The added value of intravoxel incoherent motion diffusion weighted imaging parameters in differentiating high-grade pancreatic neuroendocrine neoplasms from pancreatic ductal adenocarcinoma

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Abstract. The aim of the present study was to investigate the potential significance of intravoxel incoherent motion (IVIM)-diffusion weighted imaging (DWI) in differentiating high-grade pancreatic neuroendocrine neoplasms (pNENs) from pancreatic ductal adenocarcinoma (PDAC). A total of 50 patients, including 37 patients with PDAC and 13 patients with high-grade pNENs, underwent pancreatic multiple b-values DWI with 15 b-values including 0, 10, 20, 40, 60, 80, 100, 150, 200, 400, 800, 1,000, 1,200, 1,500 and 2,000 sec/mm². Standard apparent diffusion coefficient (ADCstandard) and IVIM parameter [slow apparent diffusion coefficient (Dslow), fast apparent diffusion coefficient (Dfast), fraction of fast apparent diffusion coefficient (f)] values of PDAC and pNENs were compared. P<0.05 was considered to indicate a statistically significant difference. Receiver operating characteristics analysis was performed in order to evaluate the diagnostic potential of IVIM parameters for differentiating high-grade pNENs from PDAC. Dslow of pNENs was significantly lower compared with that of PDAC (0.460 vs. 0.579x10⁻³ mm²/sec; P=0.001). Dfast of pNENs was significantly higher compared with that of PDAC (13.361 vs. 4.985x10⁻³ mm²/sec; P<0.001). Area under the curve of Dslow, Dfast and combined Dslow and Dfast was 0.793, 0.863 and 0.885 respectively. The specificity and sensitivity of Dslow ≤0.472x10⁻³ mm²/sec were 97.3 and 53.9%, respectively, for differentiating high-grade pNENs from PDAC. The specificity and sensitivity of Dfast >9.58x10⁻³ mm²/sec were 91.9 and 69.2%, respectively, for differentiating high-grade pNENs from PDAC. When Dslow and Dfast were combined, the specificity and sensitivity for differentiating high-grade pNENs from PDAC were 76.9 and 100%, respectively. Taken together, these results indicated that the diffusion-associated parameter Dslow and the perfusion-associated parameter Dfast of IVIM-DWI may differentiate high-grade pNENs from PDAC with high diagnostic accuracy, and that IVIM-DWI may be a valuable biomarker in differentiating pancreatic neoplasms.

Introduction

Pancreatic neuroendocrine neoplasms (pNENs) are the second most commonly-occurring solid neoplasms in the pancreas, accounting for <3% of all pancreatic neoplasms (1). The reported annual incidence of pNENs is approximately 2.5-5 per million persons (2). As all pNENs have the potential to become malignant, surgery is the only curative treatment option for pNENs; thus, it is recommended to all patients (3-5). Compared with pancreatic ductal adenocarcinoma (PDAC), pNENs usually demonstrate more indolent biological behaviors; pNENs exhibit a more preferable response to chemotherapy, higher resectability and longer overall survival (6). Even advanced pNENs exhibit improved longer-term survival compared with PDAC (7). As PDAC is one of the leading causes of cancer-associated mortality worldwide, with mortality rates...
of ~80.3% (8), preoperative adjuvant chemoradiation may improve the 1- and 2-year overall survival and disease free survival rates of patients (9). However, radiotherapy and chemotherapy induce numerous side effects, such as nausea, vomiting and bone marrow suppression. Therefore, it is imperative to accurately differentiate pNENs from PDAC prior to surgery.

Contrast-enhancement (CE) CT and MRI are widely accepted techniques for differentiating pNENs from PDAC. PNENs usually present with rapid and notable enhancement in the arterial phase of the CT scan due to their rich vascularity (7). However, pNENs gradually lose angiogenic potential and their microvascular density (MVD) decreases as the disease progresses (10). High-grade pNENs demonstrate lower vascularity and MVD compared with grade 1 pNENs (11,12). Therefore, high-grade pNENs often exhibit hypo-enhancement or heterogeneous enhancement in early contrast-enhanced images (13). At present, the use of CE CT or MRI exhibit difficulties when differentiating high-grade pNENs from PDAC. Hypo-enhanced pNENs in arterial phase imaging are associated with poor differentiation, increased aggressiveness and decreased 5-year survival rate (14,15). High-grade pNENs including grade 2 and 3 tumors often exhibit local invasion and/or metastases (16,17).

