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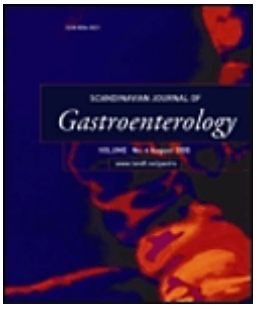

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DILATED MAIN PANCREATIC DUCT CAN BE A NEGATIVE PREDICTOR OF PANCREATITIS RELATED TO BILIARY SEMS INSERTION ACROSS THE PAPILLA

Running title: Predictors of PEP related to SEMS

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Abstract

Objectives: Post-ERCP pancreatitis (PEP) after self-expandable metallic stent (SEMS) insertion across the papilla of Vater is an important adverse event that affects the patient's quality of life (QOL). We examined the predictive factors of PEP after SEMS insertion to treat obstructive jaundice due to malignancy.

Methods: Ninety patients who underwent biliary SEMS insertion for biliary obstruction due to malignancy at Iwata City Hospital between 2010 and 2018 were reviewed. We evaluated the relationship between the incidence of PEP after biliary SEMS insertion and clinical factors. We measured the thickness of the pancreatic parenchyma and diameter of the main pancreatic duct (MPD) at the left side of the corpus vertebrae.

Results: Mild and severe PEP were diagnosed in 10 (11.1%) and 1 (1.1%) patients, respectively. Only the thickness of the pancreatic parenchyma and diameter of MPD significantly differed between the PEP and non-PEP groups. The incidence of PEP among patients whose thickness of the pancreatic parenchyma at the left side of the corpus vertebrae was less than 9.5 mm (0%) on computed tomography was lower than that in patients whose thickness was 9.5 mm or greater (34.4%). Similarly, a wider (5 mm or more) diameter of MPD (4.3%) reduced the incidence of PEP compared with a narrower diameter

(40.0%). Logistic regression analysis revealed that the probability of PEP decreases 3.91-times for every 1-mm increase in MPD diameter (95% CI 1.23-12.4, p=0.02).

Conclusion: Based on our study, a dilated MPD is a negative predictive factor of pancreatitis related to biliary SEMS insertion.

Key words: Post-ERCP pancreatitis (PEP); self-expandable metallic stent (SEMS)

Introduction

Obstructive jaundice is common in patients with pancreatobiliary malignancy. Endoscopic biliary drainage is known to be useful to improve obstructive jaundice and the quality of life (QOL) of these patients. Endoscopic self-expandable metallic stent (SEMS) insertion is accepted as a method of biliary drainage for distal malignant biliary obstruction (MBO) because its patency and cost performance are superior to those of plastic stents [1-2]. However, post-ERCP pancreatitis (PEP) after SEMS insertion across the papilla of Vater is a common complication and its incidence (2.9-10.8%) is higher than that after plastic stent insertion due to blockage of the pancreatic juice flow [3-9]. Moreover, severe PEP after SEMS insertion across the papilla can result in death [10].

Several previous studies analyzed the risk factors for pancreatitis after SEMS insertion. Pancreatic duct injection, non-pancreatic cancer and SEMS with a high axial force were reported as risk factors [8,9,11], whereas chronic pancreatitis, a dilated pancreatic duct (MPD) and endoscopic sphincterotomy (EST) were reported as negative predictors [4].

Many risk factors were analyzed in detail; however, most reports did not focus on the pancreatic condition, and few examined which pancreatic states, such as pancreatic cancer without chronic pancreatitis/ dilated MPD or non-pancreatic cancer with chronic pancreatitis/ dilated MPD, are at risk. Furthermore, it is unclear how to measure chronic pancreatitis/ dilated MPD on computed tomography (CT).

The present study investigated the risk factors for pancreatitis after SEMS insertion in patients with malignant biliary obstruction (MBO), especially those for chronic pancreatitis, and measurement of the pancreatic parenchyma and MPD on CT.

