Risk factors for pancreatic fistula after pancreaticoduodenectomy

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Introduction
Pancreaticoduodenectomy (PD) remains the gold-standard surgical procedure performed for both benign and malignant diseases of the pancreas and periampullary region, and the only hope of cure in such cases. Postoperative pancreatic fistula (POPF) is the most common major and serious complication after PD. The aim of this study was to identify the risk factors for pancreatic fistula after PD, and to correlate between these risk factors and the incidence of pancreatic fistula.

Patients and methods
This is a retrospective and prospective study that included all patients who underwent PD from January 2015 to May 2021. The study included 120 patients with periampullary lesions. The data were collected and statistically analyzed. One of the most serious complications in the early postoperative period is pancreatic fistula (pancreatic leak), which was defined as drain-fluid volume greater than 10 ml/day, with elevation of the drain-amylase level three times higher than the serum. The 120 patients were divided into two groups (group 1): patients who developed POPF, and (group 2): patients without POPF.

Results
The cohort of 120 cases that underwent PD comprised 80 males and 40 females, with the mean age of 51.3±8.2 years. Obstructive jaundice was the commonest symptom in 108 patients (90%), followed by weight loss in 72 patients (60%), and abdominal pain in 66 patients (55%). Postoperative complications occurred in 45 patients (38%). Pancreatic leakage occurred in 14 (12%) patients, bile leakage in seven (6%) patients, delayed gastric emptying in nine (7.5%) patients, and postoperative bleeding in 11 (9%) patients. Postoperative mortality occurred in 14 patients, eight of them were due to POPF and its related sepsis. With multivariate analysis of the significant risk factors, the authors found that soft pancreatic texture, pancreatic duct diameter less than 3 mm, operative time, and blood loss are independent risk factors for development of POPF.

Conclusion
POPF is still regarded as the most relevant and severe complication of pancreatic surgery. In this study, we found that soft pancreatic texture, pancreatic duct diameter less than 3 mm, operative time, and blood loss are independent risk factors for the development of POPF. However, more randomized studies, preferably multicenters, need to be conducted to better confirm which way of anastomosis and method of reconstruction decrease the incidence of POPF and its related mortality.

Keywords:
pancreatic fistula, pancreaticoduodenectomy, periampullary tumors

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Introduction

Pancreaticoduodenectomy (PD) remains the gold-standard surgical procedure performed for both benign and malignant diseases of the pancreas and periampullary region, and the only hope of cure in such cases [1].

PD is a complex and high-risk procedure. Nowadays, the mortality rate has decreased to less than 3–5%, whereas the morbidity rate remains high (30–50%), even at high-volume centers [2].

Postoperative pancreatic fistula (POPF) is the most common major complication after PD. The incidence of pancreatic fistulas after PD is reportedly 6–25%, and the mortality rate remains from 2% to 10% in high-volume centers [3].

Pancreatic fistula has been recently defined by International Study Group on Pancreatic Fistula (ISGPF) as drain output of any measurable volume of fluid on or after postoperative day 3 with amylase content greater than three times that of normal serum amylase. Three grades were applied according to the clinical impact, from grade A (none) to grade C (significant) [4].

Many scientific studies have tried to identify the risk factors for the development of pancreatic fistulas. Although several factors have been proposed as determining a risk for pancreatic fistula development, only a few are independent factors, and they vary among the different studies [2].

Aim of the work

The aim of this study was to identify the risk factors for pancreatic fistula after PD, and to correlate between these risk factors and the incidence of pancreatic fistula.

Patients and methods

Study population and design

This is a multicenter retrospective and prospective study that included all patients who underwent PD at Hepatopancreaticobiliary Surgical Department at the National Liver Institute, Menoufia University and the General Surgery Department, Faculty of Medicine, Menoufia University, from January 2015 to May 2021. The retrospective part was from January 2015 to June 2020 and the prospective was from June 2020 to May 2021.

The POPF was defined and graded according to the ISGPF published by Bassi and colleagues in 2005 and revised by the same group in 2016 [5,6]. Grade A POPF is called a biochemical fistula and is defined as measurable fluid output on or after postoperative day 3, with an amylase content higher than three times the upper normal serum level. Clinically significant POPFs are classified as grades B and C. Grade B POPF requires one of the following conditions: an endoscopic or radiological intervention, a drain in situ for more than 3 weeks, clinical symptoms without organ failure, or clinically relevant change in POPF management. Whenever a major change in clinical management or deviation from the normal clinical pathway is required or organ failure occurs, the fistula shifts to a grade C POPF [6]. The 120 patients were divided into two groups (group 1): patients who developed POPF, and (group 2): patients without POPF. Informed consents were taken from all the prospective patients, and the study was accepted from the Institutional Review Boards.

