Original Research

Predictive Risk Factors for Clinically Related Pancreatic Fistula After Pancreaticoduodenectomy: Analysis of 248 Patients

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ABSTRACT

Objective: Postoperative pancreatic fistula (POPF) affects 13-50% of patients undergoing pancreaticoduodenectomy (PD), and remains the main source of post-PD morbidity and mortality. Therefore, determining predictive risk factors for POPF remains popular today. This study aimed to determine the predictive risk factors for clinically related postoperative pancreatic fistula (CR-POPF) in the preoperative and early postoperative period in patients that underwent PD.

Methods: This is a retrospective study involving 248 patients who underwent PD between January 2015 and December 2019 in our center. We compared the groups that did and did not develop CR-POPF. We determined the risk factors affecting CR-POPF by stepwise logistic regression analysis.

Results: 141 (56.8%) of the patients included in the study were male, and the median age was 63 (56-70)/year. The CR-POPF rate was 18.1%. We found a statistically significant difference (p <0.05) in the following parameters: diabetes, smoking, preoperative leukocyte, preoperative neutrophil, postoperative first day (POD1) amylase, POD1 AST, POD1 ALT, POD1 CRP, POD1 lymphocyte-CRP ratio (LCR), postoperative third day (POD3) lymphocyte, POD3 CRP, in POD3 neutrophil-lymphocyte ratio, POD3 platelet-lymphocyte ratio (PLR), POD3 AST-ALT ratio, POD3 LCR, surgeon experience, incision type, Wirsung diameter, pancreatic tissue and operation time. In the stepwise logistic regression model, we found POD1 AST, POD3 CRP, POD3 TLR, diabetes, surgeon experience, and Wirsung diameter as predictive risk factors.

Conclusions: Despite some new methods to reduce the occurrence of POPF, the expected improvement in POPF rates is elusive. Predictive risk factors for POPF may also vary because the response of patients to trauma varies and the postoperative period is very dynamic. In our study, we found POD1 AST, POD3 CRP, POD3 TLR, diabetes, surgeon experience and Wirsung diameter as predictive risk factors for CR-POPF.

Keywords: pancreaticoduodenectomy, pancreatic fistula, predictive, risk factor

INTRODUCTION

In the United States of America, approximately 57,600 people are expected to develop exocrine pancreatic cancer per year and more than 90% of them are expected to die from this disease

[1]. The only potential curative treatment of cancers originating in the periampullary region (pancreatic head, ampulla of Vater, distal bile duct and duodenum) is pancreaticoduodenectomy (PD). Postoperative pancreatic fistula (POPF) affects 13-50%

of patients undergoing surgical resection and remains the main source of morbidity and mortality after pancreatic resection [2-4]. POPF is associated with fatal complications such as intraabdominal sepsis and hemorrhage. The literature indicates that mortality develops in 1% of all POPF patients and 25.7% of grade C POPF patients [5]. Despite numerous studies describing new methods to reduce the occurrence of POPF, there has been no significant improvement in POPF rates in the last three decades.

Until recently, literature data regarding the definition and classification of POPF were very heterogeneous. In 2005, the International Study Group of Pancreatic Surgery (ISGPS) developed a consensus definition, which facilitated the adoption of a common language in subsequent studies [6]. This definition was revised in 2016 to limit POPF reporting only to factors affecting the clinical course [2]. With the provision of a common language, studies of determining predictive risk factors for POPF have gained more importance and speed.

In this study, we aimed to determine the predictive risk factors for clinically related postoperative pancreatic fistula (CR-POPF) in the preoperative and early postoperative period in patients that underwent PD.

Main Points;

- POPF is a significant complication after PD and is associated with high morbidity and mortality rates.

- This study aimed to identify predictive risk factors for CR-POPF in the preoperative and early postoperative period in patients who underwent PD.

- The incidence of CR-POPF was 18.1% in the study population. Diabetes mellitus, surgeon experience of less than 10 years in pancreatic surgery, Wirsung diameter <4mm, POD1 AST <69 U/L, POD3 CRP >17.95 mg/dL, and POD3 PLR <225.18 were identified as predictive risk factors for CR-POPF.

