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ORIGINAL ARTICLE

The impact of postoperative exocrine index on non-alcoholic fatty liver disease following pancreaticoduodenectomy

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Abstract

Background: To study exocrine function of the remnant pancreas after pancreatoduodenectomy (PD), we propose the use of an exocrine index (PEI) that combines the volume of the remnant pancreas and the intraoperative amylase activity of the pancreatic juice. Here, we aimed to determine whether the PEI can predict non-alcoholic fatty liver disease (NAFLD) following PD.

Methods: Fifty-seven patients for whom pancreatic juice amylase activity was measured during PD were enrolled. NAFLD was defined as a liver-to-spleen attenuation ratio of <0.9 on plain CT 1 year following surgery. We retrospectively evaluated clinical parameters, including the PEI, to identify predictors of NAFLD.

Results: Fifty-four patients (95%) were regularly administered 1200 mg of pancreatic lipase. NAFLD was diagnosed in 13 participants (23%) 1 year following surgery. NAFLD was associated with pancreatic ductal adenocarcinoma ($P = .006$), soft pancreas ($P = .001$), small main pancreatic duct ($P = 0008$), low remnant pancreatic volume ($P < .001$), low intraoperative amylase activity in the pancreatic juice ($P = .001$), high pancreatic fibrosis ($P = .032$), and large body weight loss ($P = .015$). The PEI was significantly lower in the participants with NAFLD than in those without ($P < .001$). The participants were then classified into tertiles of PEI: $<5 \times 10^6$, $5\text{-}25 \times 10^6$, and $>25 \times 10^6$. The prevalence of NAFLD in these groups was 53% (10/19), 11% (2/19), and 5% (1/19), respectively. In multivariable analyses, there was a significant association between NAFLD and the PEI (P value for trend = .042).

Conclusion: The PEI, calculated using the remnant pancreatic volume and the intraoperative pancreatic juice amylase activity, predicts NAFLD development following PD.

KEYWORDS
diabetes mellitus, exocrine index, non-alcoholic fatty liver disease, pancreatic juice, pancreaticoduodenectomy

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a late complication of pancreaticoduodenectomy (PD), developing in 8%–46% of patients.[1-6] As the surgical techniques, perioperative management, and adjuvant chemotherapy have improved, the number of long-term survivors following PD has increased. Therefore, the potential long-term metabolic complications of the procedure are receiving greater attention. A previous study showed that hepatic steatosis following PD was associated with a shorter duration of disease-free survival associated with pancreatic ductal adenocarcinoma (PDAC).[7]

Previous studies have sought to identify risk factors for NAFLD following PD and have shown that poor exocrine function of the remnant pancreas is a risk factor.[1,4,5] A digestive enzyme preparation containing a pancreatic enzyme is now generally administered to patients who have undergone PD to compensate for a reduction in exocrine function and ameliorate disorders in digestion and absorption.[8] In particular, a delayed release pancreatic lipase supplement has been shown to help prevent NAFLD following PD.[9] Nevertheless, some patients develop NAFLD following PD even when taking such a supplement. Therefore, it is important to identify predictors of NAFLD in patients who have undergone PD and are taking pancreatic enzyme supplements.

We considered that the exocrine function of the remnant pancreas might represent a useful predictor of NAFLD in patients who undergo PD. The intraoperative amylase activity in pancreatic juice is reported to be a valuable predictor of POPF following PD.[10,11] Intraoperative amylase activity in pancreatic juice negatively correlates with the severity of pancreatic fibrosis,[11] suggesting that it is likely to reflect postoperative pancreatic exocrine function. Since the volume of the residual pancreas has also been reported to be a predictor of postoperative pancreatic exocrine dysfunction,[1,5,12] we focused on intraoperative amylase activity and residual pancreatic volume in pancreatic juice to predict pancreatic exocrine function more accurately. Therefore, we decided to use the above two factors' product and defined the product as PEI. In the present study, we retrospectively studied patients who underwent PD in our hospital to determine whether the PEI might represent a useful predictor of NAFLD following PD.