Data collection

Patient data were retrieved from the medical records of Hepatopancreaticobiliary Surgical Department, National Liver Institute, Menoufia University and General Surgery Department, Faculty of Medicine, Menoufia University, and were analyzed.

Inclusion criteria

The present study included 120 patients with periampullary lesions who underwent PD. The retrospective study included 100 patients, and the prospective one included 20 patients. The data were collected and statistically analyzed.

These data included patient's demographics (age – sex – BMI), and the preoperative data (clinical presentation, associated comorbidities). Preoperative laboratory and radiological investigations were done for all the patients. Operative data included type of PD (standard or pylorus-sparing), blood transfusions (type and number of units), operative time (from skin incision to skin closure), consistency of pancreas (soft or hard), type of anastomosis [pancreatojejunostomy (PJ) or pancreatogastrostomy (PG)], and pancreatic duct stenting.

Postoperative data included postoperative events in the early postoperative period, with special concern to the development of POPF and other complications. Hospital and ICU stay, histopathological examination of the resected mass, and size of the tumor were also reported. Follow-up: clinical examination, radiological, and laboratory investigations were done for all the patients.

Outcomes

The complications will be reported in the early postoperative period, which includes: first, morbidity: (1) pancreatic leak (defined as drain-fluid volume >10 ml/day, with elevation of the drain-amylase level three times higher than the serum). (2) Bile leak (defined as bilious discharge from intra-abdominal drain). (3) Delayed gastric emptying (defined as the need for nasogastric tube for more than 10 days because of persistent vomiting or sluggish intestinal movement). (4) Bleeding requiring blood transfusion. (5) Reexploration (cause, findings, and the procedure). Second, mortality: postoperative mortality (causes).

Operative technique

Incision and exploration

Exposure for a PD was performed through a bilateral subcostal incision in most of our cases and was enhanced with the use of our mechanical retracting device. At first, the extent of disease and resectability was assessed with thorough exploration.

Resection phase

An extensive Kocher maneuver is performed allowing the visualization of the superior mesenteric artery at its origin from the aorta.

The gallbladder is resected through the fundus-first technique, and is left attached, to be removed later with the whipple specimen. The gastrohepatic ligament is partially divided with an electrocautery, while small vascular and lymphatic bundles are secured by sutures and divided.

The distal common hepatic duct is divided close to the level of the cystic-duct entry site early during the operation. The bile duct is retracted caudally, and a dissection plane is opened on the anterior surface of the portal vein.

The gastroduodenal artery is identified within the hepatoduodenal ligament and is test-clamped prior to its division. After the gastroduodenal artery is divided, a plane is then created posterior to the pancreatic neck and anterior to the portal vein (PV) at their interface at the superior boundary of the pancreas.

The proximal duodenum is then separated from the pancreatic head by the creation of a tunnel ~2–3 cm distal to the pylorus. The duodenum is transected at this point [pylorus preserving pancreatoduodenectomy (PPPD)]. In cases where there is tumor encroachment upon the first portion of the duodenum, or concerning lymphadenopathy in the prepyloric region, a classic PD is performed, which involves up to 20–30% distal gastrectomy, dividing the distal stomach several centimeters proximal to the pylorus.

The pancreatic head and uncinate process are further mobilized and the right gastroepiploic artery and vein are ligated. The superior mesenteric vein (SMV) is identified as it issues from under the neck of the pancreas and crosses ventrally over the third portion of the duodenum in the groove between the uncinate process and the transverse mesocolon. Care is taken at this point to avoid injury to the SMV. A vascular tape is passed through this tunnel, to elevate the pancreatic neck.

Stay sutures are placed superiorly and inferiorly on the pancreatic remnant to reduce bleeding from the segmental pancreatic arteries running in those locations. The pancreatic neck is then divided after confirming a free plane anterior to the portal and superior mesenteric veins.

The proximal jejunum is transected ~10–15 cm distal to the ligament of Treitz. The distal line is invaginated with sutures, as this will serve as the jejunal limb for reconstruction. The proximal jejunal mesentery is taken down between clamps and 2-0 silk ties or Harmonic instrument (HARMONIC scalpel shears manufacted and supplied by ETHICON a part of Johnson and Johnson), up to the ligament of Treitz. The region is freed up enough to pass the proximal devascularized jejunum (part of the specimen) underneath the mesenteric vessels and into the right upper quadrant.