- Other factors such as smoking, midline incision, soft pancreatic tissue, and prolonged operation time were associated with increased risk of CR-POPF, but did not reach statistical significance in the logistic regression analysis.

- The study highlights the importance of identifying predictive risk factors for CR-POPF to guide treatment decisions, surgical techniques, and postoperative management to reduce the incidence and complications of POPF.

- Further studies with larger sample sizes and multicenter collaborations are needed to validate these findings and optimize strategies for preventing and managing CR-POPF after PD.

MATERIALS AND METHODS

Data from 320 patients who underwent pancreatic surgery in the General Surgery Clinic of Izmir Katip Çelebi University Atatürk Training and Research Hospital between January 2015 and December 2019 were retrospectively evaluated.

Inclusion criteria in the study:
- Patients undergoing a PD procedure
- Patients whose records are fully accessed from the hospital database

Exclusion criteria in the study:
- Patients undergoing pancreatic surgery other than PD procedure
- Patients undergoing other surgical procedures in addition to the PD procedure

Two hundred forty-eight patients who met these criteria were included in the study, and written informed consent was obtained from all patients. The study started with the approval of the ethics committee of our center with approval number 883, and all steps were carried out in accordance with the principles of the Declaration of Helsinki.

Definition of CR-POPF and Clinical Variables
POPF was defined according to the ISGPS 2016 updated consensus report [2]. The evaluated criteria were analysed according to the groups that did and did not develop CR-POPF (Grade B and C).

The analysis covers demographic data, comorbidities, preoperative biliary drainage status (internal and external), blood parameters (preoperative, intraoperative and postoperative), tumor localization, surgical technique, intraoperative findings, histopathological diagnoses, morbidity and mortality of the patients included in the study. As blood parameters, the hemogram and biochemistry parameters of the patients in the week before surgery, on the first postoperative day and on the postoperative third day, as well as the pH and lactate parameters in the intraoperative second-hour arterial blood gas were analyzed.

As intraoperative parameters, surgeon's experience (<10 years and >10 years), incision type, surgical technique, structure of pancreatic tissue (soft and hard), Wirsung diameter (<4mm and >4mm), vascular resection status, pancreaticojejunostomy

(PJ) technique, blood transfusion need and operation time were analyzed.

Delayed gastric emptying, post-PD hemorrhage and bile leakage were done according to international definitions. Delayed gastric emptying, post-PD hemorrhage, surgical site infection, bile leakage, need for reoperation, need for intensive care follow-up, early mortality and length of hospital stay were analyzed.

Surgical Technique and Follow-up

In our center, surgical techniques were personalized on a patient basis by three different surgical teams. Conventional (classical PD and pyloric-sparing PD) surgery was performed in all patients. All patients had undergone PJ as pancreatic enterostomy. Jackson-Pratt drains were placed under PJ and HJ anastomoses in all patients. The drain was terminated on the third postoperative day after confirmation that the drain amylase was within normal limits. Prophylactic somatostatin analogs were not given to any patient. Frequent vital and inflammatory markers were followed up in patients with POPF. Imaging methods were used in cases in which intraabdominal loculated fluid or abscess was suspected. If loculated fluid or abscess was detected, depending on the size or location of the fluid, conservative and percutaneous drainage methods were preferred primarily.

Statistical Analysis

The data were evaluated using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) statistical package program. Descriptive statistics were given as unit number (n), percentage (%), median (M), 25th percentile (Q1), 75th percentile (Q3), mean and standard deviation. Independent samples t-test, Mann-Whitney U test, Pearson chi-square, Fisher-exact test and Fisher Freeman Halton test were used for comparisons between groups that did / did not develop CR-POPF. Receiver Operating Characteristic (ROC) analysis was performed to determine the cut-off value of metric values with statistical significance. Risk factors affecting CR POPF were determined by stepwise logistic regression analysis. The OR values and 95% confidence intervals of the risk factors were specified. $p < 0.05$ was considered statistically significant.

