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ABDOMINAL IMAGING

ORIGINAL ARTICLE

Value of apparent diffusion coefficient for predicting malignancy of intraductal papillary mucinous neoplasms of the pancreas

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PURPOSE
We aimed to explore the potential value of the whole tumor apparent diffusion coefficient (ADC) for discriminating between benign and malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas.

METHODS
Forty-two patients underwent 1.5 T magnetic resonance imaging that included diffusion-weighted imaging (DWI, b=0.500 s/mm^2). The mean, minimum, and maximum ADC values were measured for the whole tumor. The differences between benign and malignant IPMNs were calculated for the mean ADC, ADC-min, and ADC-max values. Receiver operating characteristics (ROC) analysis was conducted to evaluate their potential diagnostic performance.

RESULTS
Fifteen of 25 benign IPMNs demonstrated low or iso-signal intensity on DWI with a b value of 500 s/mm^2 compared with normal pancreatic parenchyma, whereas all malignant IPMNs demonstrated high signal intensity. The mean value of ADC was significantly higher in benign IPMNs compared with malignant IPMNs (3.39×10^{-3} mm^2/s vs. 2.39×10^{-3} mm^2/s, $P < 0.001$), with an area under the ROC curve (AUC) of 0.92 (95% confidence interval [CI], 0.79–0.98). The ADC-min value of malignant IPMNs was also significantly lower than that of benign IPMNs (1.24×10^{-3} mm^2/s vs. 2.58×10^{-3} mm^2/s, $P < 0.001$), with an AUC of 0.94 (95% CI, 0.82–0.99). No marked difference was found between benign and malignant IPMNs for the ADC-max value (3.89×10^{-3} mm^2/s vs. 3.78×10^{-3} mm^2/s, $P = 0.299$).

CONCLUSION
Lower mean and minimum ADC values of the whole tumor might be potential predictors of malignant IPMNs of the pancreas.

Intraductal papillary mucinous neoplasms (IPMN) of the pancreas are characterized by a papillary growth of the ductal epithelium with rich mucin secretion, which ranges from adenoma to invasive carcinoma with different degrees of aggressiveness (1, 2). The mean incidences of malignancy are higher for main duct (MD)-IPMN (61.6%; range, 36%–100%) than branch duct (BD)-IPMN (25.5%; range, 6.3%–46.5%) cases, while mixed-type IPMNs and MD-IPMNs have about the same incidences of malignancy (3, 4). The decision for treatment of IPMN of the pancreas is always made according to its biological behavior; therefore, it is important to discriminate between benign and malignant IPMNs for selecting the appropriate treatment strategy.

In clinical practice, computed tomography (CT) or magnetic resonance imaging (MRI) is often performed to detect and assess IPMN (2, 5, 6). Promising results have been reported for evaluating the malignancy of IPMN according to radiologic imaging features, including a cyst larger than 3 cm, an enhanced solid component, and a marked dilatation of the main pancreatic duct ≥10 mm) (7, 8). However, a study showed that not all imaging features of the cysts should be weighted equally for assessing the malignancy of IPMN (8). The International Consensus Guidelines suggest that pancreatic cysts with "worrisome features" and cysts larger than 3 cm without "worrisome features" should be further evaluated by endoscopic ultrasonography (EUS) (2), which improves the accuracy of differentiating benign from malignant IPMNs (9). However, EUS is known to present difficulties because of its operator dependence and its low negative predictive value for fine-needle aspiration cytology (10).

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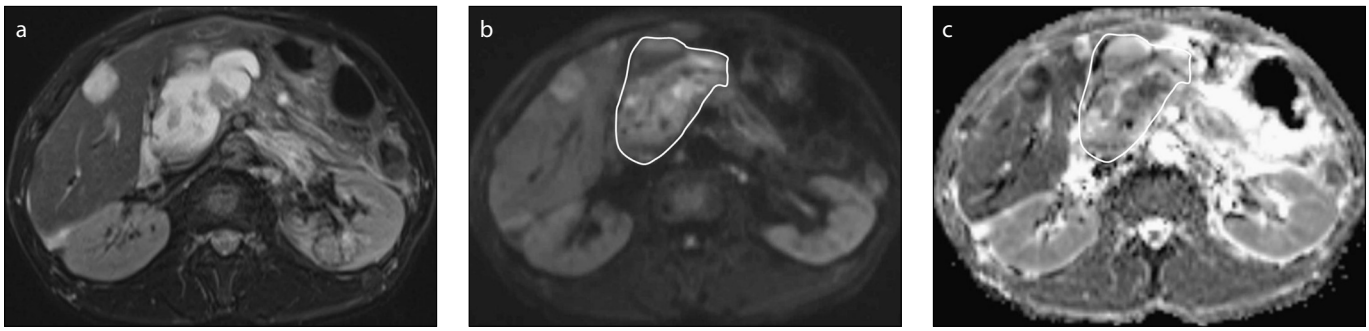