Since Le Bihan et al (18) proposed the theory of intravoxel incoherent motion (IVIM), the phenomenon that tissue perfusion effects can be separated from true tissue diffusion in IVIM diffusion weighted imaging (IVIM-DWI) was determined (19,20). Owing to the increasing concern for nephrogenic systemic fibrosis (21), IVIM-DWI may be an effective alternative to determine perfusion in tissues without contrast agents (22). An increasing number of studies have demonstrated the value of IVIM-DWI for evaluating pancreatic neoplasms (23,24). In addition, studies have applied quantitative parameters derived from IVIM-DWI to predict histological characteristics of pNENs (25,26). However, to the best of our knowledge, no published studies that compare IVIM-DWI parameters between pNENs and PDAC are currently available. Therefore, the aim of the present study was to assess the diagnostic performance of IVIM-DWI parameters for distinguishing between high-grade pNENs and PDAC.

Materials and methods

Subjects. Ethical approval was acquired from the Institutional Ethics Committee Board of Xijing hospital (Xi’an, China) and written informed consent was obtained from all participants. A total of 90 patients with suspected pancreatic solid mass were considered for inclusion in the present study between May 2014 and April 2017. A total of 40 patients were excluded due to the following exclusion criteria: i) Patients diagnosed with diseases other than PDAC and high-grade pNENs (n=36) including grade 1 pNENs (n=25), solid pseudopapillary tumor (n=7), accessory spleen located in pancreas (n=1), cholangiocarcinoma located in pancreatic segment of common bile duct (n=2) and mass-forming chronic pancreatitis (n=1); ii) patients lost to the follow-up (n=4). The recruitment process is illustrated in Fig. 1.

Image acquisition. All patients were examined on a Discovery MR750 3.0 T whole-body MR scanner (GE Healthcare Life Sciences) using a 32-channel phased-array coil. Pancreatic MR sequences comprised axial fast spin echo transverse relaxation time-weighted images (T2WI) with fat-suppression, axial breath-hold 3D liver acquisition with volume acceleration Flex (LAVA Flex) and LAVA Flex with contrast (Omniscan; GE Healthcare Life Sciences). Pancreatic multiple b-value diffusion-weighted echo-planar imaging was performed with 15 b-values, including 0, 10, 20, 40, 60, 80, 100, 150, 200, 400, 800, 1,000, 1,200, 1,500 and 2,000 sec/mm². The detailed parameters of each sequence are presented in Table I.

Image and data analysis. An abdominal radiologist with 11 years of MRI experience blinded to the histopathological results analyzed the acquired IVIM-DWI data. Following examination, all data were transmitted to a built-in AW 4.6 workstation (GE Healthcare Life Sciences) for post-processing. Functional maps of IVIM parameters and a standard apparent diffusion coefficient (ADCstandard) map were processed by mean ADC (MADC) programs on the built-in AW 4.6 workstation.

ADCstandard was calculated using a mono-exponential model including the total b-values. The equation used was as follows: S(b)/S0=exp (-b x ADCstandard) (equation 1). IVIM parameters including slow apparent diffusion coefficient (Dslow), fast apparent diffusion coefficient (Dfast) and fraction of fast apparent diffusion coefficient (f) were calculated using bi-exponential fitting by the segmented fitting method. The equation used was as follows, as proposed by Le Bihan (20): S(b)/S0=(1-f) x exp (-b x Dslow) + f x exp (-b x Dfast) (equation 2), where S(b) represents the mean signal intensity (SI) of a DW image according to a specific b-value, S0 represents the mean SI of a DW image when b=0, Dslow represents true tissue diffusivity while tissue microcapillary perfusion is mainly excluded, Dfast represents the mean velocity of the flowing blood within capillaries and the microvascular architecture and f represents the ratio of molecular diffusion within capillaries compared with the overall water molecular diffusion in a voxel. As Dfast is larger compared with Dslow by approximately one order of magnitude (22), -b x Dfast would be >3 when the b>200 sec/mm², and the f x exp (-b x Dfast) value would be >0.05x f. Therefore, f x exp (-b x Dfast) can be neglected and equation 2 can be expressed as follows: S(b)/S0=(1-f) x exp (-b x Dslow) (equation 3). As b-values were >200 sec/mm², S(b) was fitted using equation 3 according to a linear model, and Dslow was calculated. The f value was previously calculated according to equation 3; however, the accuracy was unacceptable. Therefore, the f-value was recalculated according to equation 2. Subsequently, S(b) was fitted for all b-values according to equation 2 with the Dslow value fixed by the nonlinear Levenberg-Marquardt method (19). When equation 2 was fitted, the initial estimated Dfast value was set as 10x10⁻³ mm²/sec, and the f-value was set as the previous f-value calculated from equation 3. The Dfast and f values were then acquired.