RESULTS

141 (56.8%) of the 248 patients included in the study were male and the median age was 63 (56-70)/year. 21 (8.5%) patients had a biochemical leak, 41 patients (16.5%) had Grade B, and

4 (1.6%) patients had Grade C POPF. The CR-POPF rate was 18.1%. In the evaluation of the demographic characteristics and comorbidities of the patients, the detection of more CR-POPF in the patient group with diabetes mellitus was found to be statistically significant ($p = 0.044$). In addition, less CR-POPF developed in the smoking group, and the difference between the groups was statistically significant ($p = 0.021$). Preoperative biliary drainage (PBD) was applied to 146 (58.8%) patients. It was detected that PBD was applied more in the group with CR POPF, but there was no statistical difference between the groups ($p = 0.401$) (Table 1).

In the evaluation of preoperative laboratory parameters, it was found that the group with CR-POPF had higher lymphocyte and neutrophil values, and the difference between the groups was statistically significant (p-value, respectively; 0.042, 0.022) (Table 2). In the evaluation of intraoperative parameters, more CR-POPF was observed in the patient group operated by surgeons with less than 10 years of experience in pancreatic surgery, and the difference was statistically significant ($p < 0.001$). More CR-POPF was observed in the patient group operated with midline incision and the difference between the groups was statistically significant ($p = 0.002$). Wirsung diameter <4mm and soft pancreatic tissue were more common in the CR-POPF group. The difference between the groups was statistically significant (p-value, respectively; <0.001, 0.003). In addition, the operation time was longer in the group with CR-POPF and the difference was statistically significant ($p = 0.03$) (Table 3).

In the comparison of the laboratory parameters on the postoperative first day between the groups, amylase and CRP values were higher; while AST, ALT and lymphocyte-CRP ratios (LCR) were lower in the group with CR-POPF. The difference was statistically significant between groups (p-values, respectively; 0.004, 0.005, 0.012, 0.006, and 0.005) (Table 2). In the comparison of the groups according to the laboratory parameters on the postoperative third day, it was found that CRP, neutrophil-lymphocyte ratio (NLR), thrombocyte-lymphocyte ratio (PLR) and AST-ALT ratio were higher, while lymphocytes and LCR were lower in the group with CR-POPF. The difference between the groups was statistically significant (p-values, respectively; p<0.001, p<0.001, p=0.001, p=0.016, p<0.001, and p<0.001) (Table 2). Surgical site infection, delayed gastric emptying, reoperation, Clavien Dindo ≥3a complications were found to be more common in the group with CR-POPF. In addition, the patients stayed longer in the hospital and the

difference between the groups was statistically significant (p value, respectively; p<0.001, p<0.001, p=0.005, p<0.001, p<0.001) (Table 4). On the other hand, there was no statistically significant difference between the groups in terms of 30-day mortality (p = 0.780).

Cut-off values for metric variables with statistically significant differences between groups were determined by ROC analysis (Table 5). Metric variables were categorized as being below and above the specified cut-off values.

The stepwise logistic regression model was used to determine predictive risk factors for CR-POPF. In the stepwise logistic regression model, diabetes mellitus, smoking, preoperative leukocyte, preoperative neutrophil, postoperative first day (POD1) amylase, POD1 AST, POD1 ALT, POD1 CRP, POD1 LCR, third postoperative day (POD3) lymphocyte, POD3 CRP, POD3 NLR, POD3 PLR, POD3 AST-ALT ratio, POD3 LCR, surgeon experience, incision type, Wirsung diameter, pancreatic tissue and operation time were included. The logistic regression model obtained in step 13, the last step, was statistically significant (p <0.001). It was observed that POD1 AST <69 U/L increases the CR-POPF risk 3.168 times. Similarly, POD3 CRP >17.95 mg/dL increases the risk of CR-POPF 4.871 times and POD3 TLR <225.18 increases it 3.338 times. Having diabetes mellitus as a comorbidity increases the risk of CR-POPF 2.407 times. If the surgeon's experience of pancreatic surgery is less than 10 years, the risk of CR-POPF increases 7,663 times. Wirsung diameter <4 mm increases the risk of CR-POPF by 9.945 (Table 6).

