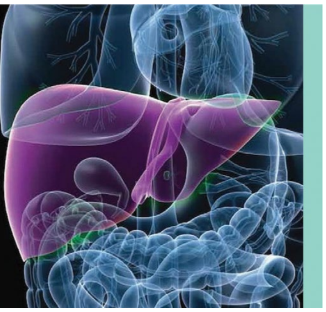

Imaging Modalities in Pediatric NAFLD

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Pediatric nonalcoholic fatty liver disease (NAFLD) comprises a spectrum of disease that can be simplified into two categories: (1) isolated/simple steatosis, 70% to 75% of cases, defined by excess liver fat without inflammation or cellular injury; and (2) nonalcoholic steatohepatitis (NASH), 25% to 30% of cases.[1] Unlike isolated steatosis, NASH reflects reactive inflammation and liver damage associated with steatosis and can ultimately progress to hepatic fibrosis and cirrhosis, eventually developing into end-stage liver disease and its related complications, including hepatocellular carcinoma.[2]

As of 2012, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHN) and as of 2016, the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommends the use of liver function tests as a part of the initial screening of NAFLD in high-risk (obese and diabetic) pediatric patients.[3,4] Unfortunately, these techniques have been shown to have low sensitivity and specificity.[3] Therefore, there is a significant role of newer quantitative imaging technologies that can be used in the screening and effective stratification of pediatric NAFLD.

ROLE OF IMAGING IN CHILDREN WITH NAFLD

Historically, the diagnosis, stratification, and management of chronic liver disease, including NAFLD, has relied heavily on liver biopsy, despite its limitations of being costly, subjective, and prone to sampling error.[5,6] The shortcomings of biopsy have meant that imaging studies are often used as surrogates for histology. These noninvasive, nonionizing quantitative imaging methods are reliable, safe, and clinically available with high repeatability and reproducibility. The aim of this article is to review the current status, diagnostic accuracy, limitations, and practical clinical use of ultrasound- and magnetic resonance imaging

Abbreviations: ARFI, acoustic radiation forces impulse; CAP, controlled attenuation parameter; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PDFF, proton density fat fraction; SWE, shear wave elastography; TE, transient elastography.

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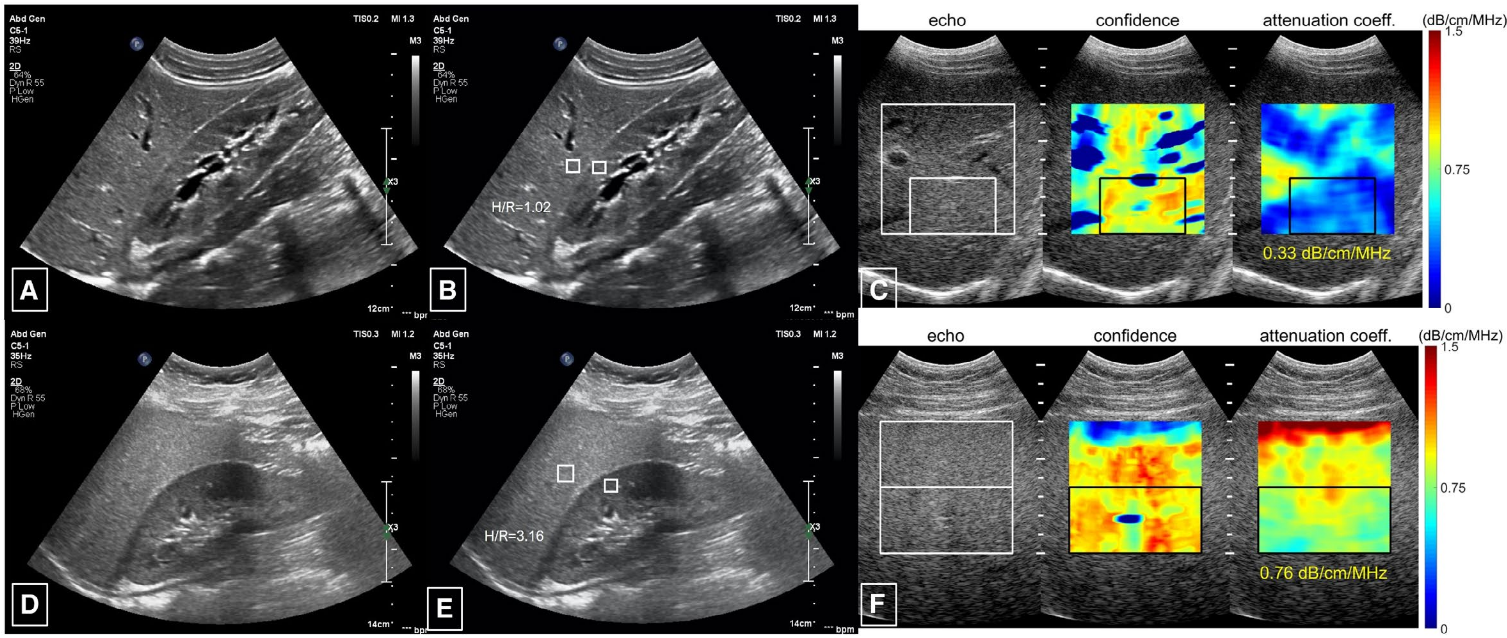