On the DW images that distinctly displayed the tumors, irregular regions of interest (ROIs) for each PDAC and pNENs were manually delineated along the edge of the tumor on three consecutive largest lesion slices. During measurement, particular efforts were made to exclude any areas of necrosis, the pancreatic duct and vessels within the tumor. Well-matched ROI copies were generated synchronously and appeared
automatically on identical locations in every functional map of IVIM-DWI parameters and ADC standard by built-in MADC software on an AW 4.6 workstation (GE Healthcare Life Sciences). The processes of ROI setting on functional parameter maps are presented in Fig. 2. The mean value of the results of three measurements was used as the final result. The ROI area range of pNENs was between 22 and 1,379 mm² with a mean area of 372.22 mm². The ROI area range of PDAC was between 136 and 1,025 mm² with a mean area of 324.58 mm².

Statistical analysis. All analyses were performed using SPSS software version 17.0 for Windows (SPSS Inc.) and MedCalc software version 12.3 (MedCalc Software). The ADC standard and IVIM-DWI parameter values are presented as the mean ± standard deviation. ADC standard and IVIM-DWI parameter values were compared using an independent sample Student’s t-test. Receiver operating characteristics (ROC) analysis was performed to evaluate the diagnostic performance of IVIM-DWI parameters and to determine the cut-off values using the maximum Youden index (the sum of specificity and sensitivity). P<0.05 was considered to indicate a statistically significant difference.

Results

Clinical and pathological characteristics of patients and lesions. The clinical and pathological characteristics of patients and lesions are summarized in Table II. A total of 50 patients including 13 cases of high-grade pNENs (grade 2, n=11; grade 3, n=2) and 37 cases of PDAC (well/moderately differentiated, n=21; poorly differentiated, n=11; confirmed by biopsy without pathological grades, n=5) confirmed by surgical pathology were included (27). The pNENs cohort (mean age, 55.1 years; age range, 42-75 years) included 8 male and 5 female patients. The clinical symptoms of the pNENs group included hypoglycemia, epigastric pain and discomfort, thrombocytopenia and splenomegaly. Among the pNENs group, one patient presented with painless jaundice. The PDAC cohort (mean age, 57.5 years; age range, 20-76 years) included 23 male and 14 female patients. The clinical symptoms of the PDAC group included marasmus, dyspepsia and abdominal and back pain. Among the PDAC group, 11 patients presented with jaundice.

Conventional MRI results. The conventional MRI results of PDAC and pNENs are presented in Table III. The mean long diameter of pNENs was 3.31 cm (range, 0.89-5.58 cm). Among the pNENs, 7 lesions were located in the head, 2 were in the body and 4 were in the tail of the pancreas. In the T1W images, 7 pNENs exhibited moderate hyperintensity, 4 exhibited slight hyperintensity and 2 exhibited moderate hypointensity. In the LAVA Flex water phase images, 12 pNENs exhibited moderate hypointensity and 1 presented with slight hypointensity. In the LAVA Flex with contrast
images, all pNENs exhibited heterogeneous mild-to-moderate hypo-enhancement on arterial phase imaging. Representative conventional images of pNENs are presented in Fig. 3A-C. In the DW images, 12 pNENs exhibited hyperintensity and 1 displayed hypointensity. Among the 12 hyperintensive pNENs, 5 (41.7%) exhibited heterogeneous SI and 7 (58.3%) exhibited homogeneous SI in DWI. In addition, 8 of 12 (66.7%) hyperintensive pNENs exhibited high SI in all b-value DW images, including low b-value (b≤200 sec/mm$^2$), moderate b-value (200 sec/mm$^2$＜b≤1,500 sec/mm$^2$) and high b-value (b>1,500 sec/mm$^2$). In addition, 4 of 12 (33.3%) hyperintensive pNENs demonstrated high SI in low and moderate b-value DW images; however, they exhibited low SI in high b-value DW images. Representative DW images of pNENs are presented in Fig. 3D-F.