The pancreatic head and uncinate process are now gently separated from the right lateral border of the PV and SMV, and subsequently the superior mesentric artery (SMA). The specimen is then removed, and hemostasis was assured.

Reconstruction phase

A defect is made in the transverse mesocolon to the right of the middle colic vessels, through which the proximal jejunal limb is delivered into the right upper quadrant. Care is taken to ensure that the jejunum lies flat without twisting its mesentery. All anastomoses are performed above the transverse mesocolon, in a retrocolic fashion.

The pancreatic remnant is mobilized for 2 cm ventrally off the splenic vein, to facilitate the PJ. The PJ is performed with an outer posterior layer of interrupted sutures placed as a horizontal mattress between the posterior aspect of the pancreatic remnant and the seromuscular layer of the jejunum.

A duct to the mucosa, or end-to-side or invagination technique of anastomosis is done using 5/0 PDS-interrupted stitches.

PG, in which the pancreatic stump is anastomosed to the posterior wall of the stomach, is done in some of the cases as preferred by some surgeons.

The hepatojejunostomy is done by making a small jejunotomy on the antimesenteric border of the jejunum, ~10 cm distal to the completed PJ. The anastomosis is created using interrupted 4-0, or 5-0

PDS sutures, depending upon the size and thickness of the bile duct.

The duodenojejunostomy or gastrojejunostomy is performed distal to the hepaticojejunostomy, in a R-en-Y manner or with enteroenterostomy before the gastrojejunostomy to prevent bile reflux into the stomach. It is performed in two layers, end-to-side fashion, using interrupted 3-0 or 4-0 PDS sutures for the outer posterior and anterior rows.

Two round-tube drains are placed exiting the abdomen on either side in the anterior axillary line, well below the lowest palpable rib. The right-sided drain is placed in the subhepatic space, and the left-sided drain is placed through the gastrocolic ligament and a few centimeters cephalad to the PJ.

Statistical analysis

All data were statistically analyzed using Statistical Package for the Social Sciences (SPSS). Quantitative data were expressed as a mean±SD, while qualitative data were expressed as frequency and percentages. Qualitative variables were compared using a χ^2–test, while quantitative continuous data were compared using the Mann–Whitney test. Multiregression model analysis was conducted for significant variables.

A *P* value less than 0.05 was considered statistically significant. A univariant analysis with nonlinear correlation (cubic-spline functions) was used to evaluate the shape of the relationship between the continuous variables and outcome.

Results

Between the first of January 2015 and the end of May 2021, 120 patients underwent PD at the university hospitals of National Liver Institute and Faculty of Medicine, Menoufia University. Patients were categorized into two groups: the first group is patients who developed pancreatic fistula (14 patients), and the second group is patients who did not develop pancreatic fistula (106 patients). Grading of group 1 (patients with POPF): grade A: two cases, grade B: three cases, and grade C: nine cases.

Demographics and preoperative comorbidities

The cohort of 120 cases who underwent PD comprised 80 (67%) males and 40 (33%) females with mean age of 51.3±8.2 years. Male sex had nearly equal distribution with female with no significant correlation between the two groups (*P*=0.29).

Patients with old age more than 60 years have liability of developing pancreatic fistula more than the patients under 50 years, with significant *P* value of 0.04. Diabetes mellitus was the most common comorbid factor in such patients, which represents 41% (50 patients), followed by hypertension by 30% (36 patients), then chronic liver diseases due to hepatitis-C virus infection by 12% (14 patients). Eight patients who developed pancreatic fistula had comorbidities (hypertension and chronic liver disease), with no significant risk factors between the two groups (*P*=0.81). Diabetes mellitus and obesity are considered as risk factors for developing POPF as shown in Table 1.

Clinical presentations of the patients

Obstructive jaundice was the commonest symptom, being reported in 108 patients (90%), followed by weight loss in 72 patients (60%). Abdominal pain was present in 66 patients (55%), anorexia in 63 patients (53%), and vomiting and itching in 50 patients (42%). No significant correlation in clinical presentation between the two groups, as shown in Table 2.

