

## Predictors of Pancreatic Leak Post Pancreaticoduodenectomy. Retrospective Study

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### ABSTRACT

**Background:** Pancreaticoduodenectomy (PD), a complex operation with a high morbidity rate, especially pancreatic fistula, is still the standard treatment for resectable pancreatic head, ampullary, distal bile duct, and duodenal tumours. Despite improvements in pancreatic fistula detection and treatment, it still has a significant death rate. As a result, it is critical to address the causes of pancreatic fistula for which this study was created.

**Objective:** This study aimed to address the different risk factors affecting the incidence of pancreatic leakage post pancreaticoduodenectomy.

**Subjects and Methods:** This is a retrospective case-control study that included all cases that experienced pancreaticoduodenectomy during the period from January 2014 to December 2021 at the National Cancer Institute (NCI), Cairo University. The cases have been categorized into two groups (cases who developed pancreatic leakage and those who did not develop it). Both groups were compared for the possible risk factors: age, gender, tumour size, LNs positivity, laboratory findings (HB, Albumin), neoadjuvants received, surgical techniques (anastomosis technique, vein resection, texture of pancreatic remnant), and postoperative nutrition plan used.

**Results:** Ninety-five cases of pancreaticoduodenectomy were done during the study period. Among them, 35 cases had developed postoperative pancreatic fistula (POPF). A significantly higher pancreatic fistula incidence was associated with the female gender, preoperative haemoglobin levels of < 12 gm/dl and albumin levels of < 3.6 gm/dl, along with soft pancreatic texture.

**Conclusion:** Pancreaticoduodenectomy is an operation with a high morbidity rate. Female gender, low HB and albumin levels, and soft pancreatic texture are risk factors for developing pancreatic fistula.

**Keywords:** Pancreatic fistula, Pancreatic leak, Pancreaticoduodenectomy, Whipple.

### INTRODUCTION

Pancreatic cancer remains one of the most lethal cancers. In the USA, it was predicted that 62210 patients would have pancreatic cancer, and about 49,830 persons would die from it in 2022, making it one of the highest mortality cancers <sup>(1)</sup>.

The pancreaticoduodenectomy remains the standard procedure for surgical treatment of resectable and marginally resectable pancreatic head cancer, and ampullary carcinoma <sup>(2)</sup>.

Although pancreaticoduodenectomy is a common procedure in cancer centres worldwide <sup>(3)</sup>, a high rate of complications is still encountered, including pancreatic fistula, problems in gastric emptying, intestinal leakage, haemorrhage and infection <sup>(4)</sup>. Among these complications, pancreatic fistula remains the most common, with an incidence range of 5-41% <sup>(5)</sup>. Pancreatic fistula mortality is still around 6-9%, despite advancements in diagnosis and management <sup>(6)</sup>. Therefore, it is crucial to address the risk factors of pancreatic fistula for which this study was accomplished. This study aimed to address the different risk factors affecting the incidence of pancreatic leakage after pancreaticoduodenectomy.

### PATIENTS AND METHODS

This was a retrospective case-control study that included all cases who underwent pancreaticoduodenectomy at the National Cancer Institute, Cairo University in the period between January 2014 and December 2021. The cases were

categorized into two groups (cases who developed pancreatic leakage and those who did not develop it). Both groups were compared for the possible risk factors, including age, gender, tumour size, LNs positivity, laboratory findings (HB, Albumin), neoadjuvants received, surgical techniques (anastomosis technique, vein resection, pancreatic remnant texture), and the adopted postoperative nutrition plan.

Postoperative pancreatic fistula (POPF) is defined as elevation of amylase level in drains after pancreaticoduodenectomy at or after day 3 postoperatively more than 3 times the upper limit of normal serum amylase level. The archived medical records were obtained from the Cancer Epidemiology & Biostatistics Department to retrieve patients' data: Age, gender, tumour size, LNs positivity, laboratory findings in the form of HB and albumin, neoadjuvants received, and surgical techniques in the form of anastomosis technique, vein resection, pancreatic remnant texture, and finally postoperative nutrition plan used.

**Ethical considerations:** This study has been approved via the Institutional Review Board (IRB) of the National Cancer Institute, Cairo University (Number: 2211-510-019). and the patients were given all the information they need about the trial. An informed written consent was taken from each participant in the study. This work has been carried out in accordance with The Code of Ethics of the

**World Medical Association (Declaration of Helsinki) for studies involving humans.**

**Statistical methodology:**

Statistical analysis of the data was accomplished by SPSS (Statistical Package for Social Science), version 24. Numerical data were described as median and range or mean and standard deviation (SD) as appropriate, while qualitative data were described as percentage and frequency.

