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What should we trust to define, predict and assess pancreatic fistula after pancreatectomy?

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Short Running Title:

Pancreatic fistula: can we go beyond the ISPGF definition?

Key-words:

Lipase, amylase, pancreatic fistula, absolute enzyme daily production

Abbreviation used:

ISGPF: *International Study Group of Pancreatic Fistula*

POPF: postoperative pancreatic fistula

POD: postoperative day

ABSTRACT

Objective: The *ISGPF* postoperative pancreatic fistula (POPF) definition using amylase drain concentration is widely used. However, the interest of lipase drain concentration, daily drain output and absolute enzyme daily production (concentration x daily drain volume) have been poorly investigated.

Material and methods: These predictive on postoperative day (POD) 1, 3, 5 and 7 were analyzed in a development cohort, and subsequently tested in an independent validation cohort.

Results: Of the 227 patients of the development cohort, 17% developed a biochemical fistula and 34% a POPF (Grade B/C). Strong correlation was found between amylase/lipase drain concentration at all postoperative days ($\rho=0.90$; $p=0.001$). Amylase and lipase were both significantly higher in patients with a POPF ($p<0.001$) presenting an equivalent under the ROC curve area (0.85 vs 0.84; $p=0.466$). Combining POD1 and POD3 threefold enzyme cut-off value increased significantly POPF prediction sensibility (97.4 % vs 77.8%) and NPV (97.1% vs 86.3%). These results were also confirmed in the validation cohort of 554 patients. Finally, absolute enzyme daily production and daily drain output were significantly higher in patients with a POPF ($p<0.001$) but did not add clinical value when compared to drain enzyme concentration.

Conclusion: Lipase is as effective as amylase drain concentration to define POPF. Absolute enzyme daily production or daily drain output do not help to better predict clinically significant POPF occurrence and severity. Lipase and amylase should mainly be used for their negative predictive value to predict the absence of clinically significant POPF and could allow early drain removal and hospital discharge.

INTRODUCTION

Following pancreatectomy, postoperative pancreatic fistula (POPF) remains one of the most frequent and life-threatening complications (1-4), despite numerous technical and pharmacologic measures used to prevent it (5, 6). As stated in the recent 2016 update of the *International Study Group of Pancreatic Fistula* (ISGPF) (7), POPF is defined as any measurable volume of drain fluid on or after postoperative day 3 with amylase concentration > 3 times the upper limit of normal serum amylase value for a specific institution and associated with a clinically relevant change in postoperative management (7). This definition, based in part on amylase, is now widely used, validated and accepted. α -amylase is a major digestive enzyme that hydrolyses long-chain carbohydrate and is secreted by both pancreas and salivary glands. Interestingly, lipase, that hydrolyzes triglycerides, is almost entirely secreted by the pancreas and is now the biological reference assay for the diagnosis of acute pancreatitis (8, 9) due to its higher specificity. On the opposite, the value of lipase for the diagnosis of POPF has not yet been extensively investigated (10). While the 2016 ISGPF definition is based on amylase level threshold, it does not take into account drain lipase concentration, absolute enzyme daily production (of either amylase or lipase) or drain output, which theoretically might influence or predict the severity of the POPF. In this setting, whether fistulas with similar total enzyme activities but different amylase values and drainage outputs have the same impact remains unknown. This information might help to better predict POPF, its severity, and tailor patient management, as an example with early drain removal (11, 12).

The aim of the present study was to investigate the value of lipase drain concentration, amylase and lipase absolute daily production and the drain daily output in the diagnosis and prediction of POPF as defined by the ISGPF and its concordance with amylase value.

MATERIALS AND METHODS

Data collection

From January 2014 to December 2017, 227 consecutive patients underwent elective pancreatectomy in the Department of Pancreatic and Endocrine Surgery, Cochin Hospital, Paris, France and are considered as the development cohort. Demographic variables, intraoperative data, postoperative course and pathology were obtained from a prospective database with additional retrospective review of medical records. An external independent cohort composed of 554 patients who underwent pancreatectomy in the Department of Hepato-Bilio-Pancreatic Surgery, Beaujon Hospital, Paris, France during the same period with available information on drain amylase and lipase concentration was used as validation cohort. Permission from Institutional Review Board (12-055) was obtained prior data review and analysis.

