

Favorable Preoperative Exocrine Function Evaluated by ^{13}C Trioctanoin Breath Test is a Significant Physiological Predictor of Pancreatic Fistula After Pancreaticoduodenectomy

Hiroyuki Kato (✉ katohiroyuki510719@gmail.com)

Fujita Health University School of Medicine, Bantane Hospital

Yukio Asano

Fujita Health University School of Medicine, Bantane Hospital

Masahiro Ito

Fujita Health University School of Medicine, Bantane Hospital

Norihiko Kawabe

Fujita Health University School of Medicine, Bantane Hospital

Satoshi Arakawa

Fujita Health University School of Medicine, Bantane Hospital

Masahiro Shimura

Fujita Health University School of Medicine, Bantane Hospital

Daisuke Koike

Fujita Health University School of Medicine, Bantane Hospital

Chihiro Hayashi

Fujita Health University School of Medicine, Bantane Hospital

Kenshiro Kamio

Fujita Health University School of Medicine, Bantane Hospital

Toki Kawai

Fujita Health University School of Medicine, Bantane Hospital

Takayuki Ochi

Fujita Health University School of Medicine, Bantane Hospital

Hironobu Yasuoka

Fujita Health University School of Medicine, Bantane Hospital

Takahiko Higashiguchi

Fujita Health University School of Medicine, Bantane Hospital

Daisuke Tochii

Fujita Health University School of Medicine, Bantane Hospital

Yuka Kondo

Fujita Health University School of Medicine, Bantane Hospital

Hidetoshi Nagata

Fujita Health University School of Medicine, Bantane Hospital

Toshiaki Utsumi

Fujita Health University School of Medicine, Bantane Hospital

Akihiko Horiguchi

Fujita Health University School of Medicine, Bantane Hospital

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Abstract

Aim

The association between the pancreatic fistula (PF) after pancreaticoduodenectomy (PD) and preoperative exocrine function has yet to be elucidated. The aim of this study is to evaluate the association between the preoperative results of ^{13}C -trioctanoin breath test and occurrence of PF, showing the clinical relevancy of the breath test to predict the PF.

Method

In the present study, the subject were 80 patients who underwent ^{13}C trioctanoin breath test prior to PD from 2006 to 2018. We conducted the uni- and multivariate analyses to reveal the preoperative predictor of PF, showing the association of the ^{13}C trioctanoin absorption and incidence of PF.

Results:

Among 80 patients (Age:68.0+/-11.9, male/female:46/34, pancreatic ductal adenocarcinoma: PDAC/non-PDAC: 30/50), the incidence of PF is 12.5% (10/80). When we compared the levels of ^{13}C trioctanoin absorption between PF and non-PF group, preoperative fat absorption level is significantly higher than in the PF group than in the non-PF group (41.2+/-5.9 vs. 33.9+/-8.1, $p = 0.019$). Moreover, optimal cut-off value of the preoperative fat absorption level to predict PF was 38.0 (sensitivity:90%, specificity:74%, AUC:0.78, $p = 0.005$). Indeed, the incidence of PF was extremely higher in the patients whose value of breath test was greater than 38.0 (33%, 9/27) compared to the patients with those less than 38.0 (1.8%, 1/53).

Conclusion

Favorable preoperative fat absorption evaluated by ^{13}C trioctanoin breath test is a feasible and objective predictor of PF after PD.

Introduction

The postoperative mortality after pancreatoduodenectomy (PD) has been reducing especially in high-volume centers because of the advancement of surgical skill and perioperative administration. 30-day and in-hospital mortality rates were reported to be 1.2 and 2.8%, respectively, by national clinical database from Japan¹. However, postoperative pancreatic fistula (PF) is still a large threat to both patients and pancreatic surgeons, because it sometimes causes the postoperative fatal intraabdominal bleeding^{2,3} and abscess^{4,5}, and its incidence is still reported to be high (11-29.4%) in patients with soft

pancreas⁶⁻⁸. Therefore, it is urgent to elucidate the global preoperative risk factor of PF and there has been several articles showing the preoperative risk factors such as obesity, fatty pancreas, narrow pancreatic duct, male and surgical technics et al⁹⁻¹¹. However, most of these predictors might affect the incidence of PF in an indirect fashion. In contrast, we conjectured that preoperative favorable exocrine function, which could be associated with normal pancreas, directly affect the incidence of PF, because excessive secretion of pancreatic juice after PD might cause the disruption of the anastomotic site. However, this assumption remains unclear because it has been still clinically challenging to address the preoperative exocrine function, which is mainly represented by fat absorption.

