



## MRE in NAFLD: Promising but Further Validation is Required

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### ABSTRACT

MR elastography is a novel method for non-invasive fibrosis assessment, not yet sufficiently validated. In a recent study in 104 patients Park, *Gastroenterology* 2017; 152: 598-602, MRE was compared to transient elastography for the diagnosis of fibrosis in non-alcoholic fatty liver disease. The current viewpoint critically appraises this study.

**Key words.** Fibrosis. Fibroscan. Non-invasive. Cirrhosis.

Non-alcoholic fatty liver disease (NAFLD) is a hugely prevalent condition affecting up to 30% of adults in the developed world. The diagnosis is associated with an increased risk of liver-related morbidity and mortality. The best determinant of major outcomes (liver-related events, need for liver transplant or death) is the presence of fibrosis on a liver biopsy. In a recent retrospective study of 619 NAFLD patients followed for a median of 12.6 years, Angulo, *et al.* highlighted the independent association of any stage of liver fibrosis on biopsy (present in > 50% of the study patients) and these outcomes. For instance, hazard ratios for factors associated with death or liver transplant included fibrosis stage 1 (HR, 1.88; 95% confidence interval [CI], 1.28-2.77), stage 2 (HR, 2.89; 95% CI, 1.93-4.33), stage 3 (HR, 3.76; 95% CI, 2.40-5.89), and stage 4 (HR, 10.9; 95% CI, 6.06-19.62) compared with stage 0. Conversely, the presence or severity of steatosis or steatohepatitis, a diagnostic feature of NAFLD and NASH, was not associated with outcomes.<sup>1</sup> This valuable study underlined the importance of liver fibrosis detection in NAFLD patients to guide management and monitoring, but also the urgent need to identify robust non-invasive fibrosis markers in order to avert the need for an invasive liver biopsy with the associated risks, cost, and impracticalities when considering such a significant patient population.

Thankfully, a burgeoning market of non-invasive tests for liver fibrosis has developed over the past decade. These tests are either blood or imaging-based, with the former often utilized as cheaper screening tools with high negative predictive values allowing the reliable exclusion of advanced fibrosis (F3-F4); while the latter techniques are performed in specialist centres, and offer the advantage of a targeted assessment for liver fibrosis along with simultaneous detection of steatosis in NAFLD. Despite very good diagnostic performance for advanced fibrosis detection in NAFLD, both non-invasive techniques tend to lack diagnostic accuracy for delineating earlier fibrosis stages, an important factor when deciding on the need for aggressive therapy and follow up. Moreover, knowing that the presence of any fibrosis on biopsy has implications for disease outcomes means that a diagnostic test with high diagnostic accuracy across all fibrosis stages would be of significant value.

In a recent prospective cross-sectional study by Park, *et al.* from California, USA, two of the most studied imaging-based techniques for the non-invasive assessment of liver fibrosis, ultrasound transient elastography (TE) or Fibroscan®, and magnetic resonance elastography (MRE) were compared.<sup>3</sup> Elastography measures liver stiffness, a surrogate of liver fibrosis, by analyzing the speed at which

mechanical waves can propagate through the liver. Both TE and MRE can also estimate liver steatosis simultaneously, using the controlled attenuation parameter (CAP) or MRI-based proton density fat fraction (MRI-PDFF) methods, respectively. One short-coming of TE is high failure rates in obese patients, which has been reduced by the advent of an XL-probe. Indeed, another recent Japanese study by Imajo, *et al.* also compared MRE with TE in NAFLD patients, but reported a 10% failure rate for TE in part due to a lack of the XL-probe.<sup>4</sup> In the Park study both the standard 'M' and XL probes were available for use, potentially allowing a more meaningful assessment of the performance of MRE *vs.* TE in fibrosis detection in NAFLD. The authors also felt that the US-based cohort would yield more generalizable results to Western NAFLD populations than that described in the Imajo paper. The Park study involved 104 consecutive NAFLD patients who had undergone a liver biopsy, MRE and TE assessment. The patient cohort was 56.7% female, with a mean ( $\pm$  SD) age of 50.8 ( $\pm$  14.6) years, BMI of 30.4 ( $\pm$  5.2) kg/m<sup>2</sup> and diabetes prevalence of 27.9%. The XL probe was used in approximately 50% of cases, although a failure rate of 6.7% was reported. At first glance, the study results were impressive; MRE significantly outperformed TE in the detection of any stage of fibrosis (stage 1 and above), with an area under the receiver operating characteristic curve (AUROC) of 0.82 (95% confidence interval [CI], 0.74-0.91), for MRE compared with an AUROC of 0.67 (95% CI, 0.56-0.78) for TE ( $p = 0.0116$ ). MRI-PDFF detected any steatosis with an AUROC of 0.99 (95% CI, 0.98-1.00), significantly higher than that of CAP (AUROC, 0.85; 95% CI, 0.75-0.96),  $p = 0.0091$ , and MRE was also significantly better at distinguishing grades of steatosis than CAP.

