Original article

Estimated functional remnant pancreatic volume predicts nonalcoholic fatty liver disease after pancreaticoduodenectomy: Use of computed tomography attenuation value of the pancreas

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Running Head: Preoperative prediction of NAFLD after PD

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ABSTRACT

Background: Nonalcoholic fatty liver disease (NAFLD) is a late complication of pancreaticoduodenectomy (PD). However, this complication is difficult to predict preoperatively. This study aimed to assess the association between NAFLD and preoperative computed tomography (CT) findings.

Methods: Medical records of 112 patients who had undergone PD and had CT scans preoperatively and 6 months postoperatively were retrospectively reviewed. We evaluated several CT findings, including the CT attenuation value of the remnant pancreas, remnant pancreatic volume (RPV), and the estimated functional remnant pancreatic volume (eFRPV) on preoperative CT. The variables, including the CT findings and histopathological findings, were compared between the patients with and without NAFLD after PD.

Results: The NAFLD group included 21 patients (18.8%). The CT attenuation value of the remnant pancreas was correlated with the pancreatic acinar cell density (r=0.537), and was lower in the NAFLD group than in the non-NAFLD group (p=0.007). The eFRPV was lower in the NAFLD group than in the non-NAFLD group (p=0.002). An eFRPV $\leq$ 47 mL·HU was an independent predictive factor for NAFLD (p=0.007; odds ratio: 6.73; 95% confidence interval: 1.70-26.70).

Discussion: The eFRPV can be used to preoperatively predict NAFLD after PD.

Key words: computed tomography, functional remnant pancreatic volume, nonalcoholic fatty liver disease, pancreatic acinar cell

Introduction

Pancreaticoduodenectomy (PD) has been established as the standard surgical procedure for the treatment of periampullary disease. Recent advances in preoperative diagnostic imaging, surgical technique, and perioperative management have improved the long-term survival of patients after PD.[1-3] Therefore, long-term nutritional management is an important issue for patients who undergo PD.[4]

Nonalcoholic fatty liver disease (NAFLD) is a late complication of PD and occurs in 8% to 37% of patients.[5-11] Some studies have suggested that the malnutrition caused by pancreatic exocrine insufficiency induces NAFLD after PD.[6,8,10] NAFLD is believed to induce nonalcoholic steatohepatitis (NASH), which is an increasingly identified aggressive variant that has a marked impact on patient health.[6] Furthermore, NAFLD may affect patients' long-term prognoses after pancreatectomy.[12] Therefore, the prevention and treatment of NAFLD after PD is clinically important.

The preoperative prediction of NAFLD after PD may be useful for the prevention and management of postoperative NAFLD. Although pancreatic exocrine insufficiency in the remnant pancreas may lead to postoperative NAFLD, preoperative evaluation of the pancreatic exocrine function is challenging and the pancreatic exocrine function of a remnant pancreas cannot be evaluated.[13]

Although there is a report that the lower computed tomography (CT) attenuation value of the remnant pancreatic parenchyma predicts postoperative NAFLD after PD,[3] the relationship between the CT attenuation value and the pathological findings of the pancreatic parenchyma was not assessed. The CT attenuation value represents the tissue density. Therefore, we hypothesized that the CT attenuation value of the remnant pancreas is associated with the pancreatic acinar cell density and can predict postoperative NAFLD after PD. The aim of this study was to evaluate the association between the CT attenuation value of the remnant pancreas and the pancreatic acinar cell density using preoperative CT and hematoxylin and eosin staining of the histopathological specimen. In addition, we investigated whether the preoperative CT findings including the CT attenuation value of the remnant pancreas and the remnant pancreatic volume predict NAFLD after PD.

Methods

Patient selection

We retrospectively examined the electronic medical records of patients who had undergone PD and had records of CTs preoperatively and 6 months postoperatively between January 2011 and December 2018 at Shiga University of Medical Science Hospital. We identified 112 patients and reviewed their clinical data for this study. All operations were performed by surgeons recognized as highly skilled by the Japanese Society of Hepato-Biliary-Pancreatic Surgery. The pancreatico-enterostomy method in this series included end-to-side pancreaticojejunostomy (PJ) with

anastomosis of the main pancreatic duct to the intestinal mucosa. Pancrelipase delayed-release supplement was used to patients by the surgeon's discretion 3 months after surgery. All patients performed blood test every 3 months. And all patients performed CT scan every 3 months or 6 months. The postoperative pancreatic fistula (POPF) was defined as the occurrence of POPF grades B and C according to the International Study Group on Pancreatic Surgery criteria.[14]

The study protocol was approved by the ethics committee of Shiga University of Medical Science (registration number 29-170) and performed according to the principles of the Declaration of Helsinki. We provided patients with the opportunity to opt-out, however, the requirement for obtaining informed consent was waived due to this study's retrospective design.

CT protocol and interpretation

CT was performed with 64- and 320-detector devices (Aquilion™ CX Edition and Aquilion™ ONE, respectively; Canon Medical Systems Corporation, Tochigi, Japan). The slice thickness was set at 5 mm in all patients in accordance with our institutional protocol. All CT findings were retrospectively reviewed by two experienced surgeons who were blinded to the laboratory results, surgical findings, postoperative findings, and final diagnoses. The CT attenuation value was determined from a Picture Archiving and Communication System (ShadeQuest/ViewR-DG; Yokogawa Medical Solutions Corporation, Tokyo, Japan). If there was a disagreement with regard to the findings the scans were reviewed by both surgeons until a consensus was reached.

The method for determining the CT attenuation value of the liver was as follows (Figure 1a): four square regions of interest (ROIs) with an area of 1.0 cm^2 were set at different sectors in the liver parenchyma on unenhanced CT images, using enhanced CT images to verify that the ROIs did not contain vessels. The CT attenuation value of the liver was defined as the mean of the attenuation value of the four ROIs. NAFLD was defined as a CT attenuation value of the liver < 40 Hounsfield units (HU).[15]

The method for determining the CT attenuation value of the remnant pancreas was as follows (Figure 1b, 1c): two square ROIs were set within the pancreatic parenchyma on unenhanced CT images in an area of the remnant pancreas in the preoperative CT. The inclusion of vessels was prevented by reviewing the enhanced CT images. The CT attenuation value of the remnant pancreas was defined as the mean of the attenuation values of the two ROIs.

