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The evolution of post-operative pancreatic fistula (POPF) classification: A single-center experience

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ABSTRACT

Background: The ISGPS classification of post-operative pancreatic fistula (POPF) was recently revised, introducing the concept of biochemical leak (BL) which replaced grade A POPF. More recently, an additional distinction on three different subclasses for grade B (B1–B3) POPF was proposed. The aim of this study was to evaluate the impact of these modifications in clinical practice.

Methods: All pancreatico-duodenectomies (PD) and distal pancreatectomies (DP) performed between 2010 and 2016 were retrospectively evaluated. Incidence and grade of POPF using the old and new ISGPS classification were evaluated. Three grade B subclasses (B1: maintenance of abdominal drain >3 weeks; B2: adoption of specific medical treatments for POPF; B3: use of radiological procedures) were evaluated for clinical severity.

Results: A total of 716 patients (502 PD, 214 DP) were evaluated. The new ISGPS classification reduced the reported rate of POPF (30.7% vs 35.2% for PD, $p > 0.05$; 28% vs 44.9% for DP, $p < 0.05$), due to the abolition of grade A POPF. Grade B1, B2 and B3 rates were 3.1%, 73.8% and 23.1% in PD and 12.3%, 47.4% and 40.3% in DP, respectively. Passing from B1 to B3, significant increases in wound infection (0–40%), mean length of stay in PD (14.7–22.5 days; $p < 0.05$) and readmission rate in DP (0–39.1%) were observed.

Conclusions: The new ISGPS classification significantly reduces the reported rate of POPF, particularly after DP. The three different grade B subclasses (B1–B3) better discriminate the severity of post-operative course, especially after PD.

Introduction

In 2005, the International Study Group of Pancreatic Fistula (ISGPF) standardized the definition of post-operative pancreatic fistula (POPF) as 'a fluid output of any measurable volume via an operatively placed drain with amylase activity greater than three times the upper normal serum value [1]. POPF was also classified into three grades (A, B, and C) according to its clinical severity [1]. This classification was a milestone in the field of pancreatic surgery and its adoption by pancreatic surgeons worldwide provided a consistent definition by which to categorize POPF and allowed comparison of post-operative results between different centers [2]. However, a lack of clarity with regard to the classification was highlighted by several papers, suggesting the need of its revision [3,4]. In 2016, the International Study Group on Pancreatic Surgery (ISGPS) updated the POPF classification [5], with the most significant modification being the removal of the grade A severity category, which was replaced by the description 'Biochemical Leak' (BL). In addition, the updated classification also clarified the definition of grade C POPF, suggesting reoperation as the key factor able to shift POPF from a grade B to grade C categorization. The benefits of the updated classification have been recently shown, with data from the Pancreas Institute, Verona, Italy, confirming the clinical relevance of the major changes in the 2016 POPF classification [6]. However, the definition of POPF grade B is only minimally modified in the updated classification [5] and it still combines a heterogeneous group of clinical conditions. More recently, Maggino et al. [7] proposed the distinction of grade B POPF in three different subcategories: B1, maintenance of abdominal drain more than three

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weeks; B2, use of antibiotics or other specific medical treatment for POPF; and B3, use of interventional procedures for the POPF treatment. The authors demonstrated that this stratification of grade B POPF better allowed the distinction of different clinical and economic conditions, proposing its adoption in the new ISGPS classification [7].

The first aim of our study was to evaluate the impact of the new ISGPS classification in terms of POPF rate in our series of consecutive pancreatic major resections (Pancreatico-Duodenectomy [PD] and Distal Pancreatectomy [DP]). Our secondary aim was to apply the stratification of grade B POPF in the three subclasses recently proposed, in order to evaluate its real usefulness in clinical practice.

Materials and methods

Consecutive cases of PD or DP, performed between 2010 and 2016 at the Pancreatic Surgery Unit of the Humanitas Research Hospital of Milan, Italy, were retrospectively evaluated from a prospective database.

