Predictive Factors of Postoperative Pancreatic Fistula in Geriatric Patients Undergoing Pancreatoduodenectomy for Periampullary Malignancy

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ABSTRACT

Objective: To identify predictive factors associated with the occurrence of postoperative pancreatic fistula (POPF) following pancreatoduodenectomy (PD) in an increasingly geriatric population.

Study Design: Observational study.

Place and Duration of the Study: Department of General Surgery, Inonu University, Malatya, Turkey, from January 2010 to April 2022.

Methodology: Demographic and clinicopathological data of 74 geriatric patients who underwent PD for periampullary tumours in the clinic at Inonu University were retrieved from the patient database. POPF was defined and categorised based on the guidelines established by the International Study Group for Pancreatic Surgery (ISGPS). The patients were stratified into two cohorts of POPF and no POPF. Univariate and multivariate analyses were conducted to compare variables between the two groups.

Results: The median age of the patient population was 72 (65-92) years, and 51 (68.9%) individuals were male. Among the 74 patients, 35 (47.3%) experienced POPF. In the multivariate analysis, hypertension (HT, p=0.012), Wirsung diameter <3.5 mm (p<0.01), and pancreaticojejunostomy (PJ, p=0.022) emerged as independent risk factors for POPF.

Conclusion: In the context of geriatric patients undergoing PD, HT, intraoperative wirsung diameter <3.5 mm, and PJ were identified as independent risk factors for POPF. These findings can guide the adoption of safer techniques in preoperative and intraoperative evaluations, as well as in postoperative follow-ups of patients presenting with these risk factors.

Key Words: *Elderly, Whipple procedure, Anastomotic leakage, Predictive factor, Postoperative pancreatic fistula, Pancreatoduodenectomy.*

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INTRODUCTION

Periampullary cancers are infrequent and have high mortality rates.[1] Their occurrence is rare, but it is elevated within the geriatric population.[2] Pancreatoduodenectomy (PD) stands as one of the most intricate surgical procedures conducted for periampullary tumour management, involving the pancreas, ampulla, distal common bile duct, and duodenum. Postoperative pancreatic fistulas (POPF) represent the most prevalent complications following pancreatoduodenectomy, leading to substantial morbidity alongside delayed gastric emptying.[3,4]

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To mitigate the occurrence of POPF, various surgical and medical approaches have been employed, including different anastomosis techniques, placement of pancreatic duct stents (either internal or external) for drainage, administration of postoperative somatostatin analogs, and utilisation of fibrin glue. These interventions aim to reduce the incidence and severity of POPF. Nevertheless, the incidence of POPF can still reach rates as high as 20%. PD has been effectively performed in geriatric patients across multiple medical centres with minimal complications. Mortality rates range from 4.5 to 6%, while the overall morbidity rate is reported at 42.7% (with a specific POPF rate of 18.6%). These figures underscore the significance of closely monitoring and managing complications, particularly POPF, in this patient population.[5,6]

Timely identification and appropriate management of POPF are crucial, particularly in the geriatric patient population, which may be more vulnerable following complications. Hence, a retrospective study was designed to investigate the predictive factors influencing the occurrence of POPF in geriatric patients undergoing PD. The aim of this study was to identify factors

contributing to POPF in this specific patient population and facilitate improved management strategies.

METHODOLOGY

After obtaining approval from the ethics committee of the university (dated 10.01.2023, Approval No. 4361), a total of 239 patients who underwent PD for periampullary tumours between January 2010 and April 2022 were identified from the database. For the study, patients below the age of 65, individuals who underwent neoadjuvant chemotherapy, as well as those with benign pathology and neuroendocrine tumours were excluded. A total of 74 geriatric patients (aged 65 years and older) with adenocarcinoma pathology were included in the study. During the postoperative follow-up period, the patients were categorised into two distinct groups: those diagnosed with POPF according to the 2016 International Study Group for Pancreatic Surgery (ISGPS) criteria, and those without POPF (Figure 1).[7] Demographic (age, gender), clinical (diabetes mellitus, hypertension, coronary artery disease, preoperative drainage, biliary leak), operation type (Pancreaticojejunostomy (PJ), pancreaticogastrostomy (PG), and *Roux-en-Y* reconstruction (R&Y)), Wirsung diameter, and pathological (tumour localisation) data, laboratory parameters (preoperative white blood cell count (WBC, 10^3/uL), neutrophil count (10^3/uL), lymphocyte count (10^3/uL), AST (U/L), ALT (U/L), GGT (IU/L), LDH (U/L), total bilirubin (mg/dL), creatinine (mg/dL), albumin level (g/dL), prognostic nutrition index (PNI), preoperative haemoglobin (Hgb, g/dL), preoperative platelet count (10^3/uL), CEA (ng/mL), CA 19-9 (ng/mL)) were obtained from the patient database. The PNI score was calculated as albumin level (g/L) + 5× total lymphocyte count (10^9/L).[8]