In terms of evaluating pancreatic exocrine functions, several articles have already reported the relevancy of various pancreatic function tests¹²⁻¹⁷. Indeed, BT- PABA (N-benzoyl-L-trypsyl-p-aminobenzoic acid), fecal chymotrypsin, fecal elastase-1 testing (FE-1), fecal fat excretion test, and ¹³C-trioctanoin breath test has been clinically employed for the evaluation of it. Among these usable testing, ¹³C-trioctanoin breath test does not have a necessity of urine or stool collection, and also is not affected by hepato-renal function of subjected patients; thus, we consider possibly more acceptable for evaluating a perioperative pancreatic exocrine function. The aim of this study is to evaluate the association between the results of ¹³C-trioctanoin breath test and occurrence of PF, showing the clinical relevancy of the breath test to predict the PF.

Patients And Methods

Among the 133 patients who underwent ¹³C-labeled trioctanoin breath test before and after pancreatectomies in our institution from 2006 to 2018, the subjects were 80 patients who underwent PD and perioperative course and factors associating PF could be precisely evaluated. ¹³C-labeled trioctanoin breath test, which directly and objectively reflects the ability of fat absorption, was performed one to three before the surgery.

All of the patients were fasted overnight prior to the breath test. Breath samples were collected in 100ml bags with a one-way check valve. Samples were obtained 15 minutes prior to the test, and 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, 180, 210 and 240 minutes after oral administration of ¹³C-labeled trioctanoin including diet (Lacol 200kcal/200ml + fat component:20g). Fat absorption was evaluated by Aa ($Aa = AUC \times Kel \times Vd$) [Kel:0.35, Vd:distribution volume], using a POCone→ which is the specific analyzer of ¹³CO₂ concentration in exhaled air. In the present study, we retrospectively compared pre-and postoperative fat absorption levels and their change rate during pancreatectomies between the groups with PF and non-PF. The medical ethics committee approved the study protocol of Fujita Health University School of Medicine (HM17165). In terms of surgical procedure of PD, we employed the inferior pancreaticoduodenal artery (IPDA) first approach to reduce the intraoperative blood loss¹⁸. A drain was removed until postoperative day (POD) 5 to 7 as long as drain discharge was clear and drain amylase level was not as three times high as the upper limit of serum amylase level (132U/ml).

In all patients, amylase level of abdominal drainage fluid were measured until day 7 after PD. Pancreatic fistula was defined and graded according to the International Study Group on Pancreatic Fistula classification¹⁹. In the present study, we divided the subject into the patients with clinically relevant PF of Grade B or C and those with non-PF or biochemical leak. To identify pre- and intra-operative risk factors of pancreatic fistula, we compared various factors between these two groups.

In terms of surgical procedure of PD, we employed the IPDA (inferior pancreatoduodenal artery)-first approach from 2007¹⁸. Briefly, IPDA is encircled and ligated before pancreatic resection, aiming the reduction of intraoperative blood loss (Fig. 1). For pancreatojejunostomy, the first-layer anastomosis was done by duct-to-mucosa anastomosis with 6–8 interrupted sutures by 5–0 PDS II (Ethicon, Inc.Somerville, NJ, USA). The second-layer anastomosis was done by the 6 to modified Kakita procedure using 3 – 0 proline²⁰. A 5F external pancreatic stent tube were inserted in the remnant main pancreatic duct in all 80 patients.

