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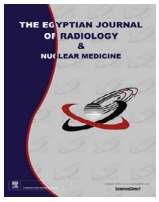

Original Article

Diffusion-weighted MRI in liver fibrosis staging: Added value of normalized ADC using spleen and renal cortex as reference organs

Tamer F. Taha Ali *, Mona AbdelGhaffar El Hariri

Department of Radiodiagnosis, Faculty of Medicine, Zagazig University, Sharkia, Egypt

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ABSTRACT

Aim: To evaluate the potential value of the spleen and renal cortex as a reference organ to improve the performance of DWI in the assessment of liver fibrosis.

Material and methods: 44 subjects were included: 30 patients with chronic viral hepatitis and 14 age matched volunteers. They were subjected to diffusion weighted MRI (DWI). Liver ADC, normalized ADC (ratio between ADC of liver to spleen (S-ADC) and renal cortex (R-ADC)) was calculated. Data was analyzed and ROC was used to evaluate the performance of ADC, S-ADC and R-ADC.

Results: No significant difference between spleen ADC and renal ADC values between patient group and control group or in-betweens different fibrosis stages. The mean liver ADC was significantly lower in cirrhotic patients than control group (1.59 ± 0.024 versus $1.55 \pm 0.036 \times 10^{-3}$ mm^2/s, $P = 0.009$) with some overlap in different fibrosis grades.

With exception to stage 1 fibrosis, the mean S-ADC value was significantly lower in patients with different hepatic fibrosis stages in comparison to control group (P 0.02–<0.001). Significant negative correlation was noted between S-ADC value and fibrosis stage ($r = -0.75$, $p < 0.001$). It had significant difference between stage 0 compared to stage 2, 3, and 4 as well as between stage 4 in comparison to stage 1, 2 and 3. S-ADC had a significant ability to differentiate between stages 0–1 Vs stage 2–4, stage 0–2 Vs stage 3–4 as well as stage 0–3 Vs stage 4.

Significant negative correlation was noted between R-ADC value and fibrosis stage ($r = -0.68$, $p < 0.001$). The mean R-ADC value was lower in patients with liver fibrosis compared to volunteers with significant difference between stage 0 and 3 and between stage 0 and 4 ($P < 0.001$). It had significant difference between stage 0 compared to stage 3, and 4 as well as in stage 4 in comparison to stage 1 and 2. R-ADC has a significant ability to differentiate between stages 0–1 Vs stage 2–4, stage 0–2 Vs stage 3–4 as well as stage 0–3 Vs stage 4.

ROC analysis showed higher performance using S-ADC in comparison to liver ADC and R-ADC while R-ADC had higher performance in comparison to liver ADC. The AUC, sensitivity, specificity, PPV, NPV and k-value for detection of fibrotic stages $\geqslant 2$ (0.85, 95.8%, 60%, 74%, 92% and 0.85 for S-ADC Vs 0.68, 66.7%, 60%, 66%, 60% and 0.28 for ADC and 0.85, 95.8%, 50%, 69%, 91% and 0.47 for R-ADC). and in detection of fibrotic stages $\geqslant 3$ was (0.86, 100%, 52%, 61%, 100% and 0.48 for S-ADC Vs 0.63, 63%, 52%, 50%, 65% and 0.14 for ADC and 0.88, 100%, 44%, 57%, 100% and 0.40 for R-ADC) while for fibrosis stage 4, the corresponding values was (1, 100%, 100%, 100%, 100% and 1 for S-ADC Vs 0.7, 81%, 54%, 37%, 90% and 0.26 for ADC and 0.65, 100%, 65%, 45%, 100% and 0.43 for R-ADC) respectively.

Conclusion: Normalized liver ADC using the spleen and kidney increases the performance of ADC in the evaluation of liver fibrosis which is highest in spleen normalized ADC.

1. Introduction

There are several causes that can lead to liver fibrosis as a long run consequence of most important are viral, metabolic, autoimmune, cholestatic and alcohol or drug-induced diseases. Liver

* Corresponding author.
E-mail address: tamerfathi2008@yahoo.com (T.F. Taha Ali).

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fibrosis progresses and distorts the hepatic architectural resulting in liver cirrhosis, hepatic dysfunction and portal hypertension [1–8].

Treatment of early fibrosis can be achieved by removing the causing agent in consistent with the usage of specific antifibrotic therapy hoping to reverse that early changes occurred. Hence it is of great value to rule out the early liver fibrosis [1,2,6]. While the liver biopsy and histological analysis is widely assigned as the gold standard for assessment of hepatic fibrosis, it carries some disadvantage. First it is relatively invasive with pain occurring in about 40% while major complications can occur in 0.5% of susceptible patients. Secondly, sample error liability and variation of results in between different observers or even in same observer with the difficulty of re-biopsy. Therefore, elaborating as reliable and non-invasive diagnostic tools for hepatic fibrosis with quantification capabilities is a real challenge [2,8,9–15].

Diffusion weighted MRI (DW-MRI) is a technique that mapping and quantifies the water molecules motion in tissues and therefore generates image contrast based on differences in its proton mobility in tissues. Quantification of water diffusion is done by the calculation of the apparent diffusion coefficient (ADC) [14,16].

DW-MRI carries frequent advantages, for example it is rapid (can be done in a breath-hold) and needs no contrast media. Recent advancement in technology are supporting the progressive application of DW-MRI in the abdomen including liver fibrosis with improving and promising results [14,16–20].