Table 1. Demographics for patients with and without CR-POPF

	Total (n=248)	No CR POPF (n=203)	CR POPF (n=45)	p value
Male sex$^\beta$	141 (56.8)	114 (56.2)	27 (60)	0.638*
Age$^\alpha$ (years)	63 (56-70)	63 (56-70)	61 (58-66)	0.347#
Diabetes mellitus$^\beta$ (Yes)	94 (37.9)	71 (35)	23 (51.1)	**0.044***
Hypertension$^\beta$ (Yes)	85 (34.2)	65 (32)	20 (44.4)	0.112*
Heart disease$^\beta$ (Yes)	59 (23.7)	46 (22.7)	13 (28.9)	0.375*
Pulmonary disease$^\beta$ (Yes)	30 (12)	26 (12.8)	4 (8.9)	0.466*
Smoking$^\beta$ (Yes)	54 (21.7)	50 (24.6)	4 (8.9)	**0.021***
ASA$^\beta$ ≥3	89 (35.8)	71 (35)	18 (40)	0.525*
CCI$^\beta$ ≥5 points	135 (54.4)	109 (53.7)	26 (57.8)	0.619*
PBD$^\beta$ (Yes)	146 (58.8)	117 (57.6)	29 (64.4)	0.401*

$^\alpha$; median (IQR), $^\beta$; numbers (%),*; Chi-square, #; Mann–Whitney U-test
ASA; physical status classification system by the American Society of Anesthesiologists, CCI; Charlson Comorbidity Index, PBD; preoperative biliary drainage

Table 2. Preoperative and postoperative laboratory data for patients with or without CR-POPF

		No CR POPF (n=203)	CR POPF (n=45)	p value
Preoperative				
	Leukocyte$^\alpha$ (10^9/L)	7.4 (6.1-9.2)	7.8 (6.9-10.2)	**0.042#**
	Hemoglobin^b (g/dL)	12.16±1.74	11.93±1.75	0.441*
	Neutrophil$^\alpha$ (10^9/L)	4.6 (3.5-5.9)	5.2 (4.4-6.6)	**0.022#**
	Lymphocyte$^\alpha$ (10^9/L)	1.8 (1.3-2.3)	1.8 (1.4-2.3)	0.313#
	Platelet$^\alpha$ (10^9/L)	270 (217-340)	301 (249-335)	0.134#
	MPV$^\alpha$ (fL)	10.5 (9.8-11.5)	10.6 (9.9-11.7)	0.652#
	Amilaz$^\alpha$ (U/L)	67 (46-97)	55 (42-99)	0.376#
	AST$^\alpha$ (U/L)	40 (22-83)	38 (19-76)	0.231#
	ALT$^\alpha$ (U/L)	55.5 (24-113)	52 (20-105)	0.403#

