

Magnetic Resonance Elastography: Proven Indications, Challenges and Future Considerations

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Introduction

Magnetic Resonance Elastography (MRE)* is a rapidly developing, non-invasive, accurate and reproducible imaging technique to assess the mechanical properties of tissue, which are dramatically affected by pathological disease processes such as inflammation, cancer and fibrosis. Physicians have long relied on the ‘palpation’ of tissue as a qualitative diagnostic tool in the detection of these pathologies, but this technique is limited

to only superficial organs and pathologies and lacks objectivity [1]. Developed by Dr. Richard Ehman and colleagues at Mayo Clinic, MRE serves as a technique to quantitatively evaluate the propagation of mechanical shear waves through tissue. Using a modified phase-contrast magnetic resonance imaging (MRI) technique that generates spatial maps and measurements of shear wave displacement patterns called elastograms, MRE can be implemented onto a conventional MRI system with a few hardware and software modifications [2]. While the technique has been reported in a variety of organs including brain [3–7], breast [8–12], blood vessels, heart [13–15], lung [16–20], pancreas and kidneys [21, 22], MRE is developing as a safe, reliable and non-invasive alternative to liver biopsy in the detection and staging of chronic liver fibrosis [2, 23–26]. To date, MRE has also been compared to other non-invasive imaging techniques including ultrasound-based transient elastography (TE) [27], diffusion-weighted imaging (DWI) [24] and conventional MR imaging markers [28]. It may be used to monitor treatment response or disease progression. Moreover, MRE has also been investigated in helping to identify individuals with steatohepatitis in patients with non-alcoholic fatty liver [29], characterize hepatic tumors [30], assess fibrosis in pediatric populations [31] and liver transplant patients with recurrent



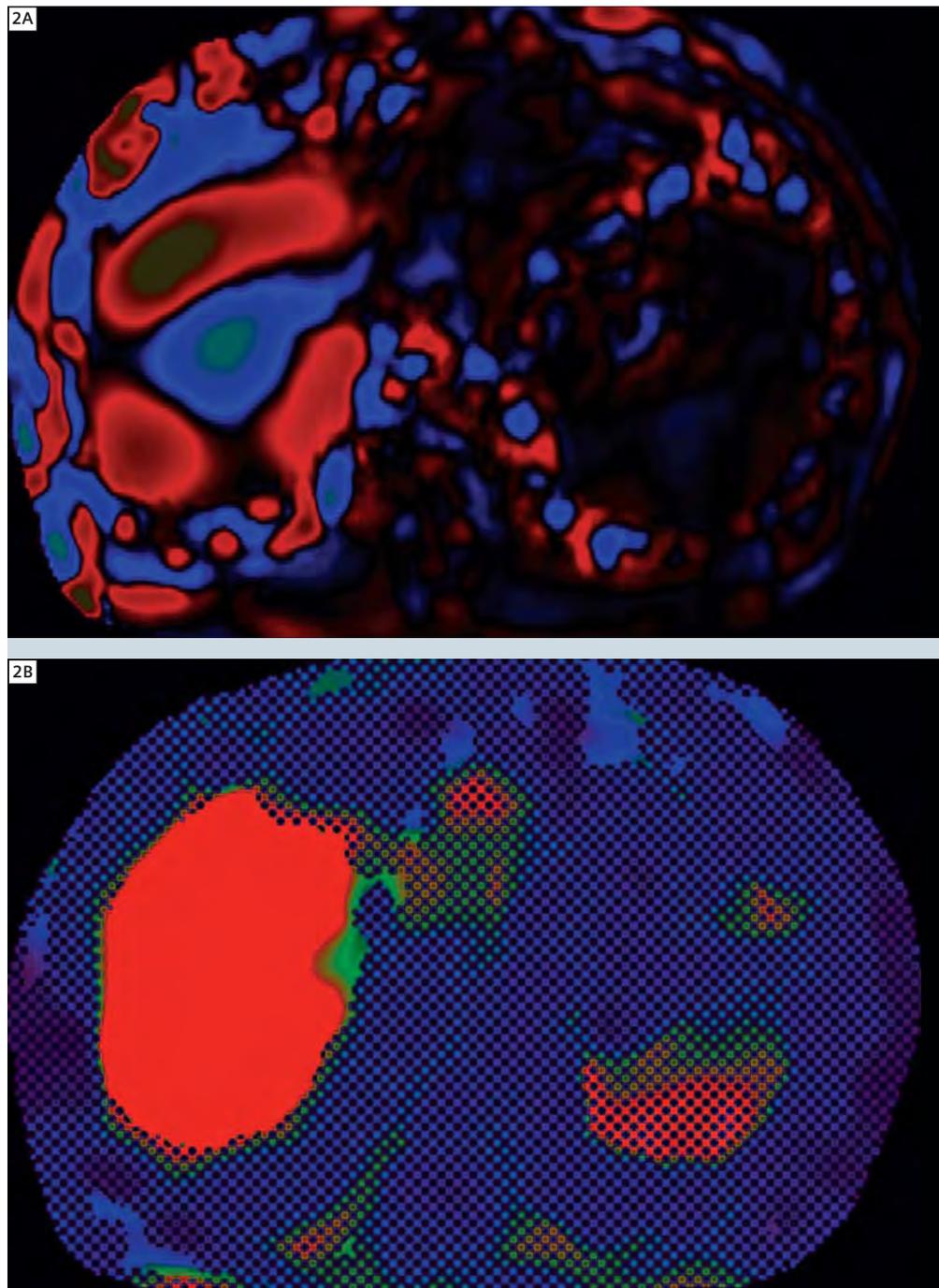
1 Photograph of an acoustical active and passive driver system for MRE with connecting tubing. The active driver is shielded from the imaging magnet and delivers vibrational energy to the passive driver at 60 Hz through the connecting tube. The passive driver is placed across the right anterior chest wall to deliver vibrations transcostally into the liver.