Restriction of the apparent water proton diffusion occurs in highly cellular tissues and with the higher density of cell membranes. While higher water molecules movement occurs in cystic or necrotic tissues. Liver fibrosis results in the accumulation of collagen, proteoglycan and glycosaminoglycans in the extracellular spaces so subsequent water molecular restriction happens [2,14,16,21].

The application of normalization of ADC by using a reference organ aims to reduce the ADC calculation variability. Spleen and renal cortex can be tried to be the reference organs [20,22–25].

The aim of the current study was to evaluate the potential value of using the spleen and renal cortex as a reference organ to normalize liver ADC in order to improve the performance of DWI in the assessment of liver fibrosis.

2. Material and methods

2.1. Subjects

The current study was approved by our institutional review board. Written informed consent was obtained from all subjects.

This prospective study included a total of 35 consecutive patients who was already diagnosed as chronic viral hepatitis on basis of clinical findings and enhanced by laboratory investigations and ongoing to percutaneous liver biopsy with normal renal function tests. Of these 35 patients, 30 patients were included in this study (patient group) with mean age 46.5 years (range 31–60 years), while 5 patients were excluded. Exclusion was due to liver biopsy contraindication (n = 3), absolute contraindication to MR study (n = 1) while last excluded patient was due to his refusal to proceed to MR study.

Fourteen control matched age subjects were enrolled with mean age 47 years (range 32–58 years), so total subjects in our study was 44 (30 males, 14 females) with mean age 47 years (range 31–60 years).

Patient group: Include thirty patients (21 males, 9 females) who were previously diagnosed as chronic viral hepatitis.

Control group: Include fourteen matched age volunteers (9 men and 5 women). Criteria of control group: have no absolute contraindication to MRI imaging, no history of acute or chronic hepatitis or diffuse hepatic disease and normal liver and renal clinical, laboratory and imaging findings apart from small hepatic cyst or haemangioma.

2.2. MRI protocol

1.5 T MR scanner (Philips Medical Systems, Achieva) was used. Phased array superficial body coil was applied. Single-shot echo-planar imaging (EPI) sequence was used to obtain DWI in a single end-expiratory breath-hold (free breathing and finger triggering pulse).

MRI parameter: TR/TE: 1300–3500, 67–83 m/s, slice thickness: 7 mm, interslice gap: 1.5 mm, field of view: 320–420 mm. number of signals averaged: 2. matrix: 192 × 256. Voxel size: 2.05 and 2.45 and tri-directional diffusion gradients (b = 500 s/mm^2). Average scan time: 6 min.

2.3. ADC mapping

A workstation with a standard software was used to obtain ADC maps for b value = 500. The mean signal intensity (SI) was

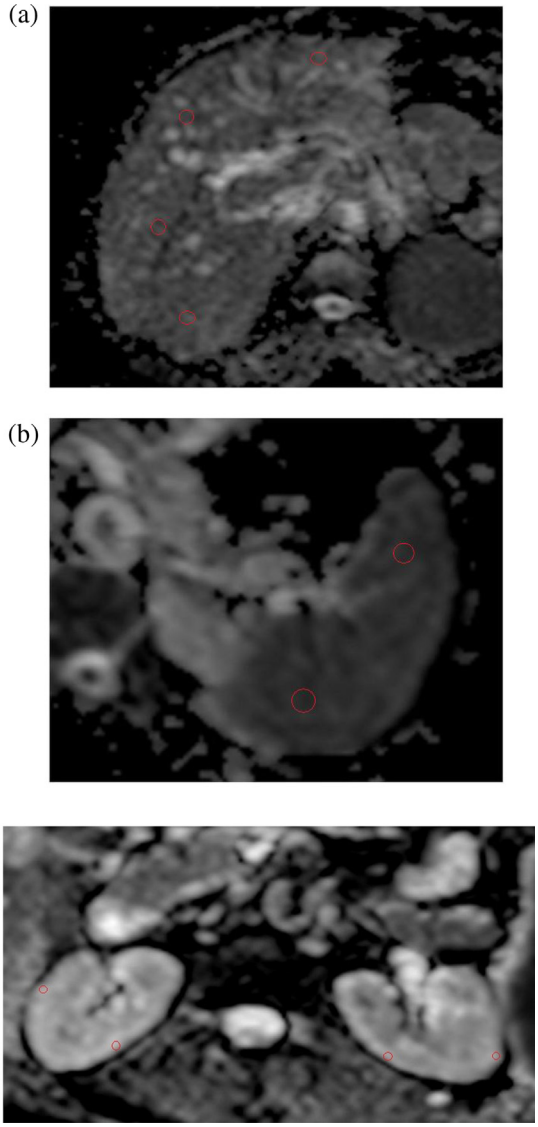

Fig. 1. ADC map. ROI application for the liver (a), spleen (b) and (c).

calculated on ADC map by applying a circular region of interest (ROIs; ranging from 10 to 20 mm^2) in the liver, spleen and renal cortex on ADC map with avoidance of vessels, artifacts and focal lesions.

Hepatic ADC was calculated as the average of the four ROIs applied to left lateral, left medial, right anterior and right posterior liver segments on 3 contiguous slices.

For the spleen ADC: 2 ROIs were positioned 3 contiguous sections with a central slice through splenic hilum level, then average was calculated.

For the renal ADC: 2 ROIs were placed at renal cortex of each kidney on 3 contiguous sections with the central one through the mid-pole level, the average was calculated.