FIG 1 Ultrasound images in a healthy child that demonstrate (A) B-mode images showing normal liver parenchyma, (B) a normal hepatorenal echogenic index, (C) a quantitative measure of attenuation in an area of liver parenchyma without blood vessels of 0.33 dB/cm/MHz, as compared with ultrasound images in a pediatric patient with (D) echogenic liver parenchyma on B-mode images, (E) elevated hepatorenal index of 3.16, and (F) increased attenuation measuring 0.76 dB/cm/MHz. Courtesy Philips Ultrasound and Stanford Lucile Packard Children's Hospital.

(MRI)-based quantitative imaging methods to diagnose, stratify, and monitor NAFLD in the pediatric population.

ULTRASOUND-BASED QUANTITATIVE IMAGING FOR FAT AND FIBROSIS

Liver Steatosis

Ultrasound-based controlled attenuation parameters (CAPs) have been around for a few years for the quantification of liver steatosis and are now well tested. A drawback of CAP is that it is a point-of-care tool and limits simultaneous liver imaging. However, innovations in CAP technology may surmount this limitation, and some studies have shown a good correlation with MRI-proton density fat fraction (MRI-PDFF) in the pediatric population.[7] Recently, several manufacturers have developed software for quantifying the attenuation of the ultrasound beam using a combination of speed of sound estimation, backscatter coefficient, attenuation coefficient, and shear wave dispersion.[8] Early results using attenuation imaging (ATI; Canon Medical Systems, Tochigi, Japan) show promising results and better area under the receiver operating characteristic curve for diagnosing >5% steatosis than CAP (0.91 versus 0.85) against MRI-PDFF as the gold standard.[9,10] Figure 1 demonstrates normal B-mode imaging, hepatorenal index (a semiquantitative measure) comparing liver/kidney parenchyma echogenicity as a ratio, and quantitative attenuation measure in a normal pediatric patient and one with hepatic steatosis.

