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Preoperative Pancreatic Stiffness by Real-time Tissue Elastography to Predict Pancreatic Fistula After Pancreaticoduodenectomy

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Abstract. *Aim: To assess the correlations among pancreatic fibrosis, pancreatic stiffness, and postoperative pancreatic fistula (PF). Patients and Methods: The study population consisted of 17 consecutively enrolled patients who underwent subtotal stomach-preserving pancreaticoduodenectomy (SSPPD). The liver fibrosis (LF) index as pancreatic stiffness was measured by real-time tissue elastography (RTE) before SSPPD. We also obtained the pathological fibrosis assessment of the pancreatic stump after SSPPD. Results: The LF index was significantly correlated with pathological pancreatic stump fibrosis. The LF index of patients without PF was significantly higher than that of patients with PF. The optimal cut-off value of the LF index to predict postoperative PF was defined as an LF index ≤1.91. Multivariate analysis revealed that a preoperative LF index ≤1.91 was an independent predictive factor of postoperative PF. Conclusion: Evaluation of pancreatic stiffness using RTE might be an objective index to estimate pancreatic fibrosis and predict postoperative PF.*

Many reports suggest that old age, narrow pancreatic duct diameter, soft pancreatic parenchyma, longer operation time, and greater intraoperative blood loss are possible causes of postoperative pancreatic fistula (PF) (1, 2). Postoperative PF is the most important complication after pancreaticoduodenectomy because it can lead to life-threatening complications, such as bleeding from adjacent major vessels (3, 4). For most pancreatic surgeons, assessment of preoperative pancreatic parenchymal texture (soft or hard) is highly correlated with occurrence of postoperative PF and is a promising field of research. However, it is difficult to assess the objective pancreatic hardness pre- and intra-operatively because it depends on the subjective tactile sense of the pancreatic surgeon.

Pancreatic parenchyma hardens because of fibrosis associated with chronic pancreatitis and pancreatic carcinoma (5). Historically, the clinical application of ultrasound (US) elastography began with realtime tissue elastography (RTE) developed by Hitachi-Aloka, so that, strain elastography (SE) (6, 7). SE estimates the stiffness of tissue by measuring the grade of strain generated by external pressure. There is a negative correlation between the grade of strain and the stiffness of the tissue (8), but there is no published research describing the relationship between pancreatic stiffness and postoperative PF.

In this study, we aimed to evaluate not only the relationship between pancreatic fibrosis and stiffness by RTE, but also the relationship between conventional tactile sense-based or elastography-based pancreatic hardness and fibrosis. Furthermore, we evaluated the association between preoperative pancreatic stiffness by RTE and postoperative PF.

Patients and Methods

Patients and surgery. The study population consisted of 17 consecutively enrolled patients who underwent subtotal stomach-preserving pancreaticoduodenectomy (SSPPD) at the Hiroshima Red Cross Hospital and Atomic Bomb Survivors Hospital between July 2014 and February 2016. Preoperative RTE imaging could not be performed in one patient because of difficulty obtaining clear images of the pancreatic body. In the remaining 16 patients, one laboratory technician (K.M.) and one surgeon (N.H.) measured the pancreatic liver fibrosis (LF) index by RTE of the pancreatic body one day prior to SSPPD.

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Key Words: Liver fibrosis index, pancreatic fibrosis, strain elastography, Masson's trichrome.