Preoperative work-up, surgical procedures

All surgical indications were discussed in a multidisciplinary pancreatic tumor board. All types of pancreatic resection, except total pancreatectomy were included. Pancreaticoduodenectomy technique was standardized and included antrectomy and reconstruction with an end-to-side pancreaticojejunostomy, hand-sewn with nonabsorbable monofilament sutures. The consistency of the pancreatic parenchyma (soft or hard) was evaluated intraoperatively using palpation of the pancreatic remnant by the surgeon. Gastrojejunostomy and hepaticojejunostomy were performed on the same jejunal loop. For distal pancreatectomy, elective ligation of the main pancreatic duct was performed whenever feasible and the pancreatic stump closed manually or stapled, according to the surgeon's choice. The pancreatic anastomosis or stump were routinely drained using a single closed-

suction silicone drain (Jackson-Pratt drain). The drain was removed from postoperative day 5. Octreotide was routinely used in patients with soft pancreatic remnant. No patients received another drug to prevent POPF.

Postoperative course and follow-up

Postoperatively, biological assessment including serum blood liver tests and amylase and lipase assay in drainage fluid was routinely performed on days 1, 3, 5 and 7. Upper normal laboratory serum amylase and lipase values were 50 IU/L and 60 IU/L, respectively. Absolute amylase and lipase daily production in the drainage is obtained multiplying amylase or lipase concentration with the daily output of the drain (ml). Postoperative mortality included all deaths occurring before hospital discharge or within 90-days. Morbidity included all complications following surgery until discharge and/or readmission and was graded according to the Dindo-Clavien classification of surgical complications (13). Postoperative pancreatic fistula, hemorrhage, chylous ascites and delayed gastric emptying were classified according to the definitions of the *International Study Group of Pancreatic Surgery* (ISGPS) (7, 14-16). Moreover, patients with clinical or radiological findings suggestive of PF (*i.e.* sepsis or hemorrhage related to peri-pancreatic collection) were classified as having a clinical fistula, regardless of the level of amylase. Patients with POPF were treated by prolonged drainage using either intraoperatively-placed drain, either a percutaneously inserted drain (placed under radiological guidance) in case of persistent or infected fluid collection, or finally by an endoscopically placed trans-papillary or transmural endogastric drain (double pigtail drain) after distal pancreatectomy for persistent fistula (17). Whenever possible, patients were discharged with drains that were subsequently removed during outpatient visits.

Statistical analysis

Values are expressed as median (range), or percentage, as appropriate. Fisher exact test was used to compare differences in discrete or categorical variables, and the Wilcoxon

rank-sum test was used for continuous variables. The Spearman correlation test was used to test the association between lipase and amylase concentrations, absolute enzyme daily production and drain output. The predictive ability of lipase concentration, absolute enzyme daily production and drain output for the occurrence of clinically relevant PF (ISGPF grade B or C) was assessed by calculating the area under the receiver operating characteristic (ROC) curve. In order to compare the correlation of lipase to amylase concentration as a diagnostic criterion of PF, the area under the curve (AUC) of ROC curves of drain amylase and lipase concentration were compared. Sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of different cut-offs were calculated. The optimal cut-off value, maximizing the balance between sensitivity and specificity, was identified through calculation of the Youden Index. For all tests, statistical significance was defined by $p < 0.05$. Data were analyzed with the STATA 12 statistical software (StataCorp. 2011. Stata Statistical Software: Release 13.1. College Station, TX: StataCorp LP).

