

Pancreatic stump closure using only stapler is associated with high postoperative fistula rate after minimal invasive surgery

Adem Yüksel, Erdal Birol Bostancı, Muhammet Kadri Çolakoğlu, Murat Ulaş, İlter Özer, Kerem Karaman, Musa Akoğlu

Department of Gastroenterological Surgery, Türkiye Yüksek İhtisas Education and Research Hospital, Ankara, Turkey

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ABSTRACT

Background/Aims: Postoperative pancreatic fistula (POPF) is the most common cause of morbidity and mortality after distal pancreatectomy (DP). The aim of the present study is to determine the risk factors that can lead to POPF.

Materials and Methods: The study was conducted between January 2008 and December 2012. A total of 96 patients who underwent DP were retrospectively analyzed.

Results: Overall, 24 patients (25%) underwent laparoscopic distal pancreatectomy (LDP) and 72 patients (75%) open surgery. The overall morbidity rate was 51% (49/96). POPF (32/96, 33.3%) was the most common postoperative complication. Grade B fistula (18/32, 56.2%) was the most common fistula type according to the International Study Group on Pancreatic Fistula definition. POPF rate was significantly higher in the minimally invasive surgery group (50%, $p=0.046$). POPF rate was 58.6% (17/29) in patients whose pancreatic stump closure was performed with only stapler, whereas POPF rate was 3.6% (1/28) in the group where the stump was closed with stapler plus oversewing sutures. Both minimally invasive surgery (OR: 0.286, 95% CI: 0.106-0.776, $p=0.014$) and intraoperative blood transfusion (OR: 4.210, 95% CI: 1.155-15.354, $p=0.029$) were detected as independent risk factors for POPF in multi-variety analysis.

Conclusion: LDP is associated with a higher risk of POPF when stump closure is performed with only staplers. Intraoperative blood transfusion is another risk factor for POPF. On the other hand, oversewing sutures to the stapler line reduces the risk of POPF.

Keywords: Pancreatic fistula, distal pancreatectomy, remnant pancreatic stump, endo-stapler

INTRODUCTION

Distal pancreatectomy (DP) is a standard procedure for benign or malignant lesions localized to the pancreatic body and tail. Additionally, it is performed as a part of radical tumor resection of adjacent organs (e.g., colon, stomach, and left adrenal, among others) invading the pancreas (1,2). Recently, perioperative mortality rates after DP have been reported as low as 0%-6% at tertiary centers (3). However, despite advances in surgical techniques and postoperative patient care, perioperative morbidity is still high ranging from 30% to 50% (4,5).

Postoperative pancreatic fistula (POPF) is the most common cause of morbidity and mortality after DP (6). Different definitions are used in the literature for POPF. The most widely accepted POPF definition is described by the International Study Group on Pancreatic Fistula (ISGPF) in 2005 (7). This classification compares several different studies. POPF rate after DP has been reported

as 20%-40% (8). POPF may lead to clinically significant and life-threatening complications such as intra-abdominal abscess, intra-abdominal bleeding, surgical site infections, and sepsis. These complications adversely affect patient health and have led to an increase in hospital stay and costs.

There are several studies in the literature to identify the risk factors affecting the development of POPF. In these studies, researchers were focused more on pancreatic remnant stump closure technique, simultaneous resection of other organs (6). Although, various different surgical techniques have been described, there is still no consensus regarding a standard surgical technique for pancreatic stump closure (9).

The aim of the present study is to determine the risk factors that are associated with the development of POPF after DP.

ORCID IDs of the authors: A.Y. 0000-0002-7486-9498; E.B.B. 0000-0002-0663-0156; M.K.Ç. 0000-0002-6283-943X; M.U. 0000-0002-3507-8647; İ.Ö. 0000-0001-6902-0913; K.K. 0000-0003-0143-9712; M.A. 0000-0001-9429-2689.