All statistical analyses were done by the statistical software package SPSS for Macintosh (version 24.0, IBM, Armonk, NY, USA). The results of the continuous variables were expressed as median and range, and statistical significance was evaluated by the Mann-Whitney U test. Discrete variables were evaluated by χ^2 analysis or Fisher's exact test, as appropriate. Pre- and intraoperative risk factors associated with POPF were analyzed using univariate and multivariate analysis (logistic regression analysis). Only variables with p-values less than 0.05, as determined by univariate analysis, were included in the multivariate analysis. Results were considered significant when P values were less than 0.05. Receiver operating characteristic (ROC) curve analysis were employed to estimate the best cut-off points for the ¹³C-trioctanoin breath test to predict PF. In the present study, the pancreatic configuration based on the imaging study, pancreatic texture and diameter of pancreatic duct intraoperatively evaluated were excluded by the items of univariate analysis because these factor might be strong confounding factors and the aim of this study is to find the objective, quantitative and physiological predictor of PF.

Results

Preoperative background of the 80 patients is shown in Table 1. In these 80 patients, the median age (range) was 69.5 (26-88) year-old, and males/females were 46/34. Primary disease was PDAC in 30, and non-PDAC in 50.

In terms of preoperative lab data, the detail of blood cell counts, and several nutritional markers were described also in Table.1. The median operation time (min) and intraoperative blood loss (ml) were 469 (296-842) minutes and, 325 (23-4900) g, respectively. Regarding the Incidence of PF, clinically relevant PF (more than grade B according to ISGPF criteria) was found in 10 out of 80 (12.5%). With regard to the results of breath test, the values of Aa before PD were 34.4 (16.4-69.7) dose/hour.

Pre- and intraoperative risk factors of POPF

As shown in Table 2, univariate analysis by comparing preoperative risk factors between the PF group and non-PF group identified the pancreatic ductal adenocarcinoma (PDAC) ($p=0.009$) and favorable results of ^{13}C -trioctanoin breath test ($p=0.005$) as the significant risk factor of PF. Indeed, when we compared the levels of ^{13}C trioctanoin absorption between PF and non-PF group, preoperative fat absorption level is significantly higher than in the PF group than in the non-PF group (40.2 vs. 34.4, $p=0.05$). Moreover, optimal cut-off value of the preoperative fat absorption level to predict PF was 38.0 (sensitivity:90%, specificity:74%, AUC:0.78, $p=0.005$). Indeed, the incidence of PF was extremely higher in the patients whose value of breath test was greater than 38.0 (33%, 9/27) compared to the patients with those less than 38.0 (1.8%, 1/53). By multivariate analysis as shown in Table.3, preoperative ^{13}C trioctanoin breath test $>38.0\%$ dose/h were selected as the most independent risk factors for PF ($p=0.001$, Odd's ratio:16.7).

Next, we focused on the association between the incidence of PF and the level of ^{13}C trioctanoin breath test $>38.0\%$ dose/h in only non-PDAC patients because we considered that the prediction of PF in non-PDAC cases, that is mostly soft pancreas, is urgent issue to be solved.

As the same manner of figure 2A, ROC curve revealed that the cut-off value was 37.9% dose/h (Area under the curve:AUC:0.78) (Figure 3A). As shown in figure3B, the incidence of PF was markedly high (39.0%, 9/23) in the patients with preoperative favorable fat absorption, whereas it was 3.7% (1/27) in the patients with unfavorable absorption (Figure 3b).

Discussion

In the present study, we newly elucidated the insight in which ^{13}C trioctanoin absorption ($> 38.0\%$ dose/h) were strong preoperative physiological predictor of PF after PD in not only total cohort, but also in non-PDAC patients whose pancreatic parenchyma could be soft.

^{13}C trioctanoin breath tests have been employed on the clinical settings to evaluate the pancreatic exocrine deficiency by detecting fat malabsorption through the gut after pancreatectomies^{21,22}. Until now, however, there has been few studies evaluating whether preoperative exocrine function test affect the incidence of PF after PD^{12,23}.

