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Role of abbreviated MRI protocol for screening of HCC in HCV related cirrhotic patients prior to direct-acting antiviral treatment

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Abstract

Background: Chronic HCV infection is a global health problem causing progressive hepatic fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC). Recent advantage of direct-acting antiviral drugs (DAA) with a high sustained virologic response (SVR) reduces overall HCV-related morbidity and mortality, yet recent studies report a high recurrence rate of HCC after DAA; this calls availability of a reliable screening method to properly exclude HCC before DAA treatment.

The primary objective of our cohort study was to assess the feasibility of an abbreviated MRI protocol as a screening tool for the detection of hepatic focal lesions/early HCC in patients with HCV-related liver cirrhosis.

The study included 41 patients with HCV-related cirrhosis candidates to DAA therapy. All patients underwent routine screening for HCC by combined abdominal ultrasound and serum alfa-fetoprotein. An abbreviated MRI protocol (Abr-MR) including combined T2-weighted image and diffusion-weighted imaging (DWI) followed by dynamic contrast-enhanced MRI (CE-MRI) was performed for all subjects, assessing for presence and characterization of focal lesions.

Results: For all included 41patients, no elevation of the alpha-fetoprotein was shown. Ultrasound detected a single focal lesion in one patient. Abbreviated MR demonstrated 15 focal lesions; for detected lesions, 1 lesion shows "shine though" and the rest showing moderate and high degrees of restriction. CE-MRI characterized lesions as 1 lesion = LIRADS-1, 3 lesions = LR-M, and 11 lesions = LR-5.The standard screening using combined ultrasound and alpha-fetoprotein had sensitivity, specificity, PPV, and NPV of 6.6 % (95% CI = 0.0034–0.29), 100% (95% CI = 0.89–1.000), 100% (95% CI = 0.051–1.000), and 68.8% (95% CI = 0.54–0.80). Abr-MR protocol showed sensitivity, specificity, PPV, and NPV of 100% for all parameters (95% CI = 0.79–1.000, 0.89–1.000, 0.79–1.000, and 0.89–1.000 respectively).

Conclusion: In our study, we demonstrate the superiority of a proposed cost-effective Abr-MR protocol in the detection of hepatic focal lesions and small-sized HCC compared to routine screening using alpha-fetoprotein and ultrasound in HCV-related liver cirrhosis.

Keywords: Ultrasound, Diffusion-weighted MRI, Hepatocellular carcinoma, Direct-acting antiviral

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Background

Chronic HCV infection is a global health problem that affects millions of people worldwide. HCV is associated with several hepatic and extra hepatic disorders, including several malignancies like colon cancer and cancer esophagus .The burden of HCV-related disorders is influenced by the number of new and existing cases and the natural history of the infection. The natural history of HCV is affected by several demographic, virological, clinical, and lifestyle factors [1]. In patients with chronic HCV infection, progressive hepatic fibrosis leading to cirrhosis (in 15–35% of patients after 25–30 years duration) is responsible for most of HCV-related morbidity and mortality, including hepatocellular carcinoma (HCC) [1]. In several cohort studies, the risk of HCC in HCV-infected people was tenfold higher compared to HCV-negative individuals, and risk estimates of 20–25-fold have been reported in case-control studies. Once HCV-related cirrhosis is established, HCC develops at an annual rate of up to 8% (average 2–3%), thus making cirrhosis an important precancerous condition. The interval from infection to HCC has been estimated to be 30 years, although latent periods of 40–50 years have been observed [2].

International guidelines for screening of HCC in cirrhotic patients suggest an ultrasound every 6 months as the first level of investigation. The main goal is diagnosing early HCC/dysplastic nodule; however, such a goal remains difficult due to the low sensitivity of such protocol (60%) [3].

HCC is unique in having imaging characteristics on contrast-enhanced computed tomography (CE-CT) or contrast-enhancing magnetic resonance imaging (CE-MRI) allowing for its accurate diagnosis. This primarily depends on the enhancement criteria of the suspected lesion relative to the background liver in the hepatic arterial, portal venous, and subsequent phases [4].

