For other causes such as alcoholic hepatitis, primary biliary cirrhosis, Wilson's disease, autoimmune hepatitis, sclerosing cholangitis, and drug-induced liver disease, there are insufficient data to make a clear conclusion.

For those who would like a value to rule out significant fibrosis, most studies that have used ARFI suggest that a liver stiffness value of less than 7 kPa (1.5 m/s) could help to rule out significant fibrosis [1].

However, the rules mentioned above refer to adult patients only. There is still not enough literature at this time to recommend them in pediatric patients. Moreover, according to the World Federation for Ultrasound in Medicine and Biology, there is still insufficient evidence to make a recommendation on the use of SWE for liver stiffness assessment in pediatric patients [2]. We still do not have reference values for the healthy child population. At present, in the case of liver disease associated with cystic fibrosis, autoimmune hepatitis, biliary atresia, or congenital heart disease with Fontan surgery or even NAFLD or viral hepatitis, it is recommended that each patient becomes his or her own control, using the stiffness delta changes over time to evaluate the efficacy of the treatment or the progression of disease [1].

The mean normal liver stiffness in children value varies among studies and ranges from 3.7 kPa [3] to 4.99 kPa [4]. For ARFI-based techniques, most published studies have shown that age and sex have no significant influence on liver stiffness values [1]. Some studies have reported similar or higher diagnostic accuracy of 2D-SWE than TE in assessing liver fibrosis in children [5, 6]. The intra-operator reproducibility of liver stiffness measurements by 2D-SWE has been found to be excellent in many studies [7, 8].

There are quite a lot of studies assessing usefulness and accuracy of 2D-SWE for detecting liver fibrosis in pediatric patients. However, these works mainly investigated groups of patients with various etiologies of liver diseases and their results are not consistent. It must be taken into account that there is a variety of specific pediatric etiologies of diseases, with different confounding factors as well.

NONALCOHOLIC FATTY LIVER DISEASE

With the increasing prevalence of childhood obesity, NAFLD has become the most common liver disease

among children in industrialized countries. Nonalcoholic fatty liver disease may progress from simple steatosis to nonalcoholic steatohepatitis (NASH), connected with the presence of hepatocellular damage, inflammation and fibrogenesis, subsequently leading to advanced fibrosis and cirrhosis. According to some studies, the disease in children appears to be more severe compared to adults [9]. One study reported that fifteen percent of children with NAFLD have stage 3 fibrosis or higher at diagnosis [10]. Therefore, early identification of NAFLD and the severity of liver fibrosis are crucial for treatment and prognosis. Liver biopsy is the current standard to define the presence and severity of NAFLD, including the presence of NASH and fibrosis. However, following the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children from 2018, elastography techniques would benefit from further validation studies in order to determine optimal cut-points and ability to longitudinally track fibrosis in children [11].

Studies in this field in the pediatric population are limited. The majority of them used TE for assessing liver fibrosis. Bi-dimensional shear-wave elastography also has been shown to be capable of detecting advanced liver fibrosis in pediatric NASH patients. Garcovich *et al.* conducted a study of 69 biopsy-proven NASH child patients, in whom the liver stiffness was measured using 2D-SWE [8]. It was feasible in 68 patients and these were included in the final statistical analysis. Overall, SWE was used to correctly classify 57 of 68 patients (84%). Statistical analysis revealed cut-off values of 5.1 and 6.7 kPa, suggesting the presence of any fibrosis (F1) and significant fibrosis (F2), respectively.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is the most common genetic disease occurring in Caucasians, of autosomal-recessive inheritance. It is a systemic disease, affecting the liver as well. Up to 40% of individuals with CF have cystic fibrosis-related liver disease (CFLD); however, only 5–10% will have clinically evident disease [12]. Impaired intrahepatic biliary ductal secretion due to a mutation in the CF transmembrane conductance regulator results in inspissated bile and bile duct plugging, leading to inflammation, liver injury and biliary fibrosis. Liver cirrhosis remains one of the most important non-pulmonary causes of death, accounting for 2.5% of overall CF mortality [12]. Liver biopsy is of questionable accuracy in CFLD because of the focal distribution of the fibrosis.

