



Research article

Evaluation of fatty pancreas by proton density fat fraction using 3-T magnetic resonance imaging and its association with pancreatic cancer



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ABSTRACT

Purpose: To evaluate whether pancreatic magnetic resonance imaging-proton density fat fraction (MRI-PDFF) correlates with histological pancreatic fat fraction and its possible usefulness as a biomarker of pancreatic cancer compared with pancreatic index (PI) using computed tomography (CT number of the pancreas divided by that of the spleen).

Method: We included 55 consecutive patients (24 with pancreatic cancer and 31 controls; median age, 72 years) who preoperatively underwent MRI-PDFF using IDEAL-IQ and unenhanced CT and did not receive preoperative therapy. Histologic pancreatic fat fraction was measured in non-tumorous pancreatic tissues at the resection stump. A board-certified radiologist evaluated MRI-PDFF and PI. Correlations were evaluated among MRI-PDFF, PI, and histologic pancreatic fat fraction; the usefulness of MRI-PDFF as a predictor of pancreatic cancer was assessed.

Results: Histologic pancreatic fat fraction significantly correlated with MRI-PDFF and PI ($r = 0.802$ and -0.534 , respectively; $P < 0.01$). The absolute correlation coefficient was significantly higher for MRI-PDFF than for PI ($P < 0.01$). Compared with the control group, the pancreatic cancer group had higher MRI-PDFF and histologic pancreatic fat fraction ($P < 0.01$) but lower PI ($P < 0.01$). In multivariate analysis, MRI-PDFF was found to be the sole independent risk factor for pancreatic cancer (odds ratio: 1.19; $P < 0.01$).

Conclusions: Pancreatic fat, which was associated with pancreatic cancer, could be quantified by MRI-PDFF measurement; therefore, MRI-PDFF should be considered as a promising and superior imaging biomarker for estimating the probability of pancreatic cancer than PI.

1. Introduction

Pancreatic cancer is the seventh leading cause of cancer-related death worldwide [1]. Pancreatic cancer-related mortality rate is estimated to be 2.5 per 100,000 people in developing countries and 14.8 per 100,000 people in developed countries, indicating that pancreatic cancer is more prevalent and fatal in developed countries [2]. Development of useful markers for predicting the risk of pancreatic cancer is critical for its early detection and can subsequently contribute to a significant reduction in mortality rates. Family history of pancreatic

cancer, smoking, age, obesity, and certain diseases such as chronic pancreatitis and diabetes mellitus have been reported as the risk factors for pancreatic cancer [3–6]. Additionally, recent studies have reported fatty infiltration of the pancreas to be an important risk factor for pancreatic cancer [6–10]. Further, recent studies have reported (i) pancreatic index (PI) determined by computed tomography (CT), i.e., CT number of the pancreas divided by that of the spleen, and fatty infiltration to be significantly correlated and (ii) that PI is useful in predicting pancreatic cancer [10,11]. However, pancreatic fat fraction cannot be quantitatively measured using CT [12]. In contrast, magnetic

Abbreviations: CT, computed tomography; MR, magnetic resonance; PDFF, proton density fat fraction; PI, pancreatic index; ROC, receiver-operating characteristics; ROI, region of interest

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resonance (MR) imaging can directly measure the fat fraction, thereby possibly proving superior to CT in evaluating fatty infiltration of the pancreas. Measurement of the liver fat fraction has become possible by measuring proton density fat fraction (PDFF) using MR imaging [13,14]. The purpose of the current study was to evaluate whether PDFF measured by MR imaging (MRI-PDFF) correlates with histological pancreatic fat fraction and its possible usefulness as a biomarker of pancreatic cancer compared with PI.

2. Materials and methods

This study was approved by our institutional review board, and informed consent was waived because of the retrospective nature of the study.

3. Patients

In total, 281 consecutive patients who underwent pancreatectomy between January 2014 and April 2018 at our institution were evaluated. Inclusion criteria were as follows: patients who preoperatively underwent MR imaging using IDEAL-IQ and unenhanced CT and those who did not receive preoperative therapy. Accordingly, 175 patients without preoperative MR imaging and 43 who underwent preoperative therapy were excluded. Among the remaining 63 patients, 5 whose MR images showed pancreatic atrophy with extensive pancreatic ductal dilation and 3 without non-tumorous pancreatic parenchyma that could be analyzed histologically were excluded. Finally, 55 patients (31 males and 24 females; median age, 72 years; range, 31–89 years) were evaluated. Among these patients, 24 had pancreatic cancer, 6 had neuroendocrine tumor, 7 had intraductal papillary mucinous adenoma (5 branch duct, 1 main duct, and 1 mixed), 6 had cholangiocarcinoma, 3 had ampullary cancer, 3 had mucinous cystic neoplasm, 3 had solid pseudopapillary neoplasm, 2 had serous cystic neoplasm and 1 had pancreatic intraepithelial neoplasia (Fig. 1). The median interval between pancreatectomy and MR imaging was 50 days (1–300 days), between pancreatectomy and CT was 57 days (10–405 days), and

