

RAPID COMMUNICATION

## Risk factors affecting pancreatic fistulas after pancreaticoduodenectomy

Yun-Mee Choe, Keon-Young Lee, Cheong-Ah Oh, Joung-Bum Lee, Sun Keun Choi, Yoon-Seok Hur, Sei-Joong Kim, Young Up Cho, Seung-Ik Ahn, Kee-Chun Hong, Seok-Hwan Shin, Kyung-Rae Kim

Yun-Mee Choe, Keon-Young Lee, Cheong-Ah Oh, Joung-Bum Lee, Sun Keun Choi, Yoon-Seok Hur, Sei-Joong Kim, Young Up Cho, Seung-Ik Ahn, Kee-Chun Hong, Seok-Hwan Shin, Kyung-Rae Kim, Department of Surgery, Inha University Hospital, Incheon 400-711, South Korea

**Author contributions:** Choe YM and Ahn SI contributed equally to this work; Choe YM, Lee KY, Oh CA, Lee JB, Choi SK and Hur YS designed the research; Choe YM, Lee KY, Oh CA, Lee JB, Choi SK, Hur YS, Kim SJ, Cho YU and Ahn SI performed the research; Hong KC, Shin SH and Kim KR contributed new reagents/analytic tools; Oh CA and Lee JB analyzed the data; Choe YM, Lee KY, Lee JB and Ahn SI wrote the paper.

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Correspondence to: Seung-Ik Ahn, MD, Department of Surgery, Inha University Hospital, 7-206, 3 Ga Shinheung-dong, Jung-Gu, Incheon 400-711, South Korea. [siahn@inha.ac.kr](mailto:siahn@inha.ac.kr)

Telephone: +82-32-8902250 Fax: +82-32-8903097

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### Abstract

**AIM:** To analyze the risk factors of pancreatic leakage after pancreaticoduodenectomy.

**METHODS:** We retrospectively reviewed 172 consecutive patients who had undergone pancreaticoduodenectomy at Inha University Hospital between April 1996 and March 2006. We analyzed the pancreatic fistula rate according to the clinical characteristics, the pathologic and laboratory findings, and the anastomotic methods.

**RESULTS:** The incidence of developing pancreatic fistulas in patients older than 60 years of age was 21.7% (25/115), while the incidence was 8.8% (5/57) for younger patients; the difference was significant ( $P = 0.03$ ). Patients with a dilated pancreatic duct had a lower rate of post-operative pancreatic fistulas than patients with a non-dilated duct ( $P = 0.001$ ). Other factors, including clinical features, anastomotic methods, and pathologic diagnosis, did not show any statistical difference.

**CONCLUSION:** Our study demonstrated that pancreatic fistulas are related to age and a dilated pancreatic duct. The surgeon must take these risk factors into consideration when performing a pancreaticoduodenectomy.

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**Key words:** Pancreaticoduodenectomy; Pancreatic fistula; Pancreatic leakage

**Peer reviewer:** Justin H Nguyen, MD, Division of Transplant Surgery, Mayo Clinic, 4205 Belfort Road, Suite 1100, Jacksonville, Florida 32256, United States

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### INTRODUCTION

Pancreaticoduodenectomy (PD) is a commonly performed surgical procedure for managing duodenal trauma and various benign and malignant diseases of the periampullary region.

This procedure was first described by Whipple *et al*<sup>[1]</sup> in 1935. At that time, PD was technically difficult to perform and the mortality rate was reported to be > 30%<sup>[1]</sup>. Despite marked progress in the procedure and in the treatment of perioperative patients, the mortality rate is still reported to be 2%-10% in most hospitals<sup>[2,3]</sup>. The incidence of pancreatic fistulas remains a major cause of postoperative complications; it is reported that the incidence of pancreatic fistulas after PD is 6%-25%<sup>[4-12]</sup>. It is known that such pancreatic fistulas induce abscess formation, vascular injuries, rupture of pseudoaneurysms, and postoperative delayed hemorrhage, all resulting from inflammation around leakage sites due to stasis of fluid, including active pancreatic enzymes<sup>[13-16]</sup>.

The aim of this study was to analyze the independent risk factors for pancreatic fistulas after PD.

### MATERIALS AND METHODS

Between April 1996 and March 2006, 172 consecutive patients who had undergone PD at Inha University Hospital were retrospectively reviewed. The operations were performed by five surgeons, and pancreatic fistulas were investigated retrospectively by review of the patients'

medical records. A pancreatic fistula was defined as follows: from the 7th postoperative day on, the drainage output was > 50 cc a day and the drainage fluid amylase level was 3 times higher than the serum level<sup>[6]</sup>.