SSPPD was performed as previously described by Tatsumi C et al. (8). The pancreatic parenchyma was surgically divided, and reconstruction was performed using the modified Child's method. The main pancreatic duct was anastomosed to the jejunum with 6-0 PDS intermittent sutures. A 4-8 French (Fr) polyvinyl catheter with multiple side holes (MD-41515 pancreatic duct tube; Sumitomo Bakelite, Tokyo, Japan) was inserted as an external drain or an internal stent in all patients. Next, 3-0 TE Prolene sutures were used to anastomosis the pancreas and the seromuscular layer of the jejunum. The external drain was typically removed on postoperative day 21. Then, end-to-side hepaticojejunostomy was performed by single-layer anastomosis using continuous or interrupted sutures with 5-0 or 6-0 PDS-II 10-15 cm distal to the pancreaticojejunostomy site. Gastrojejunostomy was performed via the antecolic route by two-layer anastomosis with 4-0 PDS-II and 3-0 silk 35-45 cm distal to the hepaticojejunostomy site. Next, polyethylene glycolic acid felt (Neoveil® 50×50 mm; Gunze, Kyoto, Japan) and fibrin glue (Bolheal®, The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) were applied to the pancreaticojejunostomy site. Nineteen Fr closed drains (J-VAC Suction Reservoir; Johnson and Johnson, Somerville, NJ, USA), from which postoperative drain fluid was collected, were inserted at the anterior pancreaticojejunostomy site. We graded the PF using the International Study Group of Pancreatic Fistula (ISGPF) classification (9).

Diagnosis of tactile sense-based pancreatic hardness was performed by two hepatobiliary-pancreatic surgeons (T.M. and H.K.) who were blinded to the preoperative pancreatic RTE stiffness value. The study protocol conformed with the updated ethical guidelines of the 2013 Declaration of Helsinki and was approved by our Institutional Review Board.

Preoperative pancreatic stiffness by real-time elastography. Preoperative RTE was performed using HI VISION Ascendus® (Hitachi-Aloka Medical, Tokyo, Japan, Figure 1A) in the pancreas mode LF index. Patients were fasting and were placed in the supine position. Conventional B-mode ultrasonography was used to visualize the pancreatic body parenchyma at a depth of 7 cm from the transducer (10). The region of interest of the strain image was approximately 2.5 cm^2 and was located at the pancreatic body above the confluence of the abdominal aorta, distant from the pancreatic tumors (Figure 1B). The LF index and Mean relative strain value (MEAN) were measured in each patient (11). The pancreatic LF index was measured three times in each of the 16 patients; the mean LF index of the three values was calculated and used in the analyses.

Pathological assessment of the pancreas. Pancreatic tissue samples were obtained 0.1-0.5 cm from the pancreatic stump, fixed in formalin, and stained with Masson's trichrome (MT). The slides were evaluated by an experienced pathologist (W.H.) and blinded to each patient's clinical data, LF index, and postoperative course. The degree of pancreatic fibrosis was indicated as a percentage of fibrosis of the slides (Figure 1B), calculated as the ratio of fibrosis (blue-stained area) to acinous cells (red-stained area) in the ×40 field of vision using video diagnosis software (ImageJ 1.50i; Wayne Rasband, National Institutes of Health, Bethesda, MD, USA,). We choose 10 sites at random and examined the correlation between the percentage of fibrosis and the LF index.

Statistical analysis. Continuous data were expressed as mean±standard deviation (SD). Quantitative and categorized variables were compared using the Wilcoxon rank-sum test and Fisher's exact test, respectively. The correlations of the LF index, percentage of fibrosis, and relative strain were evaluated using Spearman's rank correlation test. Multivariate analysis was performed to evaluate the ability of the preoperative LF index to predict the risk of postoperative PF. Because of their clinical significance, seven potentially important pre- and intraoperative factors were included in the analysis: age (≤82 years *vs.* >82 years), sex, presence of diabetes mellitus (yes *vs.* no), body mass index (>21.4 kg/m^2 *vs.* ≤21.4 kg/m^2), amount of blood loss (>245 ml *vs.* ≤245 ml), main pancreatic duct (MPD) diameter (≤3 mm *vs.* >3 mm), and LF index (≤1.91 *vs.* >1.91). The cut-off values were calculated by receiver operating characteristic (ROC) curve analysis regarding the presence of PF. The results were expressed as adjusted odds ratios (OR), and p values were calculated using the likelihood ratio test. Values of $p<0.05$ were considered statistically significant. All statistical analyses were performed using JMP software version Pro12 (SAS Institute, Cary, NC, USA).

