Risk factors for postoperative pancreatic fistula after pancreaticoduodenectomy National Liver Institute Experience.

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Abstract

AIM

To analyze the risk factors for pancreatic fistula after pancreaticoduodenectomy.

METHODS

We conducted a retrospective analysis of 310 successive cases of pancreaticoduodenectomy performed at department of hepatopancreaticobiliary surgery, National liver institute, Menoufia University from 1st Jan 2015 to 31st Dec 2023 . Pancreatic fistula was diagnosed in strict accordance with the definition of pancreatic fistula from the International Study Group on Pancreatic Fistula. The risk factors for pancreatic fistula were analyzed by univariate analysis and multivariate logistic regression analysis.

RESULTS

A total of 90 (29.0%) cases of pancreatic fistula occurred after pancreaticoduodenectomy, including 18 (16.2%) cases of grade A pancreatic fistula, 59(53.1%) cases of grade B, and 13 (11.7%) cases of grade C. Univariate analysis showed no significant correlation between postoperative pancreatic fistula (POPF) and the following factors: age, hypertension, alcohol consumption, smoking, history of upper abdominal surgery, preoperative jaundice management, preoperative bilirubin, preoperative albumin, pancreatic duct drainage, intraoperative blood loss, operative time, intraoperative blood transfusion, Braun

anastomosis, and pancreaticoduodenectomy (with or without pylorus preservation). Conversely, a significant correlation was observed between POPF and the following factors: gender (male *vs* female: 55.6% *vs* 44.4%, $P = 0.671$), diabetes (non-diabetic *vs* diabetic: 38.9% *vs* 61.1%, $P = 0.010$), body mass index (BMI) (≤ 25 *vs* > 25: 44.4% *vs* 55.6%, $P = 0.301$), , pancreaticojejunal anastomosis technique (pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis *vs* pancreatic-jejunum single-layer mucosa-to-mucosa anastomosis: 55.6% *vs* 40.0%, $P = 0.019$), diameter of the pancreatic duct (≤ 3 mm *vs* > 3 mm: 53.3% *vs* 46.7%, $P = 0.014$), and pancreatic texture (soft *vs* hard: 54.4% *vs* 45.6%, $P = 0.036$). Multivariate logistic regression analysis showed that gender (male), BMI > 25, Diabetes, pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis, pancreatic duct diameter ≤ 3 mm, and soft pancreas were risk factors for pancreatic fistula after pancreaticoduodenectomy.

CONCLUSION

Gender (male), BMI > 25,Diabetes, pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis, pancreatic duct diameter ≤ 3 mm, and soft pancreas were risk factors for pancreatic fistula after pancreaticoduodenectomy.

Keywords: Pancreaticoduodenectomy, Pancreatic fistula, Pancreaticojejunal anastomosis, Pancreatic duct, Complications

Core tip: Pancreaticoduodenectomy remains the standard surgical approach for tumors involving the lower bile duct, the pancreatic head, the duodenal papilla, and the ampulla. This operation is considered risky because of high rates of postoperative mortality and complications. In this study, we collected a large sample of 310 cases and analyzed several potential risk factors for pancreatic fistula. A statistical analysis of the case data showed that gender (male),BMI >25, Diabetes, pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis, pancreatic duct diameter ≤ 3 mm, and soft pancreas were risk factors for pancreatic fistula after pancreaticoduodenectomy.

INTRODUCTION

Pancreaticoduodenectomy is the primary treatment for malignant tumors involving the pancreatic head, the lower bile duct, and the duodenal ampulla[1,2]. The safety of pancreaticoduodenectomy has been greatly improved; however, perioperative mortality rate still ranges from 0%-5%[3-5]. Studies have reported that the incidence of pancreatic fistula after pancreaticoduodenectomy is approximately 11.4%-64.3%[6-16]. Pancreatic fistula remains the most common complication after pancreaticoduodenectomy, and this complication prolongs hospital stays and leads to high medical expenses. Pancreatic fistula is associated with delayed gastric emptying, abdominal abscesses, infection at the incision, sepsis, and bleeding after pancreaticoduodenectomy[17-20]. Several approaches may reduce the incidence of pancreatic fistula after pancreaticoduodenectomy; however, to date, a definitive approach that prevents pancreatic fistula is still lacking[21-23]. In this study, we conducted a retrospective analysis of 310 successive cases of pancreaticoduodenectomy performed over more than 3 years in the Department of Hepatobiliary Surgery of theNational liver institute Menofia university , to determine the potential risk factors for pancreatic fistula.