*This technology is not currently available with Siemens scanners in the US.

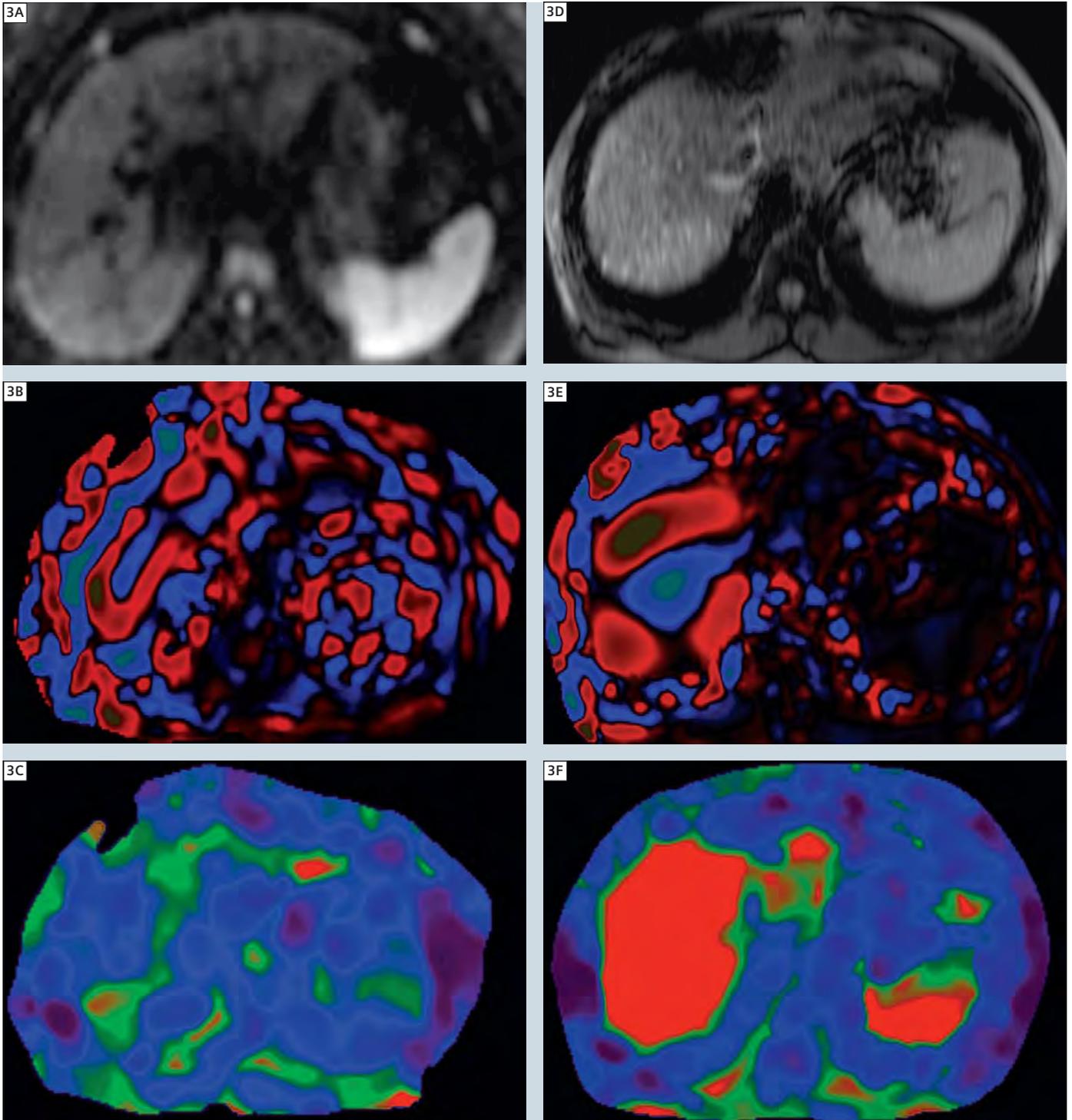
hepatitis C [32] and serve as a guide for MR-guided biopsies [33]. The following provides a summary of some of the proven indications, challenges and future considerations for MRE as an evolving imaging technique.

