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Diffusion-weighted MRI for hepatocellular carcinoma screening in chronic liver disease: Direct comparison with ultrasound screening

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Title

Diffusion weighted MRI for HCC screening in chronic liver disease: direct comparison with ultrasound screening.

Running Title

HCC screening with DWI.

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Key words
Hepatocellular carcinoma
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Abstract:

Introduction
Ultrasound is a widely utilized method of screening patients with chronic liver disease for hepatocellular carcinoma (HCC). However the sensitivity of ultrasound for small tumours is limited. We have prospectively compared ultrasound screening with diffusion weighted (DWI) MRI for detecting HCC.

Methods
Patients with chronic liver disease referred for ultrasound screening underwent a liver ultrasound and a liver MRI comprising free breathing DWI. Each test was independently read to determine the accuracy of each modality for detecting HCC.

Results

192 patients were recruited and HCC was diagnosed in 6 patients (3%); all of whom were detected at ultrasound screening, and 5 detected at MRI screening. Ultrasound had false positive studies 20 times (10%) while DWI MRI had 3 false positive examinations (2%) p=>0.05. The sensitivity, specificity, positive predictive value and negative predictive values for ultrasound are 100%, 90%, 23% and 100% respectively while for MRI are 83%, 98%, 63% and 99%.

Conclusion

In patients with chronic liver disease undergoing surveillance for hepatocellular carcinoma, DWI MRI screening shows similar sensitivity to screening ultrasound but with a significantly lower false positive rate.

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Diffusion weighted MRI for hepatocellular carcinoma screening in chronic liver disease: direct comparison with ultrasound screening.

Introduction

In 2008 there were an estimated 748,300 new cases world wide of hepatic cancer and an estimated 695,500 deaths (1). Many of these cases occur in the developing world. However the incidence of hepatocellular carcinoma (HCC) is also increasing in developed countries (2). Hepatocellular carcinoma risk factors include viral hepatitis (Hepatitis B and Hepatitis C viruses), autoimmune hepatitis, alcoholic cirrhosis and non-alcoholic steatohepatitis (NASH) cirrhosis. The incidence in developed countries may continue to increase further as the obesity epidemic continues, with NASH-related cirrhosis having a cumulative HCC incidence of 2.6%(3).

Identification of patients at risk of HCC allows enrolment within a screening program that usually comprises ultrasound examinations and alpha-fetoprotein (AFP) measurement performed at 6 monthly intervals (4). Ultrasound (US) screening has been shown to reduce mortality from HCC (5), however other studies show limited mortality benefit and considerable cost associated with current screening regimens (6, 7) because many of the tumours identified in screening programs are not suitable for treatment with curative intent at the time of diagnosis.

Combining ultrasound with AFP increases sensitivity but it also increases the false positive rate (8) and therefore expense. For a screening test to be effective it must be able to reliably identify early HCC. A meta-analysis has shown that ultrasound had a sensitivity of 63% (95% confidence interval 49-76%) for the detection of early HCC(9) with substantial variation in sensitivity between studies. The sensitivity of ultrasound is related to lesion size with studies reporting a sensitivity of 21% for HCC under 2cm, and 62% for HCC measuring 2-4cm (10). The limitation of identifying small HCC's coupled with variable screening intervals explains why only a minority of screened patients with newly detected HCC are considered resectable at the time of diagnosis (11).

Recent improvement in both hardware and software technology has enabled the already established MR diffusion weighted imaging (DWI) sequence to be applied to abdominal organs including liver imaging(12, 13). Diffusion weighted images are generated based upon local variations in Brownian motion of water molecules. Focal areas of restricted diffusion appear as high signal intensity on DWI images, while areas with free diffusion appear as low signal intensity. Due to alterations in factors such as extracellular matrix, solid tumours exhibit restricted diffusion compared to background liver (14) generating an inherent contrast difference and therefore improving lesion conspicuity and providing a method for lesion detection. We have prospectively investigated the role of diffusion weighted hepatic MRI for HCC screening in the setting of chronic liver disease. We elected to use DWI as a standalone sequence, as for MRI to be a logistically practical screening method, it is vital that the total scan time is quick. This dictates that the minimal number of sequences should be employed.

