



## Evaluation of ADC<sub>ratio</sub> on liver MRI diffusion to discriminate benign versus malignant solid liver lesions

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### ABSTRACT

**Purpose:** The aim of this project is to investigate the usefulness of the absolute liver lesion ADC value and ratio of Apparent diffusion coefficient (ADC) values of a liver lesion and liver parenchyma to discriminate between a benign and malignant lesion.

**Methods:** Liver MRI scans performed between January 2009 and June 2015 were retrospectively analysed. Scans were performed on either a 1.5 T or 3 T MRI unit. The type of liver lesion (benign or malignant) was determined by its radiological appearance, histology result and clinical management. Lesions with undetermined diagnosis or MRI studies degraded by artifacts were excluded. Liver cysts were also excluded from the analysis. ADC value of a lesion and liver parenchyma was measured and ADC<sub>ratio</sub> was calculated. The values were analysed using independent samples *t*-test

**Results:** Data set contained 39 benign lesions and 36 malignant lesions. Mean ADC value for benign lesions was 1678, and the mean value for malignant lesions was 1097 with a statistically significant difference of  $p < 0.001$ . All lesions with ADC value below 955 were malignant, while all lesions with ADC value above 1880 were benign. ADC value of 1260 was identified as the best available cut-off value for differentiating benign and malignant lesions, achieving sensitivity of 92%, specificity of 80% and an overall accuracy of 89%. The mean lesion to liver ADC<sub>ratio</sub> for benign lesions was 1.3467 and for malignant lesions was 0.9038 with a statistically significant difference of  $p < 0.001$ . All lesions with ADC<sub>ratio</sub> measuring  $< 0.9$  were malignant while lesions with ADC<sub>ratio</sub>  $> 1.5$  were benign. ADC<sub>ratio</sub> of 1.1 was identified statistically as the best available cut-off value for differentiating benign from malignant lesions, with sensitivity of 82%, specificity of 86% and an overall accuracy of 92%.

**Conclusion:** Our dataset indicates that lesion to background liver ADC<sub>ratio</sub> is superior in discriminating between benign and malignant focal lesions compared to absolute ADC values of the hepatic lesions.

### 1. Introduction

Magnetic Resonance Imaging (MRI) has superior sensitivity and specificity in diagnosing focal liver lesions when compared to Computer Tomography (CT) and Ultrasound (US) [1]. Diffusion weighted imaging (DWI) is one of the non-contrast MRI sequences which is playing increasing role in the hepatic MRI interpretation [2,3]. It was initially utilised in neuroradiology but eventually applied into abdominal imaging [4,5]. Diffusion restriction within the tissue of interest demonstrated on DWI can be quantitatively measured by Apparent diffusion coefficient (ADC) map [1,6]. ADC is a composite coefficient that reflects both microcirculation and pure diffusion. Its measurement is influenced

by water diffusion, tissue perfusion and flow. The decrease in true diffusion may be influenced by differences in tumour cellularity, architecture, and grade [7].

There has been promising evidence that ADC may be a viable tool to help discriminate benign versus malignant character of a hepatic lesion [1,6,8–13]. However, there have been conflicting reports in literature regarding the usefulness of DWI in this regard. A few research studies found that ADC is not a reliable tool for such a task [4,14,15]. Even so, there are two meta-analysis which found that ADC is useful in discriminating the lesions [11,12].

Some solid hepatic benign lesions for example, focal nodular hyperplasia, hepatic adenoma and haemangioma can demonstrate similar