Transient elastography is the most often used for liver stiffness measurement in children with CF, but many studies have indicated similar or higher diagnostic accuracy of 2D-SWE than TE, and it was also confirmed in CF pediatric patients [13].

It was proven that liver stiffness increases with time in patients with CF and that the degree of worsening is greater in patients who will develop CFLD [14].

Some studies have shown that CF patients have significantly increased liver stiffness compared to controls (mainly conducted with TE [15], some with 2D-SWE [16]).

Calvopina *et al.* compared liver stiffness measured using 2D-SWE in patients with CFLD, CF patients with no evidence of liver disease (CFnoLD) and controls [17]. Liver stiffness measurements were significantly higher in CFLD (8.1 kPa) vs. CFnoLD (6.2 kPa) and Controls (5.3 kPa). They also reported cut-off values of 6.85 kPa and 9.05 kPa for detecting CFLD and advanced CFLD respectively.

Earlier, similar results were obtained by Kitson *et al.* with TE [18]. They concluded that liver stiffness > 6.8 kPa predicts CFLD.

Moreover Calvopina *et al.* concluded that the combination of elastography and aspartate aminotransferase-to-platelet ratio index (APRI) proved to have 14.8 times higher sensitivity in the detection of CFLD (AUC = 0.84) compared with single tests [17]. APRI is an indirect biochemical marker of hepatic fibrosis.

AUTOIMMUNE LIVER DISEASES

Autoimmune hepatitis (AIH) is an autoimmune liver disorder, progressive in nature. It is a rare cause of end-stage liver disease in children, but most frequent among autoimmune liver diseases in the pediatric group of patients. Other diseases in this group include primary biliary cholangitis and primary sclerosing cholangitis. Similarly to other liver diseases, presence of advanced fibrosis is associated with worse outcome in AIH. Cirrhosis is present in 28–33% of adults at presentation as well as in 38% of children [19]. Moreover, it is well known that AIH is more aggressive in childhood than in adulthood [20].

Liver biopsy is needed to confirm the diagnosis and to evaluate the severity of liver damage. Noninvasive methods of liver fibrosis assessment are substantially limited by active liver inflammation.

According to Practice Guidance and Guidelines from the American Association for the Study of Liver Diseases, elastography may be used to assess the stages of hepatic fibrosis noninvasively, but mainly to evaluate progress of the disease [19]. They referred to a study which pointed out that accuracy of TE in quantifying fibrosis is impaired when undertaken within the first 3 months of treatment – because of active inflammation [19]. The transient elastography results correlate with histological grade of inflammation rather than stage of fibrosis. After at least 6 months of successful immunosuppressive therapy to reduce hepatic inflammation, TE can accurately diagnose cirrhosis and distinguish advanced stages of fibrosis from less severe stages. Similar results were revealed in pediatric patients with TE [21]. The results of ARFI elastography

methods are comparable to TE in many studies, which may constitute a premise for extrapolation for 2D-SWE.

One study which assessed liver fibrosis with 2D-SWE in a pediatric population distinguished a group with AIH [22]. This group showed similar levels of liver stiffness values with the various chronic liver diseases group at all fibrosis stages, excluding biliary atresia. Statistical analysis revealed optimal cut-off value for detecting advanced fibrosis (\geq F3) of 8.7 kPa.

WILSON'S DISEASE

Wilson's disease is a rare inherited disorder of copper metabolism with copper accumulation in hepatocytes and the central nervous system, leading to liver toxicity and progressive neuropsychiatric disturbances. Predominant hepatic manifestation is present in up to 60% of cases. Adequate therapy improves hepatic function and the long-term outcome in 80% of Wilson patients, whereas up to 13% of cases have progressive disease and may require liver transplantation [23].

Only a few studies have been dedicated to liver stiffness measurements in patients with Wilson's disease, even in the adult population, and even fewer were performed with 2D-SWE.

