# Chronic Hepatitis and Fibrosis Assessed by Magnetic Resonance Elastography (MRE)

**Y. Wang[1], F. H. Miller[1], R. McCarthy[2], Z. Chen[2], L. Sternick[2], D. Ganger[2], R. Ehman[3], R. Omary[1], J. Levitsky[2], B. Bolster[4], S. Shah[4], S. Zuehlsdorff[4], P. Nikolaidis[1], and V. Yaghmai[1]**

[1]Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [2]Northwestern University Feinberg School of Medicine, [3]Mayo Clinic, [4]Siemens Healthcare

**INTRODUCTION:** Liver fibrosis results from chronic liver disease, including chronic viral hepatitis, non-alcoholic steatohepatitis (NASH), inborn errors of metabolism, and toxic damage. Characterizing severity of fibrosis is essential for prediction of disease progression and therapy. Recently, ultrasonographic (US) elastography and magnetic resonance elastography (MRE) have been used to detect and quantify liver fibrosis [1, 2, 3, 4]. A significant correlation between elasticity of liver tissue and severity of fibrosis has been demonstrated on both transient US elastography and MRE. Besides fibrosis, other causes of elevated pressure include acute liver injury, hepatitis, portal vein hypertension and cellular infiltration, which may all increase liver stiffness. Salameh et al documented that steatohepatitis can be detected by increased stiffness value on MRE using an animal model [4]. Therefore, the purpose of our study was to evaluate the capability of MR elastography (1) in detecting histologic activity before the appearance of fibrosis in patients with various chronic liver diseases; (2) in discriminating histologic activity from tissue lacking inflammation and fibrorsis, and tissue with various stages of fibrosis and inflammation.

**MATERIALS AND METHODS:** This prospective study was approved by our institutional review board (IRB). All patients gave written informed consent. From October 2008 to October 2009, the final cohort included 12 normal volunteers and 64 patients with chronic liver disease who underwent routine abdominal MRI and MRE using 1.5-T MR system (Magnetom Espree, Siemens Healthcare, Erlangen, Germany). Fibrosis staging was performed using classification systems developed for the specific liver disease etiologies under study. Severity of liver fibrosis was confirmed by histopathologic analyses according to the METAVIR system in patients with chronic liver disease, except for liver steatohepatitis which was evaluated by the Brunt system. Based on the Batts-Ludwig system, grading of activity refers to the degree of hepatocellular necroinflammatory activity. The shear stiffness of liver tissue was compared among stages of fibrosis using the Kruskal-Wallis H test. Based upon the METAVIR system, Brunt system, and Batts-Ludwig system, the overall predictive power of liver stiffness in distinguishing tissue without inflammation and fibrosis from tissue with inflammation and without fibrosis was determined by constructing a receiver operating characteristic (ROC) curve of the sensitivity versus 1–specificity and calculating the area under the curve (AUC). The capability of MR elastography in discriminating tissue with inflammation and without fibrosis from tissue with various severity levels of fibrosis was also determined by ROC.

**RESULTS:** In the group of patients who showed no fibrosis on histopathologic analysis, the stiffness values of liver tissue with inflammation (3.46±0.82kPa) was higher than that of liver parenchyma lacking inflammation (2.80±1.44kPa; $P$=0.002). With a shear stiffness cut-off value of 2.88 kPa, a combination of sensitivity (82.6%), specificity (70.6%), positive predictive value (PPV, 79.2%), and negative predictive value (NPV, 77.8%) was observed. The AUC of MRE was 0.79 (95% confidence interval [CI], 0.63 to 0.90; $P$=0.0001). Liver tissue with inflammation and without fibrosis (3.46±0.82kPa) had a lower liver stiffness value than that of tissue with any amount of fibrosis (F1-4; 7.15±3.15kPa; $P$<0.0001). With a shear stiffness cut-off value of 5.02 kPa, a combination of sensitivity (76.8%), specificity (100%), PPV (100%) and NPV (74.2%) was observed. The AUC of MRE was 0.90 (95% CI, 0.79 to 0.96; $P$=0.0001). The shear stiffness of parenchyma with inflammation and without fibrosis was lower than that of parenchyma with mild fibrosis (F1; 3.71±0.67 kPa), but a significant difference was not observed (P=0.384). In addition, compared to moderate fibrosis (F2, 4.43±1.20kPa) and late-stage of fibrosis (F3-4; 8.97±2.70 kPa), the stiffness value of tissue with inflammation and without fibrosis was lower and significant differences were seen ($P$=0.009 and $P$<0.0001).

