Original Article

The clinical value of the apparent diffusion coefficient of liver magnetic resonance images in patients with liver fibrosis compared to healthy subjects

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Abstract

Background: Fibrotic tissue forms following chronic inflammation in the liver, which may progress over time to cirrhosis. Liver biopsy is the gold standard for the diagnosis of liver fibrosis, and there has been a considerable interest in developing noninvasive methods. **Objectives:** In the present study, we evaluated the efficacy of the apparent diffusion coefficient (ADC) of the liver in the diagnosis and staging of liver fibrosis. **Patients and Methods:** This case–control study was conducted on 40 patients with chronic liver disease and 31 healthy controls who were subjected to diffusion-weighted magnetic resonance imaging (MRI). Diagnostic values for different stages of fibrosis were determined using receiver-operating characteristic (ROC) curves based on the sensitivity and specificity. **Results:** Of 37 patients in the case group, 12 were males (32.4%) and 25 (67.5%) were females, whereas in the control group of 31 patients, 11 were males (35.5%) and 20 (64.5%) were females. In the ROC analysis, area under the curve separating stage one or lower fibrosis from stage two or greater fibrosis groups with a *b*-value of 600 s/mm^2 was 0.893 (98% confidence interval (CI): 0.795–0.955), and that with a *b*-value of 1000 s/mm^2 was 0.946 (98% CI: 0.813–0.946). **Conclusion:** Our results are in line with the previous studies, which showed that liver ADC values could be considered as a method for the diagnosis and staging of liver fibrosis.

Keywords: Apparent diffusion coefficient, biopsy, diffusion, fibrotic tissue, liver

Introduction

Liver fibrosis is a wound-healing response induced by chronic damage, which is defined by the accumulation of extracellular fibers such as collagen, glycosaminoglycans, and proteoglycans. Liver fibrosis is generally caused by viral infections, alcohol, drug use, fatty liver, and autoimmune and metabolic diseases. Although liver fibrosis in the early stages is reversible, the progressive form can lead to cirrhosis. The point at which liver fibrosis become irreversible is not fully understood, but even in the early stages of cirrhosis, it may be reversible;[1-5] therefore, diagnosis of fibrosis in its early stages is crucial.

Liver biopsy is currently considered as the gold standard for assessing fibrosis,[6] but liver biopsy has some limitations: it is an aggressive procedure, it may lead to complications, and it is usually not favored by patients. Besides, biopsy only extracts a small part of the liver parenchyma, and since fibrosis is not distributed equally across the liver, it is exposed to sampling variation errors.[7,8] There is also interobserver and intraobserver variability in the samples.[9,10] Therefore, noninvasive assessment of hepatic fibrosis was considered. Two major groups of

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noninvasive methods are available: (1) serologic tests such as the fibro test and (2) imaging techniques such as ultrasonic elastography and magnetic resonance-based imaging. The diffusion-weighted (DW) imaging technique, a type of magnetic resonance imaging (MRI), is sensitive to the diffusion of water molecules in tissues. The accumulation of extracellular fibers in fibrotic livers can restrict the diffusion of water molecules, which can be displayed on DW images, and its value can be measured quantitively on apparent diffusion coefficient (ADC) maps. Previous studies have shown that hepatic ADC in patients with liver cirrhosis is lower than that of controls.[11-20] Research on the relationship between DW images and fibrosis stages has revealed various results.[17,21,22]

The present study evaluates the clinical value of DW imaging in the diagnosis and staging of liver fibrosis.

Patients and Methods

Study design and population

In this case–control study, from October 2015 to October 2017, 40 patients (above 18 years) with impaired liver enzymes who were referred to an interventional radiologist for liver biopsy and 31 healthy controls were subjected to DW MRI. Control groups included individuals who were referred for MRI for reasons other than liver disease and did not have a history of liver disease. To evaluate the liver, before DW imaging, in-phase and out-phase sequences were taken. People with fatty liver or liver mass were excluded.

The study protocol was fully explained to the patient and informed consent was obtained from all of them before enrollment. This study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences.

Tissue sampling

Ultrasound-guided liver biopsy was performed from the fifth segment of the liver by interventional radiologists. Three samples of liver were obtained. Samples were studied by a 10-year experienced pathologist. The pathologist was blinded to the imaging findings. Fibrosis stages were described based on the METAVIR score[23] as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis.