We measured the remnant pancreatic volume (RPV) on preoperative CT images using CT volumetry. The method for determining the RPV was as follows (Figure 1d, 1e): first, we determined the cut line of the pancreas from the location of the PJ in the postoperative CT because of its retrospective study. Subsequently, the pancreatic parenchyma was manually outlined on each slice using a free-hand ROI and the area of each ROI was automatically calculated. Major vessels and pancreatic ducts were excluded. The product of the pancreatic area and the slice thickness represented the volume of the pancreas on a single slice. The total pancreatic volume was computed

by summing all slice volumes.[16] The estimated functional remnant pancreatic volume (eFRPV) was calculated as follows: (CT attenuation value of the remnant pancreas) × (RPV) × 1/10 (mL·HU).

Histopathological specimens

Formalin-fixed paraffin-embedded hematoxylin and eosin stained sections of pancreatic resection stumps were retrieved for all patients. These were analyzed for the percentage of the pancreatic acinar cells and the degree of fibrosis. First, three fields of view of the pancreatic resection stump were randomly selected and the percentage of the pancreatic acinar cells was measured by Image J (National Institutes of Health) at 100× magnification (Figure 1f, 1g). The average of these percentages was defined as the pancreatic acinar cell density. Next, the degree of fibrosis was scored on a scale of 1 to 12 in the three randomly selected fields as previously described by Kloppel and Maillet.[17] The average of these scores was defined as the fibrotic score. These factors were evaluated by an experienced pathologist (A.M.) and the author (H. M.), who were blinded to clinical outcomes and reached agreement on each patient's scores.

Clinical data collection and statistical analysis

Patient characteristics, including preoperative laboratory data, intraoperative findings, postoperative findings, CT findings, and histopathological findings were compared between the

patients with postoperative NAFLD (NAFLD group) and the patients without postoperative NAFLD (non-NAFLD group).

Categorical variables are expressed as numbers and percentages (%), whereas continuous variables are expressed as medians with interquartile ranges. Fisher's exact test (for categorical variables) and the Mann–Whitney U test (for continuous variables) were used to evaluate the significance of differences between the two groups. To determine an optimal cut-off value for the eFRPV, we used a receiver operating characteristic (ROC) curve analysis based on the presence of NAFLD. The optimal cut-off point was defined as the point on the ROC curve closest to the (0, 1) point. Multivariate analysis of preoperative evaluable factors was performed using a logistic regression model. In the two-tailed tests, $p < 0.05$ was considered a statistically significant difference. Confidence intervals (CIs) were determined at the 95% level. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R software (The R Foundation for Statistical Computing, version 2.13.0, Vienna, Austria).[18]

Results

Patient characteristics

A total of 112 patients were enrolled. Each patient had histological slides of the pancreatic resection margin available. There were 73 males (65.2%) and 39 females (34.8%), with a median age

of 69 years (range: 28-87 years). Nearly one-third of the patients (33/112; 29.5%) had diabetes mellitus. Pancreatic cancer was diagnosed in 49 patients (43.8%) and chronic pancreatitis was diagnosed in three patients (2.7%). All patients did not use the agents and did not have other factors which induce NAFLD. Neoadjuvant chemotherapy was performed in eight patients (7.1%). One patient (0.9%) was performed pylorus preserving PD. Thirty-three patients (29.5%) occurred POPF and 10 patients (8.9%) occurred delayed gastric emptying. All patients did not perform total parenteral nutrition or enteral nutrition. Fifty-one patients (45.5%) received adjuvant chemotherapy after PD and 20 patients (17.9%) could not complete adjuvant chemotherapy. Thirty-six patients (32.1%) received S-1 and 15 patients (13.4%) received gemcitabine. The recurrences were occurred in 12 patients (10.7%) within 6 months after PD. The median CT attenuation value of the remnant pancreas in the preoperative CT was 38.6 HU (range: 13.0-56.4 HU) and that of the liver was 57.5 HU (range: 16.7-108.5 HU). The CT attenuation value of the liver in the postoperative CT was 55.1 HU (range: -31.9-70.6 HU). The median pancreatic acinar cell density at the pancreatic resection margin was 69.2% (range: 13.0-94.1%), and the median fibrotic score was 5 (range: 2-12).

Preoperative CT attenuation value of the remnant pancreas and pancreatic acinar cell density

Figure 2a shows the scatter diagram of the relationship between the preoperative CT attenuation value of the remnant pancreas and the pancreatic acinar cell density. We observed a positive correlation between these two factors (Pearson's correlation coefficient: $r = 0.537$, $p <$

0.001). We evaluated the power of the CT attenuation value of the remnant pancreas for predicting the pancreatic acinar cell density via an ROC curve analysis (Figure 2b). The area under the ROC curve was 0.829 (95% confidence interval (CI): 0.753-0.905). At a CT attenuation cutoff value of 37.0 HU, the sensitivity and specificity for predicting pancreatic acinar cell density ≥ 50% were 71.4% and 85.2%, respectively. In regard to the fibrotic score, we observed a negative correlation between the preoperative CT attenuation value of the remnant pancreas and fibrotic score (Pearson's correlation coefficient: $r = -0.532$, $p < 0.001$) (Figure 2c). In terms of POPF, The CT attenuation value of the pancreas was significantly higher in POPF group than non-POPF group. (40.58 HU vs 36.44 HU, $p = 0.001$).

