MR Elastography for the Assessment of Hepatic Fibrosis in Patients with Chronic Hepatitis B: Does Histological Necroinflammation Influence the Measurement of Liver Stiffness?

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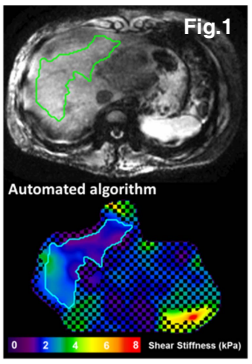
Target audience: Magnetic resonance elastography (MRE) physicians, scientist, and physicists interested in MRE for liver fibrosis.

Purpose: Chronic liver disease has emerged as a significant global health problem, which leads to liver fibrosis and liver cirrhosis [1]. Chronic hepatitis B (CHB) is different from chronic hepatitis C (CHC) in both clinical course and pathological changes [2]. CHB displays a fluctuating pattern of liver inflammation and fibrosis progression characterized by recurrent episodes of abnormal liver function, whereas CHC has a more severe and continuous progressive course [2]. Moreover, studies showed that the fibrotic pattern was differenent histologically between CHC and CHB, presenting higher perisinusoidal fibrosis amount in CHC for F≤2 patients [3]. Hence, comparing liver tissue with the same fibrosis stage both CHC and CHB patients, CHB-infected tissues has less collagen and more variable inflammatory grade than tissues with CHC. MRE, as an emerging technology, is increasingly being used clinically as a noninvasive method to stage liver fibrosis and currently is the only imaging technique to detect early stage of fibrosis [4]. However, MRE studies with homogenous HBV etiology are rare [5]. We suppose that the cut-off stiffness values for MRE that optimize the sensitivity and specificity in CHC might cause over- or underestimation of the real fibrosis stage in CHB. Hence, the aim of this study was to evaluate the performance of MRE for assessing the severity of liver fibrosis in patients with CHB and to further explore the latent impact of inflammation on liver stiffness in a cohort of 113 CHB patients.

Methods: This prospective study was approved by our institutional review board with written informed consent obtained from all participants. Between Mar 2012 and Oct 2013, one hundred and thirteen CHB patients (48 women and 65 men) were enrolled in the study. The median age was 42 years (range, 19-62 years). The fibrosis stage (F) and the necroinflammatory activity grade (A) were evaluated by METAVIR scoring system. Each subject underwent MRE at 3.0T (GE, SIGNA EXCITE HD), equipped with an 8-element torso phased-array coil. Three Axial slices were acquired using a 2D gradient-echo MRE sequence. Low-amplitude mechanical waves at 60Hz were generated in the right upper abdomen using an active acoustic generator (Mayo Clinic). The MRE imaging parameters were as follows: TR/TE =50/27.9ms (50/24.0ms); phase offsets = 4 (4); Asset=1 (2); flip angle = 30° (30°); FOV = 34 - 40 cm. Each slice was obtained in one breath hold of 28s (14 s) at the end of expiration (The parameter differences were due to scanner updates for two groups of 42 and 71 patients respectively). The MRE stiffness images were calculated from the acquired wave images using an algorithm that directly solves the Helmholtz wave equation with 4 2D directional filters (radial Butterworth bandpass filter cutoff frequencies of 2 and 128 cycles/FOV) [6,7]. The shear stiffness of the tissue, in kPa, was determined at each pixel shown in elastogram. All of the raw data was analyzed by an in-house fully automated algorithm for liver stiffness measurements described by Dzyubak et al. [8], as shown in Fig.1. A receiver operating characteristic curve analyses with area under the curve (AUC) was used to evaluate the diagnostic performance of stiffness. Multivariate linear regression analysis was conducted to identify independent predictors of the liver stiffness (variables: F stage and A grade). One-way ANOVA followed by Bonferroni's post-hoc comparisons tests were performed to compare the means among the groups and between each pairwise group.



Results: Since 95 patients (84.0%) had non-advanced liver fibrosis (≤ F2), the liver stiffness has a left skewed distribution (normal distribution was achieved after log-transform), as shown in table 1, Fig.2. A strong positive correlation between shear stiffness and fibrosis stage was observed (r = 0.91, P < 0.001, *Spearman* correlation test). The AUC shows that MRE has a high accuracy for diagnosing fibrosis in all groups (AUC greater than 0.9 for F1-F4, respectively), and has a moderate diagnostic accuracy (AUC between 0.8 and 0.9) for inflammation. All of the diagnostic performances [sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV)] for fibrosis are higher than 0.85, except for the NPV for predicting ≥ F1 (0.25). Multiple linear regression analysis showed that 89.5% of the total variability in liver stiffness could be explained by the two variables in this model overall (R^2 = 0.90, F = 477.5, P < 0.001). Both F stage and A grade were independent factors contributing to liver stiffness (β=0.80, 0.28; P< 0.001).As shown by the Bonferroni post hoc multiple comparison test using logged mean stiffness, liver parenchyma with moderate to severe chronic hepatitis and without fibrosis (F0/A2-3) had a higher value than that of tissue with mild to no inflammation and no fibrosis (F0/A0-1) (P<0.001), but had similar value to the tissue with mild fibrosis and mild to no inflammation (F1/A0-1) (P=1.00). Likewise, liver parenchyma with moderate to severe chronic hepatitis (F1/A2-3) had slightly higher value than that of tissue with mild fibrosis and mild to no inflammation (F1/A0-1) (P= 0.05), but had similar value to the tissue with moderate fibrosis and mild to no inflammation (F2/A0-1) (P= 0.49), Fig.3.