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Address for Correspondence: Adem Yüksel E-mail: drademyuksel@gmail.com

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MATERIALS AND METHODS

After obtaining approval from the ethics committee, 96 patients who underwent DP between January 2008 and December 2012 in Türkiye Yüksek İhtisas Teaching and Research Hospital, Department of Gastroenterological Surgery were retrospectively analyzed.

Demographic data including age, gender, the American Society of Anesthesiologists (ASA) score, diabetes mellitus, smoking, albumin, creatinine and hemoglobin values, indication of operation, preoperative tumor size, body mass index (BMI), surgical technique, additional organ resection, closure techniques of the pancreatic remnant stump, operative time, blood loss and blood transfusions, hospital mortality, need for reoperation, duration of hospitalization, and re-hospitalization for each patient were analyzed.

Surgical technique

All surgical procedures were performed by or under supervision of two gastrointestinal surgeons. Resection was performed with conventional surgery or minimally invasive surgery (laparoscopic) technique. Resection was classified as spleen protective DP, DP with splenectomy, or DP plus splenectomy along with multi-organ resection. Multi-organ resection was defined as DP with resection of an abdominal organ other than the spleen.

Transection and closure of the remnant pancreatic stump were performed by LDP with endo-stapler using blue (3.5 mm) or green (4.8 mm) cartridges according to the thickness of the pancreas.

On the other hand, three different stump closure techniques were used for open surgery following pancreatic transection with electrocautery or a scalpel:

- 1) closure of remnant pancreatic stump with continuous suture: remnant pancreatic stump was closed with continuous oversewing non-absorbable 2-0 polypropylene or absorbable 2-0 polyglactin suture, depending on the surgeon's preference.
- 2) closure of remnant pancreatic stump with continuous suture after pancreatic duct ligation: following transection of the pancreas, the orifice of the pancreatic duct was ligated with non-absorbable 4-0 polypropylene suture, and pancreatic remnant stump was closed with continuous oversewing non-absorbable 2-0 polypropylene or absorbable 2-0 polyglactin suture.

- 3) closure of remnant pancreatic stump with stapler and suture: closure of the pancreatic stump was performed with linear stapler using blue or green cartridges according to the thickness of the pancreas. In addition, the stapler line was closed with continuous non-absorbable oversewing 2-0 polypropylene or absorbable 2-0 polyglactin suture.

As a consequence, all pancreatic resections were performed by distal approach in patients who underwent open surgery, and any additional effort was performed after transection to identify the orifice of the remnant pancreatic duct. However, if the pancreatic duct was visible, ligation of the pancreatic duct was preferred. The groups were performed retrospectively according to the surgical interventions mentioned above.

Fistula definitions

Mortality is defined as death occurring within 30 days after surgery. Hospital readmission is defined as hospitalization during the first month after discharge. POPF is defined according to the definition of ISGPF in 2005 (7). POPF is defined when the amylase level in drain fluid is three times higher than the serum amylase on the third postoperative day. ISGPF classifies the severity of POPF according to the clinical condition of the patient as Grades A, B, and C. Grade A fistula has no clinical impact, whereas patients with Grade B fistula often require supportive treatment such as total parenteral nutrition or enteral nutrition. Grade C is associated with severe clinical complications and requires invasive therapy.

Management of POPF

In the case of POPF, wide-spectrum antibiotic treatment was started empirically and changed according to drain fluid or wound culture results. Octreotide, a somatostatin analog, was started immediately to decrease the leak flow rate. Additionally, ultrasound or CT guided percutaneous drainage was performed in the presence of intra-abdominal fluid collection. In the cases where the leak flow rate does not fall, endoscopic stent placement into the duct of Wirsung was performed.

