The diagnostic value of normalized ADC using spleen as reference organ in assessment liver fibrosis

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Abstract

Background: To investigate the value of liver ADC normalization using spleen as a reference organ in liver fibrosis assessment compared to Fibroscan.

A total of 60 participants were included, 30 HCV positive patients and 30 in control group. We calculated mean spleen apparent diffusion coefficient (ADC), liver mean ADC, and normalized liver ADC (defined as the ratio of liver ADC to spleen ADC) which were compared between cirrhotic patients and the control group. Data was analyzed, and ROC was used to evaluate the performance of nADC.

Results: No significant difference between spleen ADC values of patient and control groups or in-between different fibrosis stages. A negative correlation between liver ADC and nADC values with increasing fibrosis stages. We also found that the mean liver ADC and nADC value in patients with hepatic fibrosis were significantly lower than that of control group (1.53×10^{-3} mm^2/s vs 1.65×10^{-3} mm^2/s). After analysis with ROC, nADC shows higher diagnostic performance compared to liver ADC. nADC area under the curve (AUC) was 0.878 for detection of stage ≥ F2 with sensitivity and specificity of 87% and 80% respectively while ADC AUC was 0.548 with sensitivity and specificity of 62% and 72% respectively ($p = 0.021$); ≥ F3 AUC of nADC was 0.891 with sensitivity and specificity of 88.7% and 80% respectively while ADC AUC is 0.603 with sensitivity and specificity of 72% and 72% respectively ($p = 0.023$), and F4 stage nADC AUC was 0.879 for with sensitivity and specificity of 90% and 80% respectively, while ADC AUC was 0.648 with sensitivity and specificity of 80% and 72% respectively ($p = 0.054$).

Conclusion: Normalized liver ADC using the spleen as reference organs increases the diagnostic performance of MR in evaluation liver fibrosis compared to ADC alone.

Keywords: MRI DWI, Hepatitis C virus, Liver fibrosis, Liver cirrhosis, Fibroscan

Background

HCV (hepatitis C virus) causes liver cell injury which may be acute or chronic. In the chronic stage, the injury by fibrous tissue accumulates in extracellular space. Hepatitis C viral infection is the most common cause of liver fibrosis in Egypt [1].

Liver fibrosis plays a rule in other liver lesions pathogenesis as HCC (hepatocellular carcinoma), portal hypertension, and cirrhosis [2].

The assessment of liver fibrosis in patients with viral hepatitis is essential to follow-up on the disease progression as well as to detect patients who need antiviral treatment [3].

Liver biopsy is the gold standard for evaluating changes in fibrosis. It is considered a safe procedure but still invasive and had some contradictions and complications [4]. So, we needed a non-invasive procedure that offers a safe, fast, and reproducible way for assessing hepatic fibrosis to monitor the response of treatment [5].

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Non-invasive radiological methods that were investigated are Fibroscan, (MRE) magnetic resonance elastography, diffusion-weighted imaging (DWI), perfusion-weighted imaging, and MR spectroscopy [6].

Fibroscan is a non-invasive method for evaluating liver fibrosis in chronic liver injury. However, it has some limitations in different situations as in obese patients, ascites, and narrow intercostal spaces [7].

Diffusion-weighted imaging (DWI) is also a promising non-invasive method as it assesses tissue diffusivity which is being low in HCV patients with fibrosis due to the accumulation of fibrous tissue within the extracellular matrix. Multiple studies confirmed this hypothesis as patients with livers fibrosis had low ADC compared to normal individuals [8].

However, other studies revealed using different b values could lead to variable ADC measurements as well as breathing methods like breath-hold, free-breathing, or respiratory triggered techniques, which can affect ADC quantification [9].

To reduce the variability of ADC values, researchers suggested that normalization of ADC using a reference organ that remains relatively constant across patients or systems could be the solution to this problem. Multiple studies showed that normalized ADC (using the spleen) as reference organ improves the diagnostic performance in assessing liver fibrosis than using ADC alone. The spleen may be an ideal reference organ because it maintains a relatively stable ADC even in the setting of liver disease [10].

Methods
Subjects
A total of 30 HCV patients were included in the study after obtaining approval from the local ethics committee and informed consent from the patients. The clinical diagnosis of all the patients was established based on the patient's clinical symptoms, physical findings, and laboratory tests. The ADC values of the patients were compared with their normal counterparts. The control group for this study consisted of another 30 patients who underwent abdominal MRI owing to pancreatic, adrenal, and renal pathology but who had no known hepatic disorders.

