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Comparison of the fibrosis degree using acoustic radiation force impulse elastography and diffusion-weighted magnetic resonance imaging in chronic hepatitis cases

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SUMMARY

OBJECTIVE: The aim of this study was to investigate the correlation of fibrosis stages in cases of chronic hepatitis by comparing shear wave elastography and diffusion-weighted magnetic resonance imaging.

METHODS: A total of 46 chronic hepatitis patients with an age range of 20–50 years were classified into three groups based on their fibrosis stages. Comparison group 1: the presence of fibrosis (S0 and S1≤); comparison group 2: the presence of significant fibrosis (≤S2 and S3≤); and comparison group 3: the presence of cirrhosis (≤S4 and S6). Shear wave velocities were measured by acoustic radiation force impulse elastography. Diffusion-weighted magnetic resonance imaging was performed on a 3.0 Tesla MRI device.

RESULTS: In comparison group 1 (S0 and S1≤), the area under the curve, sensitivity, and specificity of acoustic radiation force impulse values were 0.784, 87, and 60%, respectively, while these values were 0.718, 80, and 66%, respectively, for apparent diffusion coefficient . In comparison group 2 (≤S2 and S3≤), the area under the curve, sensitivity, and specificity of acoustic radiation force impulse values were 0.917, 80, and 86%, respectively, and the apparent diffusion coefficient values were 0.778, 90, and 66%, respectively. In comparison group 3, the area under the curve, sensitivity, and specificity of acoustic radiation force impulse values were 0.977, 100, and 95%, respectively. There was no statistically significant difference between the apparent diffusion coefficient values of the cases in the three groups (p=0.132).

CONCLUSION: Noninvasive methods are gaining importance day by day for staging hepatic fibrosis. Acoustic radiation force impulse elastography was evaluated as a more reliable examination than diffusion-weighted magnetic resonance imaging in revealing the presence of fibrosis, determining significant fibrosis, and diagnosing cirrhosis.

KEYWORDS: Hepatitis. Elastography. ARFI imaging. Diffusion weighted MRI.

INTRODUCTION

Hepatic fibrosis occurs as a result of chronic liver diseases. In response to liver injury, hepatic lobules collapse, fibrous septa form, and hepatocyte regeneration nodules form. Fibrosis, for which acute pathologies are reversible, progresses to portal hypertension and cirrhosis. Factors that cause liver fibrosis are viral hepatitis (B, C, and D), metabolic causes (hemochromatosis, alpha-1 antitrypsin deficiency, Wilson disease, galactosemia, tyrosinemia, and type IV glycogen storage disease), hepatic venous obstruction, toxins and drugs (alcohol, amiodarone, methotrexate, etc.), primary biliary cirrhosis, autoimmune hepatitis, helminths (schistosomiasis), cryptogenic cirrhosis, and nonalcoholic steatohepatitis, which is a risk factor for the development of hepatocellular carcinoma[1-4]. The incidence of hepatocellular carcinoma increases in patients who develop fibrosis and cirrhosis[5,6]. Additionally, recent studies have reported that

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nonalcoholic fatty liver disease may be a potential risk factor for the development of hepatocellular carcinoma[6,7]. Noninvasive fibrosis grading imaging techniques have recently gained much attention, as advanced diagnostic tools are important in slowing the fibrosis development process and therefore in mitigating the incidence of hepatocellular carcinoma.

Ultrasound (US) is generally the preferred imaging method for radiological evaluation of the liver. US elastography plays an important role in the characterization of diffuse liver diseases and focal liver lesions[8].

Acoustic radiation force impulse (ARFI) is an up-to-date method that has been widely used in recent years. It provides information for tissue characterization according to the response of tissues to applied force. The fact that US elastography can be used to image tissues was first demonstrated in 1987[9,10].

Diffusion-weighted magnetic resonance imaging (DW-MRI) can provide additional information about many pathologies in addition to conventional MRI sequences.

Determining the stage of fibrosis development in chronic hepatitis patients is of great importance in terms of preventing the progression to cirrhosis with appropriate treatment methods and determining the response to the treatment applied. Today, percutaneous liver biopsy remains the gold standard diagnostic test for staging fibrosis. Therefore, this study aimed to investigate the correlation between fibrosis stages in cases of chronic hepatitis by comparing shear wave elastography and DW-MRI.

METHODS

Patient selection

Between September 2014 and May 2015, 46 patients (40 males and 6 females) who were followed up with after receiving a diagnosis of histopathologically proven viral hepatitis (HBV and HCV), steatohepatitis, or autoimmune hepatitis across the various clinics of Health Sciences University, Gulhane School of Medicine, were evaluated prospectively. US examinations, measurement of ARFI values, and DW-MRI examinations were conducted for all patients at least 1 week before biopsy. The patients were classified into three groups as follows: comparison group 1, presence of fibrosis (S0 and S1≤); comparison group 2, presence of significant fibrosis (≤S2 and S3≤); and comparison group 3, presence of cirrhosis (≤S4 and S6).

