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Variabilities in apparent diffusion coefficient (ADC) measurements of the spleen and the paraspinal muscle: A single center large cohort study

Yukun Chen [a,1], Panpan Yang [a,1], Caixia Fu [b], Yun Bian [a], Chengwei Shao [a], Chao Ma [a,c,*], Jianping Lu [a]

[a] Department of Radiology, Changhai Hospital of Shanghai, Naval Medical University, Shanghai, 200433, China
[b] Application Developments, Siemens Shenzhen Magnetic Resonance Ltd., Siemens Healthineers, Shenzhen, 518057, China
[c] College of Electronic and Information Engineering, Tongji University, Shanghai, 201804, China

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ABSTRACT

Purpose: Evaluation of the variabilities in apparent diffusion coefficient (ADC) measurements of the spleen (ADC_{spleen}) and the paraspinal muscles (ADC_{muscle}) to identify the reference organ for normalizing the ADC from the abdominal diffusion weighted imaging (DWI).

Methods: Two MRI scanners, with 314 abdominal exams on the GE and 929 on the Siemens system, were used for MRI examinations including DWI (b-values, 50 and 800 s/mm^2). For a subset of 73 exams on the Siemens system a second exam was conducted. Four regions of interest (ROIs) in each exam were placed to measure the ADC_{spleen} and the bilateral ADC_{muscle}. ADC variability between patients (on each scanner separately), ADC variability due to ROI placement between the two ROIs in each organ, and variability in the subset between the first and second exams were assessed.

Results: The ADC_{spleen} was more scattered and variable than the ADC_{muscle} in the comparability (n = 929 and 314 for two MRI scanners, respectively) and repeatability (n = 73) datasets. The Bland-Altmann bias and limits of agreement (LoAs) for the ADC_{spleen} (ICC, 0.47; CV, 0.070) and ADC_{muscle} (ICC, 0.67; CV, 0.023) in the repeatability datasets (n = 73) were −0.1 (−25.7%–25.6%) and −0.3 (−8.8%–8.1%), respectively. For the Siemens system, the Bland-Altmann bias and LoAs for the ADC_{spleen} (ICC, 0.72; CV, 0.061) and ADC_{muscle} (ICC, 0.53; CV, 0.030) in the comparability datasets (n = 929) were 2.1 (−20.0%–24.2%) and 0.7 (−10.0%–11.4%), respectively. Similar findings have been found in the GE system (n = 314). The CVs for the ADC_{muscle} measurements were lower than those of the ADC_{spleen} both in the repeatability and the comparability analyses (all $p < 0.001$).

Conclusion: Paraspinal muscles demonstrate better reference characteristics than the spleen in estimating ADC variability of abdominal DWI.

* Corresponding author. Department of Radiology, Changhai Hospital of Shanghai, Naval Medical University, No. 168 Changhai Road, Shanghai, 200433, China.
E-mail address: mengqihi@gmail.com (C. Ma).
[1] These authors contributed equally to this work.

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1. Introduction

Diffusion-weighted imaging (DWI) is a quantitative MRI technique to measure the changes in the extent and direction of random water motion in the tissue microenvironment modified by interactions with the hydrophobic cell membranes, intracellular organelles, and macromolecules under physiological and pathological conditions [1]. The apparent diffusion coefficient (ADC) derived from the DWI data is a quantitative measure of promising clinical value for the diagnosis and treatment evaluation of diseases [2,3]. Multiple studies have reported that the ADC is lower for malignant lesions compared to benign tissues [4–6]. However, ADC of the normal and neoplastic tissues vary significantly across studies [7,8]. The variations in ADC of abdominal organs and neoplastic lesions between studies can be attributed to the use of different MRI scanners, DWI sequences, acquisition parameters, motion artifacts, susceptibility factors, regions of interest (ROIs), and others [1,4].

Therefore, normalization would be useful to decrease variations in the ADC measurements of normal tissues and tumors [8–10]. In abdominal DWI studies, the spleen and paraspinal muscles are commonly used as references for normalizing the ADC. Currently, there is no consensus on whether the spleen or paraspinal muscle is a better choice as a reference organ for DWI studies of abdominal tissues [11–18]. In this study, we compared the variability in ADC measurements of the spleen and paraspinal muscles in a large cohort of patients to determine the preferred reference organ that can be used to normalize the ADC of the abdominal tissues.

2. Methods

2.1. Patients

The Biomedical Research Ethics Committee of our institution approved this study and the requirement for informed consent from the patients was waived. This study enrolled 1243 patients (835 males, 408 females; mean age, 57.0 ± 12.8 years; age range: 18–91 years) with a total of 1321 liver MRI examinations between June 2019 and May 2020. Patients younger than 18 years old, patients with DWI artifacts, and patients with spleen deficiency or spleen diseases were excluded. Fig. 1 shows the details of the patient enrollment including the inclusion and exclusion criteria. Among the enrolled participants, 73 patients underwent two follow-up MRI examinations with a mean time interval of 134 ± 78 days (range, 1–306 days) in an MRI scanner (Magnetom Skyra scanner) to measure the repeatability of the ADC for the spleen (ADC_{spleen}) and the paraspinal muscle (ADC_{muscle}). Two MR scanners, with 314 abdominal exams on the GE (Discovery MR750) and 929 on the Siemens (Magnetom Skyra) systems, respectively, were used for the comparability analysis, which is assessed from the difference between two regions of interest (ROIs) for the paraspinal muscle (left and right in the muscle) and the spleen.

