Early and Sustained Elevation in Serum Pancreatic Amylase Activity

A Novel Predictor of Morbidity After Pancreatic Surgery

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Objective: To characterize early postoperative serum pancreatic amylase (spAMY) trends after pancreatic resections.

Summary Background Data: A postoperative spAMY elevation is a common finding but uncertainties remain about its meaning and prognostic implications.

Methods: Analysis of patients who consecutively underwent pancreatectomy from 2016 to 2019. spAMY activity was assessed from postoperative day (POD) 0 to 3. Different patterns of spAMY have been identified based on the spAMY standard range (10–52 U/l).

Results: Three patterns were identified: (#1) spAMY values always < the lower limit of normal/within the reference range /a single increase in spAMY > upper limit of normal at any POD; (#2) Sustained increase in spAMY activity on POD 0 + 1; (#3) Sustained increase in spAMY activity including POD 1 + 2. Shifting through spAMY patterns was associated with increase morbidity (21% in #1 to 68% in #3 at POD 7; log rank < 0.001). Almost all severe complications (at least Clavien-Dindo ≥3) occurred in patients with pattern #3 (15% vs 3% vs 5% in #1 and #2 at POD 7, $P = 0.006$), without difference considering > 3-times or > the spAMY normal limit ($P = 0.85$). POPF (9% in #1 vs 48% in #3, $P < 0.001$) progressively increased across patterns. Pre-operative diabetes (OR 0.19), neoadjuvant therapy (OR 0.22), pancreatic texture (OR 8.8), duct size (OR 0.78), and final histology (OR 2.2) were independent predictors of pattern #3.

Conclusions: A sustained increase in spAMY activity including POD 1 + 2 (#3) represents an early postoperative predictor of overall and severe early morbidity. An early and dynamic evaluation of spAMY could crucially impact the subsequent clinical course with relevant prognostic implications.

Keywords: postoperative hyperamylasemia, postpancreatectomy acute pancreatitis, serum amylase trend

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The increase in serum pancreatic enzymes is a key factor in the diagnosis of acute pancreatitis (AP) and has been extensively described over the years.[1] Currently, the meaning and implications of an increase in serum pancreatic enzymes after partial pancreatic resections is a matter of vibrant debate.[2–4] As this finding could be relatively common in the first few postoperative days, it has traditionally only been considered as an indirect sign of postoperative pancreatic fistula (POPF) or a minor postoperative epiphenomenon, with no actual use in clinical practice.[5] By contrast, several studies have already described the possible prognostic implications of a postoperative increase in serum pancreatic enzymes for short-term outcomes.[2,6–9] Recently, the utility of postoperative serum pancreatic enzymes has been reappraised following the observation of postoperative hyperamy- lasemia (POH) in the absence of any clinically relevant change in the postoperative course.[10,11] However, almost all previous studies have assessed the prognostic value of serum pancreatic enzymes based on a single postoperative measurement,[5,8,12] and never as a result of a dynamic evaluation of their trend over time. Conversely, given the early onset of POH, the detection of patients at high risk for subsequent complications could remarkably affect their management.

The aims of this study are to describe the elevation in serum pancreatic enzymes after partial pancreatectomy, to characterize its trend over time, to evaluate the association with postoperative morbidity, and to identify potential predictors of its occurrence.

METHODS

This study was performed in line with the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE), and it was approved by the Institutional Review Board (Ethics Committee of the Provinces of Verona and Rovigo; approval number: 1101CESC). Written informed consent for data retrieval was obtained from all patients.

Inclusion and Exclusion Criteria

Patients who consecutively underwent pancreaticoduo denectomy (PD) and distal pancreatectomy (DP) between January 2016 and December 2019 were considered eligible and included in a prospectively maintained database. All surgeries were performed at the Department of General and Pancreatic Surgery, The Pancreas Institute, University of Verona Hospital Trust. Patients with incomplete data for postoperative serum amylase activity were excluded.

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Pancreatic Amylase Measurement and Classification

According to the institutional protocols, serum pancreatic amylase (spAMY) activity is routinely assessed 2 hours after completion of the surgical procedure on postoperative day (POD) 0, and at 7 am on POD 1, POD 2, and POD 3. In case of altered spAMY values, the assessment is continued beyond POD 3 until normalization. According to laboratory results, the standard range for spAMY activity is 10 to 52 U/L. Six patterns of postoperative amylase have been identified based on the spAMY standard range: (I) spAMY values less than the lower limit of normal (LLN) at all postoperative measurements; (II) spAMY values within the reference range at all postoperative measurements. Patients with postoperative increased spAMY values greater than the upper limit of normal (ULN) are divided according to 4 observed categories: (III) a single postoperative spAMY value greater than the ULN (spAMY >52 U/l in a single postoperative measurement regardless of whether it was recorded on POD 0, 1, or 2); postoperative spAMY values greater than the ULN in 2 consecutive measurements, namely (IV) spAMY >52 U/l on both POD 0 and POD 1; (V) spAMY >52 U/l on both POD 1 and POD 2; and (VI) spAMY values greater than the ULN at all measurements (POD 0–1–2).

For each group showing an increase in spAMY activity, patients were further stratified based on the spAMY ULN (> 52 U/L), and more than 3 times the upper limit (>156 U/L, Atlanta criteria for AP[1]).

Data Collection

Demographics, operative details, postoperative data were collected from medical records. Preoperative characteristics (including age, sex, BMI [kg/m^2], comorbidities, neoadjuvant therapy, and American Society of Anesthesiologists [ASA] score), and intraoperative data (including the type of surgery [PD or DP], vascular resection, estimated blood loss, and operative time) were retrieved. The surgical technique for PD and DP has been described elsewhere by our group.[13–16]

Both pylorus-preserving and Whipple PDs with either pan- creatojejunostomy or pancreaticogastrostomy were included. For DP, information on the type of approach (minimally invasive pancreatic surgery [MIPS, either laparoscopic or robot-assisted] or open DP), spleen preservation (either according to the Kimura[17] or Warshaw[18] technique), the level of the transection line (transection at the left of the portal vein axis, at the level of the pancreatic body-tail, or at the pancreatic neck), and pancreatic stump management (with or without a triple row staple reinforced with a polyglycolic acid felt [NEOVEIL Endo GIA Reinforced Reload with Tri-Staple Technology 60 mm; COVIDIEN, North Haven, CT, USA]) was also retrieved. The pancreatic texture was only assessed for PD due to the absence of standardization and reporting for DP performed with the MIPS approach. The size of the main pancreatic duct was measured in the pancreatic remnant from the outer dimensions using a sterile disposable ruler, and the pancreatic thickness was intraoperatively measured during DP at the pancreatic transection line. The pancreatic stump area was also calculated after DP by approximating the shape of an ellipse using major and minor axes that were retrieved from pathological reports. No prophylactic octreotide or steroids were administrated.