TB[α] (mg/dL)	2.6 (0.8-7.3)	2.3 (0.6-5)	0.483[#]
DB[α] (mg/dL)	1.8 (0.4-5)	1.4 (0.3-4)	0.461[#]
CRP[α] (mg/L)	1.40 (0.4-3.26)	2.5 (0.7-3.4)	0,189[#]
Ca 19-9[α] (U/mL)	43 (15-214)	25.5 (11-84)	0.094[#]
NLR[α]	2.46 (1.8-3.8)	2.77 (2-4.1)	0.363[#]
PLR[α]	157.14 (112.8-229)	152.78 (120.5-195.8)	0.777[#]
LCR[α]	1.08 (0.4-3.8)	0.91 (0.4-3)	0.713[#]
POD1			
Leukocyte[α] (10^9/L)	14.59 (11.5-17.2)	14.95 (12.2-19.1)	0.222[#]
Hemoglobin[b] (g/dL)	11.67±1.48	11.79±1.59	0.620[*]
Neutrophil[α] (10^9/L)	12.63 (10-15.2)	13.36 (10.9-16.5)	0.128[#]
Lymphocyte[α] (10^9/L)	0.85 (0.6-1.3)	0.72 (0.6-1.3)	0.743[#]
Platelet[α] (10^9/L)	278 (213-354)	299 (244-368)	0.140[#]
Amilaz[α] (U/L)	176 (46-176)	176 (87.5-339.5)	**0.004[#]**
AST[α] (U/L)	83 (48-139)	52 (37.5-89.5)	**0.005[#]**
ALT[α] (U/L)	84 (47-149)	65 (34.5-89.5)	**0.012[#]**
TB[α] (mg/dL)	2.23 (1-4.2)	1.56 (0.9-3.6)	0.284[#]
DB[α] (mg/dL)	1.6 (0.5-3)	0.80 (0.5-2.5)	0.190[#]
CRP[α] (mg/L)	10.29 (5.9-14.8)	13.87 (9.1-20.4)	**0.006[#]**
NLR[α]	13.98 (9.5-21.7)	17.70 (10.9-21.9)	0.169[#]
PLR[α]	325 (216-470)	386.46 (227.8-568.3)	0.147[#]
LCR[α]	0.09 (0.1-0.2)	0.06 (0.03-0.1)	**0.005[#]**
AST-ALT ratio[α]	0.97 (0.8-1.3)	1.02 (0.8-1.3)	0.497[#]
POD3			
Leukocyte[α] (10^9/L)	12.08 (9.6-14.4)	11.76 (9.2-16.3)	0.729[#]
Hemoglobin[b] (g/dL)	9.88±1.26	9.72±1.11	0.424[*]
Neutrophil[α] (10^9/L)	10.14 (7.6-12.1)	9.99 (7.9-14.4)	0.342[#]
Lymphocyte[α] (10^9/L)	1.18 (0.9-1.6)	0.84 (0.6-1.2)	**<0.001[#]**
Platelet[α] (10^9/L)	232 (182-297)	232 (178-266)	0.695[#]
Amilaz[α] (U/L)	34 (18-52.8)	48 (23.5-59)	0.113[#]
AST[α] (U/L)	34 (23-58)	33 (24-61)	0.955[#]
ALT[α] (U/L)	38 (23-75)	37 (21.5-54.5)	0.22[#]
TB[α] (mg/dL)	1.71 (0.8-3.1)	1.17 (0.8-2.7)	0.415[#]
DB[α] (mg/dL)	0.99 (0.4-2.1)	0.5 (0.4-1.9)	0.237[#]
CRP[α] (mg/L)	17.15 (12.1-20.4)	22.39 (17.6-27.5)	**<0.001[#]**
NLR[α]	8.75 (5.8-12.2)	12.49 (8.5-19.4)	**<0.001[#]**
PLR[α]	201.64 (146.8-257.7)	276.19 (172.5-386.4)	**0.001[#]**
LCR[α]	0.07 (0.04-0.1)	0.03 (0.02-0.05)	**<0.001[#]**
AST-ALT ratio[α]	0.83 (0.6-1.2)	1.02 (0.8-1.3)	**0.016[#]**

[α]; median (IQR), [#]; Mann–Whitney U-test,[*]; Independent samples t test, [b]; mean and standard deviation

POD1; postoperative day 1, AST; aspartate aminotransferase, ALT; alanine aminotransferase, TB; total bilirubin, DB; direct bilirubin, CRP; C-reactive protein, NLR; neutrophil-lymphocyte ratio, PLR; platelet-lymphocyte ratio, LCR; lymphocyte-CRP ratio