Figure 1. a–c. A 60-year-old man with malignant intraductal papillary mucinous neoplasms (IPMNs) of the pancreas (main duct type, invasive carcinomas). T2-weighted image **(a)**, diffusion-weighted image **(b)**, and corresponding apparent diffusion coefficient (ADC) map **(c)** demonstrated a dilated main pancreatic duct with mural nodules (confirmed by pathology) and showed a high signal intensity on DWI. A region of interest (ROI) was drawn on diffusion-weighted image referring to T2-weighted image. Then, the ROI was copied from the diffusion-weighted image to the corresponding ADC map.

Diffusion-weighted imaging (DWI) is widely performed in clinical practice and has been shown to be valuable in distinguishing between benign and malignant tumors (11, 12). DWI can provide qualitative and quantitative information reflecting changes at a cellular level and yields unique insights into tumor cellularity and the integrity of cell membranes (12). Recently, studies have suggested that quantitative measurement of the apparent diffusion coefficient (ADC) may have potential value for the characterization of cystic pancreatic lesions (13–16). However, there is no consensus on the true value of ADC measurement appropriate for the evaluation of malignancy of IPMN.

The purpose of this study is to assess the diagnostic performance of quantitative ADC measurement for predicting malignancy of IPMN of the pancreas.

Methods

Patients

This retrospective study was approved by the Institutional Review Board of Zhongshan Hospital, Fudan University and the requirement for informed consent was waived. We retrospectively analyzed 42 patients who were diagnosed with IPMNs of the pancreas at our institution between January 2010 and June 2015. Inclusion criteria comprised histopathologically proven IPMNs with pathologic results by surgical resection and availability of preoperative MRI, including DWI and magnetic resonance cholangiopancreatography (MRCP). Exclusion criteria comprised unresectable disease and insufficient MRI quality due to motion or metal artifacts. The median interval between MRI examination and surgical treatment of IPMNs was seven days (range, 2–12 days).

Main points

- Discriminating benign from malignant IPMN is important for selecting the appropriate treatment strategy in clinical practice.
- Quantitative measurement of apparent diffusion coefficient (ADC) may have potential value for evaluation of malignancy in patients with IPMN.
- Whole tumor ADC analysis revealed lower mean ADC and ADC-min values; these parameters might be used as potential predictors of malignant IPMNs of the pancreas.
- The mean ADC (AUC: 0.92) and ADC-min (AUC: 0.94) were significantly better than ADC-max (AUC: 0.53) for assessment of malignant IPMNs.

MRI protocol

Images were obtained on a 1.5 T MRI system (Magnetom Avanto; Siemens Medical Solutions). Three scan trace DWI (b=0.500 s/mm^2) with a single-shot, echo-planar sequence was performed in the axial plane, which were obtained after acquisition of T1-weighted axial images (TR/TE of 209/4.8), T2-weighted axial images (TR/TE of 2000/70), and two-dimensional MRCP images in the same imaging session. DWI parameters were as follows: TR/TE, 2600/66; matrix, 128×112; field of view, 380–400×300–324 mm; 7 cm section thickness with 2.1 mm gap, and 1500 Hz/pixel bandwidth. A parallel imaging technique was obtained using generalized autocalibrating partially parallel acquisition with an R factor of 2. ADC maps were calculated for each diffusion study by the standard console software of the system. For dynamic contrast enhancement, we performed a three-dimensional T1-weighted gradient echo sequence (volumetric interpolated breath-hold examination) with a fat-suppression technique, before and after the injection of the contrast media (Magnevist, Bayer Schering Pharma AG, 0.1 mmol/kg). The following parameters were used: TR/TE, 5.04/2.31; flip angle, 12°; 256×192 matrix; field of view, 380–400×300–324 mm; slab thickness, 24 cm resulting in an interpolated 4 mm section thickness; and 300 Hz/pixel/bandwidth. The arterial phase was obtained at 20–30 s, the portal venous phase at 70–80 s, and the equilibrium phase at 180 s after the injection of contrast media.

