

## Original Article

# The biomechanics and pathology in the duct-to-mucosa pancreaticojejunostomy

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**Abstract:** Background: Pancreatic fistula (PF) remains a significant problem causing the majority of mortality and morbidity after pancreaticoduodenectomy (PD). The aim of the research was to assess the surgical outcomes of duct-to-mucosa pancreaticojejunostomy (PJ) and invagination PJ after PD. Methods: Between 2011 and 2015, 120 patients in our hospital underwent duct-to-mucosa PJ after PD. All patients were recorded with variables factors and the risk factors for PF were studied by statistical analysis. To compare the difference between the duct-to-mucosa PJ and invagination PJ, the beagles (n=24) were divided into the group of duct-to-mucosa PJ (group A, n=12) and invagination PJ (group B, n=12). Enteric cavity physical pressure was measured following the postoperative 10 days at the identical pressure in 6 Beagles and bursting pressure was detected by artificial high pressure by double, triple, quadruple above the average pressure, and in the tenth day the breaking strength and pathology were assessed. Results: The incidence of PF is 7/120 (5.83%) and the operative mortality rate is 1/120 (0.83%). The pancreatic duct diameter and texture are related to PF by single factor analysis (\*P<0.05) and the independent determinants of PF by logistic regression analysis (\*P<0.05). The group A was the same as the group B in enteric cavity physical pressure after postoperative from 1 to 10 days. No PF was observed postoperative day from 1 to 10 days by double, triple and quadruple pressure in the group A but the group B had 2 beagles which appeared in double pressure on postoperative day 3 and day 5. Bursting pressure was  $272.13 \pm 22.20$  mmHg in group A on postoperative day 10 whereas  $141 \pm 14.51$  mmHg in group B (\*P<0.05). Breaking strength was  $9.35 \pm 0.35$  N in group A and  $6.5 \pm 0.30$  N in group B on postoperative day 10 (\*P<0.05). Anastomotic stoma was well repaired by granulation tissue in group A but no regeneration of the epithelium was found in group B. Conclusion: Anastomotic strength of duct-to-mucosa PJ was stronger than the invagination PJ and the healing in the former operating methods was safer and rapider.

