Magnetic resonance elastography is accurate in detecting advanced fibrosis in autoimmune hepatitis

Jin Wang, Neera Malik, Meng Yin, Thomas C Smyrk, Albert J Czaja, Richard L Ehman, Sudhakar K Venkatesh

Abstract

AIM
To assess the value of magnetic resonance elastography (MRE) in detecting advanced fibrosis/cirrhosis in autoimmune hepatitis (AIH).

METHODS
In this retrospective study, 36 patients (19 treated and 17 untreated) with histologically confirmed AIH and liver biopsy performed within 3 mo of MRE were identified at a tertiary care referral center. Liver stiffness (LS) with MRE was calculated by a radiologist, and inflammation grade and fibrosis stage in liver biopsy was assessed by a pathologist in a blinded fashion. Two radiologists selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease which can progress to advanced fibrosis and cirrhosis[1,2]. Hepatic fibrosis scores increase in 25% of patients despite corticosteroid therapy[3]. Cirrhosis develops in 3% of treated patients per year[4], and 1%-6% of individuals with cirrhosis develop hepatocellular carcinoma (HCC)[5,6]. The prevention and reversal of hepatic fibrosis are key objectives in AIH, and the safe and reliable assessment of hepatic fibrosis is essential[7].

Histological evaluation is the gold standard for assessing hepatic fibrosis, but is suboptimal for monitoring disease progression due to its invasiveness, sampling error, and inter-observer variation[8,10]. Noninvasive tests of hepatic fibrosis include laboratory and radiological tests, which have been validated in chronic viral hepatitis, but have not been rigorously assessed in AIH. Laboratory-based methods for staging liver fibrosis include the FibroTest[11,12], the serum aspartate aminotransferase/platelet ratio index (APRI)[12], the Fibrosis 4 (FIB-4) test[13], and the enhanced liver fibrosis test[14]. These tests may detect cirrhosis, but their ability to reflect the stages of fibrosis in AIH is uncertain[15,16].

The radiological tests of hepatic fibrosis include transient elastography by ultrasonography (TE), acoustic radiation force impulse (ARFI) imaging, and magnetic resonance elastography (MRE). TE has had high sensitivity and specificity for advanced stages of fibrosis and cirrhosis in chronic viral hepatitis, but its performance may differ in AIH[17,18]. Serum alanine aminotransferase (ALT) levels greater than twice the normal limit have reduced the accuracy of TE in detecting early stages of fibrosis in chronic hepatitis B, and AIH is characterized by chronic inflammation of fluctuating intensity[19,20]. Acute liver damage, as may occur in AIH, can also increase liver stiffness (LS) to levels suggestive of cirrhosis, only to resolve spontaneously with recovery[21]. Obesity can reduce the accuracy of TE and can be an important consequence of corticosteroid-treated AIH[22,23]. The technical specifications of TE may also limit its utility in patients with ascites[24]. The correlation between LS and acute liver inflammation has expanded the clinical applications of TE to include the diagnosis of acute cellular rejection after liver transplantation[25].

Early studies with TE in AIH have reported that TE is an accurate and reliable non-invasive tool in assessing liver fibrosis in AIH[26,27]. However one study by Hartl et al[28] and another case series by Romanque et al[29] demonstrated that inflammation impacts the accuracy of TE in evaluation of fibrosis. The same confounding factors that limit TE also affect the performance of ARFI. Although ARFI can differentiate normal from fibrosis secondary to chronic immune-mediated liver

Core tip: Magnetic resonance elastography (MRE) provides a non-invasive imaging-based biomarker with excellent diagnostic accuracy for detecting advanced fibrosis and cirrhosis in patients with autoimmune hepatitis (AIH). The diagnostic performance of MRE is superior compared to conventional laboratory tests and morphology assessment with conventional magnetic resonance imaging. MRE may have utility in assessing disease progression during therapy, anticipating complications of cirrhosis, and evaluation of the risk of hepatocellular carcinoma in patients with AIH.
disease\textsuperscript{[29]}, it has been outperformed by TE in diagnosing early fibrosis and distinguishing normal from fibrosis stage 1\textsuperscript{[30-32]}. The attributes that could support current diagnostic, prognostic, and therapeutic efforts to improve outcomes in AIH may reside in MRE.