If deemed necessary, during PD, an externalized transanasto- motic stent (PankreaPlus polyvinyl catheter; Peter Pflugbeil Gmbh Medizinische Instrumente) was placed according to the operator's choice. The placement of drains could be omitted in patients undergoing PD who were deemed at negligible/low risk for POPF according to the Fistula Risk Score (FRS).[19] Drains were routinely placed during DP. In the case of drain placement, early removal on POD 3 was promoted on the basis of the POD 1 drain fluid amylase (DFA) value.[20,21]

The patients' pathological reports were reviewed. Given that previous studies have highlighted a histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis as a risk factor for several postoperative complications including POH,[5,11,19] such cases were defined as having a "high-risk pathological diagnosis."

Outcome Metrics

Postoperative morbidity was defined according to the International Study Group for Pancreatic Surgery definitions of POPF,[22] delayed gastric emptying (DGE),[23] post-pancreatectomy hemorrhage (PPH),[24] and chyle leak.[25] The updated definition of POPF was retrospectively applied to all patients operated in 2016. Abdominal abscess was defined as fluid collection within the abdominal cavity with radiological or clinical signs of infection. Sepsis was defined according to the 2016 updated criteria.[26] Only an unplanned need for intensive care was defined as intensive care unit (ICU) stay. Mortality was defined as postoperative death recorded out to the point of 90days postoperatively. The severity of complications was assessed according to the Clavien-Dindo (CD) classification system.[27] Due to the existence of different etiologies, post-operative complications are likely to have different patterns of onset (early or late), as previously reported.[24,28] Given the early onset of spAMY alteration, the association of spAMY with early postoperative morbidity was investigated. As it is not possible to objectively define a threshold to separate early from late complications, the time trend of morbidity was examined, and the time-to-complication occurrence was retrieved. The analysis was focused on complications graded as CD $\geq$ II,[27] namely a complication requiring a relevant change in the postoperative course, and on severe complications graded as CD $\geq$ III.[27]

The primary objective of the study was to characterize the early postoperative spAMY trend after a partial pancreatic resection. As a secondary objective, the correlation between early spAMY patterns and postoperative morbidity was explored with the purpose of identifying clinically relevant spAMY trends. Eventually, predictors of the spAMY pattern associated with the worst postoperative outcome were explored.

Statistical Analysis

Continuous variables are reported as the median and interquartile range. Differences were assessed with the Mann-Whitney or Student *t* test when appropriate. Categorical variables are reported as frequencies, and differences were assessed through the chi-square test or Fisher exact test where appropriate. Correlations between spAMY and DFA values were assessed using Pearson or Spearman correlation tests where appropriate. The cumulative incidence curves for morbidity were plotted using the Kaplan–Meier method, and the statistical significance of differences in morbidity rates was determined using the log-rank test or Breslow test where appropriate. The analysis of predictors of the spAMY pattern associated with the worst postoperative outcome was carried out using a logistic regression with a stepwise backward elimination model. The variables were assessed for multicollinearity and were removed from the model when necessary. Diagnostic accuracy analysis was also used to assess the ability of specific spAMY patterns to predict early postoperative morbidity. A 2sided *P*-value <0.05 was considered statistically significant. Statistical analyses were performed

TABLE 1. Patients Characteristics and Postoperative Outcomes of the Overall Population and Stratified According to the Type of Surgery

	Overall (n = 983)	PD (n = 720)	DP (n = 263)
Age (yr, median, IQR)	64 (55–71)	65 (56–72)	61 (49–70)
Sex			
Male	519 (52.8%)	406 (56.4%)	113 (43%)
Female	464 (47.2%)	314 (43.6%)	150 (57%)
BMI (Kg/m^2, median, IQR)	24 (22–27)	24 (22–27)	25 (22–28)
spAMY POD 0 (U/l, median, IQR)	44 (17–85)	39 (11.5–86)	53 (33–80.7)
spAMY POD 1 (U/l, median, IQR)	48 (12–124)	38 (8–153.75)	62 (38–93)
spAMY POD 2 (U/l, median, IQR)	34 (10–68)	24 (7-83)	41 (29–55)
spAMY POD 3 (U/l, median, IQR)	20 (6–34)	14 (4–32)	28 (20–37)
CRP POD 2 (mg/L, median, IQR)	174 (116–243)	179 (122–244)	159 (105–243)
Smoke	233 (23.7%)	168 (23.3%)	65 (24.7%)
Alcohol	50 (5.1%)	28 (3.9%)	22 (8.4%)
Diabetes	182 (18.5%)	137 (19%)	45 (17.1%)
ASA score			
1	43 (4.4%)	18 (2.5%)	25 (9.5%)
2	766 (77.9%)	559 (77.%)	207 (78.7%)
3	174 (17.7%)	143 (19.9%)	31 (11.8%)
Neoadjuvant therapy	241 (24.5%)	194 (26.9%)	47 (17.9%)
High-risk pathological diagnosis	421 (42.8%)	260 (36.1%)	161 (61.2%)
Vascular resection	131 (13.3%)	110 (15.3%)	21 (8%)
Operative time (min, median, IQR)	385 (300–450)	417 (360–474)	260 (210–347)
EBL (mL, median, IQR)	400 (250–628)	450 (300–700)	200 (150–400)
POPF (total n.)	225 (22.9%)	153 (21.3%)	72 (27.4%)
grade			
BL	70 (7.1%)	22 (3.1%)	48 (18.3%)
B	186 (18.9%)	122 (16.9%)	64 (24.3%)
C	39 (4.0%)	31 (4.3%)	8 (3%)
Abscess	275 (28%)	161 (22.4)	114 (43.3%)
Biliary fistula	43 (4.4%)	42 (5.8%)	0
Chyle leak	46 (4.7%)	30 (4.2%)	16 (6.1%)
PPH (total n.)	108 (11%)	85 (11.8%)	23 (8.7%)
grade			
A	37 (3.8%)	27 (3.8%)	10 (3.8%)
B	40 (4.1%)	31 (4.3%)	9 (3.4%)
C	32 (3.3%)	28 (3.9%)	4 (1.5%)
DGE (total n.)	132 (13.4%)	125 (17.4%)	7 (2.7%)
grade			
A	30 (3.1%)	27 (3.8%)	3 (1.1%)
B	69 (7.0%)	66 (9.2%)	3 (1.1%)
C	33 (3.4%)	32 (4.4%)	1 (0.4%)
Sepsis	140 (14.2%)	109 (15.1%)	31 (11.8%)
Relaparotomy	78 (7.9%)	63 (8.8%)	15 (5.7%)
Clavien dindo score			
Uneventful	351 (35.7%)	311 (43.2%)	40 (15.2%)
I	162 (16.5%)	57 (7.9%)	105 (39.9%)
II	317 (32.2%)	237 (32.9%)	80 (30.4%)
≥ III	153 (15.6%)	115 (16%)	38 (14.4%)
LOS (days, median, IQR)	9 (7–19)	9 (7–21)	8 (7–12)
Mortality	19 (1.9%)	18 (2.5%)	1 (0.4%)