Image evaluation

The ADC values of IPMNs were measured by a single radiologist (R.S.X.) who had 10 years of experience for reading abdominal magnetic resonance images and was blinded to the pathology results and clinical data. For each patient, the radiologist drew freehand the region of interest (ROI) along the border of IPMN on the b500 images and compared them with the same slices of T2-weighted images. Then, the radiologist copied ROI to the corresponding ADC map (Figs. 1, 2). The radiologist recorded the mean ADC value of each slice of the tumor and then calculated the mean ADC value of IPMNs by averaging the ADC values of the whole tumor. Furthermore, the radiologist recorded the lowest ADC (ADC-min) and the largest ADC (ADC-max) values among all the voxels in each tumor.

Standard of reference

We selected the pathology results of the surgical resection specimens as the standard of reference. All the resection specimens were handled by an experienced pathologist.

The classification of IPMN included BD-IPMN, MD-IPMN, or mixed-type IPMN. The histologic type was categorized as low-grade

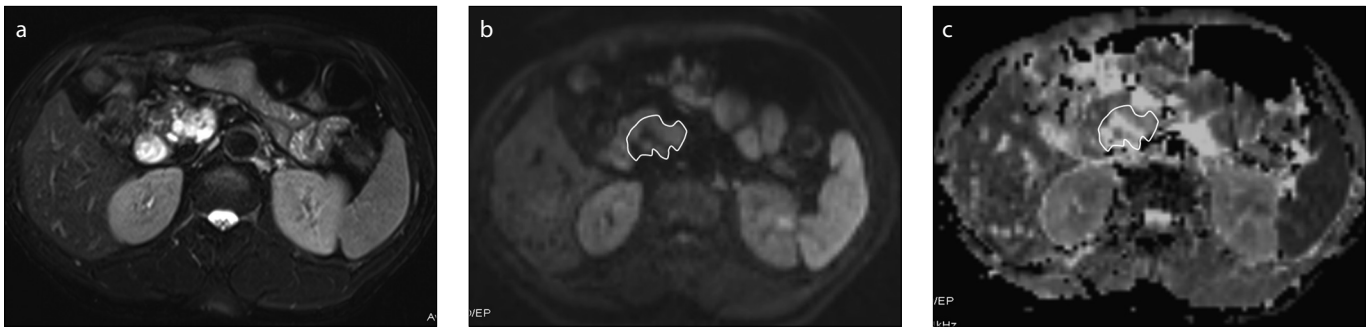

Figure 2. a–c. A 57-year-old man with benign intraductal papillary mucinous neoplasms (IPMNs) of the pancreas (mixed type, intermediate-grade dysplasia). T2-weighted image **(a)**, diffusion-weighted image **(b)** and corresponding ADC map **(c)** showed clustered cystic lesions in the uncinate process and depicted low iso-signal intensity on DWI. A ROI was drawn on the diffusion-weighted image compared with the T2-weighted image. Then, the ROI was copied from the diffusion-weighted image to the corresponding ADC map.

Table 1. Baseline characteristics of patients with intraductal papillary mucinous neoplasm of the pancreas

		All n=42	Benign n=25	Malignant n=17	*P*
Age (year)		61.95±11.47	60.64±12.63	63.88±9.56	0.38
Male/female		25 (59.5)/17 (40.5)	15 (60)/10 (40)	10 (58.8)/7 (41.2)	0.94
Hemoglobin		132.67±14.04	136.48±10.56	127.06±16.79	0.05
Glucose		6.20±1.56	6.45±1.72	5.83±1.24	0.21
Location					
	Head	20 (47.6)	12 (48.0)	8 (47.1)	0.42
	Body/tail	16 (38.1)	11 (44.0)	5 (29.4)	
	Neck	5 (11.9)	2 (8.0)	3 (17.6)	
	Diffuse	1 (2.4)	0 (0)	1 (5.9)	
Surgical resection					
	Whipple operation	20 (47.6)	14 (56.0)	6 (35.3)	0.15
	Distal pancreatectomy	14 (33.3)	8 (32.0)	6 (35.3)	
	Total pancreatectomy	3 (7.1)	0 (0)	3 (17.6)	
	Central segmentectomy	5 (11.9)	3 (12.0)	2 (11.8)	
Platelet ($\times 10^9$)		191.17±62.36	198.52±67.99	180.35±53.13	0.36
Serum CEA	High	6 (14.3)	2 (8.0)	4 (23.5)	0.20
	Low	36 (85.7)	23 (92.0)	13 (76.5)	
Serum CA19-9	High	10 (23.8)	2 (8.0)	8 (47.1)	0.01
	Low	32 (76.2)	23 (92.0)	9 (52.9)	
Serum albumin	High	38 (90.5)	22 (88.0)	16 (94.1)	0.64
	Low	4 (9.5)	3 (12.0)	1 (5.9)	
Symptomatic	Yes	33 (78.6)	19 (76)	14 (82.4)	0.72
	No	9 (21.4)	6 (24)	3 (17.6)	