One of them, which was devoted to assessing diagnostic performance of TE and 2D-SWE for evaluation of hepatic involvement in Wilson's disease, was performed in a pediatric and adult population, with a median age of 16 years old [24]. Both techniques showed excellent and comparable diagnostic accuracy for differentiating the clinical categories of hepatic involvement. The other conclusion was that the assessment of hepatic manifestations in Wilson's disease can be improved by combining elastography with serologic indices. However, liver biopsy was not performed.

In a study by Stefanescu *et al.*, in nine children with Wilson's disease, liver stiffness measured with TE was the highest at the time of diagnosis and decreased during treatment in parallel with an increase in urinary copper concentration [25].

In an already mentioned study by Behairy *et al.*, TE values of liver stiffness were compared with liver biopsy in a pediatric population, and a subgroup with 20 patients with Wilson's disease was distinguished [21]. There was a good correlation of TE results with the Ishak score.

Sini *et al.* compared the results of liver stiffness evaluated by TE, serum fibrosis markers and liver biopsy results in 28 young (aged 25 ± 7 years) treated patients with Wilson's disease. In this study the METAVIR scoring system was used [26]. Liver stiffness values increased proportionally with progression of the histological fibrosis stage. The authors proposed a cut-off value of 6.6 kPa for significant fibrosis and a cut-off value 8.4 kPa for advanced fibrosis. Yet, liver stiffness values were overlapping in different fibrosis categories and the TE values did not

differ significantly between METAVIR F1 vs. F2, F2 vs. F3, F3 vs. F4 subgroups. There was a significant difference only between F1 vs. F3 and F1 vs. F4. Similar results were reported by Przybylkowski *et al.* [27]. The authors evaluated liver stiffness in 60 adult patients using TE and 2D-SWE and they did not find a linear correlation between liver stiffness measurements and histological grading of liver fibrosis. They concluded that the precise assessment of liver fibrosis in patients with Wilson's disease has limited value, but repeated liver stiffness measurement may be useful in assessing progression/regression. Along with the various liver involvement patterns in Wilson's disease, copper content may play a role in the discrepancy between elastography and the histological liver fibrosis assessment.

BILIARY ATRESIA

Biliary atresia (BA) is a progressive disease that causes obliteration of the extra- and intrahepatic biliary tree and that clinically presents during the first few weeks of life with persistent jaundice. It rapidly progresses to cirrhosis and has a different treatment strategy from other causes of pathological neonatal liver disease, such as neonatal hepatitis. Early hepaticojejunostomy (the Kasai procedure) before 60 days of age may reestablish bile flow, thereby prolonging native liver survival. For this reason, early diagnosis is crucial.

According to many studies, elastography can be used to help differentiate BA from other non-surgical causes of neonatal jaundice, such as neonatal hepatitis and Alagille syndrome [28, 29].

Wu *et al.* found that liver stiffness > 7.7 kPa measured by TE had a sensitivity of 80% and specificity of 97% for BA diagnosis in neonates until 60 days of age [30]. Similar results were obtained in a study conducted by Shen *et al.* with 2D-SWE [31]. The cut-off value was > 7.5 kPa in infants until 60 days, with sensitivity and specificity levels reaching 73.3 and 70.1%, respectively. They also distinguished two other age groups (61–90 days and 91–120 days) and identified cut-off values for a diagnosis of BA of 10.0 kPa and 11.0 kPa, respectively.

In the above-mentioned study by Galina *et al.* a BA group of patients was distinguished [22]. Their liver stiffness was significantly higher than the other two groups at fibrosis stages \geq F2. The optimal cut-off value for detecting advanced fibrosis (\geq F3) was 16 kPa (with a value of 8.7 kPa in other chronic liver diseases).

VIRAL HEPATITIS

Globally viral hepatitis remains one of the important causes of liver disease in children – but mostly in developing countries. Children with HBV rarely have acute severe hepatitis. Most children with HBV and HCV are asymptomatic during childhood, but are at risk for developing

cirrhosis and hepatocellular carcinoma in adulthood due to their long exposure to these viruses [32].

Liver elastography has been validated for staging of liver fibrosis and diagnosis of cirrhosis in adults.

By contrast, in children liver biopsy is still considered the standard test to assess the degree of liver fibrosis [32]. The diagnostic and prognostic value of elastography in children with chronic viral infections are not yet well established, because of the limited number of studies.