All operations were performed by or under supervision of a senior pancreatic surgeon. The surgical treatment for PD included Whipple-PD or pylorus-preserving PD (PPPD). In PD, a pancreatico-jejunostomy (PJ) was the only performed pancreatic anastomosis, with a manual end-to-side pancreatico-jejunostomy in double layer performed in all cases. When feasible, a duct-to-mucosa anastomosis was also realised. No pancreatico-gastrostomies were performed and no ductal stents were used. One single jejunal loop was routinely adopted for reconstruction; in case of "high risk" pancreas (soft texture and Wirsung's diameter < 3 mm), a double isolated jejunal loop was performed (in order to avoid the mixture of pancreatic and bile fluid). In DP, the resection of the pancreatic stump was performed in different ways (cold blade, stapler), according to the pancreas' texture, surgeon's preference and kind of surgical approach (open/laparoscopic). Venous resections (tangential, complete with end-to-end reconstruction) were performed in case of infiltration of spleno-mesenteric axis; no arterial resections were performed in our series. In case of infiltration of adjacent organs (colon, left adrenal gland, stomach), a resection of these organs was performed. A standard lymphadenectomy was performed in all patients [8]. In PD, two laminar drains were routinely left in place, ventral and dorsal to PJ. In DP, one or two drainages were routinely left near to the pancreatic stump and splenic area.

All post-operative courses were supervised by a specialized pancreatic team. Standardized clinical management protocols for post-operative care were followed for all patients; these protocols were updated during the study period according to the available literature and evidence. Prophylactic somatostatin analogues were administered from the day of operation until the beginning of solid oral intake for all patients; administration was continued in cases of high-flow pancreatic fistula, in addition to the use of total parenteral nutrition. Abdominal drains were not removed before post-operative day (POD) 3, according to the clinical aspect and the level of amylases. In the absence of high amylase values, all abdominal drains were removed by POD 5; in DP, some patients could maintain drainage until POD 7 due to their enrolment in scientific protocol studies. In all PDs, a routine bacteriological analysis of drain fluid was performed on POD 5; specific antibiotic therapy was started only in cases of suspected infection (e.g. fever, inflammatory syndrome at blood examination, 'sinister aspect' of drain fluid). In DPs, drain culture was not routinely performed. The decision to perform a percutaneous radiological drainage was carried out in response to the presence of fluid collection in the peripancreatic region at computed tomography (CT) scan; all drains were placed by radiologists, who were experts in the pancreatic field.

Data on patient demographics, operative procedures, perioperative outcomes and tumour histopathology were collected. Post-operative morbidity was assessed with a focus on post-operative surgery-related complications that were identified according to the most recent international definitions of the ISGPS [9,10]. Fluid collection was defined as the presence of fluid in the peripancreatic region with diameter >1 cm (including pseudocysts or abscess), identified with a CT scan performed during or within 90 days after the hospitalization for clinical reasons. Post-operative non-surgical morbidity was also recorded considering all events that deviated from the normal operative course. All post-operative complications were classified as proposed by Dindo and Clavien [11], and stratified as grades I–V. In patients with more than one complication, the highest grade was reported. The incidence and grading of POPF were compared using the 2005 and 2016 ISGPS classifications [1–5]. Grade B POPF was also stratified in three subclasses (B1-B3), according to the recent proposal of the study published by Maggino et al. [7]. These were: B1, maintenance of abdominal drain >3 weeks, without the need for any further POPF-related treatment; B2, the use of pharmacologic agents for the treatment of POPF, with or without persistent drainage >3 weeks; and B3, the adoption of any interventional (non-surgical) procedure (percutaneous drainage and/or embolization). The association between each class and various clinical outcomes (other complications, length of stay, readmission) was evaluated. Post-operative mortality was defined as deaths occurring within 90 post-operative days (90-day mortality).