Hence, CE-CT/CE-MRI is most widely used for characterizing HCC in patients with cirrhosis. This is due to the increased ability of arterial phase enhancement to visualize early, small lesions. Although the sensitivity of helical CT for depicting hepatocellular carcinoma in patients with cirrhosis has been well documented to be from 50 to 70%, CE-MRI has shown higher figures of sensitivity and specificity for HCC detection and characterization especially for early/small-sized HCC [5].

However, MRI examinations have limited accessibility, high cost, long scan time, and the risk of contrast-related side effects. When performed without the use of contrast agents, the risk of contrast-related adverse events is eliminated, and both the cost and examination time can be reduced. With this in mind, non-contrast MRI is potentially a good alternative surveillance tool for HCC [6].

Considering non-enhancing MRI adding diffusion-weighted imaging (DWI) improves detection and—to an extent—characterization of HCC. Hence, DWI carries a potential capacity for improving patient care through its capacity of insight into tumor biology [7].

Methods

patients

A prospective study done on forty-one patients with liver cirrhosis recruited from the HCV clinic at the hospital institution. The procedure was explained in full, and the informed consent was signed by them. The study was conducted during the period from May 2018 to April 2019.

Inclusion criteria

- HCV positive patients with liver cirrhosis are candidates for antiviral therapy

Exclusion criteria

- Other causes of liver cirrhosis (HBV, NASH, alcoholic liver cirrhosis, immune-related, primary biliary cholangitis, sclerosing cholangitis, and idiopathic causes of liver cirrhosis)
- Contraindication for MRI (electronic pacemakers, MRI incompatible implanted devices, intolerant patients)
- Previous locoregional therapy for focal lesion
- Contraindication to MR contrast administration(GFR < 30 ml/min)

Technique

All patients are subjected to clinical and laboratory assessment, including viral markers, liver function tests, HCV-PCR, and serum alpha-fetoprotein assay.

A liver ultrasound was performed by using (GE healthcare) machine with curvilinear probe (3–5 MHz) and applied gel on patient lying supine on the examination table.

After completion of the sonographic assessment, MRI examinations were performed including the Abr-MRI and CE-MRI protocols. The MR performed with 1.5 T machine (Philips Achieva; Philipsmedical systems, Eindhoven, Netherland), using 16-channel phased-array torso coil (Sense XL Torso; Philips Healthcare) covering the length of the abdomen.

Patients were positioned supine—head first—on the MRI table, then the abbreviated MRI (Abr-MR) was performed including T2 weighted fast spin-echo (T2-FSE) and T2 weighted imaged spectral resaturation with inversion recovery (T2- SPIR), and diffusion-weighted image (DWI) map was performed for using 3 *b* values 0, 200, and 800 (with TR 1300 ms & TE 64 ms), with

corresponding ADC mapping. CE-MRI was performed afterward using gadopentetate dimeglumine (Omnivist ®) injected through an antecubital intravenous catheter at a rate of 3 ml/min over 15 s and a dose of 0.2 ml/kg followed by saline chaser of 30–40 ml at a rate of 1–2 mL/s. Dynamic contrast-enhanced sequences were acquired using T1 weighted high-resolution isotropic volume examination (THRIVE) acquired before (pre-contrast) and after contrast injection at 15 20 s (arterial phase), 40 s (portal phase), 60 s (venous phase), and 180 s (delayed phase). All contrast sequences were acquired at the axial plane.

Statistical data analysis

Data were coded and entered using the statistical package SPSS version 25. It was summarized using descriptive statistics: frequencies were stated as numbers of observations and percentages for categorical variables. Means and standard deviations were used as measures of central tendency for parametric numerical variables.

Inferential statistical analyses for assessment of the relation between categorical variables were performed using both contingency tables with chi-squared tests for observed and expected values and testing for correlation using the spearman-rho test. All tests are considered statistically significant at a p value equal to or less than 0.05.