We compared the pancreatic fistula rates based on gender, age, anastomotic method, preoperative serum total bilirubin level, serum albumin level, white blood cell (WBC) count, histologic diagnosis, texture of the remnant pancreas, and size of the pancreatic duct. The methods used for anastomosis included end-to-end anastomosis (dunking) between cross-sections of the jejunum and the pancreatic stump, and a pancreatic duct-to-jejunal mucosal anastomosis. The results were compared based on whether or not a feeding tube was placed into the duct, serving as a stent for the reconstruction and exteriorization of the duct from the anastomotic site through the lateral abdominal wall.

In all cases, somatostatin was used prophylactically for 7 d postoperatively. The statistical analyses of the correlations among multiple clinical factors were performed using independent t-tests and  $\chi^2$  tests, and a significant difference was considered when  $P < 0.05$ . The assessment of the statistical significance was carried out using multivariate analyses.

## RESULTS

Leakage of the pancreaticojejunostomy occurred in 30 of 172 patients (17.4%), and the frequency of such leakage was analyzed and compared according to gender, age, anastomotic methods, operative findings, preoperative serum total bilirubin and albumin levels, preoperative WBC, and histopathologic diagnosis (Table 1).

Reoperations were carried out in 5 of 30 patients (16.7%) with leakage of the pancreaticojejunostomy; 4 patients had total pancreatectomies and 1 patient had a segmental resection of the small bowel. Among 172 patients, there were 4 deaths and the mortality rate was 2.3%; 1 patient underwent reoperation and 3 patients died during conservative management. There were 4 deaths in groups with leakage of the pancreaticojejunostomy.

Five surgeons operated on 95, 26, 19, 19, and 13 patients, respectively, in our hospital. The occurrences of pancreatic fistulas according to the surgeons were 17.9% (17/95), 23.1% (6/26), 15.8% (3/19), 10.5% (2/19), and 15.4% (2/13), respectively. There was no significant correlation between the surgeons and pancreatic fistulas ( $P = 0.867$ ).

The mean age of the patients was 62.2 years, with a range of 33-87 years. Pancreatic fistulas occurred in 25 patients over 60 years of age (21.7%), and in 5 of 57 patients under 60 years of age (8.8%). The difference in the pancreatic fistula rates between the two groups was significant ( $P = 0.016$ ).

With regard to gender, anastomotic method, pancreatic stenting, texture of the remnant pancreas, preoperative serum albumin level, total bilirubin level, and WBC count, there were no significant differences in pancreatic fistula rates.

The pancreatic duct size was included in the pathology

**Table 1** Pancreatic fistula rate based on clinical factors

Factors		Number of patients (%)	Leakage (%)	P value
Age (yr)	≥ 60	115 (66.9)	25 (21.7)	0.016
	< 60	57 (32.1)	5 (8.8)	
Gender	Male	116 (67.4)	19 (16.4)	0.606
	Female	56 (32.6)	11 (19.6)	
Type of anastomosis	Duct-to-mucosa	133 (77.3)	22 (16.5)	0.582
	End-to-end	39 (22.7)	8 (19.6)	
Pancreatic stent	Yes	58 (33.7)	11 (19.0)	0.712
	No	114 (66.3)	19 (16.7)	
Texture of remnant pancreas	Hard	61 (58.5)	7 (16.3)	0.392
	Soft	43 (41.5)	7 (23.0)	
Pancreatic duct size	Dilated	60 (44.1)	4 (6.6)	0.001
	Non-dilated	76 (55.9)	21 (27.6)	
Pre-op bilirubin	≥ 1.3 mg/dL	92 (54.5)	15 (16.3)	0.674
	< 1.3 mg/dL	80 (46.5)	15 (18.8)	
Pre-op albumin	≥ 3.1 g/dL	138 (80.2)	23 (16.7)	0.607
	< 3.1 g/dL	34 (19.8)	7 (20.6)	
Pre-op WBC	≥ 10000/mm <sup>3</sup>	29 (16.9)	7 (24.1)	0.349
	< 10000/mm <sup>3</sup>	143 (83.1)	23 (16.1)	

reports and the patients were divided into 2 groups based on the main duct size, as follows: (1) patients with a dilated pancreatic main duct, defined as having a visible main duct and (2) a non-dilated pancreatic main duct, defined as having a non-visible main duct. Only 136 of 172 patients were classified according to pancreatic duct size. The number of patients with dilated and non-dilated pancreatic main ducts was 60 and 76, respectively. Pancreatic fistulas developed in 4 of 60 patients in the group with a dilated pancreatic main duct (6.6%), and in 21 of 76 patients in the group with a non-dilated pancreatic main duct (27.6%); there was a significant difference between the two groups ( $P = 0.001$ ; Table 1).