Statistical analysis

Results are reported as mean and standard deviation for numerical variables (after verification of the normality of the distribution) and as counts and percentages for categorical data. Comparison between groups was performed using the student's *t*-test for paired data with equal variance for numerical data (after verification of the normality of the distribution) and with the Chi-square for the categorical data. A value of $p < 0.05$ was considered significant. Analyses were performed with STATA IC (version 15.0).

Results

A total of 716 consecutive patients that underwent major pancreatic resection during the study period (502 PD and 214 DP) were included and retrospectively evaluated.

PD: clinical data and outcomes

Clinical and pathological data of patients who underwent PD are shown in Table 1. The cohort included 291 males (58.0%) and median age was 67.8 (19–90) years. The majority of operations were PPPD (87.6%) and the median operative time was 481 (255–805) minutes. Thirty-three patients (6.6%) received neoadjuvant treatment. Vascular resection was necessary in 34 patients (6.8%). Pancreatic ductal adenocarcinoma (PDAC) was the reason for surgery in almost half the patients (48.4%). Overall morbidity was 49.6%, although severe complications (grade IIIb–V) were observed in only a minority of patients (8.6%). Median length of hospital stay was 11 (3–108) days. The 90-day mortality rate was 2.0%.

Rates of each post-operative complication (except for POPF) are reported in Table 2. Post-pancreatectomy haemorrhage (PPH) was observed in 12.1% of patients and delayed gastric emptying (DGE) in 6.6% of patients. Placement of a radiological drain (biliary or abdominal) or arterial embolization was necessary in 11.5% and 3.0% of patients, respectively. Other non-surgical complications

Table 1
Clinico-pathological data of the entire cohort.

	Pancreaticoduodenectomy (N = 502)	Distal pancreatectomy (N = 214)	P-value
Sex (male/female), n (%)	291 (58.0%)/211 (42.0%)	104 (48.6%%)/110 (51.4%)	< **0.05**
Median age, years	67.8 (19–90)	67.8 (21–85)	< **0.05**
Type of operation, n (%):			
Whipple	62 (12.4%)		
PPPD	440 (87.6%)		
Open DP		118 (55.1%)	
LPS DP		46 (21.5%)	
Converted DP		25 (11.7%)	
DP + multivisceral resection		25 (11.7%)	
Median operative time, min	481 (255–805)	273 (118–591)	< **0.05**
Splenectomy, n (%)		167 (78.0%)	
Vascular resection, n (%)	34 (6.8%)	12 (5.6%)	0.56
Resection of adjacent organs, n (%)	3 (0.6%)	16 (7.5%)	< **0.05**
Neoadjuvant treatment, n (%)	33 (6.6%)	0 (0%)	
Preoperative biliary stent, n (%)	264 (52.6%)		
Histology, n (%)			< **0.001**
Pancreatic ductal adenocarcinoma	243 (48.4%)	101 (47.2%)	
Ampullary cancer	77 (15.3%)	–	
Distal cholangiocarcinoma	34 (6.8%)	–	
Intraductal papillary mucinous neoplasm (IPMN)	32 (6.4%)	11 (5.1%)	
Neuroendocrine tumours	29 (5.8%)	52 (24.3%)	
Chronic pancreatitis	26 (5.2%)	–	
Adenocarcinoma-IPMN	24 (4.8%)	–	
Duodenal adenocarcinoma	9 (1.8%)	–	
Serous cystoadenoma		11 (5.1%)	
Mucinous cystoadenoma		16 (7.5%)	
Other histologies	28 (5.6%)	23 (10.7%)	
Overall morbidity, n (%)	299 (49.6%)	91 (42.5%)	< **0.05**
Clavien-Dindo, n (%)			0.31
I-IIIa	256 (51.0%)	83 (38.8%)	
IIIb-V	43 (8.6%)	8 (3.7%)	
Mortality, n (%)	10 (2.0%)	0 (0%)	0.03
Length of stay, days (median)	11 (3–108)	7 (3–32)	< **0.05**

Table 2
Summary of post-operative outcomes after Pancreatico-Duodenectomy (PD) and Distal Pancreatectomy (DP).

