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HEPATOBILIARY

Whole-lesion histogram analysis metrics of the apparent diffusion coefficient: a correlation study with histological grade of hepatocellular carcinoma

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Abstract

Purpose The study evaluated the relationship between the histological grade of hepatocellular carcinoma (HCC) and the histogram-derived parameters of apparent diffusion coefficient (ADC) obtained from the whole-lesion assessment of diffusion-weighted magnetic resonance (MR) imaging in the liver.

Methods A total of 51 patients were included. The parameters were correlated with the Edmondson-Steiner grades by using the Spearman correlation coefficient (ρ). The differences of ADC parameters between different tumor histological grades were compared using the Mann–Whitney U test. The extent to which each parameter aided in differentiating tumors with poor performance (III, IV) and fair performance (I, II) was assessed by using the area under the receiver operating characteristic curve (Az).

Results The 25th percentile ADC exhibits the most negative correlation with histological grade ($\rho = -0.397$), followed by the 30th percentile ADC ($\rho = -0.395$), the minimum ADC value ($\rho = -0.390$) and the 20th percentile ADC ($\rho = -0.385$), whereas the minimum ADC value yielded the highest Az (0.763) in the discrimination of tumor foci with poor differentiation from fairly differentiated HCCs. The minimum ADC of 4.15×10^{-3} mm^2/s or lower was considered to indicate poorly differentiated performance, and the corresponding sensitivity and specificity were 66.7 and 90.9%, respectively.

Conclusion The 25th percentile ADC showed a stronger correlation with the histological grade of HCC than other ADC parameters, and the minimum ADC value might be an optimal metric for determining poor and fair differentiations of HCC in DWI.

Keywords Hepatocellular carcinoma · Diffusion-weighted imaging · ADC histogram · Histological differentiation

Introduction

Hepatocellular carcinoma (HCC) is a well-known malignant tumor with high incidence and carries a poor prognosis. Primary hepatic carcinoma is the sixth most common cancer and the third most common contributor to worldwide cancer mortality [1, 2]. Even after undergoing curative resection, high recurrence rates in HCC (50–60% at 3 years and 70–100% at 5 years) have been documented in patients with evidence of the significantly dismal outcome of HCC [3]. Histological grading is typically based upon the biological behavior of HCC, thus supplying valuable prognosis information. The classical and most commonly adopted grading system for HCC is the Edmondson–Steiner system, which was published in 1954 [4]. Edmondson–Steiner grading is a crucial and efficient predictor for long-term survival of patients [5, 6]. However, no reliable imaging modalities are

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available to accurately assess the Edmondson–Steiner grade of HCC.

Diffusion-weighted imaging (DWI) can noninvasively identify water molecule diffusion in vivo and enables characterization of pathological grade. DWI has been increasingly used in the characterization of liver diseases due to the recent availability of the echo planar imaging (EPI) technique with the ability to breathing and cardiac movement. Several studies have evaluated associations between quantitative diffusion-weighted imaging and Edmondson–Steiner grade [7–10]. The ADC is a parameter that can be measured by most clinical commercial MR imaging platforms. However, the best parameter derived from multiple pixels, which are derived in a voxel-by-voxel manner from liver whole lesions, is equivocal for evaluating the correlation of ADC values with HCC grading. Certain studies have used the mean and minimum ADC values for correlation between ADC values and grade of HCC [8, 11, whereas others have used the ADC histogram markers of standard deviation, maximum, mode, percentiles (5th, 10th, 25th, 50th, 75th, and 90th), skew, and kurtosis [12].

To investigate the robust ADC histogram parameters for predicting the histological grade of HCC, standardization of measured ADC parameters is a crucial procedure. The arbitrariness of the region of interest (ROI) imposes a significant challenge to eliminating bias, which contributes to the limited application of ADC parameters. When the ROI is interspersed with lesions on a slice, the measured ADC might be artificially inconsistent with another slice [12]. Furthermore, the entire three-dimensional (3D) analysis of the lesion might better capture the heterogeneity of HCC.

The purpose of our study was to investigate the correlation between histological grade of HCC and the ADC histogram parameters derived from the whole-lesion assessment of HCC via DWI and to determine which ADC parameters might best identify different grades of HCC.

Materials and methods

This retrospective study protocol was approved by the institutional review board, and informed consent was waived.

Patients

We searched the Picture Archiving and Communication Systems (PACS) of our institution to find patients who met the following eligibility criteria: (a) underwent abdomen MR imaging at 3.0 T enrolled in the same sequence of DWI with *b* values of 0 s/mm^2 and 800 s/mm^2 between December 2015 and June 2018, (b) hepatectomy performed at our institution within 3 months after MRI, and (c) tumors pathologically confirmed as HCC. Patients who (a) had undergone previous locoregional treatment or surgery for HCC ($n=15$), (b) had imaging with artifacts or incomplete acquisition resulting in nondiagnostic examination ($n=8$), or (c) had blurred liver lesion boundaries due to an infiltrative features ($n=5$) were excluded.