RESULTS

Clinical characteristics, intraoperative data and postoperative course

Overall, 227 consecutive patients (men 54.6%; n=124) undergoing elective pancreatic surgery were included. Pancreatic resections were mainly performed for pancreatic adenocarcinoma (67%; n=154), neuroendocrine tumors (15%; n=35) or intraductal papillary mucinous neoplasms (5%; n=13). In addition to pancreatectomy, associated organ resection (right or left colectomy, nephrectomy, hepatectomy...) were performed in 20.7% (n=47) of patients, mainly associated with distal pancreatic resection. As summarized in **Table 1**, overall morbidity rate was 55.1% (n=124) with severe complications (Dindo-Clavien ≥ 3) in 34.7% (n=78) of patients. 90-days mortality rate was 6% (n=14). Regarding pancreatic fistula, 39 patients (17%) developed a biochemical leak (grade A), while 77 patients (34%) developed a POPF including 58 (25.6%) and 19 (8.4%) with a grade B or grade C POPF, respectively. Clinically significant POPF occurred more frequently following distal pancreatectomy (p=0.006), when pancreatectomy was associated with adjacent organ resection (p=0.003), in soft pancreas (p=0.001) or when the main pancreatic duct diameter was < 5 mm (p=0.011). Finally, hospital stay was significantly longer in patients presenting a POPF (p=0.0001).

Table 1: Patient characteristics, intraoperative data, and postoperative course according to postoperative pancreatic fistula (POPF) occurrence in the development cohort				
	Overall (n=227)	POPF		p
		No (N=150)	Yes (N=77)	
Male gender	54.6% (124)	51.3 % (77)	59% (46)	0.327
BMI (kg/m2)	23.4 (21-26.5)	23 (21-26)	24.5 (21-27)	0.186
ASA (III/IV)	7% (16)	8% (12)	5.2% (4)	0.58
Procedure				
<i>Pancreaticoduodenectomy</i>	59.4% (135)	66.6% (100)	45.4% (35)	0.006
<i>Distal pancreatectomy</i>	34.3% (78)	27.3% (41)	48% (37)	
<i>Other procedure</i>	6.1% (14)	6% (9)	6.5% (5)	
<i>Associated procedure</i>	20.7% (47)	14.6% (22)	32.4% (25)	0.003
Pancreatic adenocarcinoma or chronic pancreatitis	70.9% (161)	73.0% (109)	66.6% (52)	0.35
Intraoperative blood loss (mL)	500 (250-800)	400 (250-900)	500 (250-700)	0.82
Pancreas				
<i>Soft (vs hard)</i>	44.1% (64)	30.6% (31)	75% (33)	<0.001
<i>Main pancreatic duct \geq 5 mm</i>	30.2% (33)	37.8% (28)	12.5% (4)	0.011
Postoperative course				
<i>Overall mortality</i>	6.1% (14)	4% (6)	10.4% (8)	0.079
<i>Overall morbidity</i>	55.1% (124)	39.6% (59)	85.5% (65)	<0.001
<i>Severe morbidity (\geq grade 3)</i>	34.7% (78)	18.8% (28)	65.8% (50)	<0.001
Biochemical leak	17% (39)	17% (39)	-	-
Postoperative hemorrhage	14.5% (33)	5.3% (8)	32.5% (25)	<0.001
Delayed gastric emptying	22.9 % (52)	25.3% (38)	18.2% (14)	0.14
Hospital stay (days)	21 (15-30)	17 (13-25)	29 (22-45)	<0.001