Table 1 Comparison between the two groups regarding the demographics and preoperative comorbidities

Characteristics	All patients (*N*=120 patients) [mean±SD/ number (%)]	Group 1: developed POPF (*N*=14 patients) [mean±SD/number (%)]	Group 2: not developed POPF (*N*=106 patients) [mean±SD/number (%)]	Test	*P* value
Age	51.3±8.2	62.5±8.4	49.3±7.4	87.2	**0.041**
Sex				4.1	0.29
Male	64 (53.3)	7 (50)	57 (53.77)		
Female	56 (46.7)	7 (50)	49 (46.23)		
Comorbidites					
Hypertension	36 (30)	6 (42)	30 (28.3)	1.8	0.82
Chronic liver disease	14 (11.6)	2 (14)	12 (11.3)	2.4	0.71
Diabetes mellitus	50 (41.6)	3 (21.4)	47 (44.3)	105	**0.021**
Obesity	40 (33.3)	8 (57)	32 (30)	102	**0.023**

POPF, postoperative pancreatic fistula. Patients with old age more than 60 years have liability of developing pancreatic fistula more than the patients under 50 years, with significant *P* value of 0.04.

Table 2 Comparison between the two groups regarding the clinical presentation of the patients

Characteristics	All patients (*N*=120 patients)	Group 1: developed POPF) (*N*=14 patients) [*N* (%)]	Group 2: not developed POPF) (*N*=106 patients) [*N* (%)]	Test	*P* value
Jaundice	108 (90)	12 (85.7)	96 (90.5)	1.6	0.42
Weight loss	72 (60)	8 (57)	64 (60.3)	1.4	0.48
Abdominal pain	66 (55)	7 (50)	59 (55.6)	1.8	0.38
Anorexia	63 (53)	7 (50)	56 (52.8)	1.1	0.82
Itching	50 (42)	6 (42.8)	44 (41.5)	1.2	0.75
Vomiting	50 (42)	7 (50)	43 (40.5)	2.5	0.23

POPF, postoperative pancreatic fistula.

Table 3 Comparison between the two groups regarding the preoperative laboratory data

Characteristics	All patients (*N*=120 patients) (mean±SD)	Group 1: developed POPF (*N*=14 patients) (mean±SD)	Group 2: not developed POPF (*N*=106 patients) (mean±SD)	Test	*P* value
Total bilirubin	4.75±1.9	5.2±0.8	4.3±3.1	0.4	0.52
ALK phosphatase	131±16.2	153.2±21.4	109.8±11.5	1.4	0.26
GGT	72.5±4	70.5±3.6	74.6±4.5	0.12	0.7
TLC	7.6±2.7	7±1.8	8.2±3.6	1.5	0.21
Hemoglobin	11.15±1.65	10.8±1.5	11.5±1.8	2.4	0.15
CRP	63.7±4.3	57±4.8	70.4±3.8	0.01	0.92
Albumin	3.2±59	3±0.5	3.4±0.68	3.1	0.12
ALT	67.7±10.9	73.8±19.5	61.7±2.3	1.1	0.28
AST	67.6±14.4	73.1±23.7	61.2±5.2	1.02	0.29
CA 19-9	204.4±18.75	263.8±16.5	145±21	1.2	0.27

ALK phosphatase, alkaline phosphatase; ALT; alanine aminotransferase; AST, aspartate transaminase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase; POPF, postoperative pancreatic fistula; TLC, total leukocytic count.

Indications of PD

A total of 86 patients (72%) had pancreatic head lesions, 22 patients (18%) had ampullary masses, and eight patients (7%) had tumors in the distal part of CBD, while four patients (3%) had tumors of the duodenum. Patients with biliary tumors (ampulla and distal CBD) (25%) had high susceptibility of developing POPF than pancreatic head tumors.

Preoperative laboratory data

Preoperative complete blood count: Preoperative complete blood count was done for all the patients and showed different degrees of anemia reported in 26 (22%) patients and leukocytosis in 23 (19%). Mean preoperative hemoglobin value for all patients was 11.15 mg, with no significant correlation between the two groups (*P*=0.15).

Preoperative liver-function tests: Preoperative liver-function tests were done a day before the operation for all the patients and showed that most of them had high bilirubin, being reported in 78 (65%) patients. In total, 41 patients (34%) had hypoalbuminemia. Mean albumin level for all the patients was 3.2 mg, with no significant correlation between the two groups (*P*=0.12).

Preoperative CA19.9: CA19.9 was done preoperatively for all the patients. It was elevated in 77 (64%) patients, with no significant correlation between the two groups (*P*=0.27) as shown in Table 3.

