Predictive Factors of Pancreatic Fistula After Pancreaticoduodenectomy and External Validation of Predictive Scores

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Abstract. *Background/Aim:* The Fistula Risk Score (FRS), as other risk scores, is a validated model predicting the development of a clinically relevant post-operative pancreatic fistula (CR-POPF) after pancreaticoduodenectomy (PD). We evaluated risk factors related with CR-POPF and correlated four predictive scores with the likelihood of developing CR-POPF in our cohort. *Patients and Methods:* The records of 107 patients who underwent PD from 2007 to 2015 were obtained from a prospectively maintained database and reviewed. CR-POPFs were categorized by the International Study Group of Pancreatic Fistula (ISGPF) standards. Firstly, a univariate and multivariate analysis of risk factors related to CR-POPF was performed, and then the data were correlated with FRS, Wellner's, Robert's and Yamamoto's scores. *Results:* In total, 30 patients developed a CR-POPF. On multivariate analysis, abdominal thickness ($OR=1.02$, $p=0.010$), Wirsung's duct diameter ($OR=0.57$, $p=0.029$), pancreatic consistency ($OR=3.18$, $p=0.011$) and histological diagnosis of the lesion ($OR=1.65$, $p=0.012$) represented independent predictive factors of CR-POPF. FRS ($R^2=0.596$, $p=0.001$), Wellner's score ($R^2=0.285$, $p=0.005$) and Roberts' score ($R^2=0.385$, $p=0.002$) correlated with the likelihood of developing CR-POPF. *Conclusion:* Abdominal thickness, Wirsung's duct diameter, pancreatic consistency and histological diagnosis were independent predictive factors of CR-POPF. Predictive scores reflected the likelihood of CR-POPF, FRS being the score with the highest predictive value.

Pancreaticoduodenectomy (PD) remains the surgical procedure of choice for the vast majority of the head of pancreas lesions. Despite the reduction in mortality to 1-5%, post-operative morbidity remains significant at 30-50% (1-4), pancreatic fistula (PF) being the real Achilles heel of this technique (5-7). The International Study Group of Pancreatic Fistula (ISGPF) recently updated the definition and grading of postoperative pancreatic fistula, that had previously classified PF into three categories (8, 9). The previous type A is now considered as a biochemical leak and types B and C are classified as clinically relevant post-operative PF (CR-POPF).

The rate of CR-POPF has been correlated to several factors on multivariate analysis, including, body mass index (BMI), sex, age, neoadjuvant treatment, histological diagnosis of tumour, pancreatic consistency, Wirsung's duct diameter, as well as the type of pancreatic anastomosis or the use of external drain (10-17).

So far, there has not been an ideal strategy to nullify the risk of CR-POPF, however based on these factors, a number of groups have proposed predictive scores to stratify the risk of developing CR-POPF. These scores, if reliable, could represent a useful tool in order to improve the management of patients undergoing PD.

The aim of the present study was to evaluate the risk factors related to the development of CR-POPF and correlate predictive scores.

Patients and Methods

A retrospective analysis was undertaken to identify all consecutive PDs performed at the La Princesa University Hospital from 2007 to 2015.

Preoperative assessment included a staging computed tomography (CT). The size of pancreatic duct and the intrabdominal thickness were retrospectively reviewed; the latter being defined as the distance from the posterior surface of the rectus abdominis to the aortic back wall at the level of the umbilicus. The main pancreatic

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A: Fistula Risk Score. Adapted from (10)

Risk factor	Parameter	Points*
Gland texture	Firm	0
	Soft	2
Pathology	Pancreatic adenocarcinoma or	0
	Ampullary, duodenal, cystic, islet	1
Pancreatic duct diameter, mm	=5	0
	4	1
	3	2
	2	3
	=1	4
Intraoperative blood loss, mL	400	0
	401-700	1
	701-1,000	2
	1,000	3

*Total 0 to 10 points

C: Roberts' score. Adapted from (17)

Factors
$\exp[-3.206 + 0.107[BMI] - 0.404[\text{pancreatic ductwidth mm}]]$
$1 + \{\exp[-3.206 + 0.107[BMI] - 0.404[\text{pancreatic ductwidth mm}]]\}$

B: Wellner's score. Adapted from (11)

Factor	Value*
Age >66 years	+1
Preoperative diagnosis other than pancreatic carcinoma or chronic pancreatitis	+1
History of smoking	-1
History of weight loss	-1
History of acute pancreatitis	-1

*Value -3 to +2 points

D: Yamamoto's score. Adapted from (13)

Risk factor	Parameter	Points*
MPD index	<0.25	2
	=0.25	0
Relation to portal vein on CT	Involved portal vein	0
	Away from portal vein	2
Gender	Male	1
	Female	0
Intra-abdominal fat thickness	=65 mm	0
	>65 mm	1
Diagnosis	Pancreatic cancer	0
	Disease other than pancreatic	1

*Total 0 to 7 points

MPD: main pancreatic duct

Figure 1. Resume of prognostic scores: A: Fistula Risk Score (10); B: Wellner's Score (11); C: Robert's Score (17); D: Yamamoto's Score (13).

duct (MPD) index was defined as the ratio of the diameter of MPD to the diameter of the short axis of the pancreatic body.