To predict the development of PF preoperatively, a lot of researchers seek to find the relevant risk factors such as high BMI^{24,25}, fatty pancreas^{10,24,26}, male^{27,28} and untreated jaundice²⁹, and also developed the way of its prediction using various imaging modalities such as CT configurations (narrow main pancreatic duct¹⁰, thick pancreatic parenchyma¹⁰, pancreatic border⁶, CT attenuation value³⁰), MRI findings³¹, and pancreatic ultrasound elastography^{32,33} et al. Even though these predictors might be clinically useful, most of these factors are strongly associated with the soft parenchymal condition, which cause a technical difficulty of anastomosis. Therefore, whether these risk factors are reproducible or not is also depending on the type of pancreato-enteral anastomosis and maturity of those procedures. On the other hands, the data obtained from ^{13}C trioctanoin breath test is more objective and quantitative,

and especially in patients with Aa > 38.0 %dose/h, the PF incidence is extremely high regardless of parenchymal condition. Previous article mentioned the recovery of the ¹³C-labeled trioctanoin absorption after PD positively associated with output of pancreatic enzymes such as lipase, amylase, and chymotrypsin ¹⁵. Thus, we speculated the active production of pancreatic juice might be one of the major causes of PF after PD, and considered that outcome of the present study represented this aspect. In fact, our speculation is supported by the result showing that postoperative maximum drain amylase level (U/L) is significantly higher in patients with Aa > 38.0% dose/h than that in those with Aa < 38.0 (Fig. 4).

According to the previous reports regarding the association between PF and results of pancreatic exocrine function test, several reports revealing that higher preoperative level of FE-1 was positively associated with the developments of postoperative PF^{12,30}. However, there has been no study revealing the association between the result of ¹³C-labeled trioctanoin and occurrence of PF. Therefore, to the best of our knowledge, Aa > 38.0% dose/h is considered to be first physiological quantitative predictor of PF.

Clinical application of this study is challenging, because prevention of PF is quite difficult even if risky patients were identified preoperatively. the administration of octreotide or somatostatin analogs is well-accepted pharmacological treatment with PF targeting the secretion of pancreatic juice^{34,35}. The effect of somatostatin analogs is to reduce the volume of fistula output, thereby potentially alleviating the PF³⁶. Octreotide also has been considered to reduce the volume and potency of both pancreatic exocrine secretions and hormone production³⁷. Since our study demonstrate that the favorable preoperative exocrine function, which in turn high output of pancreatic juice, is regarded as the risk factor of PF, administration of these drugs might become a key treatment of PF in these risky patients. However, prospective or randomized control study should be needed to show this hypothesis.

The present research has several limitations. The first is that this study included only small number of patients. The second limitation is that the present analysis was a retrospective analysis, and we could not identify the precise mechanism how favorable pancreatic exocrine function cause the PF postoperatively. Therefore, the study is regarded as only an exploratory research. Nonetheless, our study could draw significant attention to the association between PF and preoperative pancreatic exocrine function. In conclusion, favorable pancreatic exocrine function evaluated by ¹³C trioctanoin breath test preoperatively, is a feasible and objective predictor of PF after PD, paying attention to the development of PF in such high-risk patients.

Abbreviations

pancreatic fistula (PF), pancreaticoduodenectomy (PD), pancreatic ductal adenocarcinoma (PDAC), fecal elastase-1 testing (FE-1), the inferior pancreaticoduodenal artery (IPDA), postoperative day (POD), Receiver operating characteristic (ROC), Area under the curve (AUC)

Declarations

Availability of data and materials

The datasets analyzed during the current study available from the corresponding author on reasonable request.

Authors' contributions

HK analyzed and drafted the manuscript. UA and AH participated data collection and assisted with data interpretation. MI, NK, SA, MS, DK, C, KK, TK, TO, HY, TH, DT, UK, HN TU, and AH reviewed and revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This retrospective study was approved by the ethics committee of Fujita Health University School of Medicine (HM17165). and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients before treatment.

Data availability statement:

All the data generated or analyzed during this study are included within the article.