Clinical features of the NAFLD and non-NAFLD groups

Twenty-one patients (18.8%) were categorized to the NAFLD group. The clinical features of each group are shown in Table 1. The prevalence of pancreatic cancer was significantly higher in the NAFLD group than in the non-NAFLD group ($p < 0.001$), and the prevalence of liver dysfunction, which was defined as the patients with medication for hepatitis or liver cirrhosis, was significantly higher in the NAFLD group ($p = 0.038$). The proportion of patients who received neoadjuvant chemotherapy was significantly higher in the NAFLD group than in the non-NAFLD group ($p = 0.006$). Preoperative creatinine levels were significantly lower in the NAFLD group than in the non-NAFLD group ($p = 0.015$). There were no significant differences between the groups in

prognostic nutritional index (p = 0.679) or controlling nutritional status (CONUT) score (p = 0.774). The pancreatic stiffness was recorded as harder in the NAFLD group than in the non-NAFLD group (p = 0.001). The proportion of patients who received postoperative pancreatic enzyme supplementation was significantly higher in the NAFLD group than in the non-NAFLD group (p = 0.031). The proportion of patients who received adjuvant chemotherapy was significantly higher in the NAFLD group than in the non-NAFLD group (p < 0.001). However, there was no significant difference between the groups in the proportion of patients who received adjuvant chemotherapy completely among the patients who received adjuvant chemotherapy (p = 0.545). In terms of the prevalence of recurrence, there was no significant difference between the groups (p = 1.000). In regard to the postoperative nutritional status, the postoperative total protein level (p = 0.006), albumin level (p = 0.049), total cholesterol level (p < 0.001), and prognostic nutritional index (p = 0.014) were significantly lower in NAFLD group than non-NAFLD group. Furthermore, postoperative CONUT score was significantly higher in NAFLD group than non-NAFLD group (p = 0.037). In the postoperative CT findings, CT attenuation value of the liver was significantly lower in the NAFLD group than non-NAFLD group (17.19 HU vs 56.66, p < 0.001). As to the long-term outcomes, NAFLD group was significantly poorer overall survival (OS) rate than non-NAFLD group (5-year OS, 34.1% vs 64.4%; log-rank, p = 0.007). Nobody progressed to NASH. In the NAFLD group, 16 patients were used pancrelipase delayed-release supplement 3 months after surgery by the surgeon's discretion, and 13 patients (81.2%) were recovered to over 40 HU of CT attenuation value

of the liver within 2 years. On the other hand, 5 patients were not used pancrelipase delayed-release supplement, and only one patient (20.0%) was recovered to over 40 HU of CT attenuation value of the liver.

Preoperative CT findings and pancreatic acinar cell density in the NAFLD and non-NAFLD groups

Table 1 shows the preoperative CT and histopathological findings of the NAFLD and non-NAFLD groups. The preoperative CT attenuation value of the remnant pancreas (NAFLD group, 31.0 HU; non-NAFLD group, 39.3 HU; p = 0.007) and the remnant pancreatic volume (NAFLD group, 10.3 mL; non-NAFLD group, 15.4 mL; p = 0.007) were significantly lower in the NAFLD group than in the non-NAFLD group. The pancreatic acinar cell density was significantly lower in the NAFLD group than in the non-NAFLD group (44.6 % vs 69.7 %, p = 0.003). Furthermore, the eFRPV was significantly lower in the NAFLD group than in the non-NAFLD group (32.8 mL·HU vs. 60.6 mL·HU, p = 0.002).

eFRPV as an independent predictive factor for NAFLD after PD

We evaluated the clinical significance of the eFRPV for predicting NAFLD by performing the ROC curve analysis. The area under the ROC curve was 0.721 (95% CI: 0.591-0.850) and an eFRPV cut-off value of 47.0 mL·HU provided a sensitivity and specificity of 81.0% and 65.6%, respectively, for predicting NAFLD (Figure 3).

Results of a multivariate analysis of preoperative evaluable factors are shown in Table 2. An eFRPV ≤ 47 mL·HU (odds ratio (OR): 6.73; 95% CI: 1.70-26.70; p = 0.007) and liver dysfunction (OR: 10.70; 95% CI: 1.15-98.80; p = 0.037) were independent predictive factors for postoperative NAFLD.

Discussion

In this study we clarified two important clinical discoveries. First, the preoperative CT attenuation value of the remnant pancreas is correlated with the pancreatic acinar cell density at the pancreatic stump after PD. Second, an eFRPV ≤ 47 mL·HU, which is calculated using the preoperative CT attenuation value of the remnant pancreas and the remnant pancreatic volume, is an independent predictor of NAFLD after PD. NAFLD is a late complication of PD and is induced by malnutrition that is caused by pancreatic exocrine insufficiency.[6,8,10] It is important to prevent NAFLD after PD because NAFLD affects the patient's long-term prognosis after pancreatectomy.[12] Recently, pancrelipase delayed-release supplement was reported to improve the pancreatic exocrine dysfunction and NAFLD after PD.[19,20] Our findings may be useful to identify patients at risk for pancreatic exocrine insufficiency who may benefit from perioperative nutritional management.

We found that the preoperative CT attenuation value of the remnant pancreas is correlated with the pancreatic acinar cell density at the pancreatic stump after PD. Previous studies have reported the pancreatic acinar cell density to be associated with the presence of POPF after PD.[21,22] Other reports

have demonstrated that the CT attenuation value of the pancreas is associated with POPF after PD.[23-25] Moreover, Nahm et al. reported the association of the pancreatic acinar cell density, the CT attenuation value, and POPF.[26] Our study also revealed a relationship between the CT attenuation value and the pancreatic acinar cell density.

Pancreatic juice is secreted from acinar cells[27] and the reduction of the pancreatic acinar cell density is significantly correlated with postoperative pancreatic exocrine insufficiency after pancreatectomy.[28] A low CT attenuation value of the remnant pancreas may be associated with pancreatic exocrine insufficiency of the remnant pancreas. Yet, it is difficult to evaluate the pancreatic exocrine function preoperatively.[13] The ^{13}C-labeled mixed triglyceride breath test is reported to be a non-invasive and feasible method of assessing the pancreatic exocrine function.[29] However, this method cannot preoperatively evaluate the pancreatic exocrine function of the remnant pancreas. In contrast, the results of our study suggest that the CT attenuation value of the remnant pancreas can be used preoperatively to evaluate the pancreatic exocrine function of the remnant pancreas after PD.

In this study an eFRPV $\leq$ 47 mL·HU was found to be an independent predictive factor for NAFLD after PD. Previous reports have demonstrated that the remnant pancreatic volume is associated with pancreatic exocrine insufficiency after PD and that these factors may become the risk factors for NAFLD, which is consistent with the results of our study.[11,30] Another report has suggested that the CT attenuation value of the pancreas is associated with NAFLD after PD, which is

also consistent with the results of our study.[3] We hypothesized that the eFRPV could be calculated preoperatively by multiplying the remnant pancreatic volume and the CT attenuation value of the remnant pancreas, due to the correlation between the CT attenuation value of the remnant pancreas and the pancreatic acinar cell density.