Liver Fibrosis

Similar to CAP, transient elastography (TE) by Echosens (Paris, France) is a point-of-care technology that has been extensively studied to stage liver fibrosis. TE has shown excellent diagnostic performance in children.[11] Ultrasound imaging-based technologies, such as acoustic radiation forces impulse (ARFI) and shear wave imaging, have shown superior results compared with TE.[12] In addition, ultrasound-based imaging techniques allow for comprehensive gray-scale and color Doppler assessment of the liver parenchyma as compared with isolated quantitative measures that are typically the product of TE (Fig. 2). TE is also limited and not very successful in the presence of obesity and ascites.[13]

MRI-Based Quantitative Imaging for Fat and Fibrosis

MRI provides a comprehensive morphological and functional evaluation of the abdomen in a single

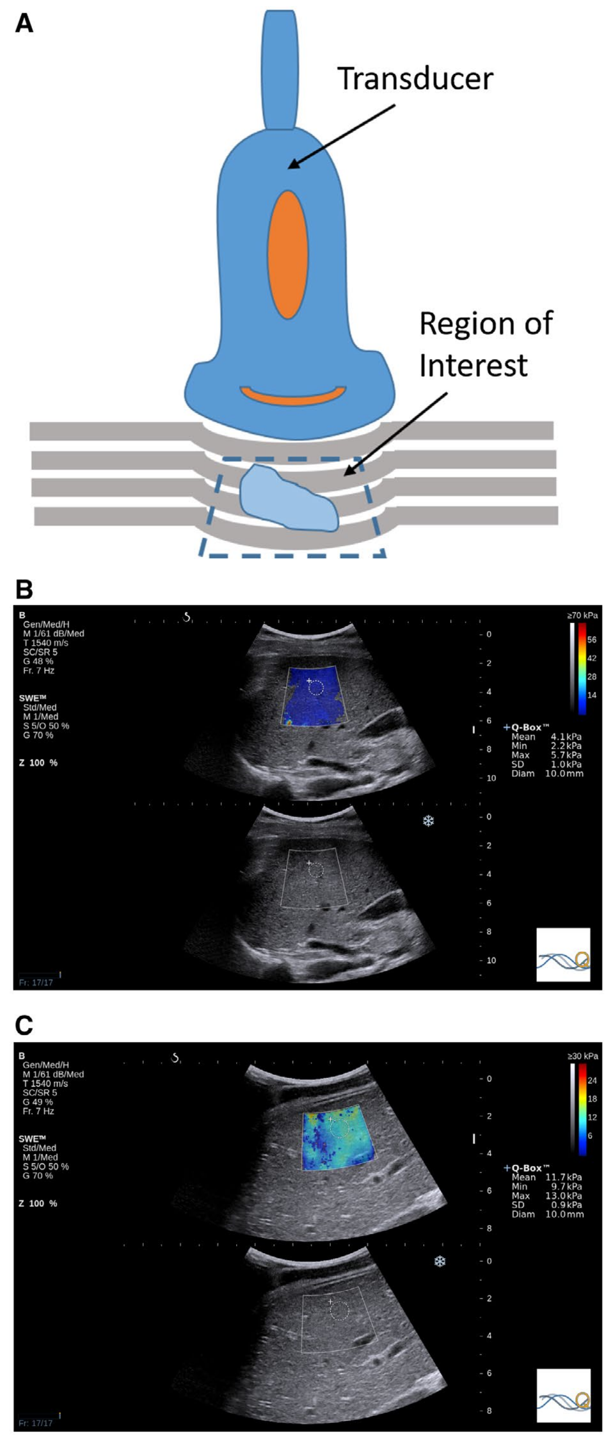

FIG 2 (A) Illustration of quantitative ultrasound ARFI using compression: a vertical load is applied with the transducer to induce tissue displacement, which is captured by multiple B-mode ultrasound images, providing a qualitative assessment of relative tissue stiffness. TE and pulsed SWE have a fixed sampling area size, although pulsed SWE allows the depth and location to be chosen. Two-dimensional SWE has the ability of pulsed SWE sampling area placement with the additional ability to change the size. Two-dimensional SWE ultrasound elastography values in (B) a 16-year-old girl with no fibrosis (mean stiffness, 4.1 kPa) and (C) an 18-year-old boy with F4 fibrosis, as confirmed by biopsy (mean stiffness, 11.7 kPa).