Technique of Fibroscan
All patients were examined by TE, transient elastography (Fibroscan®502; Echosens, Paris, France). Measurements of liver stiffness were performed by 5 years experienced internist on the right lobe of the liver through intercostal spaces in correspondence to the mid-axillary line, while patients are lying in the supine position with the right arm in maximal abduction. A median of 12 valid readings was calculated. The results were expressed in

kilopascals (kPa) and interpreted as follows: F0 (control group), < 5 kPa; F1, 5–7 kPa; F2, 7–9.5 kPa; F3, 9.5–12.5 kPa; and F4, > 12.5 kPa.

MRI examination
1.5T machine (Achieva, Philips medical system, Eindhoven, Netherlands), using Torso phased-array coil to acquire DWI of liver and spleen, three b values were taken of 0, 400, 800 mm²/s, then on FujifiLN, synapse 3D, and V4.4EU. We calculated mean spleen apparent diffusion coefficient (ADC), liver mean ADC, and normalized liver ADC (defined as the ratio of liver ADC to spleen ADC) which were compared between cirrhotic patients and patients in the control group

The examination protocol included
DWI performed using single-shot echo-planar imaging (EPI) fat suppressed sequence in the axial plane, during a single end-expiratory breath-hold, using b values of 0, 400, and 800 s/mm² using the following parameters (Table 1).

Quantitative image analysis
A single radiologist with 3 years of experience in body MR imaging drew regions of interest (ROIs) on DWI, and they were identically positioned on corresponding ADC maps by applying the copy and paste functions of the PACS system at the same points measured by the Fibroscan. The surface area of the ROIs was 20 mm². Five ROIs inserted on the liver one at the left lobe, one at the caudate lobe, and 3 separate points in the right lobe as follows: one at the anterior segment and two at the posterior segment, one at segment 6, and other at segment 7. The mean hepatic ADC value was calculated by taking the mean of the total of five ADC measurements obtained. For the spleen ADC measurements, a circular ROI of approximately 20 mm² was used. The measurements were taken from parenchyma areas at

Table 1 DWI performed using single-shot echo-planar imaging (EPI) fat suppressed sequence in the axial plane, during a single end-expiratory breath-hold, using b-values of 0,400, and 800 s/mm2 using the following parameters

	DWI
TR (ms)	1,600–3,400
TE (ms)	80
SNR	0
NEX	2
ST (mm)	3
Gap (mm)	0
FOV (cm)	421
Matrix	Up to 256 × 256

least 1 cm away from the capsule and not crossing major vascular structures as far as possible. Three ROIs were drawn as one each from the inferior pole, the interpolar section, and the superior pole. The mean spleen ADC value was calculated from the mean of the three measurements (Fig. 2). Then, normalized ADC value was calculated by dividing mean liver ADC over mean spleen ADC.

Data management and analysis
The collected data was revised, coded, tabulated, and introduced to a PC using Statistical package for Social Science (SPSS 20). Data was presented, and suitable analysis was done according to the type of data obtained for each parameter.

Analytical statistics
One tailed t-test is to compare between control and patients' groups.

Mann-Whitney test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.

Correlation analysis (using Spearman's method) is to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r_s r" defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables. Liver ADCs, spleen ADCs, and normalized liver ADCs were correlated with fibrosis scores.

The ROC curve (receiver operating characteristic) provides a useful way to evaluate the sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups.

Differences in ADC values were statistically significant when $p < 0.05$.

Results
Total participants are 60 in this study: 30 controls (19 females and 11 males of mean age 34 ± 10 years) and 30 patients: 16 females and 14 males with mean age 47 ± 11, F1 ($n = 6$), F2 ($n = 6$), F3 ($n = 8$), and F4 ($n = 10$).

There was significant difference between the mean liver ADC value of the liver in the control group (1.65×10^{-3} mm^2/s) compared to patients (1.53×10^{-3} mm^2/s with $p = 0.04$). As well as the nADC, there was significant difference between cases (nADC = 1.39) and controls (nADC = 1.87 with $p = 0.006$) (Table 2).

Correlations between fibrosis stage, liver ADC, and normalized liver ADC

- Mean ADC of the liver and nADC value show negative correlation with increasing fibrosis stages (Table 3 and Fig. 1), but there were some overlaps in different stages of fibrosis.

Correlations between fibrosis stage and spleen ADC
There was no significant difference between mean spleen ADC values among participants with different fibrosis stages (Fig. 2).

Correlations between liver ADC, normalized ADC, and spleen ADC

- There was no significant correlation between mean liver ADC or nADC and mean spleen ADC in the 30 cases (Fig. 3).

Differentiating fibrosis stages using ADC and nADC

- Mean liver ADC could not differentiate each individual stages of fibrosis except between F0 versus F4.
- nADC has significant differences between F0 and F2, F3, and F4 (Table 4).

Diagnostic performance of ADC and nADC using of receiver operating characteristic (ROC) curve analysis for each stage
According to ROC analysis, nADC exhibited a good diagnostic performance for each stage of fibrosis, with AUCs higher than those of ADC.