It is important to predict postoperative NAFLD preoperatively because NAFLD after PD affects the patient's long-term prognosis.[12] NAFLD predicting scoring system has been previously reported,[6] and it cannot predict NAFLD preoperatively as it includes postoperative findings. However, our results can predict NAFLD preoperatively. Additionally, high rate of NAFLD patients with pancrelipase delayed-release supplement recovered to over 40 HU of CT attenuation value of the liver within 2 years. Therefore, our results indicate that the occurrence of NAFLD after PD may be reduced in patients with an eFRPV $\leq$ 47 mL·HU via the preoperative or early postoperative use of a pancrelipase delayed-release supplement and preoperative nutritional instruction. On the other hand, some patients did not occur NAFLD without pancrelipase delayed-release supplement. Additionally, pancrelipase delayed-release supplement is expensive medicine and much quantity to take. Therefore, our result may be useful to decide to use pancrelipase delayed-release supplement and reduce a patients' burden.

This study has some limitations. First, this was a retrospective study, and therefore, dietary intake and the degree of diarrhea could not be evaluated. Second, this study did not perform liver biopsy for confirming fatty liver, and NAFLD was defined by using only CT attenuation value of the

liver which was reported as a evaluation method of NAFLD.[15] Some reports demonstrated NAFLD by using liver/spleen ratio of CT attenuation value <0.9.[31] However, some patients cannot determine liver/spleen ratio because of the medical history of splenectomy. Indeed, in this study, 3 patients could not determine liver/spleen ratio. Additionally, liver/spleen ratio of patients with NAFLD group in this study was <0.9, and that of patients with non-NAFLD group was ≥0.9 (data was not shown). Finally, this study did not evaluate the relationship between the eFRPV and the pancreatic exocrine function directly. Future prospective studies should focus on investigating the correlation of the eFRPV and the pancreatic exocrine function using the ^{13}C-mixed triglyceride breath test or the gold-standard 72-hour fecal fat test.

In conclusion, we demonstrated that the preoperative CT attenuation value of the remnant pancreas is correlated with the pancreatic acinar cell density at the pancreatic stump after PD, and that an eFRPV ≤ 47 mL·HU is an independent predictor of NAFLD after PD. When NAFLD after PD can be predicted preoperatively, a pancreatic enzyme supplement can be administered to patients with a high risk of NAFLD in the early postoperative period. However, further studies are necessary to accumulate more cases and analyze these findings on a greater scale.

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The authors have no conflicts of interest to disclose.

Study conception and design: H. Maehira described and designed the manuscript.

Acquisition of data: H. Maehira and T. Maekawa reviewed the computed tomography findings. H. Maehira and A. Matsubara reviewed the histopathological findings. D. Yasukawa, H. Mori, K. Takebayashi, S. Kaida, and T. Miyake performed the surgery and postoperative management.

Analysis and interpretation of data: H. Maehira.

Drafting of manuscript: H. Maehira

Critical revision of manuscript: M. Tani and H. Iida revised the manuscript.

All authors read and approved the final manuscript.

REFERENCES

1. Birkmeyer JD, Sun Y, Wong SL, Stukel TA. Hospital volume and late survival after cancer surgery. Ann Surg 2007; 245: 777-83. https://doi.org/10.1097/01.sla.0000252402.33814.dd.
2. Ziegler KM, Nakeeb A, Pitt HA, Schmidt CM, Bishop SN, Moreno J, et al. Pancreatic surgery: evolution at a high-volume center. Surgery 2010; 148: 702-9. https://doi.org/10.1016/j.surg.2010.07.029.
3. Ohgi K, Okamura Y, Yamamoto Y, Ashida R, Ito T, Sugiura T, et al. Perioperative Computed Tomography Assessments of the Pancreas Predict Nonalcoholic Fatty Liver Disease After Pancreaticoduodenectomy. Medicine (Baltimore) 2016; 95: e2535. https://doi.org/10.1097/MD.0000000000002535.
4. Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, Coleman J, et al. Quality of life and outcomes after pancreaticoduodenectomy. Ann Surg 2000; 231: 890-8. https://doi.org/10.1097/00000658-200006000-00014.
5. Nomura R, Ishizaki Y, Suzuki K, Kawasaki S. Development of hepatic steatosis after pancreatoduodenectomy. AJR Am J Roentgenol 2007; 189: 1484-8. https://doi.org/10.2214/AJR.07.2809.
6. Kato H, Isaji S, Azumi Y, Kishiwada M, Hamada T, Mizuno S, et al. Development of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) after

pancreaticoduodenectomy: proposal of a postoperative NAFLD scoring system. J Hepatobiliary Pancreat Sci 2010; 17: 296-304. https://doi.org/10.1007/s00534-009-0187-2.

7. Yu HH, Shan YS, Lin PW. Effect of pancreaticoduodenectomy on the course of hepatic steatosis. World J Surg 2010; 3: 2122-7. https://doi.org/10.1007/s00268-010-0636-8.

8. Tanaka N, Horiuchi A, Yokoyama T, Kaneko G, Horigome N, Yamaura T, et al. Clinical characteristics of de novo nonalcoholic fatty liver disease following pancreaticoduodenectomy. J Gastroenterol 2011; 46: 758-68. https://doi.org/10.1007/s00535-011-0370-5.

9. Song SC, Choi SH, Choi DW, Heo JS, Kim WS, Kim MJ. Potential risk factors for nonalcoholic steatohepatitis related to pancreatic secretions following pancreaticoduodenectomy. World J Gastroenterol 2011; 17: 3716-23. https://doi.org/10.3748/wjg.v17.i32.3716.

10. Nakagawa N, Murakami Y, Uemura K, Sudo T, Hashimoto Y, Kondo N, et al. Nonalcoholic fatty liver disease after pancreatoduodenectomy is closely associated with postoperative pancreatic exocrine insufficiency. J Surg Oncol 2014; 110: 720-6. https://doi.org/10.1002/jso.23693.