MRE (Figure 1) has had excellent performance parameters for all stages of fibrosis in diverse liver diseases\textsuperscript{[33-37]}, and it has outperformed TE for staging liver fibrosis in patients with diverse chronic liver diseases\textsuperscript{[38]}. Furthermore, MRE is unaffected by body habitus or hepatic steatosis\textsuperscript{[39,40]} and it can distinguish early from late stages of fibrosis and late stages of fibrosis from cirrhosis in liver diseases outside of AIH. It also may have prognostic implications via the assessment of splenic stiffness and the prediction of portal hypertension and esophageal varices\textsuperscript{[41]}. Our goals were to determine the accuracy of MRE in the diagnosis of advanced hepatic fibrosis or cirrhosis in patients with AIH and to compare the findings to those of APRI, FIB-4, and magnetic resonance imaging (MRI).

**MATERIALS AND METHODS**

**Patient selection**

This retrospective study was approved by the Institution Review Board and informed consent was waived. We performed a search in the hospital database for patients who underwent MRE between 2007-2015 and had a diagnosis of AIH based on histology and by International AIH Group criteria\textsuperscript{[42-45]}. One hundred and thirty-eight patients met these criteria, of whom 62 were excluded as the interval between liver biopsy and MRE exceeded 3 mo. Another 40 patients were excluded due to overlapping features of another chronic liver disease. The final study group comprised of 36 patients. Of these, 17 patients were treatment-naïve and 19 patients had received immunosuppression treatment either at our institution or elsewhere. The treatment naive patients had MRE performed within 3 mo of liver biopsy (mean 5 d; range 0 to 42 d). The treated patients had diagnosis of AIH and received treatment for variable period ranging from 1 mo to 25 years with a mean duration of 5.5 years. The time interval between liver biopsy and MRE in this group was 8.2 d (range 0 to 85 d).

**Laboratory parameters**

Laboratory tests performed within two weeks of MRE were recorded for each patient, and included international normalized ratio (INR), platelet count, serum aspartate amino transferase (AST) and ALT levels, AST/ALT ratio, AST to Platelet Ratio Index (APRI), and FIB-4 score. The APRI was calculated using the equation (AST × 100)/platelet count (10\textsuperscript{9}/L)\textsuperscript{[46]}. The FIB-4 score as calculated using the equation patient age [(years)] × AST (U/L)/[platelet count (10\textsuperscript{9}/L) × ALT (U/L)]\textsuperscript{[7,47,48]}.
**Histological assessment**

Liver biopsy specimens were reviewed and scored by an experienced hepatopathologist who was blinded to patient data and MRE results. Portal-periportal and lobular inflammation activity grade and fibrosis stage were scored according to Batts et al\[49\]. Fibrosis was staged on a 0-4 scale on Masson Trichome stain. Interface hepatitis was defined as a portal-periportal inflammation score of $\geq 2$. Liver fibrosis stage was scored on a 5-point ordinal scale (0, 1, 2, 3, and 4). All patients with liver biopsy evidence of stage 3 (bridging fibrosis) or stage 4 (cirrhosis) were classified as having advanced fibrosis.

**MRE**

MRE of the liver was performed according to technique described previously\[37\]. A pneumatic passive driver was placed overlying the liver which transmitted acoustic vibrations generated at 60 Hz to produce propagating shear waves in the liver which were imaged using a standard MRE sequence as described previously\[50\]. Four slices were obtained through the largest cross section of the liver in each patient. Total acquisition time was approximately 2 min.

MRE data were processed by an inversion algorithm installed on the scanner to produce stiffness maps and wave images. Regions of interest were drawn by a single experienced abdominal radiologist over the liver and excluded artifacts, vessels $> 3$ mm in size, liver edges and fissures. LS levels above 2.5 kPa were interpreted as elevated\[33\].

**MRI morphologic features**

Two radiologists in consensus evaluated the liver on T2-weighted, T1-weighted, diffusion weighted and post gadolinium enhanced MRI images, and the results required consensus. The following features were assessed: (1) liver parenchyma signal: homogeneous, heterogeneous, patchy/segmental; (2) fatty change; (3) parenchymal enhancement: homogeneous, heterogeneous; (4) surface nodularity: absent, equivocal, present; (5) narrowed hepatic veins: yes/no; (6) presence/absence of the following signs: expanded gall bladder fossa sign, increased hilar periportal space ($> 10$ mm), hepatic notch sign, creeping mesenteric fat sign; (7) splenomegaly; (8) collaterals; (9) caudate-to-right lobe liver ratio; (10) modified caudate-to-right lobe liver ratio; and (11) ascites. An overall impression of the presence of cirrhosis was entered as absent, equivocal, or present.

