Prediction of pancreatic fistula after pancreatoduodenectomy by preoperative dynamic computed tomographic imaging and fecal elastase-1 levels

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Prediction of pancreatic fistula after pancreatoduodenectomy by preoperative dynamic computed tomographic imaging and fecal elastase-1 levels

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The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

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December 2015

This certifies that the Master's Thesis
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December 2015

ACKNOWLEDGEMENTS

I would like to thank to professor Jeong-Sik Yu, Department of Radiology, Gangnam Severance hospital for the invaluable guidance and enthusiastic support. I am also very grateful to professor Se Joon Lee and professor Joon Seong Park, thesis committee members for sincere advice. As a radiology fellow in Gangnam Severance hospital, I wish to express my gratitude to every professor in the department.

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ABSTRACT

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Objective:

The aim of this study was to evaluate the stand-alone and combined abilities of preoperative dynamic computed tomography (CT) and fecal elastase-1 levels to predict the developement of pancreatic fistulae after pancreatoduodenectomy.

Materials and Methods:

For 146 consecutive patients from January 2006 to March 2015, the preoperative dynamic CT images and medical records of the preoperative fecal elastase-1 levels and postoperative pancreatic fistulae (POPF) were reviewed. The CT attenuation values were measured on the unenhanced images (P) and images obtained in the arterial (A) and equilibrium phases (E) after contrast administration. The three CT enhancement ratios were calculated as (A - P)/P, (E - P)/P and (E - P)/(A - P). The correlation of the CT enhancement ratios and preoperative fecal elastase-1 levels with the development of POPF was performed using the independent two-sample *t*-test, logistic regression models, receiver operating characteristic (ROC) curve analysis and Youden method. The

combined ability of the CT and fecal elastase-1 level findings for the prediction of POPF developement was assessed by ROC comparison and tree analysis.

Results:

The mean values of (E - P)/P and (E - P)/(A - P) were significantly higher among the patients without POPF (n = 107) than among the patients with POPF (n = 39) (2.256 ± 3.633 vs. 1.038 ± 0.508; *P* = 0.001 and 1.116 ± 1.395 vs. 0.713 ± 0.294; *P* = 0.006, respectively). In the logistic regression analyses, (E - P)/P and (E - P)/(A - P) were significant predictors for the development of pancreatic fistulae (odds ratio [OR] = 0.243, *P* = 0.002 and OR = 0.176, *P* = 0.014, respectively). The mean preoperative fecal elastase-1 levels were higher (OR = 1.003, *P* = 0.034) in the POPF group than in the non-POPF group. In the ROC comparison, there were no significant differences in the areas under the curve (AUC) between the prediction values of CT enhancement ratios and fecal elastase-1 combined and those of CT enhancement ratios alone (*P* = 0.897, *P* = 0.917). Tree analysis revealed that the CT enhancement ratios of the equilibrium phase were more powerful and effective predictors of POPF than the fecal elastase-1 levels.

Conclusion:

The CT enhancement ratios of the equilibrium phase and the preoperative fecal elastase-1 levels might be useful predictors of the risk of developing a pancreatic fistula following pancreatoduodenectomy. Furthermore, CT enhancement ratios of the equilibrium phase alone could be powerful enough to predict the pancreatic fistula.

Key words : CT attenuation; Pancreas; Fibrosis; Fistula; Pancreatoduodenectomy

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I. INTRODUCTION

The rate of mortality following pancreatoduodenectomy (PD), with or without pylorus preservation, has significantly declined over the last decades.[1,2] However, the post-PD morbidity rate is still high (30 - 60%).[1-4] Postoperative pancreatic fistula (POPF) following PD is the main cause for post-PD morbidity, and results in longer hospital stays, increased costs of hospitalization and treatment, or even death.[5-8] Therefore, identifying patients at high risk for POPF is important for decreasing the post-PD morbidity and improving the clinical outcome. In previous studies, several factors including a soft pancreas, pancreatic duct size, fatty pancreas and obesity were recognized as the risk factors for POPF.[5-11] Of these factors, the presence of a 'soft' or 'normal' pancreatic texture is the most widely accepted risk factor for developing a pancreatic fistula following PD.[5,9,12] On the other hand, pancreatic fibrosis with a 'firm' or 'hard' pancreatic texture is thought to decrease the risk of POPF. Previous studies have reported that the

rate of POPF is low in the fibrotic pancreases with firm parenchyma.[9-11,13]

Therefore, the preoperative assessment of pancreatic fibrosis might be helpful not only in predicting the development of pancreatic fistulae after PD, but also in preoperative patient counseling and postoperative management. Thus far, only a few studies have evaluated whether the degree of pancreatic fibrosis can be reliably estimated and quantified radiologically.[14-18] On dynamic computed tomography (CT) or magnetic resonance (MR) images, a fibrotic pancreas with autoimmune pancreatitis or chronic pancreatitis shows delayed enhancement with a slow increase followed by a slow decline or a plateau, whereas a normal soft pancreas shows rapid enhancement and a rapid decrease.[14-18] On the other hand, the normal exocrine pancreatic function of the 'soft' pancreatic tissue, as compared to that of the 'hard' fibrotic pancreatic tissue in patients with chronic pancreatitis, has been reported as one of the risk factors for POPF.[19,20]

Fecal elastase-1 is a pancreas-specific enzyme and has been proposed as a suitable marker for pancreatic insufficiency.[21-23] Fecal elastase-1 is not degraded during intestinal transport and reaches concentrations in feces 5–6 times those in the duodenal juice. Concentrations of elastase-1 greater than 200μg/g stool indicate normal exocrine pancreatic function and those ≤200μg/g stool suggest exocrine pancreatic insufficiency.[22]

We hypothesized that the equilibrium-phase dynamic CT images, which can better reveal parenchymal fibrosis than those acquired at the earlier phases, and the combined evaluation of the preoperative CT data and fecal elastase-1 levels could provide more accurate information for predicting the development of POPF. The aim of this study was

to evaluate the stand-alone and combined abilities of preoperative dynamic CT and fecal elastase-1 levels to predict the development of pancreatic fistulae after pancreatoduodenectomy.