Results

Clinical characteristics of patients with subtotal stomach-preserving pancreaticoduodenectomy. The background characteristics of the patients who underwent SSPPD are summarized in Table I. The study subjects consisted of 11 men and 5 women, ranging in age from 45-83 years (median=78 years). Using RTE, the median LF index and MEAN were 6.1 (range=0.7-11.3), and 55.8 (range=5.5-113), respectively. On pathological assessment, pancreatic stump fibrosis was 29.4% (range=12.1-74.8%). Final diagnosis after SSPPD was pancreatic cancer in seven patients, intraductal papillary mucinous carcinoma in three, pancreatic neuroendocrine tumor in two, ampulla of Vater carcinoma in three, and bile duct cancer in one. Four of 14 (28.5%) had clinically relevant PF of Grade B or higher.

Relationship between percentage of fibrosis and pancreatic stiffness parameters measured by real-time elastography. The preoperative pancreatic LF index was significantly correlated with the pathological percentage of pancreatic stump fibrosis (Spearman's rank correlation coefficient [ϱ]=0.58, p=0.018) (Figure 2A). The preoperative pancreatic MEAN was significantly correlated with the pathological percentage of pancreatic stump fibrosis (Spearman's rank correlation coefficient [ϱ]=–0.61, p=0.011) (Figure 2B).

Relationship between intraoperative tactile sense-based pancreatic hardness and parameters of pancreatic fibrosis. The pathological percentage of fibrosis of hard pancreases (based on the surgeon's tactile sense) was significantly higher than that of soft pancreases (p=0.034) (Figure 3A). The LF index of tactile sense-based hard pancreases was also significantly higher than that of soft pancreases (p=0.0017) (Figure 3B).

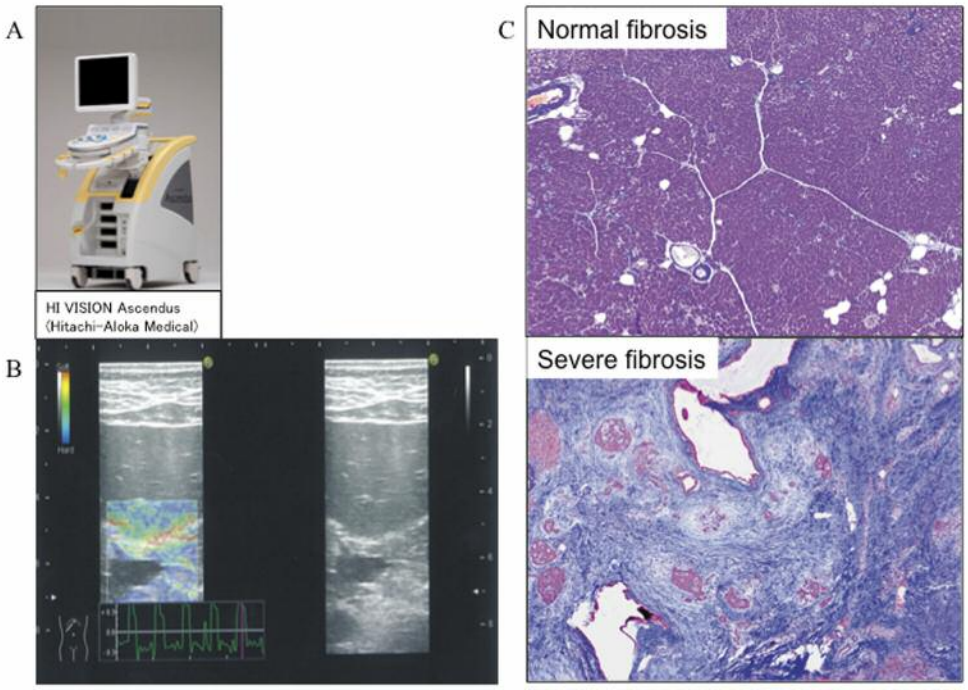

Figure 1. *A. Photograph of the HI VISION Ascendus® (Hitachi-Aloka Medical, Tokyo, Japan) ultrasound. B. Preoperative real-time tissue elastography imaging was performed using HI VISION Ascendus®. C. Normal and severe pancreatic fibrosis stained with Masson's trichrome. The slides show fibrosis (blue-stained area) and acinous cells (red-stained area) in the 40× field of vision.*