Data are presented as mean±standard deviation or n (%).
CEA, carcino-embryonic antigen; CA19-9, carbohydrate antigen 19-9.

dysplasia, intermediate-grade dysplasia, high-grade dysplasia, or invasive carcinoma. The tumor was categorized as benign lesion (low-grade dysplasia or intermediate-grade dysplasia) or malignant lesion (high-grade dysplasia or invasive carcinoma).

Statistical analysis

Statistical analysis was performed using MedCalc (MedCalc for Windows, version 11.5.0.0, www.medcalc.be). The mean ADC, ADC-min, and ADC-max of the benign tumors were compared with the malignant tumors using a Student's *t*-test when the data were normally distributed or the Mann-Whitney U test when the data were not normally distributed. Receiver operating characteristics (ROC) analyses were performed to determine their potential diagnostic performance for differentiating benign and malignant IPMNs. Areas under the ROC curve (AUC) with 95% confidence intervals (95% CI) were calculated. The cut-off values were determined according to Youden index and differences in diagnostic performance were analyzed by comparing the ROC curves using the method of Delong et al. (17) in MedCalc. *P* values of <0.05 were considered statistically significant.

Results

A total of 42 patients, 25 men (59.5%) and 17 women (40.5%) aged 61.95±11.47 years, meeting all the criteria were included. Twenty-five patients were classified as benign IPMNs (10 were low-grade dysplasia, 15 were intermediate-grade dysplasia) and 17 were classified as malignant IPMNs (12 were high-grade dysplasia, five were invasive carcinoma). The numbers of BD-IPMN, MD-IPMN, and mixed-type IPMN were 13, 10, and 19, respectively. Of the 42 patients, 20 underwent Whipple surgery, 14 underwent distal pancreatectomy, three underwent total pancreatectomy, and five underwent central segmentectomy. The main patient characteristics are summarized in Table 1.

The median size of IPMNs was 24.3 mm (range, 10.3–122.8 mm). The sizes of malignant IPMNs (median size, 33.2 mm; range, 11–122.8 mm) were larger than the benign lesions (median size, 22.7 mm; range, 10.3–52.9 mm; $P = 0.02$). The median diameter of PD was 5.4 mm (range, 1–70 mm). The diameter of PD of the malignant IPMNs (median size, 8 mm; range, 2–70 mm) was also

Table 2. Diagnostic performance of mean, minimum and maximum ADC in assessing malignant intraductal papillary mucinous neoplasms of the pancreas by ROC analyses

	AUC	Sensitivity	Specificity	PPV	NPV	Cutoff
Mean ADC	0.92	76.5 (13/17)	100 (25/25)	100 (13/13)	86.2 (25/29)	≤2.66×10^{-3}
95% CI	0.79–0.98	50.1–93.2	86.3–100	75.3– 100	68.3–96.1	
ADC-min	0.94	82.4 (14/17)	100 (25/25)	100 (14/14)	89.3 (25/28)	≤1.47×10^{-3}
95% CI	0.82–0.99	56.6–96.2	86.3–100	76.8–100	71.77–97.7	
ADC-max	0.53	11.8 (2/17)	100 (25/25)	100 (2/2)	62.5 (25/40)	≤3.01×10^{-3}
95% CI	0.37–0.68	1.5–36.4	86.3–100	15.8–100	45.8–77.3	

Data are presented as % (n/N).
ADC, apparent diffusion coefficient; ROC, receiver operating characteristics; AUC, area under the ROC curve; PPV, positive predictive value; NPV, negative predictive value; ADC, apparent diffusion coefficient; CI, confidence interval.