Materials and methods

Study design

This was a retrospective and observational study performed at Iwata City Hospital.

Patients

We retrospectively reviewed 204 patients who underwent biliary SEMS insertion for biliary obstruction due to malignancy at Iwata City Hospital between 2010 and 2018. We diagnosed malignancy based on clinical, laboratory, radiological and pathological examinations.

The exclusion criteria were as follows: (1) age <20, (2) insertion not across the papilla of Vater, (3) replacement of SEMS, (4) intestinal reconstruction after operation, such as Billroth II gastrectomy or Roux-en-Y bypass and (5) insertion via the transhepatic biliary drainage route.

All patients provided informed consent for ERCP. This study was approved by the ethics committee of Iwata City Hospital (approval number: 2018-059). The study protocols conformed to the ethical guidelines of the Declaration of Helsinki.

Measurement of the pancreas

We measured the thickness of the pancreatic parenchyma and diameter of the MPD at the left side of the corpus vertebrae on CT. The thickness of the pancreatic parenchyma was calculated as the diameter of the MPD (*white double arrow*) subtracted from

the diameter of the pancreas (*white double arrowhead*), as shown in Figure 1.

Definition of PEP

We used the following consensus guideline criteria (Cotton classification) to define the diagnosis and severity of PEP [12]: new or worsening abdominal pain continuing for at least 24 hours after ERCP in conjunction with increased serum amylase levels greater than 3-times the normal upper limit. We performed CT for all patients suspected of having pancreatitis to confirm the diagnosis radiologically.

Study outcomes

The primary objective was to assess the relationship between PEP risk after SEMS insertion across the papilla of Vater and the thickness of the pancreatic parenchyma or diameter of the MPD on CT before SEMS insertion. The secondary objectives were (1) to define thresholds of the PEP risk related to the thickness of the pancreatic parenchyma and diameter of the MPD using receiver operating characteristics (ROC), and (2) to compare serum amylase levels before and after SEMS insertion between patients with/without PEP.

Statistical analysis

We used the frequency, percentages, means (±SD) and medians for analysis. The Mann-Whitney U test, Fisher's exact test and chi-square test were used to compare categorical variables. Welch's t test was used to compare continuous variables. The Cochran-Armitage test for trends was used to compare the trend of continuous variables.

We considered a two-tailed P-value<0.05 significant. The thickness of the pancreatic parenchyma and diameter of the MPD were plotted on a ROC curve. The area under the ROC curve (AUC) and the most appropriate cut-off points were calculated to classify pancreatic parenchyma atrophy and dilated or patent MPD. The most appropriate cut-off values were established as those with the highest sum of sensitivity and specificity.

The logistic regression model was used to calculate the adjusted odds ratio (OR) with the 95% confidence interval (CI) for risks of PEP associated with factors. The multivariate logistic regression model was performed with adjustments for potential confounding factors that were significantly different by single variable analysis, as listed in Table 1.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R

Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [13].

Results

Clinical characteristics

We identified 204 patients who underwent biliary SEMS insertion for MBO at Iwata City Hospital between 2010 and 2018. After excluding 114 patients, 90 patients were included in the current analysis.

Pancreatitis related to SEMS insertion across the papilla of Vater developed in 11 of 90 patients (12.2%). Mild and severe PEP were diagnosed in 10 (11.1%) and one (1.1%) patient, respectively. The clinical characteristics are summarized in Table 1. The etiology of MBO was pancreatic cancer in 60 (67%), cholangiocarcinoma in 13 (14%), metastatic lymph node in 10 (11%) and ampullary cancer in seven (7.8%). Covered, partially covered and uncovered SEMS were inserted in 76 (84%), eight (8.9%) and six (6.7%) patients, respectively. The Wallflex was used in all patients (Microvasive Endoscopy; Boston Scientific Corp., MA,

USA). EST was implemented in 80 (89%). Pancreatic duct injections were required in nine (10%).