MATERIALS AND METHODS

Patients and data collection

We reviewed the data from 310 successive cases of pancreaticoduodenectomy performed in the Department of Hepatobiliary Surgery of National liver institute, Menoufia University from 1st Jan 2015 to 31st Dec 2023 . The following patient data were collected: gender, age, hypertension, diabetes, alcohol consumption, smoking, body mass index (BMI), history of upper abdominal surgery, preoperative jaundice management, blood sugar, preoperative bilirubin, preoperative albumin, pancreatic duct drainage, intraoperative blood loss, intraoperative blood transfusion, operative time, pancreaticojejunal

anastomosis technique, Braun anastomosis, pylorus preservation, diameter of the pancreatic duct, and pancreatic texture. Additionally, all postoperative complications and postoperative pathological findings (especially information about pancreatic fistula) were recorded. All 310 cases were included in this comprehensive study.

Preoperative preparation

Prior to surgery, the patients underwent routine tests, examinations, and evaluations of organ function. To date, no uniform standard exists for preoperative jaundice management. We believe that patients with obstructive jaundice who have a poor mental state, severe dehydration, poor nutrition, or severe jaundice should undergo jaundice management and supportive therapy to improve their nutritional intake and replenish fluids. Patients should subsequently undergo surgery after their general condition has improved.

Surgical approach

In this study, 250 patients underwent classic pancreaticoduodenectomy, of whom 11 had portal vein resection and reconstruction. Additionally, 60 patients underwent pylorus-preserving pancreaticoduodenectomy, of whom 3 had portal vein resection and reconstruction. Child's technique (pancreaticojejunal anastomosis, biliary-jejunal anastomosis, and gastrojejunal anastomosis in sequential order) was used for the gastrointestinal reconstruction. The following two approaches were used for pancreaticojejunal anastomosis: (1) pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis in 208 patients; and (2) pancreatic-jejunum single-layer mucosa-to-mucosa anastomosis in 90 patients.

Classification and detailed definition of postoperative pancreatic fistula

Pancreatic fistula was defined according to the International Study Group on Pancreatic Fistula (ISGPF) as any measurable volume of

drainage fluid output *via* operatively or postoperatively placed drains on or after postoperative day 3 with amylase content greater than three times the upper normal serum value. Three grades of pancreatic fistulas were determined according to their clinical severity. The grades were determined only after complete healing of the fistula (Table (Table1)[24].

Table 1

Criteria utilized to grade postoperative pancreatic fistula

Grade	A	B	C
Clinical conditions	Well	Often well	Ill appearing/bad
Specific treatment[1]	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/positive	Positive
Persistent drainage (after 3 wk)[2]	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

[1]Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue, and/or minimally invasive drainage;
[2]With or without a drain *in situ*. CT: Computed tomography; POPF: Postoperative pancreatic fistula; US: Ultrasonography.

Statistical analysis

All clinical data were entered into an Excel spreadsheet, and SPSS 19.0 software was used for statistical analyses. Measurement data are expressed as the mean ± SD. A *t*-test was performed for between-group comparisons. Categorical variables were analyzed using Fisher's exact test and the χ^2 test. All variables were incorporated into a univariate analysis. $P < 0.05$ was considered statistically significant. Statistically significant variables demonstrated in the univariate analysis were incorporated into a multivariate logistic regression analysis to identify

the independent risk factors for pancreatic fistula after pancreaticoduodenectomy.

RESULTS

Overall characteristics of patients and complications

This study included 178 male patients and 138 female patients with a mean age of 57.40 ± 12.54 years. The mean hospital stay was 15.64 ± 6.94 d. The condition (confirmed by postoperative pathology) of the 310 patients is shown in Table2,Figure 1. Among the 310 patients, 170 (52.7%) experienced complications, and 90 (29.0%) had POPF, including 18 (16.2%) cases of grade A pancreatic fistula, 59(53.1%) cases of grade B, and 13 (11.7%) cases of grade C. The following complications were identified: 30 (9.7%) cases of gastric leakage, 78 (25.2%) cases of delayed gastric emptying, 44 (14.2%) cases of abdominal infection, and 92 (29.7%) cases of incision infection. Moreover, 15 (2.78%) patients underwent a second operation, and 6 (1.11%) patients died after surgery due to abdominal bleeding associated with a pancreatic fistula as shown in Table 3, Figure 2 .