MR data acquisition

Images were collected on a 3-Tesla (3T) MR unit (MAGNETOM Skyra, Siemens Healthcare, Erlangen, Germany) with an 18-channel phased-array body coil and spine coil. The baseline MR imaging included a T1-weighted turbo field echo in-phase and opposed-phase sequence, a breath-hold multishot T2-weighted sequence, and a respiratory-triggered heavily T2-weighted sequence. Echo-planar diffusion weighted imaging was acquired using respiratory triggering before administration of contrast. A single shot echo planar imaging diffusion sequence (DW-EPI) was acquired in combination with parallel imaging using an array spatial sensitivity encoding technique (ASSET) factor of 2 to minimize geometrical distortions (Table 1).

Histopathologic analysis and volume measurement

All specimen sections were fixed in 10% formaldehyde solution and embedded in paraffin. A staff hepatic pathologist at our institution analyzed each lesion and assigned histopathological grades, which were defined as well (Edmondson grade I), moderate (Edmondson grade II), or poorly differentiated (Edmondson grades III or IV). The higher grade was finally determined if a lesion expressed mixed histological grades.

Subsequently, using software (*FireVoxel*, 285; https://wp.nyu.edu/firevoxel/downloads/), two radiologists with experience in interpreting abdominal MRI results and working in consensus traced the boundary of the HCC and

Table 1 Magnetic resonance imaging pulse sequence parameters

Parameter	TSE T2WI	3D VIBE	DWI EPI (0, 400, 800 s/mm^2)
TR (ms)	3960	4.15	5000
TE (ms)	96	2.01	55
No of signals acquired	2	1	1
Matrix size	320×320	167×256	160×160
FOV	36×36	36×36	240×240
Flip angle (degrees)	160	9	90
Section thickness (mm)	6	3	6
Intersection gap (mm)	1.2	0.6	1.2

TR repetition time, *TE* echo time, *FOV* Field of view, *TSE* turbo spin echo, *3D VIBE* three-dimensional Volumetric interpolated breath-hold examination, *EPI* echo planar imaging

delineated the regions of interest (ROIs). The ROI encircled each slice of lesion components on the DWI ($b = 0$ s/mm^2), which included the regions of the lesion portion as much as possible and contained cystic, necrotic, or hemorrhagic areas in the lesions for more complete information (Figs. 1, 2). A voxel-based parametric map analysis of each volume of ROI was performed (Fig. 2), and software (version 22, SPSS) was used to calculate the 5th percentile ADC to 95th percentile ADC base at 5 intervals.

Statistical analysis

The Spearman correlation coefficient (ρ) was used to assess the correlation between the ADC parameters (minimum, maximum, mean, standard deviation, inhomogeneity, skewness, kurtosis, entropy, and 5th–95th percentile ADC base at 5 intervals) and histopathological grades of HCC. The differences in ADC parameters between the tumor histological grades were compared using the Mann–Whitney U test. Binary categories (poorly differentiated HCC vs. nonpoorly differentiated) were identified for receiver operating characteristic (ROC) analysis.

The ADC parameters were tabulated according to histopathological grades. Box plots of the ADC parameters were plotted for each histopathological grade subgroup of lesions. The ADC parameters with different status of histopathological grades in three subgroups were tested and compared using the Mann–Whitney U test. The area under the ROC curve (Az) was calculated to assess the ability of each ADC parameter in discriminating the histopathological grades (poorly differentiated HCC vs. nonpoorly differentiated). The cut off values of each parameter were determined by the maximal Youden index (sensitivity + specificity − 1). All statistical analyses were performed with software (version 22, SPSS), and $P < 0.05$ was indicated as statistically significant.