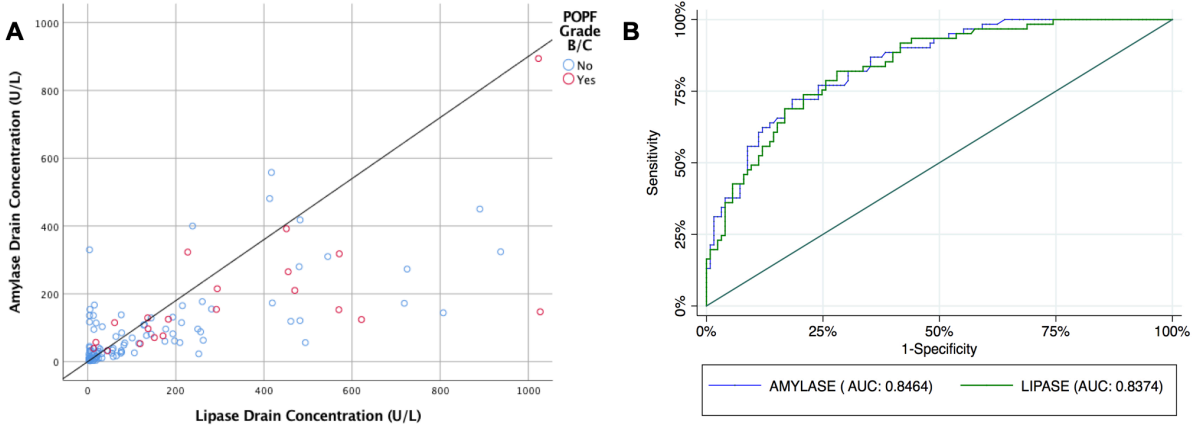
Amylase and lipase drain concentration

Amylase and lipase drain concentrations were significantly and positively correlated (Spearman's $\rho=0.90$; $p=0.001$), at all postoperative days (1, 3, 5 and 7) (**Figure 1A**) and were both significantly higher in patients with a POPF ($p<0.001$). Amylase and lipase median concentrations progressively lowered from POD1 to POD 5 (**Table 2**).

Figure 1: Correlation between the amylase and lipase value in drain on POD 3

A: Correlation between amylase and lipase drain concentration on POD 3

B: Comparison of POD 3 amylase and lipase ROC-AUC curves for POPF prediction using the threefold concentration cut-off.



In total, one hundred sixteen patients (51.1%) presented an amylase value superior to 3 times the upper normal laboratory value in the drainage fluid on and after POD3. The median lipase concentration level was significantly higher in patients with a positive threefold drain amylase concentration than in those with a negative drain amylase concentration (943 U/L vs 32 U/L; $p < 0.001$). Fourteen patients (6.1%) had negative threefold drain amylase concentration but developed either a Grade B (9 patients) or a Grade C (5 patients) POPF after drain removal, discovered on imaging or after secondary drainage/ surgery. Ninety percent of the patients presenting a threefold-elevated amylase drain concentration had also a threefold elevation in lipase drain concentration. Eight patients (7%) with a POPF were missed using a threefold lipase concentration cut-off on POD3 but were detected with the threefold amylase concentration cut-off (**Table 3**).

Table 2: Correlation between amylase and lipase drain concentration on POD 1, 3 and 5 and occurrence of POPF				
	Overall group	POPF		p
		No	Yes	
Postoperative day 1				
<i>Amylase concentration > 3N</i>	66.7% (n=142)	53.5% (n=76)	93% (n=66)	<0.001
<i>Amylase absolute concentration (U/L)</i>	446 (66-1804)	148 (37-681)	1799 (823-5794)	<0.001
<i>Lipase concentration > 3N</i>	67.8% (n=145)	53.9% (n=76)	94.5% (n=69)	<0.001
<i>Lipase absolute concentration (U/L)</i>	909 (77-4854)	179 (20-2028)	4678 (1471-20975)	<0.001
Postoperative day 3				
<i>Amylase concentration > 3N</i>	46.8% (n=87)	30.4% (n=38)	80.3% (n=49)	<0.001
<i>Amylase absolute concentration (U/L)</i>	130 (32-847)	56 (16-167)	1086 (182-5966)	<0.001
<i>Lipase concentration > 3N</i>	53.6% (n=103)	39.1% (n=50)	82.8% (n=53)	<0.001
<i>Lipase absolute concentration (U/L)</i>	221 (20-2506)	75 (13-470)	2460 (455-13613)	<0.001
<i>% Decrease of amylase concentration (POD1-POD3)</i>	70%	65.5%	35%	<0.001
<i>% Decrease of lipase concentration (POD1-POD3)</i>	75%	65.7%	41%	<0.001
Postoperative day 5				
<i>Amylase concentration > 3N</i>	34.3% (n=62)	16.5% (n=20)	70% (n=42)	<0.001
<i>Amylase absolute concentration (U/L)</i>	42 (13-585)	24 (9-60)	768 (87-5296)	<0.001
<i>Lipase concentration > 3N</i>	39.3% (n=77)	23.7% (n=31)	70.8% (n=46)	<0.001
<i>Lipase absolute concentration (U/L)</i>	58 (7-1553)	14 (5-88)	768 (89-5127)	<0.001
<i>% Decrease of amylase concentration (POD1-POD5)</i>	90%	86%	55%	<0.001
<i>% Decrease of lipase concentration (POD1-POD5)</i>	93.6%	93.4%	46%	<0.001