The surgical team was composed of surgeons experienced in pancreatic surgery who did not change over the study period. Classic Whipple was the standard surgical procedure. Tumours involving superior mesenteric vein (SMV) or portal vein (PV) were treated by *en-bloc* resection of the vein. Pancreas consistency was assessed intraoperatively. The anastomotic technique employed was a pancreaticojejunostomy, either duct to mucosa in two layers or a dunking pancreaticojejunostomy. Two intraoperative drains were placed at the end of the procedure and somatostatin analogues were used in all patients. Postoperative antibiotics and total parenteral nutrition were used in case of infection or delayed gastric emptying.

The incidence of pancreatic fistula was assessed following the ISGPF classification (8). Biochemical fistulas (Grade A) were characterized by elevated drain amylase (>3 times the upper limit of serum amylase concentration on post-operative day 3). Clinically relevant pancreatic fistulas (CR-POPF) included Grade B and C. All patients managed using antibiotic therapy, supplemental nutrition (total parenteral nutrition), transfusion, continued drainage for more than 3 weeks or additional percutaneous drains were considered as Grade B PF. Grade C PF included patients requiring operative intervention under general anaesthesia.

Four pancreatic scores were analysed; Callery's score (10), also known as Fistula Risk Score (FRS) (Figure 1A), Wellner's score (11) (Figure 1B), Yamamoto's score (13) (Figure 1C) and Roberts's score (12, 17) (Figure 1D). Each risk factor was associated with discrete numerical values as described by the different predictive scores. The weighted aggregate of these risk factors was used to calculate individual fistula risk score (from 0 to 10 in FRS; from -2 to +3 in Wellner's score; from 0 to 7 in Yamamoto's score and as discrete variable in Roberts's score).

All statistical analyses were performed using SPSS® 21.0 for Windows (SPSS, Chicago, IL, USA). Descriptive values are expressed as percentage or mean±standard deviation (SD) and median with interquartile range. Fisher's exact test was used for comparison of categorical variables and the Student's *t*-test was used for continuous variables. For the multivariate analysis, only parameters with a *p*-value <0.01 in the univariate model were entered in the Cox regression model. Coefficient of determination (R²) was used to assess the reliability of pancreatic scores. The differences were considered significant at *p*-value<0.05.

Results

The study included 107 patients, as shown in Table I. Mean age was 66.3±9.7 years; 67 patients (62.6%) were male, mean BMI was 25.9 (±4.3). Venous infiltration was detected on preoperative CT in 19 cases (17.7%), Wirsung's duct diameter was 3.6 mm (±1.7) and abdominal thickness was 136.5 mm (±31.4). Pancreas was soft in 42 cases (39.3%), the anastomosis was an end to side, duct to mucosa, in 89 patients (83.1%). The majority of resected lesions originated from the pancreas. Thirty patients (28.0%) presented a CR-POPF, 20 (18.7%) being PF type B and 10 (9.3%) PF type C.

On univariate analysis, smaller Wirsung's duct diameter (2.8±1.0 mm vs. 4.0±1.7 mm, *p*=0.001); a wider abdominal thickness (145.7±31.6 mm vs. 130.1±29.1 mm, *p*=0.012); softer pancreas (83.1% vs. 17.0%, *p*=0.001); no vascular resection (5.3% vs. 94.7%, *p*=0.021); dunking pancreaticojejunostomy (22.4% vs. 77.5%, *p*=0.009) and a lower percentage of