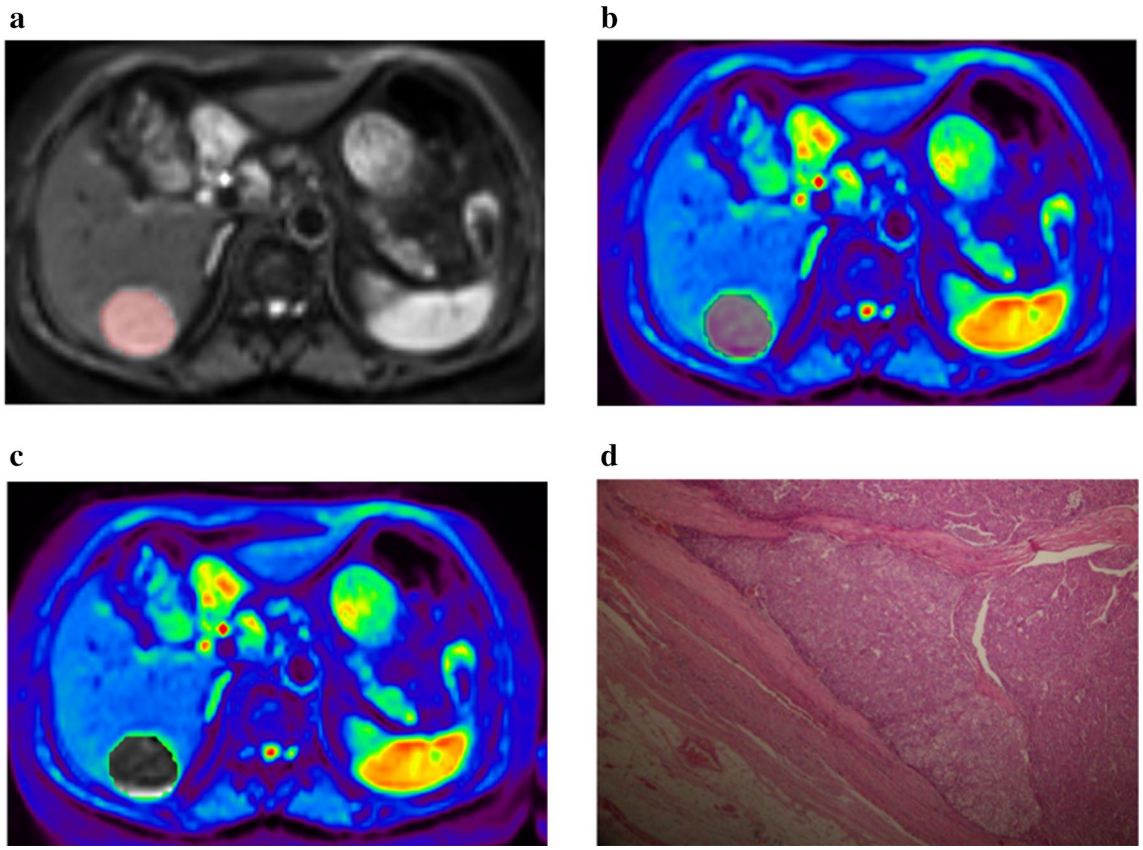

Fig. 1 Images from a 65-year-old woman. Process of creating the ADC histogram. **a** To create an ROI on diffusion-weighted imaging ($b = 0$ s/mm^2), the ROIs were set at the entire tumor through all slices on the diffusion-weighted images. **b** The diffusion in the lesion is well visualized by changing the images into rainbow colors. Calculation of the ADC map within our ROI. **c** To convert the ADC map into decimal format, we multiplied the parametric maps by 100000 and dropped all digits after the decimal point. **d** Photomicrograph of histopathological staining (hematoxylin–eosin stain × 100) shows HCC with Edmondson–Steiner grade of II

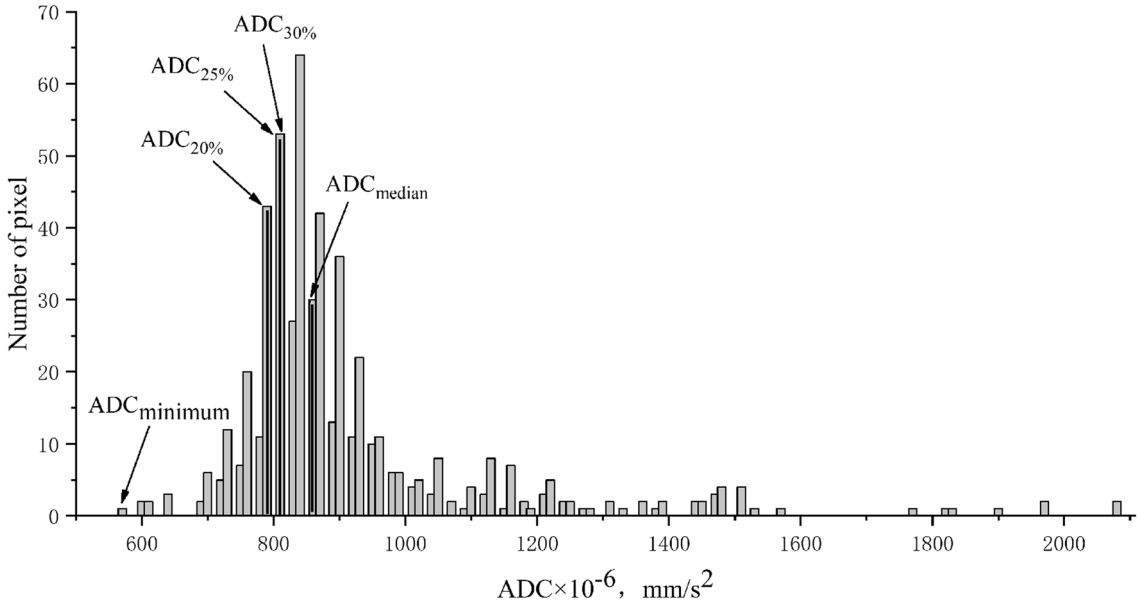

Fig. 2 Data acquired from each slice were summed to derive the voxel-by-voxel ADC values for the entire tumor, and the ADC histogram parameters were generated (the same patient as in Fig. 1)