Statistical analysis

Data analysis was performed using Statistical Package for Social Sciences for Windows 11.5 (SPSS Inc.; Chicago, IL, USA) package program. The average difference between the groups in terms of its significance was assessed by Student's t-test, and the significance of

difference in terms of median values was evaluated by Mann-Whitney U test. Categorical variables were evaluated with Pearson's chi-square test or Fisher's exact test. In order to determine the most predictive factors to distinguish groups with or without POPF development, we used a multivariate logistic regression analysis method. Variables with a value of $p < 0.25$ after univariate statistical analysis were included in multivariate logistic regression models as candidate for risk factors. Odds ratio of each variable and 95% confidence intervals were calculated. A p value < 0.05 was considered as statistically significant.

RESULTS

The mean age was 54.1 ± 14.3 years (range: 21-83 years). A total of 45 patients (46.9%) were men, and 51 patients (53.1%) were women. Overall, 20 patients (20.8%) had ASA-I score, 46 patients (47.9%) had ASA-II score, and 30 patients (31.3%) had ASA-III score. Table 1 shows the

Table 1. Distribution of patients regarding indications of distal pancreatectomy

Variables	n=96
Benign	26 (27.1%)
IPMN*	5 (5.2%)
Mucinous neoplasia	6 (6.2%)
Serous cyst	9 (9.4%)
Other	6 (6.2%)
Malignant	12 (12.5%)
Adenocarcinoma	8 (8.3%)
Mucinous cyst adenocarcinoma	2 (2.1%)
Other	2 (2.1%)
Extrapancreatic malignancy	22 (22.9%)
Gastric adenocarcinoma	20 (21%)
Colon adenocarcinoma	2 (2.1%)
NET**	25 (26.0%)
Non-functional NET	18 (18.7%)
Insulinoma	5 (5.2%)
Other	2 (2.1%)
Pancreatic pseudocyst	4 (4.2%)
Chronic pancreatitis	3 (3.1%)
Other	4 (4.2%)
GIST***	2 (2.1%)
Solid pseudopapillary neoplasia	2 (2.1%)

*IPMN: intraductal papillary mucinous neoplasia; **NET: neuroendocrine tumor; ***GIST: gastrointestinal stromal tumor

indications for DP. Resections were performed in 24 patients (25%) by LDP and in 72 patients (75%) by open surgery. None of the patients with LDP were converted to open surgery. Spleen preserving DP was performed in 13 patients (13.5%), and DP with splenectomy was performed in 83 patients (86.4%). In 43 patients (44.8%), one or more additional organ resection was performed within DP. Overall, 72 patients underwent open surgery. Transection of the pancreas was performed in 38 patients (52.8%) by electrocautery and in 34 patients (47.2%) by scalpel. No significant difference was found between the usage of scalpel and electrocautery regarding the rate of POPF (electrocautery (POPF developed in 11 patients) vs scalpel (POPF developed in 9 patients), $p=0.15$). The mean operation time was 240 ± 80.4 min. The median intraoperative blood loss was 125 ml (min-max: 10-1200). Intraoperative erythrocyte suspension replacement was required in 10 patients (10.4%).

Remnant pancreatic stump was most commonly closed using stapler and sutures. In 4 patients (4.2%) of the endo-stapler group, tissue adhesive Tisseel® (Baxter, Deerfield, IL, USA) was additionally used. POPF developed in 32 patients (33.3%). Grade B fistula developed in 18 patients (56.2%), Grade A fistula in 11 patients (34.4%), and Grade C fistula in 3 patients (9.4%). POPF was significantly higher in patients undergoing laparoscopic surgery where the stump closure was performed with only stapler ($p < 0.001$). On the other hand, POPF occurred significantly less in the open surgery group in which the pancreatic stump closure was achieved using stapler plus oversewing sutures ($p < 0.001$) (Table 2). Table 3 shows the other complications out of POPF.