The mean long diameter of PDAC was 4.03 cm (range, 2.05-6.82 cm). Among the PDAC cohort, 20 lesions were located in the head, 6 in the neck, 8 in the body and 3 in the tail of the pancreas. In the T2W images, 29 PDAC exhibited moderate hyperintensity, 5 exhibited slight hyperintensity, 1 exhibited isointensity and 2 exhibited slight hypointensity. In the LA VA Flex water phase images, 26 PDAC exhibited moderate hypointensity, 7 exhibited slight hypointensity, 1 exhibited slight hyperintensity and 3 exhibited isointensity. In the LA VA Flex with contrast images, all PDAC exhibited heterogeneous hypo-enhancement with different degrees in arterial phase imaging. Representative conventional images of PDAC are presented in Fig. 4A-C. In the DW images, 36 PDAC cases exhibited significant hyperintensity and 1 exhibited slight hypointensity. In addition, 27 of 36 (75%) hyperintensive PDAC exhibited heterogeneous SI and 9 (25%) indicated homogeneous SI in DWI. Among the 36 hyperintensive PDAC, 27 (75%) demonstrated high SI in all b-value DW images; however, 9 (25%) exhibited high SI in low and moderate b-value DW images only. Representative DW images of PDAC are presented in Fig. 4D-F.

Comparison of IVIM-DWI parameters. IVIM-DWI parameters of PDAC and pNENs are presented in Table IV. The mean $D_{slow}$ value was significantly lower in pNENs compared with that in PDAC (0.460x10$^{-3}$ vs. 0.579x10$^{-3}$ mm$^2$/sec; $t$=3.509; $P$=0.001) (Fig. 5A), whereas the mean $D_{fast}$ value was significantly higher in pNENs compared with that in PDAC (13.361x10$^{-3}$ vs. 4.985x10$^{-3}$ mm$^2$/sec; $t$=5.071; $P$<0.001) (Fig. 5B). For ADC$_{standard}$ and $f$, no significant differences were observed between pNENs and PDAC (0.818x10$^{-3}$ vs. 0.863x10$^{-3}$ mm$^2$/sec; $t$=0.961; $P$=0.341; and 59.5 vs. 55.8%; $t$=0.872; $P$=0.388, respectively) (Fig. 5C and D).

ROC curves for differentiating pNENs from PDAC using $D_{slow}$ and $D_{fast}$ are presented in Fig. 6. The optimal cut-off values and AUC in differentiating pNENs from PDAC are listed in Table V. The AUC for $D_{slow}$ and $D_{fast}$ were slightly larger compared with that for $D_{slow}$ or $D_{fast}$ alone (0.863 vs. 0.793; $P$=0.499), whereas the AUC for combined $D_{slow}$ and $D_{fast}$ was slightly larger compared with that for $D_{slow}$ or $D_{fast}$ alone (0.885 vs. 0.793; $P$=0.257; 0.885 vs. 0.863; $P$=0.757, respectively). When $D_{slow}$ value was ≥0.472x10$^{-3}$ mm$^2$/sec, the specificity and sensitivity for differentiating pNENs from PDAC were 97.3 and 53.9%, respectively. When $D_{fast}$ value was >9.58x10$^{-3}$ mm$^2$/sec, the specificity and sensitivity for differentiating pNENs from PDAC were 91.9 and 69.2%, respectively. When $D_{slow}$ and $D_{fast}$ were combined, the specificity and sensitivity for differentiating high-grade pNENs from PDAC were 76.9 and 100%, respectively.