**Keywords:** Pancreaticoduodenectomy, pancreaticojejunostomy, pancreas fistula

## Introduction

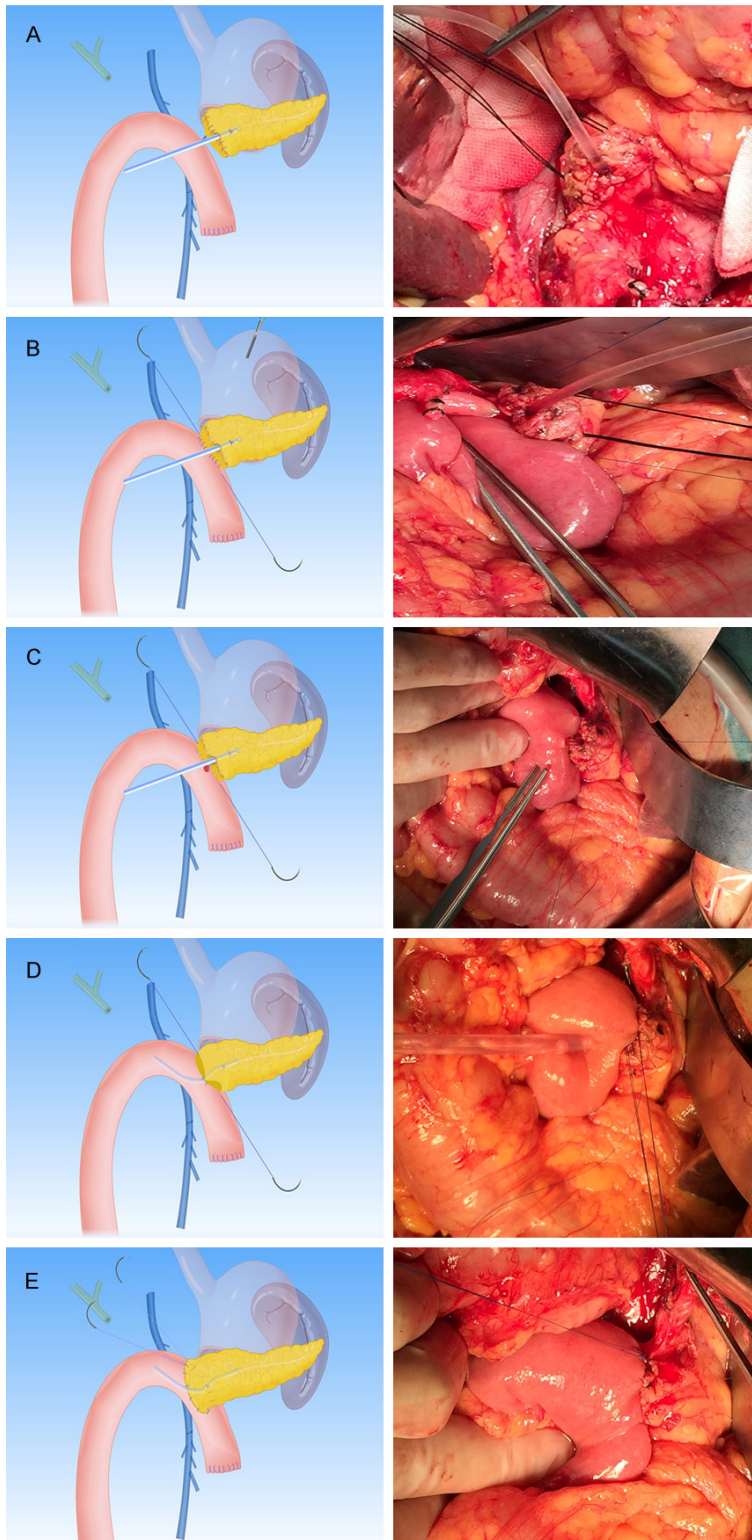
At present, PD is the main surgery to cure the benign and malignant diseases of the pancreas and periampullary region. After the complicated operation, a series of possible serious complications exists such as hemorrhage, PF, bile leakage, peritonitis, pancreatitis, sepsis, sero-peritoneum and multiple organ dysfunction syndrome (MODS). Among the anastomosis, the PJ remains the key procedure in the reconstruction of alimentary tract after PD, which could give rise to massive hemorrhage and fatal infections. Thanks to the quickly development of surgical techniques, PJ in PD has been down to 5% [1], but the postoperative complications are as high as 30-50% [2-5]. Among this,

the rate of PF is 10% on average. To decrease the rate of PF, much attempt to improve the surgical procedures has been done, which including the duct to mucosa PJ [6-8], invagination PJ [9], pancreaticogastrostomy [10]. In our research, 120 cases of PD in five years from 2011 to 2015 summarized by our medical centre along with the animal experiment to confirm that the duct-to-mucosa PJ is superior in decreasing the incidence of PF.

## Methods

### General information

In five years from 2011 to 2015, our medical team has implemented 120 cases of PD and all



**Figure 1.** Technique of surgery. A. After the cutting surfaces of pancreatic stump sutured, a 4-5 cm silastic tube with an appropriate diameter is placed into the pancreatic duct if the duct is dilated and fixed on the wall of the pancreatic duct with a 4/0 absorbable suture. B. The jejuna seromuscular layer is sutured continuously to the posterior lip of the pancreatic stump (including the partial pancreatic parenchyma) with a 4/0 prolene. The prolene should not be cut off and leaved to suture the anterior part. C. A small hole

is punctured on the jejuna mucosa and its posterior border is sewed to the posterior wall of the pancreatic duct with a 3/0 fine absorbable suture. D. This stent-tube is fixed in the anastomosis with sutures, 3 interrupted sutures are added at 3, 6, 9 o'clock direction. E. The incisal margin anterior to the jejuna seromuscular layer is sutured continuously to the anterior lip of the pancreatic stump.

of them conducted PJ. There were 43 men and 77 women with the age ranging from 21 years to 81 years. Postoperative pathology confirmed that 17 cases were periaampular tumors, 29 cases were malignant duodenal tumors, 47 cases were pancreatic head carcinoma, 22 cases were distal bile duct cancer, 1 case was lymphoma, 1 case was islet cell tumor, 1 case was sclerosing cholangitis and 2 cases were pancreatic benign tumor. The hemobilirubin was elevated in 75 cases and obstructive jaundice was occurred in 28 cases. Percutaneous transhepaticchoangial drainage (PT-CD) was conducted in 25 cases of the 28 cases prior to surgery. The volume and amylase contents of the drainage fluid were observed and detected every day postoperatively. PF was diagnosed according to the definition of the International Study Group of Pancreatic Surgery (ISGPS) [11], that is, amylase level in draining fluid was three times higher than the normal amylase level after the third postoperative day and the drain output exceeds 50 mL at the same time. According to the ISGPF clinical criteria, PF severity was classified into three grades. If the amylase contents of the drainage fluid was three times less than the serum level, the drain was removed from day 6 to day