Normalized hepatic ADC was calculated as the ratio between the hepatic ADC to each of spleen ADC (S-ADC) and renal cortex (R-ADC) (Fig. 1).

2.3.1. Histopathologic examination

All patients in the patient group (thirty) had percutaneous liver biopsy that was done after the MRI examination (mean delay, 30 days; range, 10–52 days). Sonographic guidance was used to do biopsy by an experienced hepatologist using a needle of 18–20 gauges through trans- or sub costal approach. The right hepatic lobe was sampled. The specimens length of $\geqslant$1.5 cm were fixed in formalin and stained with hematoxylin–eosin, stain for reticulin, and Masson trichrome. The biopsy specimens should include $\geqslant$10 portal tracts and regenerating nodules to be satisfactory.

Patients were classified according to the METAVIR scoring system criteria which composed of F0: normal/no scarring, F1:minimal scarring, F2: Scarring which extends outside the blood vessels contained areas, F3: Bridging fibrosis, F4: cirrhosis [26].

2.3.2. Data analysis

A commercially available PC-based software package (SPSS) is used for data analysis and to test significance of statistical difference. The specificity, sensitivity and accuracy of liver ADC as well as S-ADC and R-ADC were calculated. Comparison between two groups was done using Student's *t*-test while one Way Anova test was applied for comparison between more groups. Pearson's correlation between the liver ADC, S-ADC and R-ADC values and pathological grade was done. Cohen's kappa (κ) is used to measures inter-rater agreement.

MCnemar test was used to calculate concordance between the ADC and normalized ADC values.

Analysis of receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) was done. The threshold ADC, S-ADC, R-ADC for the maximum sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy in the differentiation between different stage

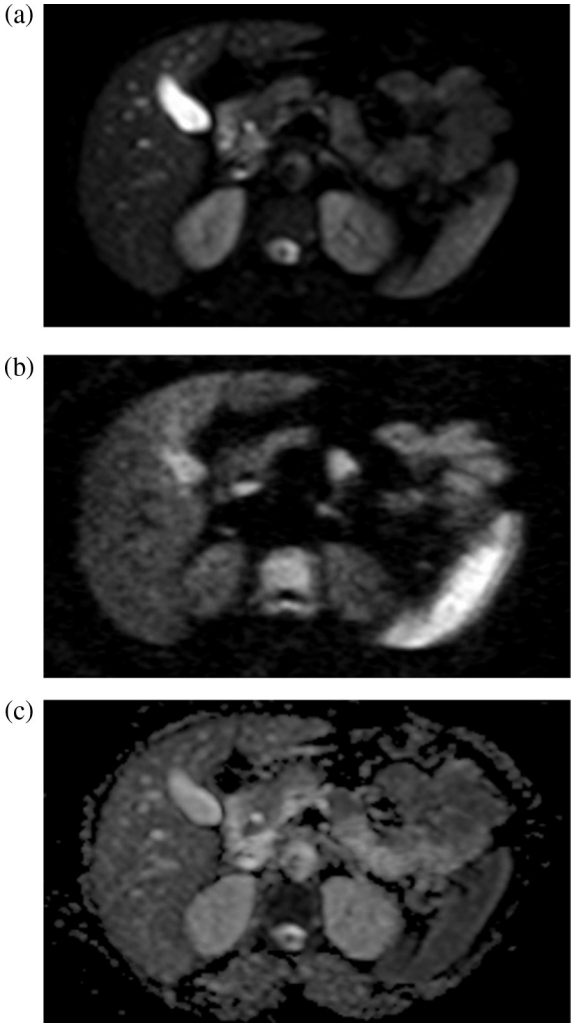

Fig. 2. DWI at b = 0 (a), b = 500 (b), and ADC map (c) for a volunteer (stage 0 fibrosis): liver ADC = 1.61 $\times$ 10^{-3} mm^2/s, S-ADC = 1.40 and R-ADC = 0.69.

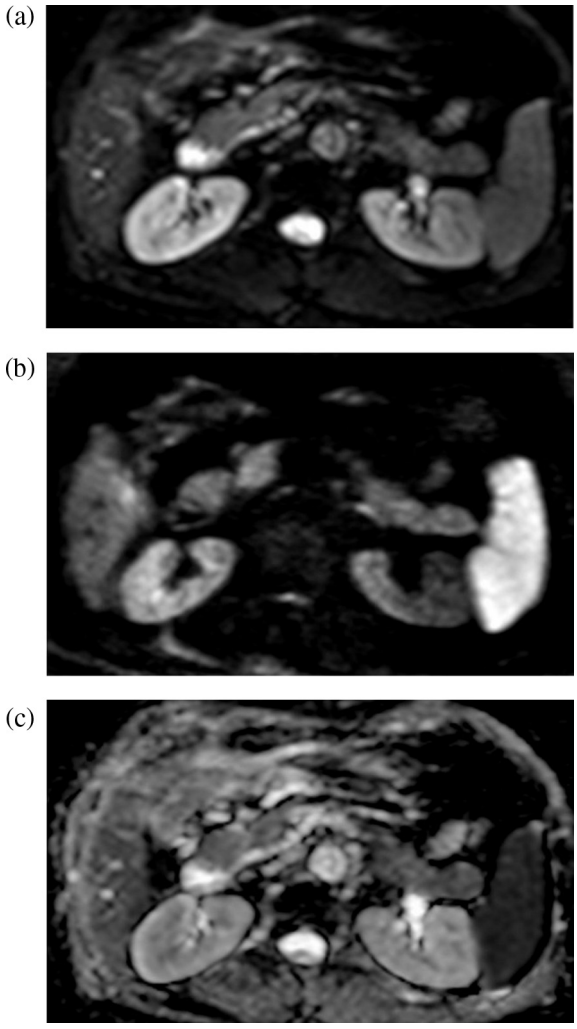

Fig. 3. DWI at b = 0 (a), b = 500 (b), and ADC map (c) for a patient with stage 1: liver ADC = 1.57 $\times$ 10^{-3} mm^2/s, S-ADC = 1.36 and R-ADC = 0.68.

was estimated. The P-value $\leqslant 0.05$ was considered significant at confidence interval 95%.