2 | PATIENTS AND METHODS

2.1 | Patients and intraoperative procedures

Between November 2014 and April 2020, 77 patients underwent PD because of pancreatic tumors at the Jikei University Hospital, and the amylase activity of the pancreatic juice of each was measured intraoperatively. Of these, 18 were excluded because of death within 1 year of the surgery, and data for the remaining 59 patients were studied. The study was approved by the Institutional Ethics Committee of the Jikei University School of Medicine (27-177 [8062]) and conformed to the provisions of the Declaration of Helsinki, as revised in Fortaleza, Brazil, October 2013.

In patients with PDAC or tumors with malignant potential, the pancreas was transected at the level of the portal vein and radical lymph node dissection was performed, according to the anterior artery first approach. The bile duct was dissected at the common hepatic duct. After pancreatectomy, a pancreatic stent was inserted into the pancreatic duct and pancreatic juice was collected using a 2.5-ml syringe for the intraoperative measurement of the amylase activity. An end-to-side pancreatojejunostomy was performed using either the Blumgart or Kakita method, with external stenting, according to the surgeon's preference. Reconstruction was performed using the modified Child method, with Braun anastomosis. At the end of the procedure, two drains were placed close to the pancreatic and biliary anastomoses, and these were usually removed between postoperative days (POD) 3 and 5. Postoperative pancreatic fistula (POPF) was defined according to criteria established by the 2016 update of the International Study Group on Pancreatic Fistula, and grades B and C are defined as POPF[13] and grade A is considered to represent biochemical leakage.

We routinely prescribed 1200 mg/day of a delayed-release pancreatic lipase supplement (LipaCreon, Eisai Co Ltd, Tokyo, Japan) after the patients became able to receive sufficient oral nutrition. If there were signs of allergy, this medication was discontinued.

2.2 | Measurement of the volume of the remnant pancreas

To facilitate earlier and more accurate detection of POPF after drain removal, routine postoperative computed tomography (CT) imaging was performed between POD 5 and 7. This was performed using a 64-slice multi-detector row CT (SOMATOM Definition AS+, Siemens, Erlangen, Germany) at our hospital. Contrast-enhanced CT was performed after a rapid bolus injection of iodinated contrast agent at 2.5-4.0 ml/s using a power injector. We imaged the arterial, portal, and venous phases at 35, 70, and 180 s, respectively. The slice thickness was 1 mm, and the reconstruction interval was 5 mm. We evaluated and measured the remnant pancreas using the portal phase images, Synapse Vincent software (Fujifilm Medical, Tokyo, Japan), and its Liver Analysis Application (Figure 1A). As the length of the remnant pancreas was traced, the software automatically contoured the remnant pancreas in each CT slice and calculated the volume of the remnant pancreas in cubic centimeters. The outlines drawn by the software for each CT slice were then made manually and corrections were made if necessary.

2.3 | Calculation of the PEI

The PEI was calculated as the product of the intraoperative amylase activity of the pancreatic juice and the residual pancreatic volume after surgery.

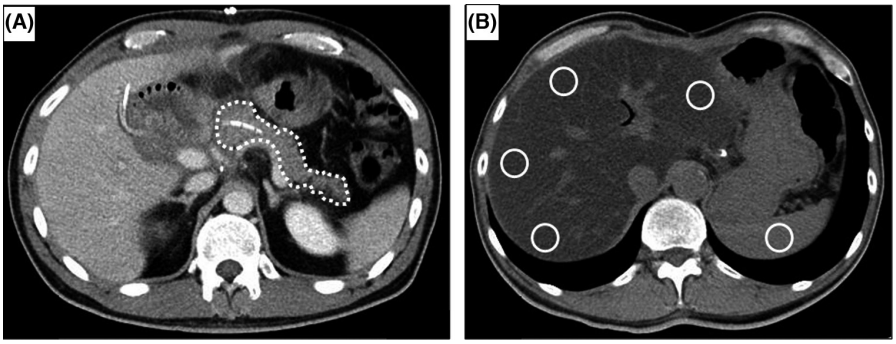

FIGURE 1 Representative computed tomography (CT) images showing the volume of remnant pancreas after pancreatoduodenectomy. A, Synapse Vincent software was used to evaluate the volume of the remnant pancreas (the area within the white dotted line). B, Mean CT attenuation values in four sectors of the liver and the median value of all the sectors of the spleen