**Figure 2.** Evaluation of the anastomotic stoma. A. The contrast agent was infused into enteric cavity utilizing the artificial high pressure created by altitude difference. B. To evaluate the fracture pressure of anastomotic stoma, solution bottle containing 1% methylthionine chloride was encased by sphygmomanometer cuffs and pressure was increased slowly until the mercury column took a nose dive. The same time methylthionine chloride was leaked from the anastomotic stoma and the maximum pressure was recorded. C. The anastomotic strength was measured subsequently according to de Waard JW and Zilling TL.

8 regardless of the volume drained. Abdominal CT was checked in all patients routinely to identify intraabdominal fluid collection.

## Surgical procedures

Firstly, after the cutting surfaces of pancreatic stump sutured, a 4-5 cm silastic tube with an appropriate diameter is placed into the pancreatic duct if the duct is dilated and fixed on the wall of the pancreatic duct with a 4/0 absorbable suture (**Figure 1A**). Then the jejuna seromuscular layer is sutured continuously to the posterior lip of the pancreatic stump (including the partial pancreatic parenchyma) with a 4/0 prolene. The prolene should not be cut off and leave to suture the anterior part (**Figure 1B**). A small hole is punctured on the jejuna mucosa and its posterior border is sewed to the posterior wall of the pancreatic duct with a 3/0 fine absorbable suture (**Figure 1C**). This stent-tube is fixed in the anastomosis with sutures, 3 interrupted sutures are added at 3, 6, 9 o'clock direction (**Figure 1D**). Finally, the incisal margin anterior to the jejuna seromuscular layer is sutured continuously to the anterior lip of the pancreatic stump (**Figure 1E**). Routine using of antibiotics and octreotide in all cases of patients undergoing PD.

## Animal experiment

**Animal:** Beagle, 24, male and female unlimited, about 10-12 kg (provided by Laboratory Animal Center of Nantong University). All animal work was performed in accordance with the institutional guidelines and was approved by the Animal Ethics Committee of Nantong University.

**Surgical procedures:** After anesthetized by injection of pentobarbital sodium intraperitoneally (5%, 2.4 ml/kg), an abdominal incision was operated and group A (duct-to-mucosa PJ) was conducted as described above. Group B (invagination PJ) was operated as follows. After PD, the pancreatic stump was isolated about 2-3 cm long and the wedgy cutting surfaces was sutured. The seromuscular layer of jejunal posterior wall and pancreatic capsule of the posterior cutting ends (including the partial pancreatic parenchyma) were sewed up with interrupted sutures. And then the whole layer of the posterior jejunal wall with the posterior lip of the pancreatic cutting end was sutured. When the inverting sutures between the whole layer of jejunal anterior wall and the anterior lip of pancreatic cutting end were completed, the pancreatic stump was invaginated into the jejunum. The seromuscular layer of the jejunal anterior wall and the pancreatic capsule were sewed up with interrupted sutures.

**Experimental methods:** Enteric cavity physical pressure was measured following the operative 10 days at the identical pressure in six Beagles and anastomotic stomas were detected with artificial high pressure by double, triple, quadruple above mentioned average pressure, and in the tenth day the anastomotic strength in vivo and histopathological findings were assessed.

To assess the enteric cavity physical pressure of anastomotic stomas, drainage tubes were inserted into enteric cavity 2 cm away from the stomas and the physical pressure was measured at three certain time (two hours before feeded).