11. Sato R, Kishiwada M, Kuriyama N, Azumi Y, Mizuno S, Usui M, et al. Paradoxical impact of the remnant pancreatic volume and infectious complications on the development of nonalcoholic fatty liver disease after pancreaticoduodenectomy. J Hepatobiliary Pancreat Sci 2014; 21: 562-72. https://doi.org/10.1002/jhbp.115.

12. Okamura Y, Sugimoto H, Yamada S, Fujii T, Nomoto S, Takeda S, et al. Risk factors for hepatic steatosis after pancreatectomy: a retrospective observational cohort study of the importance of

nutritional management. Pancreas 2012; ;41: 1067-72. https://doi.org/10.1097/MPA.0b013e31824c10ab.

13. Vujasinovic M, Valente R, Del Chiaro M, Permert J, Löhr JM. Pancreatic Exocrine Insufficiency in Pancreatic Cancer. Nutrients 2017; 9: 183. https://doi.org/10.3390/nu9030183.
14. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 years after. Surgery 2017; 161: 584-591. https://doi.org/10.1016/j.surg.2016.11.014
15. Hamer OW, Aguirre DA, Casola G, Sirlin CB. Imaging features of perivascular fatty infiltration of the liver: initial observations. Radiology 2005; 237: 159-69. https://doi.org/10.1148/radiol.2371041580.
16. Geraghty EM, Boone JM, McGahan JP, Jain K. Normal organ volume assessment from abdominal CT. Abdom Imaging 2004; 29: 482-90. https://doi.org/10.1007/s00261-003-0139-2.
17. Klöppel G, Maillet B. Pseudocysts in chronic pancreatitis: a morphological analysis of 57 resection specimens and 9 autopsy pancreata. Pancreas 1991; 6: 266-74.
18. Kanda Y. Investigation of the freely available easy-to use software ‘EZR’ for medical statistics. Bone Marrow Transplant 2013; 48: 452-8. https://doi.org/10.1038/bmt.2012.244.
19. Nagai M, Sho M, Satoi S, Toyokawa H, Akahori T, Yanagimoto H, et al. Effects of pancrelipase on nonalcoholic fatty liver disease after pancreaticoduodenectomy. J Hepatobiliary Pancreat Sci 2014; 21: 186-92. https://doi.org/10.1002/jhbp.14.

20. Sato T, Matsuo Y, Shiga K, Morimoto M, Miyai H, Takeyama H. Factors that predict the occurrence of and recovery from non-alcoholic fatty liver disease after pancreatoduodenectomy. Surgery 2016; 160: 318-30. https://doi.org/10.1016/j.surg.2016.04.009.
21. Umezaki N, Hashimoto D, Nakagawa S, Kitano Y, Yamamura K, Chikamoto A, et al. Number of acinar cells at the pancreatic stump predicts pancreatic fistula after pancreaticoduodenectomy. Surg Today 2018; 48: 790-5. https://doi.org/10.1007/s00595-018-1656-5.
22. Nahm CB, Brown KM, Townend PJ, Colvin E, Howell VM, Gill AJ, et al. Acinar cell density at the pancreatic resection margin is associated with post-pancreatectomy pancreatitis and the development of postoperative pancreatic fistula. HPB (Oxford) 2018; 20: 432-40. https://doi.org/10.1016/j.hpb.2017.11.003.
23. Deng Y, Zhao B, Yang M, Li C, Zhang L. Association Between the Incidence of Pancreatic Fistula After Pancreaticoduodenectomy and the Degree of Pancreatic Fibrosis. J Gastrointest Surg 2018; 22: 438-43. https://doi.org/10.1007/s11605-017-3660-2.
24. Hanaki T, Uejima C, Amisaki M, Yosuke A, Tokuyasu N, Honjo S, et al. The attenuation value of preoperative computed tomography as a novel predictor for pancreatic fistula after pancreaticoduodenectomy. Surg Today 2018; 48: 598-608. https://doi.org/10.1007/s00595-018-1626-y.
25. Maehira H, Iida H, Mori H, Kitamura N, Miyake T, Shimizu T, et al. Computed Tomography Enhancement Pattern of the Pancreatic Parenchyma Predicts Postoperative Pancreatic Fistula

After Pancreaticoduodenectomy. Pancreas 2019; 48: 209-215. https://doi.org/10.1097/MPA.0000000000001229.

26. Nahm CB, Lui I, Naidoo CS, Roseverne L, Alzaabi S, Maher R, et al. Density and enhancement of the pancreatic tail on computer tomography predicts acinar score and pancreatic fistula after pancreatoduodenectomy. HPB (Oxford) 2019; 21:6 04-11. https://doi.org/10.1016/j.hpb.2018.09.014.

27. Low JT, Shukla A, Thorn P. Pancreatic acinar cell: new insights into the control of secretion. Int J Biochem Cell Biol 2010; 42: 1586-9. https://doi.org/10.1016/j.biocel.2010.07.006.

28. Yuasa Y, Murakami Y, Nakamura H, Uemura K, Ohge H, Sudo T, et al. Histological loss of pancreatic exocrine cells correlates with pancreatic exocrine function after pancreatic surgery. Pancreas 2012; 41: 928-33. https://doi.org/10.1097/MPA.0b013e31823d837d.

29. Hirono S, Murakami Y, Tani M, Kawai M, Okada K, Uemura K, et al. Identification of risk factors for pancreatic exocrine insufficiency after pancreaticoduodenectomy using a 13C-labeled mixed triglyceride breath test. World J Surg 2015; 39: 516-25. https://doi.org/10.1007/s00268-014-2832-4.

30. Okano K, Murakami Y, Nakagawa N, Uemura K, Sudo T, Hashimoto Y, et al. Remnant pancreatic parenchymal volume predicts postoperative pancreatic exocrine insufficiency after pancreatectomy. Surgery 2016; 159: 885-92. https://doi.org/10.1016/j.surg.2015.08.046.