II. MATERIALS AND METHODS

1. Patients and Clinical Data Collection

This retrospective study was approved by the institutional review board for clinical studies, and the requirement for informed patient consent was waived. We identified 347 consecutive patients who underwent PD with or without pylorus preserving surgery between January 2006 and March 2015. Of the 347 patients, 155 had undergone preoperative dynamic CT. Two of the patients without enough pancreatic parenchyma to indicate the region of interest (ROI), which was of at least 3-mm diameter on the CT images, were excluded later during the review process. Of the remaining patients, 146 patients with medical records of POPF were recruited for this study. 73 of the 146 patients had medical records of their preoperative fecal elastase-1 levels.

2. Definition of Postoperative Pancreatic Fistula

Postoperative pancreatic fistula was defined and classified according to the definition of the International Study Group on Pancreatic Fistula (ISGPF).[24] A grade A fistula is transient and asymptomatic, evident only by elevated drain amylase levels. A grade B leakage necessitates changes in patient management or adjustments in the clinical treatment plan, including the introduction of antibiotic therapy, supplemental nutrition,

somatostatin analogs, and percutaneous drainage. A grade C fistula is the most severe and necessitates major deviations in the clinical management. Furthermore, a grade C fistula might result in sepsis, organ dysfunction, and even death and may require surgical exploration for definitive management. For the purpose of this study, the patients were divided into two groups: non- POPF group and POPF group (grade A, B, or C).

3. CT Protocol

Preoperative dynamic CT was performed using one of two scanners: a 16-slice multidetector CT (MDCT) scanner (Somatom Sensation 16, Siemens Medical Solutions, Erlangen, Germany), or a 64-slice MDCT scanner (Somatom Sensation 64, Siemens Medical Solutions, Erlangen, Germany).

All the patients were instructed to fast for at least 5 hours before they underwent CT examination. Each patient was administered 150 mL of a nonionic contrast material (Ultravist 300, Schering AG, Berlin, Germany) intravenously by means of a power injector (EnVision CT, Medrad, Pittsburgh, Pa) at a rate of 3 mL/second. The CT images were acquired in a craniocaudal direction with the following parameters: detector collimation , 16 × 0.75 mm; table feed, 12 mm per rotation; section width, 3 mm; reconstruction increment, 3 mm with 3-mm-thick sections; pitch, 1.2; tube voltage, 120 kVp; and tube current, 160 mAs. Unenhanced scanning (i.e., the first pass) was performed first, followed by contrast-enhanced CT. In order to determine the time of peak aortic enhancement, a bolus injection of 20 mL of contrast material was administered, and sequential dynamic sections were acquired every 2 seconds, starting from the hepatic

hilum. Based on the findings of a previous study on multidetector row helical CT, we calculated the start time for the arterial phase (i.e., the second pass) by adding 15 seconds to the time of peak aortic enhancement calculated at the hepatic hilum. The ensuing average start time for the arterial phase was 34 seconds (range, 30–38 seconds). The portal venous phase scan was acquired at 70 seconds after the start of the contrast material injection. The equilibrium phase scan was acquired at 3 minutes after the start of the contrast material injection. Since our institute was a tertiary referral hospital, and there were many patients referred here from other institutes, our study included 60 CT images acquired at other hospitals using non-unified dynamic imaging protocols.

4. CT Evaluation

Two radiologists, blinded to the patients' clinical data, analyzed the preoperative CT images. The CT attenuation values of the pancreatic parenchyma were measured on the unenhanced images and the images obtained in the arterial and equilibrium phases after contrast administration, by placing the region of interest (ROI) in the pancreas over the superior mesenteric vein in an area unaffected by the tumor. The largest possible circular or oval ROI was placed with every effort to avoid the pancreatic mass, pancreatic duct, and partial volume averaging from the extrapancreatic structures. The smallest ROI was approximately 3 mm in diameter in cases where the pancreatic parenchyma was atrophic. The mean value of the CT attenuations were calculated, and the three attenuation parameters were calculated as follows: (arterial phase(A) - unenhanced phase(P))/unenhanced phase(P), (equilibrium phase(E) - unenhanced

phase(P))/unenhanced phase(P) and (equilibrium phase(E) - unenhanced phase(P))/(arterial phase(A) - unenhanced phase(P)).

5. Fecal Elastase-1 Measurement

The fecal elastase-1 test was performed to assess exocrine pancreatic function. All of the samples were collected 4 days preoperatively. The fecal elastase-1 concentrations were measured using a commercially available enzyme-linked immunoassay (ELISA) kit (Schebo Biotech AG, Giessen, Germany).

6. Statistical Analysis

The mean CT attenuation values and fecal elastase-1 levels of the patients with POPF (grade A, B, or C) and those of the patients without POPF were compared using the independent two-sample *t*-test. Logistic regression models were used to evaluate the risk factors for the development of POPF for univariate analysis. To evaluate the efficacy of the risk factors in the prediction of POPF development and to establish the optimal cut-off points, the receiver operating characteristic (ROC) curve and Youden analyses were performed. The ROC comparison was performed to compare the ability of the clinical cut-off value of fecal elastase-1 to discriminate the POPF from non-POPF cases with that of the cut-off value obtained using the Youden method. For the combined assessment of the ability of the CT and fecal elastase-1 findings to predict POPF development, the ROC comparison and tree analysis were performed. A P-value < 0.05 was considered statistically significant. All of the statistical calculations were performed using the SAS

software (release 9.2; SAS Institute Inc., Cary, NC, USA).