MR images

MRI was performed at 1.5 Tesla (Optima, General Electric Health Care, Milwaukee, WI, USA), with a 16-element phased-array torso coil. The parameters for routine MRI sequences were as follows: coronal two-dimensional fast imaging employing steady-state acquisition: repetition time (TR)/echo time (TE) = 4/2.2 ms; flip angle = 70°; field of view (FOV) = 48 × 48 cm; axial 3D dual echo (in phase − out phase): TR/TE = 6/4 − 2 ms; flip angle = 12°; FOV = 48 × 48 cm. Respiratory-triggered DW images were obtained by using single-shot spin-echo echo-planar (SS-SE-EPI). The image parameters for DW-MRI at *b*-values of 600 and 1000 s/mm^2 were as follows: FOV: 35 × 30; matrix size: 128 × 128; TR: 2000–4000 ms; TE: 60–70 ms. Number of excitation time (NEX): 10; flip angle = 90°; section thickness: 6 mm; phase-encoding direction: anteroposterior; direction of motion probing: phase, frequency, and section.

ADC calculation

According to the protocol and parameters listed, for each *b*-value, six axial images were taken. Automatic voxel-by-voxel analysis on a workstation (Functool, General Electric Medical System, Milwaukee, WI, USA) was used to obtain gray-scale-coded ADC map images for *b*-values of 600 and 1000 s/mm^2. ADC map images were evaluated by a radiologist who was blinded to biopsy results. Three out of six axial images of the liver that were of better quality were selected. The ADC values were measured by locating six round region of interest (ROIs) approximately 1 cm in diameter, excluding large vessels and motion artifacts and 1 cm away from the liver capsule. ROIs were placed in six different parts of axial liver images (two in the posterior part of the right lobe, two in the anterior part of the right lobe, one in the medial part of the left lobe, and one in lateral part of the left lobe). The average ADC values of ROIs was considered as the final ADC value of the liver. These calculations were performed for each *b*-value independently, and liver ADC was calculated separately according to each *b*-value.

Statistical analysis

Analysis was performed using the SPSS-19 and MedCalc-15 software. On the basis of ADC values, each followed a normal distribution, and a parametric *t*-test was used (independent-samples *t*-test). The ADC values and biopsy findings were analyzed using an independent-samples *t*-test, analysis of variance, and Tukey's *post hoc* test. Diagnostic values for different stages of fibrosis were determined using receiver-operating characteristic (ROC) curves based on the sensitivity and specificity determined based on METAVIR score.

Results

The case group consisted of 40 patients who were referred for liver biopsy because of impaired liver enzymes, and 31 liver disease-free individuals who were referred to the same center for MRI formed the control group. Both the case and control groups were subjected to DW-MRI. According to biopsy results, one patient had hemochromatosis, one patient had Wilson's disease, and another had normal results without fibrosis. As the deposition of metals in hemochromatosis and Wilson's disease may affect MRI signals, these two patients were excluded. Furthermore, patients who had normal liver biopsy results were excluded too. Consequently, the case group was decreased to 37 patients [Table 1]. Of 37 patients in the case group, 12 were males (32.4%) and 25 (67.5%) were females. Hence, in the control group of 31 patients, 11 were males (35.5%) and 20 (64.5%) were females. The mean age of the case group was

40.70 ± 13.50 years and the mean age of the control group was 39.42 ± 12.67 years.

The mean and standard deviation of liver ADC based on the *b*-value of 600 and 1000 s/mm^2 are stratified according to the fibrosis stage in Table 2. The comparison of mean ADCs at a *b*-value of 600 s/mm^2 showed significant differences for F0 vs. F2, F0 vs. F3, F0 vs. F4, F1 vs. F3, and F1 vs. F4 ($P = 0.001$, $P < 0.001$, $P < 0.001$, $P = 0.006$, and $P = 0.001$, respectively); at a *b*-value of 1000 s/mm^2, they showed significant differences for F0 vs. F2, F0 vs. F3, F0 vs. F4, and F1 vs. F4, and $P < 0.001$, $P < 0.001$, $P < 0.001$, and $P = 0.003$, respectively, was reported. In other groups, the difference was not statistically significant [Table 3].