When the incidence of pancreatic fistulas was compared based on histopathologic diagnosis, pancreatic fistulas occurred in 6 of 37 patients (16.2%) diagnosed with carcinomas in the pancreatic head, in 8 of 46 patients (17.4%) diagnosed with carcinomas in the common bile duct (CBD), in 8 of 34 patients (23.5%) diagnosed with carcinomas of the ampulla of Vater, in 1 of 10 patients (10.0%) diagnosed with duodenal cancer, in 3 of 9 patients (33.3%) diagnosed with intraductal papillary mucinous tumors, in 0 of 6 patients (0%) diagnosed with chronic pancreatitis, in 2 of 22 patients (9.1%) diagnosed with gastric cancer and pancreatic invasion, in 1 of 4 patients (25.0%) with trauma to the pancreas, and in 1 of 4 patients (25.0%) diagnosed with gallbladder (GB) cancer (Table 2). Although patients diagnosed with chronic pancreatitis and gastric cancer with pancreatic invasion tended to develop pancreatic fistulas less frequently than other patients, there was no significant difference in the correlation between histopathologic diagnosis and pancreatic fistulas.

## DISCUSSION

PD is technically difficult, and as a result, relatively high mortality (15%-30%) and complication rates (50%-75%) were reported before the 1980s. With advances in surgi-

Table 2 Pancreatic fistula based on histopathologic diagnosis

Name of disease	Number of patients (%)	Leakage (%)
Pancreatic head cancer	37 (21.5)	6 (16.2)
CBD cancer	46 (26.7)	8 (17.4)
Ampulla of Vater cancer	34 (19.8)	8 (23.5)
Duodenal cancer	10 (5.8)	1 (10.0)
Chronic pancreatitis	6 (3.5)	0 (0)
Intraductal papillary mucinous tumor	9 (5.2)	3 (33.2)
Gastric cancer	22 (12.8)	2 (9.1)
GB cancer	4 (2.3)	1 (25)
Trauma	4 (2.3)	1 (25)

cal techniques and perioperative care, the mortality rate associated with PD has since improved<sup>[17]</sup>.

Most complications after PD commonly arise from failure in healing of the pancreaticojejunostomy, and have been described as pancreatic fistulas or anastomotic leakages by various authors.

Berberat *et al*<sup>[18]</sup> defined a pancreatic fistula as an anastomotic leak of the pancreaticojejunostomy demonstrated radiographically or intraoperatively, and as a prolonged or elevated output of amylase-rich fluid through an intraoperatively-placed drain (> 3 times the normal serum amylase level). Lowy *et al*<sup>[19]</sup> divided pancreatic fistulas into clinical leakage and biochemical leakage, in which the former referred to the amylase level of the fluid obtained through an intraoperatively-placed drain to be > 3 times the normal serum amylase level, with a high fever, leukocytosis, sepsis, and the need for drainage, while the latter referred to asymptomatic patients. We favor the definition described by Yeo *et al*<sup>[6]</sup> i.e. from the 7th postoperative day on, the drain output is > 50 cc a day and the drain fluid amylase level is 3 times higher than the serum amylase level. Using the Yeo *et al*<sup>[6]</sup> definition, we analyzed the risk factors for pancreatic leakage.

To place a tube as a stent and to determine how a pancreaticojejunostomy relates to pancreatic fistula formation requires more research<sup>[20]</sup>. Yeo *et al*<sup>[21]</sup> reported that pancreatic fistulas were correlated with anastomotic technique, operative time, a surgeon's skills and experience in performing a PD, tumor location, and co-morbid illnesses<sup>[21]</sup>. Bartoli *et al*<sup>[17]</sup> reported a difference in the degree of fibrosis of the remnant pancreas, and that anastomotic leakage occurred in 5% of patients with chronic pancreatitis and in 33% of patients with carcinoma of the CBD. Patients in whom the pancreatic texture has a hard consistency have been reported to be at lower risk for pancreatic leakage than those patients who have a pancreatic parenchyma with a soft or intermediate consistency<sup>[22,23]</sup>. The texture of the pancreatic parenchyma has been reported to be correlated with the pancreatic duct diameter<sup>[24]</sup>, in considering the ease in performing a pancreatic duct-to-jejunum mucosa anastomosis, such a simple comparison requires more consideration. The pancreatic duct diameter has been correlated with pancreatic leakage<sup>[5]</sup>, and our study showed that 136 (79.1%) patients had evidence of pancreatic duct dilatation by histopathologic reports, confirming the correlation be-

tween pancreatic duct size and pancreatic fistula development ( $P = 0.001$ ). None of the 6 patients with chronic pancreatitis developed pancreatic leakage, and chronic pancreatitis induced pancreatic fistula less often than other pancreatic diseases; however, there was no statistical significance. We considered this result to reflect a small number of the population and because of the possible prediction of pancreatic duct dilatation in chronic pancreatitis, pancreatic duct diameter could be correlated with pancreatic leakage. However, in considering factors related to the texture of the remnant pancreas, the incidence of pancreatic fistulas in patients with a hard texture of the remnant pancreatic parenchyma was 16.3% (7/43) and was lower than that in patients with a soft texture [23% (14/61)], but this finding lacked statistical significance ( $P = 0.392$ ). These results are considered to have no statistical significance because pancreatic texture was demonstrated in only 104 of 172 patients (60.5%).