Table 3. Intraoperative data for patients with or without CR-POPF

		No CR POPF (n=203)	CR POPF (n=45)	p value
Location[β]	Distal bile duct	16 (7.9)	7 (15.6)	0.253[*]
	Duodenum	7 (3.4)	2 (4.4)	
	Head of pancreas	77 (37.9)	11 (24.4)	
	Ampulla vateri	93 (45.8)	22 (48.9)	
	Uncinate process	10 (4.9)	3 (6.7)	
Surgeon experience[β]	<10 years	56 (27.6)	28 (62.2)	**<0.001[*]**
	≥10 years	147 (72.4)	17 (37.8)	
Incision type[β]	Midline	25 (12.3)	14 (31.1)	**0.002[*]**
	Subcostal	178 (87.7)	31 (68.9)	
Surgical technique[β]	Classical	132 (65)	32 (71.1)	0.435[*]
	PPPD	71 (35)	13 (28.9)	
Wirsung diameter[β]	<4 mm	85 (41.9)	37 (82.2)	**<0.001[*]**
	≥4 mm	118 (58.1)	8 (17.8)	
Pancreas texture[β]	Soft	108 (53.2)	35 (77.8)	**0.003[*]**
	Hard	95 (46.8)	10 (22.2)	
PJ technique[β]	Duct to mucosa	134 (66)	27 (60)	0.445[*]
	Others	69 (34)	18 (40)	
Vascular resection[β]	No	188 (92.6)	43 (95.6)	0.745[*]
	Yes	15 (7.4)	2 (4.4)	
Intraoperative transfusion[β]	No	95 (46.8)	19 (42.2)	0.577[*]
	Yes	108 (53.2)	26 (57.8)	
Intraoperative pH[α]		7.41 (7.37-7.45)	7.39 (7.35-7.43)	0.684[#]
Intraoperative laktat[α] (mmol/L)		1 (0.8-1.4)	1.1 (0.9-1.9)	0.119[#]
Operative time[α] (min)		315 (260-359)	330 (300-380)	**0.03[#]**

[α]; median (IQR), [β]; numbers (%),[*]; Chi-square, [#]; Mann–Whitney U-test

PPPD; pylorus-preserving pancreaticoduodenectomy, PJ; pancreaticojejunostomy

Table 4. Postoperative outcome in relation to CR-POPF

	Total (n=248)	No CR POPF (n=203)	CR POPF (n=45)	p value
Histopathology[β] (Adenocarcinoma)	191 (77.01)	161 (79.3)	30 (66.7)	0.068[*]
SSI[β] (Yes)	102 (41.12)	72 (35.5)	30 (66.7)	**<0.001[*]**
DGE[β] (Yes)	61 (24.6)	30 (14.8)	31 (68.9)	**<0.001[*]**
PPH[β] (Yes)	33 (13.3)	25 (12.3)	8 (17.8)	0.329[*]
Biliary leakage[β] (Yes)	7 (2.8)	6 (3)	1 (2.2)	>0.999[*]
Clavien Dindo[β] ≥3a	59 (23.1)	40 (19.7)	19 (42.2)	**0.001[*]**
Reoperation[β] (Yes)	21 (8.5)	12 (5.9)	9 (20)	**0.005[*]**
ICU follow-up[β] (Yes)	60 (24.2)	50 (24.6)	10 (22.2)	0.733[*]
Length of stay[α] (days)	10 (7-15)	9 (7-14)	19 (14-24)	**<0.001[#]**
30-day mortality[β] (Yes)	24 (9.7)	19 (9.4)	5 (11.1)	0.780[*]

[α]; median (IQR), [β]; numbers (%),[*]; Chi-square, [#]; Mann–Whitney U-test

SSI; surgical site infection, DGE; delayed gastric emptying, PPH; post-pancreaticoduodenectomy hemorrhage, ICU; intensive care unit

Table 5. ROC analysis for metric variables with statistically significant differences

		AUC-ROC (%95)	Cut off value	p value	Sensitivity (%)	Specificity (%)
Preoperative						
	Leukocyte (10⁹/L)	0.597 (0.508-0.685)	7.65	0.042	53.3	54.2
	Neutrophil (10⁹/L)	0.609 (0.522-0.697)	4.85	0.022	55.6	57.1
POD1						
	Amilaz (U/L)	0.635 (0.541-0.728)	174	0.005	60	48.8
	AST (U/L)	0.633 (0.544-0.721)	69	0.005	62.1	62.2
	ALT (U/L)	0.62 (0.533-0.707)	73.5	0.012	58.6	60
	CRP (mg/L)	0.631 (0.538-0.724)	12.35	0.006	57.8	58.6
	LCR	0.633 (0.546-0.720)	0.0781	0.005	60.1	60
POD3						
	Lymphocyte (10⁹/L)	0.683 (0.593-0.774)	0.95	<0.001	64.4	65
	CRP (mg/L)	0.716 (0.632-0.801)	17.95	<0.001	66.7	67.5
	NLR	0.696 (0.608-0.784)	10.26	<0.001	64.4	63.5
	PLR	0.658 (0.561-0.756)	225.18	0.001	64.4	64.5
	AST-ALT ratio	0.615 (0.525-0.705)	0.94	0.016	60	60.1
	LCR	0.743 (0.659-0.827)	0.052	<0.001	68.9	68
Operative time (min)		0.603 (0.515-0.691)	329.5	0.03	55.6	55.7