The numerical variables' normality was verified according to Kolmogorov-Smirnov and Shapiro-Wilk tests. The numerical variables of the two groups were compared by the nonparametric t-test and Mann-Whitney U test. The Fisher's exact and Chi-square tests, as appropriate, were adopted for comparing the qualitative data. Statistical significance was considered at P value  $\leq 0.05$ . All tests were 2 tailed.

**RESULTS**

During the study period, 95 cases had experienced pancreaticoduodenectomy (PD). Mild male predilection was present in the current cohort, as 57 (60%) patients were males. Patients' ages ranged from 20-72 years, with a median of 55 years.

Pancreatic fistula occurred in 35 (36.8%) cases. Among them, 7 cases were grade A, 23 cases were grade B, while the remaining 5 cases were grade C. 29 cases with POPF were successfully managed conservatively, 4 cases needed surgical intervention and were successfully managed, while the other 2 cases (5%) died at 18<sup>th</sup> and 29<sup>th</sup> day postoperatively with septic shock. The preoperative risk factors of post-PD pancreatic fistula are illustrated in table (1).

**Table (1):** Preoperative risk factors of post-PD pancreatic fistula

	Pancreatic leakage		p value
	No (n=60) N (%)	Yes (n=35) N (%)	
<b>Age (years)</b>			
<55	32 (53.3%)	18 (51.4%)	0.858
$\geq 55$	28 (46.7%)	17 (48.6%)	
<b>Gender</b>			
Female	18 (30%)	20 (57.1%)	<b>0.009</b>
Male	42 (70%)	15 (42.9%)	
<b>Biliary stent insertion</b>			
No	12 (20%)	10 (28.6%)	0.339
Yes	48 (80%)	25 (71.4%)	
<b>Tumor Size (cm)</b>			
$\leq 3.5$	34 (56.7%)	16 (45.7%)	0.302
$> 3.5$	26 (43.3%)	19 (54.3%)	
<b>LN's Metastasis</b>			
Negative	42 (70%)	24 (68.6%)	0.884
Positive	18 (30%)	11 (31.4%)	
<b>Pathology Type</b>			
Ductal Adenocarcinoma	40 (66.6%)	21 (60%)	
Ductal Adenosquamous carcinoma	3 (5%)	0 (0%)	
Ampullary adenocarcinoma	4 (6.7%)	4 (11.4%)	
Solid pseudopapillary neoplasm	7 (11.7%)	3 (8.5%)	
Neuroendocrine	2 (3.3%)	3 (8.5%)	
Peripheral nerve sheath tumor	0	1 (2.9%)	
Duodenal GIST	0 (0%)	1 (2.9%)	
Insulinoma	0 (0%)	1 (2.9%)	
Pancreatitis	4 (6.7%)	1 (2.9%)	
<b>HB (gm/dl)</b>			
<12	19 (31.7%)	19 (54.3%)	<b>0.030</b>
$\leq 12$	41 (68.3%)	16 (45.7%)	
<b>Albumin (gm/dl)</b>			
< 3.6	15 (25%)	18 (51.4%)	<b>0.009</b>
$\geq 3.6$	45 (75%)	17 (48.6%)	
<b>Neoadjuvant therapy received</b>			
No	58 (96.7%)	33 (94.3%)	0.624
Yes	2 (3.3%)	2 (5.7%)	

Female gender, HB less than 12 gm/dl, and albumin less than 3.6 gm/dl were associated with a higher incidence of postoperative pancreatic fistula (p value= 0.009, 0.03, 0.009, respectively). Different pancreatico-enteric anastomosis techniques were used (Table 2).