2.2. DWI

MRI examinations were performed on two 3.0-T scanners, namely, MAGNETOM Skyra (Siemens Healthcare, Erlangen, Germany) and Discovery MR750 (GE Healthcare, Wisconsin, USA). Both were equipped with embedded body coils for signal transmission. Magnetom Skyra was equipped with a combination of a 32-channel posterior spine coil and an 18-channel anterior body coil, whereas

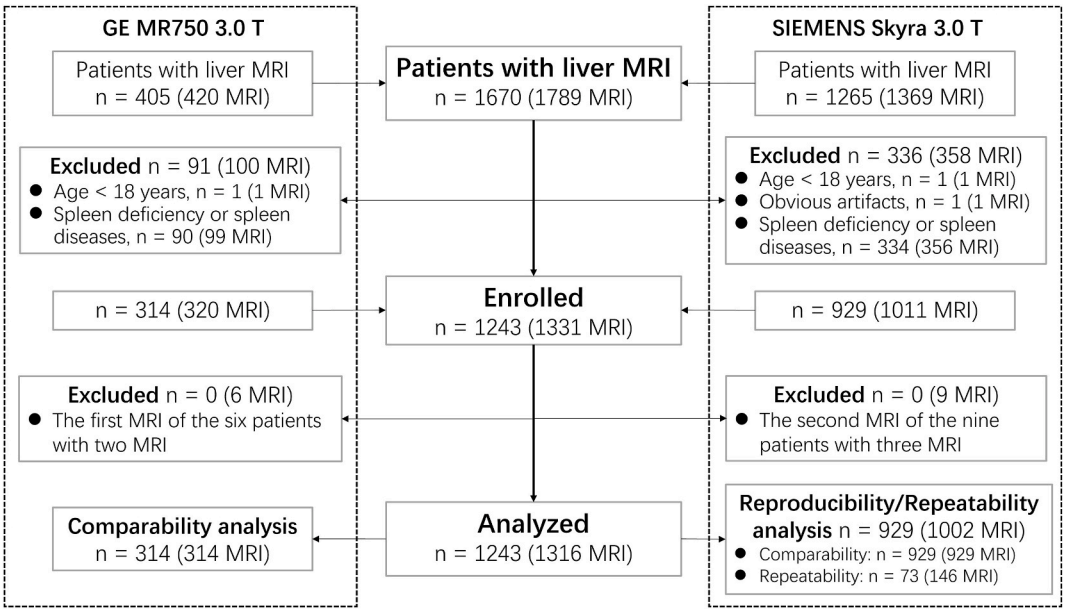

Fig. 1. Flowchart of the patient enrollment criteria in this study.

the Discovery MR750 was equipped with a 32-channel anterior body coil. DWI was performed using the axial single-shot echo-planar-imaging sequence with three orthogonal diffusion gradients. Patients underwent routine clinical liver MRI protocols including free breathing DWI with b values of 50 and 800 s/mm^2. The DWI acquisition parameters in the Magnetom Skyra were as follows: time of repetition = 5000 ms, echo time = 54 ms, matrix = 128 × 104 (reconstruction matrix = 256 × 208), slice/gap thickness = 6 mm/1.2 mm, field of view = 340–400 mm^2, pixel bandwidth = ~2300 Hz, partial Fourier Factor = 6/8, use of parallel imaging = 2, measurement time = ~90 s, average = 1 and 4 for b_{50} and b_{800}, number of slices = 26, respectively. The DWI acquisition parameters in the Discovery MR750 were as follows: time of repetition = 3586 ms, echo time = 77.5 ms, matrix = 128 × 128 (reconstruction matrix = 256 × 256), and slice/gap thickness = 6 mm/1 mm, field of view = 340–400 mm^2, pixel bandwidth = ~1953 Hz, partial Fourier Factor = none, use of parallel imaging = 2, measurement time = ~80 s, average = 1 and 6 for b_{50} and b_{800}, number of slices = 30, respectively. Written informed consent for the publication of the MRI images was obtained from patient.

2.3. DWI data analysis

The ADC maps were generated inline during DWI acquisition using a mono-exponential model. ADC_{spleen} and ADC_{muscle} were measured on a PACS system version 6.0 (GE Healthcare, Milwaukee, WI, USA). Four regions of interest (ROIs) (mean area, 152 ± 3 mm^2; range 144–167 mm^2) [Fig. 2(a-d)]were drawn within the homogenous parts of the spleen (two ROIs) and the bilateral paraspinal muscles for each patient to measure the ADC_{spleen} and ADC_{muscle}, which were also used to calculate the normalized ADC including ADC_{spleen} to ADC_{muscle} ratio ($rADC_{sp/m}$) and the ADC_{muscle} to ADC_{spleen} ratio ($rADC_{m/sp}$). In the repeatability analysis, two DWIs were acquired in the Magnetom Skyra MRI scanner for each of the 73 patients, and average ADCs of twice measurements of the spleen or the paraspinal muscles in each patient were used to evaluate the repeatability of the ADCs and the rADC. In the comparability analysis, the ADCs of bilateral paraspinal muscles and ADC_{spleen} with two different ROIs in each patient were used to evaluate the comparability of the ADCs and the rADC.

2.4. Statistical analysis

Statistical analysis was performed using the MedCalc software version 13.0.0.0 (MedCalc Software, Ostend, Belgium). In order to better reveal which one of the paraspinal muscle and the spleen is a better reference for normalizing the ADC of tissues, we further