2.4 | Evaluation of pancreatic stump

Paraffin-embedded sections from pancreatic stump were stained with hematoxylin and eosin and reviewed by an experienced gastrointestinal pathologist who was blinded to the surgical outcome. The degree of fibrosis was assessed quantitatively by calculating the ratio of the dimension of intralobular and interlobular fat to the total area of each specimen as described in the previous report.[11]

2.5 | Definition of NAFLD

The livers of the patients were evaluated 1 year after surgery. CT imaging was performed using the same 64-slice multi-detector row CT, with a slice thickness of 1 mm and a reconstruction interval of 5 mm. NAFLD was defined as a liver-to-spleen attenuation ratio of <0.9 on an unenhanced abdominal CT scan.[6,12,14,15] We used the mean pixel density in four sectors of the liver and the median density for all the sectors of the spleen (Figure 1B). Two reviewers analyzed the CT images (MT and TG).

2.6 | Identification of risk factors for NAFLD

First, we investigated the relationships between the clinicopathologic variables of patients who underwent PD and the subsequent prevalence of NAFLD by univariate analysis. The variables included preoperative factors, intraoperative factors, postoperative factors, CT findings 1 year after surgery, and the PEI.

Next, to assess the utility of the PEI, the patients were categorized into tertiles of PEI (n = 19, each group); those with PEI ≤5 × 10^6 as a "low PEI" group, those with PEI 5-25 × 10^6 as an "intermediate PEI" group, and those with PEI <25 × 10^6 as a "high PEI" group, and multivariate ordinal logistic regression analyses were performed to evaluate the relationship between the PEI and the incidence of NAFLD. We also evaluated the relationships between the clinicopathologic variables of patients who underwent PD and diabetes mellitus (DM), a pancreatic endocrine disease, using univariate analysis, and then performed multivariate ordinal logistic regression analyses to evaluate the relationship of PEI with the incidence of DM.

2.7 | Statistical analysis

Statistical analyses were performed using STATA/SE (STATA Statistical Software, version 14.0; Stata Corp., College Station, TX, USA). Continuous variables are expressed as medians and interquartile ranges, while categorical variables are expressed as absolute numbers. Clinical datasets were compared using the Mann-Whitney U-test or chi-square test, as appropriate. Multivariate analyses were performed using the ordinal logistic regression model, and all the variables with $P < .05$ in the univariate analysis were included. A two-tailed α level of 0.05 was used.

3 | RESULTS

3.1 | Patient characteristics and the incidence of postoperative NAFLD

The characteristics of the 59 patients are shown in Table 1. Of these, 54 (95%) were administered 1200 mg of pancreatic lipase daily. NAFLD was diagnosed in 13 patients (23%) 1 year following surgery. The median volume of the remnant pancreas was 32 ml (range, 22-46 ml), the median intraoperative amylase activity of the pancreatic juice was 550 × 10^3 IU/L (range, 53-879 × 10^3 IU/L), and the median PEI was 16 × 10^6 (range, 2-33 × 10^6).