AUC; area under curve, POD1; postoperative day 1, AST; aspartate aminotransferase, ALT; alanine aminotransferase, TB; total bilirubin, CRP; C-reactive protein, NLR; neutrophil-lymphocyte ratio, PLR; platelet-lymphocyte ratio, LCR; lymphocyte-CRP ratio

Table 6. Analysis to identify risk factors for CR-POPF

		OR	95% CI	p value
Step 13	POD1 AST <69 U/L	3.168	1.293-7.764	**0.012**
	POD3 CRP >17.95 mg/L	4.871	2.013-11.787	**<0,001**
	POD3 PLR <225.18	3.338	1.417-7.863	**0.006**
	POD3 AST-ALT ratio <0.94	2.031	0.868-4.751	0.102
	Diabetes mellitus (Yes)	2.407	1.019-5.687	**0.045**
	Surgeon experience <10 years	7.663	3.082-19.050	**<0,001**
	Wirsung diameter <4 mm	9.945	3.580-27.631	**<0,001**

POD1; postoperative day 1, POD3; postoperative day 3, CRP; C-reactive protein, PLR; platelet-lymphocyte ratio

DISCUSSION

One of the most important causes of morbidity and mortality after PD is POPF. It is the most common mortal complication regardless of the surgical procedure type. POPF causes life-threatening (at a rate of 40%) intraabdominal abscesses and PPH [2,7,8]. In our study, CR-POPF was found to be associated with surgical site infection, delayed gastric emptying, reoperation, ≥3a morbidity according to Clavien Dindo classification and long hospital stay. Although CR-POPF is not associated with early mortality, it will cause a delay in adjuvant therapy and a decrease in long-term survival. Therefore, anticipating or early detecting CR-POPF before it develops is very important for treatment modifications.

Knowing the risk factors for POPF after PD can provide more enlightening information to the patients in the preoperative period and can contribute to more accurate operation decisions in borderline respectable patients. In addition, surgical techniques and postoperative management can be reviewed depending on the potential risk of developing POPF. For example; for a patient with a high risk of POPF, different options such as pancreaticoenterostomy techniques, internal or external stenting during PJ anastomosis, or feeding jejunostomy may be considered. Also, prophylactic somatostatin analogs can be added to the postoperative treatment algorithm. In the group with low risk of POPF, drains may not be used and accelerated

treatment protocols may be considered.

Whether diabetes mellitus is, a risk factor for POPF is controversial [9-13]. Srivastava et al. [12] and Cheng et al. [13] reported that preoperative diabetes mellitus is a risk factor for POPF after PD. In our study, 51.1% (23 patients) of the patients who developed CR-POPF had diabetes mellitus. In the the analysis, we found a statistically significant difference was found between the groups. In the logistic regression analysis, the patient group with diabetes mellitus as a comorbidity had a 2.407 times higher risk of CR-POPF.

In our study, 66.1% (164 patients) of the patients were operated by surgeons with an experience of more than 10 years of pancreatic surgery. In this group, the incidence of CR-POPF was 10.3%. In the patient group operated by surgeons with an experience of less than 10 years of pancreatic surgery, the incidence of clinically significant CR-POPF was 33.3%. In our study, pancreatic surgery experience less than 10 years was found to be a risk factor for CR-POPF. Søreide et al. concluded in their review that the hospital volume and surgeon experience do not have an effect on CR-POPF, and that CR-POPF rates did not decrease after the centralization of pancreatic surgeons in Sweden and Finland [14]. In their single-center study involving 1003 PD patients, Schmidt et al. defined surgeons who performed 50 or more PD procedures as "experienced" and they reported that less CR-POPF was detected in the experienced surgeon group [15]. Although some studies contend that surgical experience is not related to CR-POPF, our study and other studies in the literature point out surgical experience as one of the most important criteria for both CR-POPF and surgical success.