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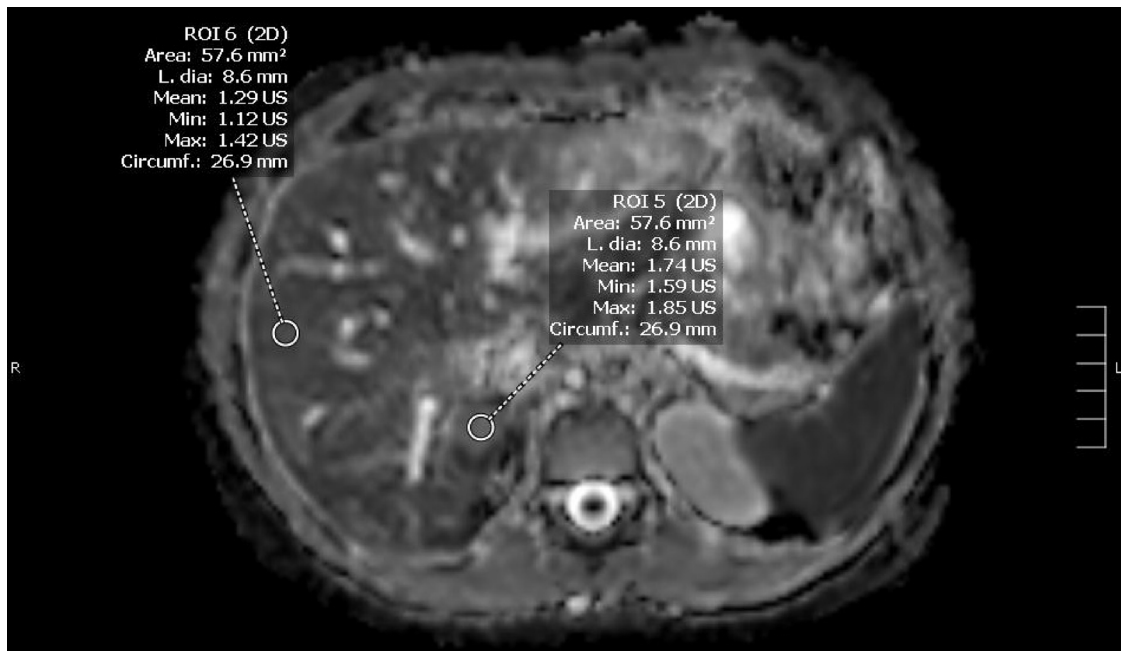


Fig. 1. Example of lesion and liver ROIs acquired of a benign lesion (haemangioma).

ADC values to malignant hepatic lesions [16]. This significantly limits the reliability of ADC as a discriminating tool. Many studies conducted to assess the discriminating ability of ADC also included simple cysts [6,8,11]. As ADC value of simple cysts is usually significantly higher than solid lesions, inclusion of cysts in the category of benign lesions may have led to a significant difference in ADC values between benign and malignant lesions, leading these investigators to believe that ADC and DWI are useful tools. Unfortunately Testa et al have indicated that exclusion of simple cysts undermines ADC as an effective discriminating tool [6].

ADC cut-off values are fraught with difficulty due to wide variation in b-values used for acquisition across the literature and different institutional practices [17]. Calculation of ADC values in a particular lesion can vary with MRI equipment, scanning protocol and analysis software platform used for calculation. ADC values can also vary within the same patient in two different sets of examinations due to variation in biological parameters e.g. vascularity, membrane permeability changes. The ratio of ADC values between a lesion and the background liver can potentially negate these external factors and provide a more accurate representation of change in the diffusion with respect to normal tissue. In an earlier study,  $ADC_{ratio}$  values were found to have better sensitivity and specificity than stand-alone ADC values in the interpretation of hepatic malignancies [18].

The aim of this project is to investigate the usefulness of  $ADC_{ratio}$  of a solid liver lesion to liver parenchyma to discriminate between benign and malignant lesions.

## 2. Material and methods

Ethics approval was obtained from institutional Human Research Ethics Committee.

### 2.1. Data acquisition

The liver MRI scans performed between January 2009 and June 2015 were retrospectively analysed. Studies without focal liver lesions were excluded.

The type of liver lesion (benign or malignant) was determined by its radiological appearance, histology result and clinical management. Radiological appearance for benign lesions are determined by the

presence of well described radiological features [19]. Apart from radiological appearance, associations were also made with patients' clinical history of metastatic malignancy, with and without histological confirmation. Patients with liver lesions that were treated with chemotherapy were also presumed to have malignant disease. Only pre-treatment liver MRIs were assessed.

Studies without liver lesions or lesions less than 10 mm were excluded. MRI studies without a complete hepatic liver MR sequences or heavily degraded by artefact were also excluded. Simple hepatic cysts were also excluded from the analysis.