**Table 1.** Single factor analysis of pancreatic fistula

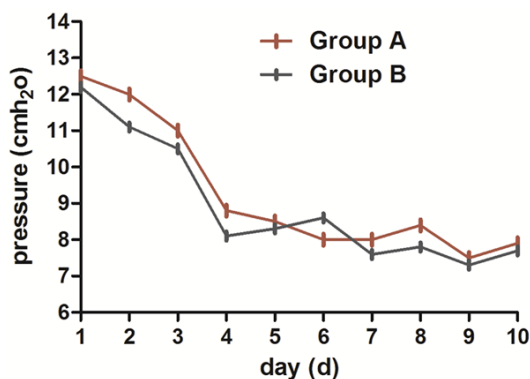
Risk factors	PF (+)	PF (-)	P
	7	113	
Age (y)	64.00±9.04	60.42±10.03	0.360
Gender (male/female)	2/5	41/72	0.680
Hemobilirubin (umol/L)	179.57±216.49	91.40±95.43	0.324
Hemoglobin (g/L)	117.43±11.79	126.18±18.14	0.211
Albumin (g/L)	34.87±2.20	36.67±5.41	0.384
CEA (ng/ml)	2.24±1.32	4.46±8.8	0.507
CA19-9 (U/ml)	1169.24±2770.73	987.33±2580.14	0.857
Pancreatic duct (<3/3≥ mm)	6/1	53/60	0.046*
Pancreatic texture (soft/hard)	6/1	47/66	0.023*

\*P<0.05 was considered significant.

**Table 2.** Logistic Regression Analysis of pancreatic fistula

	Hazard ratio	P	95% CI
Pancreatic duct (<3 mm)	7.185	0.007*	0.005-0.437
Pancreatic texture (soft)	7.905	0.005*	0.004-0.376

\*P<0.05 was considered significant.



**Figure 3.** Enteric cavity physical pressure. Enteric cavity physical pressure was usually higher before the recovery of gastrointestinal functions (on postoperative day 1, the pressure is 12.5 cm H<sub>2</sub>O on average in group A and 12.2 cm H<sub>2</sub>O in group B, on postoperative day 10, the pressure is 7.9 cm H<sub>2</sub>O in group A and 7.7 cm H<sub>2</sub>O in group B). But both the two pancreaticojejunostomy had the same enteric cavity physical pressure following the operation the first ten days.

The effect of artificial high pressure on anastomotic stoma. The jejunum was fixed on the abdominal wall 10 cm away from the distal of anastomotic stomas by 10 fine silk and the silk was penetrated outside. It would be fastened once measured. The contrast agent was infused into enteric cavity utilizing the artificial high pressure created by altitude difference (Figure 2A). The anastomotic fistula was ob-

served by X-ray at the artificial high pressure by double, triple, quadruple above mentioned average pressure.

The anastomotic strength in vivo and histopathological findings were assessed on the tenth day. To evaluate the fracture pressure of anastomotic stomas, solution bottle containing 1% methylthionine chloride was encased by sphygmomanometer cuffs and pressure was increased slowly until the mercury column took a nose dive. Meanwhile methylthionine chloride was leaked from the anastomotic stoma and the maximum pressure was

recorded (Figure 2B). The anastomotic strength was measured subsequently according to de Waard JW and Zilling TL (Figure 2C) [12, 13]. Briefly, the remaining pancreas was belayed by a proper ferrule and stress was increased by the wall pulley at the speed of 0.05 N/s in the horizontal direction. The maximum was recorded as the anastomotic strength.

The anastomotic stoma was completely resected and evaluated by histology.

#### Statistical analysis

Statistical analysis was performed using SPSS 19 software. Statistical differences were identified using student t test and logistic regression analysis when *p*-value of less than 0.05 were obtained.

#### Result

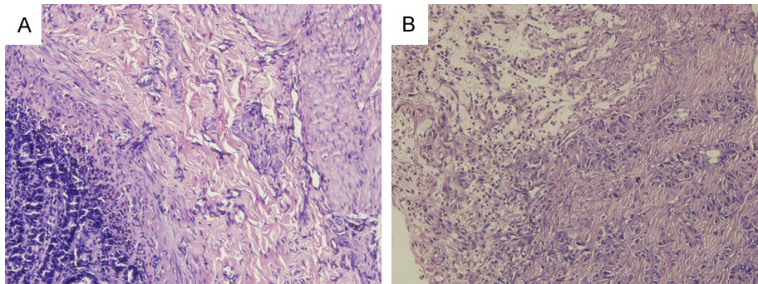
##### Patient

PD was successfully operated in all 120 cases. The average volume of drainage was 142±32 mL and amylase content of drainage was 886±146 U/L on the first postoperative day. On postoperative day 3, the average volume of drainage was 64±12 ml and amylase content in the drainage was 315±36 U/ L. Among those cases, amylase content in the drainage was more than 330 U/ L in 7 cases, 1 cases of post-

**Table 3.** The fracture pressure and anastomotic strength of anastomotic stoma

	Group A	Group B	P
The fracture pressure (mmHg)	272.13±22.20	141±14.51	P<0.05
The anastomotic strength (N/S)	9.35±0.35	6.5±0.30	P<0.05

\*P<0.05 was considered significant.