**Table (2):** Perioperative risk factors associated with pancreatic leak

	Pancreatic leakage		P value
	No (n=60) N (%)	Yes (n=35) N (%)	
<b>Pancreatic-enteric anastomosis type</b>			
Pancreatico-gastrostomy	13 (21.7%)	9 (25.7%)	0.652
Pancreatico-jejunostomy	47 (78.3%)	26 (74.3%)	
<b>Technique of pancreatico-jejunostomy *</b>			
Blumgart	13 (27.7%)	3 (11.5%)	0.127
Cattel-Warren	34 (72.3%)	23 (88.5%)	
<b>Pancreatic stent insertion</b>			
No	52 (86.7%)	32 (91.4%)	0.484
Yes	8 (13.3%)	3 (8.6%)	
<b>Pancreatic Texture</b>			
Firm	56 (93.3%)	22 (62.9%)	<0.001
Soft	4 (6.7%)	13 (37.1%)	
<b>Gastrojejunostomy technique</b>			
Loop	52 (86.7%)	32 (91.4%)	0.484
Roux-en-y	8 (13.3%)	3 (8.6%)	
<b>Feeding tube insertion</b>			
No	49 (81.7%)	29 (82.9%)	0.884
Yes	11 (18.3%)	6 (17.1%)	
<b>Vein resection</b>			
No	56 (93.3%)	34 (97.1%)	0.422
Yes	4 (6.7%)	1 (2.9%)	
<b>Pathology margin</b>			
Negative	57 (95%)	32 (91.4%)	0.666
Positive	3 (5%)	3 (8.6%)	

\*Total number of cases underwent pancreatico-jejunostomy was 73 cases

There was no significant difference in the pancreatic leak. Soft pancreas texture represented the only intra-operative factor associated with a higher incidence of pancreatic fistula (p-value <0.001). Furthermore, the multivariate analysis ascribed female gender and soft pancreas as the only significant risk factors for the pancreatic leak (Table 3).

**Table (3):** Multivariate analysis (logistic regression) of risk factors associated with pancreatic leak

	Beta coefficient	Standard error	p value	Odds ratio	95% C.I.for OR	
					Lower	Upper
<b>Gender</b>	1.532	0.699	<b>0.028</b>	4.627	1.177	18.193
<b>Pancreatic Texture</b>	1.830	0.928	<b>0.045</b>	6.235	1.011	38.457

Post-pancreaticoduodenectomy pancreatic fistula delayed oral feeding and resulted in a prolonged hospital stay, with a mean of 27.9 days compared to only 12.9 days (p-value <0.001) in cases who did not have pancreatic fistulae (Table 4).

**Table (4):** Effects of pancreatic leak on postoperative hospital stay

	Pancreatic leakage		P value
	No (n=60) Mean (SD)	Yes (n=35) Mean (SD)	
<b>Duration till starting oral fluid (day)</b>	5.60 (2.78)	9.35 (6.1)	<b>0.002</b>
<b>Duration till stating regular diet (day)</b>	7.96 (2.96)	17.25 (9.25)	<b>&lt;0.001</b>
<b>Duration of hospital stay (day)</b>	12.88 (7.99)	27.97 (13.72)	<b>&lt;0.001</b>

## DISCUSSION

Pancreaticoduodenectomy (PD) operation is the standard procedure for treating pancreatic head, and ampullary cancers <sup>(7)</sup>. Despite, the improvement of anastomotic techniques, the rate of complications remains high <sup>(8)</sup>. Pancreatic fistula, delayed gastric emptying, bleeding, bile and intestinal contents leakage, wound infection, and intra-abdominal abscess are the most frequent consequences that influence the death rate, hospitalization, and expenditures <sup>(9)</sup>.

After pancreatic resection, postoperative pancreatic fistula (POPF), which affects 13-41% of patients, represents the main cause for mortality and severe morbidity <sup>(10)</sup>. POPF patients have a mortality risk of at least 1%, which increases to about 25% for those with grade C POPF <sup>(11)</sup>. Morbid sequelae such as intra-abdominal sepsis and bleeding are connected with POPF <sup>(12)</sup>.

There was a debate about the effect of age as a potential predisposing factor for developing POPF. **Elmelegy et al.** <sup>(13)</sup> reported that patients older than 60 years had a considerably greater incidence of POPF after PD. Conversely, **Williamsson et al.** <sup>(14)</sup> reported no correlation between age and the development of POPF, which agrees with our findings. Nevertheless, **Wente et al.** <sup>(15)</sup> reported that the older group would have a greater mortality rate due to POPF, as reported by 1.9% for patients < 75 years versus 5.9% for patients ≥ 75 years (p=0.037). The same regarding gender, where males were associated with a higher incidence of POPF as reported by **Shamali et al.** <sup>(16)</sup>. In contrast, our results revealed that females were highly affected by POPF (p=0.009).