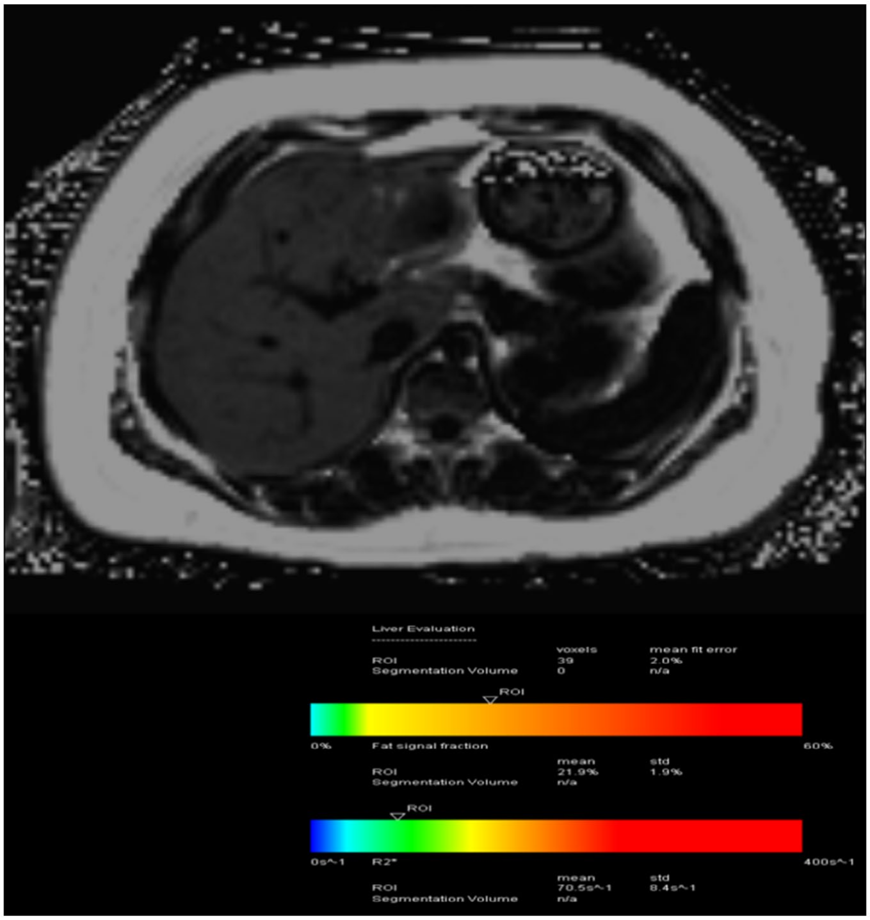

FIG 3 A 15-year-old boy with a history of NAFLD with elevated liver function tests and obesity demonstrates a fat fraction of 21.9%. Using PDFF, we have the potential to get (near) full organ coverage with an acquisition time of one breath hold (~15 seconds).

noninvasive, radiation-free examination with excellent spatial, soft tissue contrast and temporal resolution.[14,15] For these reasons, MRI is now starting to become a preferred imaging modality for evaluating pediatric patients with NAFLD.

Liver Fat

MRI-based PDFF can accurately detect and quantify hepatic steatosis independent of age, sex, and body mass index.[16] PDFF entails a rapid (single breath hold, ~12–15 seconds) scan and does not require intravenous contrast material.[16,17] PDFF pulse sequences can cover large portions of the liver and are carefully crafted to enable quantification of hepatic steatosis by separating water and fat signals (Fig. 3). PDFF-based estimated liver fat fraction has shown a high diagnostic accuracy compared with histological grade among pediatric patients with NAFLD[18] and is emerging as the noninvasive method of choice to estimate, on a continuous scale, hepatic PDFF.