31. Ricci C, Longo R, Gioulis E, Bosco M, Pollesello P, Masutti F, et al. Noninvasive in vivo quantitative assessment of fat content in human liver. J Hepatol 1997; 27: 108-113. https://doi.org/10.1016/S0168-8278(97)80288-7

Figure Legends

Figure 1 Measurement of CT findings and pancreatic acinar cell density

(a) The CT attenuation value of the liver was defined as the mean of the attenuation value of four ROIs in different sectors in the liver. **(b)** The CT attenuation value of the remnant pancreas was defined as the mean of two ROIs in the remnant pancreas on preoperative unenhanced CT. **(c)** The vessels were excluded by reviewing the preoperative enhanced CT. **(d)** The cut line of the pancreas was determined by the location of the pancreatojejunostomy in the postoperative CT images. **(e)** Subsequently, the remnant pancreatic parenchyma was manually outlined on each CT slice using a free-hand region of interest in the preoperative CT images and the volume of the remnant pancreas was calculated using all outlined areas and the slice thickness. **(f)** The pancreatic acinar cell density was measured by Image J (f, except red area) at 100x magnification of hematoxylin and eosin stained tissue **(g).**

Abbreviations: CT, computed tomography; ROI, region of interest

Figure 2 Relationship between the preoperative CT attenuation value of the remnant pancreas and the pancreatic acinar cell density

(a) The scatter diagram shows the relationship between the preoperative CT attenuation value of the remnant pancreas and the pancreatic acinar cell density. These two factors are positively correlated, with a Pearson's correlation coefficient of 0.537. **(b)** The ROC curve of the CT attenuation value of the remnant pancreas for the analysis of the pancreatic acinar cell density ≥ 50% has an area under the

curve of 0.829. A cutoff value of 37.0 HU predicts pancreatic acinar cell density ≥ 50% with a sensitivity and specificity of 71.4% and 85.2%, respectively. (c) The scatter diagram shows the relationship between the preoperative CT attenuation value of the remnant pancreas and the fibrotic score. These two factors are negatively correlated, with a Pearson's correlation coefficient of -0.532. *Abbreviations: CT, computed tomography; HU, Hounsfield units; ROC, receiver operating characteristic*

Figure 3 The estimated functional remnant pancreatic volume as a predictor of nonalcoholic fatty liver disease.

The ROC curve of the eFRPV for the prediction of NAFLD has an area under the curve of 0.721. A cut-off value of 47.0 mL·HU predicts NAFLD with a sensitivity and specificity of 81.0% and 65.6%, respectively. *Abbreviations: eFRPV, estimated functional remnant pancreatic volume; NAFLD, nonalcoholic fatty liver disease; ROC, receiver operating characteristic; HU, Hounsfield units*

Tables

Table 1. Clinical features of the NAFLD and non-NAFLD groups

	NAFLD group (n=21)	non-NAFLD group (n=91)	P-value
Background			
Sex, male / female	10 / 11	63 (69.2%) / 28 (30.8%)	0.077
Age, years	68 (62-71)	69 (62-75)	0.438
Body mass index, kg/m^2	22.0 (19.4-23.3)	21.48 (19.6-23.8)	0.864
Prevalence of hypertension	5	31 (34.1%)	0.444
Prevalence of diabetes mellitus	9	21 (23.1%)	0.099
Alcohol intake >20g/day	6	28 (30.8%)	1.000
Use of steroid agent	0	2 (2.2%)	1.000
Preoperative biliary drainage	10	41 (45.1%)	1.000
Neoadjuvant chemotherapy	5	3 (3.3%)	0.006
Preoperative NAFLD	1	1 (1.1%)	0.341
Prevalence of liver dysfunction	3	3 (3.3%)	0.038
Pathological diagnosis			< 0.001

Pancreatic cancer	19	30 (33.0%)
Intraductal papillary mucinous neoplasm	1	14 (15.4%)
Chronic pancreatitis	1	2 (2.2%)
Pancreatic neuroendocrine neoplasm	0	4 (4.4%)
Bile duct cancer	0	21 (23.1%)
Cancer of the papilla of vater	0	12 (13.2%)
Others	0	8 (8.7%)

Preoperative laboratory data

Hemoglobin, g/dL	13.0 (11.8-13.6)	12.6 (11.9-13.8)	0.911
White blood cell count, /μL	5000 (4400-7500)	5300 (4350-6400)	0.765
Platelet count, /μL	22.2 (18.9-28.7)	21.5 (17.9-26.1)	0.293
Prothrombin activity, %	99 (88-103)	94 (87-103)	0.740
Aspartate aminotransferase, U/L	29 (20-41)	22 (19-33)	0.174
Alanine aminotransferase, U/L	24 (18-65)	22 (16-48)	0.365
Alkaline phosphatase, U/L	343 (241-433)	267 (200-440)	0.256
Total bilirubin, g/dL	0.93 (0.59-1.56)	0.84 (0.58-1.34)	0.472
Creatinine, mg/dL	0.59 (0.52-0.81)	0.74 (0.63-0.90)	0.015

Amylase, U/L	68 (45-116)	79 (63-128)	0.093
Lipase, U/L	58 (15-109)	46 (31-99)	0.486
Creatine kinase, U/L	50 (30-69)	59 (38-74)	0.132
C-reactive protein, mg/dL	0.10 (0.05-0.32)	0.12 (0.05-0.37)	0.765
Preoperative nutritional status			
Total protein, g/dL	6.4 (6.2-6.8)	6.6 (6.4-7.1)	0.091
Albumin, g/dL	3.5 (3.4-4.0)	3.7 (3.4-4.0)	0.598
Cholinesterase, U/L	275 (244-292)	263 (221-295)	0.351
Total cholesterol, mg/dL	195 (164-235)	187 (148-216)	0.310
Triglyceride, mg/dL	118 (87-140)	120 (92-148)	0.967
Hemoglobin A1c, %	6.0 (5.7-6.6)	5.9 (5.6-6.7)	0.916
Total lymphocyte count, /μL	1442 (1220-1895)	1531 (1210-2056)	0.685
Prognostic nutritional index	43.73 (40.26-49.49)	45.06 (42.53-48.23)	0.679
CONUT score	2 (1-3)	2 (1-3)	0.774
Intraoperative findings			
Blood loss, mL	689 (500.0-1491)	791 (469.5-1435)	0.929