Two mortalities (2.1%) were reported. Both patients were operated for gastric cancer. One of the patients had an anastomotic leak from the esophagojejunostomy line. In addition, intra-abdominal hemorrhage occurred. The patient underwent percutaneous drainage for intra-abdominal abscess following stent placement to the esophagojejunostomy line. However, the patient died due to sepsis. The other patient died from multi-organ failure due to Grade C fistula-related intra-abdominal abscess. Duration of hospitalization and re-hospitalization period were significantly higher in patients who developed POPF ($p=0.024$ and $p < 0.001$, respectively).

When patients were compared according to demographic data and clinical characteristics, the frequency

Table 2. Distribution of patients according to pancreatic fistula type and pancreatic stump closure

Pancreatic fistula				
No		64 (66.7%)		
Yes		32 (33.3%)		
Pancreatic fistula type (n=32)				
A		11 (34.4%)		
B		18 (56.2%)		
C		3 (9.4%)		
Pancreatic stump closure		Non-fistula (n=64)	Fistula (n=32)	p
Suture	22 (22.9%)	12 (54.5%)	10 (45.5%)	0.170
Suture+ligation	17 (17.7%)	13 (76.4%)	4 (23.6%)	0.345
Stapler	29 (30.2%)	12 (41.4%)	17 (58.6%)	<0.001
Stapler+suture	28 (29.2%)	27 (96.4%)	1 (3.6%)	<0.001

Table 3. Distribution of patients according to postoperative complications out of POPF

Variables	n=96
Intra-abdominal collection	10 (10.4%)
Superficial surgical site infection	10 (10.4%)
Pneumonia	6 (6.3%)
Intra-abdominal hematoma	3 (3.1%)
Anastomotic leak	2 (2.1%)
Ileus	2 (2.1%)
Anastomotic leak+bleeding	1 (1.0%)
Intra-abdominal abscess+ pneumonia+intra-abdominal hematoma	1 (1.0%)
Postoperative diabetes mellitus	1 (1.0%)
Bleeding	1 (1.0%)
Pleural effusion	1 (1.0%)
Pulmonary embolism	1 (1.0%)
Total	39 (40.6%)

of POPF was significantly higher in smokers (p=0.028) (Table 4).

In univariate analysis, type of the surgical procedure (open vs laparoscopic) was the only significant risk factor in developing POPF (p<0.046) (Table 5).

Table 4. Demographic data and characteristics of patients with fistula and non-fistula

Variables	Non-fistula (n=64)	Fistula (n=32)	p
Age (year)	54.1±13.5	54.2±16.2	0.972
Gender			1.000
Male	30 (66.6%)	15 (34.4%)	
Female	34 (66.6%)	17 (34.4%)	
BMI (kg/m ²)	26.5±3.8	27.5±3.6	0.259
BMI			0.300
<25.0 kg/m ²	18 (69.2%)	8 (30.8%)	
25.0-29.99 kg/m ²	38 (70.3%)	16 (29.7%)	
≥30 kg/m ²	8 (50%)	8 (50%)	
Diabetes mellitus	16 (72.7%)	6 (27.3%)	0.492
Smoking	5 (38.4%)	8 (61.6%)	0.028
ASA score			0.479
I	15 (75%)	5 (25%)	
II	28 (60.8%)	18 (39.2%)	
III	21 (70%)	9 (30%)	
Hemoglobin(g/dl)	12.6±1.9	12.6±1.9	0.925
Creatinine (mg/dl)	0.75 (0.34-1.46)	0.78 (0.48-1.60)	0.337
Albumin (mg/dl)	4.4 (2.1-5.1)	4.4 (2.6-5.5)	0.892
Indication			
Benign pathology	16 (61.5%)	10 (38.5%)	0.516
Malign pathology	8 (66.6%)	4 (33.4%)	1.000
Extra pancreatic malignancy	15 (68.2%)	7 (31.8%)	0.864
Neuroendocrine tumor	18 (72%)	7 (38%)	0.511
Pseudocyst	2 (50%)	2 (50%)	0.599
Chronic pancreatitis	3 (100%)	0 (0.0%)	0.548
Other	2 (50%)	2 (50%)	0.599

*IPMN: intraductal papillary mucinous neoplasia; **NET: neuroendocrine tumor; ***GIST: gastrointestinal stromal tumor

In multivariate logistic regression analysis, type of the operation, operation time, and intraoperative blood loss and blood transfusion were included as risk factors, with a p value of <0.25. Of these, LDP (OR: 0.286, 95% CI: 0.106-0.776, p=0.014) and intraoperative blood transfusion (OR: 4.210, 95% CI: 1.155-15.354, p=0.029) were both detected as independent risk factors for POPF (Table 6).