between MR imaging and CT was 25 days (1–253 days). There were 26, 27, and 2 patients who underwent pancreaticoduodenectomy, distal pancreatectomy, and central pancreatectomy, respectively. For benign tumors, pancreatectomies were performed due to their diagnostic discrimination of benign and malignant tumor, tumor growth, and symptoms. Based on the pathological diagnosis, the patients were divided into two groups: pancreatic cancer (n = 24) and control (n = 31).

4. Pathological examination

Hematoxylin–eosin-stained slides (thickness, 2 μ m) generated from resected specimens were retrospectively analyzed by light microscopy (BZ-9000; Keyence, Osaka, Japan) by an investigator blinded to the clinical, MRI-PDFF, and PI data of the patients. Three areas of these slides (field of view: length, 5.4 mm; width, 7.2 mm) were observed by the investigator who was supervised by expert pathologists at our institute. Histologic pancreatic fat fraction was measured of non-tumorous pancreatic tissues at the resection stump using an image analysis software (ImageJ version 1.51; <https://imagej.nih.gov/>) (Figs. 2a, b and 3 a, b) [7,10]. Histologic pancreatic fat fraction was defined as the percentage of pancreatic intraparenchymal fat (intralobular and interlobular fat) of the total pancreatic parenchyma [11,15].

5. MR imaging

All MR imaging studies were performed with a 3.0-T system (Discovery MR750 3.0 T with 32-channel cardiac coil or Discovery MR750w 3.0-T with GEM body coil; GE Healthcare, Milwaukee, WI, USA). IDEAL-IQ sequence was used to determine MRI-PDFF. The IDEAL-IQ sequence parameters were as follows: repetition time (TR), 5.8 or 6.7 ms; field of view, 34 cm; matrix, 128 \times 128; bandwidth, 90.91 or 83.33 kHz; flip angle, 3°; and slice thickness, 8.0 mm; acquisition time, 23 s. At our hospital, IDEAL-IQ sequence is included in routine MR imaging protocols for upper abdominal examinations because fatty liver can be easily and quantitatively evaluated using this sequence. Other images such as diffusion-weighted, T2-weighted, MR

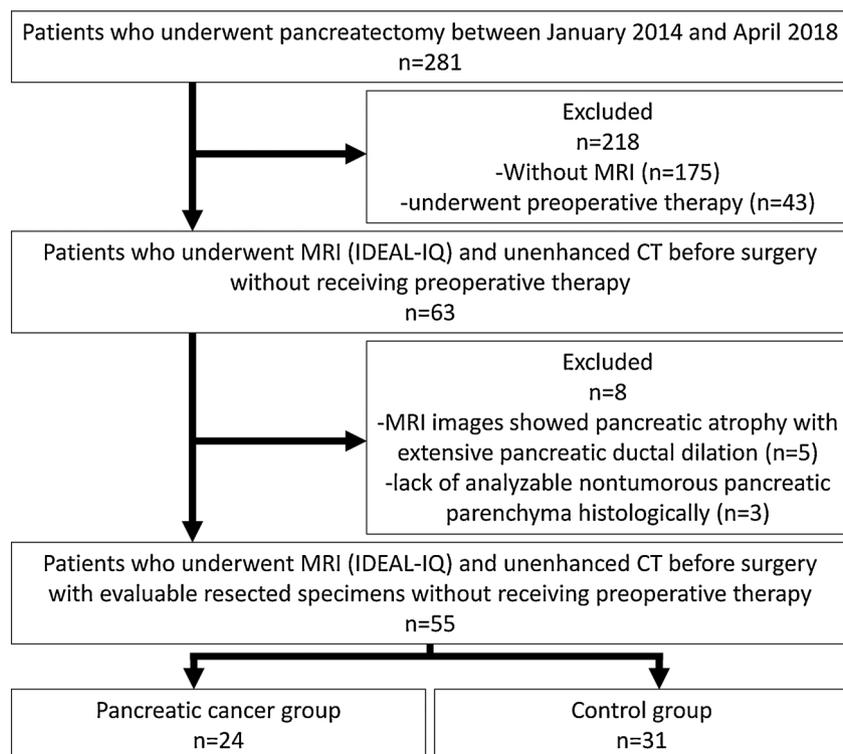


Fig. 1. Study flowchart.