Materials & Methods

The study was performed in a University affiliated tertiary hospital, with ethics approval granted by the hospital research governance review board. Written informed consent was gained from all participants. Recruitment criteria included patients aged over 18 years who were referred by the gastroenterology department with chronic liver disease for hepatocellular

carcinoma screening liver ultrasound. Exclusion criteria included the presence of a known mass as indicated on the ultrasound request form, non-English speaking (due to inability to gain informed consent), or contraindications to MRI such as pacemaker or contraindicated metallic implant. Recruited patients underwent an hepatic US followed by an hepatic MRI within a two-week period. The majority of studies were performed on the same day.

The MR scan sequence comprised respiratory-gated DWI with the following parameters: TR 2500; TE 80; slice thickness 8mm; distance factor 30%, FOV read 400mm, with effective voxel size of 2.6 x 2.1 x 8mm; and b values of 100, 400, 800 acquired with 8 averages. The US studies were reviewed by a single abdominal radiologist who was blinded to the MRI study and all prior imaging, while the MRI was reported by another abdominal radiologist, blinded to the US and all prior imaging.

Any suspicious lesion was documented with respect to size, features and hepatic segment. Prior imaging was then reviewed to determine the aetiology of the lesion and assess stability. If the lesion was new it sparked further investigation as per the AASLD guidelines(15), being repeat imaging in 3 months by the modality that identified it for lesions under 10mm, and cross sectional contrast enhanced multiphase imaging with either MRI or CT for new lesions over 10mm.

Ultrasound lesions were considered suspicious if they were solid and were not clearly focal fat infiltration or focal fat sparing. MRI lesions were considered suspicious if they had elevated signal on high b value DWI and were iso or hypointense to background liver on the ADC map.

Gold standard for the diagnosis of HCC was by the AASLD guidelines(15) of arterial phase hyperenhancement followed by washout on either CT or MRI, or by histology (biopsy or resection). The location and size of all proven HCC was correlated with the screening test result locations. Patients who elected to withdraw from the MRI component of the study were followed at future US screenings to determine if sonographic lesions became apparent.

RESULTS

192 patients were recruited with an average age of 58 years (range 22-80 years). 139 (72%) were male. The causes of chronic liver disease were HBV 108 patients (56%), HCV 56 patients (29%), alcohol 21 patients (11%), non-alcoholic fatty liver disease (NAFLD) 8 patients (4%) and 'other' 8 patients (4%) with cases of multiple causes resulting in percentages adding to over 100%. 151 (79%) patients were Childs Pugh A, 9 (5%) Childs Pugh B and one (<1%) Childs Pugh C (Table 1). 31 (16%) patients had incomplete data for Childs Pugh calculation with INR the most frequent missing measure.

Compliance rates were 192 patients having at least one simultaneous MRI and US, 91 (47%) returning for two examinations, 45 (23%) for 3 examinations, 23 (12%) for 4 exams and 6 (3%) for 5 examinations. The attrition rate was therefore approximately 50% patient loss per screening cycle.

During the study period HCC was diagnosed in 6 (3%) patients. Ultrasound detected suspicious lesions in all of these patients while MRI detected suspicious lesions in 5 i.e. one false negative patient with MRI. MRI had 3 (2%) false positive results while ultrasound had 20 (10%) patients with false positive examinations ($p < 0.05$).

Of the diagnosed HCC cohort, one patient had two lesions (31x26mm and 15 x 11mm), and five patients had a solitary tumour measuring 27mm, 24mm, 17mm, 15mm, and 8mm. The false negative MRI was in the 8mm HCC, which arose in a 14mm high-grade dysplastic nodule, located in the inferior aspect of segment 6 with the HCC component being subcapsular. An example HCC is shown in figure 1.