3.2 | Comparison of the clinicopathologic variables in patients who did or did not develop NAFLD or DM

The development of NAFLD was significantly associated with PDAC ($P = .006$), soft pancreas ($P = .001$), small main pancreatic duct ($P = .008$), low intraoperative amylase activity of the pancreatic

TABLE 1 Clinicopathological factors in patients who underwent pancreatoduodenectomy (n = 57)

Variables	
Preoperative factors	
Gender (male:female)	40 (70%):17 (30%)
Age (years)	68 (61-76)
Body weight (kg)	59.9 (51.5-66.4)
Body mass index (kg/m^2)	22.5 (20.4-23.7)
DM (yes:no)	9 (16%):48 (84%)
Dyslipidemia (yes:no)	4 (7%):53 (93%)
Primary disease (PDAC:others)	21 (37%):36 (63%)
Serum albumin level (g/dl)	3.9 (3.6-4.4)
Serum HbA1c level (%)	6 (5.6-6.5)
Operative factors	
Pancreatic texture (soft:hard)	36 (63%):21 (37%)
Main pancreatic duct size (mm)	3 (2-5)
Amylase of pancreatic juice (10^3 IU/L)	550 (53-879)
Duration of operation (min)	516 (428-606)
Intraoperative blood loss (ml)	615 (290-1010)
Postoperative factors	
Volume of remnant pancreas (ml)	32 (22-46)
POPF (yes:no)	18 (32%):39 (68%)
Postoperative hospital stay (days)	26 (22-37)
Adjuvant chemotherapy (yes:no)	34 (60%):23 (40%)
Pancrelipase (yes:no)	54 (95%):3 (5%)
NAFLD at 1 year (yes:no)	13 (23%):44 (77%)
Body weight at 1 year (kg)	54 (44.5-60.7)
Body weight ratio on post/pre	0.91 (0.83-0.97)
Serum HbA1c at 1 year (%)	5.9 (5.3-6.4)
DM at 1 year (yes:no)	17 (30%): 40 (70%)
Histopathological findings	
Pancreatic fibrosis (%)	5 (0-10)
Pancreatic intralobular fat (%)	0 (0-10)
Pancreatic interlobular fat (%)	20 (10-55)
Preoperative findings of CT images	
Pixel density on liver CT (HU)	56.3 (49.5-62.5)
Pixel density on spleen CT (HU)	44.7 (41.2-47.3)
Pixel density ratio on liver/spleen CT	1.3 (1.2-1.4)
Findings of CT images at 1 year	
Pixel density on liver CT (HU)	53.3 (43.8-58.2)
Pixel density on spleen CT (HU)	45.3 (42.2-48.1)
Pixel density ratio on liver/spleen CT	1.2 (1.0-1.3)
Volume of remnant pancreas (ml)	22 (15-30)
Change of remnant pancreas volume	0.67 (0.54-0.76)
PEI (10^6)	17 (2-33)

Note: Continuous variables are presented as median with interquartile ranges. Categorial variables are presented as patient numbers and ratios (%).

Abbreviations: CT, computed tomography; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HU, hounsfield unit; NAFLD, non-alcoholic fatty liver disease; PDAC, pancreatic duct carcinoma; PEI, postoperative exocrine index; POPF, postoperative pancreatic fistula.

juice (P = .001), low remnant pancreatic volume (P < .001), and high pancreatic fibrosis (P = .032) (Table 2). The patients who developed NAFLD lost more body weight than those without NAFLD (P = .015). The remnant pancreas volume did not significantly differ between both groups at 1 year after the surgery. The PEI of patients who developed NAFLD was significantly lower than that of patients who did not (P < .001). The administration of pancreatic lipase did not significantly differ between these groups.

The presence of DM 1 year following surgery was significantly associated with preoperative DM status (P = .001), the presence of dyslipidemia (P = .041), low liver/spleen pixel density ratio on preoperative CT (P = .029), high preoperative serum HbA1c (P = .003), small main pancreatic duct (P = .024), low intraoperative amylase activity of the pancreatic juice (P = .045), and high serum HbA1c 1 year following surgery (P < .001) (Table 3).

3.3 | Prediction of incidence of NAFLD using the PEI

The prevalence of NAFLD in the three groups was 53% (10/19) for the low PEI group, 11% (2/19) for the intermediate PEI group, and 5% (1/19) for the high PEI group, respectively (Figure 2). The pancreatic parenchyma was significantly more fibrotic in the low PEI group than in the high PEI group (Figure 3).