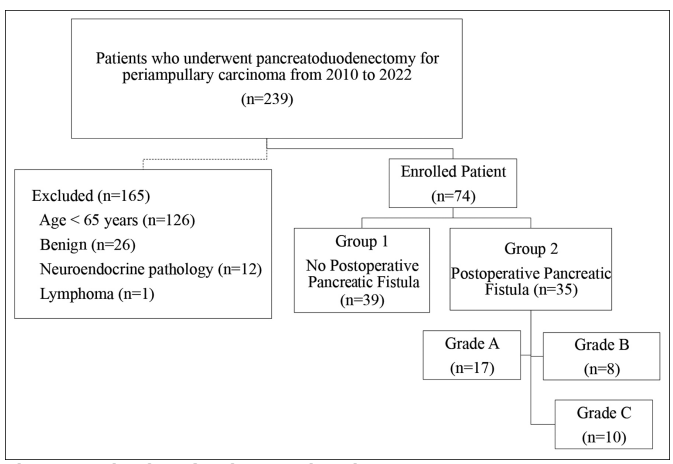

Figure 1: Selection of patients and study groups.

Postoperative complications were classified using the Clavien-Dindo (CD) classification system. Patients diagnosed with Grade A POPF were managed conservatively with oral closure and initiation of total parenteral nutrition (TPN). Grade B POPF cases underwent drainage by interventional radiology, guided by abdominal imaging to identify any additional collection sites. Furthermore, broad-spectrum antibiotics were promptly initiated. In cases of Grade C POPF, patients were promptly taken for reoperation after commencing supportive treatments for organ failure in the intensive care unit, with careful consideration of the patient's physiological condition.

Sample size was determined by performing power analysis with the G-Power 3.1 programme. According to Power (1-β) = 0.90 at a confidence level of 95%, the number of samples to be taken in each group was determined as 32. The total sample size of the two groups was determined as a minimum of 64. The normality of distribution was tested using the Shapiro- Wilk test. Equivalent nonparametric tests were used (Mann-Whitney U test). The mean, standard deviation, median, minimum, and maximum values of the variables were presented. The ideal cut-off point for Wirsung diameter, lymphocyte count, albumin level, and PNI score was determined by receiver operating characteristic (ROC) curve analysis. A Chi-square analysis was conducted for categorical variables. The frequency and percentage values of these variables were presented. Prospective selective multivariate logistic regression analysis was performed with the variables found to be statistically significant. The Hosmer-Lemeshow test was used to evaluate the goodness of fit. Statistical significance was set at $p<0.05$. The analyses were performed using SPSS v23.

RESULTS

The median age of the patients was 72 years (65-92) years, with 51 individuals (68.9%) being male. The majority of malignancies in the periampullary region consisted of pancreatic tumours (58.1%) and ampullary tumours (35.1%). Preoperative drainage catheters were inserted in 43 patients (58.1%), using either percutaneous transhepatic cholangiography or endoscopic retrograde cholangiopancreatography techniques. Pancreaticojejunostomy (PJ) was performed in 39 patients (52.7%), pancreaticogastrostomy (PG) in 17 patients (23%), and *Roux-en-Y* (R&Y) reconstruction in 18 patients (24.3%). POPF did not develop in 39 patients (52.7%) during the postoperative follow-up period. Among those who experienced POPF, 17 cases (23%) were classified as Grade A, 8 cases (10.8%) as Grade B, and 10 cases (13.5%) as Grade C. The overall morbidity rate at the 30-day follow-up was 56.7%, while the mortality rate was 9.5%.