Preoperative biliary drainage: Preoperative biliary drainage was done for 55 (46%) patients. A total of 48 (40%) of them by endoscopic retrograde cholangiopancreatography (ERCP) stenting and seven (6%) patients by percutaneous transhepatic drainage (PTD), with no significant correlation between the two groups (*P*=0.25).

Intraoperative data

Intraoperative findings: pancreatic texture: 81 (68%) patients had soft pancreas, while 39 (32%) had firm pancreas. A total of 93% of patients who developed POPF had soft pancreas, while 65% of patients without POPF had soft pancreas with high significant correlation (0.001).

The pancreatic duct diameter: Normal caliber (3 mm) was shown in 62 (52%) patients and dilated (<3 mm) in 58 (48%). Patients with pancreatic duct diameter 3 mm or less had high liability of developing POPF than patients with pancreatic duct more than 3 mm, with significant correlation (*P*=0.001).

Table 4 Comparison between the two groups regarding the intraoperative findings

Characteristics	All patients (*N*=120) [mean±SD/number (%)]	Group 1: developed POPF (*N*=14 patients) [mean±SD/number (%)]	Group 2: not developed POPF (*N*=106 patients) [mean±SD/number (%)]	Test	*P* value
Pancreas texture				112	**0.001**
Soft	81 (67.5)	13 (93)	68 (64)		
Firm	39 (32.5)	1 (7)	38 (36)		
PD diameter				160	**0.001**
≤3 mm	62 (51.6)	11 (78.5)	51 (48)		
>3 mm	58 (48.3)	3 (21.5)	55 (52)		
Tumor size	3.9±0.2	4.1±0.2	3.7±0.2	2.3	0.17

POPF, postoperative pancreatic fistula. A total of 93% of patients who developed POPF had soft pancreas, while 65% of patients without POPF had soft pancreas with high significant correlation (0.001). Patients with pancreatic duct diameter 3 mm or less had high liability of developing POPF than patients with pancreatic duct more than 3 mm, with significant correlation (*P*=0.001).

Table 5 Comparison between the two groups regarding the operative techniques and blood loss

Characteristics	All patients (*N*=120) [mean±SD/number (%)]	Group 1: developed POPF (*N*=14 patients) [mean±SD/number (%)]	Group 2: not developed POPF (*N*=106 patients) [mean±SD/number (%)]	Test	*P* value
Type of PD				8.2	0.12
Classic	87 (72.5)	9 (64)	78 (73.5)		
PPPD	33 (27.5)	5 (36)	28 (26.4)		
Anastomosis type				98	**0.012**
PG	31 (26)	4 (28.5)	27 (25.4)		
PJ (invagination)	15 (13)	0	15 (14.2)		
PJ end-to-side	34 (28)	4 (28.5)	30 (28.3)		
PJ duct-to-mucosa	40 (33)	6 (42.8)	34 (32)		
PD stent	In 34 patient (28%)	3 (21.5)	31 (29.2)	65	**0.03**
Operative time	Range: 4–11 Mean: 6.96±2.6 h	8±1.2 h	6.8±0.8 h	160	**0.005**
Blood loss	Range: 150–2500 ml Mean: 920±521.23	1250±150 ml	884±80 ml	125	**0.003**
Blood transfusion	In 86 patient (72%)	10 (71.4)	76 (71.6)	2.3	0.35

PD, pancreaticoduodenectomy; PG, pancreatogastrostomy; PJ, pancreatojejunostomy; PPPD, pylorus preserving pancreatoduodenectomy; POPF, postoperative pancreatic fistula. Mean operative time in group 1 (POPF) was 8 h, which was significantly higher than group 2 (6.8 h) with significant correlation (*P*=0.005). Mean blood loss volume in group 1 (POPF) (1250 ml) was significantly higher than group 2 (not POPF) (884 ml) with significant correlation (*P*=0.003).

The tumor size ranged from 1.5 to 8 cm (mean 3.6) with no significant correlation between two groups regarding developing POPF (*P*=0.17) as shown in Table 4.

Operative technique, operative time, intraoperative blood loss, and blood transfusion: Most of the patients underwent classic whipple PD 87 (72.5%), while 33 (27.5%) patients underwent PPPD. PG was done in 31 (26%) cases, PJ end-to-end drinking or invagination) in 15 (13%) cases, PJ end-to-side in 34 (28%) cases, and PJ with duct-to-mucosa in 40 (33%) cases. In total, 71.4% of patients (10 patients) who developed POPF had undergone PJ, while 28.5% patients (four patients) with POPF had undergone PG. Duct-to-mucosa PJ was considered a risk factor for developing of POPF (42.5% of cases with duct-to-mucosa anastomosis developed POPF) with significant correlation (*P*=0.012).