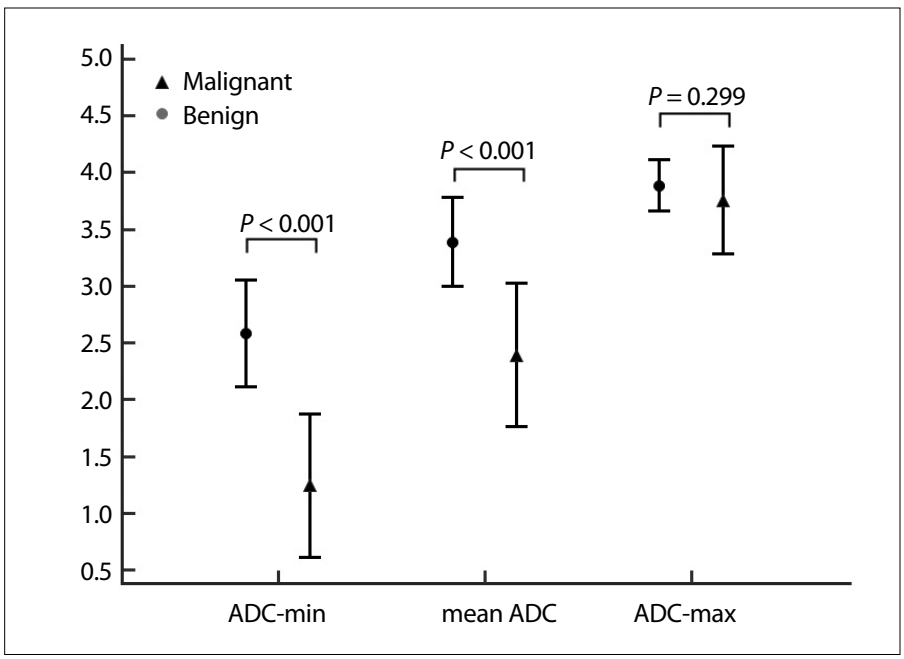

Figure 3. Mean and standard deviation for the mean, minimum, and maximum ADC values between benign tumor and malignant intraductal papillary mucinous neoplasms of the pancreas.

significantly larger than that of the benign lesions (median size, 4.1 mm; range, 1–10.3 mm; $P = 0.01$). Five invasive carcinomas and four of 12 high-grade dysplasias showed a mural nodule or thick septa within the cyst, while none of benign IPMNs depicted a mural nodule or thick septa. Fifteen of 25 benign IPMNs demonstrated low or iso-signal intensity on DWI with a b value of 500 s/mm^2 compared with normal pancreatic parenchyma, whereas all the malignant IPMNs demonstrated a high signal intensity. Six of 17 malignant IPMNs showed atrophy of pancreatic parenchyma, while four of 25 benign IPMNs had atrophy ($P = 0.30$).

The mean value of ADC was significantly higher in benign IPMNs compared with malignant IPMNs (3.39±0.39×10^{-3} mm^2/s vs. 2.39±0.63×10^{-3} mm^2/s, $P < 0.001$). The mean value of ADC-min of malignant IPMNs was also significantly lower in comparison with benign IPMN (1.24±0.34×10^{-3} mm^2/s vs. 2.58±0.47×10^{-3} mm^2/s, $P < 0.001$). However, there was no significant difference between benign and malignant IPMNs for the mean value of ADC-max (3.89±0.22×10^{-3} mm^2/s vs. 3.78±0.48×10^{-3} mm^2/s, $P = 0.299$). ADC parameters of benign and malignant groups are provided in Fig. 3. The median ADC parameters of malignant IPMNs with and without a mural nodule/thick septa were 2.04×10^{-3} mm^2/s (range, 1.01–3.22×10^{-3} mm^2/s) vs. 2.53×10^{-3} mm^2/s (range, 1.94–3.72×10^{-3} mm^2/s) for mean ADC ($P = 0.148$), 0.76×10^{-3} mm^2/s (range, 0.23–1.40×10^{-3} mm^2/s) vs. 1.44×10^{-3} mm^2/s (range, 0.95–2.72×10^{-3} mm^2/s) for ADC-min ($P = 0.008$) and 4.01×10^{-3} mm^2/s (range, 2.28–4.10×10^{-3} mm^2/s) vs. 3.9×10^{-3} mm^2/s (range, 3.01–4.10×10^{-3} mm^2/s) for ADC-max ($P = 0.561$), respectively.

