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Diffusion-weighted MRI in staging of post hepatitis C fibrosis: does ADC value challenge liver biopsy?

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Abstract

Background: There is obvious interest in finding a non-invasive diagnostic tool to detect the development of hepatic fibrosis and distinguish between its various stages. Chronic inflammation of the liver secondary to viral hepatitis, autoimmune conditions, sclerosing cholangitis, drug toxicity, chronic alcohol intake, different metabolic disorders, and steatosis lead to fibrosis and maybe cirrhosis. The current study aimed to assess the usefulness of diffusion-weighted magnetic resonance imaging (DW-MRI) in diagnosis of post hepatitis C fibrosis and detection of its stage.

Results: A prospective study had included 232 participants; 120 patients had chronic hepatitis C with/without HCC and 112 subjects had normal liver. There was no significant difference between the two groups regarding age or gender (p 0.192 and 0.227 respectively). DW-MRI was performed using 1.5 T machine. The mean liver ADC values and normalized liver ADC (liver ADC/spleen ADC) were measured at b value 800 s/mm^2; both were significantly lower among cases than controls. Cutoff values of liver ADC were 1.531×10^{-3} mm^2/s, 1.409×10^{-3} mm^2/s, 1.192×10^{-3} mm^2/s, and 1.093×10^{-3} mm^2/s for METAVIR stages ≥ F1, ≥ F2, ≥ F3, and F4, respectively. Normalized liver ADC showed larger area under the curve (AUC) than mean liver ADC in all differentiation categories except for differentiating between F0 and all other fibrosis stages.

Conclusion: In line with the literature, DW-MR imaging using b value of 800 s/mm^2 has proved to be a valuable diagnostic technique for detection and staging of post hepatitis C fibrosis/cirrhosis being noninvasive procedure with acceptable accuracy. DWI using liver/spleen ADC values raised the diagnostic performance with AUC more than 90% in all fibrosis stages on METAVIR score.

Keywords: Liver fibrosis, Cirrhosis, Diffusion magnetic resonance imaging, Hepatitis C

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Background

Chronic liver disease represents a common health problem with many etiologies, primarily viral infection by hepatitis B and C viruses. Liver fibrosis acts as a repair process responding to the chronic hepatic injury whatever the cause. Unfortunately, in most cases, it progresses to liver cirrhosis, which poses a serious threat to human health by its subsequent complications [1]. It is so vital to diagnose fibrosis before developing early or advanced cirrhosis.

Liver biopsy is the gold standard for staging fibrosis and assessment of inflammatory necrotic changes [2, 3], yet it is an invasive tool and has underlying risk of bleeding. In addition, biopsy is limited by inter-observer variance and sampling fallacy [4]. Development of non-invasive and accurate alternatives was necessary, e.g., transient elastography (fibroscan) and magnetic resonance (MR) elastography to diagnose liver fibrosis and its stage [5]. Latterly, use of diffusion-weighted MR imaging in assessment and staging of liver fibrosis has been encountered [6].

Diffusion-weighted imaging (DWI) is a developed technique of magnetic resonance imaging (MRI) used specifically in assessment of the microscopic construct of the tissues. It depends on the water molecules' motion within the tissues [7]. Many studies had designated the efficacy of quantitative apparent diffusion coefficient (ADC) measurement by this imaging technique in liver fibrosis [2]. ADC is the most frequently used DWI parameter that allows valuable idea about inflammation, tissue perfusion, and local cell breakdown. Previous researches have declared that water diffusion may be reduced by extracellular collagen deposition and proteoglycans in cases of liver fibrosis, therefore, such cases reported lower ADC values [6].

Our present study aimed to evaluate DWIs as a noninvasive technique to diagnose liver fibrosis and its stage compared to the liver biopsy and histopathological correlation.

Methods

Patients and control group

This prospective study was conducted in the period between October 2017 and March 2020 with participation of 120 patients, 84 males (70%) and 36 females (30%), age range 32–77 years with mean ± SD 57.48 ± 9.95. The included patients were proved to have chronic hepatitis C by polymerase chain reaction (PCR) elicited during a national screening program. Excluded patients were those with concomitant positive hepatitis B surface antigen, patients with positive antinuclear antibody, patients with illness since childhood and probability of metabolic disorders, and patients on long-term chemotherapy. Fifty cases with hepatocellular carcinoma (HCC) representing 41.67 % and 70 cases without HCC representing 58.33 %.