Relationship between pancreatic fistula (Grade B or higher) and parameters of pancreatic fibrosis. The pathological percentage of fibrosis of patients without PF was not significantly higher than that of patients with PF (p=0.225) (Figure 4A), but the LF index of patients without PF was significantly higher than that of patients with PF (p=0.045) (Figure 4B). Therefore, the optimal cut-off value of the LF index to predict postoperative PF was derived from the ROC analysis. That LF index was 1.91 (sensitivity 75%, specificity 83%) and the area under the curve was 0.85 (Figure 5).

Relationship between patient characteristics and liver fibrosis index-based pancreatic hardness. Based on the above optimal cut-off value of the LF index, the study population was divided into two groups: hard pancreas was defined as an LF index-based hardness >1.91, while soft pancreas was defined as an LF index ≤1.91 (Table II). The hard pancreas group had a higher prevalence of diabetes mellitus (p=0.01), greater preoperative LF index (p=0.002), greater percentage of fibrosis (p=0.004), greater estimated blood loss, smaller pancreatic duct diameter (p=0.009), lower drain amylase level on postoperative day one (p=0.01), and lower incidence of postoperative PF (p=0.03) than the soft pancreas group.

Table I. *Clinical characteristics of patients with subtotal stomach-preserving pancreaticoduodenectomy.*

Variables	(N=16)
Age at enrollment (years)	78 (45-83)
Gender (male/female)	11/5
Body mass index (kg/m^2)	22 (18-28)
Presence of diabetes mellitus (%)	6/10
HbA1c (%)	6.1 (4.5-8.1)
Preoperative LF index	2.8 (0.7-11.3)
Mean relative strain value (MEAN)	55.8 (5.5-113)
Fibrosis (%)	29.4 (12.1-74.8)
Diagnosis	
Pancreas cancer	7
IPMC	3
PNET	2
Ampulla of Vater carcinoma	3
Bile duct cancer	1
Operation time (minutes)	434 (306-583)
Estimate blood loss (g)	243 (50-815)
Pancreatic duct diameter (mm)	3.8 (1-7)
Postoperative pancreas fistula (ISGPF Grade B or higher, %)	25

HbA1c: Hemoglobin A1c; LF index: liver fibrosis index; IPMC: intraductal papillary mucinous carcinoma; PNET: pancreatic neuroendocrine tumor; ISGPF: International Study Group of Pancreatic Fistula. Values are expressed as mean (range).