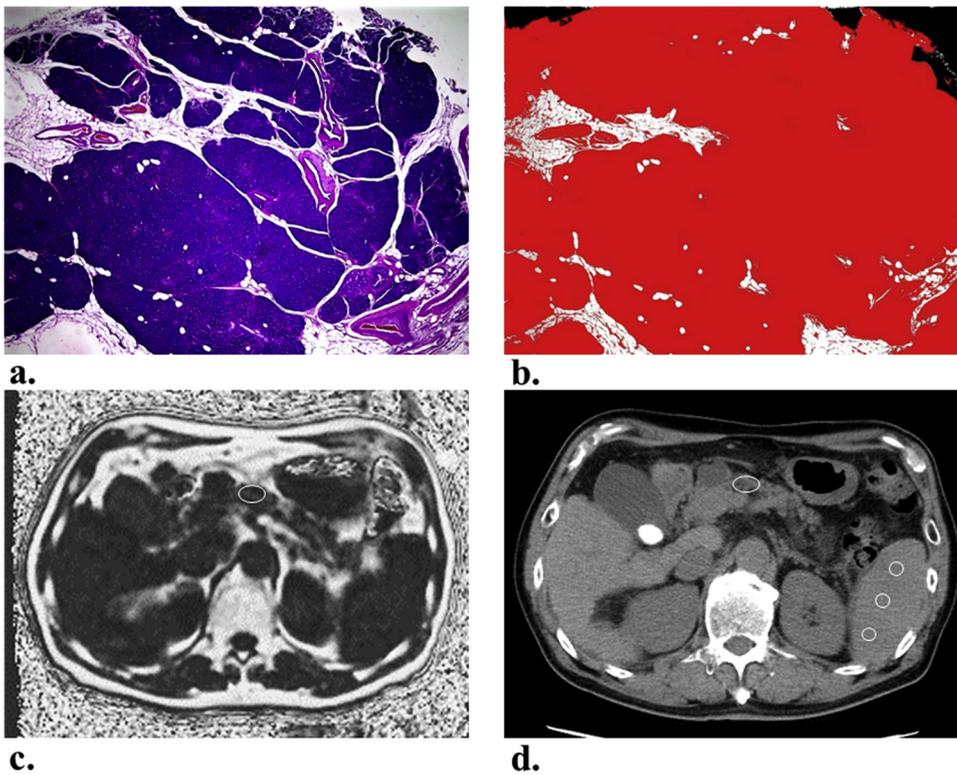


Fig. 2. Representative images of a 69-year-old male who underwent pancreatectomy for pancreatic adenocarcinoma.

(a and b) Hematoxylin–eosin-stained slide (field of view: length, 5.4 mm; width, 7.2 mm) scanned with a color scanner showing total areas of intraparenchymal fat and pancreatic parenchyma measured with an image analysis software to calculate histologic pancreatic fat fraction (6.30% in this patient). (c) An ROI location for the pancreas on PDFFF maps is shown (MRI-PDFF: 5.14% in this patient). (d) An ROI location for the pancreas and three ROIs for the spleen on unenhanced CT are shown (PI: 0.65 in this patient). ROI, region of interest; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; PI, pancreatic index.