A control group of 112 was assumed to have healthy liver with normal laboratory and imaging findings; excluding those with fatty liver and whom had any hepatic focal lesions either cystic or solid in nature (70 males (62.5%) and 42 females (38.5%), age range 45–67 years with mean ± SD 58.93 ± 6.49).

Liver biopsies were taken ultrasound guided in the day after the MRI procedure using 18-gage core needle. An interventional radiologist of more than 5 years' experience in organ core biopsies did this work for all patients in the ultrasonography unit. The Institutional Research Ethics committee had approved the study with a written informed consent from each case.

Examination technique and image analysis

Using a 1.5-T closed MR system (Siemens Magnetom Aera); complete dynamic protocol was performed using the body coil. The DWI images were obtained with these parameters: TR 5500/TE 62.0/slice thickness 6.5 mm/inter-slice gap 3.25 mm/FOV 306 × 380 mm/Matrix 216 × 268/number of excitations 2/ b1-values of 400/90/b2 800/90 s/mm^2.

The images were sent to the workstation (NUMARIS/4 syngo MR E11 4VE11C) where ADC values were calculated by locating 6 rounded regions of interest (ROIs) approximately 6 cm^2 as follows: two ROIs in the right lobe of the liver, another two ROIs in the left lobe, and the last two ROIs were in the spleen excluding the organ vessels and images with artifacts as shown in (Figs. 1, 2, 3, and 4). The mean ADC of both hepatic lobes represented liver ADC, and ratio of this ADC value to the mean spleen ADC value was the normalized liver ADC using the spleen as a reference organ.

The measurement of ADC values was calculated by a radiologist of more than 12 years' experience with nearly standardized location of each ROI from the start.

The liver biopsies were reported using the METAVIR score as follows: F0 = no fibrosis, F1 = portal fibrosis, F2 = periportal fibrosis, F3 = septal fibrosis, and F4 = cirrhosis [8, 9]. Each histopathological interpretation was performed by two pathologists of more than 10 years' experience with a higher consultation by a professor of pathology of more than 20 years' experience using a multi-head microscope.

Statistical analysis

Data were analyzed using SPSS statistical package version 23 (SPSS Inc. Released 2015. IBM SPSS statistics for windows, version 23.0, Armonk, NY: IBM Corp).

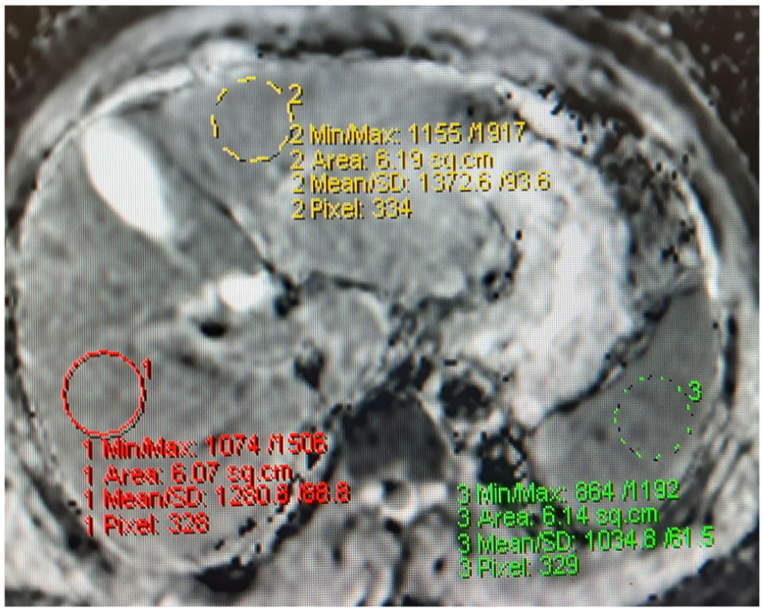

Fig. 1 DW-MR (b = 800) image and ADC map of the liver and the spleen for a case of F2 stage [mean liver ADC value = 1376.3 mm^2/s, mean spleen ADC value = 1009.6 mm^2/s, and liver/spleen ADC = 1.36]

- Tests for significance of the differences between two groups were Student's t test and Mann Whitney's test.
- For more than two groups, ANOVA test with Tukey test and Kruskal Wallis test with Tamhane's test were used.
- Chi-square test ($\chi 2$) was used to study association between qualitative variables. Whenever any of the expected cells were less than five, Fisher's exact test was used.
- Receiver operator characteristic (ROC) with respective points of maximal accuracy for sensitivity and specificity were generated to determine biomarker performance.
- Two-sided P value of < 0.05 was considered statistically significant.