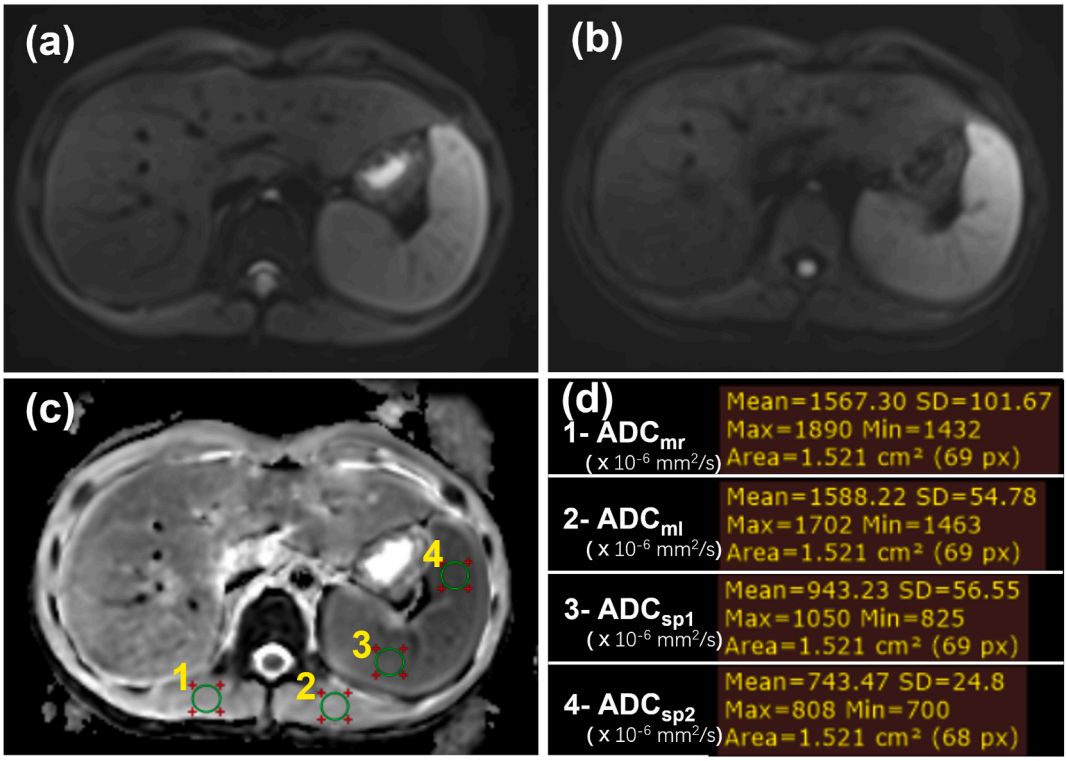

Fig. 2. ADC measurements in the paraspinal muscle and the Spleen. (a) DWI image with b_0. (b) DWI image with b_{800}. (c) Four same-size regions of interest (ROIs) for ADC measurements. (d) Results of ADC_m and ADC_{sp} measurements. The unit of ADC values is 10^{-6} mm^2/s.
ADC = apparent diffusion coefficient, DWI = diffusion weighted imaging, ADC_m = ADC values of the paraspinal muscles, ADC_{sp} = ADC values of the spleen, ADC_{mr} = ADC_m in the right paraspinal muscle, ADC_{ml} = ADC_m in the left paraspinal muscle, ADC_{sp1} = ADC_{sp} of the first ROI in the spleen, ADC_{sp2} = ADC_{sp} of the second ROI in the spleen.

compared the variabilities of the relative values (rADC) in addition to the variabilities of the ADC values of the paraspinal muscle and the spleen. The variability in the ADC and rADC were analyzed by calculating the intraclass correlation coefficient (ICC) for single measurements, Bland-Altman analysis, %repeatability coefficient (%RC) [4], histogram analysis, and the coefficient of variation (CV). The multiple regressions of standard deviations (SDs) for the ADCs (ADC_{spleen} and ADC_{muscle}) of repeated DWI scans were performed with time delay, mean ADC, age, and sex, to demonstrate the absence of biological changes in spleen and muscle. Linear regression analysis and correlation coefficient were performed to determine the correlations between age/gender and the ADCs as well as the rADC of the spleen and paraspinal muscle. Independent samples t-tests were used to compare the differences in the ADC and rADC of the spleen and the paraspinal muscles between the Magnetom Skyra and Discovery MR750 scanners as well as those between different genders. A p-value below 0.05 was considered statistically significant.

3. Results

3.1. Repeatability analysis of the ADC and rADC

The multiple regressions of SDs for the ADC_{spleen} and ADC_{muscle} of repeated DWI scans were performed with time-delay, mean ADC, age, and sex, with p values of 0.70 and 0.25, respectively. The results demonstrate the absence of biological changes in the spleen and muscle for ADC measurements except for no abnormal image changes. Histograms show the ADCs (Fig. 3a) and the normalized ADCs (Fig. 3b) of the spleen and the paraspinal muscle for the 73 patients based on two DWI acquisitions. The %RC for the ADC_{muscle} and ADC_{spleen} were 8.4% and 25.4%, respectively. The SDs of ADC and rADC values *vs.* the mean values were shown in Fig. 4(a–d). Bland-Altman data for the repeatability analyses of the ADCs and the normalized ADCs is summarized in Table 1. The ICC values for the ADC_{muscle} and ADC_{spleen} were 0.67 and 0.47, respectively. The ICC values for the $rADC_{m/sp}$ and $rADC_{sp/m}$ were 0.40 and 0.39, respectively. In comparison with the raw ADC data, $rADC_{m/sp}$ values with the normalized ADC showed lower repeatability with the Bland-Altman bias, and limits of agreement (LoAs) for the ADC_{muscle} and $rADC_{m/sp}$ were −0.3 (−8.8%–8.1%) and −0.3 (−28.6%–29.1%), respectively. The Bland-Altman bias and LoAs for the ADC_{spleen} and $rADC_{sp/m}$ were −0.1 (−25.7%–25.6%) and 0.3 (−29.1%–28.6%), respectively. The CV for the ADC_{muscle} was lower than that of ADC_{spleen}, $rADC_{m/sp}$, and $rADC_{sp/m}$ (all $p < 0.001$; Table 1).