Operation time, minutes	537 (489.0-566)	463 (403.5-586)	0.106
Presence of transfusion	5	18 (19.8%)	0.765
Diameter of MPD, mm	5 (2-6)	3 (3-5)	0.060
Pancreatic stiffness, soft / hard	4 / 17	53 (58.2%) / 38 (41.8%)	0.001
Postoperative findings			
Complication ≥ grade3	9	45 (49.5%)	0.635
Postoperative pancreatic fistula grade B/C	3	30 (33.0%)	0.114
Postoperative pancreatic enzyme supplementation	16	45 (49.5%)	0.031
Adjuvant chemotherapy	17	34 (37.4%)	<0.001
Adjuvant chemotherapy completely	9/17	22/34	0.545
Recurrence within 6 months	2	10 (8.9%)	1.000
Postoperative nutritional status (6 months after surgery)			
Total protein, g/dL	6.3 (5.6-6.7)	6.8 (6.3-7.1)	0.006
Albumin, g/dL	3.5 (3.2-3.7)	3.8 (3.2-4.0)	0.049

Cholinesterase, U/L	183 (138-220)	213 (164-269)	0.077
Total cholesterol, mg/dL	123 (110-129)	148 (126-178)	0.001
Triglyceride, mg/dL	79 (71-102)	77 (67-115)	1.000
Hemoglobin A1c, %	5.7 (5.3-6.2)	5.8 (5.4-6.4)	0.368
Total lymphocyte count, /μL	1084 (930-1288)	1385 (933-1774)	0.057
Prognostic nutritional index	40.14 (36.83-43.28)	43.98 (39.21-48.34)	0.014
CONUT score	5 (3-9)	3 (2-4)	0.037
Preoperative CT findings			
CT attenuation value of the liver, HU	55.9 (51.2-60.2)	57.7 (52.7-62.4)	0.222
CT attenuation value of the remnant pancreas, HU	31.0 (27.7-38.8)	39.3 (33.1-45.7)	0.007
Remnant pancreatic volume, mL	10.3 (5.8-15.3)	15.4 (9.6-23.8)	0.007
eFRPV, mL·HU	32.8 (17.1-46.6)	60.6(32.2-104.6)	0.002
Histopathological findings			
Pancreatic acinar cell density, %	44.6 (19.9-71.6)	69.7 (57.9-78.4)	0.003
Fibrotic score	10 (3-12)	3 (2-6)	0.003

Data are expressed as median with interquartile range for continuous data or as number and percentage for categorical data.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; CONUT, controlling nutritional status; MPD, main pancreatic duct; CT, computed tomography; HU, Hounsfield units; eFRPV, estimated functional remnant pancreatic volume

Table 2. Multivariate analysis of preoperative evaluable factors

Factors	Odd's ratio	95% confidence interval	P-value
Neoadjuvant chemotherapy	3.98	0.74-21.40	0.108
Prevalence of liver dysfunction	10.70	1.15-98.80	0.037
Creatinine	0.19	0.01-2.79	0.224
eFPRV ≤ 47 mL·HU	6.73	1.70-26.70	0.007

Abbreviations: eFRPV, estimated functional remnant pancreatic volume

Figure 1

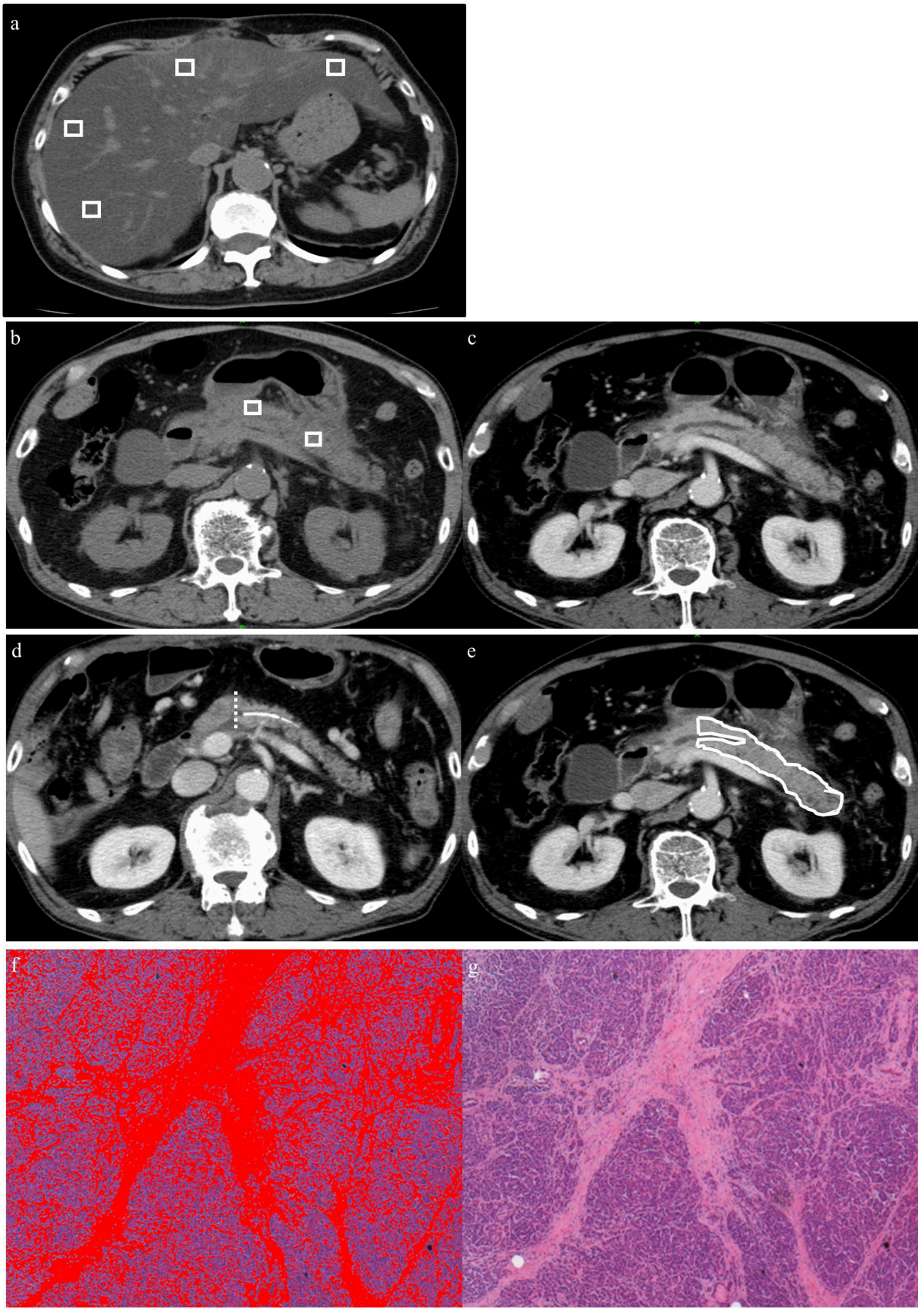
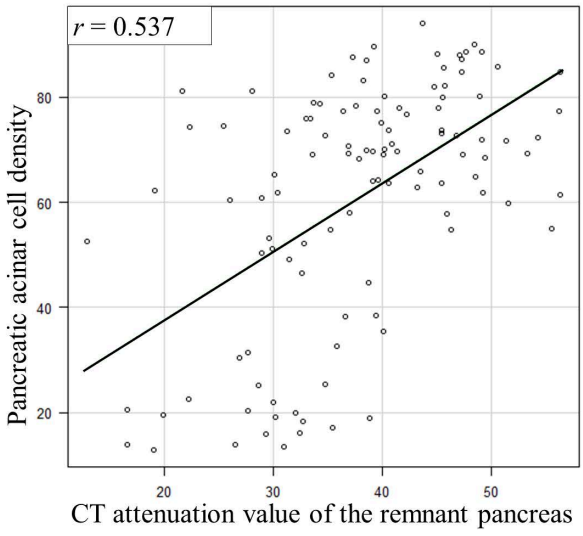