III. RESULTS

1. Patients Population and Outcomes

Of the 146 patients, 82 (56%) were male and 64 (44%) were female; the mean age of the patient population was 62 years. 15 patients had benign diseases (intraductal papillary mucinous neoplasm, 9; solid pseudopapillary tumor, 2; benign neuroendocrine tumor, 1; serous cystadenoma, 1; chronic pancreatitis, 1; and choledochal cyst, 1), and 131 patients had malignant diseases (malignant pancreatic diseases, 45; common bile duct cancer, 45; ampullary cancer, 40; and duodenal cancer, 1). Based on the ISGPF definition, 39 (26.7%) of the patients presented POPF (grade A, 26; grade B, 9; and grade C, 4); theses patients constituted the POPF group for this study and the rest of the patients (n = 107; 73.3%) made up the non-POPF group.

2. CT Assessment

The mean values of (A - P)/P show a decreasing trend with the increase in the grade of POPF (Table 1). The mean values of (E - P)/P and (E - P)/(A - P) also show a decreasing trend with the increase in the grade of POPF (Table 1).

Table 1. Mean values of the three CT attenuation ratios according to the POPF grade.

Calculated parameters	Non-POPF (n = 107)	Grade A POPF (n = 26)	Grade B POPF (n = 9)	Grade C POPF (n = 4)	Mean values
(A - P)/P	2.08 ± 1.534	1.555 ± 0.796	1.589 ± 0.473	1.242 ± 0.325	1.933 ± 1.381
(E - P)/P	2.256 ± 3.633	1.02 ± 0.548	1.186 ± 0.47	0.821 ± 0.202	1.93 ± 3.163
(E - P)/(A - P)	1.116 ± 1.395	0.698 ± 0.298	0.774 ± 0.349	0.669 ± 0.109	1.009 ± 1.216

A, arterial phase; P, unenhanced phase; E, equilibrium phase.

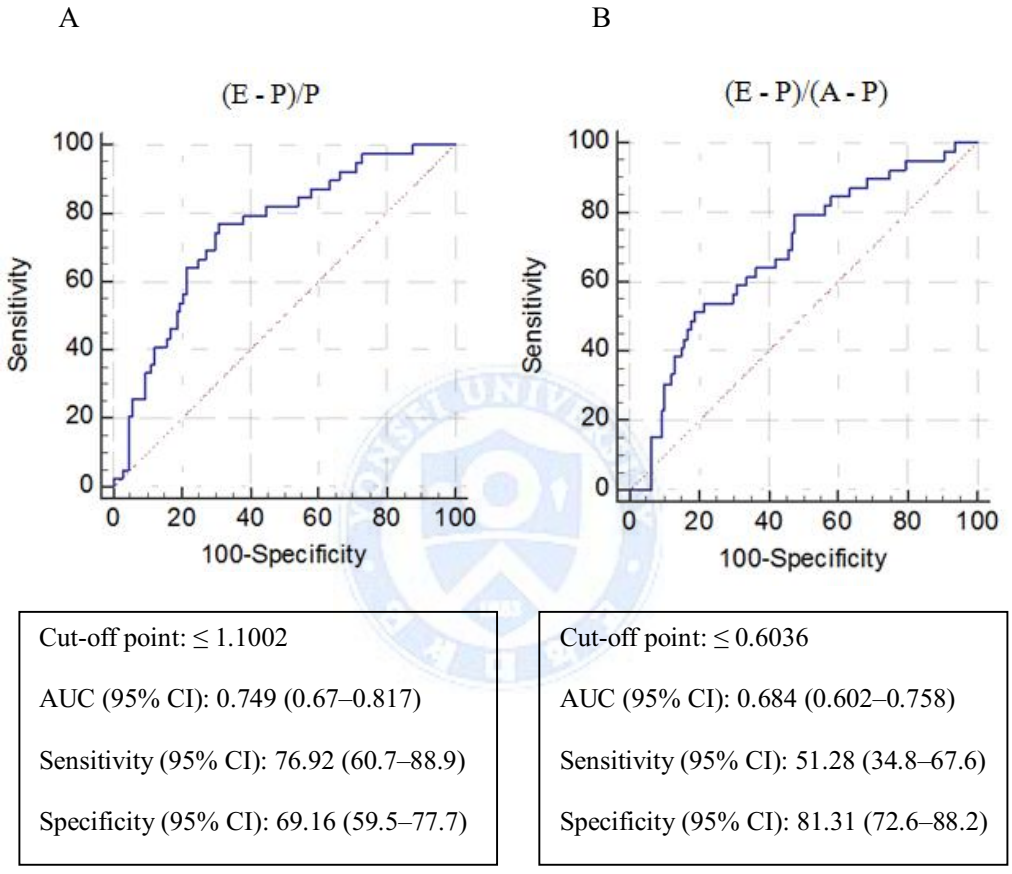
In the non-POPF group, the pancreas showed delayed enhancement compared to the pancreatic enhancement pattern seen in the POPF group. Therefore, the mean values of (E - P)/P and (E - P)/(A - P) of the non-POPF group were significantly higher than those of the POPF group (2.256 ± 3.633 vs. 1.038 ± 0.508; $P = 0.001$ and 1.116 ± 1.395 vs. 0.713 ± 0.294; $P = 0.006$, respectively). In logistic regression analyses, the values of (E - P)/P and (E - P)/(A - P) were found to be significant predictors for the development of pancreatic fistula (odds ratio (OR) = 0.243, $P = 0.002$ and OR = 0.176, $P = 0.014$, respectively).