The optimal cut-off values of nADC liver and ADC for each fibrosis stages are shown in Table 5.

Table 2 Mean liver and spleen ADC and nADC in control and patients' groups

		Control group (No=30)	Patient group (No=30)	t-test	P-value	Sig
Mean ADC liver	Mean±SD	1.65±0.9	1.53±0.41	1.72778	0.0468*	S
	Range	0.9-2.3	0.9-2			
Mean ADC spleen	Mean±SD	0.85±1.61	1±0.33	1.29422	0.242	NS
	Range	0.6-1.8	0.8-1.7			
Normalized ADC	Mean±SD	1.87±0.50	1.39±0.49	-6.12057.	0.001*	S
	Range	1.1-3	0.94-2			

One tailed T-Test, P*=significant

Table 3 Negative correlation was noted between liver ADC value as well as nADC with increasing fibrosis stage

Fibrosis stage	NO	Mean Liver ADC ($\times 10^{-3}$ mm^2/s)	Mean Spleen ADC ($\times 10^{-3}$ mm^2/s)	Mean nADC
Control group F0	30	1.65	0.87	1.8
F1	6	1.59	1.1	1.45
F2	6	1.55	1.13	1.42
F3	8	1.5	1	1.4
F4	10	1.48	1	1.38
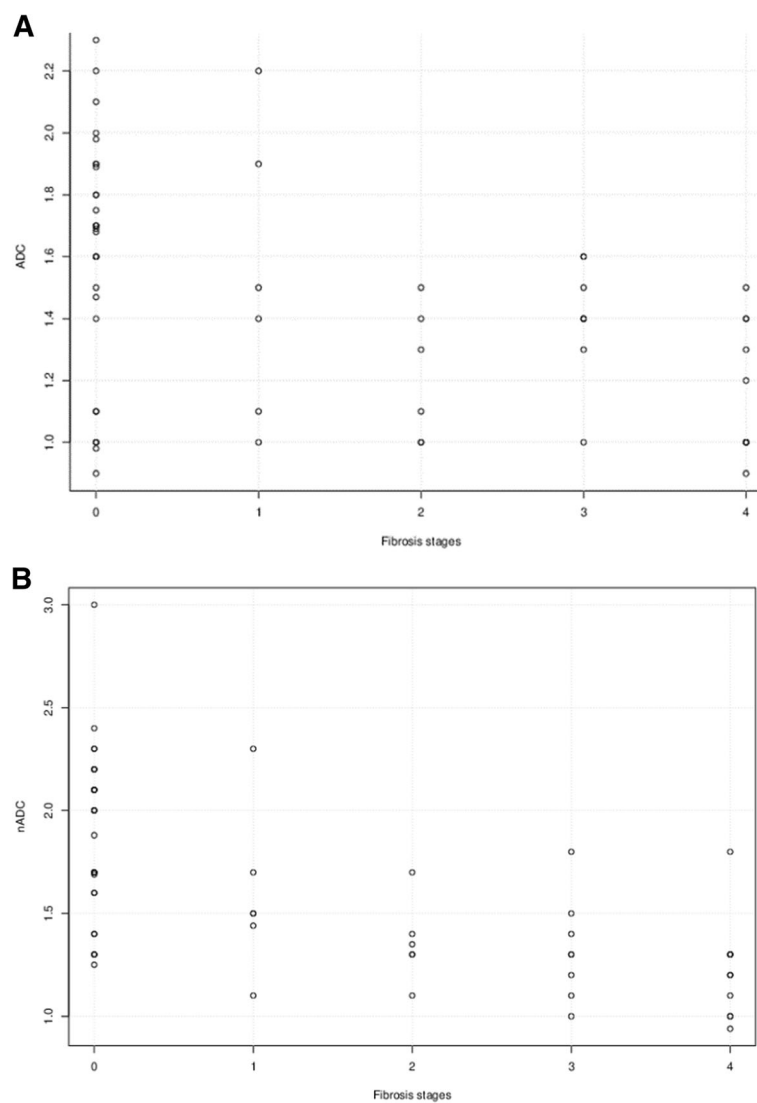
Fig. 1 a, **b** shows negative correlation between mean liver ADC of control group and different fibrosis stages groups. (Spearman's rank correlation coefficient rs = -0.6 ,95% CI: −0.446–0.015, p = 0.0374), also negative correlation between nADC of control group and different liver fibrosis stages groups. (Spearman's rank correlation coefficient rs = - 0.82 ,95% CI:−0.634–0.285, p <0.001)