N: upper limit of normal serum amylase value

Table 3: Amylase, lipase and pancreatic fistula				
Amylase on and after POD3	< 3N		>3N	
	(n=99)		(n=116)	
Lipase on and after POD3	< 3N	>3N	< 3N	>3N
		87.7% (n=87)	12.1% (n=12)	9.3% (n=10)
POPF	1 % (n=1)	0 % (n=0)	7 % (n=8)	51 % (n=59)
NPV	96.2%			

N: upper limit of normal serum amylase value, POD: postoperative day, POPF: postoperative pancreatic fistula, NPV: negative predictive value

When comparing ROC under the curve (AUC) area (**Figure 1B**) between amylase and lipase drain concentration to diagnose POPF at POD3, no significant differences were observed (0.85 vs 0.84; $p=0.446$). Optimal lipase cut-off drain concentration value for detecting a biochemical leak (BL) on POD3 was found to be three times the upper normal serum enzyme value (180 U/L) just as for amylase (150 U/L). Optimal enzyme cut-off value for predicting a POPF (Grade B or Grade C) on POD 3 were six times the upper normal amylase value (300 U/L) and five times the normal upper lipase value (287 U/L). Combination of POD1 and POD3 threefold enzyme concentration cut-off (amylase or/and lipase) increased significantly POPF prediction sensibility (97.4% or/and 94.8%) and NPV (97.1% or/and 94.2%). Predictive values of the optimal amylase and lipase cut-off concentrations are shown in **Table 4**.

Table 4: Sensitivity, specificity, positive predictive value and negative predictive value of various drain variables for the prediction of POPF				
	Se (%)	Spe (%)	PPV (%)	NPV (%)
Amylase – Lipase concentration				
POD3				
<i>Amylase concentration > 3N (150 UI/L)</i>	77.8	69.8	56.3	86.3
<i>Lipase concentration > 3N (180 UI/L)</i>	82.8	60.9	51.5	87.6
<i>Amylase concentration > 6N (300 UI/L)</i>	72	81	65	85
<i>Lipase concentration > 5N (287 UI/L)</i>	80	71	57	87
<i>Amylase concentration > 6N (300 UI/L) AND Lipase concentration > 5N (287 UI/L)</i>	70	83	67	85
<i>Amylase concentration > 6 N (314 UI/L) OR Lipase concentration > 5 N (287 UI/L)</i>	81	70	57	88
POD 1-3				
<i>Amylase concentration > 3N (150 UI/L)</i>	97.4	44.7	47.4	97.1
<i>Lipase concentration > 3N (180 UI/L)</i>	94.8	43.33	46	94.2
<i>Amylase concentration > 6N (300 UI/L)</i>	94	58	53	95
<i>Lipase concentration > 5N (287 UI/L)</i>	95	30	41	92
<i>Amylase concentration > 6N (300 UI/L) AND Lipase concentration > 5N (287 UI/L)</i>	97	55	52	98
Amylase – Lipase absolute daily production (POD3)				
<i>Absolute amylase daily production > 13 UI /24h</i>	90	60	51	93
<i>Absolute lipase daily production > 11 UI /24h</i>	92	58	51	94
Drain volume (POD3)				
<i>Volume < 30 mL</i>	37	76	44	70

N: upper limit of normal serum amylase value, Se: sensibility, Spe: specificity, PPV: positive predictive value, NPV: negative predictive value

Absolute Enzyme daily production and Drain Output

As shown in **Table 5**, absolute enzyme daily production was significantly higher in POPF group on all postoperative days. Daily drain output was significantly lower in POPF group on all postoperative days, even if this small difference does not seem clinically relevant. **Table 4 shows** the sensibility, specificity, PPV and NPV of the optimal values of these various drain variables. Comparing the various ROC-AUC of lipase and amylase absolute daily production on POD 1, 3, 5 and 7, no significant differences were observed (results not shown). Although absolute enzyme daily production and daily drain output were strongly associated with the presence of a POPF ($p < 0.001$) they were not associated with an improved predictive value as compared to enzyme drain concentration.