Discussion

The present study identified statistically significant differences in $D_{fast}$ and $D_{slow}$ between PDAC and pNENs. The differences in ADC$_{standard}$ and $f$ exhibited no significance between PDAC and pNENs. The ADC value is the most commonly used parameter for evaluating tissue diffusion that serves as a marker of cellularity (28,29), which is additionally decreased

| Table I. MRI parameters. |
|--------------------------|
| **Parameters** | Axial FSE T2WI | Axial LAVA Flex | DWI |
| Repetition time, ms | 10,000 | 4.3 | 6600 |
| Echo time, ms | 70 | 1.6 | 81.5-82.3 |
| Slice thickness, mm | 4.0 | 4.0 | 4.0 |
| Slice gap, mm | 0.5 | 0.0 | 1.0 |
| Matrix size, slices | 320x320 x NS | 260x210 x NS | 128x128 x NS |
| Field of view, mm | 360x360 | 360x324 | 380x304 |
| Number of excitations$^a$ | 1.5 | 1 | 1-8 |
| Flip angle, $^\circ$ | 110 | 14 | 90 |
| Bandwidth, Hz/pixel | 62.5 | 200 | 250 |
| Acquisition Time, sec | 120-240 | 480-660 |

$^a$Specific number of excitations for each b-value is as follows: 10 (4), 20 (2), 40 (1), 60 (1), 80 (1), 100 (1), 150 (2), 200 (2), 400 (4), 800 (4), 1,000 (6), 1,200 (6), 1,500 (6) and 2,000 (8) s/mm$^2$; the numbers in brackets represent the number of excitations. FSE, fast spin echo; T2WI, fast spin echo transverse relaxation time-weighted imaging; LAVA, liver acquisition with volume acceleration; DWI, diffusion weighted imaging; NS, number of slices.
in solid malignant tumors compared with benign tumors or cystic lesions (30). The ADC value can be a surrogate biomarker for tumor cell proliferation and predict the grade of a variety of neoplasms (31,32). However, previous studies have demonstrated that not both water diffusion within tissue microstructures and the undirected movement of particles within the capillaries can influence the obtained ADC value (19,33). The present study revealed that the ADC_{standard} of PDAC was slightly higher compared with that of pNENs. The measurement of the ADC value is biased by the effects of microcirculatory perfusion, which may impact the accuracy of ADC in evaluating pancreatic lesions (33).

The IVIM-derived parameter D_{slow} represents the pure diffusion component reflecting tissue microstructure without...
The predominant histological features of PDAC include not only the dense tumor cellularity, but also progressive fibrosis (35). Restrained molecular diffusion in PDAC may be attributed to an exceeding cellular structure and extracellular fibrosis (36). Previous studies have demonstrated that the lower $D_{\text{slow}}$ value of pNENs (grade 2 or 3) may be caused by the increased tumor cellularity (25,37). However, necrosis is also one of the pathological features in PDAC and may be associated with increasing diffusion (30). The results of the present study demonstrated that 75.0% hyperintensive PDAC appeared as heterogeneous SI in DW images, whereas only 41.7% hyperintensive pNENs exhibited heterogeneous SI in DW images. This may be the cause for the results obtained in the present study, as the $D_{\text{slow}}$ of PDAC was significantly higher compared with that of pNENs. Therefore, $D_{\text{slow}}$ may be more useful compared with conventional ADC in differentiating pNENs and PDAC by eliminating microperfusion effects in a capillary bed.

The results of the present study demonstrated that $D_{\text{fast}}$ of PDAC was notably lower compared with that of pNENs. The $f$ of PDAC was slightly lower compared with that of pNENs. $D_{\text{fast}}$ is associated with blood flow and velocity within microcirculation (19,22). Parameter $f$ is associated with the proportion of protons in microcirculation within a voxel (29).

### Table II. Clinicopathological characteristics of patients and lesions.

| Characteristics | PDAC | pNENs |
|-----------------|------|-------|
| Sex, n          |      |       |
| Male            | 23   | 8     |
| Female          | 14   | 5     |
| Grading         |      |       |
| Well/moderately differentiated (21) | Grade 2 (11) |
| Poorly differentiated (11) | Grade 3 (2) |
| Confirmed by biopsy |       |
| Clinical symptoms |      |       |
| Painless jaundice | 11   | 1     |
| Hypoglycemia    | 0    | 3     |
| Epigastric pain and discomfort | 0    | 6     |
| Thrombocytopenia and splenomegaly | 0    | 1     |
| Marasmus        | 21   | 0     |
| Dyspepsia       | 13   | 0     |
| Abdominal and back pain | 16   | 0     |

PDAC, pancreatic ductal adenocarcinoma; pNENs, pancreatic neuroendocrine neoplasms. *According to 2010 WHO Classification of Tumors of Digestive System (27). **According to 2017 World Health Organization Neuroendocrine Tumor Classification Guideline (3).