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Tables

Table 1. Background of 80 patients who underwentpancreaticoduodenectomy

	PD (n=80)
Pre-operative variables	
Age (years)	69.5 (26-88)
Gender (male / female)	46/34
Body weight (kg)	51.5 (33.0-96.0)
Diagnosis PDAC/ non PDAC	30/50
Hemoglobin (g/dl)	12.7 (8.7-15.9)
White blood cell counts (/mm ²)	5200 (620-11300)
Neutrophil (/mm ²)	3200 (1365-8512)
Lymphocyte (/mm ²)	1470 (400-2940)
Total protein (mg/dl)	6.9 (5.7-8.3)
Albumin (mg/dl)	4.0 (2.5-5.0)
Serum amylase (U/l)	90 (12-604)
Total cholesterol	182 (120-282)
Breath test (%dose/h)	34.4 (16.4-69.7)
Intra-operative variables	
Operation time (min)	469.0 (296-842)
Blood loss (g)	325 (23-4900)
Post-operative variables	
Pancreatic fistula (yes/no)	10/70

Table. 2 Univariate analysis for identifying risk factor of PF

	non-PF (n=70)	PF (n=10)	P-value
Pre-operative variables			
Age (years)	69.0 (43-88)	71.0 (26-79)	0.961
Gender (male / female)	38/32	8/2	0.114
Body weight (kg)	50.6 (33.0-83.5)	63.9 (44.3-96.0)	0.075
Diagnosis PDAC/ non PDAC	30/40	0/10	*0.009
Hemoglobin (g/dl)	12.8 (8.9-15.6)	12.1 (9.1-15.9)	0.708
White blood cell counts (/mm ²)	5100 (3300-11300)	4950 (2100-8000)	0.782
Neutrophil (/mm ²)	3245 (2046-8512)	2718 (1365-4880)	0.106
Lymphocyte (/mm ²)	1428 (630-2438)	1760 (400-2940)	0.135
Total protein (mg/dl)	6.9 (4.7-8.3)	6.6 (6.7-7.8)	0.923
Albumin (mg/dl)	4.0 (2.5-4.7)	4.0 (2.7-5.0)	0.857
Serum amylase (U/l)	90 (12-604)	94.5 (45-218)	0.903
Total cholesterol	179 (120 -282)	195 (120-282)	0.295
Breath test (%dose/h)	33.4 (16.3-69.6)	40.2 (29.1-51.4)	*0.005
Intra-operative variables			
Operation time (min)	466.5 (296-842)	489.0 (338-607)	0.813
Blood loss (g)	325.5 (23-4900)	321.0 (205-1545)	0.745

Table. 3 Results of multivariate analysis for identifying risk factor of PF There is no patients with PF in PDAC group PDAC:pancreatic ductal adenocarcinoma

Variables	Odd's ratio	95% CI	P-value
PDAC	Not applicant*	0.00-0.00	0.998
Preoperative breath test (>38)	16.7	0.007-0.522	0.001