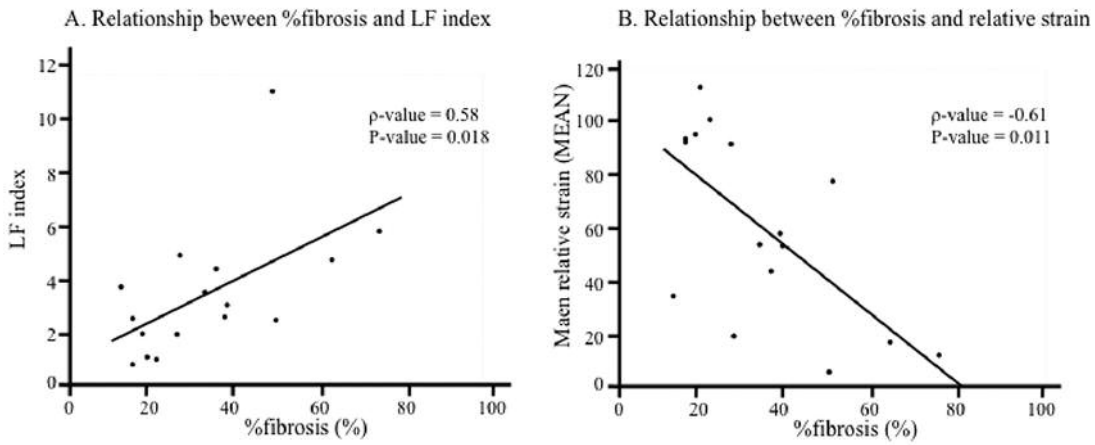

Figure 2. *Relationships between percentage of fibrosis and preoperative pancreatic stiffness measured by real-time tissue elastography. A. The preoperative pancreatic liver fibrosis index was significantly correlated with pathological percentage of pancreatic stump fibrosis (Spearman's rank correlation coefficient ϱ=0.58, p=0.018). B. Preoperative pancreatic Mean relative strain was significantly correlated with the pathological percentage of pancreatic stump fibrosis (Spearman's rank correlation coefficient ϱ=–0.61, p=0.011).*

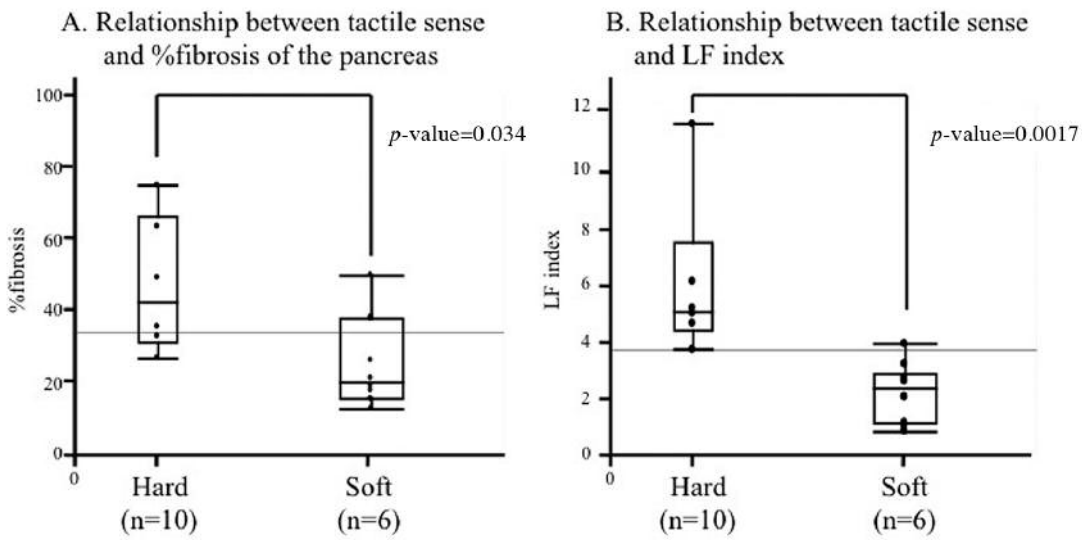

Figure 3. *Relationship between intraoperative tactile sense-based pancreatic hardness and parameters of pancreatic fibrosis. A. The pathological percentage of fibrosis of hard pancreases based on the surgeon's tactile sense was significantly higher than that of soft pancreases (p=0.034). B. The liver fibrosis index of hard pancreases was also significantly higher than that of soft pancreases (p=0.0017).*

Multivariate analysis of pre- and intraoperative factors predicting postoperative pancreatic fistula. Multivariate analysis revealed that a soft pancreas was an independent predictive factor of Grade B or higher postoperative PF (OR=33.5; p=0.019) (Table III). Other independent predictors of postoperative PF were MPD diameter ≤3 mm (OR=41.8; p=0.008) and presence of diabetes mellitus (OR=50.3; p=0.019).