In the multivariable analysis, compared with the high PEI group, the odd ratios for NAFLD following PD were 1.77 (95% confidence interval [CI], 0.14-22.3) for the intermediate PEI group, and 12.5 (95% CI, 0.89-174.7) for the low PEI group (P-value for trend = .042) (Table 4). There was no significant association between incident DM and the PEI in patients who underwent PD (P-value for trend = .588).

4 | DISCUSSION

In the present study, the incidence of NAFLD 1 year after PD was 22.8% and 1200 mg/day of delayed-release pancreatic lipase supplement was being administered postoperatively by 95% of the patients. Ordinal logistic regression analysis revealed a relationship of PEI with incident NAFLD, but there was no relationship of PEI with DM.

The etiology of NAFLD following PD is thought to involve impairments in digestion, absorption, nutrition, and/or pancreatic exocrine function,[14,15] and several studies have shown that a small remnant pancreas is also a predisposing factor.[1,4,5] The volume of the remnant pancreas is considered to be a good indicator of pancreatic exocrine function and, in the present study, the volume of the remnant pancreas was significantly lower in patients with NAFLD than in those without. However, the method of measuring the remnant pancreatic volume has not been standardized.[1,4,5] Here, we used CT images 5-7 days after PD and Synapse Vincent software to measure the volume.

The intraoperative amylase activity of pancreatic juice is routinely measured in our hospital. It is a useful predictor of POPF following PD[10,11] and it correlates negatively with the severity of

TABLE 2 Comparison of the clinicopathological factors according to the positive of NAFLD in patients who underwent pancreatoduodenectomy (n = 57)

Variables	NAFLD (n = 13)	Non-NAFLD (n = 44)	*P*-value
Preoperative factors			
Gender (male:female)	7 (54%):6 (46%)	33 (75%):11 (25%)	.143
Age (years)	67 (62-76)	71 (60-76)	.775
Body weight (kg)	60 (52.8-64)	59.5 (50.5-67.1)	.754
Body mass index (kg/m^2)	22 (22-24)	22 (20-24)	.582
DM (yes:no)	1 (8%):12 (92%)	8 (18%):36 (82%)	.362
Dyslipidemia (yes:no)	1 (8%):12 (92%)	3 (7%):41 (93%)	.914
Primary disease (PDAC:others)	9 (69%):4 (31%)	12 (27%):32 (73%)	.006
Serum albumin level (g/dl)	3.8 (3.6-4.6)	3.9 (3.5-4.4)	.555
Serum HbA1c (%)	6.1 (6.0-6.2)	5.9 (5.5-6.6)	.390
Operative factors			
Pancreatic texture (soft:hard)	3 (23%):10 (77%)	33 (75%):11 (25%)	.001
Main pancreatic duct size (mm)	4 (3-6)	2 (2-4)	.008
Amylase, pancreatic juice (10^3 IU/L)	7 (2-434)	682 (227-895)	.001
Duration of operation (min)	578 (469-626)	514 (426-595)	.238
Intraoperative blood loss (ml)	725 (305-1235)	565 (270-944)	.274
Postoperative factors			
Volume of remnant pancreas (ml)	22 (15-25)	41 (26-48)	<.001
POPF (yes:no)	2 (15%):11 (85%)	16 (36%):28 (64%)	.153
Postoperative hospital stay (days)	23 (19-38)	28 (23-37)	.321
Adjuvant chemotherapy (yes:no)	9 (69%):4 (31%)	25 (57%):19 (43%)	.423
Pancrelipase (yes:no)	11 (85%):2 (15%)	43 (98%):1 (2%)	.063
Body weight at 1 year (kg)	46.3 (42-55)	54.4 (45.5-61.7)	.061
Body weight ratio on post/pre	0.82 (0.74-0.89)	0.93 (0.85-0.98)	.015
Serum HbA1c at 1 year (%)	5.6 (5-6.2)	5.9 (5.3-6.4)	.246
DM at 1 year (yes:no)	4 (31%): 9 (69%)	13 (30%):31 (70%)	.932
Histopathological findings			
Pancreatic fibrosis (%)	5 (5-10)	0 (0-10)	.032
Pancreatic intralobular fat (%)	0 (0-10)	0 (0-10)	.934
Pancreatic interlobular fat (%)	20 (10-58)	30 (15-60)	.715
Preoperative findings of CT images			
Pixel density on liver CT (HU)	60 (50.5-62.5)	56.2 (49.3-62.3)	.634
Pixel density on spleen CT (HU)	45.4 (41.2-46.8)	44.2 (41.1-47.4)	.947
Pixel density ratio on liver/spleen CT	1.3 (1.1-1.4)	1.3 (1.2-1.4)	.790
Findings of CT images at 1 year			
Pixel density on liver CT (HU)	23 (8-39)	57 (51-59)	<.001
Pixel density on spleen CT (HU)	45 (43-47)	45 (42-48)	.909
Pixel density ratio on liver/spleen CT	0.6 (0.2-0.9)	1.2 (1.1-1.3)	<.001
Volume of remnant pancreas (ml)	20 (12-26)	23 (17-30)	.147
Change of remnant pancreas volume	0.88 (0.66-1)	0.62 (0.51-0.82)	.043
PEI (10^6)	0.1 (0.04-10)	24 (7-56)	<.001