Table 5: Correlation between amylase, lipase absolute daily production and 24h drain output on POD 1, 3 and 5 and occurrence of POPF				
	Overall group	POPF		p
		No	Yes	
Postoperative day 1				
<i>Amylase</i> absolute daily production (U/24h)	70 (12-298)	27 (6.7-146)	269 (110-593)	< 0.001
<i>Lipase</i> absolute daily production (U/24h)	175 (9-698)	29 (4-250)	647 (212-1627)	< 0.001
<i>24h volume in drain (mL)</i>	150 (95-300)	172 (100-300)	125 (50-250)	0.045
Postoperative day 3				
<i>Amylase</i> absolute daily production (U/24h)	17 (3.5-64)	6 (1.75-28.7)	66 (22-314)	< 0.001
<i>Lipase</i> absolute daily production (U/24h)	20 (2.7-150)	5 (1-45)	186 (35-1204)	< 0.001
<i>24h Volume in drain (mL)</i>	100 (25-228)	150 (45-300)	95 (25-200)	0.017
Postoperative day 5				
<i>Amylase</i> absolute daily production (U/24h)	6.7 (0.9-35)	2.3 (0.7-8.4)	41.4 (13-174)	< 0.001
<i>Lipase</i> absolute daily production (U/24h)	6 (0.8-79)	2.1 (0.6-9.6)	177 (22-606)	< 0.001
<i>Volume in drain (mL)</i>	75 (22-235)	80 (25-290)	75 (11-175)	0.028

External Validation Cohort

In the external validation cohort database, 125 patients (12.8%) with recorded amylase and lipase drain concentrations on POD1 and 554 patients (57%) with recorded POD3, POD5 and POD7 amylase and lipase drain concentrations were included. When compared with the development cohort, significant differences were found in patient's age, operative time, intraoperative blood loss, postoperative morbidity and hospital stay while POPF rate was comparable (**Table 6**).

Table 6: Clinical, demographic and operative characteristics of patients in the development and validation cohort

	Development Cohort n=227 (%)	Validation Cohort n= 554 (%)	p
Age (years)	66 (55-73)	61 (50-68)	<0.001
Male gender	122 (53.7)	286 (51.6)	0.400
BMI (kg/m²)	23.4 (21-26)	24 (21.4-27)	0.100
ASA (III/IV)	16 (7.0)	44 (7.9)	0.660
Procedure			
<i>Pancreaticoduodenectomy</i>	135 (59.5)	324 (58.4)	<0.001
<i>Distal pancreatectomy</i>	78 (34.4)	143 (25.8)	
<i>Other procedure</i>	14 (6.2)	107 (19.3)	
Intraoperative blood loss, mL	500 (250- 800)	250 (100- 400)	<0.001
Pancreas			
<i>Soft (vs hard)</i>	100 (44.1)	348 (62.8)	0.140
<i>Main pancreatic duct \geq 5 mm</i>	104 (45.8)	144 (26)	<0.001
Postoperative course			
<i>Overall mortality</i>	14 (6.1)	15 (2.7)	<0.001
<i>Postoperative pancreatic fistula</i>	76 (33.9)	156 (28.1)	0.070
<i>Severe morbidity (\geq grade 3)</i>	76 (33.5)	89 (16)	<0.001
Hospital stay (days)	21 (15-30)	15 (11-24)	<0.001

Amylase and lipase drain concentration

As in the development cohort, amylase and lipase drain concentrations were significantly and positively correlated (Spearman's $\rho=0.92$; $p<0.001$), at all postoperative days while both amylase and lipase median concentrations progressively lowered from POD1 to POD 7 (data not shown).

Median amylase concentration on POD1 was 2028 U/L (IQR 811 – 7765 U/L), significantly higher in patients who developed a POPF (4151 vs 1543 U/L, $p=0.001$). Similarly, median lipase concentration on POD1 was 9178 U/L (IQR 2963 – 24696 U/L), significantly higher in patients who developed a POPF (17820 vs 7861 U/L, $p=0.001$). When comparing ROC – AUC between amylase and lipase drain concentration to diagnose POPF at POD3, no significant differences were observed (0.776 vs 0.759; $p=0.40$). Amylase drain concentration superior to 6N was strongly associated with lipase drain concentration superior to 5N on POD3 ($p=0.001$) with negative predictive values of 88% and 90.5% respectively (data not shown). Finally, when POD1 and POD3 cut-offs (concentration > 3N) were combined NPV raised to 91% for amylase and 94% for lipase drain concentration.