Results

A total of 51 patients with 51 HCCs (median age 51 years; age range 36–76 years), consisting of 40 men (median age 51 years; age range 43–79 years) and 11 women (median age 52 years; age range 36–65 years), were included in the study. The tumor diameter ranged from 6 to 118 mm (32.50 ± 20.40 mm). The interval time between specimen collection and MR examination ranged from 2 to 62 days, with a median time of 8 days. Pathological examinations revealed 8 well differentiated, 25 moderately differentiated, and 18 poorly differentiated HCCs(III15, IV3). Among the tumors, there were 42 HCCs with cirrhosis which was caused by hepatitis B (32 cases), alcohol (3 cases), hepatitis C (5 cases), and non alcoholic fatty liver disease (2 cases). Elevated alpha-fetoprotein (AFP) was detected higher than normal in 36 cases (> 5.8 IU/ml). The intraclass correlation coefficient of ADC values between the two reviewers was good (ICC = 0.78, 95% confidence interval 0.61–0.87) of 20 patients with randomly chosen lesion diameters.

The parameters of the ADC histograms associated with each histological grade are summarized in Table 2 (Fig. 3). Of the ADC parameters, the 25th percentile ADC exhibits the strongest correlation with histological grade ($\rho = -0.397$), followed by the 30th percentile ADC ($\rho = -0.395$), the minimum ADC value ($\rho = -0.390$) and the 20th percentile ADC ($\rho = -0.385$). The Mann–Whitney *U* test showed significant differences between well differentiated and poorly differentiated HCC ($P = 0.011$) and between moderately differentiated and poorly differentiated HCC ($P = 0.045$), whereas the difference comparison using the 25th ADCs for well differentiated HCC with moderately differentiated HCC was not statistically significant ($P = 0.162$).

The parameters of the ADC histograms of poorly differentiated HCC and well and moderately differentiated HCC are shown in Table 3. In the discrimination of tumor foci with poorly differentiated HCCs from nonpoorly differentiated HCCs, the minimum ADC value yielded the highest Az (0.763; 95% confidence interval 0.618, 0.907), followed by the 30th percentile ADC (Az = 0.715; 95% confidence interval 0.557, 0.873) and the 25th percentile ADC (Az = 0.712; 95% confidence interval 0.553, 0.871). The area under the ROC curve of the mean ADC value for discrimination between poorly and nonpoorly differentiated HCCs was 0.694 (95% confidence interval 0.519, 0.868, Fig. 4). The minimum ADC value cutoff of 415×10^{-6} mm^2/s had a sensitivity and specificity for discrimination of poorly differentiated HCC from nonpoorly differentiated HCC of 66.7% and 90.9%, respectively.

When looking at the spread of parameters related to tumor grades correlated with size thresholds larger than 2 cm (39 HCCs, Table 4), 30th percentile ADC value yielded the highest Az (0.778; 95% confidence interval 0.623, 0.933), followed by 25th percentile ADC (Az = 0.772; 95% confidence interval 0.612, 0.932). The Az of mean ADC and the minimum ADC value for discrimination between poorly and nonpoorly differentiated HCCs was 0.736 (95% confidence interval 0.554, 0.918) and 0.683 (95% confidence interval 0.496, 0.870, Fig. 5). The 30th percentile ADC value cutoff of 93×10^{-6} mm^2/s had a sensitivity and specificity for

Table 2 The parameters of ADC histograms correlation with histological grades. Spearman correlation coefficients (ρ) are given

	Well diff HCC	Mod diff HCC	Poor diff HCC	ρ	*P* value
Minimum	648 ± 276	628 ± 171	439 ± 179	−0.390	0.005*
Maximum	2350 ± 485	2051 ± 504	2013 ± 513	−0.191	0.179
Mean	1257 ± 112	1206 ± 167	1114 ± 186	−0.340	0.015*
Standard deviation	2330 ± 960	269 ± 101	272 ± 91	0.115	0.422
Inhomogenity	0.21 ± 0.06	0.22 ± 0.07	0.25 ± 0.08	0.147	0.302
Skewness	1.42 ± 1.49	0.45 ± 0.67	0.48 ± 0.73	−0.148	−0.300
Kurtosis	6.79 ± 11.19	0.71 ± 1.70	0.77 ± 2.49	−0.143	0.317
Entropy	3.17 ± 1.28	3.80 ± 0.33	3.88 ± 0.27	0.214	0.131
5th	855 ± 148	786 ± 145	687 ± 187	−0.310	0.027*
10th	937 ± 119	873 ± 141	770 ± 195	−0.320	0.022*
15th	988 ± 109	930 ± 140	823 ± 181	−0.359	0.010*
20th	1039 ± 112	975 ± 140	868 ± 179	−0.385	0.005*
25th	1076 ± 117	1012 ± 147	9010 ± 168	−0.397	0.004*
30th	1107 ± 124	1048 ± 153	945 ± 165	−0.395	0.004*
35th	1138 ± 134	1075 ± 152	977 ± 167	−0.352	0.011*
40th	1160 ± 130	1108 ± 155	1011 ± 175	−0.336	0.016*
45th	1187 ± 129	1137 ± 158	1040 ± 174	−0.335	0.016*
50th	1218 ± 130	1175 ± 169	1087 ± 181	−0.317	0.023*
55th	1236 ± 135	1199 ± 170	1117 ± 192	−0.315	0.025*
60th	1261 ± 143	1230 ± 184	1156 ± 199	−0.288	0.041*
65th	1297 ± 154	1264 ± 187	1195 ± 210	−0.277	0.049*
70th	1335 ± 157	1303 ± 197	1239 ± 222	−0.256	0.070
75th	1369 ± 168	1351 ± 212	1279 ± 228	−0.237	0.094
80th	1420 ± 172	1404 ± 225	1325 ± 235	−0.234	0.098
85th	1477 ± 177	1463 ± 234	1385 ± 248	−0.209	0.140
90th	1569 ± 177	1562 ± 271	1458 ± 260	−0.196	0.167
95th	1752 ± 127	1691 ± 332	1593 ± 301	−0.214	0.132