**Statistical analyses**

Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium). Statistical analysis was performed by one author (Venkatesh SK) experienced in using MedCalc statistical software. Summary statistics are presented as mean ± SD for continuous variables and as numbers and percentages for categorical variables. The relationship between MRE and serum tests was evaluated using Pearson’s correlation coefficient test. The relationships between serum tests, MRE, inflammation grade, and fibrosis stage were assessed using Spearman’s correlation coefficient. Partial correlation analysis was used to evaluate the correlation between fibrosis stage and MRE correcting for inflammation grade. Kruskal-Wallis test was performed on serum tests and MRE to determine significant differences between fibrosis stages.

The overall performance of MRE for the diagnosis of advanced fibrosis and cirrhosis was determined by analyzing the area under the receiver operating characteristic (ROC) curve. Optimal cut-off values with accuracies, sensitivities, specificities, positive and negative predictive values were reported for predicting advanced fibrosis and cirrhosis. The performance parameters of all variables were compared by analyzing ROC curves. A two-tailed $P$ value of $< 0.05$ was considered statistically significant for all analyses.

**RESULTS**

**Clinical features**

The study population had mean age of 51.6 ± 20.6 years and mean body mass index (BMI) of 27.8 ± 6.4 kg/m\(^2\). The mean FIB-4 score was significantly lower in the treated group compared to the untreated group (2.72 vs 5.99, $P = 0.025$). A trend of higher levels of serum AST and ALT levels at the time of MRE and liver biopsy was found in the untreated group but was not statistically significant. There were no significant differences in BMI, mean LS, APRI, platelet and INR values between two groups (Table 1).

**Histology findings**

Liver biopsy was performed within 3 mo of MRE study with a mean interval of 11.7 d (95%CI: 2-76 d). Histological evaluation revealed fibrosis stages of 0, 1, 2, 3 and 4 in 4, 6, 7, 6 and 13 patients, respectively. Fibrosis ($\geq F1$) was present in 32 patients (88.9%); significant fibrosis ($\geq F2$) in 27 patients (75%); advanced fibrosis ($\geq F3$) in 19 patients (52.8%) and cirrhosis (F4) in 13 patients (36.1%). Inflammation grade 0, 1, 2, 3, and 4 in 2, 7, 15, 9 and 3 patients respectively. The distribution of fibrosis stage and inflammation grade between treated and untreated patients was similar.

**Correlations between histological findings and laboratory tests**

Spearman rank correlation analysis showed significant correlation between fibrosis stage and all serum tests except AST and ALT levels (Table 2). Both APRI and INR showed significant correlations with inflammation grade. No significant differences in ALT ($P = 0.68$), AST ($P = 0.25$), AST/ALT ratio ($P = 0.07$), and APRI...
Inflammation grade

Correlation between histological findings and radiological tests

MRE correlated closely with fibrosis stage (r = 0.83, P < 0.001), and it performed better than MRI. The correlation between LS and fibrosis stages remained significant after correction for age and BMI (r = 0.75, P < 0.001), inflammation grade (r = 0.76, P < 0.001), and all laboratory tests (r = 0.68, P < 0.0001). LS was significantly higher in fibrosis stage 4 than stage 0-3; similarly stage 3 had significantly higher stiffness than stages 0-2. There were no significant differences in LS between stages 0-2 (Figure 2).

Untreated patients had a slightly higher mean LS as compared to treated patients (3.83 kPa vs 3.7 kPa), but this was not statistically significant. This trend was seen at each fibrosis stage (stage 0, 3.1 kPa vs 2.6 kPa; stage 1, 2.94 kPa vs 2.7 kPa; stage 2, 3.2 kPa vs 2.63 kPa; stage 3, 4.1 kPa vs 3.99 kPa). The only exception was cirrhotic patients where the treated patients had a higher LS compared to the untreated group (6.5 kPa vs 5.9 kPa).