	Pancreaticoduodenectomy (N = 502)	Distal pancreatectomy (N = 214)	p
Haemorrhage: n (%)	61 (12.1%)	11 (5.1%)	< **0.001**
Grade A	26 (5.2%)	5 (2.3%)	
Grade B	17 (3.4%)	3 (1.4%)	
Grade C	18 (3.6%)	3 (1.4%)	
Delayed gastric emptying: n (%)	33 (6.6%)	0 (0%)	
Grade A	30 (6.0%)		
Grade B	3 (0.6%)		
Grade C	0 (0%)		
Fluid collection, n (%)	60 (11.9%)	32 (15.0%)	0.16
Biliary fistula, n (%)	23 (4.6%)		
Gastro-jejunal fistula, n (%)	7 (1.4%)		
Chile leak, n (%)	22 (4.4%)	7 (3.3%)	0.33
Wound infection, n (%)	74 (14.7%)	2 (0.9%)	< **0.001**
Other complications, n (%)	138 (25.7%)	34 (15.9%)	< **0.001**
Radiological procedure:			0.08
a) Drainage, n (%)	58 (11.5%)	26 (12.1%)	
b) Embolization, n (%)	15 (3.0%)	2 (0.9%)	
Surgical reoperation, n (%)	32 (6.4%)	5 (2.3%)	< **0.05**

were observed in 25.7% of patients. Surgical reintervention was needed in 6.4% of patients.

DP: clinical data and outcomes

Clinical and pathological data of DP are shown in Table 1. This cohort included 110 females (51.4%) and median age was 67.8 (21–85) years. The majority of DPs were performed with an open approach (n = 118, 55.1%) and multivisceral resection was required in 25 patients (11.7%). Splenectomy was performed in 167 patients (78.0%). Median operative time was 273 (118–591) minutes. Most DP's were performed because of pancreatic ductal adenocarcinoma (PDAC) (47.2%). Overall morbidity was 42.5%, with severe complications (grade IIIb–V) observed in 3.7% of patients. Median length of hospital stay was 7 (3–32) days. No patient died during the 90-day post-operative period.

Evaluating the rate of each single complication (except for POPF) (Table 2), PPH was observed in 11 patients (5.1%), but was classified as grade C in only three patients (1.4%). A total of 12.1% of patients needed a radiological drain. Other non-surgical complications occurred in 15.9% of patients. Only five patients (2.3%) required a surgical reintervention.

POPF rate and grading according to 2005 and 2016 classifications.

Table 3 describes POPF rates and grading after PD and DP according to the 2005 and 2016 ISGPF classifications. In PDs, no significant difference in terms of overall POPF rate was observed (35.2% versus 30.7%, respectively) ($p > 0.05$), while a significant reduction of POPF rate was observed in DPs (44.9% versus 28.0%, respectively) ($p < 0.001$). This significant reduction was due to high rate of BL in the DP group (16.4%) compared with 4.6% in the PD group. Moreover, no difference was found between the two classifications in terms of rates of grade B or C POPF.

Sub-classification of grade B POPF in B1-B3

The rate of the three subclasses of grade B POPF for both surgical procedures is shown in Fig. 1. After PD, the majority of grade B POPF were classified as B2 (73.8%), followed by grade B3 (23.1%); only a minority of cases (4, 3.1%) were classified as grade B1. In comparison, B2 and B3 rates were more similar after DP (47.4% and 40.3%, respectively), while B1 was observed only in 12.3% of cases. To study the clinical significance of the sub-classification, the association between B-POPF subclasses and clinical parameters were investigated for both surgical procedures (Table 4).

After PD, moving from B1 to B3 POPF, we found an increased occurrence of other clinical conditions, even if statistical significance was reached only for wound infection (0%, 19.8%, and 40.0% for grade B1, B2 and B3, respectively) and mean length of stay (14.7, 17.5 and 22.5 days for grade B1, B2 and B3, respectively) ($p < 0.05$).