The diagnostic accuracy of ADC for assessment of hepatic fibrosis compared with liver biopsy is shown in Table 4. ROC analysis showed that hepatic ADC is a significant predictor of liver fibrosis stages. For example, to predict stage 2 or greater fibrosis with a *b*-value of 1000 s/mm^2, the area under the curve (AUC), sensitivity, and specificity were 0.908 [confidence interval (CI): 0.713–0.964], 88.8%, and 82.3%, respectively, when the cut-off ADC value was set as 1.223 × 10^{-3} mm^2/s. For stage 3 or greater with a *b*-value of 1000 s/mm^2, the AUC, sensitivity, and specificity were 0.889 (CI: 0.790–0.952), 82.3%, and 86.2%, respectively, when the cut-off value was set as 1.188 × 10^{-3} mm^2/s.

Table 1: Causes of liver disease

Biopsy results	Frequency (%)
Autoimmune hepatitis	25 (67.5%)
Primary sclerosing cholangitis	4 (10.8%)
Primary biliary cirrhosis	3 (8.1%)
Hepatitis C virus	3 (8.1%)
Hepatitis B virus	2 (5.4%)
Total	37 (100%)

Table 2: Distribution of liver ADC (value × 10^{-3} mm2/s) stratified by fibrosis stage

Fibrosis stage	Number (%)	ADC	
		b 600 s/mm^2	b 1000 s/mm^2
F0	31 (45.5%)	1.545±0.097	1.291±0.070
F1	10 (14.7%)	1.472±0.087	1.227±0.055
F2	10 (14.7%)	1.384±0.108	1.181±0.067
F3	12 (17.6%)	1.315±0.131	1.152±0.067
F4	5 (7.3%)	1.227±0.086	1.090±0.048

Table 3: Comparing liver ADC values considering various fibrosis stages

Liver fibrosis	*P*	
	b=600 s/mm^2	*b*=1000 s/mm^2
F0 vs. F1	0.319	0.068
F0 vs. F2	0.001	<0.001
F0 vs. F3	<0.001	<0.001
F0 vs. F4	<0.001	<0.001
F1 vs. F2	0.325	0.549
F1 vs. F3	0.006	0.078
F1 vs. F4	0.001	0.003
F2 vs. F3	0.530	0.840
F2 vs. F4	0.056	0.098
F3 vs. F4	0.508	0.401

Discussion

The diagnosis of liver fibrosis stage using a physical examination and laboratory findings is challenging.[19] Identifying patients with F2 stage liver fibrosis and greater is of special clinical importance because only these patients benefit from antiviral drug therapy.[24] Liver biopsy is currently the gold standard for the diagnosis and staging of fibrosis.[6] However, liver biopsy has some limitations.[7-10] Therefore, finding an alternative method has been the goal of many researchers. DW-MRI is a noninvasive, rapid imaging technique that measures the diffusion of water molecules. In fibrotic liver, the accumulation of extracellular fibers results in a reduction of water molecule motion and ADC values.[25] As expected, with the increase in fibrosis stage, ADC values are further reduced [Figure 1].[11,26] Our study consistent with previous findings showed that ADC values are lower in patients with liver fibrosis compared with healthy individuals, and with increased fibrosis, ADC values showed a greater decrease.[15,16,22,27]

Boulanger *et al.*[20] compared ADC values in 18 patients with liver fibrosis due to hepatitis C and 10 patients without liver fibrosis, using *b*-values of 50 and 250 s/mm^2. They found no significant difference between the two groups. Our findings were not in line with the above-mentioned study, as they used lower *b*-values than we did. When low *b*-values were used in DW-imaging in addition to being under the influence of diffusion, it is also under the influence of perfusion,[28-31] in order to reduce the perfusion effect, the use of higher *b*-values is recommended. However, higher *b*-values reduce the signal and consequently, the signal-to-noise ratio (SNR), making images prone to artifacts;[32] therefore, finding a proper *b*-value for assessment of liver fibrosis is essential.

Most studies using a *b*-value ≥500 s/mm^2 showed a significant correlation between liver fibrosis and the ADC values.[15,16,27,22,33,34] Taouli *et al.*[15] evaluated the ADC value in DW-MRI of 23 patients with chronic liver disease and seven healthy subjects using *b*-values of 50, 300, 500, 700, and 1000 s/mm^2. They observed a significant difference between the liver ADC of F2≤ vs. F1≥, and between F3≤ vs. F2≥ when the *b*-value was 500 s/mm^2 or higher. AUC to differentiate F2≤ from F1≥ and F3 ≤ from F2≥ using a *b*-value of 1000 s/mm^2 was 0.868 and 0.832, respectively. They concluded that using *b*-values of 500 s/mm^2 and higher can be useful in differentiating F2≤ from F1≥ and F3≤ from F2≥. In our study, there was a statistically significant difference between the ADC values of F2≤ vs. F1≥ using both *b*-values of 600 and 1000 s/mm^2. The same results were obtained when comparing F3≤ vs. F2≥. AUC to differentiate F2≤ from