### 2.2. Liver MRI technical data

Patients were examined with either a Siemens Avanto 1.5 T Scanner or Phillips Ingenia 3 T superconducting MR imaging system.

The liver MR imaging protocol included transverse T2-weighted single-shot turbo spin-echo images, transverse T1-weighted gradient echo in- and opposed-phase images, axial transverse single-shot echo-planar (SS-EPI) DW images (free-breathing respiratory triggered sequence) with 3 b values covering the whole liver and transverse T2-weighted turbo spin-echo images with fat suppression. At 3 T scanner, the highest b value was 800 or 1000sec/mm<sup>2</sup>. At 1.5 T scanner, the highest b value was 1000sec/mm<sup>2</sup>.

Dynamic post contrast images were acquired following injection of an intravenous bolus injection of contrast. The contrast injection was followed by IV injection of 20 mL of saline. Various contrast media used were 0.1 mmol/kg dimeglumine gadopentetate (Magnevist; Bayer Group, Germany) or 0.025 mmol/kg gadoxetate disodium (Primovist, Bayer Group, Germany) or 0.1 mmol/kg Gadobenate disodium (Multihance, Bracco Diagnostics, Italy). The choice of contrast utilised was determined by the reporting radiologists on the day the scan was performed.

Hepatic arterial-dominant, portal venous, and equilibrium phase (10 min post contrast injection) sequences were performed. Hepatobiliary phase was performed if hepatobiliary specific contrast agent was administered. The total examination time was approximately 30 min.

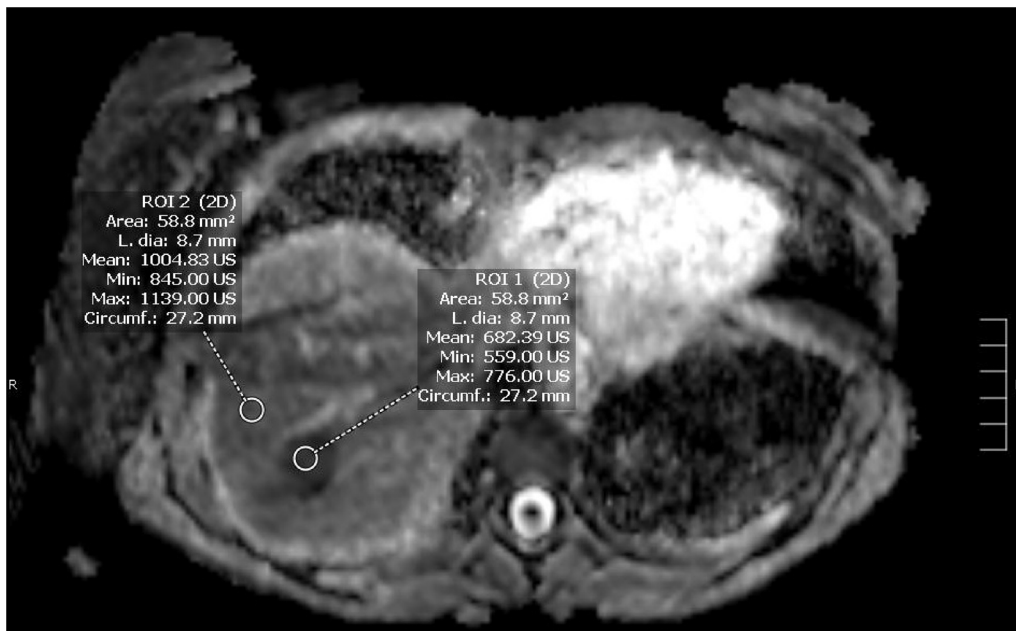


Fig. 2. Example of lesion and liver ROIs acquired of a malignant lesion (metastasis).

### 2.3. Lesion analysis

Criteria used for image quality were visual assessment of noise, motion artifacts, and image distortion. Blinded to the diagnosis, ADC value of a lesion and liver parenchyma were measured by a radiologist with 12 years' experience interpreting liver MRIs. ADC values of each lesion and background hepatic parenchyma were measured twice and an average ADC value was obtained. The area of the region of interest (lesion/background liver) was between 50–60 mm<sup>2</sup> (Figs. 1 and 2). Care was taken to avoid cystic necrotic appearing regions (bright on T2 weighted images and non enhancing on post contrast images) in a lesion as well as adjacent vessels. For a lesion with heterogeneous signal on ADC images, the ROIs were placed in the brightest and darkest regions within solid enhancing components of the lesion. For homogenous appearing lesions, ROIs were placed in the lesion at different axial slices. A similar process was repeated for the background liver, where the ROIs were measured in each liver lobe.