After DP, this association between sub-grades of POPF and other clinical conditions was not clearly evident, with only a significant increase in terms of readmission rate (0%, 3.7% and 39.1% for grade B1, B2 and B3, respectively) ($p < 0.05$).

Discussion

The first aim of the current study was to compare the two ISGPF classifications in terms of POPF rate. Our results demonstrate that the new classification reduces the reported POPF rate, particularly after DP (30.7% versus 35.2% in PD, $p > 0.05$; 28.0% versus 44.9% in DP, $p < 0.05$).

In order to understand and explain this result, it is important to clarify the main differences between the two classifications (shown in Table 5). The main innovation in the revised classification was the removal of grade A POPF and its replacement with BL. As a consequence of this modification, POPF previously classified as grade A are no longer considered true fistulas but only biochemical without any clinical implication. On the other hand, there were no significant modifications in terms of grade B and C POPF between the two classifications, although the new classification permits increased clarification of these two grades. Indeed, the original classification included some ambiguity with regard to its definition of grade B, e.g. “often well” clinical condition, “yes/no” for specific treatment (including total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage), “usually yes” persistent drainage (after 3 weeks), “yes/no” in terms of readmission. As pointed out by Hackert et al. [3], the old classification had some similar characteristics in the definition of grade B and C POPF, resulting in difficulty for the surgeon to correctly grade POPF. These ambiguities have been removed in the new classification. For example, a more stringent definition of grade C POPF has been introduced, which is now limited to scenarios of fistula-related organ failure, reoperation, or death.

Taking into account these differences between the two classifications, the significant reduction in terms of reported POPF rate is clearly explained by the abolition of grade A POPF. On the other hand, we did not find any significant difference in terms of grade B and C POPF rate between the two classifications for either surgical procedures (26.0% and 26.6% of grade B and 4.8% and 1.4% of grade C for PD and DP, respectively) ($p > 0.05$). These results confirmed that the revised ISGPF classification did not involve any substantial modification of the old definitions, given that we already considered reoperation as the key point to shift grade B to grade C POPF in the interpretation of the old classification.

Moreover, our results showed that the significant reduction of reported POPF rate was more evident in patients undergoing DP, due to a higher rate of BL in this group (16.8% compared with only 4.6% after PD). This result is explained mostly by the fact that pancreatic leak after PD often involves the presence of intestinal contamination, and, consequently, requires either antibiotic therapy or other specific treatment or maintenance of drainage for more than three weeks. This result confirmed those already published in the literature: a recent study, comparing POPF after PD and DP, demonstrated that occurrence of a clinically relevant fistula (grade B + C) was more frequent after PD [12].

One of the most important criticisms of the old ISGPS classification was the heterogeneity of grade B POPF. However, the new classification did not solve this problem. This heterogeneity can be demonstrated by two clinical examples. Patient 1 undergoes PD with drain amylase value > 3 times serum amylase after POD 3. He is discharged at POD 7 with an abdominal drain in place and receiving antibiotics (based on a routinely performed positive bacteriological culture on POD 5). The abdominal drain is removed in an outpatient setting after four weeks. Patient 2 also undergoes PD with drain amylase value > 3 times serum amylase after POD 3. At POD 5, fever and inflammatory syndrome at blood tests are present and an abdominal CT scan reveals an abdominal collection requiring the placement of abdominal percutaneous drainage. At POD 10, haemorrhage is observed and is treated by embolization of the gastroduodenal artery stump. Hospital length of stay was 20 days, with abdominal drain removal 10 days after discharge. Adopting the new classification, these two very different clinical cases are both classified as grade B POPF: Patient 1 due to the use of antibiotics and to the maintenance of abdominal drain for more than three weeks and Patient 2 because of the need for percutaneous radiological procedures (percutaneous drainage and embolization). These examples clearly demonstrate the heterogeneity of

Table 3
POPF rate and grading according to the two ISPGS classifications.