The ROC curves used to compare the diagnostic performance of ADC, ADC-min, and ADC-max for assessment of the malignant IPMNs are displayed in Fig. 4. The corresponding AUCs, sensitivities, specificities, PPVs, NPVs, and cutoff values are shown in Table 2. The mean ADC (AUC, 0.92; 95% CI, 0.79–0.98) and ADC-min (AUC, 0.94; 95% CI, 0.82–0.99) were significantly better than ADC-max (AUC, 0.53; 95% CI, 0.37–0.68; $P < 0.001$ for both). The difference in AUCs between the mean ADC and ADC-min was not significant ($P = 0.44$).

Discussion

The aim of this study was to evaluate the diagnostic performance of ADC for predicting the malignancy of IPMN of the pancreas. Our study indicated that the mean ADC and ADC-min of the whole tumor were useful for discrimination between benign and malignant IPMNs of the pancreas with high AUCs (0.92 for mean ADC and 0.94 for ADC-min) for the assessment of a malignant lesion.

We found that the mean ADC of malignant IPMN was markedly lower compared with a benign IPMN, which was consistent with previous studies. Sandrasegaran et al. (16) reported that high-grade/invasive IPMNs showed significantly lower ADC values (2.13×10^{-3} mm^2/s) than that of low-grade tumors (3.01×10^{-3} mm^2/s). Ogawa et al. (15) and Kang et al. (13) also confirmed that a lower mean ADC value was a potential useful biomarker for the assessment of malignancy for IPMN. DWI can discriminate between tissues of different cellularity by analyzing the different motion of water molecules in the extracellular space (18). The degree of restriction to water diffusion in biologic tissue is inversely correlated to the tissue cellularity and the integrity of cell membranes. The motion of water molecules is more restricted in malignant tumors with higher cellularity than in benign tumors (19). This might be one of the main reasons for malignant IPMNs showing lower ADC values in our study. On the other hand, the viscosity of the fluid and the containment properties of the fluid have an effect on the water diffusion or flow. Previous studies found that benign cystic lesions tend to have lower cyst fluid viscosity com-

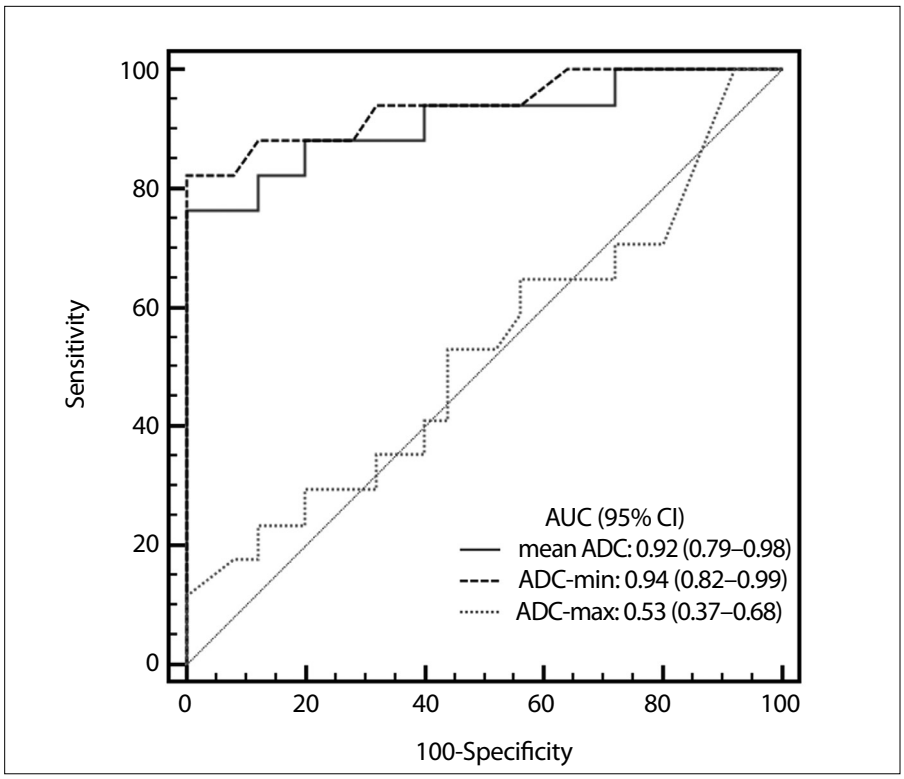

Figure 4. Receiver operating characteristic (ROC) and area under the curve (AUC) with 95% CI of the mean, minimum, and maximum ADC for identification of malignant intraductal papillary mucinous neoplasms of the pancreas.

pared with malignant cystic lesions (20, 21), which may perhaps be another explanation for why there is less-restricted diffusion in benign IPMNs (16).