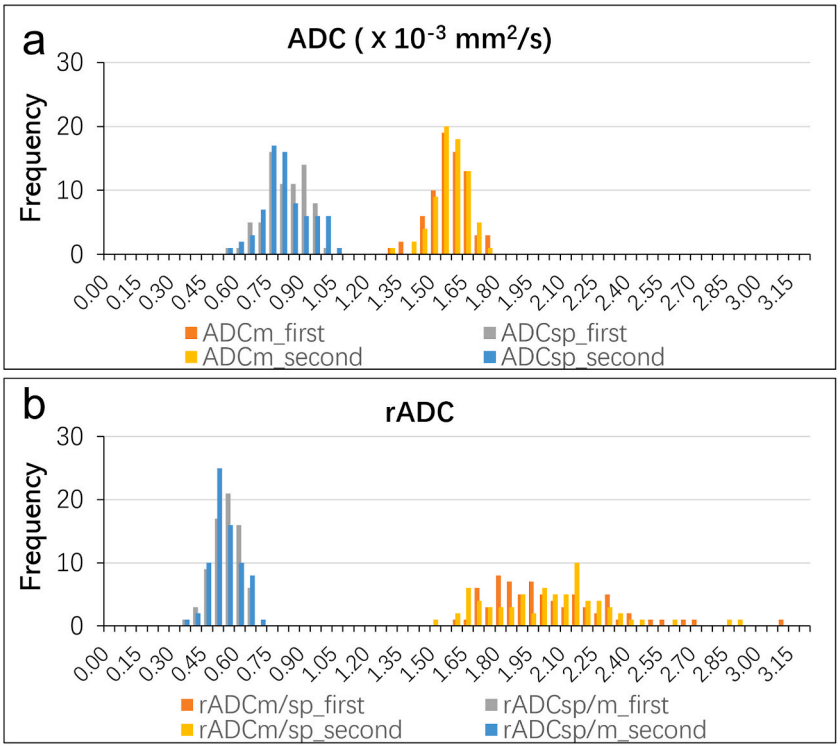

Fig. 3. Histograms of the ADCs ($\times 10^{-3}$ mm^2/s) and normalized ADCs of the spleen and the paraspinal muscle from the two follow-up DWI of 73 patients. (a) The mean ADCs ($\times 10^{-3}$ mm^2/s) for the spleen and the paraspinal muscle of 73 patients from the two follow-up DWIs. **(b)** The normalized ADCs for the spleen and the paraspinal muscles of 73 patients from the two follow-up DWIs. The histogram was generated using 65 bins with a bin size of 0.05.

ADC = apparent diffusion coefficient, DWI = diffusion weighted imaging, ADC_m = ADC of the paraspinal muscles, ADC_{sp} = ADC of the spleen, $rADC_{m/sp}$ = ADC_m to ADC_{sp} ratio, $rADC_{sp/m}$ = ADC_{sp} to ADC_m ratio.

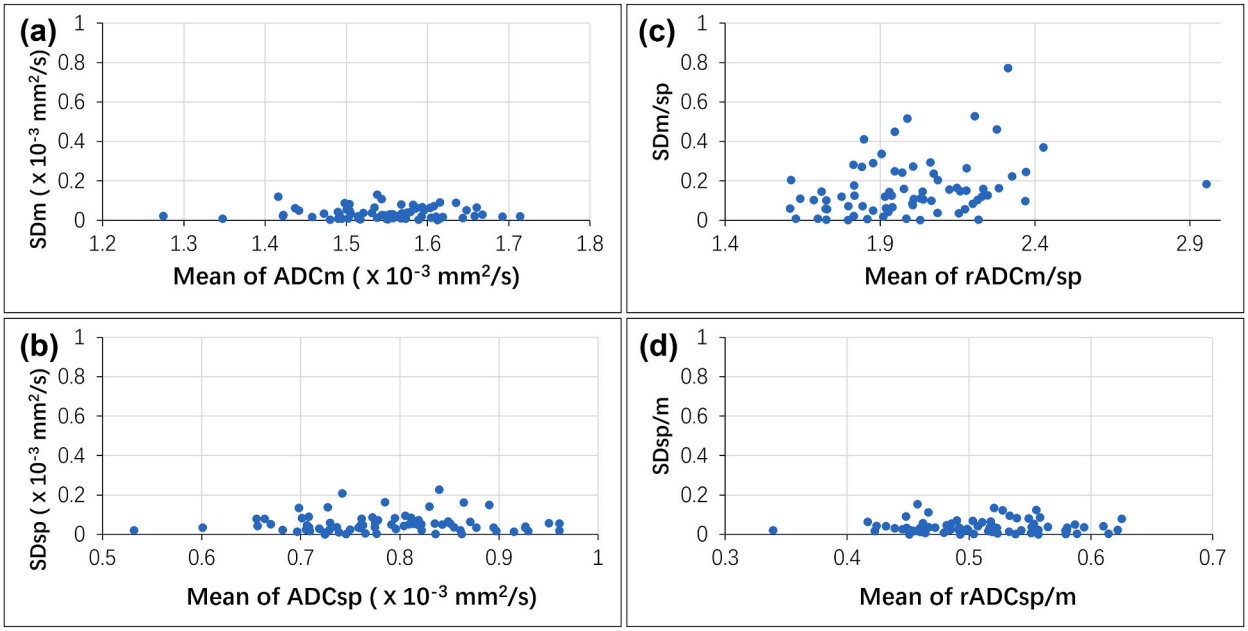

Fig. 4. Plots for the standard deviations (SDs) of the ADC ($\times 10^{-3}$ mm^2/s) and rADC of the repeatability DWI scans *vs.* the mean ADC and rADC values (n = 73). (a) The ADC_{muscle} from the two DWIs of 73 patients. **(b)** The ADC_{spleen} from two DWIs of 73 patients; **(c)** The ratios of the ADC_{muscle} to the ADC_{spleen} ($rADC_{m/sp}$); **(d)** The ratios of the ADC_{spleen} to the ADC_{muscle} ($rADC_{sp/m}$). Y-axis: SD in ADC or normalized ADC measurements; X-axis: mean ADC or normalized ADC.
ADC = apparent diffusion coefficient, DWI = diffusion weighted imaging, ADC_m = ADC of the paraspinal muscles, ADC_{sp} = ADC of the spleen, $rADC_{m/sp}$ = ADC_m to ADC_{sp} ratio, $rADC_{sp/m}$ = ADC_{sp} to ADC_m ratio.