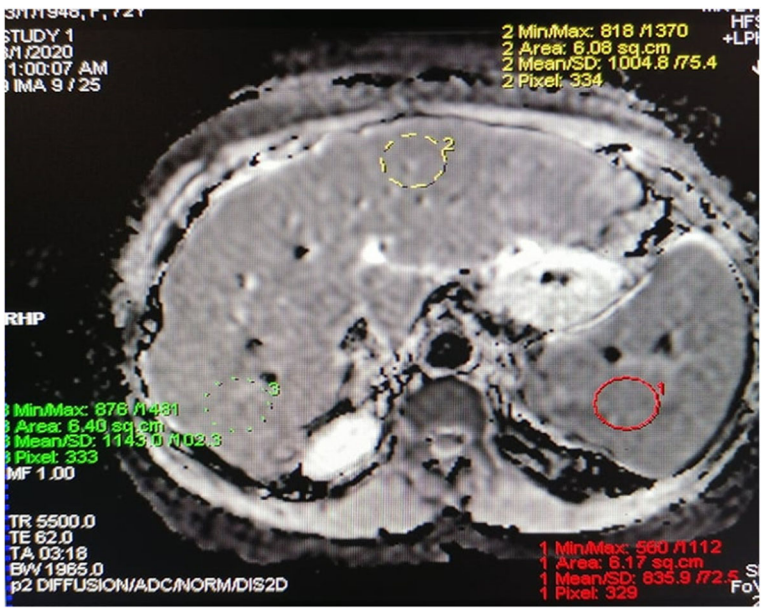

Fig. 2 DW-MR (b = 800) image and ADC map of the liver and the spleen for a case of F3 stage [mean liver ADC value = 1102.8 mm^2/s, mean spleen ADC value = 830.2 mm^2/s, and liver/spleen ADC = 1.33]

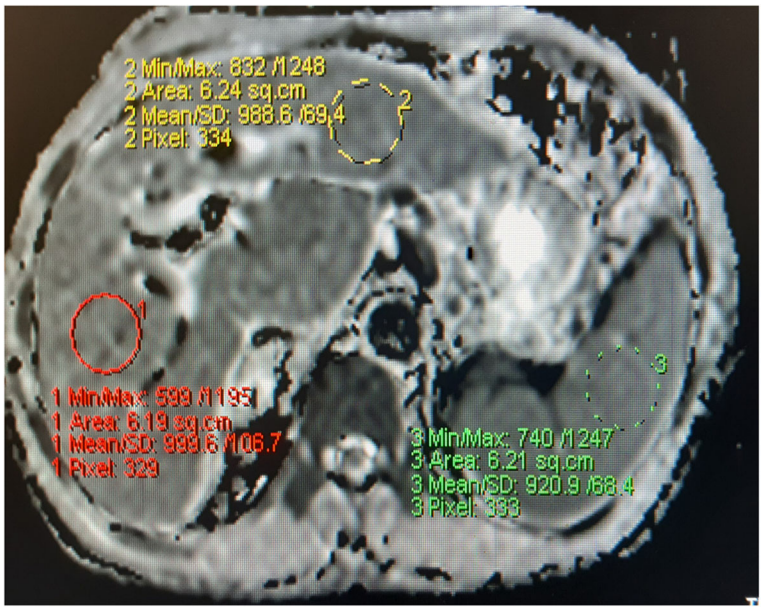

Fig. 3 DW-MR (b = 800) image and ADC map of the liver and the spleen for a case of F4 stage [mean liver ADC value = 999.8 mm^2/s, mean spleen ADC value = 915 mm^2/s, and liver/spleen ADC = 1.09]

Results

A total of 232 participants were included in this study; 120 patients had chronic hepatitis C with/without HCC, and 112 subjects had normal liver. There was no significant difference between the two groups regarding age or gender (p 0.192 and 0.227 respectively). The mean liver ADC values and normalized liver ADC (liver ADC/spleen ADC) were both significantly lower among cases than controls, yet no significant difference was noted regarding the spleen ADC values, p 0.618 (Table 1).