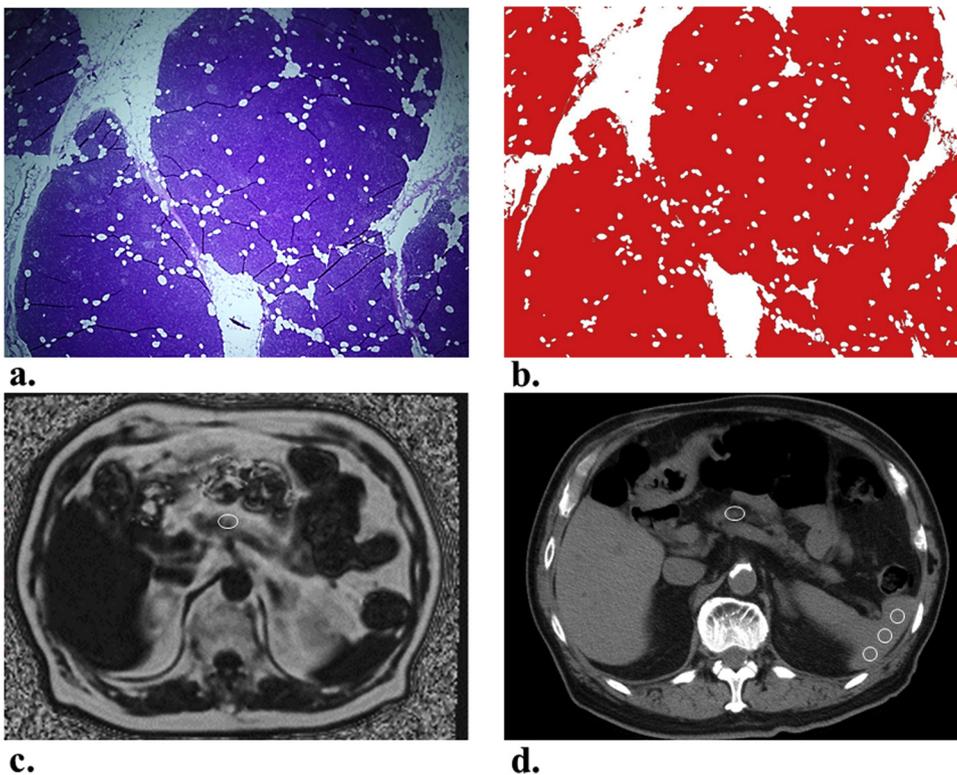


Fig. 3. Images in an 87-year-old man who underwent pancreatectomy for pancreatic adenocarcinoma (a–b) Hematoxylin–eosin-stained slide (field of view: length, 5.4 mm; width, 7.2 mm) scanned with color scanner showing total area of intraparenchymal fat and that of pancreatic parenchyma measured with image analysis software to calculate histologic pancreatic fat fraction (20.38% in this patient). (c) A ROI location for the body of the pancreas on PDFFF maps is seen (MRI-PDFF: 24.88% in this patient). (d) A ROI location for the body of the pancreas and three ROIs for the spleen are seen (PI: 0.38 in this patient).

ROI, region of interest; MRI-PDFF, proton density fat fraction measured using MRI; PI, pancreatic index.

cholangiopancreatography, and dynamic contrast-enhanced images were obtained; however, they were not used for analyses in the current study.

6. CT imaging

CT was performed using 320-channel (Aquilion One Genesis

Edition; Canon Medical Systems, Otawara, Japan), 160-channel (Aquilion Precision; Canon Medical Systems), or 64-channel CTs (Discovery CT 750 HD or Discovery CT 750 HD Freedom Edition; GE Healthcare). Scanning parameters were as follows: collimation, 0.625×64 or 0.5×80 mm; pitch, 1.375 or 0.813 mm/rotation; rotation time, 0.4 or 0.5 s/rotation; exposure parameters of 120 kV and auto exposure control with a noise index standard deviation of 13.8 or 15;