ASA indicates American Society of Anesthesiologists; BL, Biochemical leak; BMI, body mass index; CRP, C Reactive Protein; DGE, delayed gastric emptying; DP, distal pancreatectomy; EBL, estimated blood loss; High-risk pathological diagnosis, histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis; IQR, interquartile range; LOS, length of hospital stay; PD, pancreaticoduodenectomy; POD, postoperative day; POPF, postoperative pancreatic fistula; PPH, post pancreatectomy hemorrhage; spAMY, serum pancreatic amylases.

with SPSS software (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, NY).

RESULTS

A total of 983 patients undergoing partial pancreatic resections were considered for the analysis, namely 720 (73.2%) who underwent PD and 263 (26.8%) who underwent DP. The overall baseline, operative characteristics, and postoperative outcomes are listed in Table 1.

Postoperative spAMY Patterns

The 6 postoperative spAMY patterns were investigated. All patients with increased values on POD 3 showed a sustained increase in spAMY activity in the previous days. Almost all patients (99.1%) with early and sustained spAMY activity (POD 0- 1) were in range on POD3. In contrast, only 38.5% and

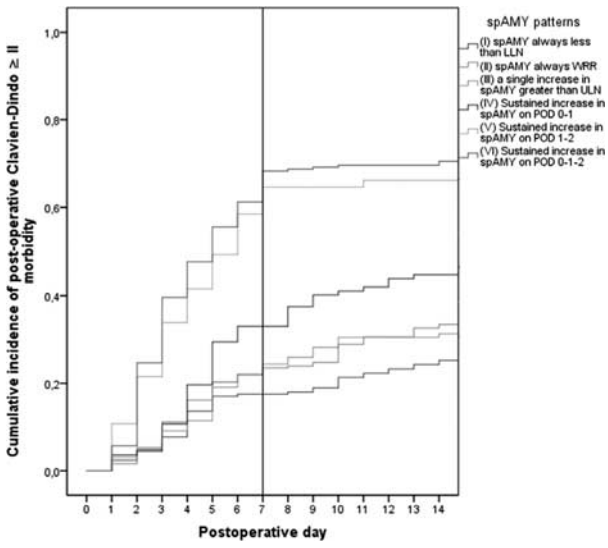

FIGURE 1. The Kaplan–Meier curves for the cumulative incidence of postoperative Clavien-Dindo ≥ II morbidity in different spAMY patterns. CD indicates Clavien Dindo Score; LLN, lower limit of normal; POD, postoperative day; spAMY, pancreatic serum amylases; ULN, upper limit of normal; WRR, within the reference range.

36.6% of patients with a sustained increase of spAMY activity on POD 1–2 and POD 0–1–2, respectively, had values within the range on POD3.

Figure 1 shows the Kaplan–Meier curves for the cumulative incidence of postoperative CD ≥ II morbidity for the 6 spAMY patterns. The cumulative incidence of early CD ≥ II morbidity was markedly different among the six spAMY patterns. Shifting through spAMY patterns was associated with an escalation of postoperative morbidity (Table 2). No significant difference was observed when comparing the pattern with a spAMY WRR to those with values always less than the LLN or with a single increase in spAMY activity ($P = 0.09$ and $P = 0.93$, respectively), and when comparing patients with a sustained increase in spAMY activity on POD 1–2 to those on POD 0–1–2 ($P = 0.54$). For this reason, these patterns were considered together in the following analyses.

Three spAMY patterns were eventually defined (Fig. 2):

- #1: spAMY values always less than the LLN/spAMY values always WRR/a single increase in spAMY activity greater than the ULN.
- #2: Sustained increase in spAMY activity greater than the ULN on POD 0 + 1.
- #3: Sustained increase in spAMY activity greater than the ULN including on POD 1 + 2.

For all spAMY trends, most postoperative complications were clustered in the first week after the index surgery. Because the curves diverged early and had reached the maximum difference by POD 7, this threshold was used to differentiate early from late morbidity in subsequent analyses.

Clinical Characteristics and Postoperative Outcomes Associated With Different Postoperative spAMY Patterns

Table 3 shows that patients with a sustained spAMY pattern, namely #3 and #2, had a significantly lower incidence of preoperative diabetes, neoadjuvant therapy, and vascular resections. Considering only PDs, approximately half of patients with #1 were considered to have a negligible or low risk of POPF according to the FRS, while almost all patients at high risk (FRS 7–10) were clustered in #2 and #3. Notably, about 7% of patients with #3 were intraoperatively considered to be at low risk of POPF (FRS 1–2).