Data are mean ± standard deviation ($\times 10^{-6}$mm^2/s)

Well diff HCC: Well differentiated hepatocellular carcinoma

Mod diff HCC moderately differentiated hepatocellular carcinoma, *Poor diff HCC* poorly differentiated hepatocellular carcinoma

*$P < 0.05$

discrimination of poorly differentiated HCC from nonpoorly differentiated HCC of 53.3% and 95.8%, respectively.

Discussion

Recently, an increasing number of studies have attempted to investigate the correlation between quantitative analysis of DWI and histological grade of HCC [8, 11–19] because DWI has been routinely applied to differentiate liver lesions. However, the optimal ADC parameter for characterization of HCC grade has yet to be determined. Various investigators have suggested that an ADC value such as the mean ADC [8, 11–19] or minimum ADC [12, 16] correlate with the histological grade of HCC. Furthermore, in previous studies, except for that of Moriya et al. [12], who directly compared all of the ADC parameters [mean, standard deviation, minimum, maximum, mode, skewness, kurtosis, and percentiles (5th, 50th, 75th, and 90th)] in the same patient cohort, the ADCs were derived from single or multiple portions of slice-based ROIs within tumors [8, 11, 13, 14]. Most studies focused only on the mean ADC value or minimum ADC (MinADC) value. We found that if additional ADC parameters were derived from histograms of whole lesions, the 25th percentile ADC was the parameter that correlated best with the histological grade of HCC. The minimum ADC value was the most valuable in discrimination of tumor foci with poorly differentiated HCCs from nonpoorly differentiated HCCs. Nakanishi et al. [16] and Moriya et al. [12] also reported that the minimum ADCs in poorly differentiated HCC were significantly lower than those in the other histological grades, although Nakanishi et al. [16] did not perform ADC histogram analysis. In addition, when each slice of the lesions was considered, the 25th percentile ADC