### 2.4. Data analysis

All statistical analysis was performed using SPSS 24 (IBM). ADC values were obtained for both the neoplastic lesion and the surrounding liver parenchyma, and ADC<sub>ratio</sub> was then calculated. Levene's test was performed to ensure equal variance between the benign and malignant groups. Student T-tests were used to analyse benign and malignant ADC values and ADC<sub>ratio</sub>.

Receiver operative characteristic curves were generated to assess the ability to differentiate benign and malignant neoplasms based on ADC value and ADC<sub>ratio</sub>. Cut-off values for benign and malignant neoplasms were determined for both ADC values and ADC<sub>ratio</sub>. A P value of < 0.05 was considered statistically significant for all statistical analyses.

Further stratification of data into 1.5 T and 3 T groups, with subsequent analysis was performed.

## 3. Results

A total of 188 patients had hepatic MRI from January 2009 to June 2015. 113 patients were excluded due to various reasons detailed in Table 1. The 75 patients were included. The data was comprised of 39

Table 1

Patient demographics, results and variance stratified into 1.5 T and 3 T groups.

|                                  | 1.5 T | 3 T | Total |
|----------------------------------|-------|-----|-------|
| Total Included                   | 38    | 37  | 75    |
| Benign lesion                    | 20    | 19  | 39    |
| Malignant lesion                 | 18    | 18  | 36    |
| Total Excluded                   | 78    | 35  | 113   |
| No lesion/ simple cyst           | 28    | 11  | 39    |
| Incomplete MRI sequences         | 7     | 4   | 11    |
| Lesion < 10 mm                   | 16    | 6   | 22    |
| Significant degraded by artifact | 27    | 14  | 41    |
| Total MRI performed              | 116   | 72  | 188   |

Table 2

Number of cases obtained from data collection.

|                           | 1.5 T  | 3 T    |
|---------------------------|--------|--------|
| Age (Mean)                | 54     | 58     |
| Gender (numbers)          |        |        |
| Male                      | 16     | 20     |
| Female                    | 20     | 19     |
| Mean ADC <sub>ratio</sub> |        |        |
| Benign                    | 1.3352 | 1.3575 |
| Malignant                 | 0.9379 | 0.8411 |
| MediADC <sub>ratio</sub>  |        |        |
| Benign                    | 1.3179 | 1.3889 |
| Malignant                 | 0.9551 | 0.8394 |
| Variance                  |        |        |
| Benign                    | 0.065  | 0.089  |
| Malignant                 | 0.032  | 0.05   |

benign lesions (13 FNH, 25 haemangioma, 1 abscess) and 36 malignant lesions (27 HCC, 1 cholangiocarcinoma, 8 metastases). Levene's test demonstrated equal variances between the analysed groups (Table 2).

### 3.1. ADC value

Mean ADC value for benign lesions was 1678, and mean value for malignant lesions was 1097. These means were statistically significant (p < 0.001). All lesions with ADC value below 955 were malignant, while all lesions with ADC value above 1880 were benign.