Comparing postoperative outcomes, the presence of a sustained increase in spAMY activity greater than the ULN including POD 1 + 2 (#3) appeared to have the worst postoperative outcome. Indeed, pattern #3 was associated with increased overall and severe (at least as CD ≥ III) early morbidity, overall and grade C POPF, overall and severe PPH, sepsis, relaparotomy, and ICU stay. Pattern #2 exhibited a greater postoperative burden than #1, with an increased rate of overall early postoperative complications, POPF, biochemical leak (BL), and DGE, but no significant difference in CD severe morbidity.

Due to existing concerns regarding the mechanism underlying postoperative spAMY increases, the relationship between spAMY and DFA was also explored. As shown in Supplemental Figure A1 (Supplemental Digital Content 1, http://links.lww.com/SLA/D130), there was a poor correlation between POD1 spAMY and POD 1 DFA ($r = 0.001$, $P = 0.967$).

TABLE 2. Cumulative Incidence of Postoperative Clavien-Dindo ≥ II Morbidity in the Different spAMY Patterns

	Population (Overall n = 983)	Cumulative Incidence of CD ≥ II Morbidity by POD 7	*P* value
(I) spAMY always less than LLN (n = 206) (< 10 U/l)	21%	17.4%	0.095
(II) spAMY always WRR (n = 242) (10–52 U/L)	24.6%	23.5%	0.93
(III) A single increase in spAMY greater than ULN (n = 131) (> 52 U/L on POD0/POD1/POD2)*	13.3%	24.4%	0.024
(IV) Sustained increase in spAMY on POD 0–1 (n = 112) (> 52 U/L on POD 0 + 1)†	11.4%	33%	0.002
(V) Sustained increase in spAMY on POD 1–2 (n = 65) (> 52 U/L on POD 1 + 2)	6.6%	64.6%	0.54
(VI) Sustained increase in spAMY on POD 0–1–2 (n = 227) (> 52 U/L on POD 0 + 1 + 2)	23.1%	68.2%	

*the 7.6% of these patients (n = 10) showed a single increase in spAMY activity greater than 3 x ULN (> 156 U/l). No significant difference ($P = 0.86$) was observed compared with patients with a single increase in spAMY activity within 53–156 U/L.

†the 16.1%of these patients (n = 18) showed a sustained increase in spAMY activity on POD 1 + 2 with at least 1 value greater than 3 × ULN (> 156 U/l). No significant difference ($P = 0.49$) was observed compared with patients with a sustained increase in spAMY activity within 53–156 U/L on both POD 0 + 1.CD indicates Clavien Dindo Score; LLN, lower limit of normal; POD, post-operative day; spAMY, pancreatic serum amylases; ULN, upper limit of normal; WRR, within the reference range.