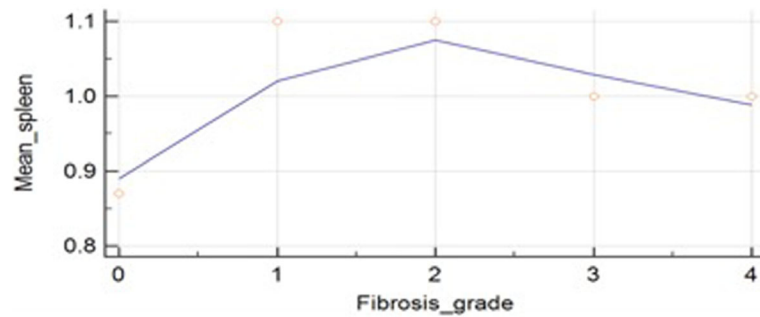
Fig. 2 Shows no significant correlation between mean spleen ADC in different fibrosis stages. (Spearman's rank correlation coefficient rs = 0.105; 95% CI: −0.153–0.350, p = 0.866).
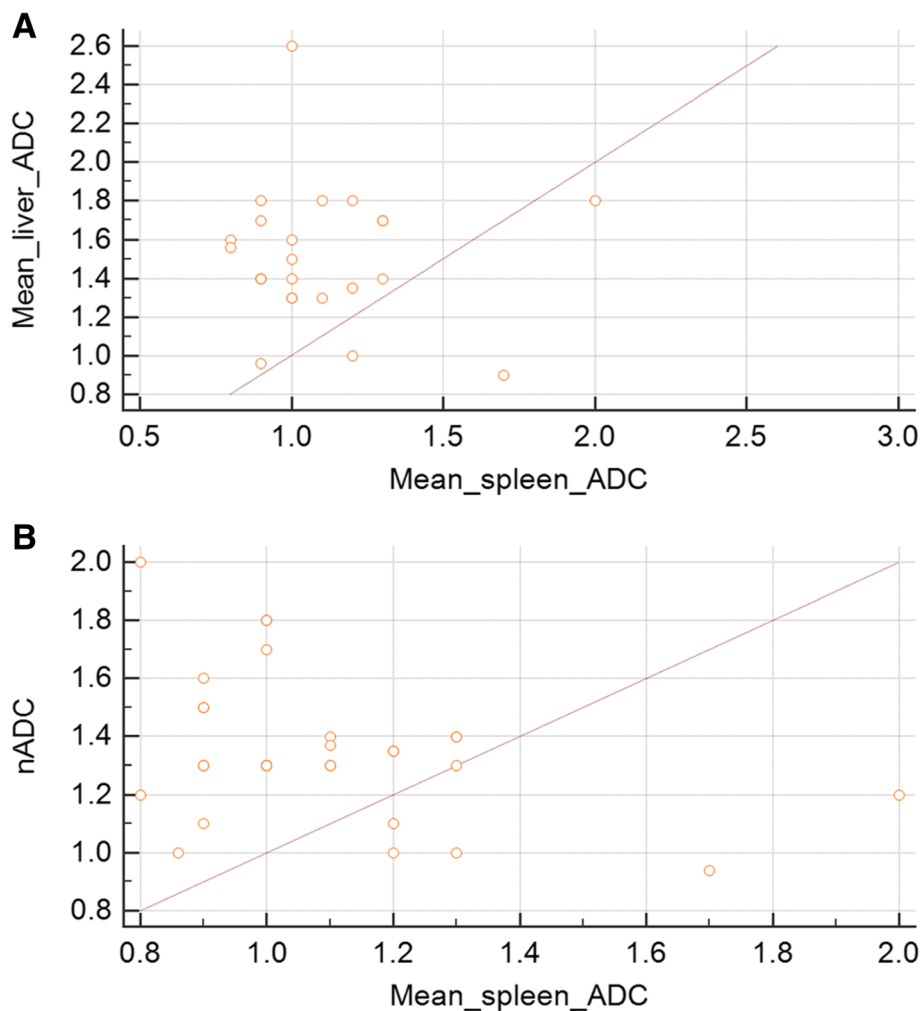
Fig. 3 a, **b** shows no significant correlation between liver and mean spleen ADC (n = 30) of patients with different stages of fibrosis (Spearman's rank correlation coefficient rs = 0.00335; 95% CI: −0.357–0.363, p = 0.9), also no significant correlation between nADC and mean spleen ADC(Spearman's rank correlation coefficient rs = - 0.225; 95% CI: −0.538–0.125, p = 0.1743). (Image quality adjusted)

Table 4 ADC and nADC comparison among different fibrosis stages

Fibrosis stage	Liver ADC p-value	nADC p-value
F0 vs F1	0.63836	0.05574
F0 vs F2	0.5485	0.01287*
F0 vs F3	0.13888	0.00138.*
F0 vs F4	0.02869*	0.00026*

*=significant *p*-value using Mann-Whitney U Test

Comparing diagnostic performance of liver apparent diffusion coefficient (ADC) versus normalized liver ADC for detection of fibrosis stages ≥ F2, ≥ F3, and F4 using ROC curves analysis