The site of the tumour may affect the rate of POPF. **Yang et al.** <sup>(17)</sup> stated that Vatar ampullary carcinoma was accompanied with an elevated risk of developing POPF than other pathologies that underwent PD. This was mainly owed to the higher incidence of obstructive jaundice, which may interfere with protein synthesis in the liver and negatively affect the anastomosis healing. Also, the pancreatic remnant in pancreatic ductal tumours was usually firm due to pancreatitis, resulting in safer anastomosis. Low haemoglobin level results in poor tissue oxygenation and poor healing. In the current study, a preoperative haemoglobin level of less than 12 gm/dl was a significant risk factor for developing POPF. This is consistent with the conclusion reached by **Sert et al.** <sup>(18)</sup> who reported a coincidence between POPF incidence and low haemoglobin levels.

The role of perioperative albumin level as predisposing or predictor of a pancreatic leak is unclear. In the current study, preoperative albumin less than 3.6 gm/dl was associated with a significant (p= 0.009) higher incidence of POPF. Conversely, **Fujiara et al.** <sup>(19)</sup> stated that POPF was not correlated to preoperative albumin, but it likely occurred in patients with low

postoperative albumin (p= 0.04). This may be because albumin is among the negative acute phase proteins, which declines during inflammatory processes such as POPF. Therefore, it may be used as a predictor for pancreatic leak rather than a predisposing factor.

Different techniques have been used for pancreatico-enteric anastomosis. There is debate in the literature about the best technique. According to the meta-analysis study of **Lyu et al.** <sup>(20)</sup> which included 7 randomized controlled trials with 1184 PD patients, there were no significant differences between pancreaticojejunostomy and pancreaticogastrostomy for the rate of POPF. This is in concurrence with the present study findings. In contrast, **Topal et al.** <sup>(21)</sup> conducted a multicentre study on 329 patients and indicated less incidence of POPF in cases who underwent pancreaticogastrostomy compared to those experiencing pancreaticojejunostomy (8% versus 19.8 respectively; p=0.002).

Many techniques have been developed for pancreaticojejunostomy. The most commonly used are the standard Cattell-Warren and Blumgart techniques. **Kleespies et al.** <sup>(22)</sup> reported that the Blumgart procedure outperforms the Cattell-Warren technique in early outcomes (complication rate: 17% versus 36%; POPF: 4% versus 13%).

Also, **Kalev et al.** <sup>(23)</sup> indicated that the rate of POPF grade c was less in cases that underwent the Blumgart technique (p=0.03). In the current study, no considerable difference in the incidence of pancreatic leakage was found due to the reduced number of patients who underwent the Blumgart technique.

The role of stenting of pancreaticoenteric anastomosis as a preventive measure for POPF is unclear. The underlying idea is to prevent the pancreatic duct from being accidentally sutured shut, while simultaneously rerouting pancreatic juice farther downstream and away from the pancreatic anastomosis. The use of external stents has been linked to lower rates of POPF, according to many RCTs but not the internal stents (24-26). The soft pancreatic texture is a crucial risk factor for developing POPF because it makes sutures insecure. Many surgeons prefer to use the invagination technique in pancreaticojejunostomy in cases with a soft pancreas. **Martin et al.** <sup>(27)</sup> reported a significantly higher incidence of pancreatic leakage post-PD in cases with a soft pancreas, the same results in the current study (p < 0.001).

As reported in this study, the statistical mean of hospital stay was longer in cases that developed POPF than those who did not develop (27.9 versus 12.7 days, respectively; p < 0.001). The development of POPF and its consequences significantly strain the health system since they increase the length of hospital stays and the number of secondary readmissions while necessitating comparatively more intensive care unit stays, complete

parenteral nutrition, and interventional radiology operations.

Although the current study had multiple limitations due to its retrospective nature and the small number of cases compared to the numerous risk factors examined, but it highlighted the effect of preoperative low haemoglobin and albumin and the effect of pancreatic texture on the development of POPF. A multicentre prospective study is recommended while exploring the influence of different techniques in pancreaticoenteric anastomosis on developing POPF because it requires a large number of cases.

## CONCLUSION

Pancreaticoduodenectomy is an operation with a high morbidity rate. Female gender, low HB and albumin levels, and soft pancreatic texture are risk factors for developing pancreatic fistula.

## DECLARATIONS

- **Consent for publication:** I attest that all authors agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

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