Figure 2

a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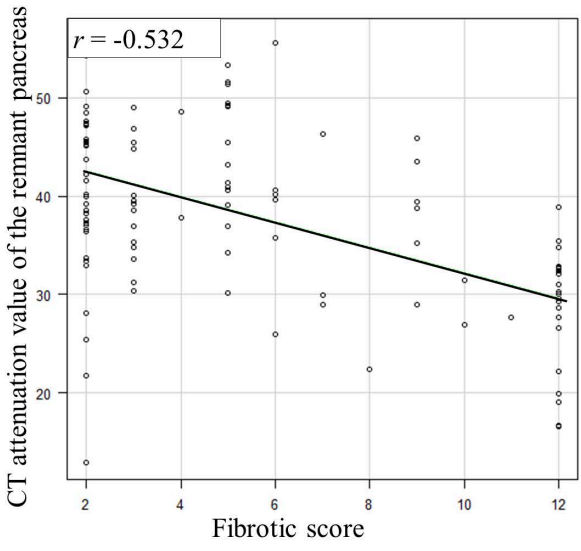
Pancreatic acinar cell density
CT attenuation value of the remnant pancreas
20
40
60
80
20
30
40
50

c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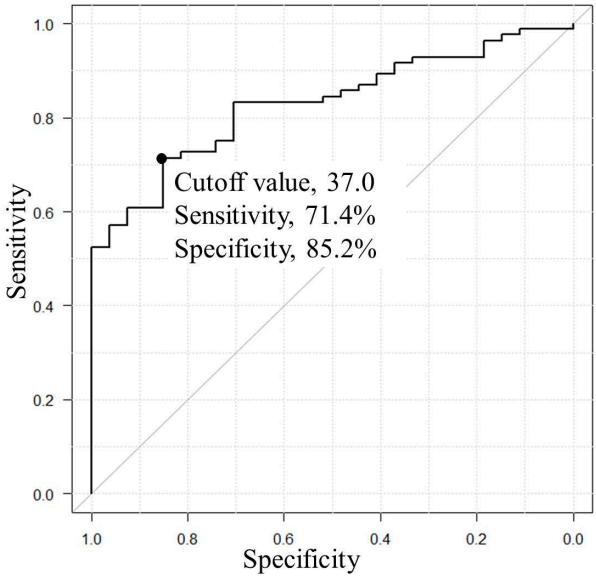
CT attenuation value of the remnant pancreas
Fibrotic score
20
30
40
50
2
4
6
8
10
12

b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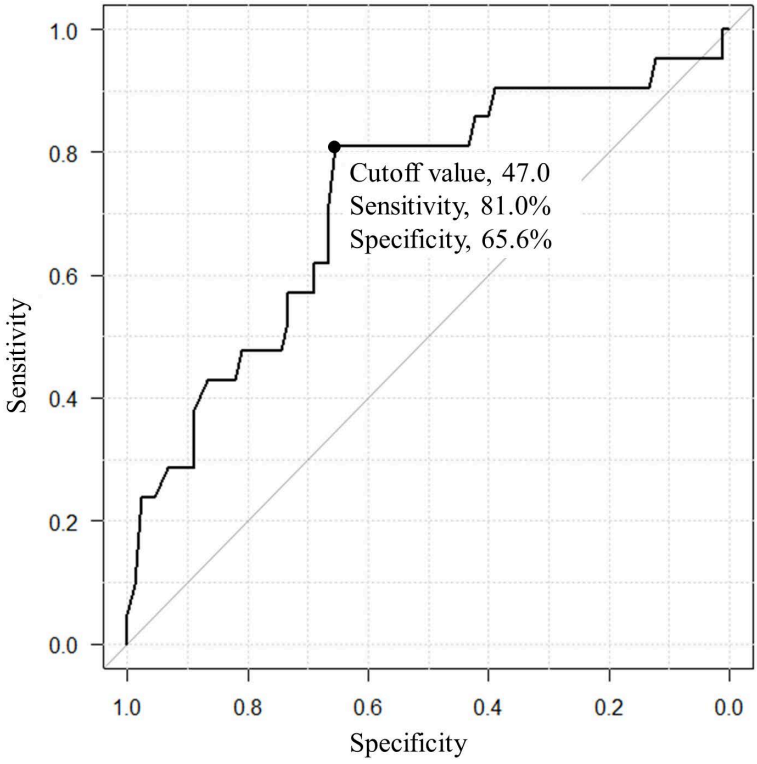
Sensitivity, 71.4%
Specificity, 85.2%
Sensitivity
Specificity
0.0
0.2
0.4
0.6
0.8
1.0

Figure 3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Specificity, 65.6%
Sensitivity
Specificity
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0.4
0.2
0.0