Note: Continuous variables are presented as median with interquartile ranges. Categorial variables are presented as patient numbers and ratios (%).
Abbreviations: CT, computed tomography; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HU, Hounsfield unit; NAFLD, non-alcoholic fatty liver disease; PDAC, pancreatic duct carcinoma; PEI, postoperative exocrine index; POPF, postoperative pancreatic fistula.

TABLE 3 Comparison of the clinicopathological factors according to the positive DM in patients who underwent pancreatoduodenectomy (n = 57)

Variables	DM (n = 17)	Non-DM (n = 40)	*P*-value
Preoperative factors			
Gender (male:female)	13 (76%):4 (24%)	27 (68%):13 (33%)	.498
Age (years)	68 (59-77)	70 (61-76)	.855
Body weight (kg)	64 (52.6-67.1)	58.2 (50.5-64.8)	.407
Body mass index (kg/m^2)	22 (21-23)	23 (20-24)	.827
DM (yes:no)	7 (41%):10 (59%)	2 (5%):38 (95%)	.001
Dyslipidemia (yes:no)	14 (82%):3 (18%)	39 (98%):1 (3%)	.041
Primary disease (PDAC:others)	9 (53%):8 (47%)	18 (45%):22 (55%)	.583
Serum albumin (g/dl)	4.1 (3.3-4.5)	3.8 (3.6-4.3)	.720
Serum HbA1c level (%)	6.4 (6-8)	5.8 (5.5-6.2)	.003
Operative factors			
Pancreatic texture (soft:hard)	7 (41%):10 (59%)	14 (35%):26 (65%)	.658
Main pancreatic duct size (mm)	5 (2-7)	3 (2-4)	.024
Amylase, pancreatic juice (10^3 IU/L)	7 (2-434)	710 (46-885)	.045
Duration of operation (min)	520 (425-572)	516 (443-620)	.398
Intraoperative blood loss (ml)	670 (445-1055)	530 (260-1030)	.303
Postoperative factors			
POPF (yes:no)	6 (35%):11 (65%)	12 (30%):28 (70%)	.694
Volume of remnant pancreas (ml)	26 (22-45)	36 (22-47)	.172
Postoperative hospital stay (days)	23 (19-33)	28 (23-38)	.190
Adjuvant chemotherapy (yes:no)	10 (59%):7 (41%)	24 (60%):16 (40%)	.934
Pancrelipase (yes:no)	16 (94%):1 (6%)	39 (98%):1 (3%)	.525
Body weight at 1 year (kg)	54.7 (47.2-62.5)	53.7 (43.1-60)	.360
Body weight ratio on post/pre	0.91 (0.86-0.97)	0.9 (0.82-0.98)	.542
Serum HbA1c at 1 year (%)	7.1 (6.4-8.2)	5.4 (5.1-5.9)	<.001
NAFLD at 1 year (yes:no)	4 (24%): 13 (76%)	9 (23%):31 (78%)	.932
Histopathological findings			
Pancreatic fibrosis (%)	5 (0-10)	5 (0-10)	.204
Pancreatic intralobular fat (%)	0 (0-10)	0 (0-10)	.567
Pancreatic interlobular fat (%)	30 (20-95)	20 (10-48)	.125
Preoperative findings of CT images			
Pixel density on liver CT (HU)	54.8 (46.4-62.1)	56.6 (50.8-62.5)	.307
Pixel density on spleen CT (HU)	45.8 (42.9-46.6)	43.6 (41-47.4)	.253
Pixel density ratio on liver/spleen CT	1.2 (1.1-1.3)	1.3 (1.2-1.4)	.029
Findings of CT images at 1 year			
Pixel density on liver CT (HU)	56 (46-60)	52 (42-58)	.147
Pixel density on spleen CT (HU)	46 (43-49)	45 (42-48)	.412
Pixel density ratio on liver/spleen CT	1.2 (1.0-1.3)	1.1 (1.0-1.3)	.264
Volume of remnant pancreas (ml)	22 (16-27)	22 (15-29)	.936
Change of remnant pancreas volume	0.9 (0.59-0.98)	0.64 (0.5-0.79)	.063
PEI (10^6)	6 (1-18)	24 (2-47)	.078