According to ROC curves analysis, nADC liver exhibited a good diagnostic performance for moderate (> F2) and severe (> F3) fibrosis stages compared to ADC as they show a larger area under the curve (AUCs) (Table 6, Fig. 4). There is a statistically significant difference between the area under the receiver operating characteristic curve (AUC) of nADC liver vs ADC liver except for the F4 stage; our results were as follows (Figs. 5, 6, 7):

Table 5 The optimal cut-off values of nADC liver and ADC for each fibrosis stages

Variable	ADC	nADC liver
F0 vs F1		
Optimal cut-off value	1.55 ($\times 10^{-3}$ mm²/s)	1.44
Sensitivity (%)	70%	83%
Specificity (%)	66%	67%
AUC (95% CI)	0.588(379 to 775)	0.717(507 to 874)
F0 vs F2		
Optimal cut-off value	1.53 ($\times 10^{-3}$ mm²/s)	1.41
Sensitivity (%)	72%	84%
Specificity (%)	55%	66%
AUC (95% CI)	0.617(407 to799)	0.729(520-883)
F0 vs F3		
Optimal cut-off value	1.51 ($\times 10^{-3}$ mm²/s)	1.4
Sensitivity (%)	80%	80%
Specificity (%)	50%	75%
AUC (95% CI)	0.644(442-818)	0.739(565-902)
F0 vs F4		
Optimal cut-off value	1.49 ($\times 10^{-3}$ mm²/s)	1.38
Sensitivity (%)	80%	90%
Specificity (%)	72%	80%
AUC (95% CI)	0.648(453-812)	0.879(589-908)

1. Fibrosis stage ≥ F2, 0.878 vs 0.548 (*p* = 0.021);
2. Fibrosis stage ≥ F3, 0.891 vs 0.603 (*p* = 0.023); and
3. Fibrosis stage F4, 0.879 vs 0.648 (*p* = 0.054).

In our study, normalized ADC was done on a single patient with moderate ascites, but he was excluded as Fibroscan results are not accurate in cases with ascites. It was classified as F4 by Fibroscan while mean liver ADC value = 1.5 and mean spleen ADC = 1.07 and nADC = 1.4 (Fig. 8).

Discussion

Hepatitis C virus (HCV) is the main agent of post-transfusion chronic hepatitis and liver fibrosis[11]. The highest incidence of HCV infection in the world is in Egypt [12], which makes a need for different laboratory and radiological methods to asses liver injury [13].

In the last few years, Fibroscan was considered as a fast, safe, and reproducible procedure to assess liver stiffness to predict liver fibrosis stage[14–16].

However, Fibroscan cannot be used in obese patients, ascites, and narrow intercostal spaces [17].

Diffusion-weighted imaging enables qualitative and quantitative assessment of tissue diffusivity. Random motion of water molecules in the liver can be quantified by calculation of the apparent diffusion coefficient (ADC). The ADC of livers with moderate or advanced fibrosis and cirrhosis has been reported to be lower than that of normal livers or livers with mild fibrosis across multiple studies [18].

DWI is a crucial sequence in the MR abdomen, but the lack of standardization of DWI acquisition techniques is a major limitation of more broad and uniform use of ADC measurements as a quantitative biomarker. The variability in reported ADC values is further complicated by the use of different *b* values and acquisition methods based on breath-hold, free-breathing, or respiratory triggered techniques, which can affect ADC quantification and that should have influenced all of the abdominal organs scanned, including not only the liver, but also the spleen, pancreas, kidney, and paraspinal muscle. So, in our study as well as previous studies, we assume that normalization using a reference organ would not be affected by different respiratory motion compensation techniques [19].

Many researchers have tried to evaluate the impact of the apparent diffusion coefficient (ADC) measurements in the assessment of liver diseases. Many studies show that the cirrhotic livers are of lower ADC values than the healthy livers [20]. This is consistent with our study as we also demonstrated a linear negative correlation between liver ADC value and fibrosis stages (*r* = − 0.63).

Table 6 nADC liver exhibited good diagnostic performance for each stage of fibrosis Compared to ADC liver

Liver ADC				nADC			
Stage	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	p-value
≥2	0.548	62%	72%	0.878	87%	80%	0.021
3-4	0.603	72%	72%	0.891	88.8%	80%	0.023
4	0.648	80%	72.2%	0.879	90%	80%	0.054

We also found that the mean liver ADC value in patients with hepatic fibrosis was significantly lower than that of volunteers (1.47×10^{-3} mm^2/s vs 1.65×10^{-3} mm^2/s, $p = 0.04$) [21, 22].

In another study done by Sandrasegaran et al. [23], ADC was able to differentiate cirrhotic from the non-cirrhotic liver with lower ADC values of the former; however, in that study, ADC could not categorize liver fibrosis in different stages; this is also confirmed by Razek et al. [24]. Earlier study done by Do et al. [25] concluded that liver ADC failed to distinguish individual stages of fibrosis, except between stages 0 and 4 mm; these results are the same to ours.