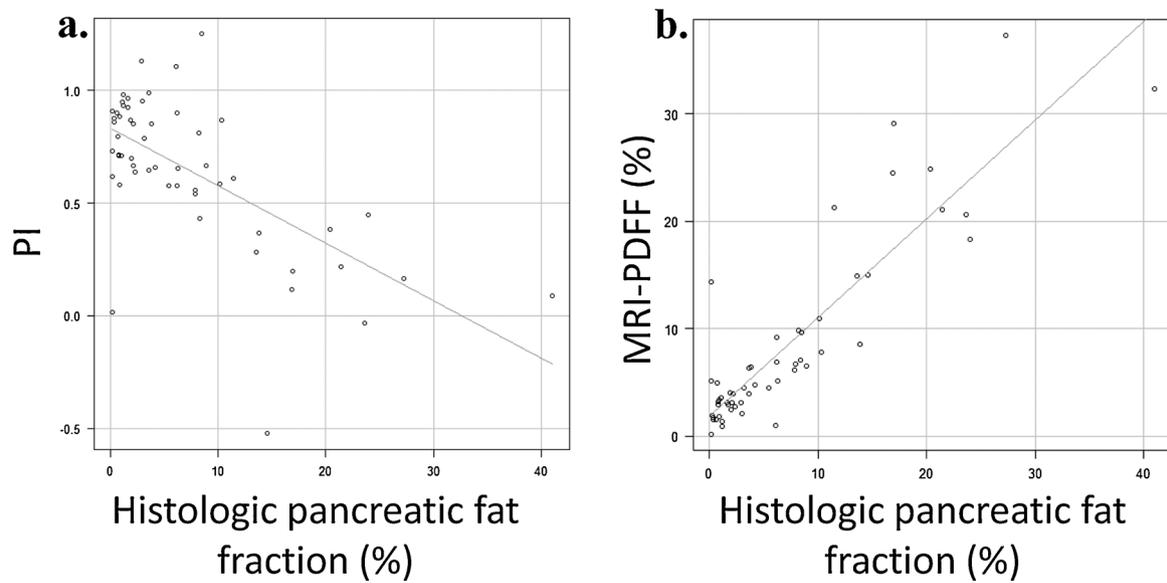


Fig. 4. Correlations among histologic pancreatic fat fraction, MRI-PDFF, and PI. (a) Histologic pancreatic fat fraction significantly correlated with MRI-PDFF ($r = 0.802$, $P < 0.01$) (b) Histologic pancreatic fat fraction correlated with PI ($r = -0.534$, $P < 0.01$). MRI-PDFF, magnetic resonance imaging-proton density fat fraction; PI, pancreatic index.