3. Results

3.1. Histopathologic data

The prevalence of fibrosis stage (F) in the current study was: stage 0 (control group; n = 14, Fig. 2), F1 (n = 6, Fig. 3), F2 (n = 5, Fig. 4), F3 (n = 8, Fig. 5) and F4 (cirrhosis, n = 11, Fig. 6).

There was no significant difference between spleen ADC and renal ADC values between patient group and control group (1.03 ± 0.06 Vs $1.13 \pm 0.09 \times 10^{-3}$ mm^2/s, p = 0.928 for spleen ADC and 2.48 ± 0.09 Vs $2.49 \pm 0.08 \times 10^{-3}$ mm^2/s, p = 0.937 for renal ADC respectively), moreover no significant difference was detected in neither of the spleen or renal ADC among patients with different stages of fibrosis (p = 0.68–0.91) (see Fig. 7).

The mean liver ADC value in volunteers was $1.59 \pm 0.024 \times 10^{-3}$ mm^2/s while in patient group was $1.56 \pm 0.044 \times 10^{-3}$ mm^2/s. The mean liver ADC value was significantly lower in cirrhotic patients (F4) in comparison to control group (1.59 ± 0.024 versus $1.55 \pm 0.036 \times 10^{-3}$ mm^2/s, P = 0.009). On the other hand liver ADC had some overlap in different fibrosis grades with insignificant difference between individual stage while significance is noted in differentiation only between stage 0–1 Vs stage 2–4 (p = 0.02) and between stage 0–3 Vs stage 4.

Significant negative correlation was noted between liver ADC value and fibrosis stage (r = -0.35, p < 0.05) (Tables 1 and 2).

The mean S-ADC value in the control group was 1.39 ± 0.059 while in patient group it was 1.295 ± 0.053.

With exception to stage 1 fibrosis, the mean S-ADC value was significantly lower in patients with different hepatic fibrosis stages in comparison to control group (P 0.02–<0.001).

S-ADC value decreased with upgrading of fibrosis stage with some overlapping in different fibrosis stages. It had significant difference between stage 0 compared to stage 2, 3, and 4 as well as between stage 4 in comparison to stage 1, 2 and 3. On the other hand there was no significant difference between the other stages.

S-ADC has a significant ability to differentiate between stages 0–1 Vs stage 2–4, stage 0–2 Vs stage 3–4 as well as stage 0–3 Vs stage 4 (Tables 1 and 2).

Significant negative correlation was noted between S-ADC value and fibrosis stage (r = −0.75, p < 0.001).

The mean R-ADC value in the control group was 0.69 ± 0.036 while in patient group it was 0.64 ± 0.114.

The mean R-ADC value was lower in patients with liver fibrosis compared to volunteers with significant difference between stage 0 and 3 and between stage 0 and 4 (P < 0.001).

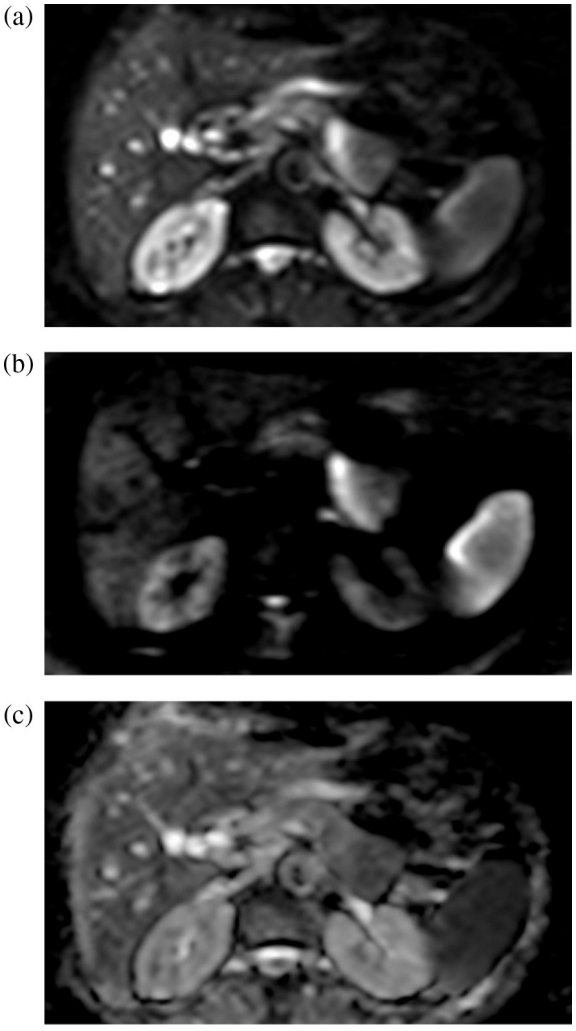

Fig. 4. DWI at b = 0 (a), b = 500 (b), and ADC map (c) for a patient with stage 2. Liver ADC = 1.56×10^{-3} mm^2/s, S-ADC = 1.34 and R-ADC = 0.66.