Diagnostic performance indices including sensitivity, specificity, positive and negative predictive values, likelihood ratios, and overall accuracy were calculated using contingency tables.

Data was presented by graphs, bar charts, and pie charts as well as tables.

Results

Our study was carried on a total of 41 patients (22 males, 19 females) with a mean age of 53.4 ± 9.17 years (males = 50.74 ± 8.5, females = 57.31 ± 8.8 years).

For the Abr-MRI, a total of 15 focal lesions were detected on either T2WI/T2-SPIR or DWI in 10 patients (male = 12, females = 3). The lesions were most frequently present in segment VIII (n = 7, 46.7%) followed by segments VI, V, and II (n = 2, 13.3%) and segments VII and III (n = 1, 6.7%). The mean diameter of the focal lesions was ranging from 1.4 to 3.8 cm. Two focal lesions seen at segment II, segment V, and segment VI and their measurements ranging from 1.9 to 2.3 cm, 1 to 4.7 cm, and 1 to 2.2 cm, respectively; seven focal lesions seen at segment VIII ranging from 2 to 4.4 cm; and one focal lesion seen at segment III and segment VII measuring 3.2 cm and 1.9 cm, respectively (Table 1).

T2WI detected only 13 lesions (intermediate to high = 1, bright/high signal = 12) and detected no lesions in 33 cases. Combining the DWI and ADC, 14 lesions exhibited true restriction (ADC = 0.72 +/− 0.08), and 1 lesion exhibited T2 shine through (ADC = 2.00) (Figs. 1b, c and 2b–d). Utilizing the T2WI/T2-SPIR only for focal lesion detection showed relatively lower figures of sensitivity (86.67%, 95% CI = 59.5–98.3%) and good negative predictive values (93.9%, 95% CI = 81.01–98.26), with otherwise excellent specificity and positive predictive values of 100%. Adding the DWI/ADC into the proposed Abr-MR protocol for detection of focal lesions increased sensitivity and NPV for 100% retaining specificity and positive predictive value at 100% also (95% CI = 0.79–1.000, 0.89–1.000, 0.79–1.000, and 0.89–1.000, respectively).

CE-MRI detected 15 lesions, which were characterized based on LI-RADS v2018 including 11 LR-5 (definite HCC), 3 LR-M (malignant—not compatible with HCC), and 1 LR-1 (hemangioma); 31 cases were negative for focal lesions (Tables 2 and 3) (Figs. 1b, c and 2b–d).

There was statistically significant difference between lesions classified as high malignant probability (LR-5, LR-M) versus low malignant probability (LR1, no lesion) based on both T2WI/T2-SPIR (χ^2 = 32.796, p < 0.001) and DWI/ADC characteristics (χ^2 = 46.00, p < 0.001); moreover, we found strong correlation between detectability (signal brightness) on T2 signal and (r = 0.838, p < 0.001) stronger correlation between diffusion restriction and probability of malignant focal lesions (r = 0.977, p < 0.001).

Additionally, the Abr-MR protocol had the same figures of specificity, sensitivity, PPV, and NPV for the detection of lesions of high malignant probability based on the presence of true diffusion restriction. Ultrasound examination in this study detected 1 focal lesion in 1 patient, with the remaining 40 no lesions detected (Figs. 1a and 2a).

Comparing the ultrasound results to the CE-MRI protocol, the ultrasound detected only 1 out of 15 focal lesions and failed to detect 14. In this study group, ultrasound showed extremely low sensitivity = 6.67% (95 CI = 0.17–31.95%) and relatively low NPV = 68.9% (95% CI = 65.92–71.71%), while it showed excellent specificity = 100% (95% CI = 88.78–100%) and PPV = 100%.