Figures

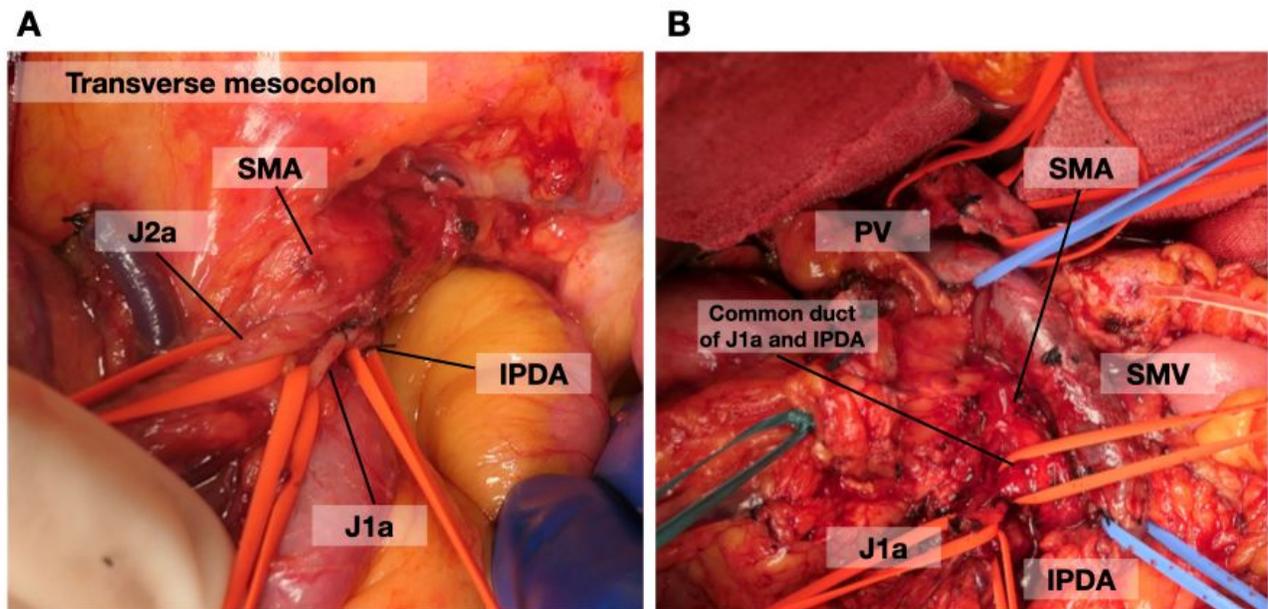


Figure.1 Procedures of pancreaticoduodenectomy

- A. IPDA first approach. Before pancreatic resection, the IPDA is encircled and ligated, reducing the amount of blood loss.
- B. The dissection of SMA plexus during PD, The common duct of IPDA and J1a is encircled and then transected. SMA:superior mesenteric artery IPDA: inferior pancreaticoduodenal artery J1a:first jejunal artery J2a:second jejunal artery PV:portal vein SMV:superior mesenteric artery