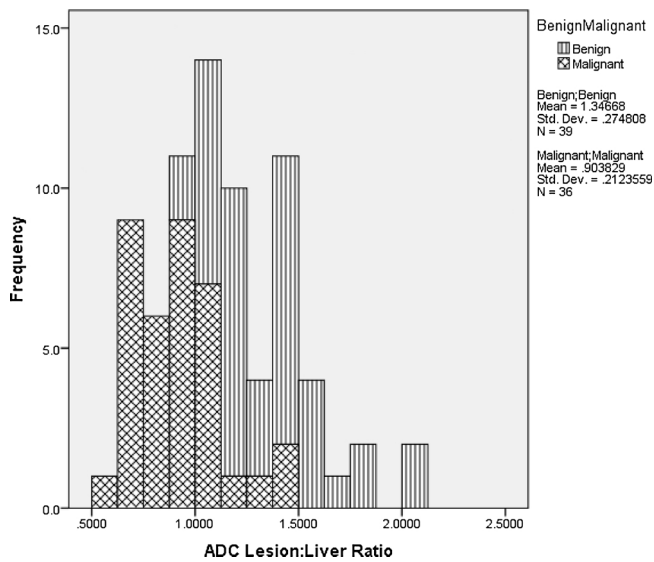


Fig. 3. Spread of all malignant and benign lesions ADC ratio in the study.

ROC curve analysis demonstrated an area under the curve of 0.89. ADC value of 1260 was determined to be the best available cut-off value for differentiating benign and malignant lesions, achieving sensitivity and specificity of 92% and 80%, respectively (Fig. 4).

### 3.2. ADC<sub>ratio</sub>

Mean ADC<sub>ratio</sub> for benign lesions was 1.3467 and for malignant lesions was 0.9038. There was a statistically significant difference between these values ( $p < 0.001$ ). All lesions with ADC<sub>ratio</sub> less than 0.9 were malignant while all lesions with ADC<sub>ratio</sub> greater than 1.5 were benign (Fig. 3).

ROC curve analysis demonstrated an area under the curve of 0.92. ADC<sub>ratio</sub> of 1.1 was determined to be the best available cut-off value for differentiating benign from malignant lesions, with sensitivity and specificity of 82% and 86%, respectively (Fig. 5).

### 3.3. Cutoff values

There was a statistically significant difference between ADC<sub>ratio</sub> and

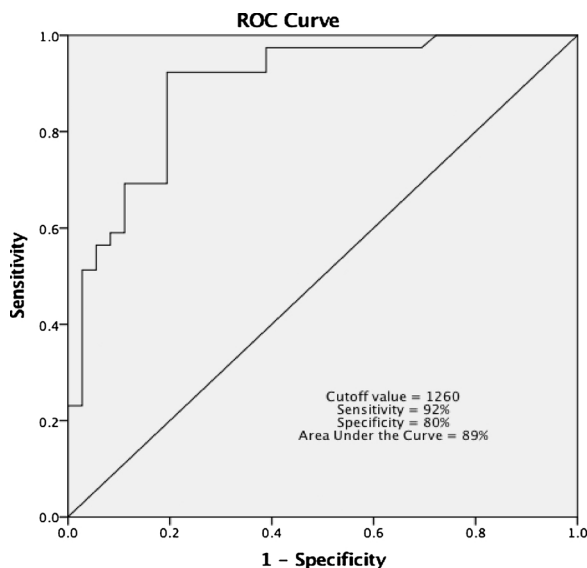


Fig. 4. Receiver operating curve demonstrating optimum ADC value cut-off.

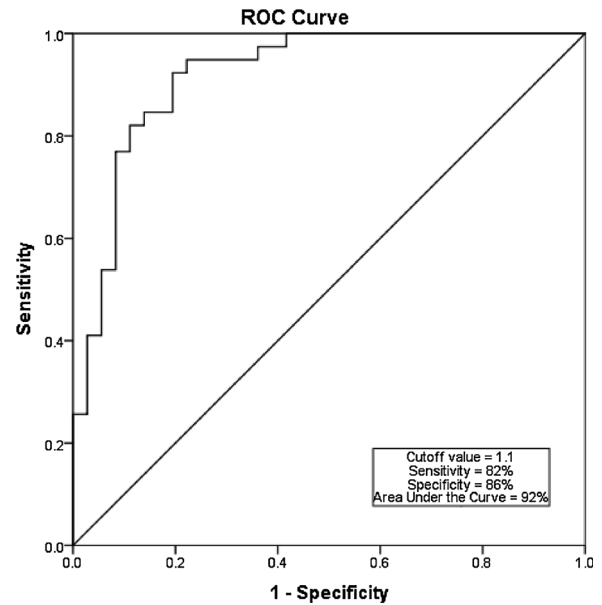


Fig. 5. ROC curve demonstrating optimum ADC ratio of 1.1 with Sens = 82% and Spec = 86%.