Table 4: Area under the receiver operating characteristics curve (AUC) and criterion (ADC) observed to maximize sensitivity and specificity for quantification of liver fibrosis (se: sensitivity, sp: specificity)

Fibrosis stage	*b* 600 (s/mm²)				*b* 1000 (s/mm²)			
	ADC cut-off	AUC (95% CI)	se	sp	ADC cut-off	AUC (95% CI)	se	sp
F0 vs. F1≤	1.458	0.861 (0.756-0.933)	75.68	87.10	1.223	0.894 (0.795-0.955)	75.68	90.32
≤F1 vs. F2≤	1.404	0.893 (0.795-0.955)	77.78	87.80	1.223	0.908 (0.813-0.964)	88.89	82.93
≤F2 vs. F3≤	1.374	0.892 (0.793-0.954)	82.35	86.27	1.186	0.889 (0.790-0.952)	82.35	86.27
≤F3 vs F4	1.352	0.927 (0.837-0.976)	100.00	82.54	1.140	0.933 (0.846-0.980)	80.00	82.54

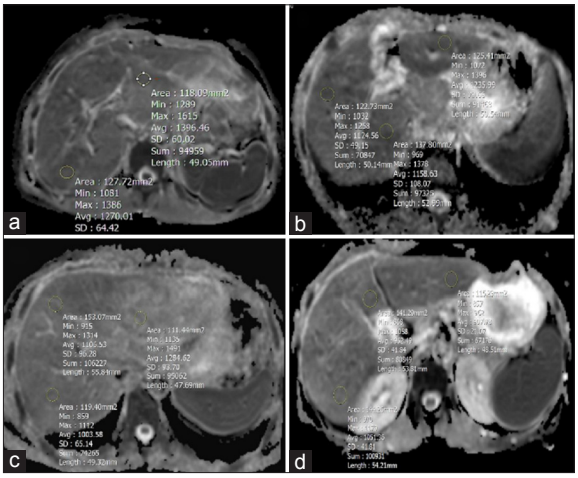

Figure 1: ADC map at the *b*-value 1000 s/mm². (a) A 48-year-old man who were referred for lumbosacral MRI due to low back pain, and considered as F0. (b) A 34-year-old woman with autoimmune hepatitis and F2 biopsy results. (c) A 38-year-old woman with autoimmune hepatitis and F3 biopsy results. (d) A 47-year-old man with chronic hepatitis B and F4 fibrosis stage

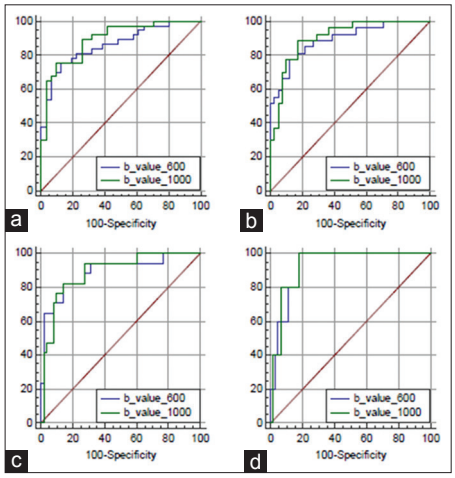

Figure 2: ROC analysis is used to differentiate F0 vs. F1 ≤ (b), ≤F1 vs. F2≤ (d), ≤F2 vs. F3≤ (a), and ≤ F3 vs. F4 (c) using liver ADC when the *b*-values were 600 and 1000 s/mm²

F1≥ and F3≤ from F2≥ at *b*-values of 600 and 1000 s/mm² were 0.893 and 0.903, and 0.892 and 0.889, respectively, which is consistent with the results of Taouli's study [Figure 2].

Kocakoc *et al.*[21] studied 44 patients with chronic liver disease and 30 healthy controls, assessing the role of DW images in the diagnosis of hepatic fibrosis using three different *b*-values (100, 600, and 1000 s/mm²). They concluded that only ADC values obtained by a *b*-value of 1000 s/mm² were statistically significant. In their study, the Ishak classification scoring system for fibrosis stage was used. AUC for identification of significant fibrosis (Ishak ≥3) was 0.759, which in our study for F2 and higher at the *b*-value of 1000 s/mm² was 0.903. In order to increase SNR and reduce image artifacts, we increased NEX to 10, while in the Kocakoc's study NEX was one. This and the use of different fibrosis scoring systems might explain the differences between our study and that of Kocakoc in the results when the *b*-value was 600 s/mm² and the AUC.