MRE protocol in our institution

MRE is well tolerated by patients, it is non-invasive and does not require contrast material. To perform hepatic MRE, mechanical waves are generated in the liver with a special MRI-compatible driver system (Resoundant Inc, Rochester, MN, USA). The system consists of an active driver, located outside the magnet room, which generates continuous low frequency vibrations. These vibrations are transmitted via a flexible tube to a drum-like passive driver (19 cm diameter, 1.5 cm thick flat and disc shaped), which is placed directly against the anterior right chest wall over the liver and held in place by an abdominal binder (Fig. 1). The propagating shear waves are imaged with a modified phase difference gradient-echo sequence which incorporates first moment nulled cyclic motion encoding gradients sensitive to through-plane motion. The Resoundant system is synchronized to these gradients via a trigger provided by the imager. The trigger time is stepped to provide a sample of the propagating wave field at four different phase offsets. The parameters of the MRE sequence are as follows: repetition time (TR) / echo time (TE), 50/22.9 msec; flip angle 25°; bandwidth 260 Hz/pixel; acquisition matrix 256 x 64; section thickness 5 mm; field-of-view (FOV) 390 x 390 mm². The scanning time of each trans-axial slice is 21 seconds with breath-hold. Four trans-axial slices at different anatomic levels are acquired. The resulting phase images depicting the waves in the liver for each slice are automatically processed using an inversion algorithm to generate quantitative images depicting the stiffness of the liver (elastograms) [23, 34–36].



2 (2A) Wave image shows the propagation of the shear waves through the hepatic parenchyma. (2B) Color-coded elastogram shows markedly elevated stiffness values with a mean 15 kPa consistent from severe fibrosis.



3 Example anatomic images, wave images and shear stiffness maps (elastograms) in a normal patient with elevated liver enzymes (3A–C) and biopsy-proven stage 4 fibrosis (F4) (3D–F). Shear stiffness was measured to be 2.1 kPa in the normal patient and 14 kPa in the patient with F4 fibrosis.

MR Elastography analysis

To analyze the MRE results, regions of interest (ROI) are placed on the MR elastograms. When placing an ROI, care is taken to avoid bile ducts and large vessels within the liver, motion artifacts, the region immediately below the driver, and the left lobe of liver (which is prone to artifacts due to transmitted cardiac motion). For the measurement of shear stiffness using MRE, the ROIs are first visually transposed onto the wave images to ensure that they were placed in regions with adequate wave quality. A region is determined to have adequate wave quality if the propagating waves had both good amplitude and the presence of a clear dominant propagation direction. Subsequently, the ROI locations are visually transposed onto the quantitative elastogram image and mean stiffness values (in kilopascals, kPa) are calculated (Figs. 2A, B).