Regarding the histopathological results, according to the METAVIR scoring system, 21 cases were of stage F1,

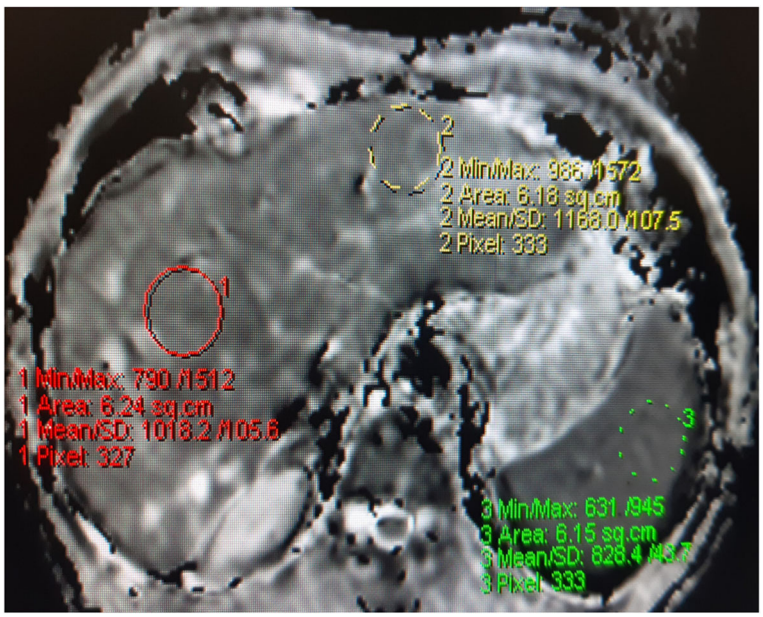

Fig. 4 DW-MR (b = 800) image and ADC map of the liver and the spleen for a case of F4 stage with HCC [mean liver ADC value = 1093.5 mm^2/s, mean spleen ADC value = 868.4 mm^2/s, and liver/spleen ADC = 1.26]

Table 1 Age and different ADC measurements between cases and control group

Variable	Cases (n = 120) mean ± SD	Controls (n = 112) mean ± SD	P value
Age	57.48 ± 9.95	58.93 ± 6.49	0.192
Liver ADC	1142.96 ± 158.76	1659.43 ± 101.71	< 0.001
Spleen ADC	806.52 ± 100.36	813.18 ± 101.40	0.618
Liver/spleen ADC (normalized liver ADC)	1.43 ± 0.25	2.07 ± 0.27	< 0.001

40 cases were of stage F2, 36 cases were of stage F3, and finally 23 cases were of stage F4. There was no significant difference regarding age among patients with different stages of fibrosis. There were significant differences regarding the measurements of the liver ADC and normalized liver ADC values among patients with different stages of fibrosis. Patients with F1 had the highest measures followed by F2 followed by F3 and finally F4 had the lowest measurements, with significant difference among each other as elicited in Table 2.

The mean liver ADC and normalized liver ADC showed significantly larger measurements among patients with stage F1 than all other fibrosis stages. Patients with stages F2 and F3 had significantly larger measurements than those of stage F4, with no significant difference was found between grades F2 and F3.

Among the case groups (n = 120), there was no significant difference between patients with and patients without HCC regarding the age, liver ADC, spleen ADC, and normalized liver ADC as shown in Table 3.

There was no significant difference between patients with mild (F1 and F2) fibrosis and severe (F3 and F4) fibrosis regarding age (p 0.0151). Spleen ADC was significantly smaller (p < 0.001) while liver ADC and normalized liver ADC were significantly larger in patients with mild fibrosis than severe fibrosis (p 0.001 and < 0.001 respectively) as shown in Table 4.

The ROC curve analysis for liver ADC and normalized liver ADC showed good performance of both measures. Mean liver ADC best performed in differentiating between F0 (control group) and all other fibrosis groups. Normalized liver ADC best performed in differentiating between F4 and all other fibrosis grades. Normalized liver ADC showed larger area under the curve (AUC) than mean liver ADC in all differentiation categories except for differentiating between F0 and all other fibrosis stages as demonstrated in Table 5, Figs. 5 and 6.