ROC analysis showed that MRE (cut off, 4.1 kPa) predicted advanced fibrosis (≥ stage 3) with 0.97 accuracy (95%CI: 0.85-0.99), 89.5% sensitivity (95%CI: 67%-99%), 100% specificity (95%CI: 80.5%-100%), 100% positive predictive value (PPV, 95%CI: 80.5%-100%), and 89.5% negative predictive value (NPV, 95%CI: 67%-99%). Similarly, a cut-off of 4.5 kPa predicted cirrhosis with 0.98 accuracy (95%CI: 0.87-1.00), 92.3% sensitivity (95%CI: 85%-99%) and 96% specificity (95%CI: 78%-99.9%), 92.3% PPV (95%CI: 64%-99.8%) and 88% NPV (95%CI: 68.8%-97.5%).

Comparison between radiological tests and laboratory tests

Comparison of ROC curves for MRE and laboratory tests showed that MRE performed significantly better...
than ALT, AST, AST/ALT, APRI, FIB-4, INR and platelet counts for the detection of advanced fibrosis (Table 3, Figure 3A). FIB-4 performed better than AST, ALT and APRI for detecting advanced fibrosis, and all the laboratory tests performed better than the serum ALT level in making this distinction. Similarly for cirrhosis, MRE performed significantly better than all laboratory tests (Table 3, Figure 3B). FIB-4 only performed better than the serum ALT level in detecting cirrhosis, and the serum ALT level was worse than all other laboratory tests in making this distinction. We also analyzed diagnostic performance of MRE and laboratory tests for two study groups. In the untreated group of 17 patients MRE performance was better than laboratory tests for both advanced fibrosis (0.93 vs 0.51-0.86) and cirrhosis (0.95 vs 0.57-0.95). In the treated group of 19 patients, MRE performance was also better than serum tests for advanced fibrosis (0.98 vs 0.59-0.87) and cirrhosis (1.0 vs 0.64-0.89).

**DISCUSSION**

A non-invasive, accurate method of detecting advanced fibrosis and cirrhosis in patients with AIH is required to assess disease progression during therapy, anticipate complications of cirrhosis, and evaluate the risk of HCC. Our study demonstrates high accuracy of MRE in detecting advanced fibrosis and cirrhosis in patients with AIH.
AIH, and its superiority to laboratory assessment and conventional MRI. Our findings are consistent with other studies that demonstrate greater diagnostic accuracy of MRE over laboratory assessment in detecting advanced fibrosis and cirrhosis in patients with diverse chronic liver diseases. Furthermore, our study indicates that the laboratory and histological indices of liver inflammation do not compromise the accuracy of MRE in assessing hepatic fibrosis in AIH.

Untreated patients showed mildly higher LS as compared to treated patients which was not statistically significant, likely related to the presence of inflammation in the untreated group, and the subset of untreated AIH patients did have higher inflammation grades. This finding suggests that hepatic inflammation could have an impact on determinations of LS by MRE, and it was similar to that in patients with chronic viral hepatitis in whom the presence of chronic inflammation has been shown to increase LS by MRE. In our study, there was no significant difference in the distribution of inflammation grades between the treated and untreated groups, and fibrosis stages were detected with similar accuracy in the treated and untreated patients. Our study also showed that cirrhotic livers in untreated patients had higher mean stiffness as compared to cirrhotic livers in untreated patients. The exact reason is not known, however it is possible that the fibrosis content in treated patients is likely to be more as the duration of disease was longer in these patients. This needs to be confirmed in studies with a larger number of participants.

Recent studies performed with TE and ARFI in AIH have shown that both techniques are useful in assessment of significant fibrosis and cirrhosis in AIH. In one study with nearly 100 patients, Hartl et al. showed excellent diagnostic performance of TE for diagnosis of cirrhosis. They also showed that liver inflammation has a major impact on LS in first few months of AIH treatment and its diagnostic performance improves after 6 mo of immunosuppression treatment. In our study we also showed that untreated patients had higher stiffness compared to treated patients. In addition the diagnostic performance of MRE in treated patients was slightly better than that in untreated patients, however the numbers of patients in our study groups are too small to draw conclusions. In another study of only 15 patients, Efe et al. showed that ARFI is able to accurately differentiate significant fibrosis from non-significant fibrosis. There are no comparison studies between MRE, TE and ARFI and future studies combining all three modalities may be useful for determining their utility in different clinical scenarios.