MRE in the detection and staging of liver fibrosis

Liver biopsy is currently the gold standard for detecting fibrosis and cirrhosis. As an invasive procedure, it has an increased risk for potential complications such as procedural pain, bleeding, pneumothorax, biliary tree puncture and death (approximately 1 in 10,000–12,000) [37]. From a clinical perspective, one of the greatest limitations with biopsy is a significant sampling error of up to 14.5% and 25% when determining presence or absence of cirrhosis [38]. Based on recent studies, MRE is receiving attention as a non-invasive alternative. Thus far, MRE has shown that it can be an accurate method for both the detection (Figs. 3A–F) and staging (Figs. 4A–D) of hepatic fibrosis [2, 23–26]. Receiver operating characteristic (ROC)

analysis by Yin et al. comparing 50 patients with biopsy-proven liver disease and 35 healthy controls showed 98% sensitivity and 99% specificity for the detection of liver fibrosis with a shear stiffness cutoff value of 2.93 kPa [26]. ROC analysis also showed that MRE was able to discriminate between patients that had moderate to severe fibrosis (F2–F4) and those that had mild fibrosis based on the METAVIR histopathological staging system (F0–F1) [26]. The ability to distinguish moderate to severe fibrosis from mild fibrosis is clinically significant, as treatment is advised for a score of F2 or greater by the American Association for the study of liver diseases [39]. More recent studies by Wang et al. [24], Rustogi et al. [28], Kim et al. [40] and Huwart et al. [25] have demonstrated comparable sensitivity and specificity ranges (Table 1).

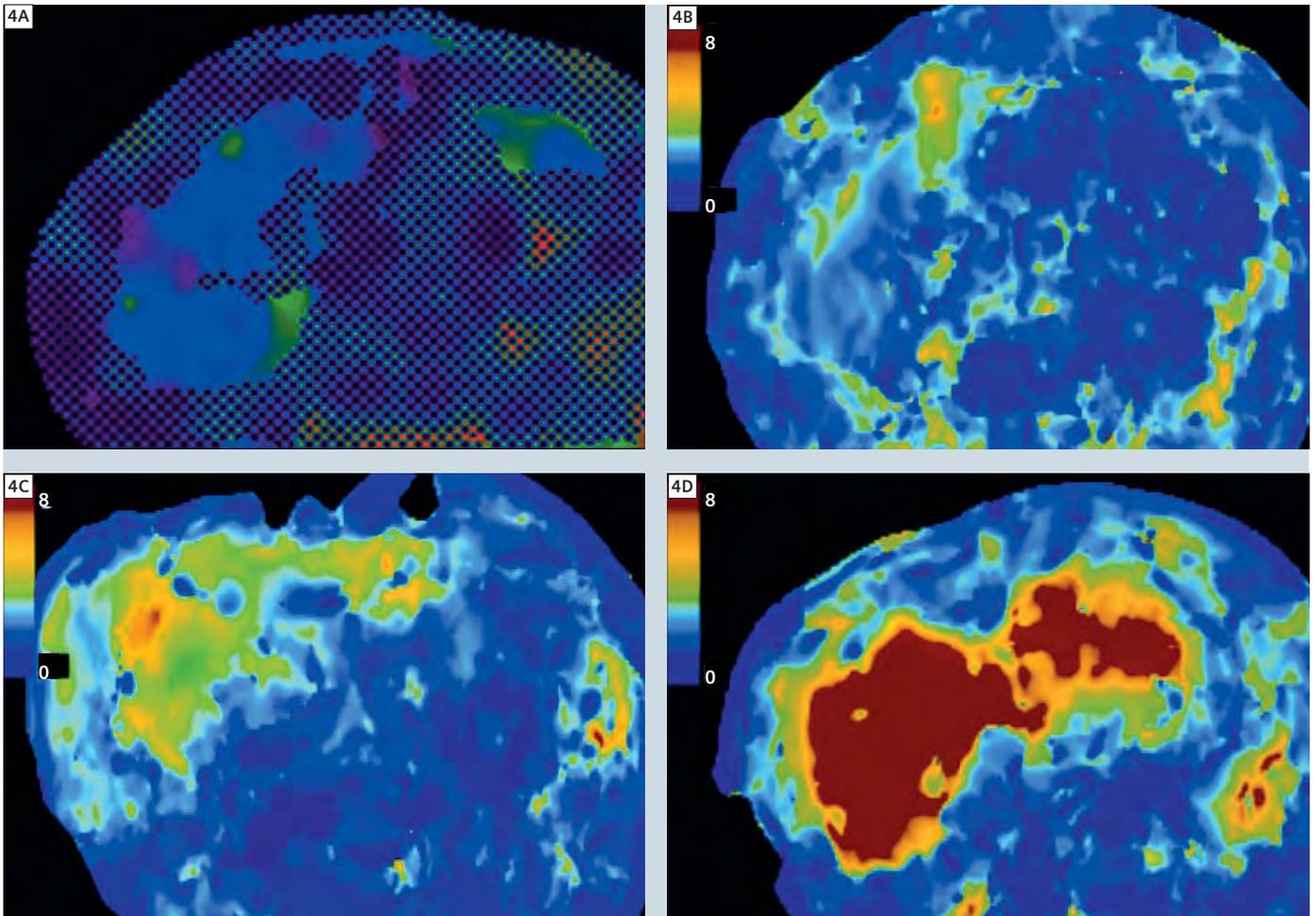
MRE versus other non-invasive assessments of liver fibrosis