The operative time in our patients ranged from 4 to 11 h (mean 6.2±2.3 h). Mean operative time in group 1 (POPF) was 8 h, which was significantly higher than group 2 (6.8 h) with significant correlation (*P*=0.005).

Pancreatic duct stenting had been used in 34 (28%) patients aiming to avoid postoperative pancreatic leak. Only three patients who underwent pancreatic duct stenting develop POPF. In addition, 29.2% of cases who did pancreatic stenting do not develop POPF with significant correlation (*P*=0.03).

Table 6 Multivariate analysis of significant risk factors

Parameter	*B*	SE	Wald	Expected *B*	Confidence interval (CL=95%)	*P* value
Age (≥60 years)	1.08	0.24	2.51	1.01	0.41–1.09	0.1
Diabetes mellitus	0.59	0.41	12.5	0.62	0.4–1.15	0.06
Obesity	1.01	0.35	4.3	0.98	0.8–1.4	0.12
Biliary masses	1.1	0.25	7.3	1.02	1.06–1.45	0.24
Pancreas texture (soft)	1.3	0.28	17.5	1.22	0.9–1.8	**0.03**
PD diameter (<3 mm)	1.5	0.16	20.5	1.4	0.79–0.2.2	**0.01**
Pancreatojejunostomy (duct-to-mucosa)	1.1	0.17	8.8	1.02	0.99–1.62	0.09
Operative time	1.2	0.28	15.4	1.1	0.98–1.5	**0.04**
Blood loss	1.1	0.34	13.2	1.05	1.01–1.2	**0.05**

As regards intraoperative blood loss, the minimum blood loss intraoperatively was 150 ml, while the maximum blood loss was 2500 ml (mean 870). Mean blood loss volume in group 1 (POPF) (1250 ml) was significantly higher than group 2 (not POPF) (884 ml) with significant correlation (P=0.003).

Most of our patients received intraoperative blood transfusion, 86 (72%) patients. Thirty-four (28%) patients did not receive blood transfusion. These data are shown in Table 5.

Postoperative data

Postoperative morbidities: Postoperative complications occurred in 45 patients (38%). Pancreatic leakage occurred in 14 (12%) patients, bile leakage in seven (6%), delayed gastric emptying in nine (7.5%) patients, and postoperative bleeding in 11 (9%) patients. Six (5%) patients had hematemesis and melena due to bleeding peptic ulcers, and in the other two (1.5%) patients, the cause of the bleeding cannot be defined in the form of melena. Wound infection developed in 25 (21%) patients, and wound dehiscence developed in seven (6%) patients. Seven cases (6%) of these patients underwent reoperation: pancreatic leak complicated with wound dehiscence in three (2.5%) patients to repair postoperative bile leak complicated with wound dehiscence in three (2.5%), and control of bleeding in one (1%) patient.

Postoperative mortality

Postoperative mortality occurred in 14 patients (11.7%), eight of them (6.7%) due to POPF and related sepsis.

Postoperative hospital and ICU stay

Postoperative ICU stays ranged from 1 to 22 days (mean: 4.3±3.8). The hospital stays were defined as the time from the day of admission in the surgical department, till the day of discharge, and it ranged from 2 to 67 days (mean: 15.6±12.5). Interestingly, patients who developed POPF (group 1) had longer hospital stay and ICU stay (23, 12 days, respectively) than group 2 (12, 5.5 days, respectively), with significant correlation (0.002, 0.002).

Multivariate analysis of significant risk factors

We did regression-analysis model for significant risk factors. We found that soft pancreatic texture, pancreatic duct diameter less than 3 mm, operative time, and blood loss are independent risk factors for development of POPF as shown in Table 6.

Discussion

PD is the standard surgical treatment for tumors of the pancreatic head, proximal bile duct, duodenum, and ampulla, and represents the only hope of cure in cases of malignancy. PD is the gold-standard surgical procedure performed for both benign and malignant diseases of the pancreas and periampullary region [1].

When it was first introduced, and until the late 1970s, the reported mortality and morbidity rates were high (>20%). Nowadays, the mortality rate has decreased to less than 3–5%, 2–4 whereas the morbidity rate remains high (30–50%), even at high-volume centers. POPF is the most common major complication after PD. It is a potentially serious and life-threatening event that may lead to prolonged hospital stay and increased costs [2].