The optimal cut-off point of (E - P)/P for the discrimination of the patients developing POPF from those without PAF was determined to be 1.1002 (areas under the curve (AUC), 0.749; sensitivity, 76.92%; and specificity, 69.16%) and that of (E - P)/(A - P) was determined to be 0.6036 (AUC, 0.684; sensitivity, 51.28%; and specificity, 81.31%) (Fig. 1).

Fig. 1—Receiver operating characteristic (ROC) curve of the CT attenuation ratios.

A. CT attenuation ratio calculated as (E - P)/P

B. CT attenuation ratio calculated as (E - P)/(A - P)



Cut-off point: ≤ 1.1002	Cut-off point: ≤ 0.6036
AUC (95% CI): 0.749 (0.67–0.817)	AUC (95% CI): 0.684 (0.602–0.758)
Sensitivity (95% CI): 76.92 (60.7–88.9)	Sensitivity (95% CI): 51.28 (34.8–67.6)
Specificity (95% CI): 69.16 (59.5–77.7)	Specificity (95% CI): 81.31 (72.6–88.2)

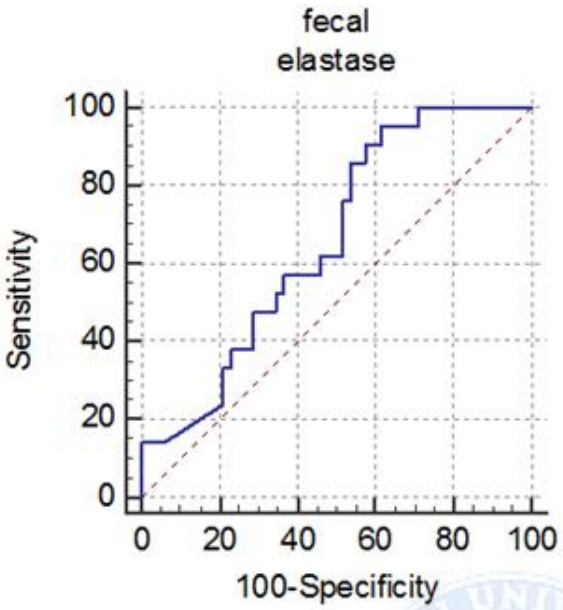
CT, computed tomography; CI, confidence interval; AUC, areas under the curve;

E, equilibrium phase; P, unenhanced phase; A, arterial phase

3. Fecal Elastase-1 Assessment

Of the 73 patients whose records of preoperative fecal elastase-1 levels were available, 21 (28.8%) developed POPF (grade A, 15; grade B, 4; and grade C, 2). The non-POPF group was composed of the remaining 52 patients. The mean preoperative fecal elastase-1 level of the POPF group was significantly higher than that of the non-POPF group (359.44 vs. 252.03; P = 0.029). In the logistic regression analyses, fecal elastase-1 was a marginally meaningful predictive factor of pancreatic fistula (OR = 1.003, P = 0.034). According to the ROC curve and Youden analyses, the AUC was 0.657 (95% CI, 0.536–0.764) and the optimal cut-off point for the discrimination of the patients with POPF from those without POPF was 120.1 (sensitivity, 95.24%; specificity, 38.46%) (Fig. 2).

Fig. 2—ROC curve of the fecal elastase-1 levels.



Cut-off point: > 120.1

AUC (95% CI): 0.657 (0.536–0.764)

Sensitivity (95% CI): 95.24 (76.2–99.9)

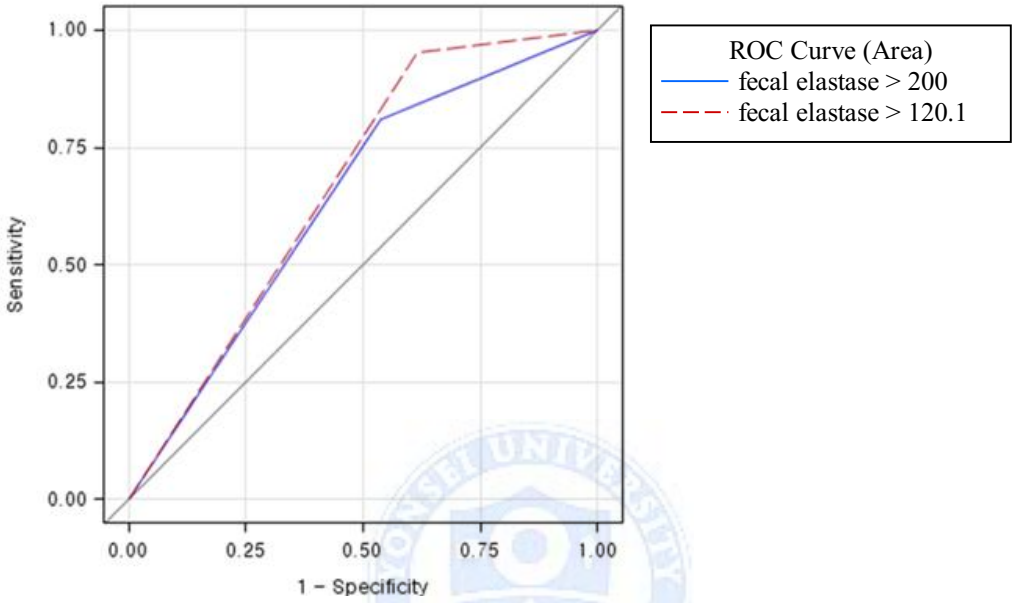
Specificity (95% CI): 38.46 (25.3–53)