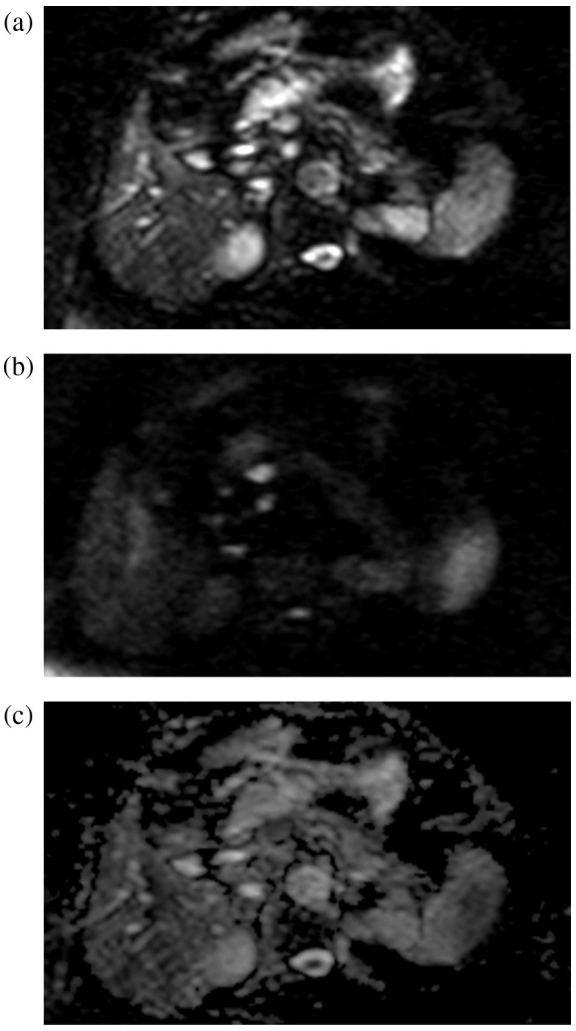

Fig. 5. DWI at b = 0 (a), b = 500 (b) and ADC map(c) for a patient with stage 3. Liver ADC = 1.57×10^{-3} mm^2/s, S-ADC = 1.32 and R-ADC = 0.64.

Fig. 6. DWI at b = 0 (a), b = 500 (b), and ADC map (c) for a patient with stage 4. Liver ADC = 1.54 × 10^{-3} mm^2/s, S-ADC = 1.20 and R-ADC = 0.60.

R-ADC value decreased with upgrading of fibrosis stage with some overlapping in different fibrosis stages. It had significant difference between stage 0 compared to stage 3, and 4 as well as in stage 4 in comparison to stage 1 and 2. On the other hand there was no significant difference between other stages.

R-ADC has a significant ability to differentiate between stages 0–1 Vs stage 2–4, stage 0–2 Vs stage 3–4 as well as stage 0–3 Vs stage 4 (Tables 1 and 2).

Significant negative correlation was noted between R-ADC value and fibrosis stage ($r = -0.68$, $p < 0.001$).

ROC analysis (Fig. 6 and Table 3) showed higher performance using S-ADC in comparison to liver ADC and R-ADC while R-ADC had higher performance in comparison to liver ADC. The AUC, sensitivity, specificity, PPV, NPV and k-value for detection of fibrotic stages ⩾2 (0.85, 95.8%, 60%, 74%, 92% and 0.85 for S-ADC Vs 0.68, 66.7%, 60%, 66%, 60% and 0.28 for ADC and 0.85, 95.8%, 50%, 69%, 91% and 0.47 for R-ADC).

In the detection of fibrotic stages ⩾3, ROC analysis showed higher performance using R-ADC in comparison to liver ADC while S-ADC had a higher performance than both liver ADC and R-ADC. The AUC, sensitivity, specificity, PPV, NPV and k-value (0.86, 100%, 52%, 61%, 100% and 0.48 for S-ADC Vs 0.63, 63%, 52%, 50%, 65% and 0.14 for ADC and 0.88, 100%, 44%, 57%, 100% and 0.40 for R-ADC).