Table 5. Univariate analysis in determining intraoperative risk factors for postoperative pancreatic fistula

Variables	Non-fistula (n=64)	Fistula (n=32)	p
Operation type			0.046
Conventional surgery	52 (72.2%)	20 (28.8%)	
Minimally invasive surgery (laparoscopy)	12 (50%)	12 (50%)	
Splenectomy	56 (67.4%)	27 (32.6%)	0.755
Multi-organ resection	31 (72.0%)	12 (38.0%)	0.310
Operation time (min)	240 (100-570)	225 (120-515)	0.674
Operating time (>240 min)	30 (73.1%)	11 (26.9%)	0.243
Intraoperative blood loss (cm ³)	100 (10-450)	150 (10-1200)	0.502
Intraoperative blood loss (≥400 cm ³)	6 (46.1%)	7 (53.9%)	0.117
Intraoperative blood transfusion (units)	0 (0-1)	0 (0-4)	0.053
Tumor size	3 (1-10)	3 (0.8-12)	0.701
Pancreatic resection length	9.1±3.1	9.9±3.6	0.309

*IPMN: intraductal papillary mucinous neoplasia; **NET: neuroendocrine tumor; ***GIST: gastrointestinal stromal tumor

Table 5. Multivariate analysis in determining intraoperative risk factors for postoperative pancreatic fistula

Variables	Odds ratio	95% CI	p
Minimally invasive surgery	0.286	0.106-0.776	0.014
Intraoperative blood replacement	4.210	1.155-15.354	0.029

*IPMN: intraductal papillary mucinous neoplasia; **NET: neuroendocrine tumor; ***GIST: gastrointestinal stromal tumor

DISCUSSION

Risk factors affecting POPF are uncertain (10,11). Various technical and demographic factors including closure technique of the remnant pancreatic stump, existence of splenectomy, indication of surgery, multi-organ resection status, prolonged operative time, and BMI have been evaluated as risk factors (1,5,12).

In some previous studies, male gender is reported as a risk factor for POPF (13). In the present study, although male patients have a higher incidence of Grade B fistula, this result was not statistically significant.

Nathan et al. (14) reported smoking as a risk factor for POPF. Similarly, smoking was also found to be a risk factor in univariate analysis of the present study. Smoking is associated with a 5.3 times higher risk of developing POPF. However, it was not identified as an independent risk factor in multivariate logistic regression analysis.

In the study by Ferrone et al. (12), multi-organ resection increases the risk of POPF. On the other hand, no significant association was found in the present study between multi-organ resection and development of POPF. Again in the study by Ferrone et al. (12), patients who underwent DP plus gastric resection comprise 15% of patients having multi-organ resection with a rate of 28% POPF. However, this rate is 71% in DP plus colon or small bowel resection. In the present study, 53.4% of patients with multi-organ resection (23/43) were composed of patients who underwent gastric resection. This might be the reason of unrelated status between multiple organ resection and POPF development of the present study.

Intraoperative blood transfusion is also evaluated as a risk factor for POPF (13-16). Several studies have shown that intraoperative blood transfusion increases the rate of surgical mortality, sepsis, pulmonary complications, or renal complications and impairs wound healing (17,18). Intraoperative blood transfusion may increase the rate of POPF by disrupting wound healing due to impaired immunity.