There is a high variability in the reported rates of POPF. The incidence of pancreatic fistulas after PD is reportedly 6–25%, and the mortality rate remains from 2% to 10% in many hospitals [3].

Many scientific studies have tried to identify the risk factors for the development of PFs. Although several factors have been proposed as determining a risk for PF development, only a few are independent factors, and they vary among the different studies [2,7].

The objective of this study was to identify the risk factors for pancreatic fistula after PD and to correlate between these of pancreatic fistula.

In this study, the number of males was more than the number of females and constitutes about 2/3 of the total number of patients, with the age of few patients more than 70 years. Male sex and old age more than 60 years had high liability of developing POPF than female sex and younger patients less than 50 years with significant correlation. Faraj *et al.* [8] demonstrated that the patients over the age of 65 undergoing PD have increased postoperative mortality rates compared with younger patients largely due to an increased risk of septic shock. Also, Greenblatt *et al.* [9], in a large multicentric study, demonstrated that older patients and male sex are preoperative risk factors associated with 30-day morbidity. However, many risk factors examined in the various studies (e.g. age, sex, ethnic group, acute and chronic pancreatitis, smoking habit, and diabetes mellitus) did not show any significant difference between patients who presented with and those who did not present with POPF [2]. This is in accordance with our study that does not show a significant difference between age and sex, and the occurrence of POPF.

The ICU stay and hospital stay were very variable. This of course depends on the mortality and complications that affect these parameters. However, the clinical presentation of our patients involved in this study was as expected, being jaundice is the most common presentation, followed by weight loss and abdominal pain. Moreover, total and direct serum bilirubin showed elevation in only about 2/3 of our patients. This is explained by the fact that many of the patients were drained preoperatively by either ERCP or PTD in about 1/2 of the patients (46%).

It has been demonstrated that preoperative release of obstructive jaundice by endoscopic or percutaneous biliary drainage neither influences postoperative mortality and morbidity when compared with the group of patients who did not receive preoperative biliary drainage nor increases operative time. On the other hand, however, many results have recommended relieving biliary obstruction preoperatively to correct the alterations induced by jaundice and to reduce perioperative mortality and morbidity after PD. Some authors explained the different results may be due to most of these trials were retrospective, and some included heterogeneous groups of patients, as well as a variety of different surgical procedures [10]. Our study shows that only two patients with normal bilirubin had POPF. However, this was not statistically different for the occurrence of the fistulas.

In this study, the consistency of the pancreas was soft in most of the cases (68%) and duct size was normal in about half the cases of PD. Soft pancreatic texture and pancreatic diameter less than 3 mm are considered independent risk factors for development of POPF by multivariate analysis.

Moreover, this study showed that tumor size is very variable and even the big size does not prevent radical surgery in selected cases. However, this study shows that there was statistical significance between the occurrence of the POPF and the soft pancreas and small duct size.

Mechteld *et al.* [11] declared that the impact of tumor size on the outcome after PD remains controversial. Moreover, he reported that the size of the pancreatic tumor was noted to impact perioperative and intraoperative management. Patients with larger tumors had longer operating times, more intraoperative blood loss, and more importantly, tumor size was associated with the surgeon's ability to achieve a microscopically (R0) negative surgical margin.

In this study, soft pancreatic remnant was a risk factor with the incidence of postoperative pancreatic leak. This was statistically significant.

This risk factor might be explained by the ability of a firm and fibrotic pancreatic stump to hold sutures securely and facilitate pancreatic anastomosis. It is also possible that the limited exocrine function of a fibrotic pancreas makes it less likely to induce leakage of pancreatic juice [12].

Many studies confirmed our results. They indicated soft pancreatic texture as an independent risk factor for POPF after PD [2,12].

As regards the pancreatic duct diameter and its effect on postoperative pancreatic leakage, we found that the pancreatic diameter was an independent risk factor.

The main pancreatic duct diameter of 3 mm or less can complicate the accomplishment of a safe pancreatic–enteric anastomosis. Moreover, it reflects the possibility that adequate anastomosis of the pancreatic duct and active exocrine function are deeply involved in the formation of POPF [13,14].

A recent study from Al Mansoura University evaluated the effect of the postoperative use of octreotide on the postoperative outcomes of PD in patients with soft pancreas and nondilated pancreatic duct. In this study, PG was used for pancreatic reconstruction. This study showed that octreotide did not affect the incidence of POPF and other complications [15].