	Pancreaticoduodenectomy (PD)			Distal pancreactomy (DP)		
	ISGPS 2005	ISGPS 2016	p	ISGPS 2005	ISGPS 2016	p
POPF, n (%)	177 (35.2%)	154 (30.7%)	>0.05	96 (44.9%)	60 (28.0%)	< **0.001**
Biochemical leak, n (%)	–	23 (4.6%)		–	36 (16.8%)	
Grade A, n (%)	23 (4.6%)	–		36 (16.8%)	–	
Grade B, n (%)	130 (26.0%)	130 (26.0%)		57 (26.6%)	57 (26.6%)	
Grade C, n (%)	24 (4.8%)	24 (4.8%)		3 (1.4%)	3 (1.4%)	

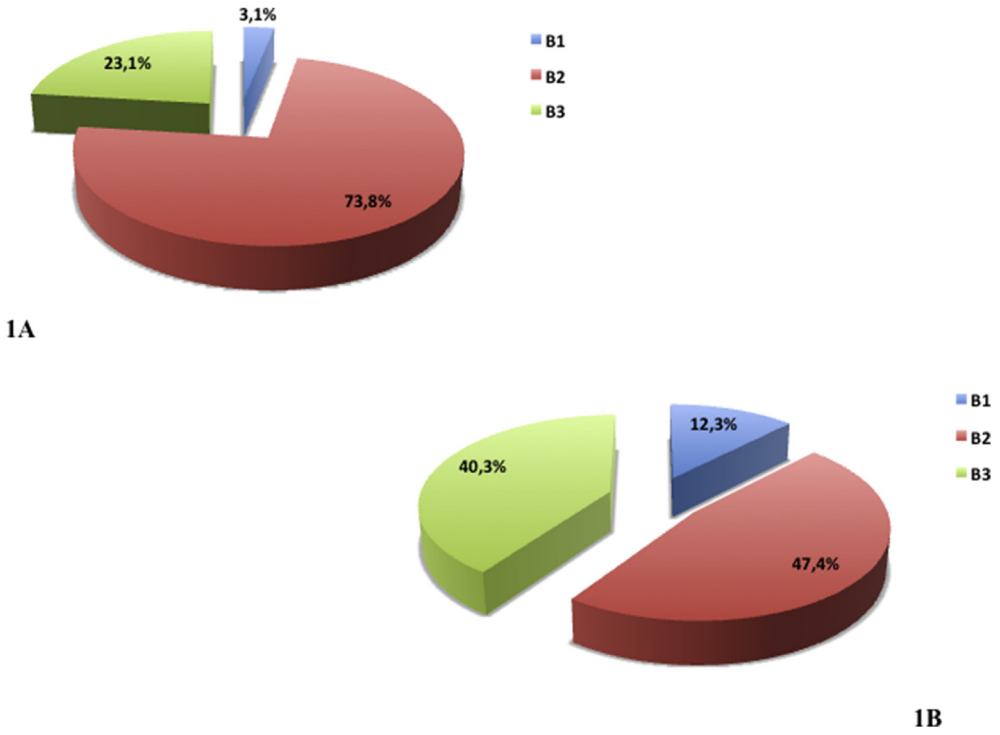

Fig. 1. Rate of three subclasses of grade B POPF (B1-B3). **1A:** Pancreatico-Duodenectomy (PD). **1B:** Distal Pancreatectomy (DP).

Table 4
Outcome measures for patients with a grade B fistula stratified by B-POPF subclass (B1-B3). **A**. Pancreatico-Duodenectomy (PD). **B.** Distal Pancreatectomy (DP).