Table I. *Univariate analysis.*

Variable	Total	No CR-POPF	CR-POPF	p-Value
N	107	77 (72.0%)	30 (28.0%)	
Demographic variable				
Age (mean, SD)	66.3 (±9.7)	66.5 (±10.4)	65.8 (±11.7)	0.767
Gender (male) (n, %)	67 (62.6%)	47 (70.1%)	20 (29.9%)	0.660
BMI (mean, SD)	25.9 (±4.3)	25.5 (±4.3)	27.1 (±3.9)	0.171
Smoker (n, %)	40 (37.4%)	30 (75.0%)	10 (25.0%)	0.660
Drinker (n, %)	22 (20.6%)	18 (81.8%)	4 (18.2%)	0.298
Previous pancreatitis (n, %)	8 (7.5%)	6 (75.0%)	2 (25.0%)	0.238
ASA (n, %)				0.394
I	6 (5.6%)	4 (66.7%)	2 (33.3%)	
II	56 (52.3%)	42 (75.0%)	13 (23.2%)	
III	45 (42.1%)	30 (66.7%)	15 (33.3%)	
Signs and symptoms				
Weight lost >5kg (n, %)	34 (31.8%)	25 (73.5%)	9 (26.5%)	1.000
CT findings				
Size of lesion (mean, SD)	2.9 (±1.5)	2.8 (±1.5)	3.1 (±1.5)	0.631
Venous infiltration (n, %)	19 (17.7%)	16 (84.2%)	3 (15.7%)	0.089
Wirsung's diameter (mm) (mean, SD)	3.6 (±1.7)	4.0 (±1.8)	2.8 (±1.0)	0.001
Abdominal thickness (mm) (mean, SD)	136.5 (±31.4)	130.1 (±29.1)	145.7 (±31.6)	0.012
Other preoperative variables				
Preoperative drain (n, %)	73 (68.2%)	52 (71.2%)	21 (28.8%)	1.000
Neoadjuvant treatment (n, %)	4 (3.6%)	3 (75.0%)	1 (25.0%)	0.639
Surgery				
Pancreas consistency (n, %)				0.001
Hard	65 (60.7%)	54 (83.1%)	11 (17.0%)	
Soft	42 (39.3%)	18 (42.8%)	24 (57.1%)	
Vascular resection (n, %)	19 (17.3%)	18 (94.7%)	1 (5.3%)	0.021
Anastomosis (n, %)				0.009
D-M PJ	89 (83.1%)	69 (77.5%)	20 (22.4%)	
Dunking PJ	18 (16.8%)	8 (44.4%)	10 (55.6%)	
Blood lost (27) (mean, SD)	418 (±320)	405 (±323)	449 (±317)	0.580
Surgical time (min) (mean, SD)	448 (±93)	456 (±97)	429 (±81)	0.202
Histopathology				
Origin (n, %)				0.008
Pancreas	60 (56.1%)	51 (85.0%)	9 (15.0%)	
Bile duct	11 (10.1%)	5 (45.4%)	6 (55.5%)	
Duodenum	5 (4.7%)	2 (40.0%)	3 (60.0%)	
Vater's tumour	21 (19.1%)	12 (57.1%)	9 (42.9%)	
Postoperative				
Fistulas (n, %)	61 (57.0%)			
Type A	16 (15.0%)			
Type B	20 (18.7%)			
Type C	10 (9.3%)			

BMI: Body mass index; ASA: American Society of Anesthesiologists Classification; CT: computed tomography; D-M PJ: duct-to-mucosa pancreaticojejunostomy; PJ: pancreaticojejunostomy; SD: standard deviation.

pancreatic lesions ($p=0.008$) (Table II) were found to be risk factors of CR-POPF.

On multivariate analysis, abdominal thickness (OR=1.02, $p=0.010$), Wirsung's duct diameter (OR=0.57, $p=0.029$), pancreatic consistency (OR=3.18, $p=0.011$) and histologic diagnosis of the lesion (OR=1.65, $p=0.012$) represented independent predictive factors of CR-POPF (Table III).

The correlation analysis between the predictive scores and the likelihood of developing CR-POPF in our cohort showed a significant association with FRS ($R^2=0.596$, $p=0.001$) (Figure 2A), Wellner's score ($R^2=0.285$, $p=0.005$) (Figure 2B) and Roberts' score ($R^2=0.385$, $p=0.002$). There was no significant correlation with Yamamoto's score (Figure 2C).

Table II. *Multivariate analysis.*

Variable	OR	95%CI	p-Value
Abdominal thickness	1.02	1.01-1.05	0.010
Wirsung' diameter	0.57	0.34-0.94	0.029
Pancreas' consistency	3.18	1.38-7.74	0.011
Vascular resection			0.279
Pancreatic anastomosis			0.058
Histologic type	1.65	1.12-2.44	0.012

OR: Odd ratio; 95%CI: 95% Confidence interval.

Table III. *Correlation analysis.*

Variable	R ²	p-Value
Callery's Score	0.596	0.001
Wellner's Score	0.285	0.005
Roberts' Score	0.350	0.002
Yamamoto's Score	--	0.244

R²: Coefficient of determination.