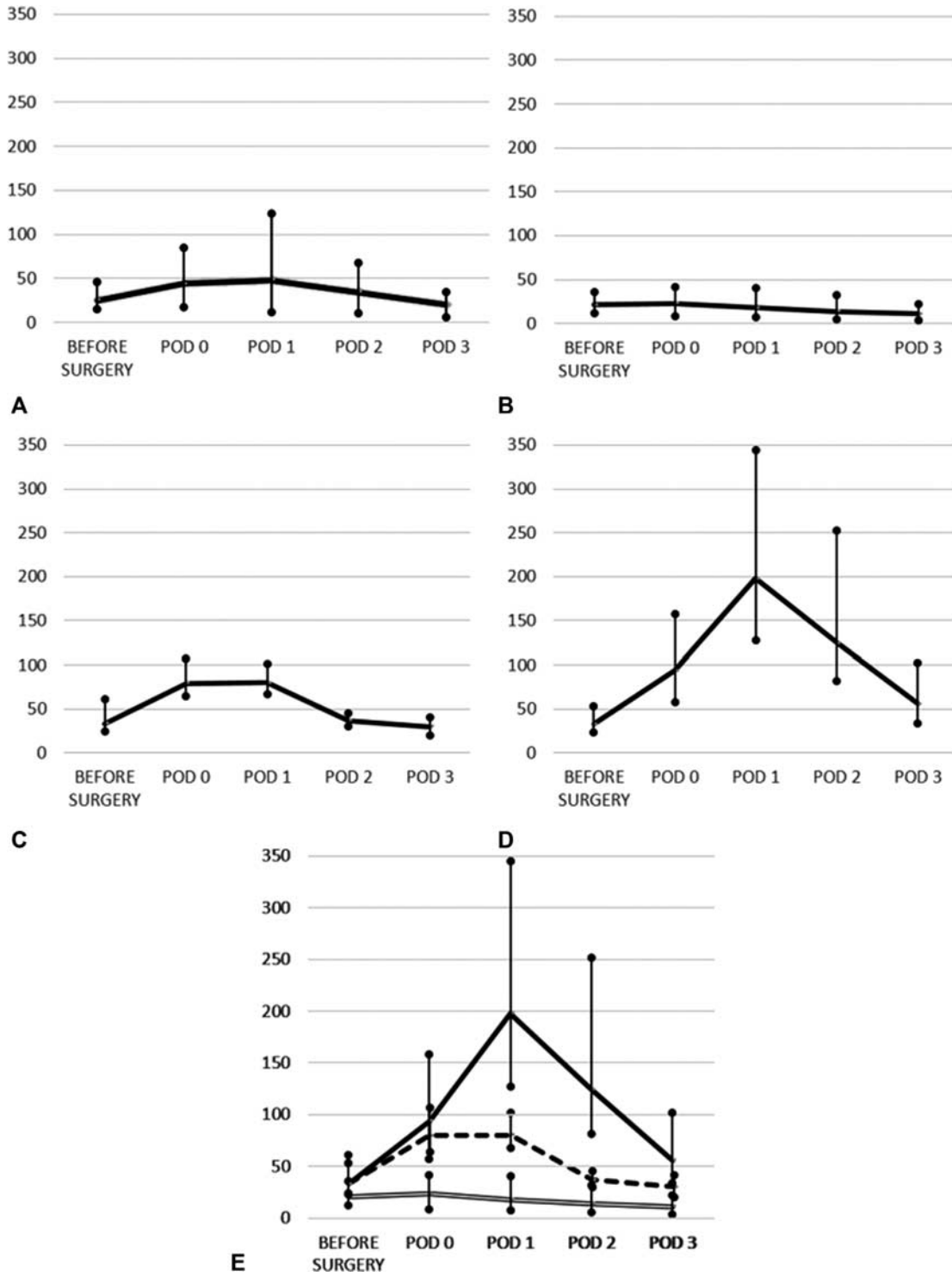

FIGURE 2. Analysis of perioperative spAMY levels [before surgery, and postoperatively on the day of surgery (POD 0), and thereafter (POD 1-3)]. (A) All patients; (B) Pattern #1 (spAMY values always less than the LLN/spAMY values always WRR/a single increase in spAMY activity greater than the ULN); (C) Pattern #2 (Sustained increase in spAMY activity greater than the ULN on POD 0 + 1); (D) Pattern #3 (Sustained increase in spAMY activity greater than the ULN including on POD 1 + 2); and (E) All patients stratified according to the spAMY pattern. LLN indicates lower limit of normal; POD, postoperative day; spAMY, pancreatic serum amylases (U/L, median, Interquartile range); ULN, upper limit of normal; WRR, within the reference range.

TABLE 3. Clinical Characteristics and Postoperative Outcomes Stratified According to Different Postoperative spAMY Patterns

	#1 spAMY Values Always Less Than the LLN/spAMY Values Always WRR/a Single Increase in spAMY Activity Greater Than the ULN. (n = 579)	#2 Sustained Increase in spAMY Activity Greater Than the ULN on POD 0 +1 (n = 112)	P^*	#3 Sustained Increase in spAMY activity Greater Than the ULN Including on POD 1 + 2 (n = 292)	$P^\dagger$
Age (yr, median, IQR)	66 (56–72)	61 (48–69)	**0.001**	63 (54–70)	0.08
BMI (Kg/m^2, median, IQR)	24 (22–27)	24 (22–28)	0.204	24 (22–27)	0.46
Smoke	144 (24.9%)	28 (25%)	1.0	61 (20.9%)	0.42
Alcohol	32 (5.5%)	4 (3.6%)	0.492	14 (4.8%)	0.78
Diabetes	149 (25.7%)	11 (9.8%)	**< 0.001**	22 (7.5%)	0.54
ASA score					
1	15 (2.6%)	13 (11.6%)	**< 0.001**	15 (5.1%)	**0.012**
2	451 (77.9%)	89 (79.5%)		226 (77.4%)	
3	113 (19.5%)	10 (8.9%)		51 (17.5%)	
Neoadjuvant therapy	189 (32.6%)	13 (11.6%)	**< 0.001**	39 (13.4%)	0.74
CRP POD 2 (mg/L, median, IQR)	155 (104–218)	202 (127.5–253)	**0.002**	212 (142–280)	0.09
High–risk pathological diagnosis	173 (29.9%)	67 (59.8%)	**< 0.001**	181 (62%)	0.73
Vascular resection	104 (18%)	7 (6.3%)	**0.001**	20 (6.8%)	1
Operative time (min, median, IQR)	395 (300–460)	349 (251–419)	**< 0.001**	385 (304–450)	**0.007**
EBL (mL, median, IQR)	420 (250–700)	354 (200–542)	**0.008**	400 (250–600)	0.16
FRS *(only PD, n = 720)*					
Negligible	50 (11.3%)	3 (5.4%)	**< 0.001**	0	**0.005**
Low	167 (37.8%)	5 (8.9%)		15 (6.8%)	
Moderate	191 (43.2%)	32 (57.1%)		146 (65.8%)	
High	34 (7.7%)	16 (28.6%)		61 (27.5%)	
POPF (total n.)	52 (9%)	33 (29.5%)	**< 0.001**	140 (47.9%)	**0.001**
Grade					
BL	23 (4%)	16 (14.3%)	**< 0.001**	31 (10.6%)	**< 0.001**
B	48 (8.3%)	31 (27.7%)		107 (36.6%)	
C	4 (0.7%)	2 (1.8%)		33 (11.3%)	
PPH (total n.)	41 (7.1%)	5 (4.5%)	0.408	62 (21.2%)	**< 0.001**
Grade					
A	22 (3.8%)	1 (0.9%)	0.407	14 (4.8%)	**0.001**
B	11 (1.9%)	3 (2.7%)		26 (8.9%)	
C	8 (1.4%)	1 (0.9%)		23 (7.9%)	
DGE (total n.)	58 (10%)	22 (19.6%)	**0.006**	52 (17.8%)	0.66
Grade					
A	14 (2.4%)	8 (7.1%)	**0.015**	8 (2.7%)	0.11
B	32 (5.5%)	11 (9.8%)		26 (8.9%)	
C	12 (2.1%)	3 (2.7%)		18 (6.2%)	
Abscess	100 (17.3%)	41 (36.6%)	**0.001**	134 (45.9%)	0.09
Biliary fistula	21 (3.6%)	4 (3.6%)	1	18 (6.2%)	0.46
Chyle leak	21 (3.6%)	7 (6.3%)	0.194	18 (6.2%)	1
Sepsis	48 (8.3%)	13 (11.6%)	0.274	79 (27.1%)	**0.001**
Respiratory failure	11 (1.9%)	3 (2.7%)	0.592	32 (11%)	**0.008**
Relaparotomy	21 (3.6%)	9 (8%)	0.044	48 (16.4%)	**0.037**
Unplanned ICU stay	26 (4.5%)	7 (6.3%)	0.465	49 (16.8%)	**0.006**
LOS (d, median, IQR)	8 (7–11)	9 (7–18)	**0.019**	15 (9–31)	**< 0.001**
Mortality	5 (0.9%)	2 (1.8%)	0.317	12 (4.1%)	0.367
Clavien Dindo Score ≥ grade II (≤ POD7)	122 (21.1%)	38 (33.9%)	**0.002**	197 (67.5%)	**< 0.001**
Clavien Dindo Score ≥ grade III (≤ POD7)	18 (3.1%)	6 (5.3%)	0.234	45 (15.4%)	**0.006**

*spAMY values always less than the LLN/spAMY values always WRR/a single increase in spAMY activity greater than the ULN versus Sustained increase in spAMY activity greater than the ULN on POD 0 + 1.