Liver Fibrosis

Magnetic resonance elastography (MRE), which can be performed during the same examination session as MRI-PDFF, allows the noninvasive measurement of liver stiffness, which reflects liver fibrosis (Figs. 4 and 5). MRE has recently been found to be accurate in identifying advanced fibrosis in children with NAFLD.[19,20] Considering that hepatic fibrosis is the strongest predictor of long-term patient outcomes and that noninvasive serum biomarkers of fibrosis in pediatric NAFLD are largely inaccurate, MRE is currently the most reliable, clinically available, noninvasive approach to assess fibrosis progression, particularly in obese patients.

MRE uses low-frequency (60-Hz) sound waves to induce shear waves in the liver, visualizes the shear waves

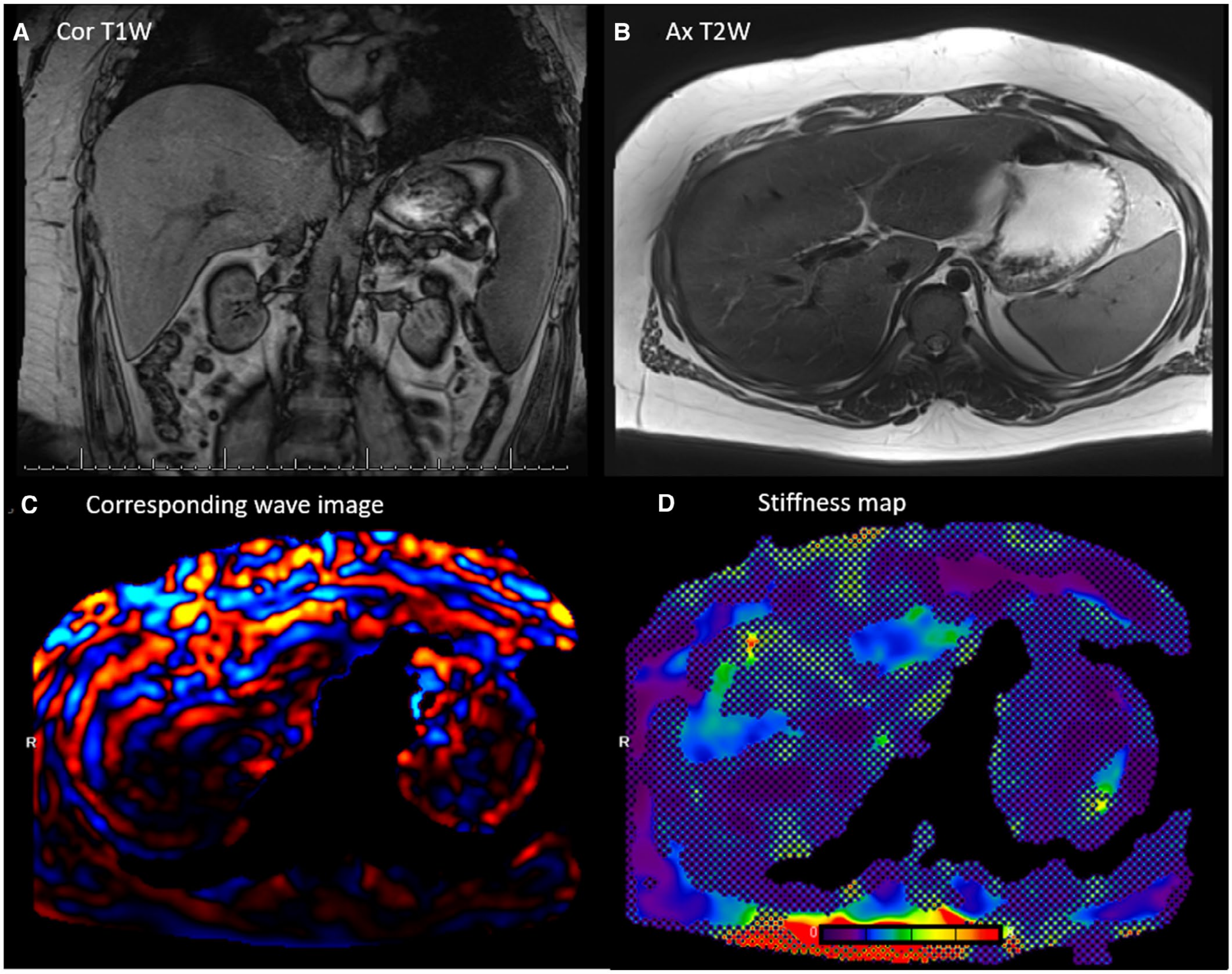

FIG 4 A 15-year-old boy with hepatosplenomegaly: (A) coronal T1W, (B) axial T2W, (C) corresponding wave image, and (D) stiffness map. Liver stiffness was measured to be 2.5 kPa using MRE, corresponding to low-grade fibrosis. MRE offers (near) full organ coverage, hence minimizing sampling errors.

by tracking tissue displacement using a modified phase-contrast sequence, and measures the speed of the propagating wave with specialized software. The sound waves are generated by a subwoofer ("active driver") outside the scan room and are transmitted to a plastic disk ("passive driver") secured by an elastic band over the right lower anterior chest wall.[21] Unlike ultrasound, uniformly similar MRE hardware and software are now clinically available on scanners manufactured by the major magnetic resonance vendors, such as Siemens, GE, and Philips.[22] Consequently, liver stiffness reports using MRE can be used across different imaging centers and hospitals. MRE can be achieved in between one and four relatively small breath holds depending on the acquisition method used.[23] MRE examinations can be performed on children awake and as young as 4 months of age, but sedation may be required for children who are claustrophobic or developmentally delayed.[24] Studies have shown that MRE can discriminate patients with moderate and severe fibrosis from those with mild fibrosis with a sensitivity of 86% and specificity of 85%.[20] In a study of 35 children with mixed chronic liver disease, Xanthakos et al.[19] observed that a cutoff stiffness value of 2.7 kPa provided 88% sensitivity and 85% specificity for detecting moderate liver fibrosis. In 468 studies performed in 372 patients, Joshi et al.[25] report MRE to have a high rate of technical success in pediatric and young adult patients. These results suggest a more widespread