A number of lesions resulted in false positive ultrasounds. These include dominant regenerative nodules (normal signal on DWI and hepatobiliary phase with no focal lesion on dynamic imaging), haemangiomas (figure 2) and focal mass-like fat. A number of lesions did not gain a definitive diagnosis but were demonstrated to be stable after over 2 years of follow up. One false positive was the result of incorrect localization with a 'new' lesion found in segment 7, subsequently demonstrated to be a known benign lesion previously labeled as segment 6.

The false positive MRI results were all less than 10mm. One was subsequently shown to be a cyst with internal haemorrhage that was stable at 18 months of follow up, and the other two had elevated signal on high b value DWI and isointensity on the ADC map. These were shown to be stable on subsequent studies.

The sensitivity, specificity, positive predictive value and negative predictive values for ultrasound are 100%, 90%, 23% and 100% respectively while for MRI are 83%, 98%, 63% and 99%.

DISCUSSION

Much of the published literature around DWI and HCC is focused on the added benefit of acquiring DWI as part of a diagnostic liver MRI examination rather than as a stand-alone sequence. Extraction of the data from these studies reveals promising, while slightly heterogenous results for DWI.

Nasu et el (16) examined the DWI and T2 characteristics of 125 HCC nodules with surgical correlation and found that 91.2% were hyperintense on DWI compared with background liver, with 69.6% being markedly hyperintense.

This compares favourably with T2 images on which only 23% of HCCs were hyperintense. The signal intensity of HCC on DWI was also noted to increase with higher grades of tumour. The median nodule size in this study was 2.9cm (range 0.8-15cm). This study excluded lesions in the lateral left lobe, which is prone to cardiac motion artifacts, excluded lesions under 8mm and excluded cases with misregistration artifact. Therefore it is reasonable to assume that the percentage of HCCs that will be hyperintense on DWI in a screening population will be less than the 91.2% that they reported.

The sensitivity of DWI for detection of HCC was assessed in a retrospective study of 91 patients with 109 HCCs (17). 70% of lesions in this study were 29mm or less in maximal diameter. Two blinded readers assessed HCC as being hyperintense to liver in 89/109 (82%) and 79/109 (72%) respectively although the sensitivity was reduced slightly in HCC less than 20mm being 74% and 64% respectively. There was good agreement between the two readers. An additional study (18) focused on small HCC's (20mm or less) and found that 78.8% of HCC in their cohort of 66 pathologically proven lesions were hyperintense to background liver on DWI. Both well and moderately differentiated tumours were found to be isointense and 8 of this studies 14 false negative DWI cases were due to fatty metamorphosis with signal potentially being nulled by fat on fat suppressed images. Interestingly hepatic fatty infiltration provided a false positive case when a regenerating nodule was found to be hyperintense compared to background fatty liver. Another retrospective study (19) examined small HCC's and determined that for lesions between 0.6-2.0cm, with an average size of 1.5cm, 27 of 34 (79%) were visible with DWI.

The accuracy of DWI for detecting HCC was assessed in a retrospective study (20) using explanted livers as the gold standard. Tumours ranged from 0.3 to 6.2 cm with a mean of 1.5cm and overall DWI had a per patient sensitivity of 75.8%. The sensitivity was related to lesion size and approached 90% for lesions over 20mm but under 32% for lesions less than 10mm. The false positive rate for the DWI data set was low.

The above studies compare favourably with the published sensitivities for ultrasound in a screening population. They also correlate well with our results with MRI detecting 5 of the 6 HCC that developed during the study. The single false negative case occurred in a sub-centimeter sub-capsular lesion at the inferior aspect of the liver where there was artifact from adjacent gas containing bowel.

There is considerable controversy surrounding HCC screening in the western world (21-23) due to the potential morbidity associated with false positive results. The major advantage of DWI over US screening in our study has been the low false positive rate of DWI. Reducing false positives is important as it will reduce the expense of screening programs as less patients will needlessly progress to more expensive diagnostic investigations such as multiphase CT and/or MRI, and fewer biopsies will be required. This should also reduce patient anxiety and may help to improve the poor compliance with screening programs which are documented to be as low as 58% (24).