The diagnostic accuracy of liver ADC and liver/spleen ADC (normalized liver ADC) to assess stage of liver fibrosis compared to the histopathological correlation revealed that both parameters were significant predictors in staging. For example, using liver ADC, ≥ F1 stage with b value 800 s/mm^2, AUC, sensitivity, specificity, and accuracy were 0.987, 96.6%, 87.4%, and 92 % respectively, the cut off ADC value was 1.531×10^{-3} mm^2/s. Using liver/spleen ADC for the same category, AUC, sensitivity, specificity, and accuracy were 0.957, 94.9%, 80.2%, and 88% respectively; the cutoff value was 1.844.

For F4 stage with liver ADC, AUC, sensitivity, specificity, and accuracy were 0.940, 87%, 85.4%, and 86% respectively; the cutoff ADC value was 1.093×10^{-3} mm^2/s. Using liver/spleen ADC for the same category, AUC, sensitivity, specificity, and accuracy were 0.986, 95.7%, 89.3%, and 90% respectively. 1.355 was the cutoff value.

Discussion

Liver fibrosis is considered a major morbidity that can lead to serious complications like portal hypertension

Table 2 Age and different ADC measurement of different fibrosis stages among cases

Variable	F1 (n = 21) mean ± SD	F2 (n = 40) mean ± SD	F3 (n = 36) mean ± SD	F4 (n = 23) mean ± SD	P value	Post hoc
Age (year)	54.52 ± 12.78	57.07 ± 8.44	56.63 ± 10.19	62.21 ± 7.93	0.059	----
Liver ADC	1280.33 ± 140.95	1139.55 ± 133.05	1158.23 ± 159.35	999.56 ± 81.09	< 0.001	P1 < 0.001 P2 0.001 P3 < 0.001 P4 0.549 P5 < 0.001 P6 < 0.001
Liver/spleen ADC (normalized liver ADC)	1.74 ± 0.26	1.46 ± 0.13	1.41 ± 0.17	1.12 ± 0.12	< 0.001	P1 0.001 P2 < 0.001 P3 < 0.001 P4 0.684 P5 < 0.001 P6 < 0.001

P1 F1 vs F2, *P2* F1 vs F3, *P3* F1 vs F4, *P4* F2 vs F3, *P5* F2 vs F4, *P6* F3 vs F4

Table 3 Age and different ADC measurements between patients with and without HCC among the cases group

Variable	With HCC (n = 50) mean ± SD	Without HCC (n = 70) mean ± SD	P value
Age	56.34 ± 11.16	59.08 ± 7.79	0.138
Spleen	803.14 ± 107.15	811.45 ± 90.40	0.660
Liver ADC	1150.43 ± 181.01	1132.50 ± 121.98	0.544
Liver/spleen ADC	1.45 ± 0.30	1.40 ± 0.16	0.547

and hepatic cellular failure [10];thus, it is more wisely to be managed in early stages. It is crucial to determine the stage of hepatic fibrosis as antiviral therapy will be beneficial to cases with ≥ F2 [11].

Previous researches had reported a relationship between the liver fibrosis and ADC values. The current study used b values 400 and 800 s/mm^2. Taouli et al. [2] stated a significant correlation on using b values of ≥ 500 s/mm^2 and Jiang et al. [12], a meta-analysis concluded that DWI of the liver is a reliable noninvasive diagnostic tool for liver fibrosis staging using b_{max} ≥ 800 s/mm^2.

The literature stated that DW-MRI had demonstrated lower ADC values in liver fibrosis than normal liver [1, 2, 12–20]. In concordance with the previous researches, the liver ADC values of the cases were significantly lower than the ADC values of the control group. Regarding the diagnostic performance in distinguishing different stages of fibrosis, Do et al. [21] had used b values of 0, 50, and 500 s/mm^2 and reported cutoff values of 1.68 × 10^{-3} mm^2/s, 1.53 × 10^{-3} mm^2/s, and 1.68 × 10^{-3} mm^2/s for METAVIR stages ≥ F2, ≥ F3, and F4, respectively. Their study group was smaller (34 patients) and inhomogeneous including many etiologies rather than viral hepatitis C.