Note: Continuous variables are presented as median with interquartile ranges. Categorial variables are presented as patient numbers and ratios (%).
Abbreviations: CT, computed tomography; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HU, Hounsfield unit; NAFLD, non-alcoholic fatty liver disease; PDAC, pancreatic duct carcinoma; PEI, postoperative exocrine index; POPF, postoperative pancreatic fistula.

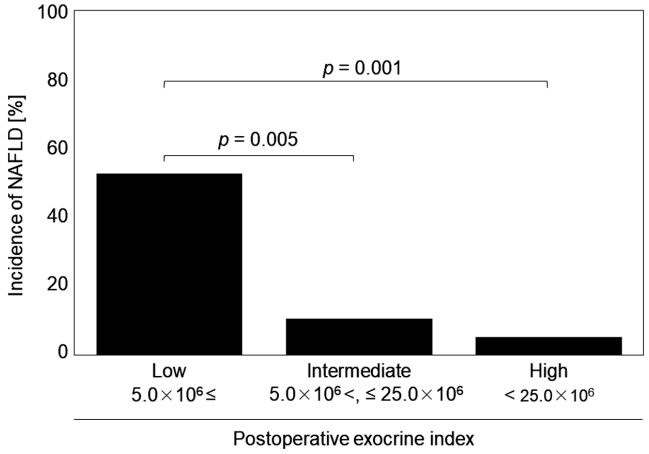

FIGURE 2 Incidence of NAFLD according to the tertile of the exocrine index (PEI). The incidences of NAFLD in the low PEI, intermediate PEI, and high PEI groups were 53% (10/19), 11% (2/19), and 5% (1/19), respectively

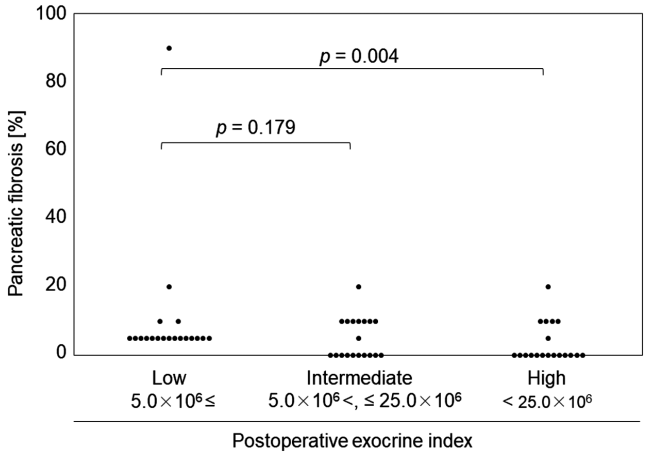

FIGURE 3 Degree of pancreatic fibrosis according to the tertile of the exocrine index (PEI). The degree of pancreatic fibrosis in the low PEI, intermediate PEI, and high PEI groups were median 5% (range, 5%-5%), median 0% (range, 0%-10%), and median 0% (range, 0%-10%), respectively