The reasons for the low false positive rate of DWI MRI include: not depicting macroregenerative and low grade dysplastic nodules, not depicting focal fatty heterogeneity and the ability to correctly classify cavernous haemangiomas which usually have elevated apparent diffusion coefficient (ADC) values (25). For small nodules, the sonographic sensitivity is low and the positive predictive value is also reduced to approximately 82%(10). In a study (26) of 442 patients, false positive ultrasounds led to 48 cross sectional investigations in 34 patients.

Due to its cross sectional nature, it is easier to directly compare the location of depicted nodules on MRI with previous studies compared with the sonographer dependent localization of lesions on previous ultrasounds. One sonographic false positive in our study was the result of incorrect localization of a previously characterized nodule. The US false positive rate is substantially higher when serum AFP levels are combined with screening ultrasound. We did not examine the effect of combining serum AFP to MRI

screening algorithms.

Enrolment in surveillance programs in the western world is sporadic and variable. In a retrospective study (27) reviewing patients with known cirrhosis and a new diagnosis of HCC, only 17% of patients had received regular surveillance in the preceding three years, 45% had no surveillance while 33% had inconsistent surveillance. If HCC screening is to be offered maximal participation of eligible candidates is mandatory. Another study (28) examining causes of screening failure in the setting of HCC surveillance, noted that compliance with screening of 31.1%. Of the late stage HCC that were diagnosed 13% were related to absence of screening and 17% due to absence follow up. Interestingly, the majority (70%) of late HCC diagnosis was the result of failure of detection. Given the deficiencies in screening relying on ultrasound and AFP, screening with DWI MRI warrants further investigation. DWI acquisition is fast, reliable and well tolerated.

There are a number of limitations in our study. Compliance was poor, with attrition of around 50% of patients per screening cycle, which is comparable with published studies (29). One reason may have been due to the inconvenience of requiring two tests on one day. Therefore, compliance would presumably improve if MRI was a replacement examination rather than an additional test.

Another limitation was the absence of a non-invasive gold standard for HCC screening. Therefore, it is possible that both US and MRI may have missed tumours that remain undetected in our patients. These HCC's however are likely to be small and slow growing given that the doubling time of tumours is related to the level of differentiation which varies between 138 days to 32 days for Edmonson grade 1 and grade 3 tumours respectively (30). It was reassuring that no patient was found to have developed a new tumour in a follow up period of at least 6 months. However, these imitations should not detract from our 'proof of concept' pilot study, although a larger trial of DWI screening for HCC is required.

Conclusion:

In patients with chronic liver disease undergoing HCC surveillance, MRI can detect the majority of clinically significant cancers and has significantly lower false positive rate than screening ultrasound. Larger scale studies are required to ensure that the comparable sensitivity and improved specificity of MRI warrants replacing US as a cost effective screening tool.

Figure legends

Figure 1: DWI image (fig 1a) with b value 800 shows a hyperintense focal lesion in segment 8, with isointensity on the ADC map (figure 1b). This was a hepatocellular carcinoma.

Figure 2: Ultrasound (fig 2a) showing a new lesion in segment 5/8 that is heterogenous. The DWI (fig 2b) shows it has high signal on b value 100, but is also hyperintense on the ADC map (fig 2c). This lesion had previously been called segment 6 and had previously been characterized as a haemangiomas on dedicated diagnostic MRI performed 2 years earlier.

Compliance with Ethical Standards:

The authors have not received any funding for the research presented in this manuscript. The research was prospectively approved by the institutional ethics review board.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and / or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed written consent was obtained from all individual participants included in the study.