Table 1 Distribution frequency of the hepatic focal lesions according to gender and liver segment

	Gender		Segment						
	Male	Female	II	III	V	VI	VII	VIII	Total
Number of lesions	12	3	2	1	2	2	1	7	15
Size of lesions			1.9 to 2.3 cm	3.2 cm	1 to 4.7 cm	1 to 2.2 cm	1.9 cm	2 to 4.4 cm	1.4 to 3.8 cm

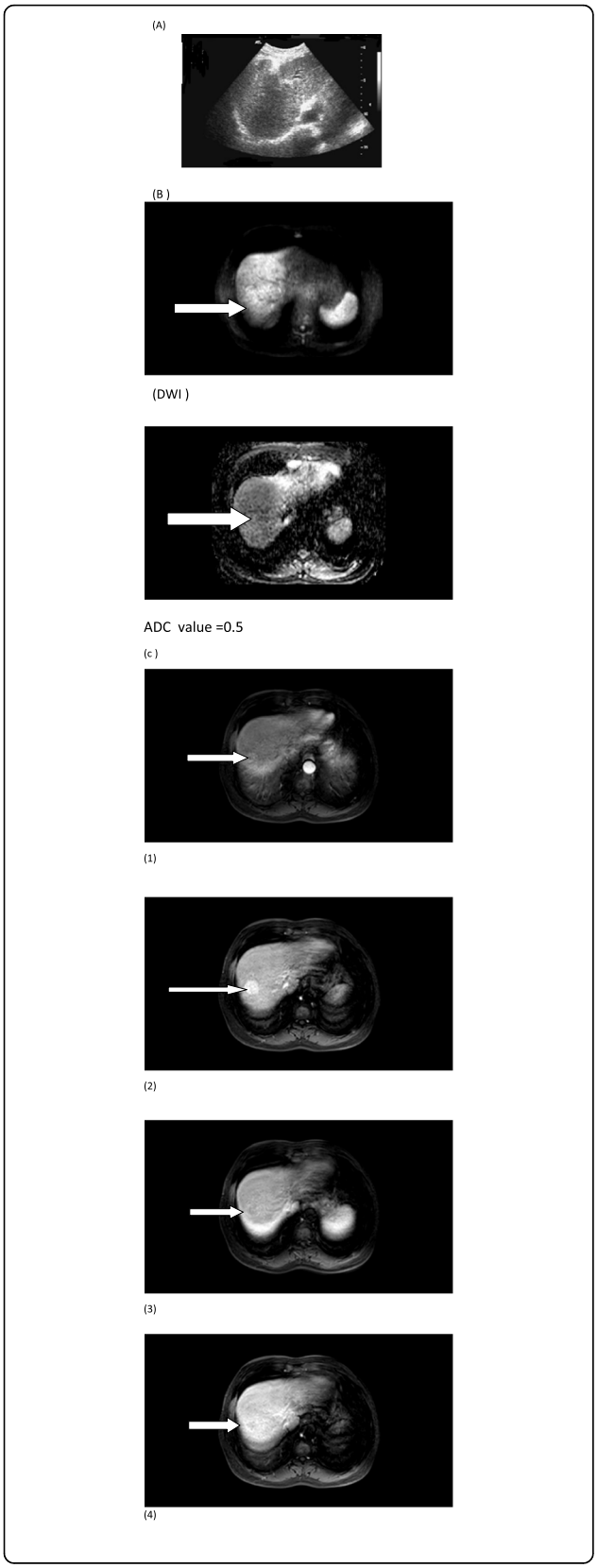

Fig. 1 A 56-year-old male patient underwent an ultrasound and abbreviated MRI protocol followed by standard contrast-enhanced dynamic MRI. **a** Ultrasound of the liver showed a coarse echo pattern with no visualized focal lesion. **b** One hepatic focal lesion is noted with true restricted diffusion at segment VIII with ADC value of 0.5; the patient underwent conventional contrast-enhanced MRI for further characterization of this focal lesion. **c** On contrast study, the lesion shows enhancement pattern consistent with HCC early arterial enhancement with washout on porto-venous with pseudocapsular enhancement