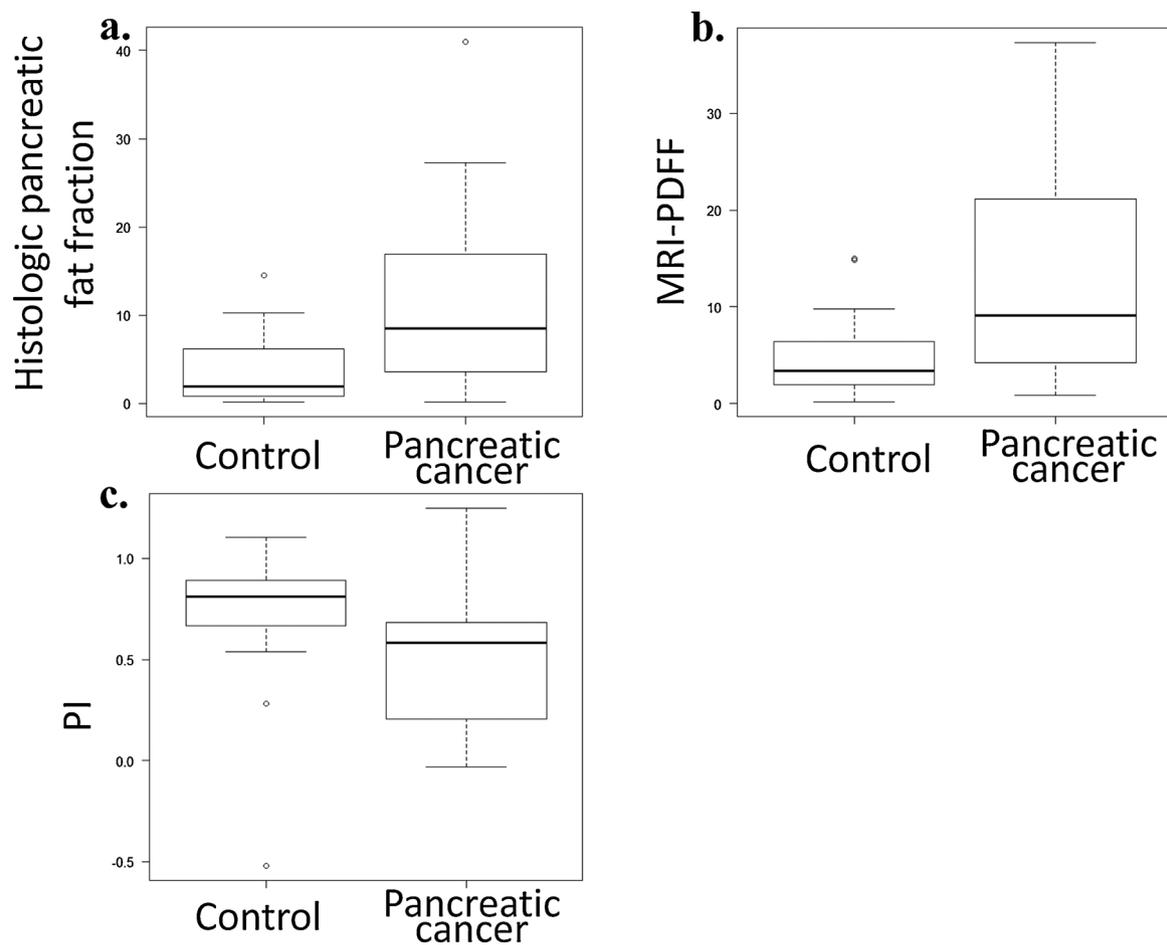


Fig. 5. (a) Box plot showing that the median histologic pancreatic fat fraction is higher in the pancreatic cancer group than in the control group (8.48% vs. 1.90%; $P < 0.001$). (b) Box plot showing that the median MRI-PDFF is higher in the pancreatic cancer group than in the control group (9.09% vs. 3.42%; $P < 0.01$). (c) Box plot showing that the median PI is lower in the pancreatic cancer group than in the control group (0.58 vs. 0.81; $P < 0.01$). MRI-PDFF, magnetic resonance imaging-proton density fat fraction; PI, pancreatic index.

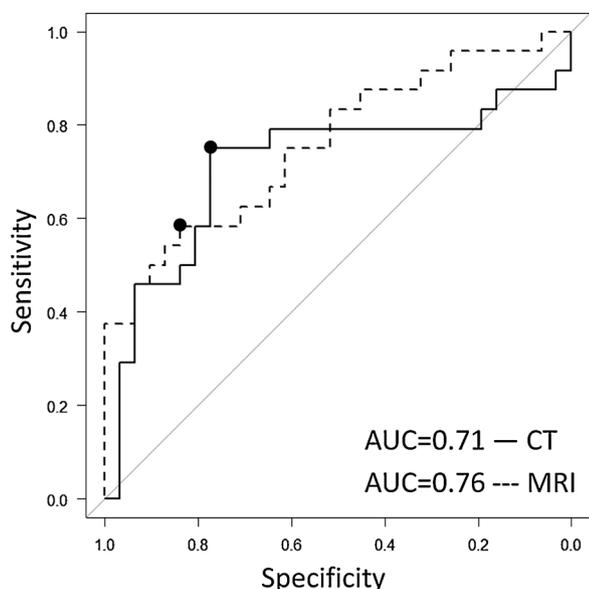


Fig. 6. ROC curves for the determination of the efficacy of MRI-PDFF and PI in detecting pancreatic cancer showing AUC values of 0.76 and 0.71, respectively. The optimal MRI-PDFF and PI cutoff values are 7.10% and 0.66, with a sensitivity of 58.0% and 75.0% and specificity of 84.0% and 77.0%, respectively. There is no statistically significant difference in terms of the AUC values between MRI-PDFF and PI.

ROC, receiver-operating characteristics; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; PI, pancreatic index; AUC, area under the curve.

Table 1

Univariate logistic regression analysis for factors associated with pancreatic cancer.

	Odds ratio	95%CI	P
MRI-PDFF	1.19	1.06–1.33	< 0.005
PI	0.11	0.02–0.78	< 0.05
Drinking	1.44	0.45–4.63	0.54
Smoking	0.92	0.31–2.68	0.87
Diabetes	1.82	0.61–5.39	0.28
BMI (kg/m ²)	0.47	0.08–2.68	0.40
Chronic pancreatitis	2.73	0.23–32.00	0.43
Gender	2.13	0.71–6.43	0.18
Age	1.04	0.99–1.10	0.10

MRI-PDFF proton density fat fraction measured using magnetic resonance imaging; PI pancreatic index; BMI body mass index.

Table 2

Results of multivariate logistic regression analyses.

	Odds ratio	95%CI	P
MRI-PDFF	1.19	1.06–1.33	< 0.01
PI	0.20	0.03–1.19	0.26
Gender	2.13	0.71–6.43	0.12
Age	1.04	0.99–1.10	0.29

MRI-PDFF proton density fat fraction measured using magnetic resonance imaging; PI pancreatic index.

and field of view, 345 mm. Unenhanced and dynamic contrast-enhanced images were obtained, but only unenhanced images were used.