ADC values when discriminating benign from malignant lesions using the above cutoff values ( $p = 0.039$ ).

### 3.4. 1.5 T vs 3 T

There was no significant difference in ADC<sub>ratio</sub> data between the 1.5 T and 3 T units ( $p = 0.80$  in the benign group and  $p = 0.060$  in the malignant group). Again, equal variances for 1.5 T and 3 T units were assumed ( $p = 0.073$  and  $p = 0.413$ , respectively). A statistically significant difference between the mean benign and malignant ADC<sub>ratio</sub> was observed in both the 1.5 T and 3 T groups ( $p < 0.001$  and  $p < 0.001$ , respectively).

## 4. Discussion

Quantitative measurements of ADC values have been shown to outperform visual inspection of ADC map in differentiating benign from malignant lesions [20]. A large number of covariates can influence ADC values. ADC<sub>ratio</sub> analysis method utilised in this study is aimed to reduce heterogeneities due to these covariates where possible, while retaining easy application for daily reporting. Lesion to normal liver ADC<sub>ratio</sub> is also easily calculated and can be used in daily practice without having the need to use new software or formulae. ADC value variability in hepatic tumour can vary by as much as 30% between two consecutive MRI scans due to rescan variability on the same patient cohort and same scanning parameters done 15 min apart [21,22]. In our opinion, utilising ratio values theoretically nulls potential heterogeneity caused by covariates, leaving the ratio reflecting true difference between the lesion and background liver. This method had also been used in previous study to access hepatic lesions [18]. The use of lesion: background ADC<sub>ratio</sub> has also been described to assess prostate lesions on MRI [23]. ADC<sub>ratio</sub> in assessment of prostate cancer was found to be superior to ADC value alone [22].

### 4.1. Factors influencing scanning parameters

Recent meta-analysis of the diagnostic capability of breath-hold diffusion-weighted imaging (DWI) for differentiation between malignant and benign hepatic lesions by Chen et al, showed that overall diagnostic performance was high. However, significant heterogeneity among studies was noted in their analysis. A number of covariates



analysed were not found to be the source of this heterogeneity. The analysed covariates included MR scanner, scanning technique, TR, TE, maximum b factor, number of b factors used, mean tumour size and mean patient age [11].

Apart from variable scanning parameters, patient related factors also have an impact on the generated ADC images. Cirrhotic livers have been reported to have lower ADC values when compared to healthy livers [5,20,24,25]. Nonalcoholic liver disease was also noted to record lower ADC values [26]. ADC value variations are demonstrated amongst different hepatic segments where hepatic segment 2 was found to exhibit higher ADC values [4,27].

DWI Images in all our patients were acquired with respiratory trigger. Respiratory triggered image acquisition yielded better image quality and signal to noise ratio when compared to breath-hold and free breathing technique [28,29]. To our knowledge, there is none or very limited literature comparing respiratory and cardiac triggered image acquisition. Up to the present time, dual respiratory and cardiac synchronisation is conducted only in animal experiments using strong magnetic fields above 4.7 T [30,31].

There was no statistical difference between measurement of ADC<sub>ratios</sub> between 1.5 T and 3 T MRI unit used in our case series. This would need to be examined by other investigators; this will be useful as the strength of MRI units varies in different institutions. To our knowledge, there is no previous study comparing the discriminating ability of ADC between images acquired on 1.5 T and 3 T MRI unit.

#### 4.2. Variability in assessing a lesion

A single ADC value may not be able to reliably represent the entire lesion [32]. This is particularly true for larger lesions. Hence, to address intralésional ADC heterogeneity, two ROIs were drawn in the lesion to obtain an average lesion ADC value. For a lesion with heterogeneous signal on ADC images, the ROIs were placed in the brightest and darkest regions within the lesion after excluding cystic necrosis. For homogenous appearing lesions, ROIs were placed in the lesion at different axial slices. A similar process was repeated for the background liver, where the ROIs were measured in each liver lobe.