The variability in reported ADC values is further complicated using different b values and acquisition methods based on breath-hold, free-breathing, or respiratory triggered techniques, which can affect ADC quantification [26, 27]. For example, in our study, mean liver ADC ($b = 800$) for the control group was $1.65 \pm 0.44 \times 10^{-3}$ mm^2/s and nADC liver 1.87 ± 0.50, while in a recent study done by Shin et al. [28], the mean liver ADCs for the control group (F0) was 1.389×10^{-3} mm^2/s, and nADC liver was 1.977.

In the study carried out by Kim et al. [29], there was no difference between spleen ADCs values between diseased and volunteers' individuals. This supports our results as there was no significant difference between spleen ADC values among patients in comparison to control ($1 \pm 0.33 \times 10^{-3}$ mm^2/s vs $0.85 \pm 1.61 \times 10^{-3}$ mm^2/s, $p = 0.24$); also, there was no significant difference in the spleen ADC between different stages of fibrosis ($r = 0.105$; $p = 0.866$).

Pervious results of Do et al. [25] showed that area under ROC curve values of nADC were higher than liver ADC values. AUC of nADC ≥ F2 stages was 0.864 with sensitivity and specificity of 90% and 77% respectively while ADC values were 0.655 with sensitivity and specificity of 61% and 61% respectively ($p = 0.013$); AUC of nADC ≥ F3 stages was 0.805 with sensitivity and specificity of 96% and 71% respectively while ADC values were 0.689 with sensitivity and specificity of 56% and 71% respectively ($p = 0.015$), and nADC AUC for F4 stage was 0.935 with sensitivity and specificity of 95% and 66% respectively while ADC AUC was 0.720 with sensitivity and specificity of 76% and 60% respectively ($p = 0.185$).

While our study reveals close results, there was a statistically significant difference between area under the receiver operating characteristic curve (AUC) of
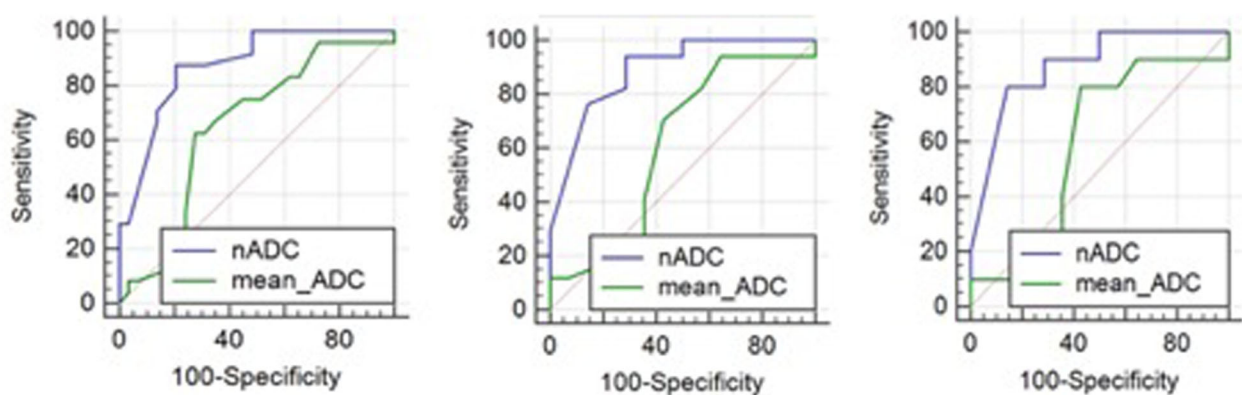