Lower values for the same stages have been elicited in our study 1.409 × 10^{-3} mm^2/s, 1.192 × 10^{-3} mm^2/s, and 1.093 × 10^{-3} mm^2/s for METAVIR stages ≥ F2, ≥ F3, and F4, respectively using b values of 400 and 800 s/mm^2. Bonekamp et al. [18] have demonstrated cutoff values of 1.33 × 10^{-3} mm^2/s, 1.31 × 10^{-3} mm^2/s, and 1.30 × 10^{-3} mm^2/s to detect METAVIR stages ≥ F2, ≥ F3, and F4, respectively using b values 0 and 750 s/mm^2. The number of cases belonging to F2 and F3 stages was notably small (2 cases for F2 and 6 cases for F3). Variable b values and different sample sizes as well as the patient's characterization regarding different causative entities might explain the difference.

Shayesteh et al. [20] with b value of 1000 s/mm^2 and 1.5 T scanner have reported somehow similar cutoff values 1.223 × 10^{-3} mm^2/s, 1.186 × 10^{-3} mm^2/s, and 1.140 × 10^{-3} mm^2/s to detect METAVIR stages ≥ F2, ≥ F3, and F4, respectively. Also, the AUC 0.908, 0.889, and 0.933 for ≥ F2, ≥ F3, and F4 respectively.

Similarly, Fujimoto et al. [16] with b values of 0 and 1000 s/mm^2 have declared close cutoff values of 1.35 × 10^{-3} mm^2/s (METAVIR ≥ F1), 1.32 × 10^{-3} mm^2/s (METAVIR ≥ F2), 1.27 × 10^{-3} mm^2/s (METAVIR ≥ F3), and 1.23 × 10^{-3} mm^2/s (METAVIR F4).

It is believed that significant periportal fibrosis (F2 stage) is considered a predictor of cirrhosis; thus, the aim of diagnosis and treatment during this stage is to manage the underlying etiology and abort its effect. Besides, high accuracy in the diagnosis of severe fibrosis (F3 and F4) is important, as these patients should be followed up and screened for development of portal hypertension and HCC [22, 23].

Regarding the values of ADC liver for cirrhosis (stage F4 by METAVIR score), our study reported 999.56 ± 81.09 mm^2/s (mean ± SD) for 23 cases. Close result was obtained by Verloh et al. [24] 1015 ± 60.2 mm^2/s for the same pathological category. But they used another scoring system instead of METAVIR (Ishak score) and a 3 T MRI system.

Again, similar values concerning F4 stage were recorded by Hu et al. [1], whom used variable b values and 1.5 T scanner. With b value 700 s/mm^2 and another scoring system similar to METAVIR, they reported 1150 ± 22 mm^2/s.

Our study revealed relatively larger area under the curve (AUC) of normalized ADC liver in diagnosis of

Table 4 Age and different ADC measurements between cases with mild fibrosis and severe fibrosis

Variable	Mild fibrosis (F1 and F2) (n = 61) mean ± SD	Severe fibrosis (F3 and F4) (n = 59) mean ± SD	P value
Age	56.19 ± 10.11	58.81 ± 9.69	0.151
Spleen ADC	764.27 ± 95.09	848.77 ± 87.41	< 0.001
Liver ADC	1188.01 ± 150.59	1096.38 ± 154.62	0.001
Liver/spleen ADC	1.56 ± 0.23	1.30 ± 0.21	< 0.001

Table 5 Comparison between mean liver ADC and normalized liver ADC regarding the diagnostic performance and cutoff values

Class	Cutoff	AUC	Sensitivity	Specificity	PPV	NPV	Accuracy
Mean liver ADC							
F0 vs ≥ F1	1531.0	0.987	96.6	87.4	89	96	92
≤ F1 vs ≥ F2	1409.75	0.968	92.8	85.6	83	94	89
≤ F2 vs ≥ F3	1192.25	0.879	88.1	80.6	61	95	83
≤ F3 vs F4	1093.0	0.940	87.0	85.4	40	98	86
Normalized liver ADC							
F0 vs ≥ F1	1.844	0.957	94.9	80.2	84	94	88
≤ F1 vs ≥ F2	1.705	0.973	96.9	87.1	85	97	87
≤ F2 vs ≥ F3	1.499	0.933	88.1	85.9	68	95	86
≤ F3 vs F4	1.355	0.986	95.7	89.3	50	99	90

significant fibrosis (≥ F2) and cirrhosis (F4) compared to ADC liver; 0.973 and 0.986 compared to 0.968 and 0.940 for ≥ F2 and F4 stages respectively. Thus, it can be considered an excellent diagnostic tool with AUC > 90% [25].