Figure 1

See image above for figure legend

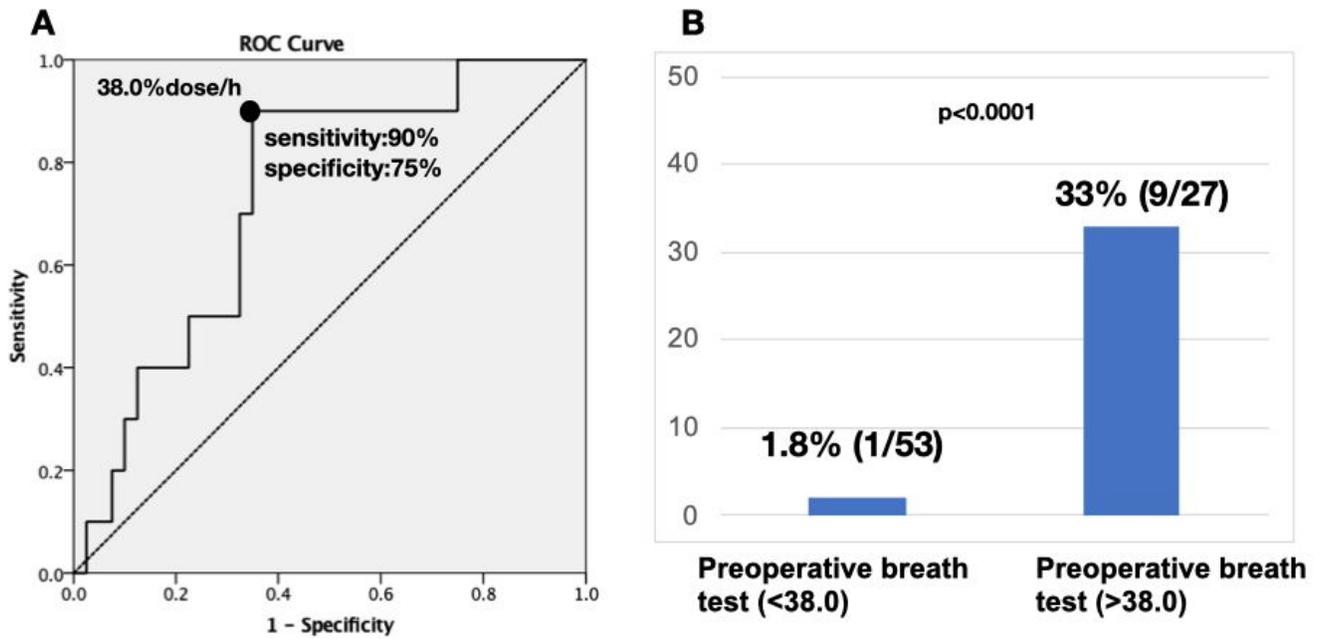


Figure.2

A. Receiver operating characteristic (ROC) curve. Cut-off point of value of ^{13}C breath test (Aa) is 38.0% dose/h (AUC:078). B. The incidence of POPF according to more than or less than cut-off value (Aa).