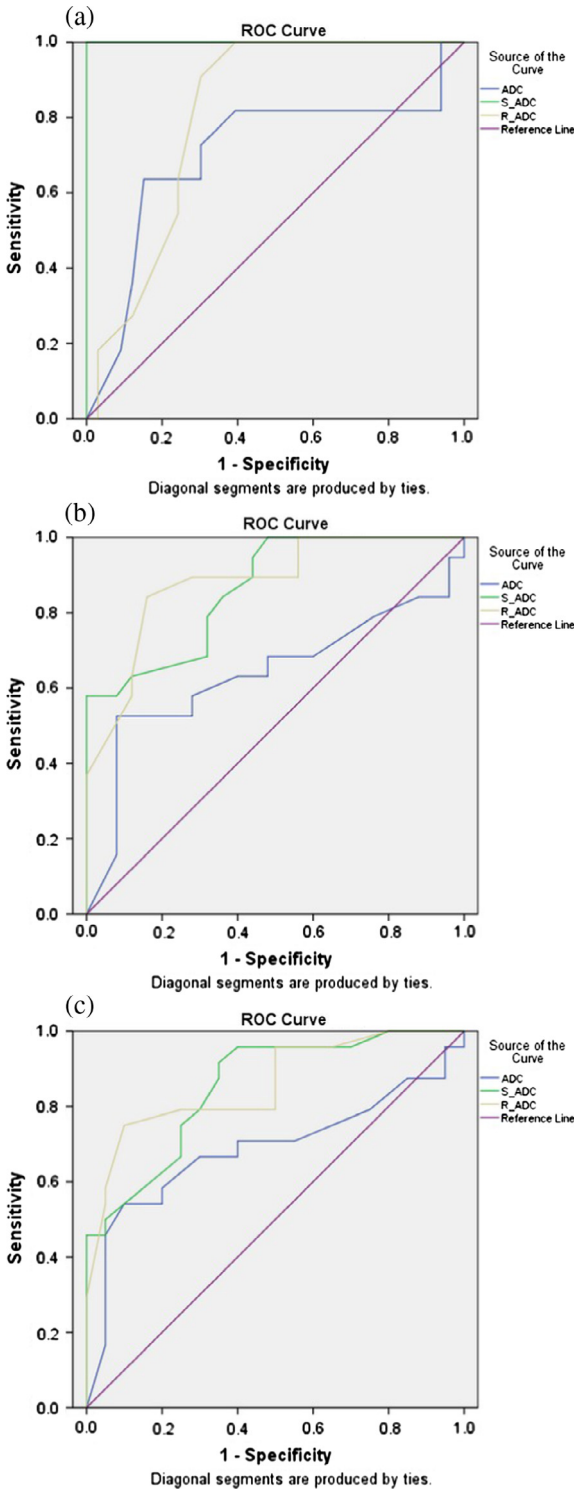

Fig. 7. ROC curves for liver ADC, S-ADC and R-ADC in differentiation of patients stratified by fibrosis stage (distinguishing of stage ⩾2 (a); distinguishing of stage ⩾ 3 (b); and distinguishing of cirrhosis [stage 4] (c). Refer to Table 3 for AUC values.

In fibrosis stage 4, S-ADC had an overall higher performance also in comparison to liver ADC and R-ADC while R-ADC had a higher performance in comparison to liver ADC. The AUC, sensitivity, specificity, PPV, NPV and k-value (1, 100%, 100%, 100%, 100% and 1 for S-ADC Vs 0.7, 81%, 54%, 37%, 90% and 0.26 for ADC and 0.65, 100%, 65%, 45%, 100% and 0.43 for R-ADC).

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Table 1
The mean ADC (±SD) of: liver, S-ADC, R-ADC, in different grades of hepatic fibrosis (according to METAVIR score).

Fibrosis stage	No	Liver ADC ($\times 10^{-3}$ mm^2/s)	S-ADC	R-ADC
F0	14	1.59 ± 0.024	1.39 ± 0.059	0.69 ± 0.036
F1	6	1.57 ± 0.031	1.35 ± 0.06	0.67 ± 0.037
F2	5	1.56 ± 0.033	1.33 ± 0.051	0.67 ± 0.037
F3	8	1.57 ± 0.045	1.32 ± 0.021	0.63 ± 0.05
F4	11	1.55 ± 0.036	1.18 ± 0.023	0.62 ± 0.023

Table 2
ADC comparison among different fibrosis stages.

	Liver ADC (P–value)	S-ADC (P–value)	R-ADC (P–value)
F0 Vs F1	0.43	0.11	0.19
F0 Vs F2	0.08	0.02	0.13
F0 Vs F3	0.40	0.005	<0.001
F0 Vs F4	0.009	<0.001	<0.001
F1 Vs F2	0.37	0.49	0.79
F1 Vs F3	0.98	0.32	0.06
F1 Vs F4	0.15	<0.001	0.01
F2 Vs F3	0.33	0.84	0.12
F2 Vs F4	0.73	<0.001	0.04
F3 Vs F4	0.11	<0.001	0.60
F0-1 Vs F2-4	0.02(S)	<0.001	<0.001
F0-2 Vs F3-F4	0.10	<0.001	<0.001
F0-3 Vs F4	0.02(S)	<0.001	0.002

4. Discussion

Applications of diffusion-weighted imaging (DWI) as a part of abdominal MRI had become feasible with the advancement of MRI techniques. Many authors have evaluated the application of measuring the apparent diffusion coefficient (ADC) as a part of evaluation of hepatic diseases [9,27–29]. Many literature had demonstrated the significance of ADC reduction in cirrhotic livers compared to the normal livers [8,10,14,16–20,30].

Girometti et al. [13] showed lower liver ADC in cirrhotic livers compared to healthy controls, and reported an area under the curve (AUC) of 0.93 for diagnosis of fibrosis, with sensitivity and specificity of 89.7% and 100% respectively in differentiating for diagnosing cirrhosis (using b-values of 0–150–250–400 s/mm^2).

In another study [2] ADC was able to differentiate cirrhotic liver from non-cirrhotic liver with lower ADC of the former, however in that study ADC could not significantly differentiate between low and high fibrosis grade. This is also confirmed by Razek et al. [8] who also showed significant correlation between the mean ADC value with METAVIR fibrosis score (r = 0.77, P = 0.01) and Taouli et al. [14] who showed also lower liver ADCs in stage $\geqslant$stage 2 compared to stage $\leqslant$1.