Discussion

Hepatocellular carcinoma (HCC) is considered the major cause of mortality in patients with hepatitis C virus (HCV)-related liver cirrhosis; hence, screening for HCC is mandatory for all cirrhotic patients. The advantage of direct-acting antiviral (DAA) therapy for HCV achieved sustained virologic responses after 12 weeks of therapy (SVR12) of 90–93%, however, several studies demonstrated conflicting results for reduction of the risk of HCC in patients treated by DAA where some studies showed no significant reduction of the risk of development of HCC following DAA treatment, whereas other studies claimed a relatively higher incidence of HCC following treatment, especially in patients with treated HCC (recurrence). Moreover, fewer studies showed that the HCC pattern in patients receiving DAA was more aggressive with relatively poor prognosis compared to patients not receiving DAA [8]. All the previous data calls for the presence of a reliable screening method to properly exclude the presence of hepatic focal lesions with the potential for being an HCC before the onset of treatment. In this study, the sensitivity of US for detection of early or small HCC was low measuring 6.6%. Multiple studies were also performed to document the efficacy of ultrasound and its combination with AFP for early detection of HCC; recent different meta-analysis studies are carried by Tzartzeva et al 2018, Singal et al 2012, and Kim 2016 et al who documented combined sensitivity of US with AFP for early stage to be 63%, 90%, and 32.6% which also decreased down to 47%, 44%, and 25% when the US used alone as a screening tool [8–10]. The low sensitivity of the US as a screening tool in this study was attributed to using US modality as the sole screening tool rather than the combined US with AFP as well as involvement of patient with only cirrhotic liver where the US shows heterogeneous hepatic texture reducing its sensitivity to discriminate small focal lesion. Albeit, the low sensitivity and negative predictive values documented by the various studies fail to reliably detect early/small HCC or dysplastic nodules despite the convenience, wide availability, and low cost of ultrasound examination for screening. It is of special importance in patients undergoing treatment by direct-acting antiviral (DAA) agents since several recent studies have established