DISCUSSION

Despite tremendous advances over the last decade in pancreatic surgery, pancreatic fistula remains a frequent, and possibly life-threatening, postoperative complication (7). Numerous tips and tricks either technical (18) or pharmaceutical (19, 20) have been published in order to prevent its occurrence or decrease its severity, with overall disappointing results (21). Various risk factors of POPF are now clearly identified. These include “*pancreas factors*” such as soft pancreatic tissue and small main pancreatic duct diameter, “*patient factors*” such as high BMI or male gender and “*procedure factors*” such as intraoperative blood loss (22-24). Despite extensive academic research including randomized controlled studies, publication of several clinical risk scores, POPF still occurs and accurate postoperative prediction remains difficult.

In the present work, exploring various POPF diagnostic factors, with a specific attention to drain-related ones, we observe a strong correlation between drain amylase and lipase concentration. Lipase drain concentration accurately classifies POPF in 83% of cases with an area under the ROC curve of 0.84, equivalent to the amylase one (0.85). Considering ISGPF 2016 definition for a biochemical leak and POPF (Grade B or/and C), a lipase threshold of three times the upper normal value (180 U/L) and five times the normal upper lipase value (287 U/L) yielded the optimal sensitivity and specificity respectively. Considering optimized enzyme cut-offs, combination of POD1 and POD3 threefold threshold increases significantly POPF prediction sensitivity (97.4% for amylase and 94.8% for lipase) and NPV (97.1% for amylase and 94.2% for lipase). The same results were confirmed in the validation cohort. If, lipase and amylase absolute daily production were significantly higher in patients with a POPF, their predictive value was comparable and finally did not offer any improved predictive value when compared to amylase and lipase drain concentration.

Lipase, although pancreas-specific, has curiously not been considered in the ISGPF 2016 definition of POPF and its prognostic value has not been extensively investigated. This is surprising since recent evidence-based guidelines recommend the use of lipase over amylase in the diagnostic of acute pancreatitis (25). Consistent with other studies, our work found a very strong correlation between amylase and lipase concentration in abdominal drains at POD1, 3, 5 and 7 (10, 26, 27). Lipase drain concentration on POD 3 had an area under the ROC curve of 0.84, equivalent to amylase (0.85), and thus accurately classifying POPF accurately in 84% of cases. The same observations were made in the validation cohort. To our knowledge, only three studies tried to correlate amylase and lipase concentration in POPF. Facy and al. found a good correlation between amylase and lipase concentration in abdominal drains on and after POD3, with lipase showing a high sensitivity and specificity for POPF prediction (10). Griffith et al. compared lipase and amylase in POPF prediction in a retrospective study of 68 patients and showed a higher lipase sensitivity compared to amylase (91% vs 81.8%) even if none of these enzymes were sensitive or specific enough to accurately rule out POPF and tailor postoperative patient management (26). Finally, Mussle et al. found that a threefold lipase concentration on POD3 may be used as an indicator of POPF. Only 7 out of 333 patients (2%) with POPF were missed with the threefold amylase analysis on POD3 but were detected using lipase analysis. The authors conclude that additional detection of POPF using lipase drain concentration is thus marginal and probably of little added clinical value (27). In the present study a lipase threshold of three times the upper normal value (180 U/L) yielded the optimal sensitivity and sensibility for diagnosis of a biochemical leak according to the ISGPF 2016 definition. Overall, we could move a step further and state that amylase and lipase could both be used to define POPF. As underlined by the serial modifications of the ISGPF consensus, POPF definition is evolving and this might justify considering the alternative use of lipase to define POPF in a next update. We can thus

propose that any measurable volume of drain fluid on or after postoperative day 3 with amylase OR lipase concentration level >3 times the upper normal laboratory limit for each institution is the necessary threshold.