Shin et al. [26] compared the diagnostic performance of ADC liver and normalized ADC liver and reported evident difference between them in diagnosing all fibrosis stages, for ≥ F2 0.631AUC, 83.4% sensitivity, 58.5% specificity, and optimal cutoff value was 1.332×10^{-3} mm^2/s using liver ADC. Normalized ADC liver for the same category revealed 0.877 AUC, 84.3% sensitivity, 86.9% specificity, and optimal cutoff value was 1.411.

For F4 stage, AUC 0.577, 43.4% sensitivity, 83.1% specificity, and optimal cutoff value was 1.189×10^{-3} mm^2/s using liver ADC. Normalized ADC liver for the same category revealed AUC 0.789, 90.2% sensitivity, 62.3% specificity, and optimal cutoff value was 1.365. This might be contributed to variable *b* values used, and their study group was inhomogeneous including only 3 cases of post hepatitis C fibrosis.

Again, Do et al. [21] have concluded that normalization of liver ADC using the spleen as a reference organ increased the diagnostic ability for hepatic fibrosis. There was larger AUC for normalized ADC liver in all fibrosis stages 0.864, 0.805, and 0.935 for ≥ F2, ≥ F3, and F4, respectively, compared to 0.655, 0.689, and 0.720 for the same fibrosis categories using the liver ADC. Their sample was heterogeneous in nature as other causes of hepatic fibrosis rather than chronic hepatitis C were included. Also different *b* values, as they used 0, 50, and 500 s/mm^2 *b* values on 1.5 T machine.

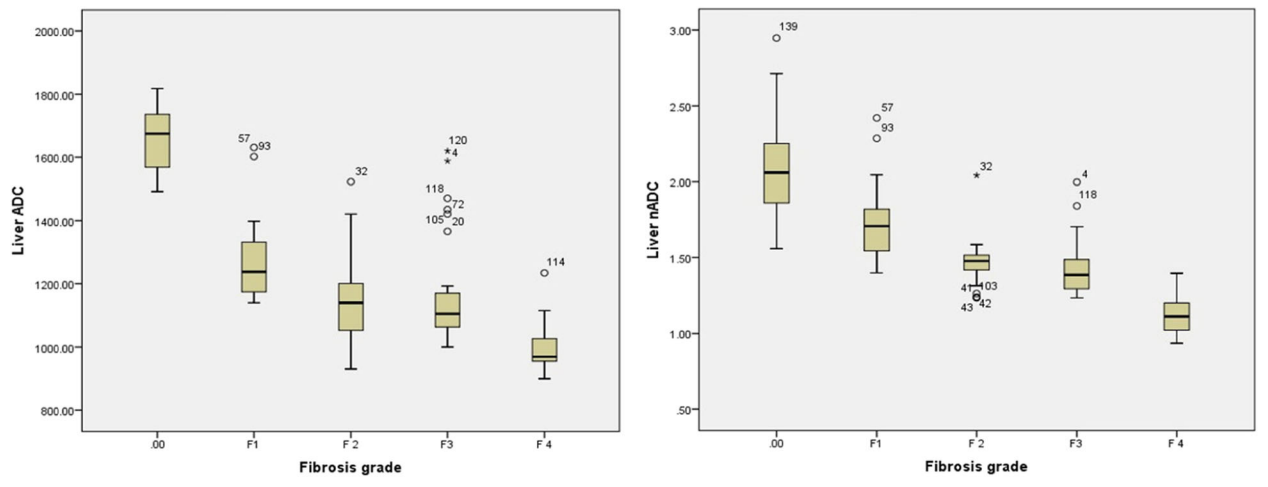

Fig. 5 Box plots showing values of ADC liver and normalized liver ADC for each stage of hepatic fibrosis. There were 112 control cases representing F0 with 21, 40, 36, and 23 patients with fibrosis stages F1, F2, F3, and F4, respectively