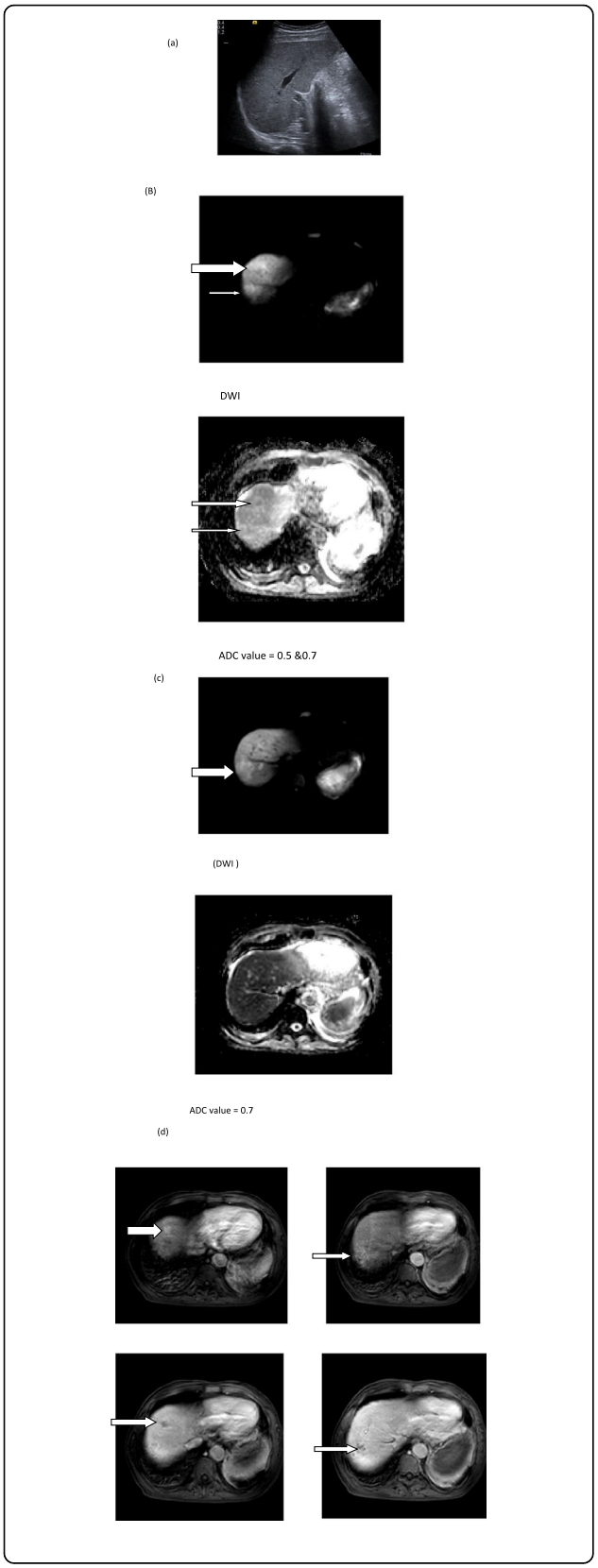

Fig. 2 A 66-year-old male patient underwent an ultrasound and abbreviated MRI followed by standard contrast-enhanced dynamic MRI. **a** US shows coarse liver echo pattern with no focal lesions. **b**, **c** Three hepatic focal lesions are noted (two at segment VIII and one at segment VI) with true restricted diffusion, with ADC value 0.5, 0.7, and 0.7, respectively; the patient underwent conventional contrast-enhanced MRI for further characterization of these focal lesions. **d** On contrast study, the lesions show enhancement pattern consistent with HCC early arterial enhancement with washout on porto-venous and delayed phase

the high incidence of tumor recurrence, rapid development or development of aggressive patterns of HCC, and most recent guidelines for DAA therapy recommend against using such therapy in patients with untreated HCC. This, in turn, calls for more reliable methods for the exclusion of HCC especially in its early stages before starting the DAA therapy. A method that has shown promising results for the detection of HCC is MRI–diffusion-weighted imaging (DWI). In our study, we aimed to examine for the feasibility of a shortened or abbreviated MRI protocol based on a combination of DWI/ADC map and T2 sequence to provide both reduced time and cost which might enable for such MRI protocol as screening for early HCC in cirrhotic patients selected for DAA therapy. In this study, we showed an impressively high sensitivity and negative predictive values (both 100%) for detection of HCC (lesions categorized as LIRADS LR-4 or LR-5) based on DWI and ADC characteristics of the lesions, in a total of 15 hepatic focal lesions detected in10 patients, indicating an extremely high reliability for exclusion of such lesions in such patient population. Moreover, the specificity and positive predictive values shown in our study for such LR-4 and LR-5 lesions were also high (92.3% and 91.6%, respectively) indicating not only the excellent ability for the exclusion of such lesions but also very good reliability for characterizing those lesions as early/small HCC. This study results agreed with Nasu et al. 2012 who showed a sensitivity of 91.2% for detection of small-sized HCC (mean diameter of 2.9 cm) based on bright DWI signal and low ADC value. Compared to the nearby liver parenchyma [11], however, the comparatively higher figure of sensitivity in this study may be attributable to the fact that Nasu et al. compared the DWI/ADC to surgical

Table 2 Frequency and percentages of the focal lesions according to the LIRADS/CE-MRI characterization

CE-MRI criteria/ LIRADS	Focal lesion	
	Frequency	Percent
LR-5	11	23.9
Negative	31	67.4
LR-1	1	2.2
LR-M	3	6.5

Table 3 Sensitivity, specificity, NPV, and PPV of US, abbreviated MRI protocol with and without ADC value in the detection of a malignant focal lesion in correlation with CE-MRI