Some of the risk factors for presenting a POPF reported in the present work are also consistent with the results of previous studies. Factors such as perioperative bleeding, main pancreatic duct diameter and pancreatic consistency are important in clearly identifying patients with a high likelihood of developing a POPF (high positive predictive value factors). This is also reflected by numerous studies attempting to define different “*fistula risk scores*” (22-24, 28, 29). In the present work, none of the drain related variables explored *i.e.* amylase or lipase drain concentration, amylase or lipase absolute daily production and 24h drain volume, were associated with a sufficiently high positive predictive value. Nevertheless, this high PPV would have been of little help as management of POPF is not specific and consists principally of close postoperative surveillance and treatment of complications, mainly involving sepsis (drainage, antibiotics, etc.). What in our opinion is important is to identify patients with a very low likelihood of developing a POPF, *i.e.* finding predictive factors with a high negative predictive value. Indeed, when disease prevalence is relatively low as it is expected for POPF, a test’s NPV is expected to be higher than its PPV since NPV increases when disease prevalence decreases. In terms of clinical practice, this allows defining a specific patient pathway with early drain removal and safe discharge (30, 31).

In this setting, many studies tried to identify ideal enzyme cut-off values for POPF prediction (32-38). As expected, the sensitivity and specificity of the enzyme cut-off values used were strictly dependent on the chosen value used: the lower is the cut-off value chosen, the higher is the sensitivity and the lower is the specificity observed. Various cut-off have thus been proposed. Molinari et al. set a threshold of drain fluid amylase of 5000IU/l at POD1, while Israel et al. and Sutcliff et al. set cut-offs of 100 IU/L and 350 IU/L, respectively (32-34).

Sensitivity (Se) and specificity (Sp) were similar (Se/Sp: 93/84%, 96/69% and 100/79%) with a very high negative-predictive value (NPV) (98%, 96% and 100% respectively). Less frequently, studies have also focused in the use of POD1 serum amylase (39) or lipase (40) and POD3 drain lipase concentration (10). Considering ISGPF 2016 definition for a biochemical leak and POPF (Grade B or/and C), a lipase threshold of three times the upper normal value (180 U/L) and five times the normal upper lipase value (287 U/L) yielded the optimal sensitivity and sensibility respectively in the present study. Lipase can be used alternatively to amylase, but with a limited added predictive value. However, when we combined POD1 and POD3 enzyme concentration cut-offs, both amylase and lipase drain concentration sensitivity (amylase: 95% vs 72%, lipase: 95% vs 80%) and NPV (amylase: 95% vs 85%, lipase: 92% vs 87%) in POPF prediction were strengthened. The same observations were made in the validation cohort. This concept is important in the era of improving postoperative monitoring of patients at low risk of developing a POPF and tailoring approach to postoperative management and early drain removal (12) (30, 31). Finally, it is of note that all these enzyme concentration cut-offs are probably not patient, pancreas or procedure specific, but rather institution dependent and thus stresses the need for a specific cut-off calculation for each surgical team, as advocated by some authors (41). Nevertheless, in the present study the same cut-offs were observed in the 2 independent cohorts.

Enzyme absolute daily production reflects the inner characteristics of a POPF. We supposed that it is possible a POPF with a daily drain output of 200 mL and amylase value of 600 U/L for example, will not have the same presentation or an equivalent severity with a POPF with a daily drain output of 100 mL and amylase value at 1200 U/L, even if the absolute enzyme daily production is the same. We found that although absolute enzyme daily production and daily drain output were both strongly associated with the presence of a POPF

($p < 0.001$) they were not associated with an improved predictive value as compared to enzyme (amylase or lipase) drain concentration. Interestingly, we noticed (**Table 5**) that POPF, compared to no fistula or BL, tends to be highly concentrated (high concentration and absolute daily production) and of low output (low daily drain output). The main limitation of this work is its retrospective nature, which is however outweighed by the large patient population included and the presence of an external validation cohort permitting to confirm our results.

In conclusion, the present study demonstrates that assessment of lipase concentration in drain can be used as an alternative to amylase drain concentration; however, it adds little clinical value compared to amylase dosage. Similarly, absolute enzyme daily production and daily drain output do not improve POPF prediction when compared to early amylase or lipase dosage in drain. Finally, combination of POD1 and POD3 enzyme drain concentration may have a strong impact in postoperative management (e.g. early drain removal) as it increases significantly negative predictive value and permits to accurately recognize patients who will not develop a POPF.

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