In the univariate analyses conducted between the two groups, statistical significance was observed for several factors. Wirsung duct diameter ($p<0.001$), WBC count ($p=0.014$), lymphocyte count ($p=0.044$), albumin level ($p=0.007$), and PNI ($p=0.009$) showed significant associations with the development of POPF. Among the categorical variables, DM ($p=0.017$), HT ($p=0.022$), and reconstruction type ($p=0.047$) were found to be statistically significant predictors of POPF (Tables I, II). The cut-off values were identified as wirsung diameter <3.5mm, albumin level <3.35, PNI <33.04, and lymphocyte count ≥1.75. In the multivariate analyses, Wirsung diameter <3.5 mm ($p<0.01$, odds ratio (OR) = 82.461, 95% confidence interval (CI): 6.542-1039.343), HT ($p=0.012$, OR=25.519, (95% CI: 2.034-320.152), and PJ ($p=0.022$, OR=15.615, 95% CI: 1.496-162.95) were identified as independent risk factors for POPF (Table III).

Table I: Analysis of categorical data between the groups.

Variable		no POPF (n=39)	POPF (n=35)	p
Gender, n (%)	Female	13(33.3%)	10(28.6%)	0.659
	Male	26(66.7%)	25(71.4%)	
Age, years (min-max)		72(65-92)	71(65-85)	0.345
ASA[a], n (%)	1	1(2.6%)	3(8.6%)	0.504*
	2	25(64.1%)	22(62.9%)	
	3	13(33.3%)	10(28.6%)	
	4	0(0%)	0(0%)	
	5	0(0%)	0(0%)	
Tumour localisation, n (%)	Pancreas	27(69.2%)	16(45.7%)	0.060*
	Vater's ampulla	9(23.1%)	17(48.6%)	
	Distal common bile duct	2(5.1%)	0(0%)	
	Duodenum	1(2.6%)	2(5.7%)	
DM[b], n (%)	Absence	33(84.6%)	21(60.0%)	0.017
	Presence	6(15.4%)	14(40.0%)	
CAD[c], n (%)	Absence	34(87.2%)	28(80.0%)	0.403
	Presence	5(12.8%)	7(20%)	
HT[d], n (%)	Absence	27(69.2%)	15(42.9%)	0.022
	Presence	12(30.8%)	20(57.1%)	
Preoperative drainage, n (%)	Absence	17(43.6%)	14(40.0%)	0.755
	Presence	22(56.4%)	21(60.0%)	
Reconstruction type, n (%)	PJ[e]	18(46.2%)	21(60.0%)	0.047
	PG[f]	7(17.9%)	10(28.6%)	
	R&Y[g]	14(35.9%)	4(11.4%)	
Bilier leakage, n (%)	Absence	39(100.0%)	32(91.4%)	0.101*
	Presence	0(0%)	3(8.6%)	
CD[h], n (%)	0	24(61.5%)	1(2.9%)	<0.001*
	1	0(0%)	0(0%)	
	2	6(15.4%)	16(45.7%)	
	3a	3(7.7%)	5(14.3%)	
	3b	3(7.7%)	4(11.4%)	
	4a	0(0%)	2(5.7%)	
	4b	1(2.6%)	2(5.7%)	
	5	2(5.1%)	5(14.3%)	

*a. ASA = American Society of Anaesthesiologists, b. DM = Diabetes mellitus, c. CAD = Coronary artery disease, d. HT = Hypertension, e. PJ = Pancreatico-jejunostomy, f. PG = Pancreaticogastrostomy, g. Roux-en-Y reconstruction, h. CD = Clavien Dindo, Pearson Chi-square test, * Fisher's exact test was considered significant at p <0.05.*

Table II: Univariate analysis of risk factors for postoperative pancreatic fistula.