Fig. 4 Receiver operating characteristic curves (ROC) for liver apparent diffusion coefficient (ADC; green line) and normalized liver ADC (blue line). It differentiates the patients into different fibrosis stages (A-detection of stage ≥ 2, left curve; B-detection of stage ≥ 3, middle curve; C-detection of cirrhosis [stage 4], right curve)
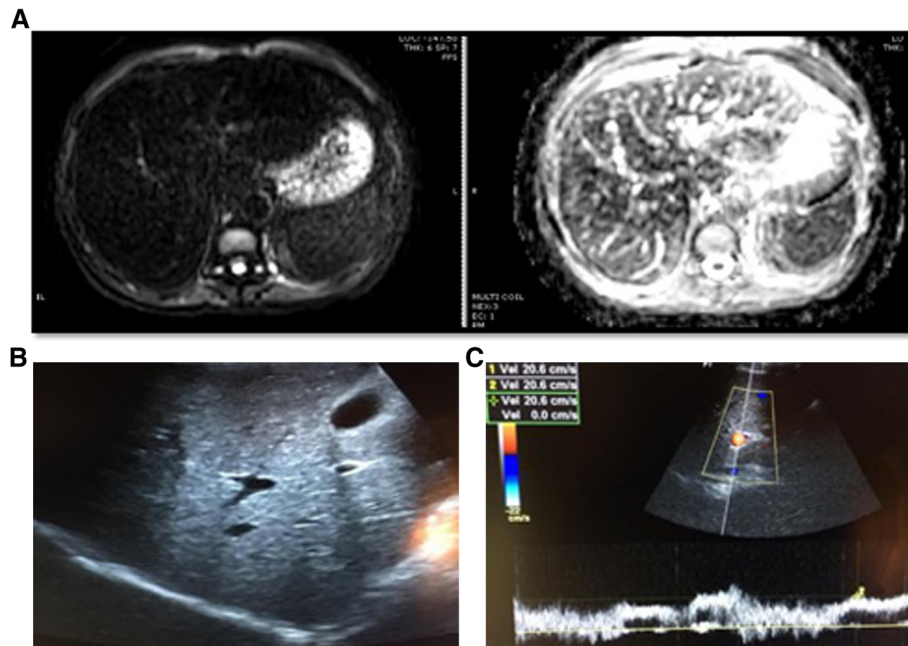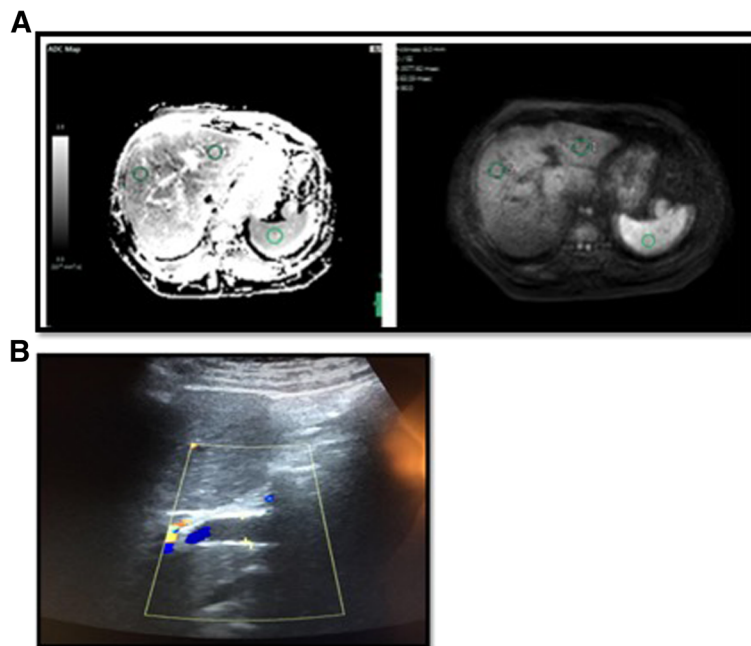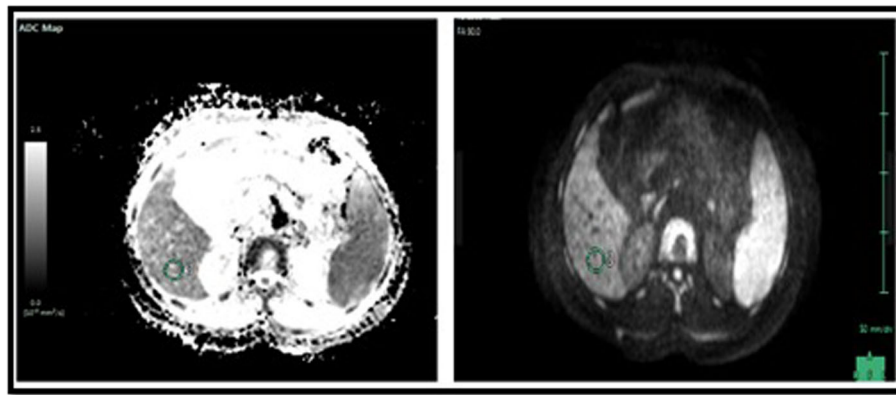
Fig. 5 a 35 years old HCV positive female patient, underwent Fibroscan with 6 kPa which was classified as F1 stage (F1=5-7 kPa), His diffusion study: reveals mildly enlarged liver with no focal lesions. The spleen was of average size with no focal lesions (**a**)-DWI at b = 800- and (**b**)-ADC map, revealed mean liver ADC = 0.95 × 10−3 mm2/s and spleen mean ADC= 0.66× 10−3 mm2/s so normalized ADC= 1.45(F1 nADC cut off = 1.44). **b** & **c** -His ultrasound study reveals (**b**)-mild hepatomegaly (16 cm) with no cirrhotic features or focal lesions and (**c**)-portal vein shows average calibre with the hepatopedal flow(numbering adjusted)