The distribution of patients with/without PEP clarified relationships with the thickness of the pancreatic parenchyma ($p<0.001$) and diameter of the MPD ($p<0.001$), and statistics by the Cochran-Armitage test for trends were collected (Figure 2). Only the thickness of the pancreatic parenchyma (14.50 mm [9.50, 24.0] vs 6.0 mm [1.00, 30.0], $p<0.001$), diameter of the MPD (2.5 mm [1.0, 5.0] vs 7.0 mm [2.50, 27.0], $p<0.001$) and incidence of pancreatic cancer (69.6% vs 36.4%, $p=0.04$) significantly differed between the PEP and non-PEP groups. There was no significant difference related to the incidence of PEP in the other factors: age, sex, etiology, staging, stent type, pre P-amylase, EST, pacreatography, NSAID use and pancreatic stenting. Logistic regression analysis of the factors to prevent PEP after SEMS insertion is shown in Table 2. As shown in Table 2, the diameter of the MPD (OR 3.91, 95% CI 1.23-12.4, $p=0.02$) was independently associated with the prevention of PEP. Thus, expansion of the MPD by 1 mm led to a decrease in the rate of pancreatitis by 3.91-times.

Next, we defined pancreatic parenchyma atrophy as a thickness of less than 9.5 mm (Figure 3A, AUC=0.8913) and dilated MPD as an MPD diameter wider than 4.0 mm

(Figure 3B, AUC=0.9396) by ROC curves.

Changes in the serum amylase levels and incidence of PEP after transpapillary SEMS insertion in patients with or without pancreatic parenchyma atrophy and a dilated MPD are summarized in Table 3. The incidences of PEP and an increased serum amylase level after SEMS insertion were significantly lower in patients with pancreatic parenchyma atrophy than in those without atrophy (0.0% vs 34.4%, $p<0.001$, and 279.6±477.5 vs 907.0±1343.7, $p<0.001$, respectively). Similarly, the incidences of PEP and an increased serum amylase level after SEMS insertion were significantly lower in patients with a dilated MPD than in those with a patent MPD (4.3% vs 40.0%, $p<0.001$, and 285.3±477.5 vs 1264.0±1505.5, $p<0.001$, respectively) (Table 3). Furthermore, the incidence of PEP after SEMS insertion was high (50%, 8/16 patients) in patients without atrophy and a patent MPD.

Pancreatic duct injections were not significantly related to the incidence of PEP, whereas the incidence of PEP after SEMS insertion with pancreatic duct injections was high in patients without atrophy (50%, 2/4 patients) and a patent MPD (50%, 1/2 patients).

We next compared the thickness of the pancreatic parenchyma (5.50 [1.00, 30.00] vs 8.00 [1.50, 24.00], $p=0.054$) and diameter of the MPD (7.00 [2.60, 27.00] vs 5.00 [1.00, 13.50], $p<0.001$) between patients with and without pancreatic cancer. The thickness of the

pancreatic parenchyma and diameter of the MPD were also different between the PEP and non-PEP groups. In the pancreatic cancer group, the thickness of the pancreatic parenchyma (14.3 mm [13.8, 15.1] vs 5.5 mm [3.0, 8.5], p=0.008) and diameter of the MPD (4.0 mm [3.7, 4.3] vs 7.0 mm [5.9, 9.5], p=0.009) significantly differed between the PEP and non-PEP groups. In the no pancreatic cancer group, the thickness of the pancreatic parenchyma (15.5 mm [9.5, 24.0] vs 7.3 mm [1.5, 15.0], p=0.002) and diameter of the MPD (2.0 mm [1.0, 2.6] vs 5.5 mm [2.5, 13.5], p<0.001) significantly differed between the PEP and non-PEP groups.

Discussion

In this study, pancreatitis related to SEMS insertion improved after conventional treatments. However, in previous case reports, several patients died due to severe PEP related to SEMS insertion across the papilla of Vater [10]. Therefore, the risks and benefits of SEMS insertion should be considered.