Transection of the pancreas with stump closure appears to be the most critical step in the development of POPF (6). Current literature does not allow recommending for the site or direction of transection (19). Effects of pancreatic transection on POPF whether by using scalpel or electrocauterization have not shown a clear superiority. In the study by Takahashi et al. (20), transection with scalpel is significantly less associated with POPF after pancreaticoduodenectomy. However, this effect is not yet been laid in the healing of the pancreatic stump following DP. Further, Dorcaratto and his colleagues (21) claimed in their study that coagulative necrosis of the transected surface caused by thermal injury with subsequent reactive fibrosis may provide a stronger "defense" against pancreatic stump leak. Results of the present study show that the rate of POPF did not significantly alter when pancreatic transection was performed by scalpel or electrocautery.

Several studies highlight the closure technique of the remnant pancreatic stump as the main risk factor in

POPF development (22-25). Therefore, many stump closure techniques have been described (24-28). However, debates continue on this issue. In the present study, four different stump closure techniques were used. Univariate analysis revealed a 10.5-fold increase in developing POPF when remnant pancreatic stump is closed only with stapler. Yoshioka et al. (27) reported in their study the POPF rate as 50% where all remnant pancreatic stumps are closed with only stapler. Kah Heng et al. (28) defined the closure of pancreatic stump with only stapler as an independent risk factor for POPF. In the DISPACT multicenter randomized controlled study, results of the comparison of suture versus stapler closure techniques showed that POPF rate is higher (36%) in the stapler group (29,30). In the present study, POPF rate after LDP was 50% (12/24). Both univariate and multivariate analyses of the present study showed LDP as an independent risk factor for POPF. In the literature, there are few studies evaluating the relationship between minimally invasive surgery and POPF. In the study by Butturini et al. (31), POPF rate is 44.4% after minimally invasive surgery. In the same study, after initiation to use different types of endo-staplers, POPF rate decreases to 16%. In the study by Soh et al. (32), POPF rate is reported as 70% after LDP. In the present study, POPF rate was 58.6% (17/29) in patients whose remnant pancreatic stump was closed with only stapler. According to these findings, closure of the pancreatic remnant stump with only stapler appears to be unsafe.

In the present study, POPF rate was 3.5% (1/28), where the remnant pancreatic stump was closed with both stapler and oversewing sutures. Similarly, Nathan et al. (14) reported a decrease in the rate of POPF (6%) after closure of the pancreatic stump with both stapler and oversewing sutures. These results suggest closure of the remnant pancreatic stump with stapler plus oversewing sutures as an ideal technique.

Soft pancreatic texture is accepted as a strong risk factor for POPF after pancreaticoduodenectomy (33,34). On the other hand, pressure of the sphincter of Oddi and thickness of the pancreas rather than softness are considered as the main risk factors for POPF after DP. Although transection of the pancreas at the level of the neck is associated with less POPF owing to thinner texture than the tail, results of previous studies are comparable (0%-27% vs 7%-21%) (19). In the present study, the length of the resected part of the pancreas was similar in patients who developed both POPF and none, suggesting that the site

of transection did not significantly alter the risk of POPF (Table 5).

The present study has several limitations. First, it is retrospective in nature. Second, the sample size is small. Third, softness of the pancreas is not clearly documented which does not allow statistical comparison.

In conclusion, results of the present study indicate that POPF rate after DP is 33.3%. The risk of POPF is determined by intraoperative variables rather than the demographic or clinicopathologic characteristics of the patients. Intraoperative blood transfusion is a risk factor for POPF. LDP is associated with a higher risk of POPF when pancreatic stump closure is performed with only staplers. On the other hand, using additional oversewing sutures to the stapler line reduces the risk of POPF.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethical Committee of Gastroenterological Surgery, Türkiye Yüksek İhtisas Training and Research Hospital (Decision Date: February 2013).

Informed Consent: Written informed consent obtained from the patients who participated in this study.

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