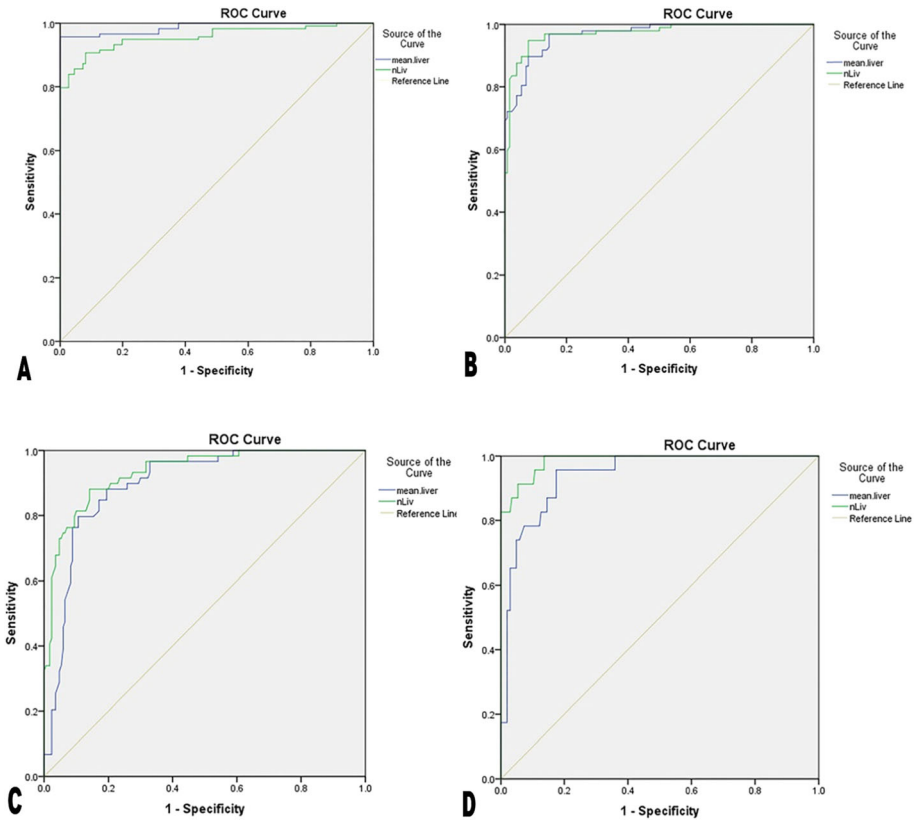

Fig. 6 Receiver operating characteristic (ROC) curve for liver ADC and normalized liver ADC in diagnosis of fibrosis stage ≥ F1 (**a**), ≥ F2 (**b**), ≥ F3 (**c**), and F4 (**d**)

Limitations of the study

Lack of confirmed F0 stage by histopathological correlation as the control group was included based on clinical, laboratory, and imaging findings. Lack of a standardized parameters for image acquisition.

Conclusion

In line with the literature, DW-MR imaging using *b* value of 800 s/mm^2 has proved to be a valuable diagnostic technique for detection and staging of post hepatitis C fibrosis/cirrhosis being noninvasive procedure with acceptable accuracy. DWI using liver/spleen ADC values raised the diagnostic performance with AUC more than 90% in all fibrosis stages on METAVIR score, thus could be considered an excellent diagnostic tool. Further studies are recommended to establish an optimized imaging protocol concerning this issue.

Abbreviations

DW-MRI: Diffusion-weighted magnetic resonance imaging; ADC: Apparent diffusion coefficient; HCC: Hepatocellular carcinoma; PCR: Polymerase chain reaction; ROIs: Regions of interest; ROC: Receiver operating characteristics; AUC: Area under the curve

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Authors' contributions

ER and DS contributed equally to the study design, data collection, analysis, and interpretation of results. All authors read and approved the final manuscript.

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Availability of data and materials

Data will be available upon request via contacting the corresponding author.

Ethics approval and consent to participate

A written consent to participate is available.
Ethics approval: by Menoufia University, Faculty of Medicine, Research Ethics Committee
The reference number is 3/2020RAD3.

Consent for publication

A written consent for publication is available.

Competing interests

The authors declare that they have no competing interests.

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