In previous studies, pancreatic cancer and EST were reported as protective factors against PEP after SEMS insertion [4]. In contrast, non-pancreatic cancer, pancreatic duct injection and SEMS inserted with a high axial force were reported as risk factors [8,9,11].

In the present study, pancreatic cancer was negatively related to PEP; however,

EST exhibited no significant relationship with PEP. The Wallflex SEMS was used in all patients in the present study, and no significant difference in the incidence of PEP between covered and uncovered types [3,5,14] or between a SEMS diameter of 8 mm and 10 mm was noted [15]. Thus, we excluded PEP risk factors related to the differences in stent type.

In previous reports, pancreatic parenchyma atrophy was a predictor of PEP [16], the incidence of PEP was only 0.5-3.4% after inserting a SEMS to treat biliary stricture in chronic pancreatitis [17,18] and pancreatic parenchyma atrophy/dilated MPD reduced the incidence of acute pancreatitis after percutaneous biliary SEMS placement across the papilla of Vater [19]. Pancreatic parenchyma atrophy was reported to reduce pancreas exocrine function [20], and the diameter and volume of pancreatic parenchyma were directly related [16]. Therefore, we measured the diameter of the pancreatic parenchyma due to its ease in clinical practice.

Although sudden pancreatic duct occlusion due to SEMS insertion is a major risk factor for PEP [10], only one report described the diameter of the MPD before SEMS insertion [4]. We therefore measured the diameter of the MPD in this study. The thickness of the pancreatic parenchyma and diameter of the MPD were measured in the pancreatic body on CT.

The thickness of the pancreatic parenchyma and diameter of the MPD were significantly different between the PEP and non-PEP groups. We defined pancreatic parenchyma atrophy as <9.5 mm and a dilated MPD as ≥4.0 mm. In each group, the incidences of PEP significantly differed; therefore, pancreatic parenchyma atrophy and a dilated MPD may be predictors of PEP after SEMS insertion across the papilla of Vater.

We separated pancreatic cancer and non-pancreatic cancer, and the thickness of the pancreatic parenchyma and diameter of the MPD significantly differed between the PEP and non-PEP groups. Furthermore, the thickness of the pancreatic parenchyma and diameter of the MPD were more atrophied and dilated, respectively, in the pancreatic cancer group than in the non-pancreatic cancer group. Based on the above, pancreatic parenchyma atrophy and a dilated MPD may be more important predictors than the presence of pancreatic cancer. Indeed, logistic regression analysis demonstrated the diameter of the MPD (OR 3.91, 95% CI 1.23-12.4) to be independently associated with the prevention of PEP.

The present study has several limitations. First, it was a retrospective observational study. Second, as our hospital is not a high-volume center, there were no experts who performed more than 200 ERCP procedures per year. Third, all patients were treated using a Wallflex SEMS, which has a high axial force, increasing the risk of PEP.

Fourth, there are many risk factors for pancreatitis and we were unable to consider them all. For example, we did not prescribe NSAIDs to prevent PEP. In addition, some important factors of the ERCP procedure for PEP were not recorded fully and unavailable in the present study. Lastly, further studies are needed to confirm the results of the present study.

SEMS insertion for MBO was reported to be superior to plastic stent insertion regarding patency and cost performance, although we should consider their risks and benefits before insertion in all cases. Graphical evaluation before ERCP can help in deciding the drainage procedure for MBO.

Figure Legends

Table 1. Characteristics of patients in the present study: PanCa, pancreatic cancer; MPD, main pancreatic duct; P-Amy, pancreatic amylase; PEP, post-ERCP pancreatitis; EST, endoscopic sphincterotomy; NSAIDs, non-steroidal anti-inflammatory drugs

Table 2. Results of multivariate analysis of factors to prevent PEP: PEP: post-ERCP pancreatitis, OR: odds ratio, CI: confidence interval, MPD: main pancreatic duct

Table 3. Serum amylase levels pre- and post-ERCP: Pre-Amy, pre-ERCP serum amylase level; Post-Amy, post-ERCP serum amylase level

Figure 1. Measurement of the pancreas: The thickness of the pancreatic parenchyma and diameter of the MPD were measured at the left side of the corpus vertebrae on CT. The thickness of the pancreatic parenchyma was calculated as the diameter of the MPD (*white double arrow*) subtracted from the diameter of the pancreas (*white double arrowhead*).