Our study has limitations. First, the study was retrospective. This was unavoidable as patients frequently received treatment at outside medical centers. This also precludes assessment of the time interval between initial diagnosis and treatment to liver biopsy and MRE. Second, our sample size is small because the timing of liver tissue examinations and the performance of MRE was variable, and overlap syndromes were excluded. Third, the reference standard was histological assessment, which is limited by sampling error and inter-observer variability. This was mitigated by applying a standardized scoring system for fibrosis and inflammation, requiring all specimens to be stained for fibrosis, and having each tissue sample re-reviewed by a pathologist specialized in autoimmune liver diseases. Fourth, our study group comprised treated and untreated patients, which was unavoidable due to the rarity of AIH and retrospective nature of the study. Fifth, patients were assessed at varying intervals during the course of their disease, and were not studied sequentially to assess for detection of small gradations of change.

MRE is a non-invasive imaging-based biomarker with superior diagnostic accuracy for detecting advanced fibrosis and cirrhosis in patients with AIH compared to conventional laboratory and MRI assessment. MRE may become useful as a non-invasive tool for staging fibrosis in AIH, evaluating response to treatment, and decision-making regarding drug administration, dose adjustment, and duration of therapy. Our study provides a foundation for future prospective studies that evaluate the role of MRE to detect changes in LS that can be used safely and repeatedly in patients with AIH of all ages, habitus, and disease severity.

### Table 3 Area under the receiver operating characteristic curves of magnetic resonance elastography and laboratory tests for prediction of advanced fibrosis and cirrhosis in autoimmune hepatitis

|                | Advanced fibrosis | Cirrhosis |
|----------------|-------------------|-----------|
|                | AUC               | 95%CI     | AUC       | 95%CI       |
| LS             | 0.966             | 0.845-0.998 | 0.980     | 0.867-1.000 |
| ALT            | 0.526             | 0.354-0.695 | 0.582     | 0.406-0.744 |
| AST            | 0.618             | 0.441-0.774 | 0.691     | 0.515-0.834 |
| AST/ALT        | 0.681             | 0.505-0.826 | 0.736     | 0.563-0.868 |
| APRI           | 0.728             | 0.554-0.862 | 0.776     | 0.606-0.898 |
| FIB_4          | 0.786             | 0.618-0.905 | 0.803     | 0.636-0.916 |
| INR            | 0.770             | 0.596-0.891 | 0.800     | 0.635-0.915 |
| Platelet       | 0.802             | 0.636-0.916 | 0.763     | 0.592-0.888 |

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; APRI: AST to platelet ratio index; FIB-4: Fibrosis 4 test; INR: International normalization ratio; LS: Liver stiffness.
Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease which can progress to advanced fibrosis and cirrhosis. Histological evaluation is the gold standard for assessing hepatic fibrosis, but is suboptimal for monitoring disease progression due to its invasiveness, sampling error, and inter-observer variation. A non-invasive, accurate method of detecting advanced fibrosis and cirrhosis in patients with AIH is required to assess disease progression during therapy, anticipate complications of cirrhosis, and evaluate the risk of hepatocellular carcinoma. Magnetic resonance elastography (MRE) has the potential to fulfill this function.

Research frontiers
MRE is a non-invasive imaging-based biomarker that has far reaching applications in the diagnosis, management, and treatment of patients with AIH.

Innovations and breakthroughs
This study provides a foundation for future prospective studies that evaluate the role of MRE to detect changes in liver stiffness that can be used safely and repeatedly in patients with AIH of all ages, habits, and disease severity.

Applications
MRE may become useful as a non-invasive tool for staging fibrosis in AIH, evaluating response to treatment, and decision-making regarding drug administration, dose adjustment, and duration of therapy.

Terminology
MRE is a magnetic resonance imaging based technique that non-invasively assesses tissue stiffness.

Peer-review
These findings represent a first effort at defining the role of MRE in the evaluation of AIH. There is robust information supporting the usefulness of this technique in accurately assessing liver fibrosis in other liver diseases, such as hepatitis C, hepatitis B and non-alcoholic fatty liver disease.