Table 1
Comparisons of the apparent diffusion coefficients (ADCs) ($\times 10^{-3}$ mm^2/s) and the normalized ADCs (rADC) for the spleen and the paraspinal muscle based on the twice diffusion weighted imaging (DWI) measurements (n = 73).

	Paraspinal muscle				Spleen			
Parameter	First DWI	Second DWI	ICC	CV of the two measurements[b]	First DWI	Second DWI	ICC	CV of the two measurements[b]
ADC ($\times 10^{-3}$ mm^2/s)	1.546 ± 0.084 (1.260–1.706)	1.551 ± 0.079 (1.290–1.728)	0.67	0.023 ± 0.019 (0.001–0.085) *,†	0.786 ± 0.095 (0.517–0.979)	0.787 ± 0.104 (0.547–1.000)	0.47	0.070 ± 0.060 (0.001–0.281) *
rADC	1.996 ± 0.277 (1.557–3.084)	2.003 ± 0.278 (1.468–2.858)	0.40	0.078 ± 0.068 (0.001–0.333)†	0.510 ± 0.064 (0.324–0.642)	0.509 ± 0.070 (0.350–0.681)	0.39	0.078 ± 0.068 (0.001–0.333)
CV of ADC[a]	0.052 $\times 10^{-3}$ mm^2/s				0.126 $\times 10^{-3}$ mm^2/s			
CV of rADC[a]	0.139				0.131			

Data are represented as means ± standard deviation; Data in parentheses represent the range of the values.
ADC, apparent diffusion coefficient; CV, coefficient of variation, rADC, ratio of ADC.
*, †P values < 0.001; [a]The mean CV values of all the measured ADC values for paraspinal muscle or spleen; [b]CV was calculated from the two ADC measurements for paraspinal muscle or spleen from each of the 73 patients.

3.2. Comparability analysis of the ADC and rADC

We analyzed the ADCs and normalized ADCs of the spleen and the paraspinal muscle for 929 patients based on the DWIs acquired on the Magnetom Skyra. The ICC values for the ADC_{muscle} and ADC_{spleen} were 0.53 and 0.72, respectively. The ICC values for the $rADC_{m/sp}$ and the $rADC_{sp/m}$ were 0.93 and 0.73, respectively. The Bland-Altman bias and LoAs for the ADC_{muscle} and $rADC_{m/sp}$ were 0.7 (−10.0%–11.4%). The Bland-Altman bias and LoAs for the ADC_{spleen} and $rADC_{sp/m}$ were 2.1 (−20.0%–24.2%). The %RC for the ADC_{muscle} and ADC_{spleen} were 10.8% and 22.5%, respectively. We then analyzed the ADCs and the normalized ADCs of the spleen and the paraspinal muscle for 314 patients based on the DWIs acquired on the Discovery MR750. The ICC values for the ADC_{muscle} and $rADC_{m/sp}$ were 0.43 and 0.85, respectively. The Bland-Altman bias and LoAs for the ADC_{muscle} and the $rADC_{m/sp}$ were 0.9 (−8.7%–10.6%). The ICC values for the ADC_{spleen} and the $rADC_{sp/m}$ were 0.57 and 0.62, respectively. The Bland-Altman bias and LoAs for the ADC_{spleen} and the $rADC_{sp/m}$ were −0.3 (−16.8%–16.2%). The %RC for the ADC_{muscle} and ADC_{spleen} were 9.8% and 16.5%, respectively. The above results are shown in Table 2 and Fig. 5(a–d). The CVs for the ADC_{muscle} and $rADC_{m/sp}$ were lower than the CVs for the ADC_{spleen} and $rADC_{sp/m}$ ($p < 0.001$).

Table 2
Comparisons of the two measurements of the ADC ($\times 10^{-3}$ mm^2/s) and rADC for the spleen and the paraspinal muscles of the 2 patient cohorts.

Parameter	Magnetom Skyra (n = 929)						
	Paraspinal muscle				Spleen		
	Right	Left	ICC	CV of two measurements[b]	First ROI	Second ROI	ICC
ADC ($\times 10^{-3}$ mm^2/s)	1.558 ± 0.092 (1.123–1.912)	1.546 ± 0.081 (1.127–1.811)	0.53	0.030 ± 0.025 (0.000–0.149)	0.801 ± 0.123 (0.506–1.329)	0.783 ± 0.116 (0.446–1.357)	0.72
rADC	2.005 ± 0.295 (1.146–3.021)	1.989 ± 0.286 (1.201–3.040)	0.93	0.030 ± 0.025 (0.000–0.149)	0.517 ± 0.081 (0.324–0.850)	0.505 ± 0.077 (0.292–0.887)	0.73
CV of ADC[a]	0.049 $\times 10^{-3}$ mm^2/s				0.140 $\times 10^{-3}$ mm^2/s		
CV of rADC[a]	0.143				0.144		

Data are represented as means ± standard deviation; Data in parentheses represent the range of values.
ADC, apparent diffusion coefficient; CV, coefficient of variation; rADC, the ratio of ADCs.
[a]The mean CV values of all the measured ADC values for the paraspinal muscle or spleen; [b]CV was calculated from the two ADC measurements for Paraspinal muscle or spleen from each of the 73 patients.