Table (2): Distribution of the studied cases according to the type of the tumor (n = 310)

	No.	%
Pancreatic headTumor Size		
Less than 3cm	90	29.0
More than 3cm	164	52.9
Pancreatic head tumors	254	81.9
Lowe bile duct tumors	18	5.8
Ampulla tumors	24	7.7
Duodenal papillary tumors	10	3.2

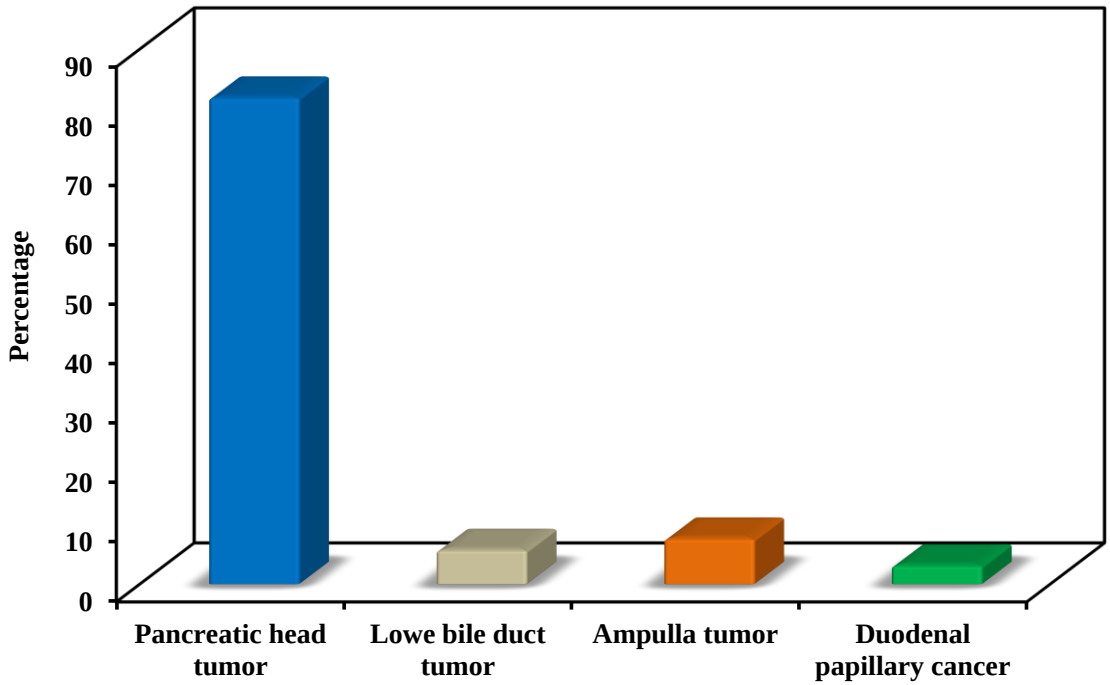

Figure (1): Distribution of the studied patients according to the type of the tumor (n = 310)

Table (3): Distribution of the studied cases according to post-operative complications (n = 310).

	No.	%
Wound infection	92	29.7
Wound dehiscence	44	14.2
Gastric leak	30	9.7
Delayed gastric emptying	78	25.2
Pancreatic leak	90	29.0