†Sustained increase in spAMY activity greater than the ULN on POD 0 + 1 versus Sustained increase in spAMY activity greater than the ULN including on POD 1 + 2. ASA indicates American Society of Anesthesiologists; BL, Biochemical leak; BMI, Body Mass Index; CRP, C Reactive Protein; DGE, delayed gastric emptying; EBL, estimated blood loss; FRS, fistula risk score; High–risk pathological diagnosis, histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis; ICU, intensive care unit; IQR, interquartile range; LLN, lower limit of normal; LOS, length of hospital stay; POD, postoperative day; POPF, postoperative pancreatic fistula; PPH, post pancreatectomy hemorrhage; spAMY, serum pancreatic amylases; ULN, upper limit of normal; WRR, within the reference range.

Characteristics of Pattern #3: A Sustained Increase in spAMY Activity Greater Than the ULN including POD 1 + 2

A comparison of patient characteristics and postoperative outcomes of pattern #3, stratified according to different spAMY cut-offs is shown in Table 4. Of the total patients, 28.8% had a spAMY activity within 53 to 156 U/l on POD 1 + 2 (#3a), 34.6% had 1 spAMY value greater than 3 times the ULN (> 156 U/l) regardless of whether it was on POD 1 or 2 (#3b), and 36.6% had a spAMY activity greater than 3 times the ULN on both days (#3c). Lower but still sustained increased values (#3a) were mainly reported after DP, whereas greater spAMY values (#3c) were

TABLE 4. Clinical Characteristics and Postoperative Outcomes of Pattern #3 (Sustained Increase in spAMY Activity Greater Than the ULN Including on POD 1 + 2; n = 292) Stratified According to Different spAMY Cut–offs

	#3a spAMY Within 53–156 U/l on both POD 1 + 2 (n = 85)	#3b spAMY With 1 Value > 3 X ULN (>156 U/l) on POD 1 or 2 (n = 100)	#3c spAMY > 3 X ULN (>156 U/l) on Both POD 1 + 2 (n = 107)	*P*
Age (years, median, IQR)	63 (51–70)	60 (55–70)	65 (55–70)	0.48
BMI (Kg/m^2, median, IQR)	24 (22–26)	25 (23–27)	24 (22–27)	0.28
Smoke	18 (21.2%)	25 (25%)	18 (16.8%)	0.35
Alcohol	7 (8.2%)	4 (4%)	3 (2.8%)	0.19
Diabetes	7 (8.2%)	6 (6%)	9 (8.4%)	0.77
Neoadjuvant therapy	8 (9.4%)	17 (17%)	14 (13.1%)	0.31
CRP POD 2 (mg/L, median, IQR)	175 (110–249.2)	212 (153–262)	245 (163.2–293.7)	**0.001**
Type of surgery				
PD	41 (48.2)	84 (84%)	97 (90.7%)	**< 0.001**
DP	44 (51.8%)	16 (16%)	10 (9.3%)	
Vascular resection	5 (5.9%)	6 (6%)	9 (8.4%)	0.72
High-risk pathological diagnosis	54 (65.5%)	57 (57%)	70 (65.4%)	0.43
Transanastomotic stent *(only PD, n = 222)*	20 (48.8%)	39 (46.4%)	28 (28.9%)	**0.02**
FRS (only PD, *n* = 222)				
Low	3 (7.3%)	5 (6%)	7 (7.2%)	0.71
Moderate	25 (61%)	53 (63.1%)	68 (70.1%)	
High	13 (31.7%)	26 (31%)	22 (22.7%)	
Operative time (min, median, IQR)				
PD	410 (371–470)	406 (346–460)	410 (365–468)	0.71
DP	235 (208–331)	290 (222–327)	300 (244–352)	0.24
EBL (mL, median, IQR)	400 (200–600)	435 (262–645)	400 (200–600)	0.34
POPF (total n.)				
Grade	30 (35.3%)	48 (48%)	62 (57.9%)	**0.008**
BL	14 (16.5%)	9 (9%)	8 (7.5%)	0.05
B	24 (28.2%)	34 (34%)	49 (45.8%)	
C	6 (7.1%)	14 (14%)	13 (12.1%)	
PPH (total n.)	15 (17.6%)	23 (23%)	24 (22.4%)	0.62
Grade				
A	5 (5.9%)	6 (6%)	3 (2.8%)	0.53
B	8 (9.4%)	7 (7%)	11 (10.3%)	
C	3 (3.5%)	10 (10%)	10 (9.3%)	
DGE (total n.)	8 (9.4%)	21 (21%)	23 (21.5%)	0.05
Grade				
A	2 (2.4%)	2 (2%)	4 (3.7%)	0.11
B	6 (7.1%)	9 (9%)	11 (10.3%)	
C	0	10 (10%)	8 (7.5)	
Abscess	32 (37.6%)	43 (43%)	59 (55.1%)	**0.04**
Biliary fistula	2 (2.4%)	7 (7%)	9 (8.4%)	0.20
Enteric Fistula	1 (1,2%)	3 (3%)	9 (8.4%)	**0.03**
Chyle leak	5 (5.9%)	3 (3%)	10 (9.3%)	0.16
Sepsis	17 (20%)	27 (27%)	35 (32.7%)	0.14
Respiratory failure	9 (10.6%)	12 (12%)	11 (10.3%)	0.91
Relaparotomy	10 (11.8%)	19 (19%)	19 (17.8%)	0.37
Unplanned ICU stay	11 (12.9%)	17 (17%)	21 (19.6%)	0.46
LOS (days, median, IQR)	11 (7–21)	15 (8–35)	21 (10–35)	**< 0.001**
Mortality	2 (2.4%)	4 (4%)	6 (5.6%)	0.52
Clavien Dindo Score ≥ grade II (< POD7)	44 (51.7%)	67 (67%)	86 (80.3%)	**< 0.001**
Clavien Dindo Score ≥ grade III (< POD7)	13 (15.3%)	14 (14%)	18 (16.8%)	0.85