3.3. Comparisons of ADC and rADC between the two MRI scanners

The mean ADC_{muscle} (1.493 x 10^{-3} mm^2/s *vs.* 1.552 x 10^{-3} mm^2/s, CV = 3.9%) and $rADC_{m/sp}$ (1.828 *vs.* 1.997, CV = 8.8%) based on the DWIs acquired with Discovery MR750 were lower than those based on the DWIs acquired with the Magnetom Skyra. However, the mean ADC_{spleen} (0.822 x 10^{-3} mm^2/s *vs.* 0.792 x 10^{-3} mm^2/s, CV = 3.7%) and $rADC_{sp/m}$ (0.551 *vs.* 0.511, CV = 7.5%) based on the DWIs acquired with the Discovery MR750-derived DWIs were higher than those based on the DWIs acquired with the Magnetom Skyra (Fig. 6).

3.4. Effects of gender and age on ADC and rADC

We analyzed the correlations of the ADC and the rADC values of the spleen and the paraspinal muscle with the age and gender of 1243 patients. The ADC_{muscle} and $rADC_{m/sp}$ for the males were higher than those for the females (both $P < 0.001$; Table 3). In both males and females, linear regression analyses and correlation coefficient results showed that the ADC_{muscle} (correlation coefficient = −0.155, $P < 0.001$; slope coefficients, −0.001) and the $rADC_{m/sp}$ (correlation coefficient = −0.097, $P < 0.001$; slope coefficients, −0.002) were inversely related to the age of the patients (Fig. 7).

The ADC_{spleen} and $rADC_{sp/m}$ for the males were lower than those for the females ($P = 0.003$ and $P < 0.001$, respectively). Furthermore, linear regression analysis and correlation coefficient results showed that the ADC_{spleen} (correlation coefficient = 0.06, $P = 0.035$; slope coefficients, 0.001) and $rADC_{sp/m}$ (correlation coefficient = 0.116, $P < 0.001$; slope coefficients, 0.001) values increased with the age of patients (Fig. 7).

4. Discussion

Our study demonstrated that the ADC_{spleen} was more scattered and variable than the ADC_{muscle} both in the comparability and repeatability analyses. This was confirmed by the larger range of LoAs, %RC and CVs for the two measurements of ADC_{spleen}. The CVs for ADC_{muscle} in the repeatability (2.3%) and the comparability (3.0% for Magnetom Skyra and 2.9% for Discovery MR750) analyses and the analysis between MRI scanners (3.9%) were consistent with those reported in the in vitro experiments using DWI phantoms [19–21]. The %RC of ADC_{muscle} was 8.4%, which was lower than that of the organs of the liver (26%) and prostate (47%) [4]. Therefore, the paraspinal muscle is a better choice as an internal reference for investigating the variability in the ADC measurements during multicenter longitudinal studies with different MRI scanners. Furthermore, in our study, the mean ADC_{spleen} and ADC_{muscle} were 0.80 x 10^{-3} mm^2/s and 1.54 x 10^{-3} mm^2/s, respectively. These values were consistent with the previously reported ADCs for these tissues [8–18].

DWI is a commonly used clinical tool for the diagnostic and treatment evaluation of various diseases. However, ~10% variability is observed in the ADCs between MRI centers because of differences in the DWI protocols, pulse sequences, and scanner operator et al. [2,4,7,22]. Previous reports have demonstrated significant differences in the ADC between abdominal tumors and normal abdominal tissues [2,7]. Therefore, the normalized ADC of the target tissues is more reliable than the raw ADC [8,15,16,18]. Some studies have shown that the paraspinal muscle is a good option as a reference organ because of low variability in its ADC under various abdominal disease conditions [13,23]. The spleen is another reference organ for normalizing the ADC of abdominal organs [15,16,18]. Song et al. suggested that the spleen was a better reference organ than the paraspinal muscle for decreasing the variability in the ADC measurements of the abdominal organs based on the ICC values [16]. Koc et al. found that the area under the receiver operating characteristic curve values of the normalized ADCs using paraspinal muscle as a reference organ are higher than those normalized using the spleen as a reference organ for distinguishing the malignant and the benign abdominal lesions [17]. Additionally, Ding et al. also reported that the paraspinal muscle was a better choice as a reference organ than the spleen for normalizing the ADC of the pancreas

Magnetom Skyra (n = 929)	Discovery MR750 (n = 314)							
Spleen	Paraspinal muscle				Spleen			
CV of two measurements[b]	Right	Left	ICC	CV of two measurements[b]	First ROI	Second ROI	ICC	CV of two measurements[b]
0.061 ± 0.053 (0.000–0.284)	1.500 ± 0.066 (1.339–1.740)	1.486 ± 0.071 (1.312–1.675)	0.43	0.029 ± 0.021 (0–0.101)	0.820 ± 0.069 (0.625–0.993)	0.823 ± 0.078 (0.607–0.996)	0.57	0.047 ± 0.036 (0–0.224)
0.061 ± 0.053 (0.000–0.284)	1.836 ± 0.158 (1.500–2.413)	1.820 ± 0.168 (1.448–2.306)	0.85	0.029 ± 0.021 (0–0.101)	0.550 ± 0.051 (0.389–0.689)	0.552 ± 0.053 (0.441–0.670)	0.62	0.047 ± 0.036 (0–0.224)
0.140 × 10^{-3} mm^2/s	0.039 × 10^{-3} mm^2/s				0.079 × 10-3 mm2/s			
0.144	0.086				0.085			