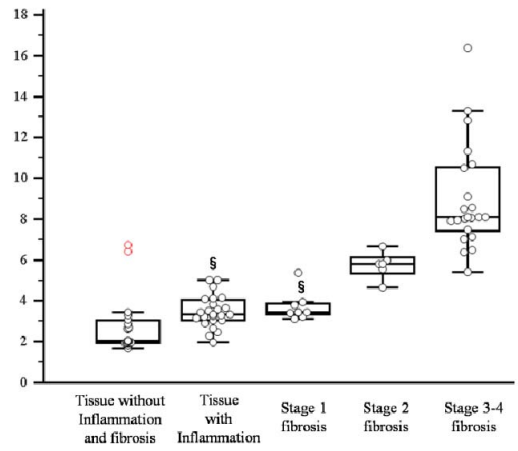


Figure 1. Box plot of shear stiffness value shows the median and distribution of various stages of fibrosis. § = median stiffness value of liver tissue with inflammation and without fibrosis is lower than that of mild fibrosis (F1) but a significant difference was not seen $P$=0.384. The circles represent the distribution of the data ranging from minimum to maximum. The line through each box represents median value and lines extend from the box to the range with the 10th to 90th percentile. The horizontal line through each box represents median value and box represents data from the 25th to the 75th percentile (middle 50% of observations). (Kruskal-Wallis H test and Mann-Whitney U test).

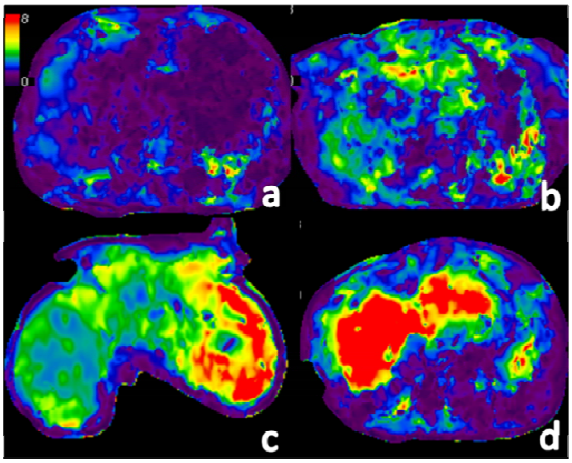


Figure 2. (a) 37-year-old female who is normal volunteer and shear stiffness value is 2.05kPa; (b) 45-year-old male who has chronic hepatitis C and only grade 1 inflammation *without fibrosis* confirmed by histopathology, shear stiffness value is 3.45kPa; (c) 20-year-old who has cystic fibrosis and stage 1 fibrosis; shear stiffness value is 3.45kPa; (d) 56-year-old female with cirrhosis and shear stiffness value is 8.02kPa..

**CONCLUSIONS:** In this blinded and prospective study, we demonstrated that liver tissue with inflammation and without fibrosis can be identified as mildly elevated shear stiffness measured on MRE. Although an overlap between liver parenchyma lacking inflammation and fibrosis and liver only containing inflammation was seen, a significant difference was still obtained. In addition, a relatively high sensitivity (82.6%) and specificity (73.7%) was obtained with optimal cut-off value of 2.88kPa. Consistent with prior studies [2, 3], increased shear stiffness measured on MRE with increasing severity of fibrosis was demonstrated in the present study. Furthermore, both mild hepatic fibrosis (F1) and liver inflammation was associated with mild elevation of stiffness value and a significant difference between them was not observed. In contrast, moderate fibrosis (F2) and advanced fibrosis to cirrhosis (F3-4) showed significant increase of shear stiffness on MRE compared to inflammation and mild fibrosis. In this clinical study, our results suggested that elastography can be used to characterize inflammation in patients with various histopathologic types of chronic liver disease. Therefore, elastography might be helpful for the early detection and therapeutic management in patients with chronic hepatitis.

References:
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