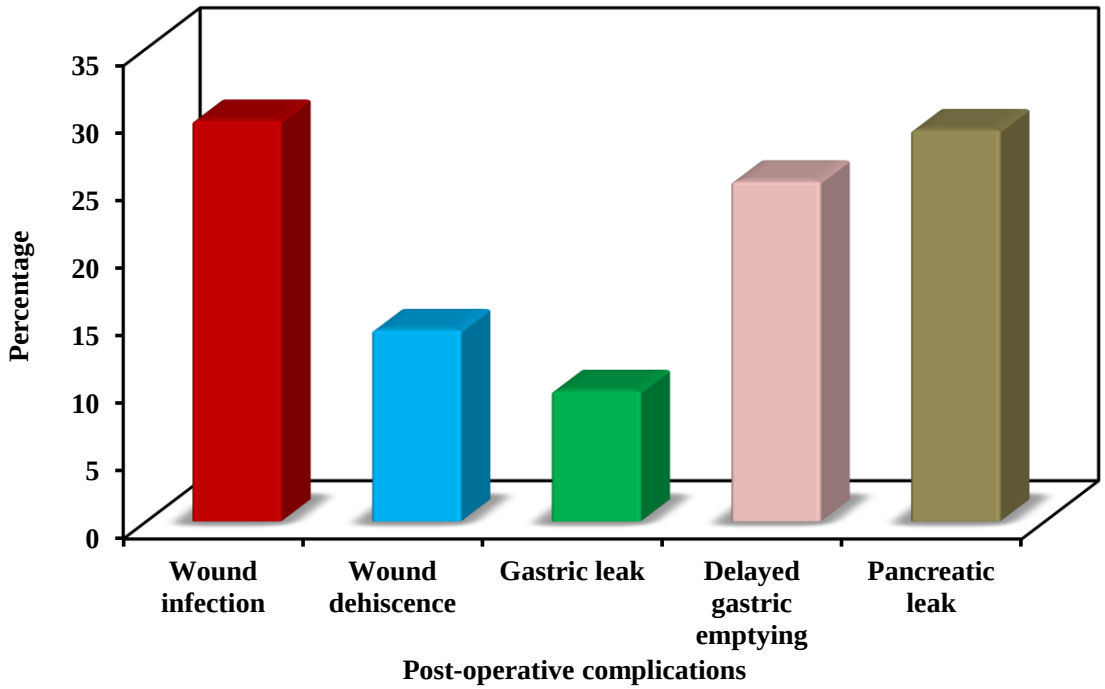

Figure (2): Distribution of the studied cases according to post-operative complications (n = 310).

Univariate analysis

Univariate analysis showed no significant correlation between POPF and the following factors: age, hypertension, alcohol consumption, smoking, history of upper abdominal surgery, preoperative jaundice management, preoperative bilirubin, preoperative albumin, pancreatic duct drainage, intraoperative blood loss, operative time, intraoperative blood transfusion, Braun anastomosis, and pancreaticoduodenectomy (with or without pylorus preservation). Conversely, a significant correlation was observed between POPF and the following factors: gender (male vs female: 55.6% vs 44.4%, P = 0.671), diabetes (non-diabetic vs diabetic: 38.9% vs 61.1%, P = 0.010), body mass index (BMI) (≤ 25 vs > 25: 44.4% vs 55.6%, P = 0.301), , pancreaticojejunal anastomosis technique (pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis vs pancreatic-jejunum single-layer

mucosa-to-mucosa anastomosis: 55.6% vs 40.0%, P = 0.019), diameter of the pancreatic duct (≤ 3 mm vs > 3 mm: 53.3% vs 46.7%, P = 0.014), and pancreatic texture (soft vs hard: 54.4% vs 45.6%, P = 0.036).
Multivariate logistic regression analysis showed that gender (male), BMI > 25, Diabetes, pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis, pancreatic duct diameter ≤ 3 mm, and soft pancreas were risk factors for pancreatic fistula after pancreaticoduodenectomy. (Table (Table4).

Table (4): Relation between Pancreatic leak and different parameters (n = 310) .

	Pancreatic leak				$\chi 2$	p
	No (n = 220)		Yes (n = 90)			
	No.	%	No.	%		
Age						
<60	132	60.0	54	60.0	0.000	1.000
≥60	88	40.0	36	40.0		
Sex						
Male	128	58.2	50	55.6	0.180	0.671
Female	92	41.8	40	44.4		
BMI						
<25	112	50.9	40	44.4	1.068	0.301
≥25	108	49.1	50	55.6		
Smoking						
No	134	60.9	54	60.0	0.022	0.882
Yes	86	39.1	36	40.0		
DM						
No	121	55.0	35	38.9	6.632*	0.010*
Yes	99	45.0	55	61.1		
HTN						
No	128	58.2	54	60.0	0.087	0.768
Yes	92	41.8	36	40.0		
Pancreatogastrostomy						
No	212	96.4	86	95.6	0.112	FEp= 0.738
Yes	8	3.6	4	4.4		
Blood transfusion						
No	160	72.7	74	82.2	3.112	0.078
Yes	60	27.3	16	17.8		
Pancreatic duct diameter						
Less than 3mm	84	38.2	48	53.3	5.997*	0.014*
Above 3mm	136	61.8	42	46.7		
Pancreatic Head Tumor						

size (n = 254)						
Less than 3cm	52	27.7	38	57.6	19.110	<0.001*
More than 3cm	136	72.3	28	42.4		
Pacreatic Texture						
Soft	91	41.4	49	54.4	4.413*	0.036*
Firm	129	58.6	41	45.6		
Pancreatojeujenal anastomosis						
No	8	3.6	4	4.4		
Single layer	54	24.5	36	40.0	7.880*	0.019*
Double layer	158	71.8	50	55.6		
Blood loss						
<500	114	51.8	40	44.4	1.389	0.239
≥500	106	48.2	50	55.6		