A meta-analysis[35] included 25 studies that assessed the role of ADC values for estimation of fibrosis stages. In this study, the AUC to differentiate F ≥ 2 in *b*-value ≥800 and <800 s/mm² were 0.918 and 0.799, respectively; and for F ≥ 3 were 0.916 and 0.836, respectively. Their findings for *b*-values ≥800 s/mm² were very close to those of our study. However, for *b*-values <800 s/mm², our findings show better estimation results for a *b*-value of 600 s/mm². As very low *b*-values such as 50–250 s/mm² were included in their study, and considering that these are contaminated by the perfusion effect, the differences may be explained.

Study limitations

In our study, there were no tissue samples from the control group and they were selected based on clinical and MRI findings. Similar numbers of patients were not used at each stage of fibrosis, and our sample size, particularly in some stage of fibrosis (F4) was low. Further research with a larger number of patients and even distribution among different stages of fibrosis is recommended.

Conclusion

Our results show that hepatic ADC value with *b*-values 600 and 1000 s/mm² could be considered as a method for diagnosis and staging of liver fibrosis. Besides, using DW-MR may lead to good estimates to differentiate fibrosis stage ≥2 from ≤1, which is of clinical importance.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bonis PA, Friedman SL, Kaplan MM. Is liver fibrosis reversible? N Engl J Med 2001;344:452-4.
2. Dienstag JL, Goldin RD, Heathcote EJ, Hann H, Woessner M, Stephenson SL, *et al.* Histological outcome during long-term lamivudine therapy. Gastroenterology 2003;124:105-17.
3. Falize L, Guillygomarc'h A, Perrin M, Lainé F, Guyader D, Brissot P, *et al.* Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. Hepatology 2006;44:472-7.
4. Mallet V, Gilgenkrantz H, Serpaggi J, Verkarre V, Vallet-Pichard A, Fontaine H, *et al.* Brief communication: The relationship of regression of cirrhosis to outcome in chronic hepatitis C. Ann Intern Med 2008;149:399-403.
5. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, *et al.* Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007;147:677-84.
6. Berg T, Sarrazin C, Hinrichsen H, Buggisch P, Gerlach T, Zachoval R, *et al.* Does noninvasive staging of fibrosis challenge liver biopsy as a gold standard in chronic hepatitis C? Hepatology 2004;39:1456-7.
7. Afdhal NH, Nunes D. Evaluation of liver fibrosis: A concise review. Am J Gastroenterol 2004;99:1160-74.
8. Kugelmas M. Liver biopsy. Am J Gastroenterol 2004;99:1416.
9. Regev A, Berho M, Jeffers LJ, Milikowski C, Molina EG, Pyrsopoulos NT, *et al.* Sampling error and intraobserver variation in liver biopsy in patients with chronic HCV infection. Am J Gastroenterol 2002;97:2614-8.
10. Bedossa P, Dargère D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology 2003;38:1449-57.
11. Namimoto T, Yamashita Y, Sumi S, Tang Y, Takahashi M. Focal liver masses: Characterization with diffusion-weighted echo-planar MR imaging. Radiology 1997;204:739-44.
12. Girometti R, Furlan A, Bazzocchi M, Soldano F, Isola M, Toniutto P, *et al.* Diffusion-weighted MRI in evaluating liver fibrosis: A feasibility study in cirrhotic patients. La radiologia medica 2007;112:394-408.
13. Moteki T, Horikoshi H. Evaluation of hepatic lesions and hepatic parenchyma using diffusion - weighted echo-planar MR with three values of gradient b - factor. J Magn Reson Imaging 2006;24:637-45.
14. Ichikawa T, Haradome H, Hachiya J, Nitatori T, Araki T. Diffusion-weighted MR imaging with a single-shot echoplanar sequence: Detection and characterization of focal hepatic lesions. AJR Am J Roentgenol 1998;170:397-402.