Variable	no POPF (n=39)		POPF (n=35)		p
	Median	(min-max)	Median	(min-max)	
Wirsung duct diameter, mm	5(2-10)		3(2-6)		<0.001
Creatinine, mg/dL	0.7(0.5-1.5)		0.7(0.4-1.3)		0.397
Total Bilirubin, mg/dL	2.6(0.3-25.3)		1.8(0.3-15.3)		0.795
AST, U/L	36(13-681)		47(12-312)		0.770
ALT, U/L	54(8-758)		52(12-538)		0.749
GGT, IU/L	99(0-1785)		227(0-2237)		0.196
LDH, U/L	204(0-509)		209(0-2237)		0.286
WBC, 10^3/uL	7.1(4.1-17)		8.7(4.7-15.9)		0.014
Hgb, g/dL	12.5(8.6-15.7)		12.6(8-15.8)		0.940
Lymphocyte, 10^3/uL	1.5(0.5-4.8)		1.9(0.5-7.6)		0.044
Neutrophil, 10^3/uL	4.2(0.7-16)		5.8(2-12.8)		0.067
Platelet, 10^3/uL	272(162-485)		265(118-530)		0.681
ICU[a] length of stay in days	3(2-4)		4(2-13)		0.066
Length of hospital stay in days	13(12-19)		23(16-33)		0.001
Albumin, g/dL	3.5(2-4.4)		3.2(2.1-4)		0.007
PNI[b]	35.06(20.09-44.03)		32.03(21.08-40.05)		0.009
CEA, ng/mL	1.9(0-515)		2.27(0-72.9)		0.418
CA 19-9, ng/mL	15(0-10942)		47.8(0-7926)		0.060
Median survival time, months	16(1-128)		15(1-144)		0.722

a. ICU = Intensive care unit, b. PNI= Prognostic nutritional index, Mann-Whitney U test results were considered significant at p <0.05.

Table III: Multivariate logistic regression analysis for postoperative pancreatic fistula.

Characteristics	Odds Ratio	95% CI[a]	p
HT[b]	25.519	2.034- 320.152	0.012
DM[c]	1.276	0.149- 10.915	0.824
Wirsung diameter <3.5mm	82.461	6.542- 1039.343	<0.01
Albumin <3.35 g/dL	0.19	0.005- 7.26	0.372
Lymphocyte <1.75 10^3/uL	0.626	0.107- 3.655	0.603
PNI <33.04[d]	5.842	0.181- 188.099	0.319
R&Y[e]	1		0.063
PG[f]	6.425	0.854- 48.342	0.071
PJ[g]	15.615	1.496- 162.95	0.022

a. CI = Confidence interval, b. HT = Hypertension, c. DM = Diabetes mellitus, d. PNI = Prognostic nutritional index, e. Roux-en-Y reconstruction, f. PG = Pancreaticogastrostomy, g. PJ = Pancreaticojejunostomy, p<0.05 was considered statistically significant.

DISCUSSION

In the study, significant differences were observed between the occurrence of POPF and the presence of HT, DM, Wirsung duct diameter <3.5 mm, albumin level <3.35 g/dL, lymphocyte count <1.75 10^3/uL, PNI <33.04, and reconstruction type after PD in geriatric patients, as determined in the univariate analyses. However, in the multivariate analyses, HT, Wirsung duct diameter <3.5 mm, and PJ as a reconstruction technique were identified as independent risk factors for POPF in geriatric patients undergoing PD. Furthermore, the study revealed a mortality rate of 9.5% and a POPF rate of 47.3% in the geriatric patient population. These high rates of mortality and POPF can be attributed to the advanced age and the malignant nature of the patients included in the study.

The recognition, management, and prevention of postoperative POPF are particularly crucial in the context of geriatric patients who undergo PD. While the literature suggested that a small pancreatic duct and a soft gland may serve as predictive factors for POPF, there was a lack of definitive evidence in this regard. In cases where POPF does occur, additional invasive procedures become necessary to mitigate associated morbidity. This can lead to prolonged hospital stays and increased mortality rates among geriatric patients with underlying comorbidities and limited organ reserve. Consequently, it is imperative to identify predictive factors that can help prevent the development of POPF in a vulnerable patient population. Scoring systems such as Callery's score and Roberts' score, which incorporate Wirsung duct diameter as a risk factor for POPF, have been developed.[9,10] Another study demonstrated that a Wirsung diameter ≤3 mm was independently associated with an increased risk of POPF.[11] It was hypothesised that a wider Wirsung diameter may lead to a lower incidence of POPF due to improved surgical anastomosis and pancreatic duct fibrosis.[11] In this study, it was also found that a Wirsung diameter <3.5 mm was an independent risk factor for the development of POPF.

The incidence of HT tends to increase with age in geriatric patients, and in this study, it was also found to be 43.2%. Importantly, HT was identified as an independent risk factor for POPF. Although recent studies have suggested that HT contributes to pancreatic damage by promoting inflammation and oxidative stress in the pancreas, the underlying pathophysiological mechanisms linking HT to an increased risk of POPF remain largely unexplored in the existing literature.[12] Further research is needed to elucidate the specific mechanisms by which HT influences the development of POPF.