	PD			
	B1 (N. 4)	**B2 (N. 96)**	**B3 (N. 30)**	**p**
DGE, n (%)	1 (25.0%)	10 (10.4%)	7 (23.3%)	0.163
PPH, n (%)	0 (0%)	8 (8.3%)	6 (20.0%)	0.154
Biliary fistula, n (%)	0 (0%)	5 (5.2%)	3 (10.0%)	0.555
Digestive fistula, n (%)	0 (0%)	1 (1.0%)	0 (0%)	0.837
Wound infection, n (%)	0 (0%)	19 (19.8%)	12 (40.0%)	< **0.05**
Other medical complications, n (%)	2 (50.0%)	34 (35.4%)	9 (30.0%)	0.695
Length of stay, mean days	14.7	17.5	22.5	< **0.05**
Readmission, n (%)	0 (0%)	8 (8.3%)	7 (23.3%)	0.062
DGE: Delayed Gastric Emptying; PPH: Post-Pancreatectomy Haemorrhage. B1: maintenance of abdominal drain >3 weeks; B2: adoption of specific medical treatments for POPF; B3: use of radiological procedures				
	DP			
	B1 (N. 7)	**B2 (N. 27)**	**B3 (N. 23)**	**p**
PPH, n (%)	0 (0%)	2 (7.41%)	0 (0%)	0.316
Wound infection, n (%)	0 (0%)	1 (3.7%)	0 (0%)	0.586
Other medical complications, n (%)	1 (14.3%)	3 (11.1%)	4 (17.4%)	0.816
Length of stay, mean days	7.2	10.4	12.5	0.107
Readmission, n (%)	0 (0%)	1 (3.7%)	9 (39.1%)	< **0.001**

PPH: Post-Pancreatectomy Haemorrhage. B1: maintenance of abdominal drain >3 weeks; B2: adoption of specific medical treatments for POPF; B3: use of radiological procedures.

grade B POPF, even when adopting the new proposed classification. This scenario was recently confirmed by Maggino et al. [7], who described the characteristics and management approaches for grade B POPF in a series of 1949 pancreatectomies performed in two high-volume pancreatic centers. POPF grade B developed in 320 patients (16.4%) and frequently required antibiotics (70.3%), prolonged drain (67.8%) or enteral/parenteral nutrition (54.7%), while percutaneous drainage was necessary in 79 patients (24.7%). The presence of three different subclasses of grade B POPF were proposed: grade B1 was associated with persistent drainage without the need for any further POPF-related treatment, grade B2 was associated with the need for pharmacologic agents, and grade B3 was associated with any interventional (non-surgical) procedure. The authors found that the rate of B subgrades was influenced by the type of resection: B1, B2 and B3 POPF rates were 18.6%, 60.6%, and 20.7% for PD and 19.7%, 40.15%, 40.15% for DP ($p < 0.05$) [7].

We decided to adopt the same sub-classification of grade B POPF, in order to validate the results of the study published by Maggino et al. [7]. After PD, the overall rate of grade B POPF was 26.0%: the majority of grade B POPF were classified as B2 (73.8%), followed by grade B3 (23.1%), with only a minority of cases ($n = 4$, 3.1%) classified as grade B1. The significantly higher rate of grade B2

Table 5
Comparison of two ISGPF classifications for POPF. **5.1.** Old classification (ISGPF 2005). **5.2.** Revised classification (ISGPF 2016).

Grade	A	B	C
Clinical conditions	Well	Often well	Ill appaering/bad
Specific treatment *	No	Yes/No	Yes
US/CT (if obtained)	Negative	Negative/Positive	Positive
Persistent drainage (after 3 weeks)	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possible Yes
Signs of infection	No	Yes	Yes
Sepsis	No	No	Yes
Readmissions	No	Yes/No	Yes/No

* Partial or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.

Grade	**BL**	**B**	**C**
Persisting pancreatic drainage >3 weeks	No	Yes	Yes
Clinically relevant change in management of POPF *	No	Yes	Yes
POPF percutaneous or endoscopic specific interventions for collection	No	Yes	Yes
Angiographic procedures for POPF related bleeding	No	Yes	Yes
Reoperation for POPF	No	No	Yes
Signs of infection related to POPF	No	Yes, without organ failure	Yes, with organ failure
POPF related organ failure	No	No	Yes
POPF related death	No	No	Yes

BL: Biochemical Leak.
* Partial or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.