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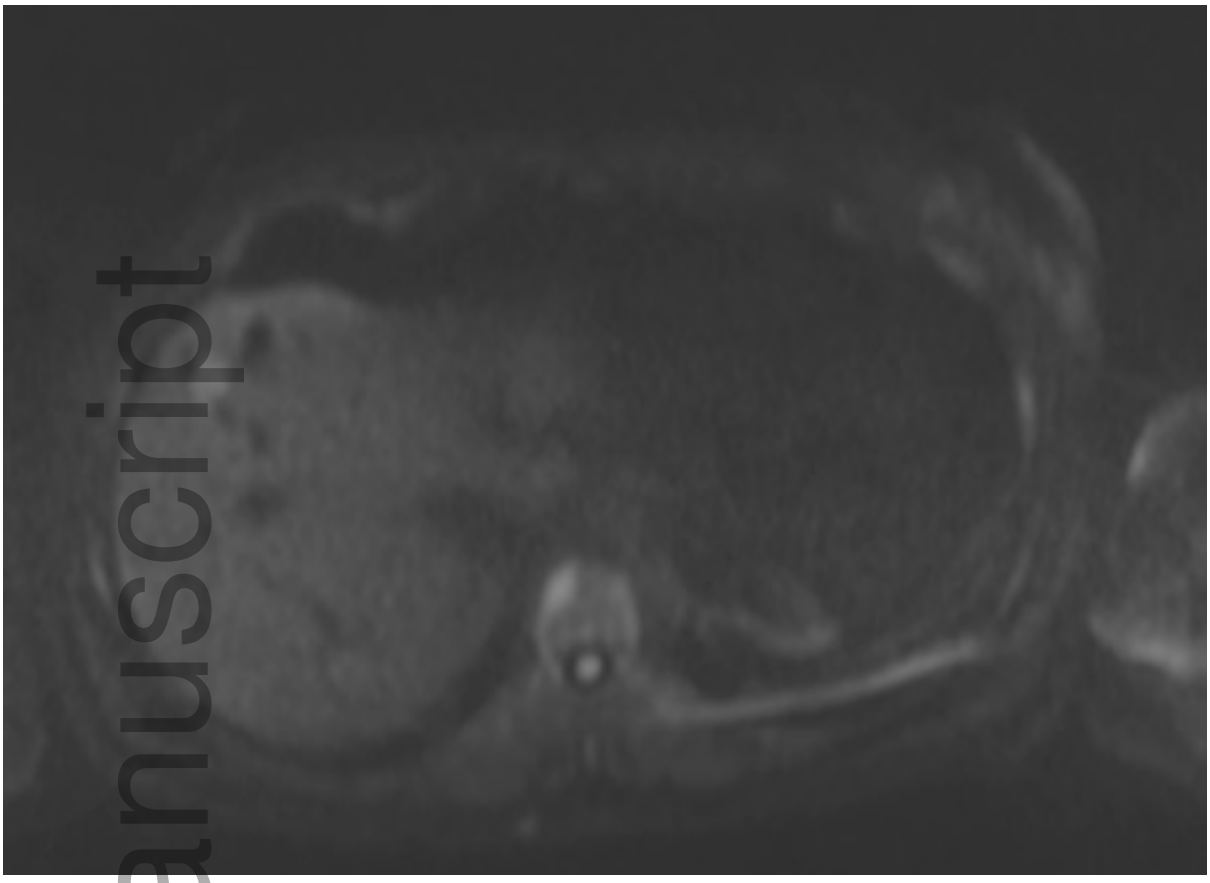
Age	58 years (range 22-80)
Male/female	139 (72%) / 53 (28%)
Cause of CLD	
HBV	108 (56%)
HCV	56 (29%)
Alcohol	21 (11%)
Hepatic steatosis	8 (4%)
other	8 (4%)
Child Pugh Status	
A	79%
B	5%
C	<1%
Incomplete data	16%

Table 1

Demographic details of the study population.