Approval for this study was obtained from the Institutional Ethical Review Board (dated May 30, 2014, decision no. 8000-259-14/1560), and the study followed the tenets of the Declaration of Helsinki.

Acoustic radiation force impulse elastography analysis

B-mode US and ARFI elastography measurements were evaluated on a Siemens Acuson S3000 device (Siemens Medical Solutions, Mountain View, CA, USA) using a 6C1 HD convex probe with Virtual Touch Quantification (VTQ) software.

The values were obtained in m/s units using a 10×5 mm region of interest (ROI) placed at least 2 cm away from the Glisson capsule. The median values of 10 shear wave velocities measured were used (Figure 1A).

Magnetic resonance imaging protocol

A Sense-XL Torso coil in a 3.0 Tesla (T) superconductive MR (Philips 3T Achieva Release 3.2.3.0) was used. DW images were obtained using the following parameters: eco-planar spin echo, the fat suppression technique, and breath hold: 1241/52 repetition time (TR)/echo time (TE); 90° flip angle; 375×302×255 mm field of view (FOV); 124×100 matrix; and 7 mm thickness. The acquisition time for the images was 3 min and 12 s. Diffusion gradient b values of 0, 100, and 800 were used in DW-MRI. These values were applied to minimize diffusion anisotropy in three orthogonal directions (x, y, and z).

The images obtained were transferred to a separate workstation (DynaCAD Version 2.1.6), and measurements from apparent diffusion coefficient (ADC) maps were made at this station (Figure 1B).

Magnetic resonance imaging analysis

ADC values were measured using circular ROIs of approximately 1 cm^2 from the right liver lobe. ADC values were measured in mm^2/s from the right liver lobe parenchyma. ROIs at least 1 cm away from the Glisson capsule, where there were no main vascular structures, focal lesions, or artifacts, were placed on ADC maps simultaneously.

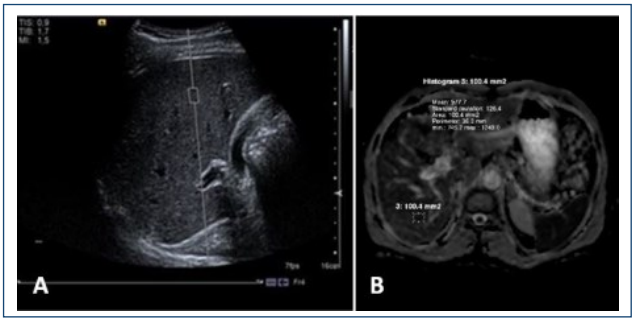

Figure 1. Placement of region of interest in acoustic radiation force impulse elastography (A) and apparent diffusion coefficient value measurement (B).

Evaluation of liver biopsy

The Ishak scoring system[11] was used to stage fibrosis. Accordingly, stage (S)0 was evaluated as no fibrosis, S1–S2 as mild fibrosis, S3–S4 as moderate fibrosis, and S5–S6 as advanced-stage fibrosis[11].

Statistical analysis

SPSS for Windows version 15.00 (SPSS Inc., Chicago, IL, USA) was used. The t-test and the Fisher-corrected chi-squared test were used to determine intergroup differences. For each group, the area under the curve (AUC), according to the ARFI and ADC values, was measured at a 95% confidence interval (CI). p-Values less than 0.05 were considered statistically significant.

RESULTS

The mean age of the 46 patients was 34.52±9.6 years, and the mean body mass index (BMI) was 25.226±3.27. The disease distribution and fibrosis stages are shown in Table 1.

The comparison of patients in group 1 was performed to detect the presence of fibrosis between patients with S0 fibrosis and patients with fibrosis at any stage (S1≤). ARFI elastography was determined to be more effective than DW-MRI in detecting any stage of fibrosis. When the optimal cutoff value for ARFI elastography was determined to be 1.25 m/s in separating the two groups, the sensitivity was 87%, and the specificity was 60%. When the optimal cutoff value for DW-MRI was determined to be 1.110×10^{-3} mm²/s, the sensitivity was 80%, and the specificity was 66%.

Comparison group 2 featured patients with S0–S2 (≤S2) fibrosis and was compared to patients with S3–S6 (S3≤) fibrosis to reveal the presence of significant fibrosis. ARFI elastography was determined to be more effective than DW-MRI in diagnosing significant fibrosis. When the optimal cutoff value for ARFI elastography was determined to be 1.52 m/s in separating the two groups, the sensitivity was 80%, and the specificity was 86%. When the optimal cutoff ADC value for DW-MRI was determined to be 1.063×10^{-3} mm²/s, the sensitivity was 90%, and the specificity was 66%.