ROC, receiver operating characteristic; AUC, areas under the curve; CI, confidence interval

Clinically, fecal elastase-1 values greater than 200μg/g stool indicate normal exocrine pancreatic function and those ≤ 200μg/g stool suggest exocrine pancreatic insufficiency.[22] In the ROC comparison of the ability of the clinical cut-off value (200μg/g stool) and that of the cut-off value obtained using the Youden method

(120.1μg/g stool), to discriminate the patients with POPF from those without, the value of AUC was slightly higher when the cut-off point was 120.1 μg/g stool; however, there was no statistically significant difference between the predictive abilities of the two (AUC = 0.669 for cut-off point = 120.1μg/g stool; AUC = 0.636 for cut-off point = 200μg/g stool; $P = 0.447$) (Fig. 3).

Fig. 3—ROC curve for the comparison of the fecal elastase-1 levels at the cut-off points of 120.1μg/g stool and 200 μg/g stool.



Cut- off point	AUC (95% CI)	*P*-value
Fecal elastase > 200	0.636 (0.526–0.746)	0.447
Fecal elastase > 120.1	0.669 (0.587–0.75)	

ROC, receiver operating characteristic; AUC, areas under the curve; CI, confidence interval

4. Combined Assessment with CT enhancement ratios and Fecal elastase-1 levels

Of the 73 patients with available preoperative dynamic CT and fecal elastase-1 level records, the AUC values of the stand-alone CT enhancement ratios were slightly higher than those of the combination of the CT enahancement ratios and fecal elastase-1 levels;

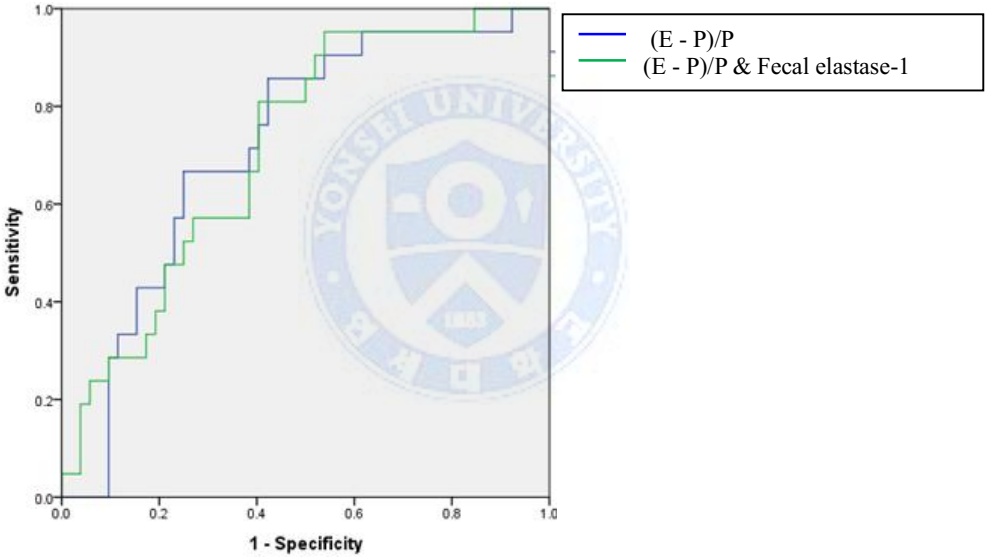
however, there were no statistically significant difference (AUC = 0.729 for (E - P)/P; AUC = 0.726 for the combination of (E - P)/P and fecal elastase-1 levels; $P = 0.897$ and AUC = 0.72 for (E - P)/(A - P); AUC = 0.716 for the combination of (E - P)/(A - P) and fecal elastase-1 levels; $P = 0.917$) (Fig. 4).

Fig. 4—ROC curve for the comparison of the abilities of the CT enhancement ratios alone and the combination of CT enhancement ratios and fecal elastase-1 levels to predict postoperative pancreatic fistulae.

A. Comparison of the abilities of (E - P)/P alone and the combination of (E - P)/P and fecal elastase-1 levels

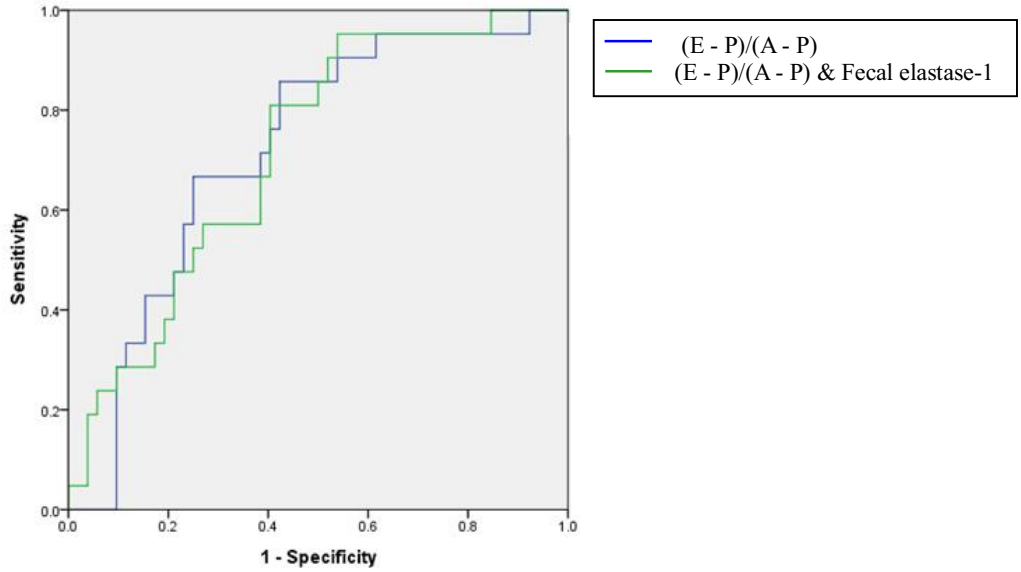
B. Comparison of the abilities of (E - P)/(A - P) alone and the combination of (E - P)/(A - P) and fecal elastase-1 levels