Discussion: In this study, we used an automated stiffness measurement algorithm which can provide results. Consistent with the previous studies with other etiologies, MRE had a similarly high diagnostic accuracy for hepatic fibrosis in CHB. MRE showed significantly higher stiffness in group F0/A2-3 vs F0/A0-1, indicating that the stiffness can be elevated by inflammation before the onset of fibrosis. Furthermore, MRE cannot distinguish between the stiffness of liver parenchyma with F0/A2-3 vs F1/A0-1 and F1/A2-3 vs F2/A0-1. Inflammation can significantly elevate liver stiffness leading to absence of significant difference with the next fibrosis stage, indicating that the chronic hepatitis might be a confounding factor causing an overestimation of true fibrosis stage in patients with F≤2 fibrosis. Clinical observation has shown that CHB infection often manifests with repeated episodes marked by fluctuating levels of serum ALT and HBV DNA. We suppose that the onset of liver injury causes the accumulation of interstitial liquid and inflammatory infiltration. This may lead to increased intrinsic stress and increase the liver stiffness. Additionally, as compared to CHC and alcoholic cirrhosis, the amount of fibrosis is lower in CHB for F≤2 patients, mainly because of the decreased perisinusoidal fibrosis amount [3]. The less amount of fibrosis and the greater variability of inflammation in CHB might partially explain the controversy of the stiffness cut-offs for CHB and CHC patients at the same fibrosis stage through different transient elastography studies [2, 3, 9]. Individual inflammation patterns and the fibrotic stages in various etiologies demand customized cut-off stiffness values for clinical use.

Fibrosis		Liver stiffness	Inflammation		Liver stiffness
Stage	No.	Median (IQR)	Grade	No.	Median (IQR)
F0	43	2.66 (2.38,3.32)	A0-1	30	2.51 (2.34,2.66)
			A2-3	13	3.56 (3.38,3.72)
F1	30	3.87 (3.71,4.12)	A0-1	12	3.76 (3.60,3.85)
			A2-3	18	4.05 (3.82,4.22)
F2	22	4.63 (4.26,4.93)	A0-1	9	4.26 (4.08,4.54)
			A2-3	13	4.85 (4.57,5.27)
F3-4	18	6.51 (5.78,6.93)	A0-1	6	5.82 (5.58,6.33)
			A2-3	12	6.80 (6.29,7.48)

Table 1

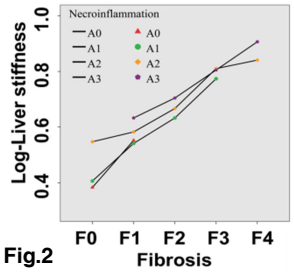


Fig.2

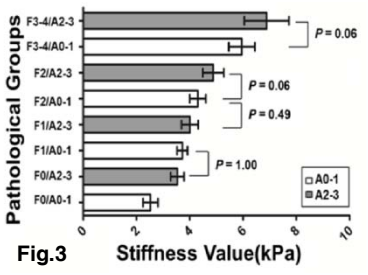


Fig.3

Conclusions: The results indicate that MR elastography is suitable for stratifying patients with liver fibrosis caused by chronic hepatitis B. For liver tissue with F≤2 fibrosis, necroinflammation accounts for a portion of the elevated liver stiffness.

References: **[1].** Ott JJ, et al.Vaccine, 2012. **32**(12):p.2212-19. **[2].**Verveer C, et al. Liver Int, 2012. **32**(4):p.622-8. **[3].**Sturm N, et al. Liver Int, 2013. **33**(3):p.428-38. **[4].** Yin M, et al. Top Magn Reson Imaging, 2009. **20**(2):p.79-87. **[5].** Venkatesh SK, et al. Eur Radiol. 2013 Aug 9. **[6].** Manduca A, et al. Med Image Anal 2001; **5**(4):p.237-54. **[7]** Manduca A, et al. Med Image Anal,2003.**7**(4):p.465-73. **[8]** Dzyubak B, et al. JMRI, 2013. **38**(2):p.371-9. **[9]**Chan HL,et al. J Viral Hepat, 2009. **16**(1):p.36-44.