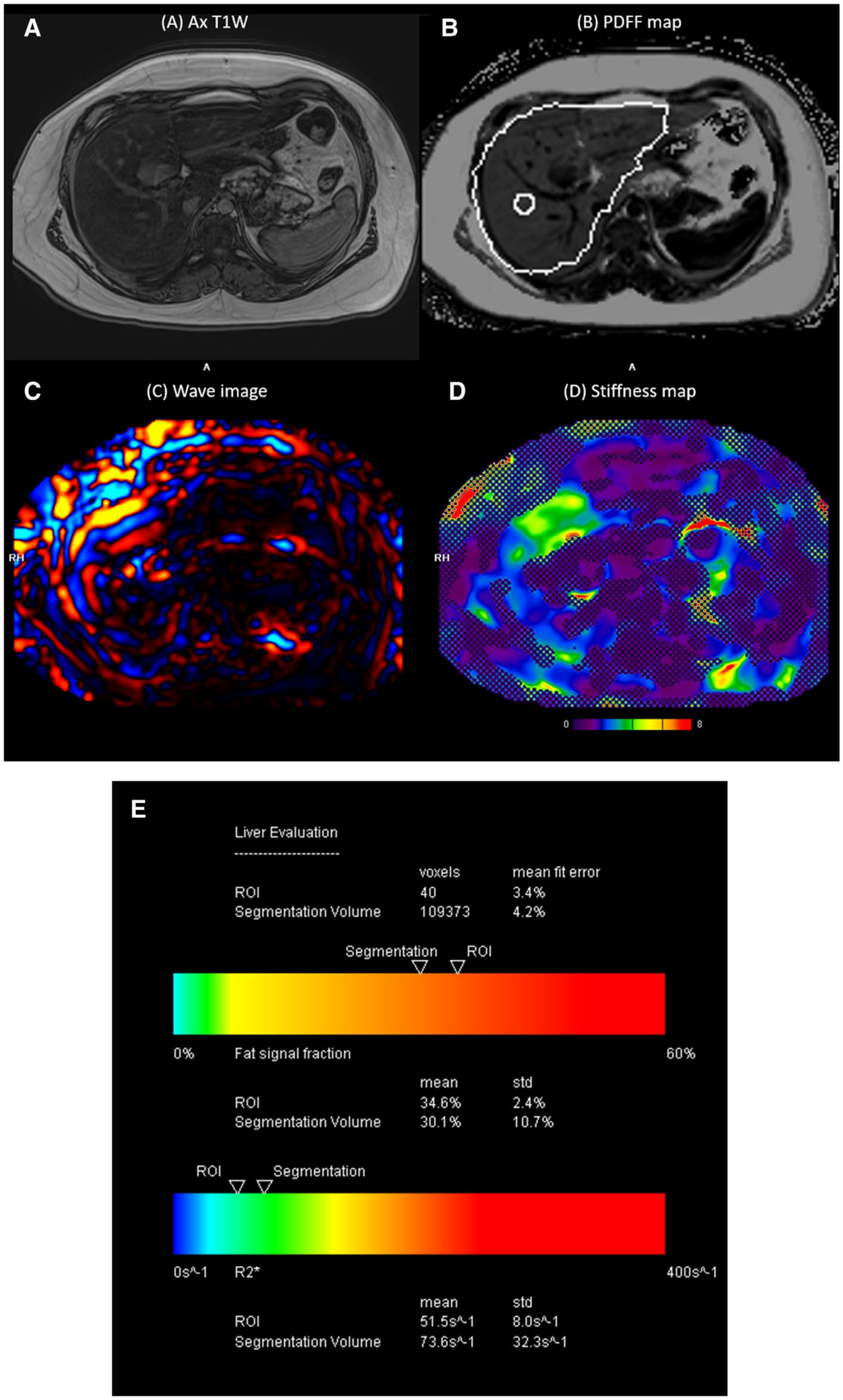

FIG 5 A 16-year-old boy with elevated liver enzymes and history of NASH. (A) Axial T1W, (B) PDFF map, (C) corresponding wave image, (D) stiffness map, and (E) automatic segmentation report chart of the entire liver showing % fat and R2* values. MRE shows elevated liver stiffness (3.8 kPa), and PDFF shows high liver fat fraction of 34.6%. Both MRE and PDFF were obtained in the same MRI scan session with one breath hold each (scan time of ~12–15 seconds for each acquisition).

TABLE 1. ADVANTAGES AND LIMITATIONS OF ULTRASOUND AND MRI FOR NAFLD

Modality	Advantages	Limitations
Ultrasound (ARFI [m/second] and CAP [fat %])	• Easier accessibility of ultrasound • Relatively lower cost • Relatively easy to use in young children • Can be integrated with a conventional ultrasound	• Small tissue sample size • Variations in vendor algorithms • Increased failure rate with obesity
MRI (MRE [kPa] and PDFF [fat %])	• Larger liver tissue sample size • Accurate in obese patients • High repeatability and reproducibility • High uniformity across multiple vendor scanner platforms • Can be integrated with a routine MRI	• Limited availability • Relatively higher cost • May need sedation/anesthesia for young children

TABLE 2. SENSITIVITY AND SPECIFICITY OF QUANTITATIVE ULTRASOUND AND MRI FOR STIFFNESS AND % FAT FOR STEATOSIS

	Ultrasound*		MRI	
Modality	Sensitivity	Specificity	Sensitivity	Specificity
Stiffness	0.95[11]	0.90[11]	0.92[32]	0.93[32]
Steatosis	0.85[33]	0.74[33]	0.83[34]	0.98[34]

For stiffness, sensitivity and specificity values shown are for detecting significant fibrosis (≥F2).