**Figure 4.** Histology assay (×20). A. In the group of duct-to-mucosa PJ, anastomotic stoma was repaired by the connective tissue and the serosa was firmly adherent to the pancreas. Inflammatory cells and capillaries of granulation tissue of pancreatic stumps decreased obviously. It's evident to observe the proliferation of fibroblast and collagenous fiber. B. In the group of invagination PJ, pathological examination revealed anastomotic stoma was full of extensive necrosis of cells in the pancreatic stump.

operative death in 30 days. On postoperative day 6, the drainage was 30±12 ml and amylase content was 162±24 U/L. According to the definition of the international team of pancreatic leakage, the incidence of PF was 5.83% (grade A is 3.33%, B level of 1.67% and C level of 0.83%). No significant differences in the age, gender, hyperbilirubinaemia, albumin were observed between the group of PF (+) and PF (-) groups (P>0.05, **Table 1**). But difference between the pancreatic duct diameter and pancreatic texture has the statistical significance (\*P<0.05, **Table 1**). In addition, the pancreatic duct diameter and pancreatic texture were shown as the independent determinants of PF on logistic regression analysis (\*P<0.05, **Table 2**).

#### Animal

In the Beagles operated by invagination PJ, two of them died after executing artificial high pressure on anastomotic stoma on the postoperative day 3 and day 5. The postmortem revealed that the leakage of contrast medium in the abdominal cavity. The X-ray radiography indicated the fistula orifice was occurred on the side of mesangial in another 2 deaths. However no deaths were reported in the group A. Also, the postmortem didn't find any abnormality.

The average time of PJ was 43.7±3.2 min in duct-to-mucosa PJ and 62.3±3.5 min in invagination PJ (\*P<0.05). It's significant that less time in the operation would lead to less chance of trauma, less pain for the patient, and ultimately speed recovery.

Enteric cavity physical pressure was usually higher before the recovery of gastrointestinal functions. But both the two PJ had the same enteric cavity physical pressure following the postoperative ten days (**Figure 3**).

The anastomotic stoma was observed by X-ray at the artificial high pressure by double, triple, quadruple above mentioned average pressure. In the group A, there was no PF in all 6 cases. But in the group

B, PF occurred in 2 cases on the postoperative day 3 and day 5 at the artificial high pressure by double above mentioned average pressure.

The fracture pressure of anastomotic stoma was 272.13±22.20 mmHg in the group A and 141±14.51 mmHg in the group B (**Table 3**, \*P<0.05).

The anastomotic strength was 9.35±0.35 N/S in the group A and 6.5±0.30 N/S in the group B (**Table 3**, \*P<0.05).

Histology was performed on the postoperative day 10. In the group A, anastomotic stoma was repaired by the connective tissue and the serosa was firmly adherent to the pancreas. Inflammatory cells and capillaries of granulation tissue of pancreatic stumps decreased obviously. It's evident to observe the proliferation of fibroblast and collagenous fiber (**Figure 4A**). But in the group B, pathological examination revealed that the anastomotic stoma was full of inflammatory cells and the granulation tissue was not obvious observed. Also, extensive necrosis of cells were existed in the pancreatic stump (**Figure 4B**).

#### Discussion

Over the past decades, substantial efforts including technical and pharmacological have

been taken to improve the safety of PJ after PD. PF remains one of the feared complications after PD in recent years, associated with alimentary tract hemorrhage, peritonitis, pancreatitis, sepsis, seroperitoneum, peritoneal abscesses, bile leakage, and delayed gastric emptying [14-16]. These consequences directly result in the increase of hospitalization expense and extension of hospitalization time [17]. What's worse, delayed hemorrhage could increase the risk of mortality rate up to 40%.