Studies have also begun to compare MRE to other non-invasive techniques in the detection and staging of liver fibrosis. One study of 141 patients with chronic liver disease comparing MRE and ultrasound transient elastography (TE) showed that MRE had a higher technical success rate (94%) than TE (84%) [25]. In addition, areas under the curve (AUC) in ROC analysis for MRE were significantly larger than those of TE, aspartate aminotransferase to platelets ratio index (APRI), and the combination of TE and APRI [25]. Significantly, MRE measurements did not seem to be influenced by the presence of obesity or ascites, which cause TE to fail, or steatohepatitis [41]. Furthermore, MRE evaluates a global view of the liver, whereas TE looks at only a 1 cm x 4 cm area over the right liver edge. While TE has also demonstrated excellent sensitivity and specificity for the detection of fibrosis compared to biopsy, it has reduced values of 70%

and 80%, respectively, compared to MRE (86% and 85% respectively) [26] in the detection of intermediate stages of fibrosis (F2–F4) [42].

More recently, the diagnostic performance of MRE was compared to diffusion-weighted imaging (DWI). ROC analysis showed that MRE had greater accuracy in assessing the severity of fibrosis compared with DWI using histopathology as a reference standard. In a group of 76 patients [32], MRE had greater predictive ability in distinguishing the stages of liver fibrosis than DWI [24]. Specifically, MRE showed greater capability than DWI in discriminating stages F2 or greater, F3 or greater and F4 as shown as significant differences in AUC analysis. While stiffness values on MRE increased in relation to increasing severity of fibrosis, no consistent relationship between apparent diffusion coefficient (ADC) values and stage of fibrosis was shown.

Another recent study has compared the diagnostic accuracy of MRE and conventional anatomic MR imaging features in the diagnosis of severe hepatic fibrosis and cirrhosis [28]. Three readers independently assessed 72 patients with liver biopsy for conventional imaging features such as caudate to right lobe ratios and expanded gallbladder fossa sign compared with shear stiffness values from MR elastograms. Sensitivity, specificity and diagnostic accuracy was calculated and intra-class correlation coefficient was used to assess inter-reader reproducibility. MRE proved to be a more accurate and reproducible technique compared to conventional imaging features with a higher intra-class correlation coefficient and better diagnostic accuracy.



4 Liver stiffness values (kPa) represented through elastograms increased in parallel with the degree of fibrosis (stages F0-F4). **(4A)** Shear stiffness was measured to be 2.1 kPa in normal liver tissue, **(4B)** 2.9 kPa in fibrosis stage F1, **(4C)** 4.1 kPa in fibrosis stage F2, and **(4D)** 10.5 kPa in fibrosis stage F4.