Figure 2. The distribution of patients demonstrating that pancreatic atrophy ($p<0.001$) and MPD dilation ($p<0.001$) are inversely related to PEP.

Figure 3. Receiver operating characteristics curve to predict pancreatic atrophy (A) and dilated MPD (B) after PEP. We defined pancreatic atrophy as a pancreatic parenchyma thinner than 9.5 mm and a dilated MPD as a MPD diameter of 4 mm or wider. The incidence of PEP in the atrophy group (0.0%) was lower than that in the non-atrophy group (34.4%) ($p<0.001$). Similarly, the dilated MPD group (4.3%) had a lower incidence of PEP than the patent MPD group (40.0%) ($p<0.001$). The data are rates of PEP ± SD.

Conflict of interest statement: There are no conflicts of interest to declare.

Funding: No financial support related to this article was received

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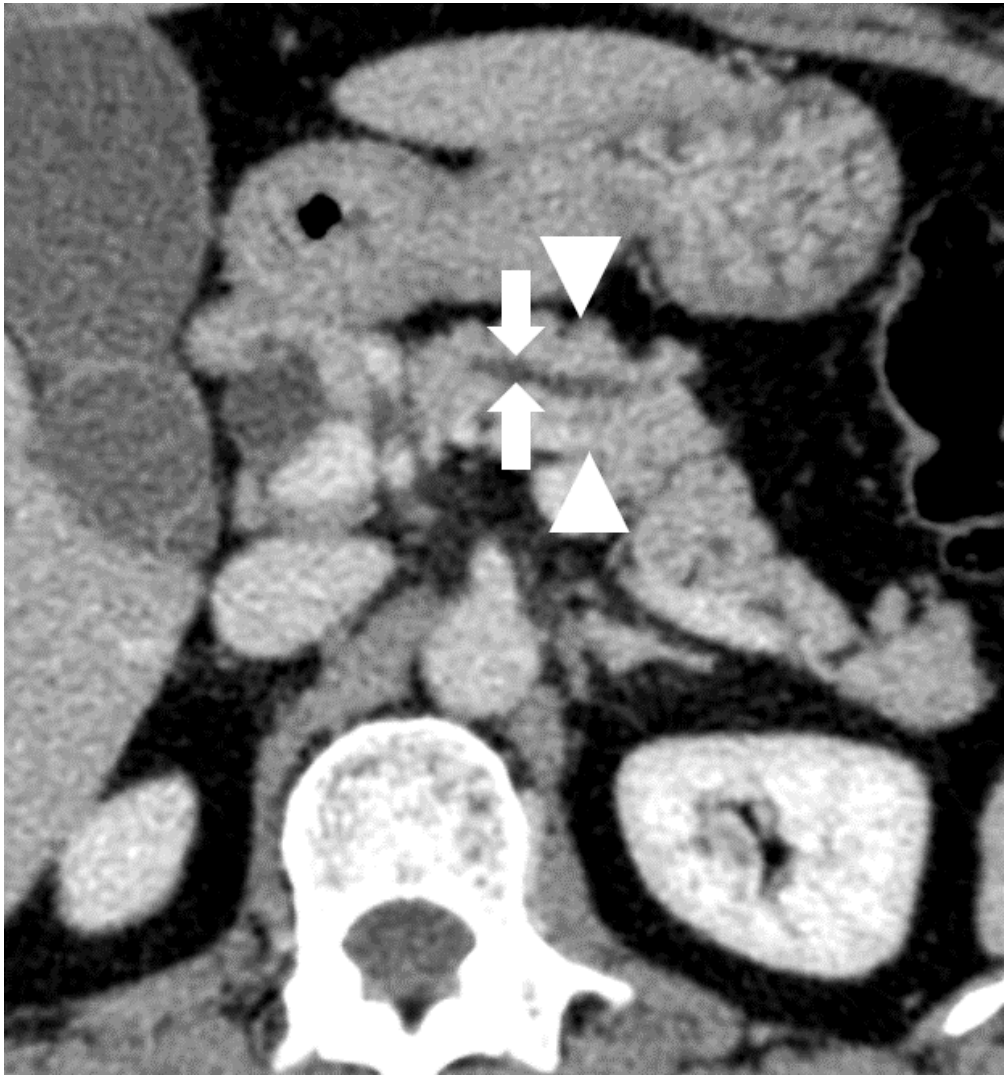
	Non-PEP (n=79)	PEP (n=11)	P
Age years, medium	78 (44-98)	82 (61-92)	= 0.74
Sex (male : female)	40 (50.6%) : 39 (49.4%)	5 (45.5%) : 6 (54.5%)	= 1
Etiology (PanCa : Other)	55 (69.6%) : 24 (30.4%)	4 (36.4%) : 7 (63.6%)	= 0.04
Stage II : III : IV	1 : 13: 46	0 : 4 : 7	= 0.22
Stent			= 1
Fully covered	66 (83.5%)	10 (90.9%)	
Partially covered	7 (8.9%)	1 (9.1%)	
Uncovered	6 (7.6%)	0	
Thickness of the pancreatic parenchyma (mm)	6.0 mm [1.00, 30.0]	14.50 mm [9.50, 24.0]	<0.001
Diameter of the MPD (mm)	7.0 mm [2.50, 27.0]	2.5 mm [1.0, 5.0]	<0.001
Pre-P-Amy (U/ml)	93.4	113.6	= 0.58
EST (with : without)	70 (88.6%) : 9 (11.4%)	10 (90.9%) : 1 (9.1%)	= 0.82
Pancreatography	72 (91.1%) : 7 (8.9%)	9 (81.8%) : 2 (18.2%)	= 0.30
NSAIDs	0	0	= 1
Pancreatic stenting	0	0	= 1