[13]. In this study, the comparability of the $rADC_{m/sp}$ value was satisfactory with the LoA ranging from −10.0% to 11.4%. However, the repeatability of the $rADC_{m/sp}$ value was not satisfactory because the LoA ranged widely from −29.1% to 28.6%. Furthermore, $rADC_{m/sp}$ was more scattered than the ADC_{muscle} in the repeatability analysis. This can be attributed to a larger variation of the ADC_{spleen} compared to the variation in the ADC_{muscle}. Therefore, the CV of the $rADC_{m/sp}$ was higher than that of the ADC_{muscle}. If the variability in the ADCs for the target tissues or tumors was lower than that of the spleen, the errors would be magnified if the spleen is used as the reference organ. Despite a good correlation with the ICC of 0.72, ADC_{spleen} was highly variable with the LoA ranging from −20.0% to 24.2%. In comparison, ADC_{muscle} was less variable with the LoA ranging from −10.0% to 11.4% despite a moderate correlation with the ICC of 0.53. Nearly 25.4% (424/1670) of patients were excluded from this study because of splenic deficiency or diseases. In such cases, the spleen could not be used for normalizing the ADC of the abdominal organs. Several consensus guidelines have been proposed regarding the use of quantitative DWI sequences, parameters, and ROI methods for the abdomen to improve the accuracy, repeatability, and comparability of the absolute ADC and normalized ADC [24–27].

In the current study, even though the correlation of the ADC_{spleen} with age is significant, the correlation coefficient is low suggesting negligible ADC dependence. These findings are inconsistent with Li et al. reports [28] but consistent with Nazarlou et al.'s findings [29]. Furthermore, our results demonstrated that the mean ADCs and normalized ADCs correlated with gender for both the spleen and the paraspinal muscle. The findings are inconsistent with Nazarlou et al.'s reports [29]. The main reason for this discrepancy may be due to the differences in the sample size and the MRI parameters used in these studies. These findings should be taken into

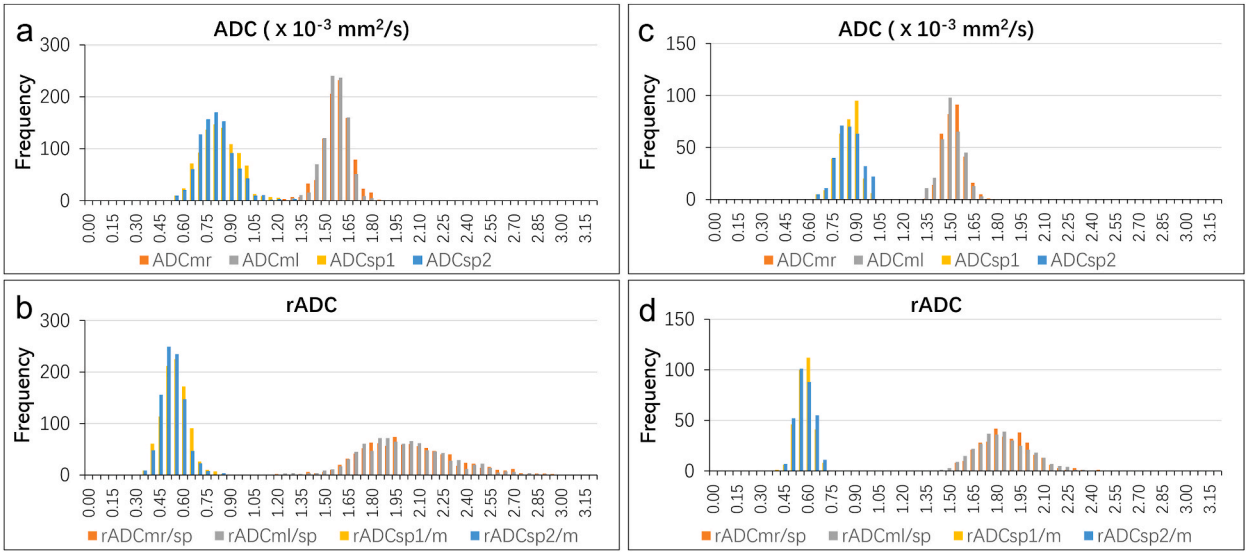

Fig. 5. Histograms of the ADCs (× 10^{-3} mm^2/s) and the normalized ADCs for the spleen and the paraspinal muscle of each patient in two cohorts with DWI acquisitions on two MRI scanners. **(a)** The mean ADC (× 10^{-3} mm^2/s) of the spleen and the paraspinal muscle of the 929 patients (Magnetom Skyra). **(b)** The normalized ADC of the spleen and the paraspinal muscle of the 929 patients (Magnetom Skyra). **(c)** The mean ADC (× 10^{-3} mm^2/s) of the spleen and the paraspinal muscles derived from the DWIs of the 314 patients (Discovery MR750). **(d)** The normalized ADC of the spleen and the paraspinal muscle derived from the DWIs of the 314 patients (Discovery MR750). The histogram was generated using 65 bins with a bin size of 0.05. The indices "1" and "2" or "r"/"l" refer to the different ROIs described in Fig. 2.
ADC = apparent diffusion coefficient, DWI = diffusion weighted imaging ADC_m = ADC of the paraspinal muscles, ADC_{sp} = ADC of the spleen, $rADC_{m/sp}$ = ADC_m to ADC_{sp} ratio, $rADC_{sp/m}$ = ADC_{sp} to ADC_m ratio.