A



	AUC (95% CI)	*P*-value
(E - P)/P	0.729 (0.613–0.845)	0.897
(E - P)/P & Fecal elastase-1	0.726 (0.609–0.843)	

B



	AUC (95% CI)	*P*-value
(E - P)/(A - P)	0.72 (0.596–0.843)	0.917
(E - P)/(A - P) & Fecal elastase-1	0.716 (0.595–0.838)	

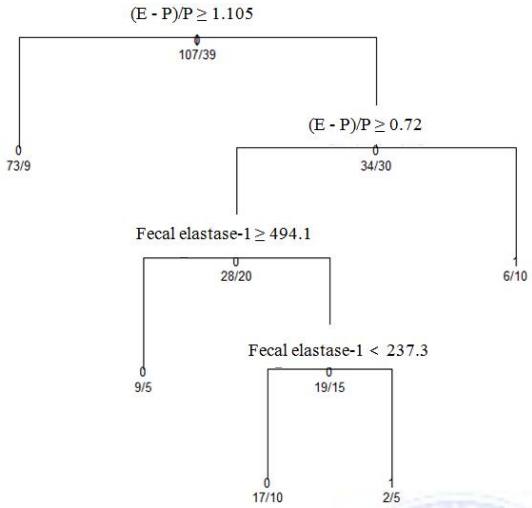
ROC, receiver operating characteristic; AUC, areas under the curve; CI, confidence interval; E, equilibrium phase; P, unenhanced phase; A, arterial phase

A tree analysis was performed to evaluate the efficacy of the CT enhancement ratios and fecal elastase-1 levels for the prediction of POPF and to establish their cut- off values when evaluated in conjunction (Fig. 5). In the tree analysis of the (E - P)/P values and fecal elastase-1 levels on conjunction, the CT enhancement ratio was the more powerful tool for the prediction of POPF. At (E - P)/P values $\geq$ 1.105, the non-occurrence of POPF could be expected regardless of the fecal elastase-1 levels; at (E - P)/P values less than 0.72, POPF could be expected to develop regardless of the fecal elastase-1 levels; and at (E - P)/P values between 0.72 and 1.105, fecal elastase-1 levels could help predict the development of POPF.

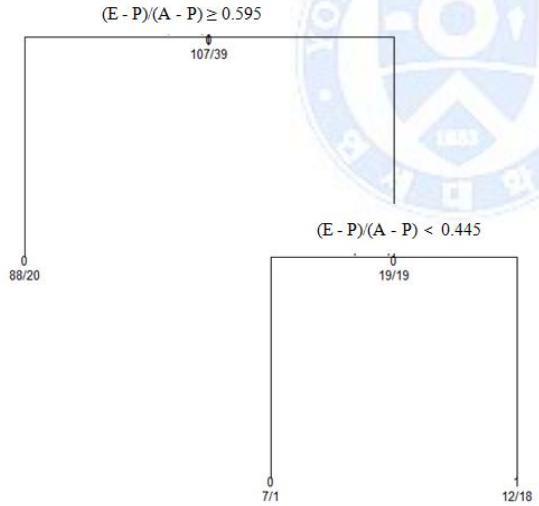
In the tree analysis of the (E - P)/(A - P) values and fecal elastase-1 levels in conjuction, the efficacy of the latter for POPF prediction could be ignored. At (E - P)/(A - P) values > 0.595, the non-occurrence of POPF could be expected regardless of the fecal elastase-1 levels.

Fig. 5—Tree analysis of the abilities of the CT enhancement ratios and fecal elastase-1 levels to predict postoperative pancreatic fistulae.

A



B



A. Combination of the CT enhancement ratio (E - P)/P and fecal elastase-1 levels

B. Combination of the CT enhancement ratio (E - P)/(A - P) and fecal elastase-1 levels

E, equilibrium phase; P, unenhanced phase; A, arterial phase

IV. DISCUSSION

The mortality rate associated with pancreatoduodenectomy has decreased to less than 5% due to advances in the postoperative care and surgical techniques.[5,12,25-32] However, the morbidity still remains high, with a rate of 30–60%, and is often related to the occurrence of POPF.[6-8] The risk factors for the development of pancreatic fistula after PD have been extensively studied.[5-10,12,25,26,28,30-33] The presence of soft pancreatic parenchyma is the most widely recognized of those risk factors.[5,9,12] On the other hand, the presence of pancreatic fibrosis with a firm pancreatic texture is thought to decrease the risk of POPF development.[14-18,34]