Discussion

Prior to this study, soft pancreas was a known cause of postoperative PF, but was not possible to diagnose objectively (1, 2, 12, 13). We aimed to provide objective diagnostic criteria for soft pancreas. In this preliminary study, we compared the tactile sense-based hardness with the LF index and found that they were significantly associated. The LF

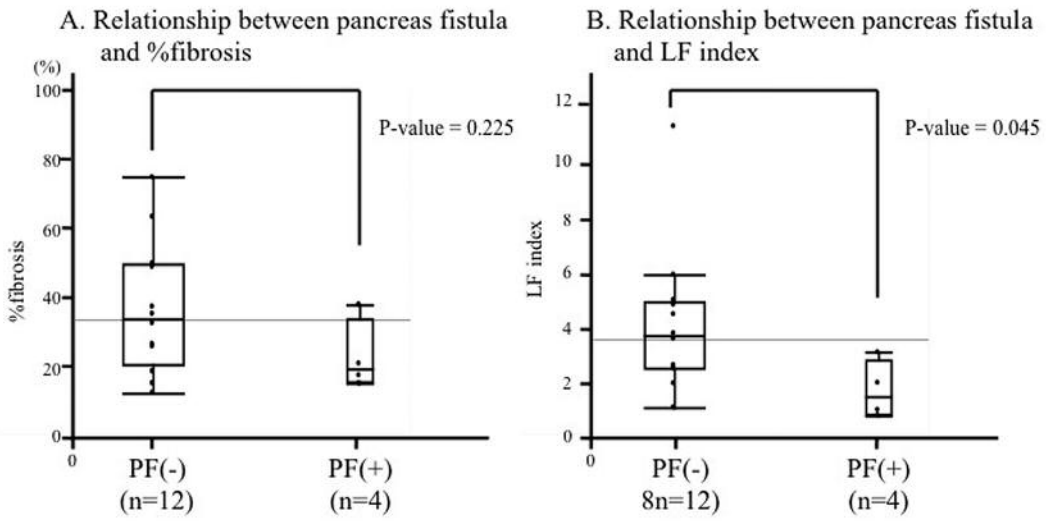

Figure 4. *Relationship between grade B and higher pancreatic fistula and parameters of pancreatic fibrosis. A. The percentage of fibrosis of patients without pancreatic fistula (PF) was not significantly higher than that of patients with PF (p=0.225). B. The liver fibrosis index of patients without PF was significantly higher than that of patients with PF (p=0.045).*

Table II. *Relationship between patient characteristics and LF index-based hardness of the pancreas.*

Variables	Hard pancreas LF index >1.91 (n=11)	Soft pancreas LF index ≤1.91 (n=5)	*p*-Value
Age at enrollment (years)	72.2±9.9	69.1±9.4	0.73
Gender (male/female)	8/3	3/2	0.61
Body mass index (kg/m^2)	22.5±1.9	21.6±4.0	0.23
Presence of diabetes mellitus (%)	54.6	0	0.01
HbA1c (%)	6.4±0.9	5.5±0.7	0.10
Preoperative LF index	4.5±2.5	1.3±0.6	0.002
%fibrosis (%)	39.4±19	19.4±4.1	0.04
Operation time (minutes)	420±75	480±60	0.10
Estimate blood loss (g)	456±284	204±129	0.03
Pancreatic duct diameter (mm)	4.7±1.5	2.3±0.8	0.009
Serum amylase level (POD1, U/L)	342±410	559±468	0.16
Drain amylase level (POD1, U/L)	991±1264	3429±2009	0.01
Serum amylase level (POD3, U/L)	60±52	97±64	0.11
Drain amylase level (POD3, U/L)	342±298	428±233	0.53
Postoperative pancreas fistula (ISGPF Grade B or higher, %)	9	60	0.03

HbA1c: Hemoglobin A1c; IPMC: intraductal papillary mucinous carcinoma; PNET: pancreatic neuroendocrine tumor; ISGPF: International Study Group of Pancreatic Fistula. Values are expressed as mean±SD.

index was traditionally used to measure liver elastography (8). However, the clinical application of elastography has expanded to evaluate the pancreas as well (14-17).

We preoperatively diagnosed soft pancreas using the LF index. To our knowledge, this is the first report using an LF index cut-off as an independent predictive factor of postoperative PF. Pancreatic fluid output is higher from a soft pancreas than from a hard pancreas. Therefore, pancreatic fluid leakage from the anastomosis of a soft pancreas has a higher volume and a higher likelihood of forming a PF.