There is no literature focusing on the relationship between incision type and CR-POPF. Although the shape of the incision varies due to the surgeon's habit, the incision type is personalized on a patient basis, like all treatment protocols. In our study, more CR-POPF was found in patients with midline incisions. Regression analysis revealed that midline incision is not a risk factor. The reason for the detection of more CR-POPF in midline incision is might be due to the use of the midline incision in the patient group at risk for CR-POPF or to the insufficient exposure in the midline incision, which may affect the quality of the PJ. Although, in our study, a difference was detected between the groups in terms of incision type, the surgeon decides the incision type depending on the patient type. In order to understand the effect of incision shape on CR-POPF, multi-center studies and larger samples are needed.

We found that Wirsung diameter less than 4 mm was a predictive risk factor for CR-POPF and it increased the risk of CR-POPF 9.945 times. In many studies, soft pancreatic tissue and the non-dilation of the Wirsung duct were found to be associated with CR-POPF [14,16-21]. However, in our study, more CR-POPF was detected in the patient group with soft pancreatic tissue, while logistic regression analysis revealed that there was no predictive risk factor.

CRP is a valuable marker with a mean half-life of approximately 19 hours. It is used to detect disease activity, inflammatory response, and postoperative recovery [22]. Clinical use of CRP has become routine today. It has been reported that pancreatic necrosis can be detected as high as 95% in acute pancreatitis [22]. However, pathology-specific cut-off values are still subject to studies, and controversial cut-off values are reported [22-24]. In our study, the CRP cut-off value for POD3 was 17.95 mg/L (ROC-AUC 0.716 95% Cl (0.632-0.801), p <0.001). It was found that the risk of CR-POPF increased 4.871 times in the patient group with POD3 CRP> 17.95 mg/L. As in our study, in many other studies, POD3 CRP value was reported to be higher in the group with CR-POPF [23-27].

Very few studies in the literature have assessed whether there is a relationship between AST and CR-POPF, and they detected no relationship [28-30]. While mild levels of AST and ALT are usually detected in some patients after pancreatic surgery, the importance of high or low levels of these values is not clear in the literature. Winter et al. [31] conducted a study in which the data of 2,894 PD patients were evaluated retrospectively. They reported that AST> 187 U/L is associated with mortality. However, this study, did not find a relationship between AST and POPF, either. In our study, we found that the CR-POPF risk increased 3.168 times in the patient group with POD1 AST <69 U/L. Ours is the first study in the literature to find a relationship between POD1 AST value and CR-POPF.

PLR as an inflammatory biomarker has been evaluated in a limited number of studies in terms of complications after pancreatic surgery and CR-POPF, and no significant relationship was detected (29,32). In our study, we found that the relationship with CR-POPF was 3.338 times higher in the patient group with PLR <225.18 on the third postoperative day. In this respect, ours is the first study to find a relationship between POD3 PLR and CR-POPF.

The major limitation of our study is its retrospective nature and small sample size. In addition, the application of PD by different teams and the application of different surgical techniques are other factors that disrupt the homogeneity of the study group. There is a need for more homogeneous, wider and multi-center studies on this subject.

CONCLUSION

Pancreatic fistula is a natural consequence of insufficient control of exocrine secretion following PD. The definition of ISGPS provided a common scientific language for POPF, which deepened the literature knowledge on POPF. However, due to different responses of patients to surgical trauma and the dynamism of postoperative processes, the expected progress has not been achieved in applications required to prevent POPF. In this respect, determining predictive risk factors for POPF is still popular today.

In our study, diabetes mellitus, surgeon having less than 10 years of pancreatic surgery experience, Wirsung diameter <4 mm, POD1 AST <69 U/L, POD3 CRP >17.95mg/L and POD3 PLR <225.18 were found as predictive risk factors for CR-POPF.

ACKNOWLEDGMENTS

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