Recent studies have shown that CT or MR perfusion imaging can detect the microcirculatory changes caused by collagen deposition in the pancreas.[14-16,18] These studies have shown that pancreatic fibrosis is characterized by delayed enhancement with a slow rise to the peak, followed by a slow decline or plateau, while the normal pancreas shows a rapid rise to the peak, followed by a rapid decline. Only a few studies have described the quantitative assessment of the pancreatic enhancement characteristics on the preoperative CT or MR images, as a method to estimate the risk of developing POPF. Dinter et al. calculated a muscle-normalized signal intensity (SI) curve with a SI ratio using dynamic contrast-enhanced MR imaging in 72 patients who underwent PD by duct-to-mucosa pancreatojejunostomy.[14] The SI ratios were grouped into two groups: rapid increase (SI ratio $\geq$ 1.1; early arterial value > portal-venous value; soft pancreas) and equilibrium increase (SI ratio < 1.1; firm or hard pancreas) groups. Leakage of the

pancreatojejunostomy occurred more frequently in the patients of the rapid increase group than in those of the equilibrium increase group (32% vs. 6%; $P = 0.006$); additionally, in multivariate analysis, the SI ratio ≥ 1.1 was the only preoperative parameter that could predict the leakage (OR = 7.9). Using a dual-phase pancreatic CT technique, Hashimoto et al. expressed the late phase/early phase ratio (L/E ratio), calculated as (hepatic phase - unenhanced phase)/(pancreatic phase - unenhanced phase), to indicate delayed phase enhancement.[35] The L/E ratio and histological grade of pancreatic fibrosis were correlated with the development of a clinically relevant pancreatic anastomotic failure (PAF, grades B and C) and the other clinical parameters. The degree of pancreatic fibrosis and the value of the L/E ratio of the PAF group were significantly lower than those of the non-PAF group (0.86 ± 0.14 vs. 1.09 ± 0.24; $P < 0.0001$ and 21.0 ± 17.9 vs. 40.4 ± 29.8; $P < 0.0001$). In the multivariate analyses, the L/E ratio and body mass index (BMI) were found to be significant predictors for the development of a clinically relevant PAF.

In the present study, we expected that the mean value of (A - P)/P of the POPF group would be higher than that of the non-POPF group. However, the actual result obtained was different from what was expected. Commonly, the pancreatic phase scans are acquired 40–70 seconds after the infusion of the intravenous contrast material, at which time, the tumor-to-pancreas attenuation difference is the greatest.[36,37] In the previous studies, that evaluated the enhancement patterns of the normal pancreas and the fibrotic pancreas with autoimmune pancreatitis or chronic pancreatitis, the early images of the pancreatic enhancement peak were obtained 25–45 seconds after the administration of the contrast material.[15,17,18,38,39] In this narrow time range of barely dozens of seconds, the

time-attenuation curve showed a steep slope. Therefore, it is possible that the values of pancreatic attenuation vary significantly with the time differences of just a few seconds during the narrowing of the time range. Furthermore, in the study of Tajima et al., the time-signal intensity curve (TIC) of the fibrotic pancreas showed a slow rise to the peak value at 1–2 min after the administration of contrast material.[17]

The patients involved in the present study also included a number of patients referred from other hospitals, which caused discrepancies in the obtaining of the early phase images for the dynamic imaging protocol. It was, therefore, difficult to measure the attenuation value of the pancreas at the arterial phase in all of the cases at a standardized time. Given this situation, it was difficult to obtain as reliable result as was expected using the arterial image data. Meanwhile, in order to express the delayed enhancement corresponding to pancreatic fibrosis, we used a 3-min delayed CT attenuation value after contrast administration, and calculated two enhancement ratios, (E - P)/P and (E - P)/(A - P), while previous studies mentioned above used CT attenuation values of hepatic or portal-venous phases 60–70 sec after the administration of the contrast material.[14,35] In most studies, the time-attenuation curve showed a plateau or gradual slope during the 3-min delay after contrast administration with higher attenuation values in the fibrotic pancreas compared to those in the normal pancreas.[15,17,18,38,39] Therefore, there would be no remarkable differences between the pancreatic attenuation values based on the difference of a few or dozens of seconds. Furthermore, in the various dynamic CT protocols of different hospitals, there were slight differences in the images of the arterial or portal venous phases, but the equilibrium phase images were acquired approximately 3

min after contrast administration, in most cases. Therefore, using the 3-min delayed CT attenuation values to express the delayed enhancement corresponding to pancreatic fibrosis seems reasonable in practice.

Pancreatic fibrosis causes the loss of the exocrine function of the pancreas. There have been several studies reporting that a soft pancreas has a good exocrine function and secretes more pancreatic juices, which contain proteolytic enzymes.[40,41] Therefore, the exocrine pancreatic function would most probably be correlated with pancreatic fibrosis, and could be used to preoperatively predict POPF development. Human fecal elastase-1 is a pancreas-specific proteolytic enzyme, and has been proposed as a suitable marker for pancreatic insufficiency.[21-23] The measurement of fecal elastase-1 levels by ELISA is sensitive, specific, and noninvasive.[42,43] In the present study, the fecal elastase-1 level was a marginally meaningful predictive factor of pancreatic fistula (OR = 1.003; $P = 0.034$). Moreover, there were no great differences in the AUC values between the CT enhancement ratios and fecal elastase-1 levels in conjuction and the CT enhancement ratios alone ($P = 0.897$, $P = 0.971$). This indicates that there is no added benefit in using the CT enhancement ratios in conjuction with the fecal elastase-1 levels for the discrimination of the patients with POPF from those without. Additionally, in results of the tree analysis of the combined evaluation of (E - P)/P values and fecal elastase-1 levels, (E - P)/P was more a powerful predictor of POPF development than fecal elastase-1. In the tree analysis of the combined evaluation of (E - P)/(A - P) values and fecal elastase-1 levels, the efficacy of fecal elastase-1 in the prediction of POPF development was negligible. These results suggest that the CT enhancement ratios indicating the delayed

enhancement of the pancreas are more powerful and effective tools than the fecal elastase-1 levels for the prediction of the POPF development. It is thought that these results are probably related to the relatively low odd ratios of the fecal elastase-1 levels (OR = 1.003, $P = 0.034$).