ASA indicates American Society of Anesthesiologists; BL, Biochemical leak; BMI, Body Mass Index; CRP, C Reactive Protein; DGE, delayed gastric emptying; DP, distal pancreatectomy; EBL, estimated blood loss; High–risk pathological diagnosis, histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis; ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay; PD, pancreaticoduodenectomy; POD, postoperative day; POPF, post–operative pancreatic fistula; PPH, post pancreatectomy hemorrhage; spAMY, serum pancreatic amylases; ULN, upper limit of normal.

significantly more frequent after PD. Further stratified subanalysis has not been performed due to the small sample size of #3c after DP. Persistent high spAMY values (#3c) were associated with an increased rate of POPF and overall early morbidity, but no significant difference was reported in early severe morbidity nor mortality compared to #3a and #3b (Fig. 3).

The predictors of pattern #3 were assessed separately for DP and PD procedures. For PD, a soft pancreatic texture (OR 8.89, CI 95% 5.28 – 14.95; $P < 0.001$), the main pancreatic duct (OR 0.78, CI 95% 0.69 – 0.87; $P < 0.001$), and a final histology different from that of pancreatic ductal adenocarcinoma or chronic pancreatitis (OR 2.23, CI 95% 1.49 – 3.34; $P < 0.001$) were independently associated with this spAMY pattern (Supplemental Table A1 - Supplemental Digital Content 2, http://links.lww.com/SLA/D131). In the multivariable model for DP patients, preoperative diabetes (OR 0.19, CI 95% 0.058 – 0.681;

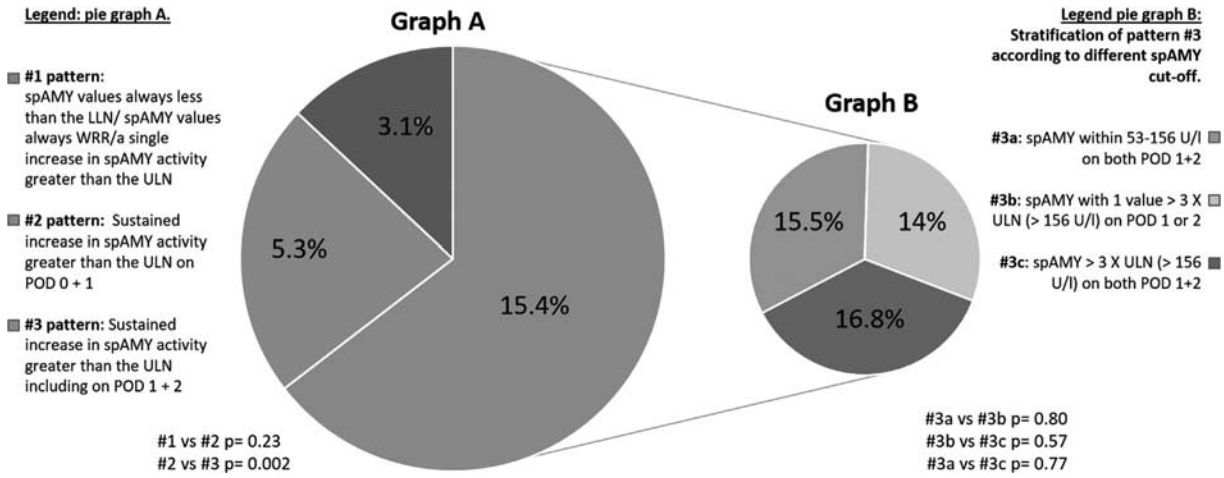

FIGURE 3. Incidence of postoperative Clavien-Dindo ≥ III morbidity within POD 7 in different spAMY patterns (pie graph A). Pattern #3, representing the group with the highest incidence of early severe complications has also been stratified according to different spAMY cut-offs (pie graph B). LLN indicates lower limit of normal; POD, postoperative day; spAMY, pancreatic serum amylases; ULN, upper limit of normal; WRR, within the reference range.

$P = 0.010$) and neoadjuvant therapy (OR 0.22; CI 95% 0.062–0.789; $P = 0.020$) were confirmed as independent predictors (Supplemental Table A2 - Supplemental Digital Content 3, http://links.lww.com/SLA/D131).

Pattern #3 showed a 55% sensitivity, 85% specificity, 68% positive predictive value, 77% negative predictive value, and 74% accuracy in predicting the occurrence of at least CD ≥ II morbidity before POD 7. When early severe morbidity (at least CD ≥ III) was considered, pattern #3 showed a 65% sensitivity, 73% specificity, 31% positive predictive value, 92% negative predictive value, and 72% accuracy (Supplemental Table A3 - Supplemental Digital Content 4, http://links.lww.com/SLA/D131).

DISCUSSION

To the best of our knowledge, this is the first study to characterize different patterns of postoperative spAMY activity after partial pancreatic resections. These spAMY trends are based on the presence of values above or below the normal range at multiple and sequential postoperative blood tests. We found that different patterns were associated with distinct rates of postoperative complications. Notably, a sustained increase in spAMY activity including POD 1 + 2 (pattern #3) was associated with the highest rate of overall and severe early postoperative complications.