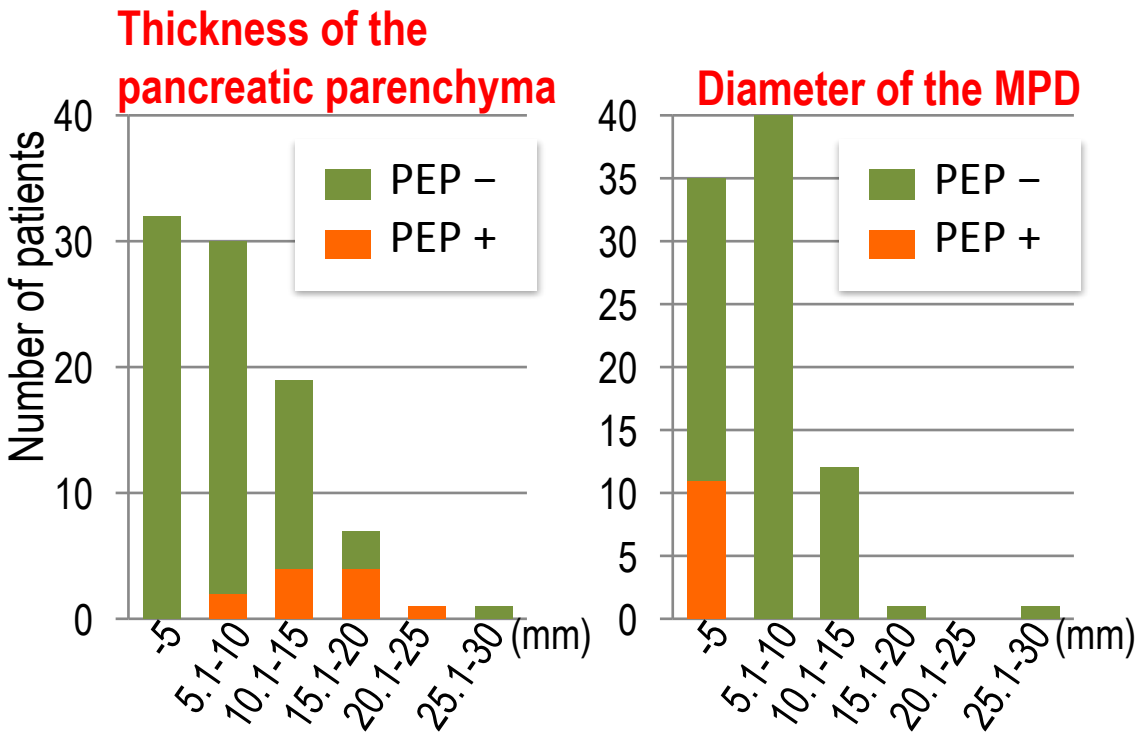
Table 2

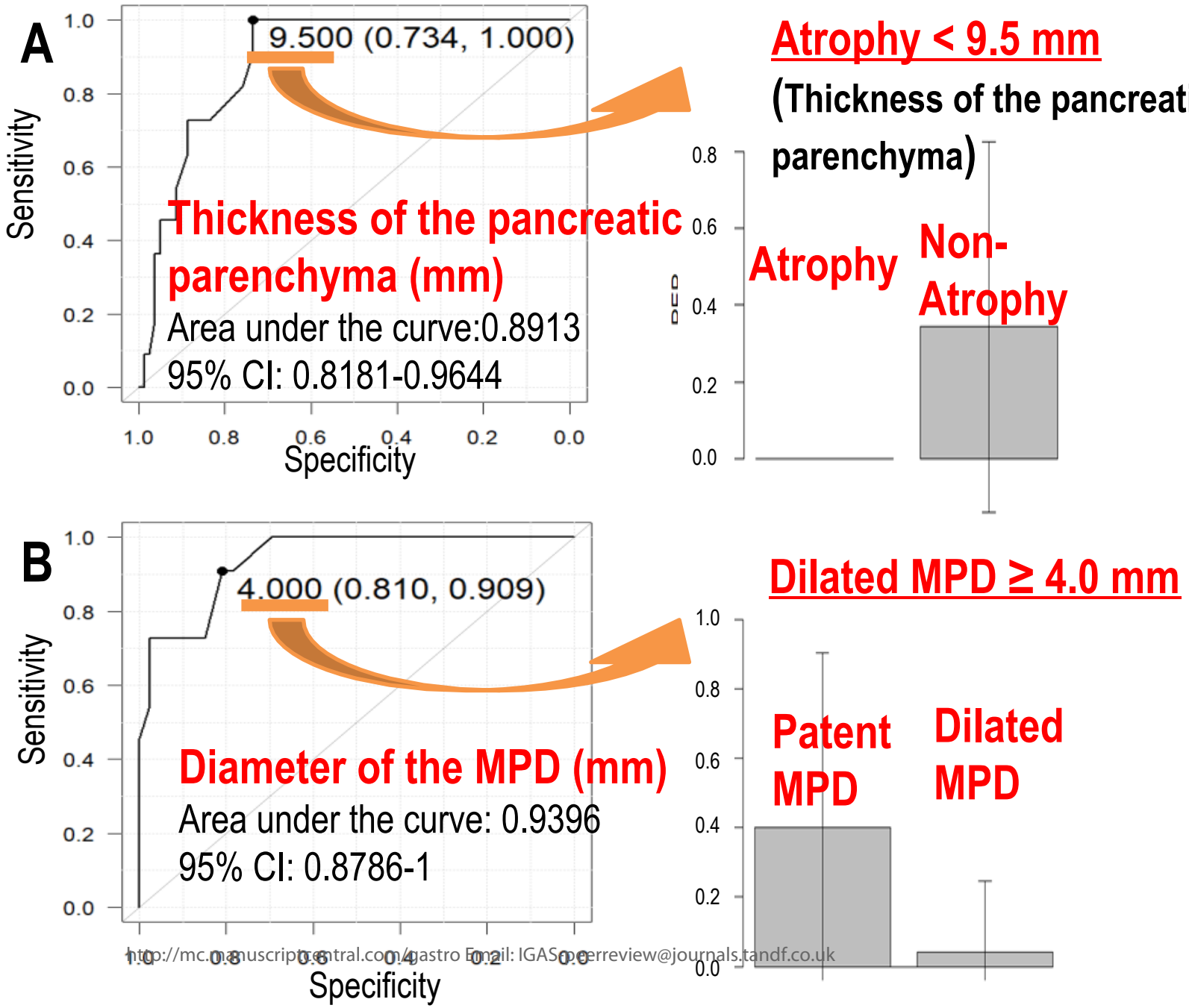
Variable	OR	95% CI	P
Pancreatic cancer	1.64	0.16-16.4	= 0.68
Thickness of the pancreatic parenchyma (mm)	0.94	0.79-1.11	= 0.47
Diameter of the MPD (mm)	3.91	1.23-12.4	= 0.02