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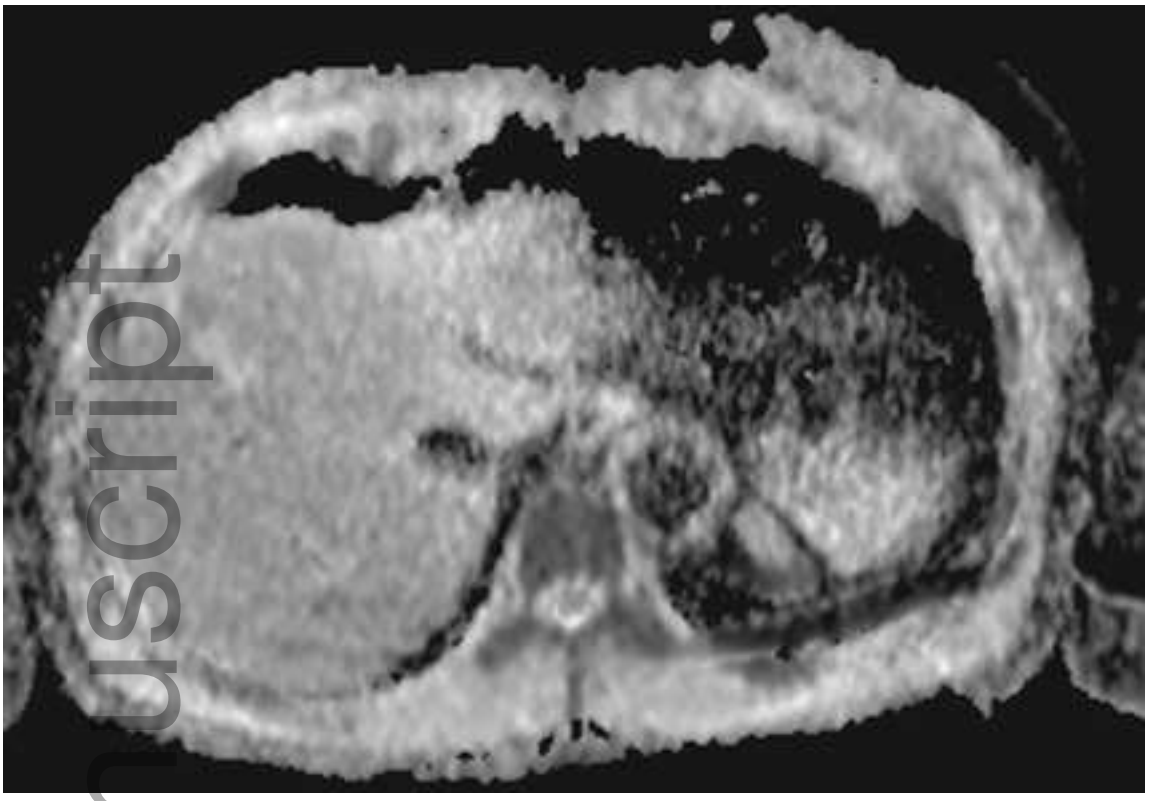

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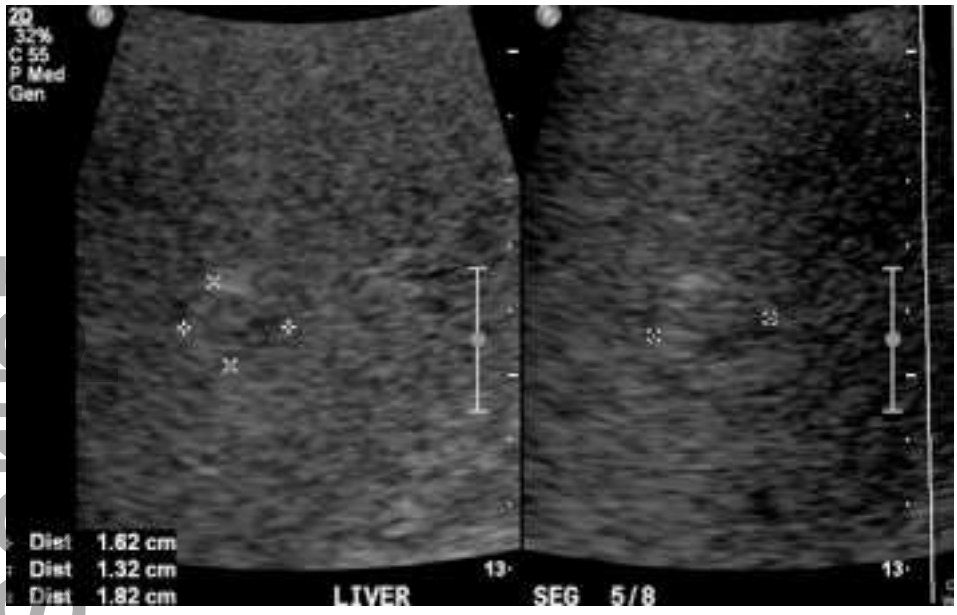