POPF is explained by the fact that pancreatic fistula after PD is often "infected" and not "sterile", due to intestinal contamination from the anastomosis (demonstrated by positive culture of the liquid drain performed routinely on POD 5). Consequently, the majority of grade B POPF after PD requires antibiotic therapy, in addition to maintenance of abdominal drain for more much time. Interestingly, only 21.4% of all grade B POPF after PD were due to the need for more invasive treatment as radiological procedures (abdominal drainage or embolization). Different results were found after DP: the overall rate of grade B POPF was 26.6%; grade B2 and B3 rates were similar (47.4% and 40.3%, respectively), while grade B1 was observed only in 12.3% of cases. The higher rate of radiological procedure after DP (40.3% of grade B3 POPF), if compared with PD, might be explained by two reasons. Firstly, it is more difficult to place the abdominal drain correctly on the pancreatic stump (particularly in minimally invasive surgery) after DP, if compared with the peri-anastomotic region after PD and, secondly, the POPF-related left upper quadrant fluid collections are generally more amenable to percutaneous drainage than the more insidious peri-anastomotic collection after PD. Thus, our results were consistent with those reported by Maggino et al. [14] for both surgical procedures.

Maggino et al. also demonstrated that these three subclasses were associated with progressively worse clinical and economic outcomes, both in PD and DP ($p < 0.05$) [7]. Moreover, the distribution of grade B POPF subclasses showed striking variability between the two institutions participating in that study: the rate of grade B1, B2 and B3 was 41.2%, 25.2%, and 33.5% versus 3.8%, 70.9% and 25.4% for institution I and II, respectively ($p < 0.05$) [7]. This shows that this sub-classification was significantly influenced by the differences in intraoperative techniques, fistula mitigation strategies and postoperative management of patients, in particular the propensity to antibiotic treatment and/or percutaneous drainage and the policy of drain placement and removal, between the two centers.

The secondary aim of our study was to evaluate the real usefulness of the distinction of grade B POPF in three subclasses (B1-B3) in our series of resected patients. Unlike Maggino et al. [7], we found different results comparing PD and DP. In PD, we observed a worsening of clinical conditions from grade B1 to B3 and, in particular, an increasing incidence of all other POPF-related complications (even if not all were statistically significant, which is probably due to the low number of cases). Moreover, we found a significant association between the subclasses of grade B POPF and the rate of wound infection (0%, 19.8%, and 40.0% for B1, B2 and B3, respectively; $p < 0.05$) and the duration of hospital stay (14.7, 17.5 and 22.5 days for grade B1, B2 and B3, respectively; $p < 0.05$). On the other hand, subclasses do not seem to be influenced by the presence of other medical complications (50.0%, 34.4% and 30.0% for grade B1, B2 and B3, respectively; $p > 0.05$)). Different results were found in case of DP, with no relationship between the subclass of grade B POPF and the incidence of other complications. However, a relationship with the readmission rate (0%, 3.7% and 39.1% for grade B1, B2 and B3, respectively; $p < 0.05$) was observed. This could be explained by the fact that many patients undergoing DP are readmitted for the presence of a fluid collection that requires percutaneous drainage and that appeared after hospital discharge (resulting in a grade B3 POPF).

Conclusions

Our study confirms that the new ISGPS classification, introducing the concept of BL which is not considered a true clinical fistula, results in a reduction in the reported rates of POPF. This phenomenon is more evident after DP compared to PD, due to the higher rate of BL (16.4% versus 4.6%). We confirmed, moreover, that grade B POPF still includes a heterogeneous group of clinical conditions. Out results appear to support the recent proposed distinction of three different subclasses of grade B POPF. However, although this proposed sub-classification was useful in PD to better discriminate the severity of clinical conditions, the same utility was not observed in DP. Moreover, the rate of different grade B POPF is dependent on the policy of post-operative management, particularly in terms of antibiotic use and drain removal. Other studies with larger cohorts of patients are needed in order to validate and to adopt this sub-classification proposal for grade B POPF.

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