MRE for the early detection of non-alcoholic steatohepatitis (NASH)

Associated with obesity and type 2 diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) is a clinical condition now estimated to affect 1 in 3 adults in the US [43]. Up to 25% of NAFLD patients develop non-alcoholic steatohepatitis (NASH), which can progress to cirrhosis in susceptible individuals [44]. Since a diagnosis of NASH currently requires an invasive liver biopsy to help detect and stage liver cell injury, MRE has been investigated as an alternative

technique that could help in early detection. Using a rat model of fatty liver disease, Salameh et al. showed that MRE could help to discriminate the presence of steatohepatitis from simple steatosis before the onset of fibrosis [45]. This led to a retrospective study of 58 NAFLD patients to investigate the variation of liver stiffness in patients ranging from simple steatosis to NASH. MRE was able to show that NAFLD patients with NASH but no fibrosis had higher hepatic stiffness measurements than patients with simple steatosis [29] (Fig. 4).

MRE in the characterization of liver tumors

While it is well known that cirrhosis is the strongest predisposing factor for the development of hepatocellular carcinoma (HCC), the detection of small tumors presents the greatest challenge to imaging in HCC [46]. The application of MRE to HCC may be a promising tool in the characterization of hepatic tumors. A preliminary investigation has shown that malignant liver tumors have a significantly greater mean shear stiffness than benign liver tumors as well as normal liver tissue parenchyma by estab-

Table 1: Selected diagnostic ranges of MRE-assessed hepatic fibrosis in patients with chronic liver disease from various studies.

Reference	N	Cutoff	Sensitivity	Specificity	Liver Stiffness, kPa
Yin et al.	85	F0-1:F2-4	86	85	4.9
		F0-2:F3-4	78	96	6.7
Huwart et al.	88	F0-1:F2-4	98	100	2.5
		F0-2:F3-4	95	100	3.1
Huwart et al.	133	F0-1:F2-4	100	91	2.5
		F0-2:F3-4	91	97	3.1
Kim et al.	55	F0-1:F2-4	89	87	3.1
Wang et al.	76	F0-1:F2-4	91	97	5.4
		F0-2:F3-F4	92	95	5.9

lishing a cutoff value of 5 kPa [30]. Since the technique can be readily combined as a complement to conventional MRI of the abdomen, it shows potential in further characterization and early detection of liver tumors [47]. A potential limitation may be in the cirrhotic liver where the background liver may be as stiff as the HCC but further investigation will be required.

MRE in the assessment of fibrosis in liver transplant recipients

MRE has also been compared to various biomarkers to assess efficacy in the staging of fibrosis in liver transplant recipients with recurrent hepatitis C (HCV) with HCC [32]. While limited by graft complications, MRE and serum panels like FIBROSpectII have high sensitivity in detecting fibrosis from recurrent HCV, but are limited by poor specificity and positive predictive value (PPV). MRE could avert the need for liver biopsy, as values below the MRE and FIBROSpectII cutoffs strongly suggested the absence of fibrosis in transplant recipients with recurrent HCV.