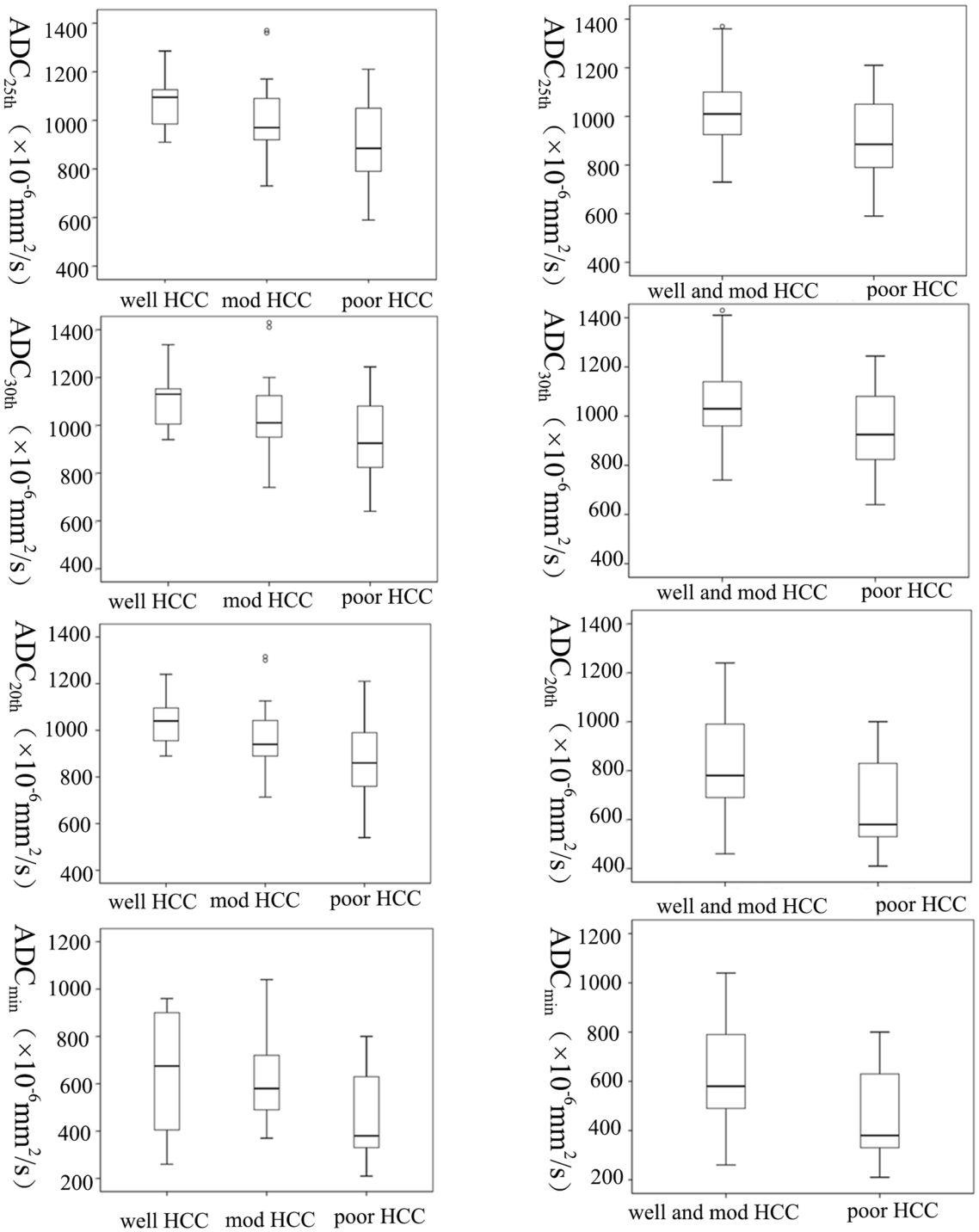

Fig. 3 Box plots show comparison of the 25th, 30th, and 20th percentile ADC values and the minimum ADC value of histological grade. The line in the box indicates the median, the height of box represents the interquartile range, the whiskers denote the lowest and highest data points within the 1.5 interquartile range, and the circles indicate outliers

and the minimum ADC value performed significantly better than the mean ADC (the parameter most commonly used in quantitative analysis of DWI of HCC) in differentiating the histological grade of HCC.

The 25th percentile ADC of the Spearman correlation coefficients describing the relationships between the ADC parameters and histological grade of HCC in our study ($\rho = -0.397$) lies within the range of previously reported

Table 3 Comparison of well differentiated and moderately differentiated hepatocellular carcinoma with poorly differentiated hepatocellular carcinoma using the parameters of ADC histograms

	Well diff HCC + Mod diff HCC	Poor diff HCC	*P* value
Minimum	633 ± 197	439 ± 179	0.002
Maximum	2124 ± 509	2013 ± 513	0.454
Mean	1218 ± 155	1114 ± 186	0.023
Standard deviation	260 ± 99	272 ± 91	0.503
Inhomogenity	2.19 ± 0.07	0.25 ± 0.08	0.237
Skewness	6.87 ± 1.00	0.48 ± 0.73	0.622
Kurtosis	21.86 ± 6.05	0.77 ± 2.49	0.454
Entropy	36.50 ± 0.72	3.88 ± 0.27	0.296
5th	803 ± 147	687 ± 187	0.058
10th	888 ± 137	770 ± 195	0.056
15th	944 ± 134	823 ± 181	0.028*
20th	990 ± 135	868 ± 179	0.016*
25th	1027 ± 141	9010 ± 168	0.013*
30th	1062 ± 147	945 ± 165	0.012*
35th	1090 ± 148	977 ± 167	0.027*
40th	1120 ± 149	1011 ± 175	0.031*
45th	1149 ± 151	1040 ± 174	0.032*
50th	1185 ± 160	1087 ± 181	0.039*
55th	1208 ± 161	1117 ± 192	0.035*
60th	1237 ± 173	1156 ± 199	0.051
65th	1272 ± 177	1195 ± 210	0.053
70th	1311 ± 187	1239 ± 222	0.079
75th	1356 ± 200	1279 ± 228	0.100
80th	1408 ± 211	1325 ± 235	0.094
85th	1466 ± 219	1385 ± 248	0.134
90th	1564 ± 249	1458 ± 260	0.150
95th	1706 ± 295	1593 ± 301	0.225

Data are mean ± standard deviation ($\times 10^{-6}$mm^2/s)

Well + Mod diff HCC well differentiated and moderately differentiated hepatocellular carcinoma, *Poor diff HCC* poorly differentiated hepatocellular carcinoma