REFERENCES
1. Mauns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, Vierling JM. Diagnosis and management of autoimmune hepatitis. Hepatology 2010; 51: 2193-2213 [PMID: 20513004 DOI: 10.1002/hep.23584]
2. Gleeson D, Heneghan MA. British Society of Gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut 2011; 60: 1611-1629 [PMID: 21757447 DOI: 10.1136/ gut.2010.235259]
3. Czaja AJ, Carpenter HA. Progressive fibrosis during corticosteroid therapy of autoimmune hepatitis. Hepatology 2004; 39: 1631-1638 [PMID: 15185304 DOI: 10.1002/hep.20235]
4. Davis GL, Czaja AJ, Ludwig J. Development and prognosis of histologic cirrhosis in corticosteroid-treated hepatitis B surface antigen-negative chronic active hepatitis. Gastroenterology 1984; 87: 1222-1227 [PMID: 6489694]
5. Montano-Loza AJ, Carpenter HA, Czaja AJ. Predictive factors for hepatocellular carcinoma in type I autoimmune hepatitis. Am J Gastroenterol 2008; 103: 1944-1951 [PMID: 18564111]
6. Yeoman AD, Al-Chalabi T, Karani JB, Quaglia A, Devlin J, Mieli-Vergani G, Bomford A, O’Grady JD, Harrison PM, Heneghan MA. Evaluation of risk factors in the development of hepatocellular carcinoma in autoimmune hepatitis: Implications for follow-up and screening. Hepatology 2008; 48: 863-870 [PMID: 18752332 DOI: 10.1002/hep.22432]
7. Czaja AJ. Review article: The prevention and reversal of hepatic fibrosis in autoimmune hepatitis. Aliment Pharmacol Ther 2014; 39: 385-406 [PMID: 24387318 DOI: 10.1111/apt.12592]
8. Soloway RD, Baggenstoss AH, Schoenfield LJ, Summerskill WH. Observer error and sampling variability tested in evaluation of hepatitis and cirrhosis by liver biopsy. Am J Dig Dis 1971; 16: 1082-1086 [PMID: 5133770]
9. Theodossi A, Skene AM, Portmann B, Knill-Jones RP, Patrick RS, Tate RA, Kealey W, Jarvis KJ, O’Brian DJ, Williams R. Observer variation in assessment of liver biopsies including analysis by kappa statistics. Gastroenterology 1980; 79: 232-241 [PMID: 7399228]
10. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009; 49: 1017-1044 [PMID: 19243014 DOI: 10.1002/hep.22742]
11. Puyana J, Imbert-Bismut F, Ratziu V, Chevret S, Jardel C, Moussali J, Messous D, Degos F. Biochemical markers of liver fibrosis in patients infected by hepatitis C virus: longitudinal validation in a randomized trial. J Viral Hepat 2002; 9: 128-133 [PMID: 11876795]
12. Angulo P, Bugianesi E, Bjornsson ES, Charatcharoenwittaya P, Mills PR, Barrera F, Hafidoddottir S, Day CP, George J. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2013; 145: 782-789.e4 [PMID: 23860502 DOI: 10.1053/j.gastro.2013.06.057]
13. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009; 7: 1104-1112 [PMID: 19523535 DOI: 10.1016/j.cgh.2009.05.033]
14. Parker J, Guha IN, Roderick P, Harris S, Cross R, Manos MM, Irving W, Zaitoun A, Wheatley M, Ryder S, Rosenberg W. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. J Viral Hepat 2011; 18: 23-31 [PMID: 20196799 DOI: 10.1111/j.1365-2893.2009.01263.x]
15. Gutkowski K, Hartleb M, Kacperek-Hartleb T, Kajor M, Mazur W, Zych W, Walewska-Zielecka B, Habiior A, Sobolewski M. Laboratory-based scoring system for prediction of hepatic inflammatory activity in patients with autoimmune hepatitis. Liver Int 2013; 33: 1370-1377 [PMID: 23651331 DOI: 10.1111/ liv.12198]
16. Abdo AA. Clinical presentation, response to therapy, and predictors of fibrosis in patients with autoimmune hepatitis in Saudi Arabia. Saudi J Gastroenterol 2006; 12: 73-76 [PMID: 19585859]
17. Sandrin L, Fouquet B, Hasquepon JM, Yon S, Fournier C, Mal F, Christidis C, Ziol M, Poullet B, Kazemi F, Beaumrad M, Palau R. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003; 29: 1705-1713 [PMID: 14698338]
18. Boursier J, Zarsi JP, de Ledinghen V, Rousselet MC, Sturm N, Leblai B, Fouach-Hubert I, Gaillous Y, Oberti F, Bertrasi S, Calès P. Determination of reliability criteria for liver stiffness evaluation by transient elastography. Hepatology 2013; 57: 1182-1191 [PMID: 22809556 DOI: 10.1002/hep.25993]
19. Kim SU, Kim DY, Park JY, Lee JH, Ahn SH, Kim JK, Paik YH, Lee KS, Chun CY, Choi EH, Song KJ, Park YN, Han KH. How can we enhance the performance of liver stiffness measurement using FibroScan in diagnosing liver cirrhosis in patients with chronic hepatitis B? J Clin Gastroenterol 2010; 44: 66-71 [PMID: 19609218 DOI: 10.1097/MCG.0b013e3181a9c57f]
20. Chan HL, Wong GL, Choi PC, Chan AW, Chim AM, Yiu KK, Chan FK, Sung JJ, Wong VW. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009; 16: 36-44 [PMID: 18673426 DOI: 10.1111/j.1365-2837.2008.01037.x]
21. Sagir A, Erhardt A, Schmitt M, Häussinger D. Transient elastography is unreliable for detection of cirrhosis in patients with acute liver damage. Hepatology 2008; 47: 592-595 [PMID: 18098325 DOI: 10.1002/hep.22056]
22. Roulet D, Czernichow S, Le Clézios H, Costes JL, Vergnaud AC, Beaumrad M. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. J Hepatol 2008; 48: 606-613 [PMID: 18222014 DOI: 10.1016/j.jhep.2007.11.020]
Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. Magnetic Resonance Imaging More Accurately Classifies Chronic Hepatitis B. Gastroenterology 2010; 139: 2356-471 [PMID: 21481295 DOI: 10.1053/j.gastro.2010.07.036]