pancreatic fibrosis.[11] Therefore, it is likely to reflect postoperative pancreatic exocrine function. The PEI is calculated as the product of the volume of the remnant pancreas and the intraoperative amylase activity of pancreatic juice and could therefore represent a predictor of subsequent exocrine function.

In the present study, 54 (95%) patients took the recommended dose (1200 mg) of daily pancreatic lipase. However, the dosage of pancreatic lipase was not assessed in the present study, and it is unclear if the dosage of the pancreatic lipase supplement could be safely adjusted based on PEI. Further study should be conducted to assess the optimal doses of pancreatic lipase for each patient.

A previous report used a pixel density of the remnant pancreas as an indicator of exocrine function.[12] Although the pixel density of the remnant pancreas was considered to have the same significance as the intraoperative amylase activity of pancreatic juice according to the pathological evaluation,[11,12] we adopted the intraoperative amylase activity because it does not cause measurement errors.

In the present study, the patients were categorized according to tertile of PEI to assess its utility, and in this way, we showed that PEI could predict NAFLD, but, in fact, PEI did not reflect postoperative pancreatic endocrine function. In a previous study, the remnant pancreatic volume was found to be a significant risk factor for DM, but this relationship was stronger in patients who underwent DP, rather than PD.[16] Another study showed that obstructive pancreatitis caused by periampullary PDAC exacerbates glucose intolerance by inhibiting insulin secretion and that treatment of the periampullary tumor by pancreatectomy sometimes permits the recovery of the function of the remnant pancreas by removing the obstruction.[17] However, the endocrine function of patients following PD cannot be explained by the remnant pancreas volume alone. Moreover, the homeostasis model assessment for insulin resistance was reported not to significantly differ between patients with NAFLD and those without.[14] Thus, insulin resistance does not seem to be related to development of NAFLD following PD but may be involved in the progression of NAFLD to non-alcoholic steatohepatitis or beyond.

The present study had two limitations. First, it was a retrospective study conducted in a single institution with a relatively small

TABLE 4 Ordinal logistic regression analysis to assess the association of PEI in relation to NAFLD and new onset of DM after pancreatoduodenectomy (n = 57)

	Univariate		Multivariate	
PEI	**Odds ratio**	**95% CI**	**Odds ratio**	**95% CI**
NAFLD				
High	1 (reference)		1 (reference)	
Intermediate	2.11	0.18-25.5	1.77	0.14-22.3
Low	20.0	2.20-181.6	12.5	0.89-174.7
P-value for trend	.002		.042	
New onset of DM				
High	1 (reference)		1 (reference)	
Intermediate	3.04	0.51-18.1	2.40	0.44-12.9
Low	1.59	0.23-10.8	1.56	0.16-15.4
P-value for trend	.670		.588	

Abbreviations: CI, confidence interval; DM, diabetes mellitus; NAFLD, non-alcoholic fatty liver disease; PEI, postoperative exocrine index.

number of participants. Second, due to its small sample size, it was unable to determine an optimal cutoff value for PEI, and it was also difficult to identify the correlation between PEI and pathological findings, so we focused on the usefulness of PEI for patients who underwent PD. Therefore, large-scale prospective studies should be conducted for further clarification.

In conclusion, the PEI, which is a combination of the volume of the remnant pancreas with the intraoperative amylase activity of the pancreatic juice, may be a useful means of predicting the development of NAFLD following PD.

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