In this study, we have confirmed this opinion, as we found that the mean liver ADC value in hepatic cirrhosis patients was significantly lower than that of control normal group ($1.55 \pm 0.036 \times 10^{-3}$ mm^2/s vs. $1.59 \pm 0.024 \times 10^{-3}$ mm^2/s, p = 0.009). This can be explained by the restricted diffusion in fibrotic changes due to presence of collagen and thus reduction of liver ADC values [31].

We also noticed a significant negative correlation between liver ADC value and stage of fibrosis (r = −0.35, p < 0.05). This is in agreement with multiple previous studies [14–16,18,20,25,30] that emphasized upon this negative correlation.

However this negative correlation was denied by Boulanger et al. [17], who compared ADC values and fibrosis scores measured using the Ishak scale with five different b values (50–50 s/mm^2).

Limitations of the absolute ADC values are attributed to reproducibility and noise effects as well as variability due to technical factors as using different b values and acquisition methods as a recognized problem [21,32–35].

The ideal b-value used in the assessment of hepatic fibrosis has not yet been fully established and may depend on the individual experiences [13,16,34–36]. ADC calculation using images obtained with higher b values are more sensitive to diffusion than those obtained using b values <500 s/mm^2. On the other hand higher b value of 800 s/mm^2 are less sensitive to the effects of microvascular perfusion which is diminished in early fibrosis, till the present time, the recommended b-value to obtain enough signals from the liver is limited up to 500 mm^2/s [8,14,16,19,31]. Chandarana and Taouli [16] used b value of 0 and 400 while Do et al. [37] measured signal intensity on b0 and b 500. In current study we used b-value of 0 and 500 s/mm^2.

This was shown in a previous study [13] which reported cirrhotic liver ADCs of 1.14×10^{-3} mm^2/s with b values of 0, 50, 250, and 400 s/mm^2 and ADCs of 0.91×10^{-3} mm^2/s with b values of 600 and 800 s/mm^2. Similar discrepancy was obtained in another study [10] between the normal liver mean ADCs between using b values of 0 and 500 s/mm^2 (ADC was $1.79 \pm 0.32 \times 10^{-3}$ mm^2/s versus $1.55 \pm 0.29 \times 10^{-3}$ mm^2/s).

So, application of a reference relatively constant organ for normalization of ADC may help to diminish the variability in ADC calculation. The spleen and renal cortex had been tried as a standard Refs. [10,29,36–39].

In a previous study [20], the spleen ADCs showed insignificant difference among healthy and chronic liver disease subjects. This is consistent with the current study as we noticed insignificant difference of spleen ADC between patient and control group ($1.13 \pm 0.09 \times 10^{-3}$ mm^2/s Vs $1.03 \pm 0.06 \times 10^{-3}$ mm^2/s, p = 0.928), or even among different stages of fibrosis (p = 0.54–0.91).

In addition, Insignificant difference of renal cortex ADC is noted also in current study between patient and volunteer group ($2.48 \pm 0.09 \times 10^{-3}$ mm^2/s Vs $2.49 \pm 0.08 \times 10^{-3}$ mm^2/s, p = 0.937), as well as among different stages of fibrosis (p = 0.61–0.87).

In our current study, the mean R-ADC value was lower in patients with liver fibrosis compared to volunteers with significant difference between stage 0 and 3 and between stage 0 and 4 (P < 0.001). R-ADC value decreased with upgrading of fibrosis stage

Table 3
Analysis for performance of Liver ADC versus S-ADC and R-ADC:

Fibrosis stage	ADC	Cutoff ($\times 10^{-3}$ mm^2/s)	AUC	Sensitivity (%)	Specificity (%)	PPV	NPV	KAPPA	P-value
F $\geqslant$ 2	ADC	1.58	0.68	66.7	60.0	66	60	0.28	0.07
	S-ADC	1.36	0.85	95.8	60	74	92	0.58	<0.001
	R-ADC	0.70	0.85	95.8	50	69	91	0.47	<0.001
F $\geqslant$ 3	ADC	1.58	0.63	63	52	50	65	0.14	0.31
	S-ADC	1.36	0.86	100	52	61	100	0.48	<0.001
	R-ADC	0.69	0.88	100	44	57	100	0.40	<0.001
F = 4	ADC	1.58	0.7	81	54	37	90	0.26	0.03
	S-ADC	1.25	1.0	100	100	100	100	1.0	<0.001
	R-ADC	0.65	0.65	100	65	45	100	0.43	<0.001

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with some overlapping in different fibrosis stages. It had significant difference between stage 0 compared to stage 3, and 4 as well as in stage 4 in comparison to stage 1 and 2. On the other hand there was no significant difference between the other stages. R-ADC has a significant ability to differentiate between stages 0–1 Vs stage 2–4, stage 0–2 Vs stage 3–4 as well as stage 0–3 Vs stage 4.

In the study carried out by Hong et al. [36], to compare the accuracy of normalized spleen and renal ADC, they reported significant reduction of normalized renal ADC (R-ADC) with higher fibrosis stages at variable b value with higher accuracy at b = 600 s/mm^2 ($r = -0.697$; $p < 0.001$), they showed that R-ADC at 3 T with b-value of 600 s/mm^2 might be more accurate than normalized spleen R-ADC in prediction of hepatic fibrosis.