*$P < 0.05$

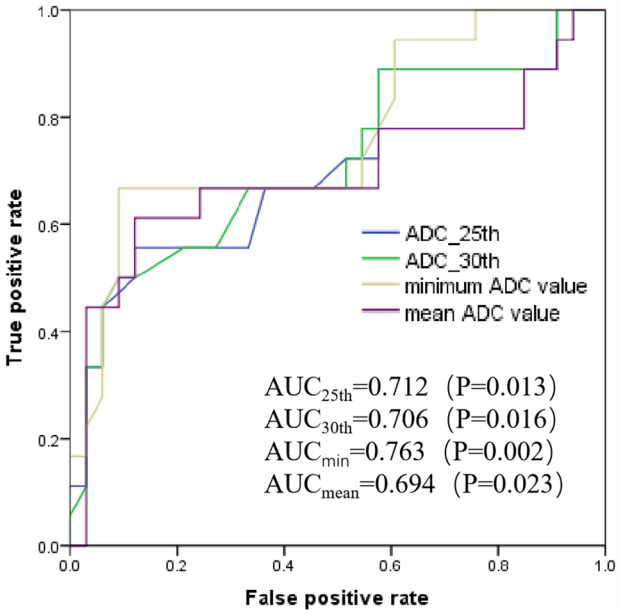

Fig. 4 Comparison of the ROC curves of the 25th and 30th percentiles, the mean ADC, and the minimum ADC parameters in the discrimination of tumor foci with poorly differentiated HCCs from non-poorly differentiated HCCs

associations between ADC parameters and histological grade of HCC [12, 13]. Moriya et al. [12] observed that the minimum ADC and 5th percentile ADC had weak correlations for each histological grade and that the minimum ADC yielded a higher Pearson's correlation coefficient. Moriya et al. delineated the ROI on the hepatobiliary phase or T2-weighted images. This discrepancy between the findings in the previous study and those of our own study might be related to the different approaches that were applied for ADC determination. Moriya et al. determined the ROI on the hepatobiliary phase or T2-weighted images and subsequently superimposed them on the ADC map. However, in our study, the ROIs were determined from diffusion-weighted images ($b = 0$ s/mm^2).

The observation that the 25th and 30th percentile ADCs and the minimum ADC outperformed the mean and median ADCs in differentiating tumors with a diagnosis of poorly differentiated HCC from higher-grade tumors might be explained by the heterogeneous histological characteristics of HCC. A proportion of normal liver tissue might influence the mean ADC and median ADC more than the 25th and 30th percentile ADCs and the minimum ADC value, thus artificially increasing the values of the former parameters [20]. Within tumors with heterogeneous cellularity, the focal areas of the hypercellular component in the tumor are represented to a greater extent by the 25th percentile ADC and the minimum ADC than by the mean and median ADCs. The minimum ADC might reflect the hypercellular component in the tumor. As the tumor histological grade increases, the cellularity of the tumor usually increases, which leads to restricted diffusion. We suggest that the results of the current study support this assumption.

Overall, the minimum ADC value supplied a low sensitivity of 66.7%, but a good specificity of 90.9% was found for diagnosis of poorly differentiated HCC. Although several studies had previously reported the histological grade of the tumor using DWI, the accuracy was relatively low. Moriya et al. [12] conducted diagnosis of poorly differentiated HCC using the minimum ADC and obtained a sensitivity of 100 and specificity of 54%. We suggest that the low sensitivity

Table 4 Histological grade of hepatocellular carcinoma > 2 cm, the parameters of ADC histograms, Spearman correlation coefficient (ρ)

	Well diff HCC	Mod diff HCC	Poor diff HCC	ρ	*P* value
Minimum	56 ± 26.91	52 ± 17	41 ± 19	−0.324	0.044*
Maximum	254 ± 38.96	219 ± 56	201 ± 55	−0.355	0.027*
Mean	122 ± 9.47	119 ± 16	108 ± 16	−0.416	0.009*
Standard deviation	24 ± 10.8	28.62 ± 10.78	26.56 ± 9.42	0.032	0.849
Inhomogenity	0.24 ± 0.051	0.24 ± 0.07	0.25 ± 0.086	0.066	0.688
Skewness	1.83 ± 1.51	0.51 ± 0.74	0.52 ± 0.76	−0.263	−0.106
Kurtosis	9.3 ± 12.04	0.98 ± 1.90	0.90 ± 2.71	−0.325	0.044*
Entropy	3.17 ± 1.47	3.90 ± 0.27	3.90 ± 0.28	0.167	0.308
5th	77 ± 24.8	73 ± 13	6413 ± 19	−0.315	0.051
10th	87 ± 16.31	84 ± 11	72 ± 18	−0.375	0.019*
15th	92 ± 11.33	91 ± 11	78 ± 17	−0.380	0.017*
20th	98 ± 9	96 ± 11	82 ± 16	−0.441	0.005*
25th	103 ± 8.92	100 ± 12	87 ± 15	−0.488	0.002*
30th	106 ± 9	105 ± 12	91 ± 14	−0.478	0.002*
35th	108 ± 8.92	108 ± 12	94 ± 14	−0.423	0.007*
40th	111 ± 9.14	112 ± 12	99 ± 14	−0.408	0.010*
45th	114 ± 10.3	115 ± 12	102 ± 14	−0.385	0.016*
50th	118 ± 11.05	116 ± 16	105 ± 16	−0.397	0.012*
55th	119 ± 12.02	123 ± 14	111 ± 15	−0.311	0.054
60th	121 ± 12.83	128 ± 15	116 ± 17	−0.260	0.110
65th	124 ± 14.5	132 ± 16	121 ± 19	−0.226	0.166
70th	128 ± 14.71	137 ± 17	126 ± 21	−0.200	0.221
75th	132 ± 16.45	142 ± 18	132 ± 23	−0.151	0.359
80th	137 ± 17.84	149 ± 21	138 ± 26	−0.128	0.438
85th	143 ± 18.41	155 ± 22	148 ± 34	−0.080	0.626
90th	153 ± 19.53	167 ± 26	160 ± 43	−0.065	0.696
95th	176 ± 14.89	182 ± 32	177 ± 49	−0.123	0.455