### Table III. Conventional magnetic resonance imaging results.

| Characteristic | PDAC, n | pNENs, n |
|----------------|---------|----------|
| Site           |         |          |
| Head of pancreas | 20   | 7        |
| Neck of pancreas | 6    | 0        |
| Body of pancreas | 8    | 2        |
| Tail of pancreas | 3    | 4        |
| T$_2$W images  |         |          |
| Moderate hyperintensity | 29 | 7        |
| Slight hyperintensity  | 5    | 4        |
| Isointensity        | 1    | 0        |
| Moderate hypointensity | 0   | 2        |
| Slight hypointensity  | 2    | 0        |
| LAVA Flex water phase images | | |
| Moderate hypointensity | 26 | 12       |
| Slight hypointensity | 7    | 1        |
| Isointensity | 3    | 0        |
| Slight hypointensity | 1    | 0        |
| LAVA Flex with contrast images | | |
| Heterogeneous hypo-enhancement | 37 | 13       |
| with a different degree | | |
| DWI             |         |          |
| Hyperintensity  | 36    | 12       |
| All b-values    | 27    | 8        |
| (0<b≤1,500 sec/mm$^2$) | 9    | 4        |
| Hypointensity   | 1    | 1        |

PDAC, pancreatic ductal adenocarcinoma; pNENs, pancreatic neuroendocrine neoplasms; LAVA, liver acquisition with volume acceleration; DWI, diffusion weighted imaging; T$_2$W, fast spin echo transverse relaxation time-weighted.
Figure 3. Grade 2 pNEN located in the head of the pancreas (white arrow). The pancreatic body and tail exhibit atrophy and the pancreatic duct exhibits dilation. (A) Axial T2W MRI with fat suppression demonstrates pNEN with heterogeneous moderate hypointensity and an obscure boundary. (B) Axial LAVA Flex water phase image displays pNEN with heterogeneous moderate hypointensity and an obscure boundary. (C) Axial arterial phase image demonstrates pNEN with mild heterogeneous enhancement. (D) Axial DWI with a b-value of 200s/mm2 demonstrates pNEN with heterogeneous hyperintensity and an obscure boundary. (E) Axial DWI with a b-value of 1,500s/mm2 demonstrates pNEN with heterogeneous hyperintensity and a clear boundary. (F) Axial DWI with a b-value of 2,000s/mm2 demonstrates pNEN with heterogeneous hyperintensity and a clear boundary. pNEN, pancreatic neuroendocrine neoplasm; LAVA, liver acquisition with volume acceleration; DWI, diffusion weighted imaging; T2W, fast spin echo transverse relaxation time-weighted.

Figure 4. PDAC located in the head of the pancreas (white arrow). The pancreatic body and tail exhibit atrophy and the pancreatic duct presents with dilation. (A) Axial T2W MRI with fat suppression displays PDAC with heterogeneous moderate hyperintensity and an obscure boundary. (B) Axial LAVA Flex water phase image demonstrates PDAC with heterogeneous moderate hypointensity and an obscure boundary. (C) Axial arterial phase image demonstrates PDAC with mild heterogeneous enhancement. (D) Axial DWI with a b-value of 200s/mm2 demonstrates PDAC with heterogeneous hyperintensity and a clear boundary. (E) Axial DWI with a b-value of 1,500s/mm2 demonstrates PDAC with heterogeneous hyperintensity and a clear boundary. (F) Axial DWI with a b-value of 2,000s/mm2 demonstrates PDAC with heterogeneous hyperintensity and a clear boundary. DWI, diffusion weighted imaging; PDAC, pancreatic ductal adenocarcinoma; T2W, fast spin echo transverse relaxation time-weighted.
significantly higher compared with that of pNENs. This may be due to Kang et al using only nine b-values in IVIM-DWI; however, 15 b-values were used in the present study. Therefore, in order to obtain high-quality IVIM-DWI, at least 10 b-values should be used (40).