There were some limitations to this study. Firstly, because of the retrospective nature of our study, there were no reference standards of the pathological fibrosis data to correlate with the CT enhancement ratios or fecal elastase-1 levels for the validation of our results. Secondly, the number of patients with the records of fecal elastase-1 levels available was quite small (n = 73); this might be the reason for the low odd ratios of fecal elastase-1 levels, which resulted in a negligible combined predictive value of the two preoperative predictive tools of POPF. Finally, the number of patients with grade C POPF was too small (n = 4) to separate the analysis of the correlation between the CT enhancement ratios/fecal elastase-1 levels and the POPF grades according to the clinical severity. However, we showed the decreasing trend of the mean values of the CT enhancement ratios according to the POPF grade.

V. CONCLUSION

Pancreatic fibrosis with a firm pancreatic texture is thought to decrease the risk of POPF; it is well correlated with the delayed enhancement of the pancreas on dynamic CT images and exocrine pancreatic insufficiency. The CT enhancement ratios indicating the delayed enhancement of the pancreas and the preoperative fecal elastse-1 levels can be used to predict the risk of developing POPF. However, the CT enhancement ratios

indicating the delayed enhancement of the pancreas are more powerful and effective tools for the prediction of the development of POPF, than the fecal elastase-1 levels. Moreover, there might be no remarkable added benefit of combining the evaluation of the CT enhancement ratios with the fecal elastase-1 levels for the discrimination of the patients with POPF from those without compared to using the CT enhancement ratio alone.

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ABSTRACT(IN KOREAN)

수술 전 역동적 조영증강 CT와 fecal elastase-1 수치 측정을 이용한 췌십이지장절제술 후의 췌십이지장 문합부 누출의 예측

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목적: 췌십이지장절제술을 시행받은 환자들을 대상으로 수술 전에 시행한 역동적 조영 증강 CT를 단독으로 이용한 것과 수술 전 시행한 역동적 조영 증강 CT와 수술 전 측정한 fecal elastase-1 수치를 조합한 것을 이용하여 수술 후 발생할 수 있는 문합부 누출을 예측할 수 있는지 알아보고자 하였다.

대상 및 방법: 2006년 1월부터 2015년 3월까지 췌십이지장절제술을 시행받은 146명의 환자를 대상으로, 수술 전 시행한 역동적 조영 증강 CT 영상과 fecal elastase-1 level 수치, 그리고 수술 후 문합부 누출 여부를 평가하였다. 조영 전 영상, 동맥기 영상, 평형기 영상에서 췌장의 감쇠치를 측정하였고, (동맥기 영상에서의 감쇠치(A) - 조영 전 영상에서의 감쇠치(P))/조영 전 영상에서의 감쇠치(P), (평형기 영상에서의 감쇠치(E) - 조영 전 영상에서의 감쇠치(P))/조영 전 영상에서의 감쇠치(P)와 (평형기 영상에서의 감쇠치(E) - 조영 전 영상에서의 감쇠치(P))/(동맥기 영상에서의 감쇠치(A) - 조영 전

영상에서의 감쇠치(P))를 계산하였다. CT 조영 증강 비율과 수술 전 fecal elastase-1 수치가 수술 후 문합부 누출과 상관관계가 있는지를 알아보기 위하여 독립표본 T검증, 로지스틱 회귀분석, ROC 곡선, Youden 분석을 이용하였다. 수술 후 문합부 누출을 예측하는데 있어서 CT와 fecal elastase-1의 조합을 평가하기 위하여 ROC 비교분석, 나무 분석법을 이용하였다.

결과: (E－P)/P 와 (E－P)/(A－P) 의 평균값은 누출이 없는 군에서 누출이 있는 군에 비해 더 컸다 (2.256 ± 3.633 vs. 1.038 ± 0.508; P = 0.001 and 1.116 ± 1.395 vs. 0.713 ± 0.294; P = 0.006, respectively). 로지스틱 회귀분석에서 (E－P)/P 와 (E－P)/(A－P) 는 문합부 누출의 유의한 예측변수였다 (OR = 0.243, P = 0.002 and OR = 0.176, P = 0.014, respectively). 수술 전 fecal elastase-1 수치 또한 문합부 누출의 유의한 예측변수였다 (OR = 1.003, P = 0.034). ROC 비교분석에서 CT와 fecal elastase-1을 조합하였을 때와 CT만 단독으로 하였을 때 문합부 누출을 예측하는데 있어서 큰 차이가 없었다. 나무 분석법에서 췌장의 지연 조영 증강을 나타내는 CT 조영 증강 비율이 fecal elastase-1에 비하여 문합부 누출을 예측하는데 더 효과적이었다.

결론: 췌장의 지연 조영 증강을 나타내는 CT 조영 증강 비율과 수술 전 fecal elastase-1 수치는 췌십이지장절제술 후 발생할 수 있는 문합부 누출 여부를

예측하는데 유용한 방법이 될 수 있다. CT와 fecal elastase-1을 조합하였을 때와 비교하여 큰 차이 없이, CT 조영 증강 비율만 단독으로 사용하여도 문합부 누출을 예측하는데 충분히 효과적이었다.

핵심되는 말 : CT 감쇠치, 췌장, 섬유화, 누출, 췌십이지장절제술