χ^2: **Chi square test** **FET: Fisher Exact test**
p: p value for comparing between the studied groups*: Statistically significant at $p \leq 0.05$

DISCUSSION

The causes of pancreatic fistula include pancreaticojejunal anastomotic leak, leak from pancreatic resection, leak associated with damage to the pancreatic capsule, and leak *via* the puncture channel. Pancreatic fistula after pancreaticoduodenectomy is a common and serious complication and the most important cause of subsequent complications and death after this procedure[8,24-26]. The dilemma of pancreatic fistula after pancreaticoduodenectomy has not yet been resolved[27]. Currently, researchers believe that the following factors are related to pancreatic fistula: gender, age, preoperative jaundice, intraoperative blood loss, operative time, pancreatic texture, BMI, diameter of the main pancreatic duct, and pancreaticojejunal anastomosis[14,28-32]. Peng et al[33] suggested that bundled pancreaticogastrostomy was a safe and effective anastomosis technique to prevent the leakage of pancreatic juice from pancreaticojejunal anastomosis. Shubert *et al*[34] believed that the clinical risk score for pancreatic fistula (CRS-PF) could effectively predict pancreatic fistula after pancreaticoduodenectomy. In this study, multivariate logistic regression analysis showed that gender (male), BMI > 25, Diabetes ,pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis, pancreatic duct diameter ≤ 3 mm, and soft pancreas were risk factors for pancreatic fistula after pancreaticoduodenectomy.

Kawai retrospectively analyzed the perioperative data from 1239 patients treated at 11 medical facilities from 2005 to 2009 and summarized that the male gender was a risk factor for pancreatic fistula after pancreaticoduodenectomy[35]. This study included 178 male patients (POPF rate: 55.6%) and 132 female patients (POPF rate: 44.4%). Univariate analysis showed that the difference in the POPF rate was (P = 0.671), suggesting that male patients were at a higher risk than female patients for the development of pancreatic fistula after pancreaticoduodenectomy.

El Nakeeb et al[36] analyzed 471 cases of pancreaticoduodenectomy and found that BMI > 25 was a risk factor for POPF. Gaujoux et al[28] analyzed 100 successive cases of pancreaticoduodenectomy and similarly found that BMI > 25 was a risk factor for pancreatic fistula after pancreaticoduodenectomy. In our study, 112patients had a BMI ≤ 25 (POPF rate: 44.4%), and 108 patients had a BMI > 25 (POPF rate: 55.6%). Univariate analysis showed that the difference in the POPF rates was (P = 0.301), suggesting that patients with a BMI > 25 were at a higher risk of developing pancreatic fistula after pancreaticoduodenectomy than patients with a BMI ≤ 25. The higher incidence of pancreatic fistula after pancreaticoduodenectomy in patients with a BMI > 25 may be associated with the following factors: increased difficulty in exposing the pancreas during surgery due to a higher volume of abdominal fat and peripancreatic fat, a higher risk of damage to the pancreatic capsule during separation due to a soft and brittle pancreas, and a higher risk of pancreatic leakage caused by damage to the pancreatic tissue and fine pancreatic ducts due to suturing and knotting during pancreaticojejunal anastomosis.

Pancreaticojejunal anastomosis is a critical step during pancreaticoduodenectomy and affects the surgical outcome. However, pancreaticojejunal anastomosis is a complex procedure during pancreaticoduodenectomy, and the choice of an appropriate pancreaticojejunal anastomosis technique should reduce the incidence of pancreatic fistula[33,37-40]. Fu et al[32] retrospectively analyzed 532 cases of pancreaticoduodenectomy and found that the pancreaticojejunal

anastomosis technique was a risk factor for pancreatic fistula after pancreaticoduodenectomy. In this study, pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis was performed in 208 patients (POPF rate: 55.6%), and pancreatic-jejunum single-layer mucosa-to-mucosa anastomosis was performed in 90patients (POPF rate: 40.0%). Univariate analysis showed that the difference in the POPF rates was significant (*P* = 0.019), suggesting that patients who underwent pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis were at a higher risk of developing pancreatic fistula after pancreaticoduodenectomy than patients who underwent pancreatic-jejunum single-layer mucosa-to-mucosa anastomosis as shown in (Figure3,4)