Figure 2

See image above for figure legend

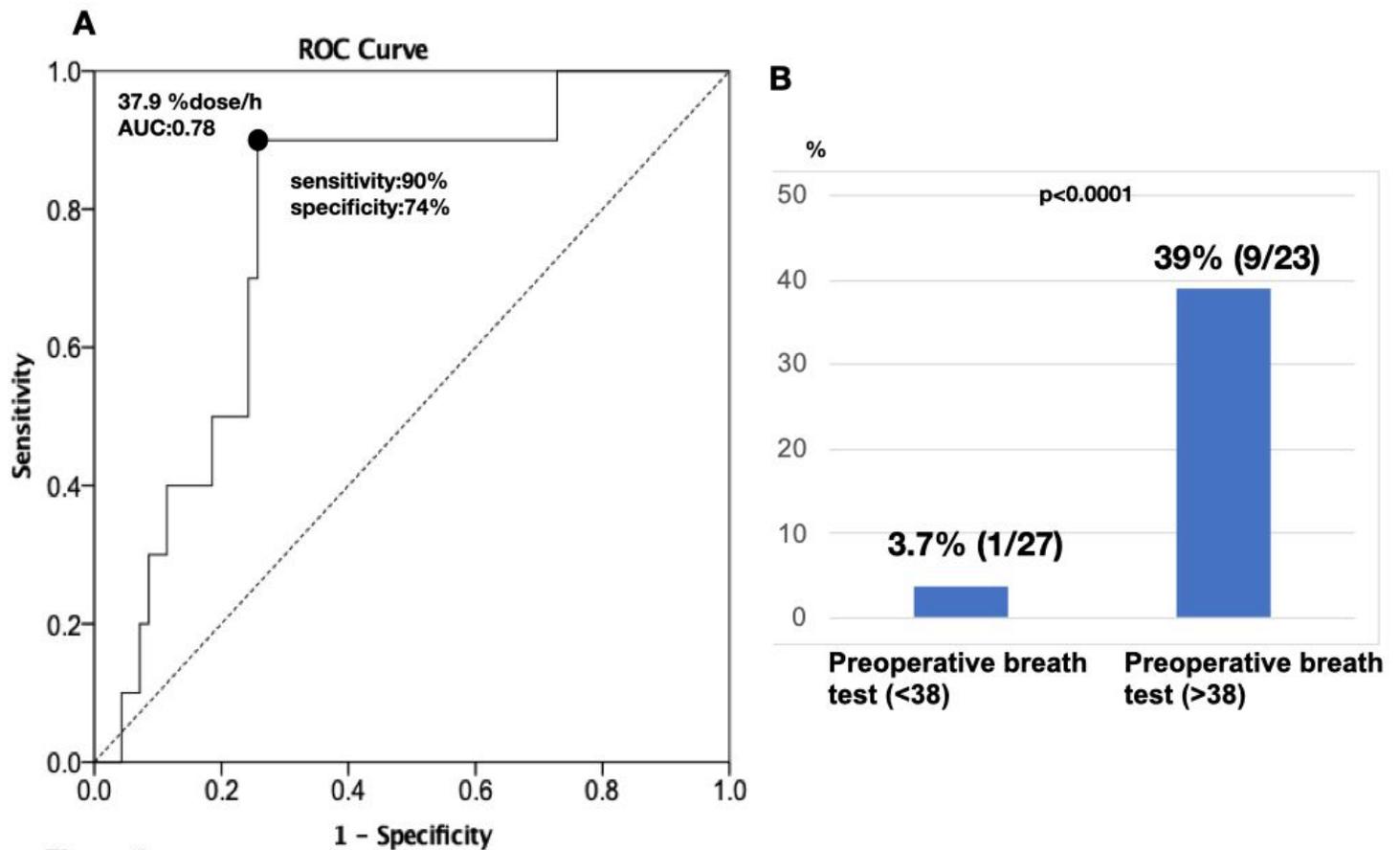


Figure.3

A. Receiver operating characteristic (ROC) curve to predict PF in 50 non-PDAC patients. Cut-off point of value of ^{13}C breath test (Aa) is 37.9% dose/h (AUC:078). B.The incidence of POPF according to more than or less than cut-off value (Aa %dose/h).

Figure 3

See image above for figure legend

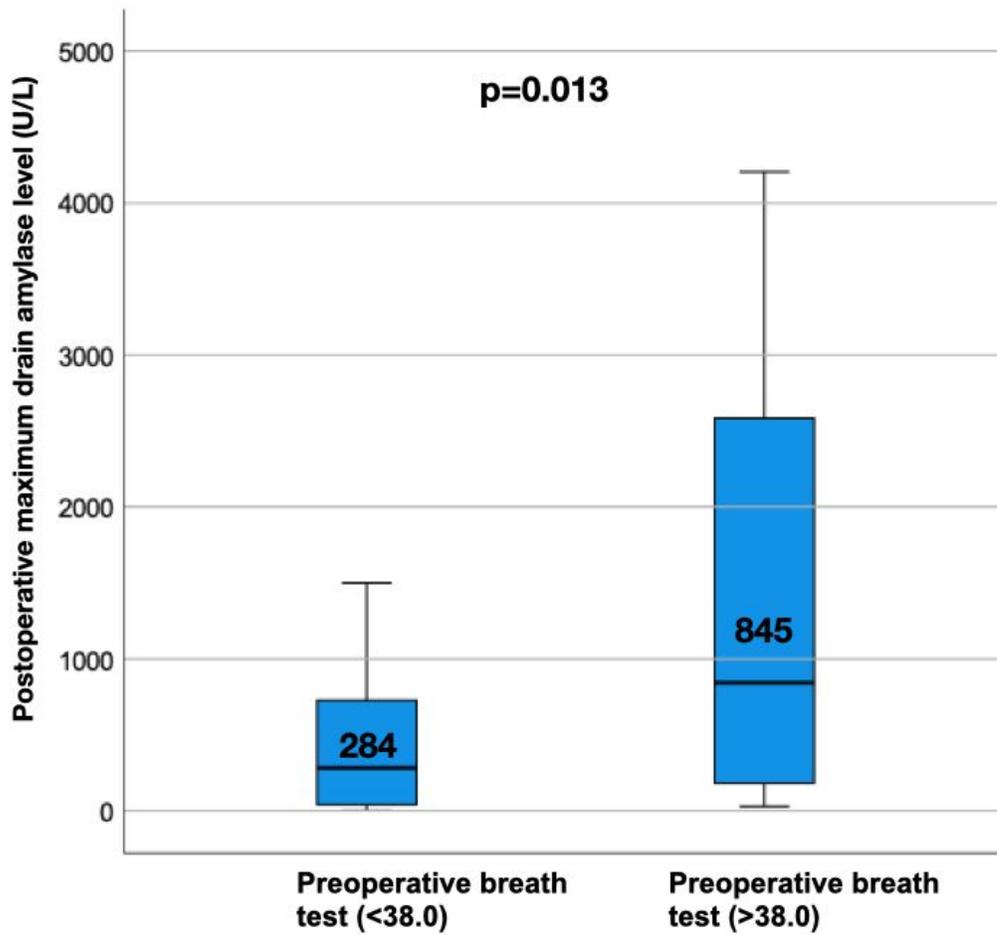


Figure.4
Comparison of postoperative maximum drain amylase level (U/L) according to the result of preoperative breath test

Figure 4

See image above for figure legend