Despite ongoing debate regarding POH in recent years,[2,8,9,29,30] the characterization of this phenomenon and its possible prognostic role remains largely unknown, mainly because POH typically occurs early after surgery.[6,11] Due to the temporary nature of POH, appropriate assessment and definition are often difficult and remain a matter of discussion. Such debate has recently seen a rise in popularity because POH has been increasingly considered as the main biochemical evidence of postoperative AP.[2,8–11,11,30,31] Although POH has been investigated as a punctual increase in pancreatic amylase activity,[2,4,8] the spAMY time trend has never been systematically evaluated. Interestingly, the present study highlighted that the presence of a single altered value of spAMY was not associated with increased morbidity. By contrast, patients with a sustained spAMY activity were found to be twice as likely to develop early complications. Based on these findings, a single postoperative serum pancreatic enzymatic assessment does not allow for proper scaling of the risk of postoperative morbidity. This finding could also explain why, despite a high sensitivity in predicting pancreatic-specific complications, the specificity of spAMY reported by previous studies was relatively low.[8,9]

The temporal course of postoperative morbidity was carefully analyzed to assess the association with different spAMY patterns. Most complications occurred within the first week after surgery, but the strongest correlation was observed with early complications occurring up to POD 7.

Escalation to higher and sustained spAMY values was associated with increased overall and severe postoperative early morbidity. Patients with spAMY activity less than the LLN, and those presenting with a spAMY pattern both WRR and/or with a single increase of spAMY activity (pattern #1) showed a low likelihood of developing severe morbidity. Conversely, it was found that almost one third of patients who presented with an increased spAMY activity on POD 0 + 1 (pattern #2) went on to develop early overall complications, although only approximately 5% were classified as severe. Given this short spAMY peak and the related intermediate burden, we could speculate that this latter pattern possibly represents the expression of a self-limiting process that does not proceed towards more severe morbidity. Finally, patients showing a sustained spAMY activity including POD 1 + 2 (pattern #3) were found to have the highest postoperative incidence of overall (68%) and severe (15%) early morbidity. In addition, pancreas-specific complications such as POPF, PPH, and abdominal abscess are of increasing severity among different spAMY patterns. Particularly, with regard to pattern #3, spAMY values greater than 3 times the ULN on both POD 1 + 2 (#3c) were associated with the highest rate of POPF and overall morbidity, but pattern #3c was almost exclusively observed after PD. This increased morbidity may be explained by the different timings of POPF[32] and the increased burden of PD compared to DP.[33] Further studies are needed to highlight possible differences and clinical relevance of spAMY patterns according to the specific operation type. Interestingly, the reduced placement of transanastomotic stents in this group (#3c) during PD might also suggest duct occlusion/ stasis of pancreatic juice as a possible mechanism.[34] By contrast, patients

with increased spAMY activity, even under the threshold of 3 times the ULN on both POD 1 + 2, still have an increased – and definitely non-negligible – risk of early severe complications. Once again, the role of a dynamic assessment of postoperative spAMY activity is reinforced by the use of the trend in values in identifying patients at risk for early morbidity.

The analysis of risk factors for the pattern of spAMY associated with the worst postoperative outcome (pattern #3) revealed that this phenomenon, even with differences compared PD to DP, is essentially linked to the presence of a healthy pancreatic parenchyma, namely a soft pancreatic texture and preserved functionality. These results are in line with those of previous studies, and such features have been already included in prognostic scores.[19,35] Nevertheless, this study adds further evidence by introducing the concept of a "postoperative continuing reassessment for early morbidity" risk until POD 2. Given that the risk of postoperative complications changes over time, the risk estimation should equally be a dynamic process. Since prevention and mitigation strategies begin either before or during the surgical procedure on the basis of well-known risk scores,[31,35–37] they may alter the clinical outcome, eventually lowering the risk of postoperative complications. Facing this challenge, the risk for early postoperative complications could be readjusted immediately after surgery through the spAMY trends analysis. Early estimation of spAMY could be used to identify patients with sustained high values, burdened by poor postoperative outcomes, in whom enhanced recovery after surgery paradigms[38] and drainage management protocols[20,39] may need to be redefined. In contrast, patients with spAMY values within or less than the reference range, with a low risk of subsequent morbidity, could benefit from enhanced recoveries and early hospital discharges.

Finally, but of outmost importance, the prognostic relevance of spAMY trends indicates the need to redefine POH. Historically, POH has been considered only as a consequence of POPF[40] or of surgical mechanical trauma[3]; however, POH has been recently interpreted as a marker of an acute inflammatory process of the pancreatic rem- nant.[5,6,9] In a nonsurgical context injuries to the pancreatic parenchyma may lead to premature activation of pancreatic enzymes and a subsequent increase in serum levels.[1] The pathological mechanism has been related to the disruption of pancreatic cells or to an alteration of the normal exocytosis process, with the secretion of the zymogen contents at the basolateral side of the acinar cells.[41,42] However, as the spAMY has a half-life of approximately 10 hours, the persistence of increased values for 48 hours, may potentially be the expression of an ongoing release and hence an AP process.

This study adds solid evidence to the increasing literature investigating POH and its clinical significance.[5,7,8] The correlation between spAMY trends and postoperative morbidity can serve as a biochemical characterization of postpancreatectomy AP. Thus, our study adds value, not only because it lays the foundation for a consensus definition of such a novel postoperative pancreas-specific complication, but also because it encourages the debate and opens discussion to further prospective validation studies to refine its sequelae and grading.

The present study has several limitations that warrant discussion. First, even though the data were prospectively collected, only patients with complete data were included, excluding those without multiple postoperative assessments of serum amylase activity. For this reason, our results may not be fully representative of the entire population of patients undergoing partial pancreatic resection. Second, the patients were not stratified according to pre- and intraoperative features and operation type to avoid reducing the statistical power and clinical utility of our results. Finally, an inherent drawback of this study is that spAMY evaluation was conducted within a singlecenter, with homogeneity among surgical approaches and postoperative management. Thus, different reference ranges or pancreatic enzymes (eg, lipase) may have been evaluated, potentially leading to different results.

CONCLUSIONS

A sustained rise in postoperative spAMY activity greater than the ULN, including POD 1 + 2, represents an early postoperative predictor of overall and severe early morbidity. A dynamic evaluation of spAMY, not limited to a single postoperative assessment, appears to be crucial. These findings are relevant for the development of the definition of postpancreatectomy AP and could prompt further appraisal of systematic measures to ultimately improve the clinical pathway of the early postoperative course.

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