Comparison group 3 was created to compare patients with S0–S4 (S4≥) fibrosis and patients with S5 and S6 fibrosis (pre-cirrhosis+cirrhosis) to distinguish cirrhosis cases. ARFI elastography was determined to be more effective than DW-MRI in diagnosing cirrhosis. In separating the two groups, when the optimal cutoff value for ARFI elastography was determined to be 1.8 m/s, the sensitivity was 100%, and the specificity was 95%.

The AUC, optimal cutoff value, sensitivity, specificity, positive predictive value, negative predictive value, and positive-negative likelihood ratio of all three groups are summarized in Table 2.

DISCUSSION

Image parameters, such as magnetic sensitivity, spatial resolution, signal-to-noise ratio, and pathophysiological factors (e.g., cellular density and tissue components), affect ADC[12]. In comparing the 3.0T MRI device to a 1.5T device, a high magnetic field was shown to increase the signal-to-noise ratio and spatial resolution while decreasing imaging time[13]. In our study, we aimed to benefit from these advantages by using the 3.0T MRI device.

In comparison group 1, the AUC value of the ARFI was 0.784, the sensitivity was 87%, and the specificity was 60%. Lupsor et al.[14] reported AUC, cutoff, sensitivity, and specificity values of 0.709, 1.19 m/s, 62.07, and 85.7%, respectively, in 112 chronic hepatitis C cases with F0 and F1≤ fibrosis. The AUC values between Lupsor et al.'s[14] study and the present study were similar. However, Lupsor et al.[14] reported lower sensitivity and higher specificity values.

In comparison group 1, the AUC of the mean ADC, cutoff, sensitivity, and specificity values were 0.718, 1.110×10^{-3} m²/s, 80, and 66%, respectively. Similar to the AUC and sensitivity values in this study, the study by Bonekamp et al.[15] accepted B values of 0–750 s/m² with a 1.5T system; the AUC, cutoff, sensitivity, and specificity values were 0.79, 1.51×10^{-3} m²/s, 75.8, and 78.2%, respectively. The specificity in Bonekamp et al.'s study was found to be higher than in the present study. The different results in our study may be due to differences in

Table 1. Distribution of disease groups according to fibrosis stages.

Pathology	S0	S1	S2	S3	S4	S5	S6	Total
HBV	6	8	8	2	4		1	28 (60.9%)
HCV	1	2						3 (6.5%)
Autoimmune hepatitis			2	2			1	5 (10.9%)
Nonalcoholic steatohepatitis	8		2					10 (21.7%)
Total	15 (32.6%)	9 (19.6%)	12 (26.1%)	4 (8.7%)	4 (8.7%)		2 (4.3%)	46

Table 2. Statistical data of acoustic radiation force impulse and diffusion-weighted magnetic resonance imaging in three comparison groups.

	ARFI elastography	DW-MRI
Comparison group 1 Presence of fibrosis (S0 and S1≤)		
Cutoff value	1.25 m/s	1.110×10^{-3}
Sensitivity (95% confidence interval)	87%	80%
Specificity (95% confidence interval)	60%	66%
Positive likelihood ratio (+LR)	2.17	2.35
Negative likelihood ratio (-LR)	0.22	0.3
Positive predictive value	68.5%	70.1%
Negative predictive value	82.19%	76.7%
AUC (95% confidence interval)	0.784	0.718
Comparison group 2 Presence of significant fibrosis (≤S2 and S3≤)		
Cutoff value	1.52 m/s	1.063×10^{-3}
Sensitivity (95% confidence interval)	80%	90%
Specificity (95% confidence interval)	86%	66%
Positive likelihood ratio (+LR)	5.71	2.65
Negative likelihood ratio (-LR)	0.23	0.15
Positive predictive value	85.1%	72.5%
Negative predictive value	81%	86.8%
AUC (95% confidence interval)	0.917	0.778
Comparison group 3 Presence of precirrhosis+cirrhosis (≤S4 and S5≤)		
Cutoff value	1.8 m/s	Statistically no significant difference (p=0.132)
Sensitivity (95% confidence interval)	100%	
Specificity (95% confidence interval)	95%	
Positive likelihood ratio (+LR)	20	
Negative likelihood ratio (-LR)	0	
Positive predictive value	95%	
Negative predictive value	100%	
AUC (95% confidence interval)	0.977	

the B values, acquisition parameters, susceptibility effects, and magnetic field strengths of the devices.