	Pre-Amy	P	Post-Amy	P	PEP +	P
Parenchyma	(mean±SD, U/L)		(mean±SD, U/L)		(%)	
Atrophy – (n=58)	123.0±117.8	0.08	907.0±1343.7	<0.001	34.4	<0.001
Atrophy + (n=32)	80.5±98.0		279.6±477.5		0.0	
MPD	(mean±SD, U/L)		(mean±SD, U/L)		(%)	
Patent (n=20)	115.5±104.7	0.37	1264.0±1505.5	<0.001	40.0	<0.001
Dilated (n=70)	90.0±107/6		285.3±477.5		4.3	

Figure 1




Thickness of the pancreatic parenchyma
Number of patients
40
30
20
10
0
PEP –
PEP +
-5
5.1-10
10.1-15
15.1-20
20.1-25
25.1-30
(mm)
Diameter of the MPD
40
35
30
25
20
15
10
5
0
PEP –
PEP +
-5
5.1-10
10.1-15
15.1-20
20.1-25
25.1-30
(mm)


A
9.500 (0.734, 1.000)
Sensitivity
Specificity
Thickness of the pancreatic parenchyma (mm)
Area under the curve:0.8913
95% CI: 0.8181-0.9644
Atrophy < 9.5 mm
(Thickness of the pancreati
parenchyma)
Atrophy
Non-Atrophy
B
4.000 (0.810, 0.909)
Diameter of the MPD (mm)
Area under the curve: 0.9396
95% CI: 0.8786-1
Dilated MPD ≥ 4.0 mm
Patent MPD
Dilated MPD

Dear Prof. Reidar Fossmark,
Scandinavian Journal of Gastroenterology

We wish to resubmit our manuscript, which has been revised based on the reviewer's comments. We also wish to thank the reviewer for the helpful comments, which have helped to significantly improve our manuscript. Part of the manuscript has been revised and displayed in blue. Included below are point-by-point responses to clarify each of the revisions made to our manuscript.

- Describe more exactly the patient selection. Were the 90 patients that were included all patients that fit in- and exclusion criteria? In other words: were these all patients treated at the institution in this time period (consecutive patients)?

Response: We revised the sentences and added how to identified and excluded patients in this study. (P9, L7-9)

- One important (possible) factor is missing completely in results, methods and discussion which is the (biliary) sphincterotomy. Could the authors provide these data, analyze and discuss them?

Response: We revised the sentences and mentioned EST procedure. (P10, L9-11; P12, L16- P13, L12)
We revised and added EST as an item in Table1.

- Results and discussion could be more concise

Response: We removed some repeated expressions in the discussion part.

Sincerely yours,
Takanori Yamada

==========

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