Despite these positive findings, several issues limit the interpretation and application of the study results. Although MRE performed well in the primary study objectives, TE seemed to grossly underperform compared to other published studies. Indeed, the study cohort suffered from a clear 'spectrum bias', where stages of fibrosis were unevenly distributed amongst the group making meaningful comparisons difficult. The vast majority of patients had no or mild fibrosis (45.6% F0; 23.3% F1; 10.7% F2; 12.6% F3; 7.8% F4). This meant that that cut-offs used to determine the diagnostic accuracy for TE were atypical; for instance a value of 6.9kPa was the threshold for distinguishing F4 from F0-3 stages, compared to a minimum of 11.7kPa in other, larger series. Unlike the Imajo study, no comparison was made with the efficacy of cheaper, more readily available, blood-based fibrosis scores such as the NAFLD fibrosis score (NFS) or the FIB-4 index. Indeed, the NFS performed as well as MRE in detecting any fibrosis, advanced fibrosis or cirrhosis in the

larger group of 127 NAFLD patients from the Imajo study. Moreover, the MR facility used in the Park study was a 3.0T MR scanner, whose use would be typically confined to research facilities and associated with a significant cost. Finally, although the detection of steatosis is useful to aid the diagnosis of NAFLD due to false negatives with standard ultrasound, the grading of steatosis does not appear to have implications for disease severity and long-term outcomes.<sup>1</sup> Nevertheless, hepatic steatosis seems to closely reflect adipose insulin resistance specifically, and highly sensitive techniques such as MRI-PDFF may yet prove useful in determining treatment choice and response for this multi-system disease in the future.

In conclusion, although MRE is a useful addition to the available non-invasive fibrosis tests, it requires further validation in larger cohorts of patients with more even distribution of fibrosis. Ultimately, what is required is a non-invasive fibrosis test that can be used sequentially and accurately reflect the progression or regression of fibrosis, and therefore be used as a surrogate marker in clinical trials. It remains to be determined if MRE is such a test.

## REFERENCES

1. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, et al. Liver Fibrosis, but No Other Histologic Features, Is Associated With Long-term Outcomes of Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2015; 149: 389-97 e10.
2. Chin JL, Pavlides M, Moolla A, Ryan JD. Non-invasive markers of liver fibrosis: adjuncts or alternatives to liver biopsy? *Frontiers in Pharmacology* 2016; 7.
3. Park CC, Nguyen P, Hernandez C, Bettencourt R, Ramirez K, Fortney L, Hooker J, et al. Magnetic Resonance Elastography vs Transient Elastography in Detection of Fibrosis and Noninvasive Measurement of Steatosis in Patients With Biopsy-Proven Nonalcoholic Fatty Liver Disease. *Gastroenterology* 2017; 152: 598-607 e2.
4. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, Fujita K, et al. Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease Than Transient Elastography. *Gastroenterology* 2016; 150: 626-37 e7.
5. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatology* 2011; 54: 650-9.
6. Brill F, Barb D, Portillo-Sanchez P, Kusi K. Metabolic and histological implications of intrahepatic triglyceride content in nonalcoholic fatty liver disease. *Hepatology* 2017; 65: 1132-44.

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