Discussion

Pancreatic fistula remains the Achilles heels of PD. Despite a consensus definition of PF (8, 9) and recent improvements in the surgical technique, the incidence of clinically relevant fistula has remained constant, between 13-36% (1, 7, 10, 18). Several groups have proposed different predictive scores of PF, based either on preoperative or both preoperative and intraoperative parameters. This series outlines that predictive factors like abdominal thickness, Wirsung's duct diameter, pancreatic consistency and histologic diagnosis of the lesion are related with an increase in the rate of CR-POPF. Furthermore, FRS, Wellner's score and Robert's score represented valid tools to assess the risk of CR-POPF. It is important to consider the magnitude of the correlation as well as the variables included in each score. While FRS takes into account both preoperative and intraoperative findings, the other two scores consider only preoperative variables. FRS was our preferred predictive score as it showed the strongest correlation with our series and at the same time it took into account Wirsung's duct diameter, pancreatic consistency and histologic diagnosis, which were independent predictive factors of CP-POPF in our multivariate analysis.

Patients with a higher predictive score should be offered the best available tools and strategy in order to minimize the risk of a CR-POPF. Several meta-analyses (19-23) have shown some advantages of pancreaticogastrostomy in reducing the incidence of pancreatic fistula. Although a reduction in mortality has never been clearly proven, the reduction of CR-

Figure 2. Correlation analysis showing the likelihood of developing CR-POPF. A: Fistula Risk Score (10); B: Wellner's Score (11); C: Yamamoto's Score (13).

POPF could help to reduce morbidity in high-risk patients. As an alternative strategy, Pessaux *et al.* (18) proposed the use of an external pancreatic drain in order to reduce the incidence of CR-POPF. Their prospective multicentre randomized clinical trial showed a decrease in PFs from 42-26%, $p=0.034$. Similar results have also been confirmed by Motoi *et al.* (24), highlighting that an external pancreatic drain could represent a useful tool, especially in patients with high predictive fistula scores. In addition to this, somatostatin analogues have shown contradictory results (25, 26), but Allen *et al.* (27) recently showed a significant decrease in CR-POPF from 21-10% ($p=0.006$) in patients treated with pasireotide, which could represent an effective tool when the likelihood of CR-POPF is high. The stratification of pancreatic fistula risk based on predictive scores is a fundamental tool in order to personalize surgical and postoperative strategies, keeping in mind all of the above strategies to reduce the incidence of CR-POPF in high-risk patients.

On the other hand, patients with lower predictive scores could be selected for not having an abdominal drain and for early feeding. A recent multicentric prospective trial by McMillan *et al.* (28) advised to omit the use of abdominal drain in low-risk patients and stratify the removal of abdominal drain in high- and intermediate-risk patients, based on postoperative drain fluid amylase. A recent prospective analysis by Bertens *et al.* (29) compared the value of drain fluid amylase (DFA) on postoperative day 1 to the FRS, highlighting both as predictors of CR-POPF. Therefore, FRS and DFA can be used as independent indicators of early drain removal.

Risk stratification of CR-POPF may have a role in selecting patients appropriate for training and evaluate surgical results. Pancreatic anastomosis is classically considered as one of the most challenging steps for both trainers to teach and trainees to learn (14). A stratification of PF risk could allow trainees to perform less risky anastomoses and at the same time establish surgical performance more accurately. In order to continue to progress and improve, outcomes after PD should be routinely stratified by risk categories based on predictive scores. These scores should become a quality control by which all PDs are evaluated. This will unify the reporting of PFs across institutions and hence make future comparisons more meaningful (30).

Our results demonstrated a correlation between CR-POPF and predictive pancreatic fistula scores, FRS being the one with the highest predictive value in our series. However, our study, presents certain limitations including the retrospective nature of analysis and the limited number of cases. Furthermore, other pancreatic fistula scores (31-33) were not analysed due to the lack of specific data related to score's variables. The routine utilization of these scores could help improve the perioperative management of patients undergoing PD, but a larger series based on multicentric studies could better compare and assess the value of different predictive scores.

Conclusion

Predictive factors like abdominal thickness, Wirsung's duct diameter, pancreatic consistency and histological diagnosis of the lesion are independent predicative factors of CR-POPF. Furthermore, a correlation between CR-POPF and predictive pancreatic fistula scores was found, FRS providing the highest predictive value. Personalizing the management of each case based on reliable predictive fistula scores could reduce severe complications related with CR-POPF, and promote an enhanced recovery.

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