37 Venkatesh SK, Yin M, Ehman RL. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. J Magn Reson Imaging 2013; 37: 544-555 [PMID: 23423795 DOI: 10.1002/jmri.23731]

38 Hwuart L, Sempoux C, Vicart E, Salameh N, Annet L, Danse E, Peeters F, ter Beek LC, Rahier J, Sinkus R, Horsmans Y, Van Beers BE. Magnetic resonance elastography for the noninvasive staging of liver fibrosis. Gastroenterology 2008; 135: 32-40 [PMID: 18471441 DOI: 10.1053/j.gastro.2008.03.076]

39 Singh S, Venkatesh SK, Wang Z, Miller FH, Motoyugi U, Low RN, Hassanain T, Ashbach P, Godfrey EM, Yin M, Chen J, Keaveny AP, Bridges M, Bolte A, Murad MH, Lomus DJ, Talwalkar JA, Ehman RL. Diagnostic performance of magnetic resonance elastography in staging liver fibrosis: a systematic review and meta-analysis of individual participant data. Clin Gastroenterol Hepatol 2015; 13: 4518-4526 [PMID: 25305349 DOI: 10.1016/j.cgj.2014.09.046]

40 Cui J, Heba E, Hernandez C, Haufe W, Hooker J, Andre MP, Valasek MA, Aryafar H, Sirlin CB, Loomba R. Magnetic resonance elastography is superior to acoustic radiation force impulse for the Diagnosis of fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease: A prospective study. Hepatology 2016; 63: 1035-461 [PMID: 26560734 DOI: 10.1002/hep.28337]

41 Talwalkar JA, Yin M, Venkatesh S, Rossman PJ, Grimm RC, Manduca A, Romano A, Kamath PS, Ehman RL. Feasibility of in vivo MR elastographic splenic stiffness measurements in the assessment of portal hypertension. AJR Am J Roentgenol 2009; 193: 122-127 [PMID: 19542403 DOI: 10.2214/AJR.07.3504]

42 Abdullahi MR, Somi MH, Faraji E. Role of international criteria in the diagnosis of autoimmune hepatitis. World J Gastroenterol 2013; 19: 3629-3633 [PMID: 23801865 DOI: 10.3748/wjg.v19.i23.3629]