On the other hand another study [38] compared the diagnostic accuracy of using the spleen and renal cortex as reference organ for normalized liver ADC. They showed that the S-ADC has a higher accuracy in the diagnosis of liver fibrosis in comparison to liver ADC and R-ADC. S-ADC had higher accuracy also in detection of fibrosis stage 2, 3 and 4. They also showed stronger correlation between fibrosis stage and S-ADC compared to liver ADC and R-ADC ($r = -0.71, -0.51, -0.41$ respectively; $P < 0.01$).

In this study, we found a significant negative correlation between each of ADC, S-ADC and R-ADC with the fibrosis grade. This correlation was higher in S-ADC ($r = -0.75$, $p < 0.001$) than R-ADC ($r = -0.68$, $p < 0.001$), and more powerful for R-ADC compared to liver ADC.

In current study, the mean S-ADC value was significantly lower in patients with different hepatic fibrosis stages in comparison to control group except for stage 1 (P 0.02–<0.001). It could significantly differentiate stage 0 from stage 2, 3, and 4 as well as stage 4 from all other stages, while no significance was noted between the other stages. S-ADC has a significant ability to differentiate between stages 0–1 Vs stage 2–4, stage 0–2 Vs stage 3–4 as well as stage 0–3 Vs stage 4.

This enhanced the opinion of the previous report [37] for encouraging the usage of the spleen as a reference organ in order to increase the capability of ADC in the detection of cirrhosis. In that study Absolute hepatic ADCs in cirrhosis were lower than normal livers but not reaching significant levels ($1.67 \pm 0.26 \times 10^{-3}$ versus $1.81 \pm 0.36 \times 10^{-3}$ mm^2/sec, $p = 0.33$) while they reported significant R-ADC differences between cirrhotic and non-cirrhotic cases (1.25 ± 0.22 vs. 1.55 ± 0.22, $p = 0.02$). The authors proposed a cutoff <1.4 to have a specificity and sensitivity of 80% and 78% respectively in the diagnosis of cirrhosis. They concluded that normalized liver ADC may be of value in the detection of early cirrhotic changes in normal appearing liver on conventional MR images.

This is also in consistent with an earlier report [10] which showed the inability of the liver ADC discriminate between different fibrosis stages except between 0 and 4.

On the other hand S-ADC had a significant difference between normal livers and stage 2–3 (intermediate fibrosis) and stage 4 (cirrhosis). Also significant difference was detected between stage 1 and 4. A trend toward significance was noted between stages 0 and 1 ($p = 0.051$) and stages 1 and 3 ($p = 0.06$). Some previous studies using liver ADC had estimated AUC values of 0.655–0.790, 0.689–0.92 and 0.720–0.93 for the detection of liver fibrosis stage $\geqslant 2$, stage $\geqslant 3$ and cirrhosis respectively [10,11,13,14].

In an earlier report [10] ROC analysis showed the superiority of S-ADC in comparison to liver ADC in the detection of stage $\geqslant 2$ (AUC: 0.864 Vs 0.655; $p = 0.013$) and stage $\geqslant 3$ (0.805 Vs 0.689; $p = 0.015$), while no significant difference was found in patients of cirrhosis (0.935 vs. 0.720; $p = 0.185$).

In the current study, ROC analysis showed higher performance using S-ADC in comparison to liver ADC and R-ADC while R-ADC had higher performance in comparison to liver ADC. The AUC, sensitivity, specificity, PPV, NPV and k-value for detection of fibrotic stages $\geqslant 2$ (0.85, 95.8%, 60%, 74%, 92% and 0.85 for S-ADC Vs 0.68, 66.7%, 60%, 66%, 60% and 0.28 for ADC and 0.85, 95.8%, 50%, 69%, 91% and 0.47 for R-ADC).

In the detection of fibrotic stages $\geqslant 3$, ROC analysis showed higher performance using R-ADC in comparison to liver ADC while S-ADC had a higher performance than both liver ADC and R-ADC. The AUC, sensitivity, specificity, PPV, NPV and k-value (0.86, 100%, 52%, 61%, 100% and 0.48 for S-ADC Vs 0.63, 63%, 52%, 50%, 65% and 0.14 for ADC and 0.88, 100%, 44%, 57%, 100% and 0.40 for R-ADC).

In fibrosis stage 4, S-ADC had an overall higher performance also in comparison to liver ADC and R-ADC while R-ADC had a higher performance in comparison to liver ADC. The AUC, sensitivity, specificity, PPV, NPV and k-value (1, 100%, 100%, 100%, 100% and 1 for S-ADC Vs 0.7, 81%, 54%, 37%, 90% and 0.26 for ADC and 0.65, 100%, 65%, 45%, 100% and 0.43 for R-ADC).

The current results are also in consistent with the previous report [38] which concluded that the usage of spleen for normalization of liver ADC can improve the potential accuracy in the detection of liver fibrosis in comparison to liver ADC and renal normalized liver ADC.

We had some limitations in current study. Variability of interval time between MRI performance and biopsy taking (mean delay, 30 days; range, 10–52 days) during which the fibrosis may undergoes progression or alteration of its degree due to ongoing medical treatment. Small number of subjects enrolled in this study was another obstacle.

In conclusion, the current results highlighted the value of application of normalized liver ADC using the spleen and kidney as reference organs to increase the performance of ADC measurement in the evaluation of liver fibrosis. Spleen normalized ADC had the highest performance power over ADC and renal normalized ADC. The usage of this tool has a promising result in the assessment of liver fibrosis that may assist to avoid or at least reduce the liver biopsies in some patients.

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