	Sensitivity	Specificity	NPV	PPV
Ultrasound	**6.6%**	**100%**	**68%**	**100%**
Abbreviated MRI without ADC value	**96.8%**	**93.3%**	**100%**	**100%**
Abbreviated MRI with ADC value	**100%**	**100%**	**100%**	**100%**

specimen and histopathological confirmation of HCC while in this study, we compared the lesions to the standard multiparametric MRI protocol and LIRADS categories. Moreover, the total number of lesions in this study [12] was less than the number included in Nasu et al. study (125). A retrospective study done by Piana et al. [5] on 91 patients with 109 HCC assessing the sensitivity of DWI for detection of HCC in correlation with histopathology; two blinded readers assess HCC being hyper intense with a sensitivity of 89/109 (82%) and 79/109 (72%) and decreased to be sensitivity of 74% and 64% in tumors less than 20 mm, and there was an agreement between the two readers. Another cohort study done by Shingaki et al. [13], focusing on small sized tumor (20 mm or less), found that sensitivity being 78.8% of HCC of 66 pathologically proven lesions were hyper intense to back ground liver. Another retrospective study by Zhao et al. [14] made on HCC lesions and determined for lesions between 0.6 and 2 cm with an average size of 1.5 cm was visible on DWI with a sensitivity of 79%. Also, a retrospective study done by Park et al. [15] to estimate the accuracy of DWI in detecting HCC using explanted liver as a gold slandered, and tumor ranged from 0.3 to 6.2 cm DWI had a sensitivity of 75.8% and approaches 90% in lesions more than 20 cm. Low et al. [12], a study for evaluation of the role of added DWI to conventional dynamic MRI study and use of conventional dynamic study alone in detection of a HCC, found that the sensitivity value for use of combined technique was 97.8%, and those use of conventional study alone without DWI was 85.11%. The positive predictive value for combined technique was 97.8%, and for the conventional technique alone was 92.8%. So in this study, the use of added DWI causes higher sensitivity in detection of HCC than dynamic MRI alone .The major advantage of DWI over the USA shown in our study is the less false-positive results, which will reduce the expense of screening programs as fewer patients will progress into an expensive diagnostic investigation as conventional dynamic contrast-enhanced MRI.

Conclusion

In our study, we were able to demonstrate the superiority of a proposed cost-effective abbreviated MRI protocol in the detection of hepatic focal lesions and small-sized HCC compared to the routine screening protocol of combined alpha-fetoprotein and transabdominal ultrasound imaging for HCV-related liver cirrhosis. The drawbacks in this study are that the MRI machine is not easily available in remote places, not cheap as US machine, some peripheral small hepatic focal lesion could be missed owing to motion artifact (respiratory motion), or at left lateral lobe due to cardiac motion; however, in comparison to the US machine, still, the MRI machine can detect the majority of clinically significant cancers and has significantly lower false-positive rate than screening ultrasound.

Also, this study can be used as an alternative for the detection and characterization of HCC, especially in patients with impaired renal function or contrast allergies precluding the use of iodinated (CT) contrast media as the majority of patients with liver cirrhosis had hepatorenal syndrome so the use of abbreviated MRI is to avoid element of nephropathy.

Abbreviations

HCC: Hepatocellular carcinoma; DWI: Diffusion-weighted image; HCV: Hepatitis C virus; DAA: Direct-acting antiviral; ADC: Apparent diffusion coefficient; NPV: Negative predictive value; PPV: Positive predictive value; MRI: Magnetic resonance imaging; SD: Standard deviation; LI-RADS: Liver imaging and data reporting system; Abr-MRI: Abbreviated MRI; NASH: Non-alcoholic steatohepatitis; SVR: Sustained virologic response

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Authors' contributions

NNA: reviewing literature, data collection and analysis, perform statistical analysis, write and revise the manuscript, and prepare figure and tables. SMELG: reviewing literature, data analysis, and manuscript editing. RZE: suggest and develop the research idea, reviewing literature, and data analysis. EMAH: reviewing literature, share in statistical analysis, data analysis, and manuscript editing. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was a prospective study. This study was approved by the Research Ethics Committee of the Faculty of Medicine at Ain shams University in Egypt on 10 May 2018: Reference Number of approval: FWA 000017585. All patients included in this study gave written informed consent to participate in this research. If the patient was unconscious at the time of the study, written informed consent for their participation was given by their legal guardian.

Consent for publication

All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was unconscious

when consent for publication was requested, written informed consent for the publication of this data was given by their legal guardian.

Competing interests
The authors declare they have no competing interests.

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