7. Quantitative assessment of images

The MRI-PDFF and PI measurements were manually performed on an image workstation (Synapse; Fujifilm, Tokyo, Japan). Mean CT number was measured on unenhanced CT. MRI-PDFF was measured on

fat fraction images derived from the IDEAL-IQ sequence. A board-certified abdominal radiologist (9 years of experience as a radiologist) carefully placed the largest possible elliptical region of interest (ROI) on the pancreas at an estimated transection line to match the measurement areas on CT and MR images with those determined on the pathological assessment [10]. The radiologist determined the estimated resection line by referring to the operation records. If the radiologist was uncertain about the transection line, a surgeon was consulted for estimating the line. Mean CT number of the spleen was measured by tracing three 1-cm² ROIs in different parts of the spleen [11,12]. PI was obtained by dividing the CT number of the pancreas by the mean CT number of the spleen (Figs. 2c, d, and 3c, d).

8. Statistical analysis

Shapiro–Wilk test was performed to determine normality. Spearman’s rho coefficient was performed to calculate the degree of association among histologic pancreatic fat fraction, MRI-PDFF, and PI. Z-values were calculated using Fisher’s r-to-z transformation to assess the significance of the difference between two correlation coefficients. Regarding histologic pancreatic fat fraction, MRI-PDFF, and PI, Mann–Whitney U-test was performed to evaluate the difference between two parameters. Receiver-operating characteristics (ROC) analysis was performed to define the Youden index-based optimal cutoff values [16] for MRI-PDFF and PI. Univariate and multivariate logistic regression analyses were performed to determine whether MRI-PDFF, PI, drinking (> 10 g/day for females and > 20 g/day for males) [17], smoking (Brinkman’s index > 200), diabetes mellitus [18], chronic pancreatitis, obesity (body mass index ≥ 25 kg/m²), age, and sex were important predictors of pancreatic cancer. For all tests, P-value < 0.05 was considered statistically significant.

9. Results

In the entire cohort of 55 patients, the median histologic pancreatic fat fraction was 3.59% (range, 0.18%–40.98%; interquartile range, 1.15%–9.53%), median MRI-PDFF was 4.93% (range, 0.20%–37.31%; interquartile range, 2.91%–9.71%), and median PI was 0.70 (range, –0.52–1.25; interquartile range, 0.55–0.88). Histologic pancreatic fat fraction was found to be significantly correlated with MRI-PDFF ($r = 0.802, P < 0.01$) and PI ($r = -0.534, P < 0.01$), and the absolute correlation coefficient was significantly higher for MRI-PDFF than for PI ($P < 0.01$) (Fig. 4a and b). The median histologic pancreatic fat fraction in the pancreatic cancer and control groups was 8.48% (range, 0.18%–40.98%; interquartile range, 3.59%–16.92%) and 1.90% (range, 0.18%–14.54%; interquartile range, 0.82%–6.16%), respectively; the fraction was significantly higher in the pancreatic cancer group than in the control group ($P < 0.001$) (Fig. 5a). The median MRI-PDFF of the pancreatic cancer and control groups was 9.09% (range, 0.90%–37.31%; interquartile range, 4.37%–21.15%) and 3.42% (range, 0.20%–14.97%; interquartile range, 2.00%–6.46%), respectively; MRI-PDFF was significantly higher in the pancreatic cancer group than in the control group ($P < 0.01$) (Fig. 5b). Further, the median PI in the pancreatic cancer and control groups was 0.58 (range, –0.03–1.25; interquartile range, 0.21–0.67) and 0.81 (range, –0.52–1.10; interquartile range, 0.67–0.89), respectively; PI was significantly lower in the pancreatic cancer group than in the control group ($P < 0.01$) (Fig. 5c).

The ROC curves for the determination of the efficacy of MRI-PDFF and PI in estimating pancreatic cancer revealed that AUC values were 0.76 (95% confidence interval [CI] 0.63–0.89) and 0.71 (95% CI, 0.56–0.87), respectively. The ROC analysis identified MRI-PDFF and PI cutoff values to be 7.10% (sensitivity, 58.0%; specificity, 84.0%) and 0.66 (sensitivity, 75.0%; specificity, 77.0%), respectively (Fig. 6). There was no statistically significant difference in terms of AUC values between MRI-PDFF and PI. In the univariate analysis (Table 1), MRI-PDFF

and PI were found to be associated with pancreatic cancer ($P < 0.005$ and $P < 0.05$, respectively). Conversely, in the multivariate analysis (Table 2), MRI-PDFF was identified as the only independent risk factor for pancreatic cancer (odds ratio, 1.19; 95% CI, 1.06–1.33, $P < 0.01$).