The present study demonstrated that the optimal AUC was achieved by combining $D_{\text{slow}}$ and $D_{\text{fast}}$ (AUC, 0.885), which was followed by $D_{\text{fast}}$ alone (AUC, 0.863 and 0.793 respectively). The highest specificity was identified for $D_{\text{slow}}$ (97.3%), which was closely followed by $D_{\text{fast}}$ (91.9%).
Dslow and Dfast were combined, the sensitivity for differentiating high-grade pNENs from PDAC was 100.0%. Therefore, Dslow and Dfast may be the ideal screening indicators in differentiating high-grade pNENs from PDAC.

There were certain limitations to the present study. For example, the sample size of the present study was relatively small, particularly regarding the limited number of high-grade pNENs due to its low incidence. However, all patients underwent surgery and were confirmed by histopathology. Secondly, the present study did not analyze the association between histopathology and IVIM-DWI parameters. This was due to the small sample size of different pathological grades pNENs and PDAC. Additional subjects need to be recruited in order to investigate the association between histopathology and IVIM-DWI parameters of pNENs and PDAC in further studies. In addition, dynamic contrast enhancement (DCE)-MRI was not performed in the present study due to the patients’ preferences. The association between DCE-MRI and IVIM-DWI parameters will be investigated in our future studies. An additional limitation of the present study was that the b-values selected may have been suboptimal. Therefore, optimal b-values should be selected in any future studies to balance the least sampling time and the reliability of parameter estimation. Finally, a control group with normal pancreas was not included in the present study. This will be evaluated in further studies with larger populations.

In conclusion, the results of the present study demonstrated that the diffusion parameter Dslow and the perfusion parameter Dfast derived from IVIM-DWI may be reliable in differentiating high-grade pNENs from PDAC with high diagnostic accuracy. In addition, IVIM-DWI may be a potential technique to function as a surrogate biomarker in distinguishing pancreatic neoplasms.

Table V. Results of the receiver operating characteristic analysis for Dslow and Dfast.

| Coefficient              | AUC (95% CI)            | Optimal cut-off               | Sensitivity (%) | Specificity (%) | P-value |
|-------------------------|-------------------------|-------------------------------|-----------------|-----------------|---------|
| Dslow                   | 0.793 (0.655-0.895)     | ≤0.472x10^{-3} mm²/sec        | 53.9            | 97.3            | 0.499a  |
| Dfast                   | 0.863 (0.736-0.944)     | >9.58x10^{-3} mm²/sec         | 69.2            | 91.9            | 0.757b  |
| Combined Dslow and Dfast| 0.885 (0.763-0.958)     | -                             | 100             | 76.9            | 0.257c  |

aDslow vs. Dfast; bDfast vs. Combined Dslow and Dfast; cDslow vs. Combined Dslow and Dfast. AUC, area under the curve; CI, confidence interval; Dslow, slow apparent diffusion coefficient; Dfast, fast apparent diffusion coefficient.

Figure 6. ROC curves of Dslow and Dfast for differentiating pNENs from PDAC. The diagonal line is the reference, which indicates the results for a test with 50% sensitivity and 50% specificity. The highest AUC was obtained for combined Dslow and Dfast, which was closely followed by Dfast and Dslow alone. ROC, receiver operating characteristics; Dslow, slow apparent diffusion coefficient; Dfast, fast apparent diffusion coefficient; AUC, area under the curve; pNENs, pancreatic neuroendocrine neoplasms; PDAC, pancreatic ductal adenocarcinoma.
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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Authors' contributions

WM, MW and NL participated in the study conception and design. ZH, YT, QP and GZ collected and analyzed the patients' clinical data. WM, MW and JR collected and analyzed the patients' imaging data. WM, MW, ZH, YT, QP, GZ, JR, YH and NL participated in the interpretation of the patients' imaging data. WM and MW prepared the first draft of the manuscript. YH and NL revised the manuscript critically for important intellectual content. NL gave final approval of the version to be published. All authors revised and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval was acquired from the Institutional Ethics Committee Board of Xijing Hospital (Xi'an, China), and written informed consent was obtained from all participants prior to collecting the data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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