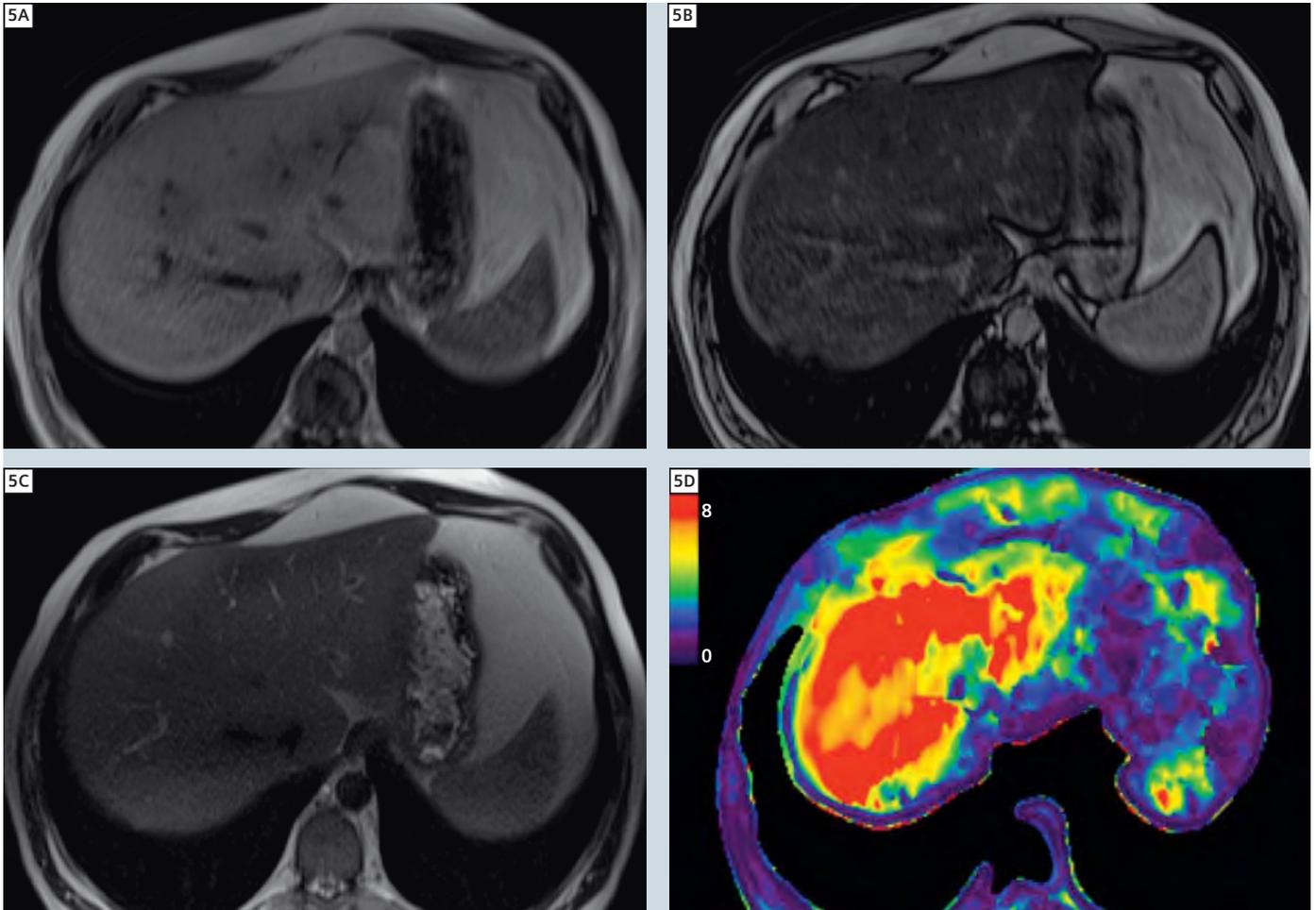
Challenges / difficulties with MRE

Future challenges and difficulties with MRE lie mainly in further technical development. The widespread use of MRE relies on the same technology and infrastructure as conventional MR imaging, and so claustrophobic or very obese patients and those with contraindications to MRI will be excluded from investigation due to an inability to enter the scanner. Other challenges include technical failure in patients with hemochromatosis and iron overload conditions because of signal-to-noise limitations [25]. Falsely elevated shear stiffness values have been reported in regions just below the passive driver used to generate shear waves. Liver stiffness can be increased without the presence of fibrosis in pathological processes such as inflammation, hepatic congestion, and vascular abnormalities [24, 28]. Since MRE is a relatively new technique, improved driver technologies [48] and refined imaging sequences [49] are currently under development to produce more accurate shear stiffness values and improve signal-to-noise ratios. Moreover, in its bid to replace liver biopsy as a non-invasive technique in

the staging of detection of liver fibrosis, MRE must be evaluated for cost-effectiveness versus other non-invasive techniques. While researchers have proposed diagnostic algorithms to help define how to stage fibrosis incorporating these techniques, these algorithms are yet to be externally validated in independent populations.

Conclusions and future outlook

MRE has received considerable interest as a quantitative technique to assess the same information evaluated pathology by the more qualitative clinical tool of palpation. As a non-invasive, accurate and reproducible technique, it is receiving consideration as a viable alternative to liver biopsy for the diagnosis and staging of hepatic fibrosis. Since many applications of MRE are currently under investigation in the liver, heart, brain and kidney, it is likely that MRE will continue to elucidate invaluable information about tissue structure and function. As the field continues to evolve rapidly, this information should help to guide clinicians and researchers improve clinical outcomes and management.



5 (5A) In-phase (top left) and (5B) out-phase (top right) images show significant SI decrease, suggesting a diagnosis of non-alcoholic steatohepatitis (NASH). (5C) Liver cirrhosis cannot be identified based on routine T2-weighted image (bottom left). (5D) MRE elastogram (bottom right) shows shear stiffness of 7.51 kPa, suggesting fibrosis stage F4.

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