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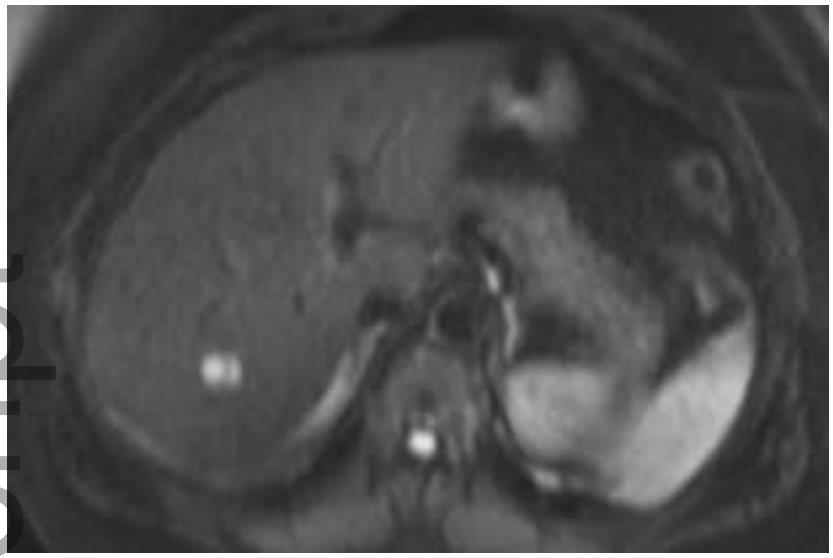

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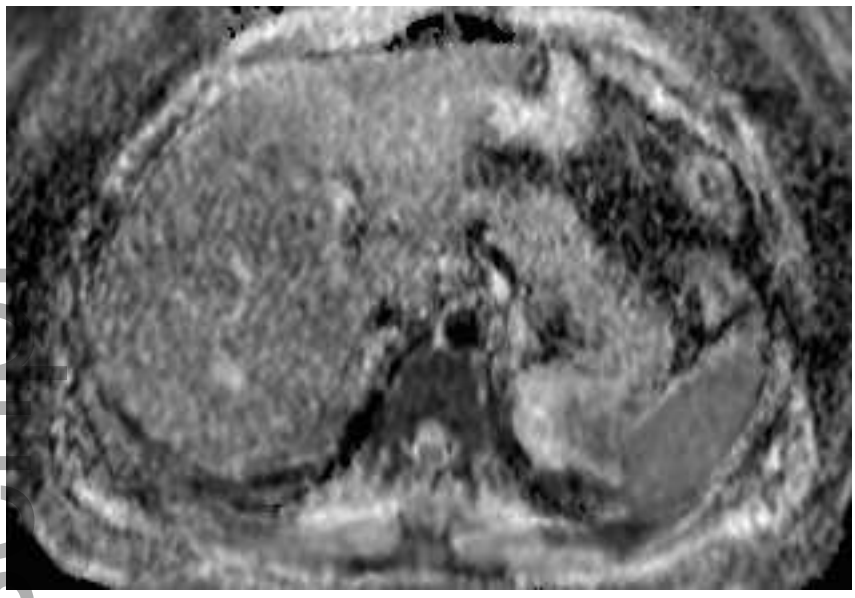

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