Another interesting finding of the present study is that the sensitivity of ADC-min improved from 76.5% to 82.4% without any loss of specificity compared with the mean ADC, which resulted in a lower overestimation of malignancy of IPMN of the pancreas for ADC-min. In our study, the mean ADC was calculated by averaging the ADC values for all voxels in the whole tumor. The subtle changes of water restriction of small foci of a malignant tumor might be averaged out by a large cystic component of tumor. However, ADC-min was the lowest ADC value among all voxels in the whole tumor. Malignant tissue tends to have lower ADC values compared with benign tissue. This may explain why ADC-min values may be particularly sensitive to subtle changes of restricted water diffusion induced by a malignancy of IPMN. Quantitative DWI assessment using ADC-min has rarely been studied so far. Nevertheless, measurement errors still occurred with ADC measurements, leading to a relatively low sensitivity. The possible explanation for this might be that *(a)* the signal-to-noise ratio of diffusion-weighted images and ADC map were low, so sometimes it was difficult to confirm the margin of the cystic tumor, especially for the small tumor; *(b)* there were artifacts on the diffusion-weighted images caused by air in the gastroenterological tract, i.e., the stomach or duodenum. Additionally, we failed to demonstrate a benefit for ADC-max for differentiating benign from malignant IPMNs. A possible explanation might be that the maximum ADC value may represent the free fluid within IPMN, which exists both in benign and malignant IPMNs.

Compared with other imaging techniques, ADC measurement can be beneficial given the fact that this technique can be performed without radiation or contrast enhancement. Although imaging features on conventional CT and MRI in combination with MRCP have been established in the 2012 International Consensus Guideline for the indications of treatment, many patients will undergo potentially unnecessary surgical resection for benign IPMNs because the specificity of the guideline is low. [18F]-2-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}F-FDG PET) seems to be valuable for evaluating the malignancy of IPMN of the pancreas (22–25). Takanami et al. (22) found that a ^{18}F-FDG PET outperformed a contrast enhanced CT for predicting malignant IPMN with mural nodules. However, another study showed a low sensitivity of PET/CT for a small cystic lesion of the pancreas ≤1 cm) (25) and its value as a treatment strategy of IPMN is yet to be established.

Our study has several limitations. First, the current study is a retrospective study with a relatively small sample size. Second, all of the patients in our study were surgically resected cases whose imaging features met the indications of resection from the 2012 International Consensus Guideline. Hence, we did not compare ADC measurement with the common imaging features. Third, we performed DWI using a relatively low b value of 500 s/mm^2 for the routine abdominal MRI in our department. We found that 10 of 25 (40%) benign IPMNs demonstrated high signal intensity on DWI (b=500 s/mm^2) compared with normal pancreatic parenchyma. In theory, malignant tumors always show higher signal intensity on DWI, because of the restricted diffusion in malignant tumors. However, the signal intensity of tissue on DWI depends on not only restricted diffusion but also the T2 relaxation time. Consequently, a tissue with a very long T2 relaxation time may depict a high signal on DWI, which might be mistaken for restricted diffusion. This is regarded as the "T2 shine-through" effect. (12). Theoretically, this effect could be sometimes eliminated by choosing a larger b value for the acquisition of DWI. Ogawa et al. (15) reported that a high signal on high b value DWI (b=1000 s/mm^2) is regarded as a useful imaging feature for predicting malignancy in patients with IPMNs. Finally, all images were assessed by a single radiologist, which might result in bias because of interobserver variations. However, this might be small for whole tumor ADC evaluation (26).

In conclusion, whole tumor ADC analysis revealed discriminative parameters (mean ADC and ADC-min) for differentiation between benign and malignant IPMNs of the pancreas. Objective information from DWI could thus be of additional value for risk stratification in patients with IPMNs of the pancreas at the time of diagnosis.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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