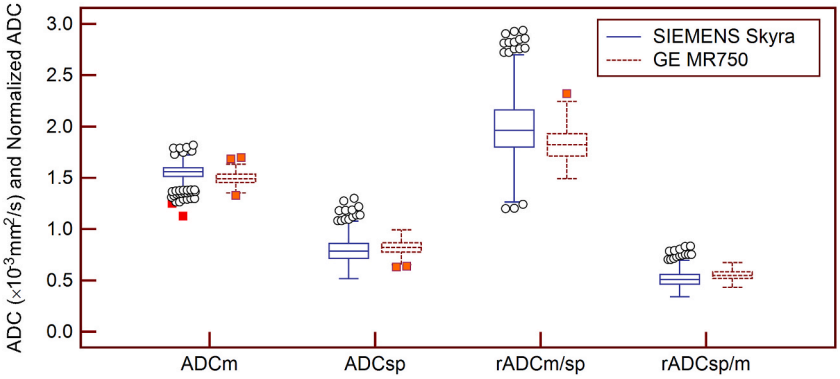

Fig. 6. The Box-and-Whisker plots show the mean ADCs ($\times 10^{-3}$ mm^2/s) and rADCs of the spleen and paraspinal muscle from the two MRI scanners. The central box represents the values from the lower to the upper quartile (25th percentile to 75th percentile). The middle line represents the median. The plots with solid blue lines represent the mean ADC and rADC values of the 929 patients from the DWIs acquired using the Magnetom Skyra. The plots with red-dotted lines represent the mean ADC and rADC values of the 314 patients from the DWIs acquired using the Discovery MR 750 scanner. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

ADC = apparent diffusion coefficient, ADC_m = ADC values of the paraspinal muscles, ADC_{sp} = ADC values of the spleen, $rADC_{m/sp}$ = ADC_m to ADC_{sp} ratio, $rADC_{sp/m}$ = ADC_{sp} to ADC_m ratio.

Table 3

The association between apparent diffusion coefficients (ADCs) ($\times 10^{-3}$ mm^2/s) and the ratio of ADCs (rADCs) for the spleen and paraspinal muscles and gender (n = 1243).

	Paraspinal muscle (n = 1243)			Spleen (n = 1243)		
Parameter	Male (n = 835)	Female (n = 408)	P*	Male (n = 835)	Female (n = 408)	P*
ADC ($\times 10^{-3}$ mm^2/s)	1.544 ± 0.073 (1.125–1.819)	1.522 ± 0.079 (1.247–1.760)	<0.001	0.793 ± 0.104 (0.515–1.276)	0.812 ± 0.098 (0.539–1.300)	0.003
rADC	1.981 ± 0.279 (1.199–2.938)	1.900 ± 0.239 (1.203–2.905)	<0.001	0.515 ± 0.071 (0.340–0.834)	0.534 ± 0.065 (0.344–0.831)	<0.001

Data are represented as means ± standard deviation; Data in parentheses represent the range of values.
ADC, apparent diffusion coefficient; rADC, the ratio of ADC.
*Independent samples *t*-test.

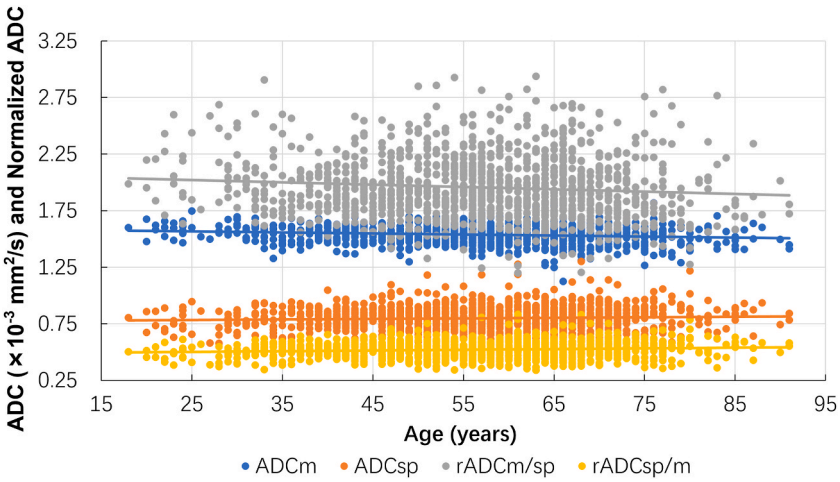

Fig. 7. The scatter diagram shows the ADCs ($\times 10^{-3}$ mm^2/s) and rADCs of the paraspinal muscle and the spleen versus the age of patients (n = 1243). Y-axis: ADC ($\times 10^{-3}$ mm^2/s) or rADC; X-axis: Patient age. The lines represent the linear regression lines.

ADC = apparent diffusion coefficient, ADC_m = ADC of the paraspinal muscles, ADC_{sp} = ADC of the spleen, $rADC_{m/sp}$ = ADC_m to ADC_{sp} ratio, $rADC_{sp/m}$ = ADC_{sp} to ADC_m ratio.

consideration in future applications.

This study has a few limitations. Firstly, our hospital performed DWI using the free-breathing method to optimize the imaging time and the signal-to-noise ratio. The free-breathing method is versatile in abdomen MRI [30]. However, abdominal DWI is also performed in many cases using the breath-hold and respiratory-triggered methods. Therefore, in future studies, the variability in ADC_{spleen} and ADC_{muscle} should be investigated for DWI studies with breath-hold and respiratory-triggered methods. Secondly, only two scanners were used, and longitudinal scans were on a single system, we did not investigate the diagnostic performance of the normalized ADC for distinguishing between different pathological types of abdominal lesions. Future studies need to investigate this because it may be clinically significant and are necessary to confirm our findings for abdominal tumors.

5. Conclusions

Our study demonstrated that the ADC_{muscle} was less variable than ADC_{spleen} and is a better choice as the internal reference to investigate ADC variability across MRI scanners. The spleen is not a suitable reference for normalizing ADC of abdominal tissues or tumors with low ADC variability.

Author contribution statement

Yukun Chen & Panpan Yang; Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Caixia Fu; Yun Bian & Chengwei Shao: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Chao Ma & Jianping Lu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Additional information

Supplementary content related to this article has been published online at [URL].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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