PJ is a kind of reconstruction between two different tissues, which is different from the reconstruction between the same tissues. So it can lead to noninfectious inflammatory response and pancreatic juice could be leaked from the unhealed anastomotic stoma and pinhole, especially when the pancreas is soft and the exocrine functions is strong. Plenty of pancreatic juice will induce the pancreas to the self digestion. Eventually, the PF occurs. In recent years, lots of studies have found that risk factors leading to PF include age, gender, BMI, diabetes, cardiovascular disease, hemobilirubin, albumin, hemoglobin, pancreatic texture, pancreatic duct diameter, operation method, pancreatic drainage, peritoneal drainage and bleeding during operation [18-20]. Among those factors, pancreas texture (soft) and pancreatic duct diameter (<3 mm) are widely recognized as the independent risk factors giving rise to PF [21]. In our study, the incidence of PF after PD is 5.83%, which is in accord with most of the reported researches [22, 23]. In addition, our study show there is no significant differences between the group of PF (+) and PF (-) groups in consideration of the age, gender, hyperbilirubinaemia, albumin. But difference between the pancreatic duct diameter and pancreatic texture has the statistical significance. Considering the pancreatic duct diameter and pancreatic texture as the objective factors, therefore the surgical procedures and quality of anastomosis of PJ performed by the surgeon is somewhat important. In general, before the recovery of gastrointestinal functions, about 1000-2000 mL liquid secreted by pancreas will accumulate around the anastomosis and trypsin-induced pancreatic tissue inflammation caused by self digestion will result in anastomotic bleeding and PF. Poor blood supply of anastomotic stoma, high tension and careless handling of pancreatic stump as the local factors can be

controlled by improving the surgical technique. The duct-to-mucosa PJ employed by us could prevent the PF happening in the following reasons: 1) Pancreatic ducts are rich in collagen fibers and elastic fibers, which make it elastically similar to the mucosa of jejunum. So the inner layer isn't easy to be ruptured and therefore avoid PF; 2) Anastomosis stoma between the pancreatic duct and jejunum requires four symmetrical sutures using absorbable suture which will make the stoma satisfactory; 3) The outer layer between the pancreatic capsule and serosa of jejunum requires continuous sutures using 4-0 prolene. Not only assuring the outer and inner layer connected firmly which could prevent the pancreatic juice from outflowing to protect the pancreatic stump, but the intestinal juice is kept out to protect the stoma; 4) The silastic tube in the pancreatic duct is inserted into the jejunal lumen could transport the pancreatic juice to the distal of jejunum which enables the pancreatic juice not to be activated around the stoma. Not only promoting the heal up of anastomotic stoma, but making the pancreatic juice outflow fluently. The absorbable suture will be decomposed on the postoperative day 30 and the silastic tube could be released into the jejunal lumen. On postoperative day 1 in the 120 cases, the volume and amylase contents of the drainage fluid is higher on account of acute stress reaction, peritoneal lavage and minor pancreatic duct in the stump of pancreas. But on postoperative day 3, the volume and amylase contents decreased significantly and returned to normal on postoperative day 6. In our animal experiment, there was no PF in the group A, but four cases in group B, which confirmed the surgical procedures we adopted was reliable.

In general, the anastomotic stoma would be stretched by intestinal pressure and the heavy intestinal loop where accumulating pancreatic juice and bile. So the fracture pressure and anastomotic strength of stoma are usually adopted to detect the stoma. The fracture pressure is the resistance to the increasing enteric cavity physical pressure and the anastomotic strength is the resistance to tensile force in longitudinal. After surgery, the enteric cavity physical pressure of anastomotic stoma and the artificial high pressure by double, triple, quadruple above mentioned average pressure were detected and recorded to monitor the serious

postoperative complications. Histopathology of the stoma on postoperative day 10 revealed that the serosa was firmly adherent to the pancreas, and the inflammatory cells decreased obviously. Finally the fibroblast and collagenous fiber proliferated obviously. But in the group B, the anastomotic stoma were full of extensive necrosis of cells in the pancreatic stump. Also, compared to the group B, the less time group A took would reduce the incidence of additional damage. As a consequence, it would have a good influence on the postoperative recovery.

## Conclusion

The research confirmed the duct-to-mucosa PJ is superior in resisting to the fracture pressure and anastomotic strength compared to traditional invagination PJ. No matter which surgical procedures to choose, it's of great importance for the surgeons to improve the surgical technique and pay attention to detail. Those efforts will be the cornerstones to decrease the rate of PF.

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## Disclosure of conflict of interest

None.

## Abbreviations

MODS, Multiple organ dysfunction syndrome; PF, Pancreatic fistula; PD, pancreaticoduodenectomy; PJ, pancreaticojejunostomy; POPF, post-operative pancreatic fistula; PTCD, Percutaneous transhepaticcholangial drainage; ISGPS, International Study Group of Pancreatic Surgery.

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