*Ultrasound stiffness sensitivity and specificity values shown are for two-dimensional SWE (measured in m/second). The sensitivity and specificity values are lower for TE and pulsed SWE in comparison with two-dimensional SWE.

deployment of MRE as a means of accurately assessing liver fibrosis in children.

Advantages and Limitations: Ultrasound Versus MRI

Although both ultrasound and MRI can be used to measure hepatic stiffness in children, each modality has relative advantages and limitations (Table 1) with their respective specificity and sensitivity (Table 2). Ultrasound-based elastography and fat measurement methods are readily available, portable, and relatively inexpensive. This method has an obvious benefit in applications to infants and young children to avoid any use of sedation/anesthesia for the purposes of diagnosis. The volume of tissue interrogated, however, is small, and ultrasound-based techniques may not perform as well in the setting of severe obesity or ascites that often accompanies fatty liver disease.[26]

MRI-based quantitative measurements have the ability to accurately and noninvasively detect and quantify hepatic stiffness and steatosis independent of age, sex, and body mass index. The measurements can be achieved with a short scan and do not require intravenous contrast material. MRI provides reproducible results, is not as limited in obesity, and hence has proved to be a stronger choice than ultrasound for imaging in this context. MRE and PDFF sample a much larger area of the liver, thereby providing a more global assessment of liver stiffness and minimizing sampling error. A distinct advantage is that PDFF-based measurements acquire R2* information (for corrections) in no additional scan time, and this can be used to rule out iron overload.[27] MRI-based measurements have been demonstrated to have high repeatability and reproducibility among scanners, field strengths, and vendor platforms.[17,22,28,29] The disadvantages of MRI in general, however, are that overall it is relatively more expensive and less readily available as compared with ultrasound.

Assessment of Cost of Imaging Examinations

A pragmatic consideration of imaging modality will, of course, include a cost assessment. Distinct Current Procedural Terminology codes were established in 2019 for both MRE (76391) and ultrasound elastography for organ assessment (76981). In the United States, reimbursement for MRE is approximately $235 compared with $110 based on the Medicare physician fee schedule (calendar year 2020),[30] although individual payer coverage decisions and reimbursement rates vary widely for these newer procedures. Both of these imaging-based elastographic methods are significantly more expensive than TE without imaging (91200), such as FibroScan, which is estimated to be around $40 per study.[30] Decisions regarding appropriate modality selection may depend on local carrier policies and out-of-pocket expenses balanced against the additional benefits of imaging-based elastographic methods in assessing anatomy and screening for lesions. The cost of these noninvasive methods is substantially less compared with percutaneous liver biopsy, which has estimated direct costs of $1500 to $3000.[31] Further research into the cost-effectiveness of specific elastography-based techniques in the diagnosis of NAFLD and related conditions is needed to better inform clinical decision making and guide health policy.

Given the high accuracy of imaging methods in the detection and measurement of hepatic fibrosis and steatosis for patients with NAFLD, there is a potential that these methods may ultimately replace more invasive procedures for the diagnosis and long-term monitoring of patients with steatosis and may be used to monitor response to treatment.

CONCLUSIONS

To summarize, the ease of availability of ultrasound is promising in evaluating steatosis and fibrosis in patients with NAFLD; MRI has advantages over ultrasound and provides comprehensive functional information with improved anatomical information. Newly developed adaptations of ultrasound and magnetic resonance quantitative imaging are becoming more widely available, precipitating a clinical shift in the diagnosis and management of pediatric NALFD. Now, it is possible to measure fat, iron, and fibrosis to enable accurate diagnosis of NAFLD in a low-cost, noninvasive manner; alleviating the need for invasive liver biopsies. These modalities allow for detailed screening and appropriate management of a disease process that is widely prevalent, has severe long-term complications, and is otherwise difficult to detect clinically.

CORRESPONDENCE

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