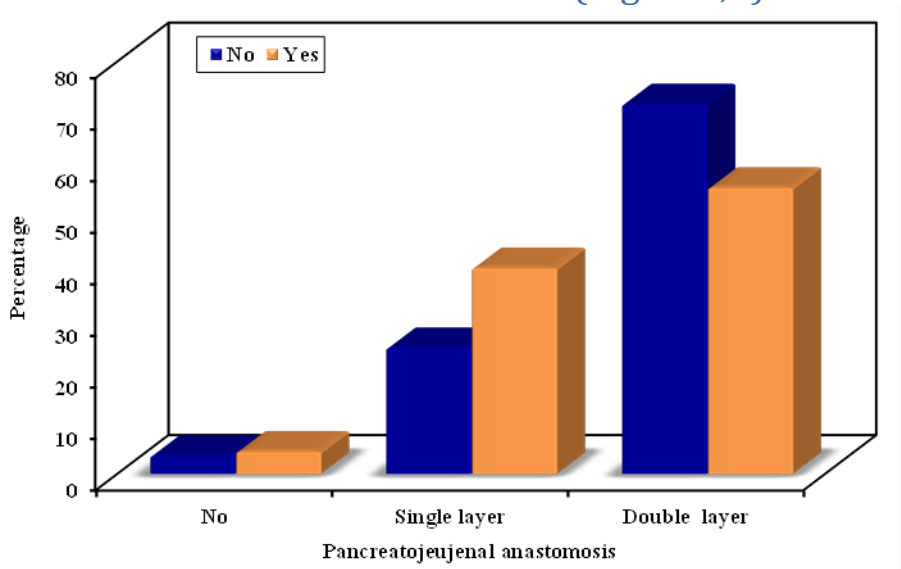

Fig. (3) : Relation between pancreatic leak and pancreatojeujenal anastomosis (n = 310). Univariate analysis showed that the difference in the POPF rates was significant (P = 0.019), suggesting that patients who underwent pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis were at a higher risk of developing pancreatic fistula after pancreaticoduodenectomy than patients who underwent pancreatic-jejunum single-layer mucosa-to-mucosa anastomosis , suggesting that pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis was an independent risk factor for pancreatic fistula after pancreaticoduodenectomy .

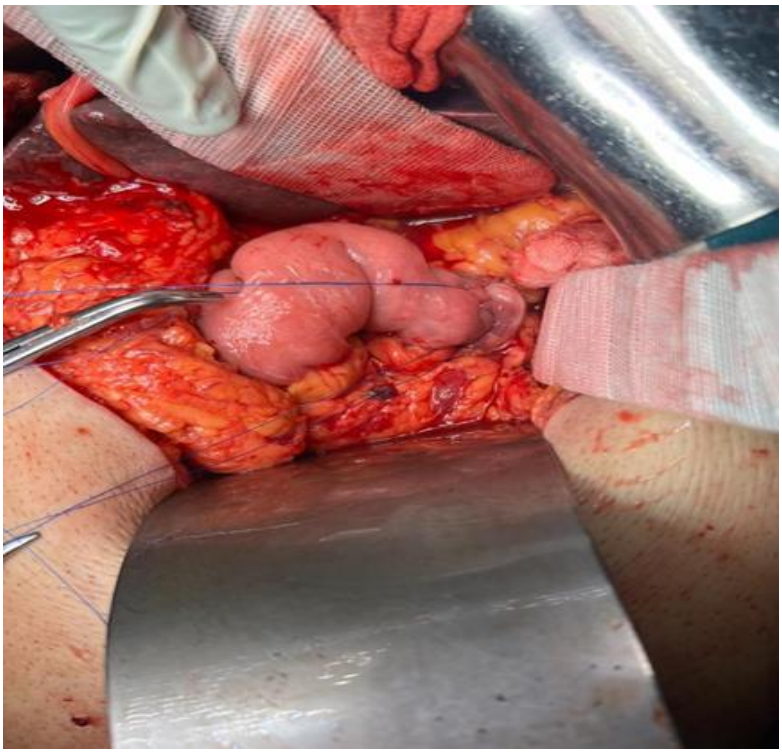

Fig. (4): Dunking Single layer pancreaticojujonostomy National Liver Institute **(Menoufia University).**