In comparison group 2, the AUC value of ARFI elastography was 0.917, and that of DW-MRI was 0.778. The sensitivity and specificity values were 80–86% for ARFI elastography and 90–66% for DW-MRI. Friedrich-Rust et al.[16] reported that the AUC, cutoff, sensitivity, and specificity values were 0.87, 1.34 m/s, 79, and 85%, respectively. In the present study, similar sensitivity and specificity values were found.

A US liver elastography consensus statement[17] claimed that most studies using ARFI report that a liver stiffness value of less than 1.5 m/s could help rule out significant fibrosis. For comparison group 2, we assumed that the cutoff value was 1.52 m/s, which is very similar to the value stated in this consensus[17].

Furthermore, in comparison group 2, the AUC of the mean ADC, cutoff, sensitivity, and specificity values were 0.778, 1.063×10^{-3} m²/s, 90, and 66%, respectively. Bonekamp et al.[15] reported that the AUC, cutoff, sensitivity, and specificity values were 0.77, 1.33×10^{-3} m²/s, 84.9, and 71.4%, respectively. Similar AUC, sensitivity, and specificity values were found in this study. Sandrasegaran et al.[18] conducted a study using B values of 50–400 s/m² in a 1.5T system and reported that the AUC, cutoff, sensitivity, and specificity values were 0.686, 1.03×10^{-3} m²/h, 72.6, and 59.3%, respectively. In our study,

it was thought that the high sensitivity and specificity values may be due to the use of the 3.0T MRI.

In comparison group 3, there was no statistically significant difference between the ADC values. There may be several reasons why we found a much better result using ARFI elastography than DW-MRI in determining cirrhosis. One of these reasons is the absence of Ishak S5 patients and the fact that there were only two S6 patients. In the present study, although no statistically significant result was obtained with DW-MRI in this comparison group, in the study by Sandrasegaran et al.[18], when the cutoff value was 0.98×10^{-3}, the AUC, sensitivity, and specificity were 0.656, 51.7, and 71.4%, respectively.

ARFI elastography showed very good performance in distinguishing the cirrhosis group from the other fibrosis groups, with an AUC of 0.977. The sensitivity and specificity values were found to be 100 and 95%, respectively. In patients (4%) with Ishak S6, the mean ARFI values were found to be significantly higher (1.89 and 1.85 m/s). In the study by Friedrich-Rust et al.[16], the AUC of 0.93 was the highest compared to the other comparison groups. The cutoff value was 1.80 m/s, and the sensitivity and specificity values were 92–86%. In this study, the highest AUC was obtained for the differentiation of cirrhosis. Fierbinteanu-Braticevici et al.[19], Karlas et al.[20], and Nierhoff et al.[21] found a sensitivity value of 100% in the differentiation of cirrhosis cases. In these studies, the values for the cirrhosis patient group compared to the whole patient group were reported to be 27[19], 26.5[20], and 6%[21], respectively.

In the US liver elastography consensus statement[17], a cutoff interval of 1.7–2.1 m/s for the ARFI value suggests advanced chronic liver disease, and further testing is required for confirmation. In our study, the cutoff value for this category (1.8 m/s) is compatible with this consensus statement[17].

There were inconsistent results regarding which b value is sufficient in DW-MRI images, especially due to the small number of studies performed with 3.0T MRI. Although a low b value is affected by capillary perfusion, the perfusion effect, especially above 300 s/m², disappears[22]. Therefore, high b values may be more valuable in determining fibrosis[23].

This study has various limitations. First, a larger patient population could not be reached. In particular, the number of patients with advanced-stage fibrosis constituted 4% of the entire study group. The second limitation was that while the liver was evaluated by ADC and ARFI elastography, steatosis, possible effects of iron load, and histological activity index were not taken into account in the comparison. The third limitation was the difficulty in placing the ROI used in ARFI elastography measurements, the difficulty in placing the ROI used during ADC measurements in the same area, and the inability to place the ROI used in ARFI measurements deeper than 8 cm. Another limitation is that the disease groups were not homogeneous because of the inclusion of both viral and non-viral hepatitis patients.

CONCLUSION

Conducting new studies involving larger populations and patient groups using a 3.0 Tesla MRI device with a high signal-to-noise ratio, spatial resolution, and short imaging time will contribute to the diagnosis and treatment follow-up of especially early-stage patients.

ETHICAL APPROVAL

Approval for this study was obtained from the Institutional Ethical Review Board (date: 30.05.2014, decision no: 8000-259-14/1560), and the study followed the tenets of the Declaration of Helsinki.

AUTHORS' CONTRIBUTIONS

MS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Visualization, Writing – original draft. **MuS:** Conceptualization, Formal Analysis, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. **CA:** Resources. **KO:** Resources. **OK:** Resources. **HTS:** Supervision, Writing – review & editing.

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