A study by Xu *et al.* found that the liver stiffness measured with TE positively correlated with the fibrosis stage in chronic hepatitis B children aged 0–6 years. The authors reported the cut-off values for significant and advanced fibrosis as 5.6 kPa and 6.9 kPa, respectively [33]. Different results were obtained by Luo *et al.*, who assessed children aged 0–16 years old with chronic hepatitis B – also with TE [34]. They identified cut-off values for diagnosis of any fibrosis and significant fibrosis as 5.9 kPa and 8.4 kPa, respectively.

A study conducted by Galal *et al.* assessed liver fibrosis in children with chronic hepatitis C measured by 2D-SWE with liver biopsy as a reference [35]. The SWE value was significantly higher in patients with significant fibrosis than in those with no or mild fibrosis – statistical analysis revealed a cut-off value of 7.6 kPa for differentiating between significant and no or mild fibrosis.

FONTAN ASSOCIATED LIVER DISEASE

Fontan surgery is the palliative procedure of choice for many patients with a single functional ventricle and establishes an altered hemodynamic physiology, resulting from a direct conduit between caval and pulmonary veins. The elevated systemic venous pressure results in chronic passive liver congestion and fibrogenesis, which are principles of Fontan-associated liver disease (FALD). Its progression takes an individual course in each patient, and the main serious complications are portal hypertension with its consequences and hepatocellular carcinoma.

The assessment of liver fibrosis with SWE or any other elastographic technique in patients with FALD is challenging, because liver congestion is a huge confounding factor in this group of patients and liver stiffness values are higher than those observed in other etiologies of chronic liver disease.

Wu *et al.* evaluated 50 post-Fontan patients for liver stiffness with TE, among whom 10 patients underwent liver biopsy [36]. Correlation of liver biopsy findings of these 10 patients with TE cut-off values as suggested by Foucher *et al.* [37] revealed that fibrosis was overestimated by at least one stage for 70% of patients and by at least two stages for 50% of patients.

Currently we are unable to distinguish with certainty liver stiffening from congestion vs. fibrosis by elastography [38].

Fontan surgery induces immediately increased liver stiffness due to hepatic congestion. Over time, signs of Fontan failure appear and the liver stiffness value increases.

Several studies have confirmed significantly higher liver stiffness compared to healthy controls. One of them, conducted by Kutty *et al.*, also showed a good correlation between liver stiffness and histopathological stage of fibrosis, but in a small group of patients [39]. Liver stiffness on average was 13.4 kPa in patients with METAVIR fibrosis stage F < 2 and 19.8 kPa in patients with F ≥ 2. The authors stated that no significant change in SWE values was observed with time since the Fontan operation.

On the other hand, Talwar *et al.* assessed liver stiffness with TE and SWE in the preoperative and postoperative period [40]. The preoperative baseline value in SWE (mean \pm SD) was 13.32 \pm 5.4 kPa. Postoperatively, the liver stiffness measurements by SWE increased over time (20.22 \pm 6.49, 21.09 \pm 7.87, and 22.83 \pm 9.19 at 3, 6, and 12 months respectively), similar to the liver stiffness measurements by TE.

Moreover, Munsterman *et al.* compared liver stiffness values by TE with liver biopsy results of adult patients after the Fontan operation [41]. Liver stiffness measurements did not correlate with histological grade of fibrosis.

The American Heart Association in its scientific statement *Evaluation and Management of the Child and Adult With Fontan Circulation* opined that elastography promises to be a valuable tool for serial evaluation of the progression of hepatic stiffness over time [38].

CONCLUSION

Bi-dimensional shear-wave elastography is an accurate and reproducible noninvasive elastographic technique of rising importance in children. Despite its limitations, it seems likely to be a great method for noninvasive liver fibrosis staging in the future. This tool can be helpful in identifying patients with higher risk of progression or with initial stage of disease in order to intensify treatment and prevent or delay serious complications. However, further studies with larger numbers of pediatric patients assessed by 2D-SWE are needed.

DISCLOSURE

The authors declare no conflict of interest.

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