The higher incidence of pancreatic fistula after pancreaticoduodenectomy in patients who underwent pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis may be related to the following factors: use of the 6-0 PDS II suture during pancreatic duct-jejunum anastomosis because the fine suture can easily cut the pancreatic duct during suturing and knotting, thereby resulting in a pancreaticojejunal anastomotic leak, and the use of the 5-0 PDS II suture to suture the pancreatic section and the jejunal seromuscular layer because this suture can easily cut the pancreas and fine pancreatic ducts during suturing and may not tightly secure the pancreatic section and the jejunal seromuscular layer, thereby resulting in pancreatic leakage and leakage from the fine pancreatic ducts. In contrast, the 4-0 Vicryl suture is used for full-layer suturing of the pancreas, the pancreatic duct, and the jejunum during pancreatic-jejunum single-layer mucosa-to-mucosa anastomosis; therefore, the suture is secure and reduces the risk of cutting the pancreas. Moreover,

the jejunal seromuscular layer covers the entire pancreatic section and presses the fine pancreatic ducts at the pancreatic section, thereby reducing pancreatic leakage[38].

A soft pancreas is a risk factor for pancreatic fistula after pancreaticoduodenectomy[35-37,41,42]. The pancreatic stumps of all cases were submitted for pathological diagnosis of the degree of pancreatic fibrosis. All cases of pancreatic texture were divided into two groups (normal soft pancreas with no significant fibrosis and hard pancreas with fibrosis. In this study, 140 patients had a soft pancreas (POPF rate: 54.4%), and 170 patients had a hard pancreas (POPF rate: 45.6%) as shown in Table 5. Univariate analysis showed that the difference in the POPF rates was significant (P = 0.036), suggesting that patients with a soft pancreas were at a higher risk of developing a pancreatic fistula after pancreaticoduodenectomy than patients with a hard pancreas.

Table (5): Distribution of the studied cases according to the operative data (n = 310)

	No.	%
Operative time		
Min – Max.	3.0 – 9.0	
Mean ± SD.	5.86 ± 1.30	
Median (IQR)	6.0 (5.0 – 7.0)	
Blood loss		
<500	154	49.7
≥500	156	50.3
Min – Max.	200.0 – 2000.0	
Mean ± SD.	545.2 ± 267.8	
Median (IQR)	500.0 (400.0 – 650.0)	
Blood transfusion	76	24.5
Pancreatic Duct diameter		
Less than 3mm	132	42.6
Above 3mm	178	57.4
Pancreatic Texture		
Soft	140	45.16
Firm	170	54.84

Type of Whipple operation		
Pyloric preserving	60	19.4
Classic	250	80.6

The higher incidence of pancreatic fistula after pancreaticoduodenectomy in patients with a soft pancreas may be related to insecure suturing and knotting, which can result in unsatisfactory pancreaticojejunal anastomosis and a higher risk of damage to the pancreatic tissue and fine pancreatic ducts during suturing and knotting of a soft pancreas, resulting in pancreatic leakage. The lower incidence of pancreatic fistula after pancreaticoduodenectomy in patients with a hard pancreas may be related to pancreatic exocrine dysfunction due to prolonged pancreatic duct obstruction and pancreatic fibrosis, secure pancreaticojejunal anastomosis, and obstructed minor ducts at the cut-surface of the hard pancreas, and this could help reduce POPF[43] and risk of damage to the pancreatic tissue and fine pancreatic ducts during suturing and knotting. Pancreatic texture is the most significant single predictor of POPF, and clinicians should select a pancreaticojejunal anastomosis technique based on the texture of the pancreas to reduce the incidence of POPF[44]

Pancreatic duct diameter ≤ 3 mm is a risk factor for pancreatic fistula after pancreaticoduodenectomy[14,37]. In this study, the diameter of the pancreatic duct was ≤ 3 mm in 132 patients (POPF rate: 53.3%) and > 3 mm in 178 patients (POPF rate: 46.7%). Univariate analysis showed that the difference in the POPF rates was significant (P = 0.014), suggesting that patients with a pancreatic duct diameter ≤ 3 mm were at a higher risk of developing a pancreatic fistula after pancreaticoduodenectomy than patients with a pancreatic duct diameter > 3 mm. The lower incidence of pancreatic fistula after pancreaticoduodenectomy in patients with a pancreatic duct diameter > 3 mm may be related to pancreatic duct obstruction, pancreatic duct fibrosis, pancreatic fibrosis, ease of suturing, and a lower risk of damage to the pancreatic duct during suturing and knotting. As a result, the incidence of pancreatic fistula after pancreaticoduodenectomy was lower in patients with