Fig. 6 a- 53 years old HCV positive male patient underwent Fibroscan with 6.3kPa which was classified as F1 stage. (F1=5-7 kPa), his Diffusion study: reveals mildly enlarged liver with no focal lesions. The spleen was of average size with no focal lesions. (**a**)- ADC map, and (**b**) - DWI at b = 800- reveals liver mean ADC = 2.4 × 10−3 mm2/s, and spleen mean ADC = 1.7× 10−3 mm2/s so normalized ADC= 1.429(F1 nADC cut off =1.44). **b**- His ultrasound study reveals mild hepatomegaly (16.5 cm) with no cirrhotic features or focal lesions. (**c**)-There was periportal fibrosis that can explain the low normalized ADC value as by further researches there might be subtypes in one stage

Fig. 7 45 years old HCV positive female patient, underwent Fibroscan with 14.5 kPa which was classified as F4stage. (F4 > 12.5 kPa). His diffusion study reveals enlarged liver with cirrhotic features denoted by nodular hepatic surface, enlarged left lobe and deep fissures yet no focal lesions. The spleen was enlarged in size with no focal lesions. (**a**)-ADC map, and (**b**) - DWI at b = 800- reveals liver mean ADC = 1.6 × 10−3 mm2/s, and spleen mean ADC = 1.7× 10−3 mm2/s so normalized ADC= 0.94. (F4 nADC cut off =1.38)

normalized liver ADC and ADC for all comparison's subsets except for diagnosis of cirrhosis (stage 4). nADC AUC was 0.878 for detection of ≥ F2 stages with sensitivity and specificity of 87% and 80% respectively while ADC value was 0.548 with sensitivity and specificity of 62% and 72% respectively (p = 0.021); nADC AUC for ≥ F3 stages was 0.891 with sensitivity and specificity of 88.7% and 80% respectively while ADC values were 0.603 with sensitivity and specificity of 72% and 72% respectively (p = 0.023), and F4 stage nADC AUC was 0.879 with sensitivity and specificity of 90% and 80% respectively, while ADC values were 0.648 with sensitivity and specificity of 80% and 72% respectively (p = 0.054). We acknowledge some limitations in current study as small number of subjects enrolled in this study and the lack of biopsy.

Conclusion

Using the spleen as a reference organ to calculate the normalized liver ADC increases the diagnostic performance of liver fibrosis than using ADC alone.

Recommendation

- We recommend using normalized ADC as a valid non-invasive option to diagnose and stage liver fibrosis in hepatitis C patients. It can be used in obese, ascetic, or narrow intercostal space patients.
- Further studies are recommended with large participants' number and to be correlated with liver biopsy results.
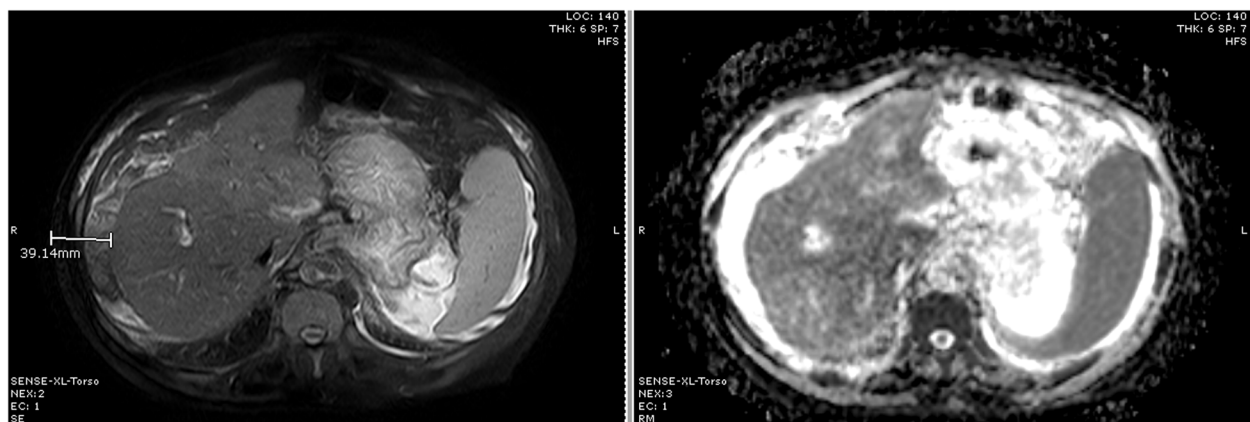- There is a potential of subgrouping each stage using color Doppler with the DWI.

Fig. 8 Excluded case as there was moderate amount of ascites, it was classified as F4 by Fibroscan while mean liver ADC value =1.5 and mean spleen ADC=1.07 and nADC=1.4

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