15. Taouli B, Tolia AJ, Losada M, Babb JS, Chan ES, Bannan MA, *et al.* Diffusion-weighted MRI for quantification of liver fibrosis: Preliminary experience. Am J Roentgenol 2007;189:799-806.
16. Lewin M, Poujol-Robert A, Boëlle PY, Wendum D, Lasnier E, Viallon M, *et al.* Diffusion-weighted magnetic resonance imaging for the assessment of fibrosis in chronic hepatitis C. Hepatology 2007;46:658-65.
17. Sandrasegaran K, Akisik FM, Lin C, Tahir B, Rajan J, Saxena R, *et al.* Value of diffusion-weighted MRI for assessing liver fibrosis and cirrhosis. Am J Roentgenol 2009;193:1556-60.
18. Soylu A, Kiliçkesmez Ö, Poturoglu S, Dolapçioglu C, Serez K, Sevindir İ, *et al.* Utility of diffusion-weighted MRI for assessing liver fibrosis in patients with chronic active hepatitis. Diagnostic and Interventional Rad 2010;16:204.
19. Koinuma M, Ohashi I, Hanafusa K, Shibuya H. Apparent diffusion coefficient measurements with diffusion-weighted magnetic resonance imaging for evaluation of hepatic fibrosis. J Magn Reson Imaging 2005;22:80-5.
20. Boulanger Y, Amara M, Lepanto L, Beaudoin G, Nguyen BN, Allaire G, *et al.* Diffusion-weighted MR imaging of the liver of hepatitis C patients. NMR Biomed 2003;16:132-6.
21. Kocakoc E, Bakan AA, Poyrazoglu OK, Dagli AF, Gul Y, Cicekci M, *et al.* Assessment of liver fibrosis with diffusion-weighted magnetic resonance imaging using different b-values in chronic viral hepatitis. Med Princip Pract 2015;24:522-6.
22. Bakan AA, Inci E, Bakan S, Gokturk S, Cimilli T. Utility of diffusion-weighted imaging in the evaluation of liver fibrosis. Eur Radiol 2012;22:682-7.
23. Curry M, Nezam H. Noninvasive assessment of hepatic fibrosis: Overview of serologic and radiographic tests. UpToDate.com, 2015.
24. Kim AI, Saab S. Treatment of hepatitis C. Am J Med 2005;118:808-15.
25. Aube C, Racineux P, Lebigot J, Oberti F, Croquet V, Argaud C, *et al.* Diagnosis and quantification of hepatic fibrosis with diffusion weighted MR imaging: preliminary results. Journal de radiologie 2004;85:301-6.
26. Taouli B, Vilgrain V, Dumont E, Daire JL, Fan B, Menu Y. Evaluation of liver diffusion isotropy and characterization of focal hepatic lesions with two single-shot echo-planar MR imaging sequences: Prospective study in 66 patients. Radiology 2003;226:71-8.
27. Bonekamp S, Torbenson MS, Kamel IR. Diffusion-weighted magnetic resonance imaging for the staging of liver fibrosis. J Clin Gastroenterol 2011;45:885.
28. Yamada I, Aung W, Himeno Y, Nakagawa T, Shibuya H. Diffusion coefficients in abdominal organs and hepatic lesions: Evaluation with intravoxel incoherent motion echo-planar MR imaging. Radiology 1999;210:617-23.
29. Le Bihan D, Breton E, Lallemand D, Aubin M, Vignaud J, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988;168:497-505.
30. Dixon W. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging: A modest proposal with tremendous potential. Radiology 1988;168:566-7.
31. Luciani A, Vignaud A, Cavet M, Tran Van Nhieu J, Mallat A, Ruel L, *et al.* Liver cirrhosis: Intravoxel incoherent motion MR imaging—pilot study. Radiology 2008;249:891-9.
32. Kim T, Murakami T, Takahashi S, Hori M, Tsuda K, Nakamura H. Diffusion-weighted single-shot echoplanar MR imaging for liver disease. AJR Am J Roentgenol 1999;173:393-8.
33. Hong Y, Shi Y, Liao W, Klahr N, Xia F, Xu C, *et al.* Relative ADC measurement for liver fibrosis diagnosis in chronic hepatitis B using spleen/renal cortex as the reference organs at 3 T. Clin Radiol 2014;69:581-8.
34. Ozkurt H, Keskiner F, Karatag O, Alkim C, Erturk SM, Basak M. Diffusion weighted MRI for hepatic fibrosis: Impact of b-value. Iran J Radiol 2014;11:e3555.
35. Jiang H, Chen J, Gao R, Huang Z, Wu M, Song B. Liver fibrosis staging with diffusion-weighted imaging: A systematic review and meta-analysis. Abdom Radiol 2016:1-12.