In this study, about 3/4 of our cases (72.5%) were treated by classic PD and the rest by PPPD, and the way of anastomosis was variable. As regards the type of pancreatic–enteric reconstruction, we found that the type of reconstruction was not a risk factor for the incidence of POPF.

McKay *et al.* [16] suggested that PG is better than PJ for reconstruction of the pancreatic remnant after PD as it results in a significant decrease in the incidence of pancreatic fistula or leak.

However, the best anastomosis technique for pancreatic surgery has remained controversial. A Belgian study reported comparative results of the occurrences of POPFs (grade B or C) in an randomized control trial (RCT) with 329 patients. They stratified the randomization according to the pancreatic duct diameter, and the results clearly demonstrated that the occurrence of POPF was significantly lower after PG than after PJ [17].

Conversely, a German multicenter RCT [18] demonstrated that there was no significant difference in the rate of grade B/grade C fistulas after PG versus PJ.

Recently, some meta-analysis results have been reported and demonstrated the apparent superiority of PG in minimizing the risk for POPF, despite the slight difference in the included studies [19,20].

Meanwhile, El Nakeeb *et al.* [21] found that PJ has physiological advantages compared with PG although the follow-up periods were relatively short.

On the other hand, for the way of anastomotic reconstruction, Berger *et al.* [22] demonstrated that the pancreatic leakage rate was higher in patients who underwent end-to-end PJ as compared with invagination PJ.

Recently, a transpancreatic U-suture technique was devised by Blumgart and colleagues, and the ratio of clinically relevant PFs was reported to be only 6.9% in the original report [23].

Other researchers have conducted confirmatory studies and reported that the occurrence rates of POPFs were less than 5% [24].

The rationale of duct-to-mucosa PJ is the secure drainage of pancreatic juice into the intestinal lumen. The anastomotic procedure, however, is not always easy, particularly with narrow pancreatic ducts. The invagination method in which the cross-sectional surface was inserted into the intestinal lumen might be a better option of duct-to-mucosa PJ as an easier reconstruction method [25].

In this study, pancreatic duct stenting technique was used in 34 patients (28%). Only three patients of them (21%) developed postoperative pancreatic leak. However, the use of this technique in reduction of the incidence of postoperative pancreatic leak was not statistically significant.

Several studies have reported that draining the pancreatic juice from the PJ anastomosis with a stent placed in the main pancreatic duct is an effective method to promote the healing of the anastomotic site by preventing pancreatic trypsin from corroding the anastomotic site during the early period after surgery, thereby reducing the rate of POPFs after PD [26].

Moreover, recent RCTs have been conducted to examine the short-term outcomes of patients with external or internal stents compared with those without stents after PJ. However, there were no differences in the incidence of POPFs or other morbidities between the stent (external or internal) and the no-stent groups [27,28].

Some studies reported that there has been no conclusion as to whether a pancreatic duct stent for internal or external drainage can reduce the pancreatic leakage rate after PD. However, the overall pancreatic leakage rate in patients with a pancreatic stent was found to be like that in patients without a stent [29]. However, it is safer to use an internal drainage stent for patients with a small pancreatic duct and a soft pancreas.

In this study, the mean of blood loss in patients with postoperative pancreatic leak was 1250 ml, while in patients without pancreatic leak, it was 870 ml. Moreover, intraoperative blood loss was found to be

statistically significant with the incidence of postoperative pancreatic leak being more liable to occur when the blood loss is about 1250 ml or more. This was in accordance with many other studies [10].

In this study, leakage from the pancreatic anastomosis (POPF) happened in 12% of cases, and mortality in our study happened in 7%, about half were due to fistula and related sepsis.

Many studies confirmed our results and demonstrated that pancreatic fistula is the most important factor strongly linked with death in most case series and remains the leading cause of morbidity after PD [30,31].

Conclusion

POPF is still regarded as the most relevant and severe complication of pancreatic surgery, and it might develop intra-abdominal infection, hemorrhage, shock, and consequently death in some cases. Furthermore, POPF leads to increased healthcare costs and prolonged hospital stay. Our study showed that soft pancreatic texture, pancreatic duct diameter less than 3 mm, operative time, and blood loss are independent risk factors for development of POPF. Several studies to reduce the incidence of POPF have been made in recent years. More randomized studies, preferably multicenters, need to be conducted to better confirm which way of anastomosis and method of reconstruction decrease the incidence of POPF and its related mortality. Therefore, innovative studies should be performed to standardize surgical techniques and perioperative management.

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Conflicts of interest

There are no conflicts of interest.

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