In this study, the incidence of pancreatic fistulas in patients with gastric cancer with pancreatic invasion was 9.1% and was lower than that in patients with other diseases, again showing no statistical significance. Among 22 patients with gastric cancer with pancreatic invasion, 13 patients were < 60 years of age, suggesting that gastric cancer with pancreatic invasion affects a younger age group when compared with 57 patients < 60 years of age in the total population of 172 patients. These results were considered to be influenced by the bias arising from the difference between the older age group, a significant factor in our study, and the younger age group of patients with gastric cancer with pancreatic invasion.

Pancreatic leakage has been related to the presence or absence of co-morbid illnesses, and age has been correlated with the occurrence of pancreatic fistulas<sup>[21-23]</sup>. In our study, there was a significant correlation between age and pancreatic fistulas ( $P = 0.03$ ).

With regard to the pancreaticojejunostomy technique, binding pancreaticojejunostomy significantly decreased postoperative complications and the pancreaticojejunostomy leakage rate<sup>[25-27]</sup>. In our study, the methods used for anastomosis were divided into end-to-end dunking anastomosis between cross-sections of the jejunum and the pancreatic stump, and pancreatic duct-to-jejunal mucosal anastomosis. The results were compared based on whether or not a feeding tube, which serves as a stent for the reconstruction and exteriorization, was placed from the anastomotic site through the lateral abdominal wall.

Many previous reports have proposed that hard texture of the pancreatic parenchyma and a dilated pancreatic duct have a lower risk of pancreatic fistula formation owing to an ability to prevent pancreatic duct dilatation and shrinkage of the pancreaticojejunostomy after PD<sup>[16]</sup>. Conversely, in the case of a small pancreatic duct and a soft pancreas, an end-to-end invagination anastomosis or binding pancreaticojejunostomy significantly decreases postoperative complications<sup>[20,27]</sup>. In our study there was no significant difference in the incidence of pancreatic fistulas as a function of anastomotic technique.

Although there is a report that the preoperative serum total bilirubin level, duration of jaundice, surgery performed under emergent conditions, and preoperative serum albumin level can affect the occurrence of pancreatic fistulas<sup>[28]</sup>, there was no significant difference among the preoperative serum total bilirubin level, albumin level, and leukocytosis in our study. The patients with pancreatic parenchyma of soft consistency produce a larger amount of pancreatic juice and have a higher risk of pancreatic leakage than those with a hard consistency<sup>[14]</sup>. Therefore, a variety of surgical methods have been attempted. Specifically, efforts to exteriorize the pancreatic fluid with a tube, to place a tube into the pancreatic duct, and to use synthetic somatostatin prophylactically have been attempted, but the reports have failed to show a statistically significant difference among the techniques<sup>[26,27]</sup>.

In this study, it was demonstrated that there were no significant differences in the incidence of pancreatic fistulas based on surgical technique. Therefore, we are of the opinion that the surgical technique should be individualized based on the patient's condition and the surgeon's preferences.

We demonstrated several risk factors related to pancreatic leakage after PD; age and pancreatic duct size were significantly correlated with an increased incidence of pancreatic fistula. In conclusion, it is important that surgeons are aware of these risk factors for pancreatic fistula formation when performing a PD.

## COMMENTS

### Background

Pancreaticoduodenectomy is technically difficult, and as a result, relatively high mortality (15%-30%) and complication rates (50%-75%) were reported before the 1980s. With advances in surgical techniques and perioperative care, the mortality rate associated with PD has since improved.

### Research frontiers

Most complications after PD commonly arise from failure in healing of the pancreaticojejunostomy, and have been described as pancreatic fistulas or anastomotic leakages by various authors.

### Innovations and breakthroughs

The incidence of developing pancreatic fistulas in patients older than 60 years of age was 21.7% (25/115), while the incidence was 8.8% (5/57) for younger patients; the difference was significant ( $P = 0.03$ ). The patients with a dilated pancreatic duct had a lower rate of post-operative pancreatic fistulas than the patients with a non-dilated duct ( $P = 0.001$ ).

### Applications

This study demonstrated that pancreatic fistulas are related to age and a dilated pancreatic duct. The surgeon must take these risk factors into consideration when performing a pancreaticoduodenectomy.

### Peer review

A well organized paper about the risk factors affecting pancreatic fistulas after pancreaticoduodenectomy.

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