43 Alvarez F, Berg PA, Bianchi B, Bianchi L, Burroughs AK, Canaleo ED, Chapman RW, Cookeley WG, Croaja AJ, Desnet VJ, Donaldson PT, Eddeleston AL, Faimboin L, Heathcote J, Homberg JC, Hoofngale JH, Kukawo S, Krawitt EL, Mackay IR, MacSween RN, Madsen MP, McFarlane IG, Meyer zum Büschenfelde KH, Zieni M. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 299-938 [PMID: 10580593]

44 Francque S, Vonghia L, Ramon A, Michaelsen P. Epidemiology and treatment of autoimmune hepatitis. Hepat Med 2012; 4: 1-10 [PMID: 24367228 DOI: 10.2147/HMдер.v1.23.3629]

45 Libman LR, Grant CR, Longhi MS, Mieli-Vergani G, Vergani D. Diagnostic criteria of autoimmune hepatitis. Autoimmun Rev 2014; 13: 435-440 [PMID: 24448295 DOI: 10.1016/j.autrev.2013.11.009]

46 Wai CT, Greenson JK, Fontana RJ, Kaibllesid JC, Marrero JA, Conjevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003; 38: 518-526 [PMID: 12883497 DOI: 10.1002/hep.10346]

47 Chen J, Talwalkar JA, Yin M, Glaser KJ, Sanderson SO, Ehman RL. Early detection of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease by using MR elastography. Radiology 2011; 259: 749-756 [PMID: 21640032 DOI: 10.1148/ radiol.11101942]

48 Kim D, Kim WR, Talwalkar JA, Kim HJ, Ehman RL. Advanced fibrosis in nonalcoholic fatty liver disease: noninvasive assessment with MR elastography. Radiology 2013; 268: 411-419 [PMID: 23547411 DOI: 10.1148/radiol.13121193]

49 Batts KP, Ludwig J. Chronic hepatitis. An update on terminology and reporting. Am J Surg Pathol 1995; 19: 1409-1417 [PMID: 7503362]

50 Venkatesh SK, Wang G, Lim SG, Wei A. Magnetic resonance elastography for the detection and staging of liver fibrosis in chronic hepatitis B. Eur Radiol 2014; 24: 70-78 [PMID: 23928932 DOI: 10.1007/s00330-013-3197-x]

51 Imaio M, Kessoku T, Honda Y, Tomono W, Ogawa Y, Mawatari H, Fujita K, Yoneda M, Taguri M, Saida Y, Sumida Y, Ono M, Eguchi Y, Inoue T, Yamanaka T, Wada K, Saito S, Nakajima A. Magnetic Resonance Imaging More Accurately Classifies Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease Than Transient Elastography. Gastroenterology 2016; 150: 626-637 [PMID: 26677985 DOI: 10.1053/j.gastro.2015.11.048]

52 Shi Y, Guo Q, Xie F, Dzyubak B, Glaser KJ, Li Q, Li J, Ehman WJG | www.wjgnet.com 867  February 7, 2017 | Volume 23 | Issue 5 |
Wang J et al. MRE in autoimmune hepatitis

RL. MR elastography for the assessment of hepatic fibrosis in patients with chronic hepatitis B infection: does histologic necroinflammation influence the measurement of hepatic stiffness? Radiology 2014; 273: 88-98 [PMID: 24893048 DOI: 10.1148/radiol.14132592]

Efe C, Gungoren MS, Ozaslan E, Akbiyik F, Kav T. Acoustic Radiation Force Impulse (ARFI) for Fibrosis Staging in Patients with Autoimmune Hepatitis. Hepatogastroenterology 2015; 62: 670-672 [PMID: 26897951]

Dhaliwal HK, Hoeroldt BS, Dube AK, McFarlane E, Underwood JC, Karajeh MA, Gleeson D. Long-Term Prognostic Significance of Persisting Histological Activity Despite Biochemical Remission in Autoimmune Hepatitis. Am J Gastroenterol 2015; 110: 993-999 [PMID: 26010310 DOI: 10.1038/ajg.2015.139]

P- Reviewer: Gallegos-Orozco JF, Lee HC S- Editor: Gong ZM L- Editor: A E- Editor: Zhang FF