Numerous studies have investigated different reconstruction techniques to prevent POPF. These studies have shown that patients who undergo PG have lower rates of POPF compared to those who undergo PJ.[13] However, it has also been observed that reconstruction techniques do not significantly impact POPF-related mortality.[14] One hypothesis is that *Roux-en-Y* (R&Y) reconstruction after PD avoids activation of trypsin from gastric contents and preserves the integrity of the PJ.[15] Nonetheless, studies have not demonstrated any superiority of R&Y reconstruction over other techniques in terms of POPF and other complications.[16]

In this study, it was found that patients who underwent PJ with R&Y reconstruction had an approximately 15-fold increased risk of developing POPF. This highlighted the importance of making the appropriate reconstruction decision intraoperatively, considering the individual patient's risk factors.[17] Clinicians should be mindful of selecting safer anastomosis techniques in patients with predictive factors to minimize the occurrence of POPF.

Meta-analyses had demonstrated that the use of pancreatic stents, either external or internal, can reduce the rates of POPF.[14] Furthermore, studies had shown that the mortality associated with POPF is lower in patients who undergo external stent placement.[14] These findings suggested that the diversion of pancreatic contents with stenting helps to prevent complications related to the anastomosis by protecting against pancreatic duct occlusion and injuries during the procedure.

However, in this study, the authors did not observe a significant difference in the rates of POPF between patients who received external stent placement and those who did not. Despite the potential benefits suggested by previous

researches, findings of this study did not support a significant impact of external stenting on POPF rates.

Previous studies in the literature suggested that DM may actually reduce the risk of POPF.[18] This could be attributed to the fact that the pancreatic tissue of patients with DM tends to be less fatty and more fibrotic, potentially leading to a more secure pancreatic anastomosis and lower risk of POPF.[19] However, this study did not find a significant association between DM and the occurrence of POPF. Despite the existing literature suggesting a potential protective effect of DM against POPF, the current findings did not support this relationship.

A previous study investigating the impact of nutritional status on postoperative outcomes following PDs demonstrated that an albumin level below 3 g/dL increased the risk of POPF in patients with high nutritional risk scores.[20] This suggested that a lower albumin level may be associated with impaired healing and increased susceptibility to complications such as POPF.

However, in this study, there was no significant association between preoperative albumin levels and the occurrence of POPF in the multivariate analysis. It is important to note that nutritional status is a complex and multifactorial aspect of patient care, and the influence of albumin levels on POPF risk may be influenced by various factors such as comorbidities, surgical technique, and overall patient health.

By identifying these predictive factors, clinicians can proactively address the risk of POPF in geriatric patients undergoing PD. This may involve implementing interventions such as pancreatic duct stenting, optimising nutritional status, and tailoring postoperative care to minimise complications. Furthermore, these findings underscore the importance of individualised approaches in surgical decision-making, taking into account patient-specific factors to achieve favourable outcomes.

Indeed, conducting multicentre studies with larger sample sizes is crucial to validate and generalise the findings of low-volume studies. Limiting the patient group to the geriatric population may result in a smaller sample size and potential limitations in terms of statistical power and generalisability of the results. Multicentre studies can help overcome these limitations by including a more diverse patient population and increasing the sample size, thus providing more robust evidence.

CONCLUSION

In the geriatric population undergoing PD, HT, Wirsung diameter <3.5 mm, and the preference for pancreaticojejunostomy (PJ) as the chosen anastomosis technique have been identified as prognostic factors for POPF. These findings provide valuable insights to guide clinicians towards safer reconstruction techniques during intraoperative anastomosis in patients with these predictive factors.

ETHICAL APPROVAL:
This study was conducted retrospectively and approved by the Ethics Committee of University Hospital, on 10th January 2023 (Approval No. 4361).

PATIENTS' CONSENT:
Since it was designed as a retrospective study, the data were collected from the hospital archive following the approval of the Ethics Committee. Informed consent was obtained from all the patients before the procedure.

COMPETING INTEREST:
All authors reported no competing interest.

AUTHORS' CONTRIBUTION:
CC, CA: Study conception and design, preparation of manuscript.
HK, KS, MK: Data collection.
CC: Analysis and interpretation of results.
CC, NTB: Drafting of discussion, literature review.
All authors reviewed the results and approved the final version of the manuscript.

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