pancreatic duct dilation than in patients without as shown in **Figure 5,6**

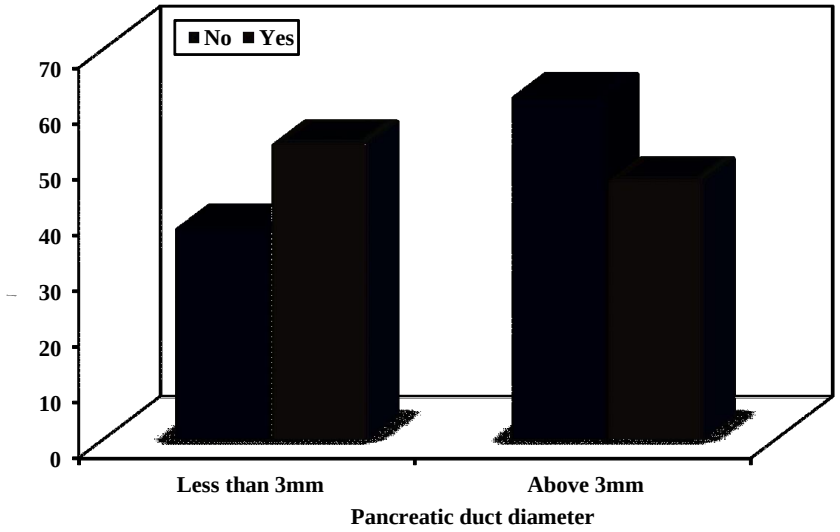

Fig (5) Relation between pancreatic leak and pancreatic duct diameter (n = 310) patients with a pancreatic duct diameter ≤ 3 mm were at a higher risk of developing a pancreatic fistula after pancreaticoduodenectomy than patients with a pancreatic duct diameter > 3 mm Univariate analysis showed that the difference in the POPF rates was significant (P = 0.014*)

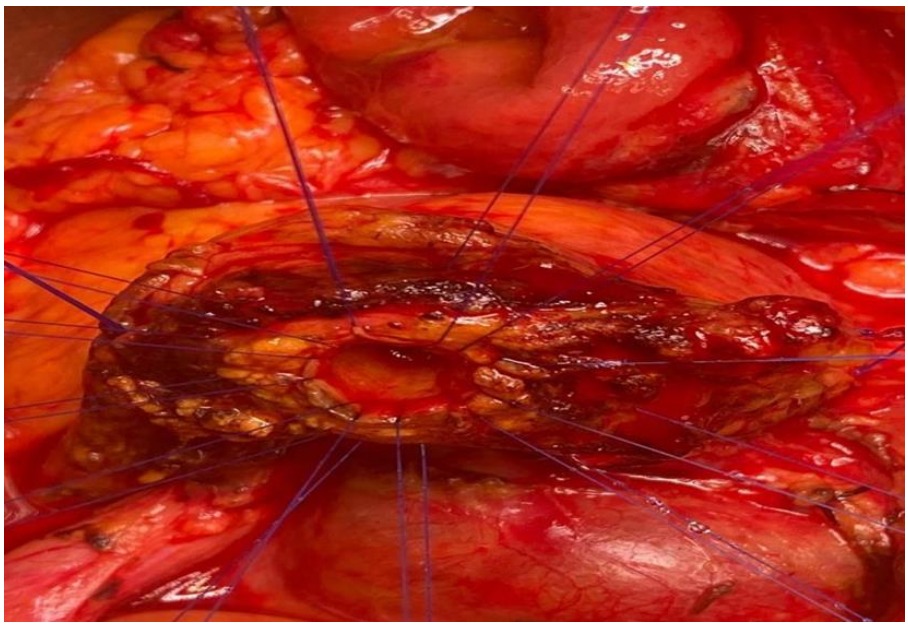

Fig. (6): Dilated pancreatic duct prepared for pancreatico-enteric anastomosis. National Liver Institute (Menoufia University).

Univariate analysis demonstrated that the incidence of pancreatic fistula after pancreaticoduodenectomy was higher in diabetic patients than in non-diabetic patients (61.1% *vs* 38.9%, $P = 0.010$) therefore, diabetes was considered a risk factor for POPF.

In conclusion, gender (male), BMI > 25,DM, pancreatic duct-jejunum double-layer mucosa-to-mucosa pancreaticojejunal anastomosis, pancreatic duct diameter ≤ 3 mm, and soft pancreas were risk factors for pancreatic fistula after pancreaticoduodenectomy.

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