10. Discussion

Fatty infiltration of the pancreas, i.e., replacement of normal pancreatic tissue with adipose tissue, has been demonstrated to be associated with obesity, diabetes mellitus, old age, metabolic factors, and nonalcoholic fatty liver disease [19–22]. Further, recent reports have suggested fatty infiltration of the pancreas to be a risk factor for pancreatic cancer [6,9,10,19,23]. Pancreatic fatty infiltration induces chronic inflammation resulting from the release of various cytokines and chemokines by the adipose tissue and leads to the development of pancreatic cancer [24–26]. However, unlike liver biopsy, pancreatic biopsy is considered technically challenging to perform. Therefore, noninvasive biomarkers of pancreatic fatty infiltration can prove to be potentially useful modalities for the detection of pancreatic cancer at an early stage. Several studies have demonstrated a correlation between fatty infiltration and PI, calculated using CT, and the usefulness of PI in early detection of pancreatic cancer [10,11]. However, the risks related to radiation exposure by CT render PI unsuitable for routine screening and surveillance. In contrast, given the absence of radiation exposure in MR imaging, it is considered a favorable screening technique.

Patel et al. demonstrated that MRI-PDFF correlated with histologic hepatic fat fraction, but pancreatic histologic fat fraction was not examined [27]. Therefore, the relationship between pancreatic histologic fat fraction and MRI-PDFF remains unclear. In the current study, we demonstrated that MRI-PDFF was correlated with histologic pancreatic fat fraction and PI. The findings that histologic pancreatic fat fraction was higher and PI was lower in the pancreatic cancer group than in the control group are consistent with the findings of some previous studies [6,10]. Similarly, the correlation coefficient is similar to those reported in earlier studies [11,28]. Furthermore, we found MRI-PDFF to be higher in the pancreatic cancer group than in the control group. Notably, the median MRI-PDFF in the pancreatic cancer group was close to that reported in a study that investigated MRI-PDFF in patients with nonalcoholic fatty liver disease [27].

In addition to the evaluation of the correlation between MRI-PDFF and histological pancreatic fat fraction, we assessed the usefulness of MRI-PDFF as an imaging predictor of pancreatic cancer compared with CT. Our analysis revealed that the absolute correlation coefficient was significantly higher for MRI-PDFF than for PI ($P < 0.01$) and that MRI-PDFF was the sole independent risk factor for pancreatic cancer as per the multivariate analysis. Additionally, lack of ionizing radiation exposure is beneficial for screening purposes. Therefore, the findings of the current study suggest that MRI-PDFF is superior to PI as a predictor of pancreatic cancer. Moreover, we determined the cutoff values of MRI-PDFF and PI for determining their usefulness in distinguishing between patients with and without pancreatic cancer. The cutoff value of 0.70 for PI that was established in a previous study is similar to the cutoff value of 0.66 obtained in this study [10].

This study has several limitations. First, interobserver variability was not assessed because the measurements were performed by the same investigator. However, the investigator carefully placed ROIs on the pancreas at an estimated transection line to match the measurement areas on CT or MR images with the area for pathological assessment. Second, regarding the imaging technique, an 8-mm slice thickness for MRI-PDFF measurement may not be optimal for measuring pancreatic fat. Additionally, the slice thicknesses were different between MR imaging and CT. Third, pancreatic sections could only be obtained from patients who had undergone pancreatectomy and the control group lacked healthy controls. Forth, it cannot be concluded that fatty pancreas is a biomarker for pancreatic cancer although the correlation between fatty pancreas and pancreatic cancer has been shown.

Pancreatic cancer and MRI-PDFF were related in multivariate analysis, and MRI-PDFF can be a biomarker; however, future studies are needed to determine whether patients with fatty pancreas are likely to develop pancreatic cancer. MRI is an expensive examination, and it is necessary to investigate further whether it can be used for medical examination in terms of cost. Fifth, in our study, the reproducibility of MRI-PDFF was not examined. However, because Kang GH et al. showed high reproducibility of MRI-PDFF for liver fat content, the reproducibility of MRI-PDFF for pancreatic fat is also expected to be high [29]. Lastly, this study was a single-center, retrospective, observational study. A multi-center, prospective study is necessary to determine the usefulness of MRI-PDFF in early detection of pancreatic cancer.

In conclusion, MRI-PDFF, which was found to be correlated well with histologic pancreatic fat fraction, should be considered for non-invasive evaluation of fatty pancreas. Furthermore, MRI-PDFF can be a potentially superior predictor of pancreatic cancer than PI.

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