In order to obtain a reading reflecting true ADC value, a region of interest (ROI) of 50 – 60 mm<sup>2</sup> was used. A study in 2013 conducted by Filipe JP and team showed that measurement above 1 cm<sup>2</sup> can provide an accurate measurement of a homogenous lesion [4]. The authors also reported that there is no difference in measuring 1 cm<sup>2</sup> of the lesion and the entire area of the lesion. Use of a circular ROI of 1 cm<sup>2</sup> needs the lesion to be at least 11.28 mm in diameter, which can potentially exclude some smaller lesions. At the same time, using a very small ROI may not be representative of ADC value. A 50-60mm<sup>2</sup> ROIs were obtained as a compromise. Use of an ROI of 50 – 60 mm<sup>2</sup> needs the lesion diameter to be between 7.07–7.74 mm. Hence, we excluded lesions smaller than 10 mm diameter, to avoid placing the ROI outside the lesion. Also, two ROIs readings were obtained to account for intralésional heterogeneity. There has been no study in the literature that has evaluated the variation in size of ROI as a factor influencing the accuracy of ADC measurement in liver lesions. While it is possible to use smaller ROI in lesions smaller than 1 cm in diameter, effectiveness of smaller ROI can be explored in future investigations.

#### 4.3. Study methods and results yield

Some studies in the past which reported DWI and ADC values to be useful in distinguishing benign vs malignant liver lesion included simple cysts [6,8,10,16]. In daily practice, simple liver cysts are easily identified as they demonstrate distinct fluid MRI signal characteristics. They highly affect the statistical analysis as they have free water mobility and very high ADC values, thus raising ADC average on the benign lesions group and consequently the cut-off point, leading to a selection bias [6]. The key requirement in daily practice is mainly to

distinguish and diagnose solid lesions. When Testa et al 2014 excluded simple cysts from their data set, accuracy of ADC to distinguish between benign and malignant lesions reduced [6]. Other investigators have reported that solid benign lesions ADC values were similar to malignant lesions [15,16]. A study excluding simple cysts conducted by Sutherland et al. concluded that DWI is unreliable in differentiating benign from malignant lesions [14]. Despite the exclusion of simple cysts, the results of our study demonstrate statistically significant ADC<sub>ratio</sub> difference between benign and malignant lesions.

We found that all lesions in our study with ADC<sub>ratio</sub> measuring < 0.9 were malignant while lesions with ADC<sub>ratio</sub> > 1.5 were benign. In theory, malignant lesions by virtue of their increased cellularity are expected to display restricted diffusion and can consequently be differentiated from less cellular, benign lesions [17]. Using pure diffusion coefficient, Wagnet et al showed that within a focal malignant lesions, the “benign” necrotic and fibrotic areas showed less diffusion restriction [33]. Despite careful exclusion of cystic necrotic regions of a lesion, our results correspondingly yield an overlap in ADC<sub>ratio</sub> between benign and malignant lesions. This may be attributed to relatively less restricted diffusion non-cystic necrosis in malignant lesions.

#### 4.4. Limitations of this study

The first is limitations inherent to retrospective analysis. The incidence of lesions in our study group may not be representative of the general population. Another limitation relates to the reference standard used and final diagnosis of the lesions. Majority of benign lesions were not biopsied and the diagnosis was established based on imaging and/or clinical management. A histological examination is an ideal gold standard. However, it can be hard to justify performing a biopsy of a lesion deemed to be benign on imaging, in view of the invasive nature and risks of a biopsy. The cases in study include pre-treatment liver MRIs hence, findings will not be directly applicable to patients who were treated with chemotherapy. ADC assessment is only applicable to solid liver lesions and not applicable to cystic metastasis. Also, our results need to be validated in larger series.

#### 5. Conclusion

Our dataset indicates that lesion to background liver ADC<sub>ratio</sub> is superior in discriminating between benign and malignant focal lesions compared to absolute ADC values of the hepatic lesions. With increasing ADC<sub>ratio</sub>, there is a trend towards benignity. A cut off of ADC<sub>ratio</sub> below 0.9 reflected malignancy while ADC<sub>ratio</sub> above 1.5 reflected benign aetiology. These cut offs can be validated further with further studies with larger number of individual malignant and benign lesions. ADC<sub>ratio</sub> did not differ between 1.5 T and 3 T MRI unit.

#### Declarations of interest

None.

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#### Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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