Pancreatic elastography is usually performed by US. There are two types of pancreatic elastographies based on different principles: strain elastography and shear wave elastography. In the former, the stiffness of a tissue is estimated by

Table III. *Multivariate analysis of pre- and intraoperative factors predicting postoperative pancreatic fistula (International Study Group of Pancreatic Fistula Grade B or higher).*

Variables	Multiple logistic regression analysis	
	Odds ratio	*p*-Value
Male sex	5.46	0.999
Blood loss >245 ml	0.87	0.617
MPD diameter ≤3 mm	41.8	0.008
LF index ≤1.91	33.5	0.019
Age ≤82 years	0.04	0.999
BMI >21.4	28.8	0.096
Presence of diabetes mellitus	50.3	0.019

MPD: Main pancreatic duct; LF: liver fibrosis; BMI: body mass index.

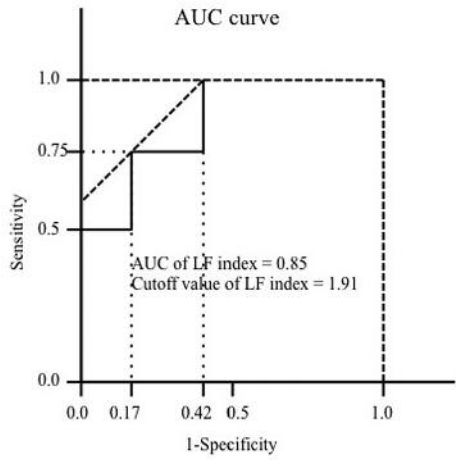

Figure 5. *Receiver operating characteristic curve analysis of the fibrosis index for predicting pancreatic fistula. The optimal cut-off value of the fibrosis index to predict postoperative pancreatic fistula was 1.91. It was obtained by receiver operating characteristic curve analysis (sensitivity 75%, specificity 83%) and the area under the curve was 0.85.*

measuring the grade of strain generated by external pressure, whereas in the latter it is estimated by measuring propagation speed of a shear wave (transverse wave) generated by an acoustic radiation impulse. Strain elastography is difficult to perform when the probe, the pancreas, and the aorta are not located in a straight line. Therefore, a high-quality elastogram of the pancreatic body can be performed easily but one of the pancreatic head and tail cannot (18). In this study, we found a limit of 7 cm in depth from the body surface to the pancreatic body.

In this study, we evaluated fibrosis using the MT stain. This method has not been published but is commonly used in the hepatic fibrosis field (19). We found that the preoperative pancreatic LF index was significantly correlated with the pathological percentage of pancreatic stump fibrosis by this MT stain. A previous report assessed fibrosis of the pancreatic parenchyma by Hematoxylin-Eosin stain (20, 21). Assessing pancreatic fibrosis using the MT stain is more precise and merits further research.

We herein used a standardized surgical procedure and postoperative management and decreased bias where possible. We concluded that the preoperative LF index might be predictive of postoperative PF. The morbidity rate of a PF ranges from 2-50% (19, 20). The incidence of grade B or higher PF in our study was 25%. This percentage of PF is consistent with prior studies and supports the reliability of this study design to evaluate complications after SSPPD.

However, there are several limitations. First, this is a preliminary study and the study population was relatively small. Further evaluation of pancreatic fibrosis by RTE in the larger cohort will be required in the future. Second, while a high-quality elastogram of the pancreatic body can be obtained easily unless a patient has severe arteriosclerosis, one of the pancreatic head and tail often cannot be obtained. Even with these limitations, pancreatic stiffness affects postoperative morbidity and merits future study. For SSPPD of the pancreatic body, evaluation of pancreatic fibrosis by RTE might be indicated.

In conclusion, our findings that the LF index correlates with pancreatic fibrosis and with postoperative PF indicate that RTE evaluation of pancreatic stiffness might be a noninvasive method to predict postoperative PF after SSPPD.

Conflicts of Interest

The Authors declare that they have no conflict of interest.

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