Data are mean ± standard deviation ($\times 10^{-6}$mm^2/s)

Well diff HCC well differentiated hepatocellular carcinoma, *Mod diff HCC* moderately differentiated hepatocellular carcinoma, *Poor diff HCC* poorly differentiated hepatocellular carcinoma

*$P < 0.05$

and specificity in our study was due to the adoption of different histological classifications (Moriya et al. applied the 5th edition [21]). In addition, the variety of the histological structures in HCC might be to blame. However, our result lies within the reported range of accuracies, and the ADC parameters showed significant differences between poorly differentiated HCC and nonpoorly differentiated HCC [8, 11–19].

Since ADC values vary between MRI scanners of different vendors, special focus should then be placed on the histogram parameters' skewness, kurtosis, and entropy, which do not depend on field strength and sequence specifics [22]. Histogram skewness and kurtosis can be attributed to the asymmetric shape of ADC value distribution. ADC Inhomogeneity and entropy represents the predictability of intensity characteristics within various tissues and increases as the distribution of signal intensities becomes more heterogeneous [23].

Our study contains several limitations. First, a small population was included in our retrospective study. Second, the sample was biased due to the inclusion of only patients who had undergone hepatectomy. Third, as a limitation of the current respiratory triggered DWSS-EPI technique, cardiac motion, which causes negligible artifacts and noise contamination, might distort the ADC values to a certain degree [24], which is a crucial disadvantage for improvement of this method. Recently, certain researchers have recommended reduction of cardiac motion [25–27]. These methods should be tested in the future when performing clinical routines. Fourth, the MR imaging examination was not exactly coregistered with the histopathology specimen. Although the ADC values were measured by each slice of the tumor in DWI, histopathological analysis was performed on multiple specimens. This sampling bias might also contribute to the discrepancy between the ADC parameters and the histopathological analysis because this multiple

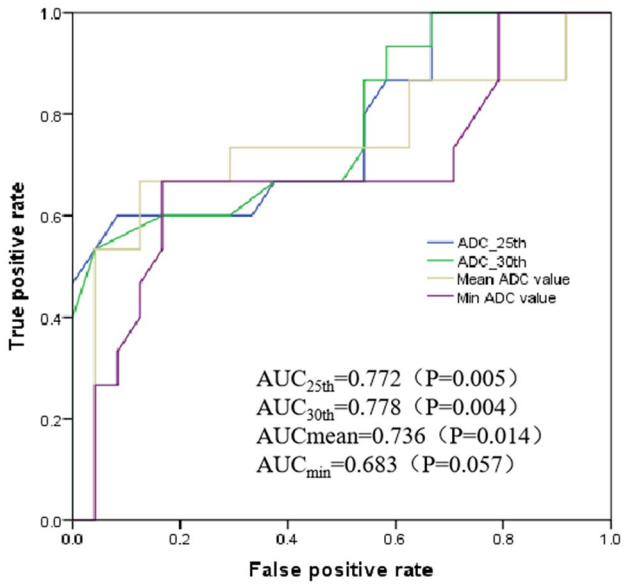

Fig. 5 Comparison of the ROC curves of the 25th and 30th percentiles, the mean ADC, and the minimum ADC parameters in the discrimination of tumor foci > 2 cm with poorly differentiated HCCs from nonpoorly differentiated HCCs

specimen method might not fully represent the histopathological heterogeneity of the tumor compared with that of whole-mount step-section specimens. Therefore, a further prospective study is needed to match the regions that are histopathologically examined and the regions in which the ADC value is measured. Finally, DWI was performed with two different *b* values (0 and 800 s/mm^2) to estimate the diffusion fraction by minimizing the perfusion fraction in our study. However, because multiple or higher *b* values could enable more precise calculation of an ADC with less perfusion contamination and less regional ADC variations, further studies using multiple or higher *b* values of abdominal DWI are also required. In addition, computed tomography angiography (CTA) technology has been proven capable of obtaining high quality images of the coronary arteries. Its principle is to identify bright blood vessels containing the contrast agent. So we have reason to believe that if there are a large number of studies similar to ours supporting our findings, we can also get a similar technique to identify bright lesions on DWI images.

In conclusion, our results suggest that if ADC parameters are determined from whole-lesion histogram analysis, the 25th percentile ADC correlates better with the histological grade of HCC and that the minimum ADC value most accurately differentiates lesions with poorly differentiated HCCs from nonpoorly differentiated HCCs compared with other ADC parameters commonly used in the literature. Therefore, DWI of HCC could supply quantitative parameters for the preoperative prediction of tumor histological grade.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts to disclose.

Informed consent Formal consent is not required for this type of study.

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