UNIVERSITÀ DEGLI STUDI DI VERONA

DEPARTMENT OF MEDICINE

GRADUATE SCHOOL OF LIFE AND HEALTH SCIENCE

DOCTORAL PROGRAM IN
INFALMMATION, IMMUNITY AND CANCER

XXXV CYCLE / 2019

TITLE OF THE DOCTORAL THESIS

Translational research in Post-pancreatectomy Acute Pancreatitis: from intraoperative spectral imaging assistance to clinical treatment.

S.S.D. MED 18

IN *CO-TUTELLE DE THÉSE* WITH THE

UNIVERSITÉ DE STRASBOURG

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Introduction

Despite significant advancements in risk stratification, mitigation strategies, and treatment, morbidity after pancreatic surgery remains a major challenge. At the beginning of the new Millennium, the International Study Group for Pancreatic Surgery (ISGPS) provided standardized definitions for post-pancreatectomy complications. Post-pancreatectomy acute pancreatitis (PPAP) eluded these endeavors, leaving its existence, precise definition, and legitimacy as a distinct clinical entity in a state of uncertainty.

Chapter 1 - Post-operative hyperamylasemia (POH) and acute pancreatitis after pancreatoduodenectomy (POAP): state of the art and systematic review[1]

The literature has suggested the occurrence of an acute inflammatory process in the pancreatic parenchyma following pancreatic resections. However, acknowledging clinically relevant post-pancreatectomy acute pancreatitis (PPAP) – at that time referred to as postoperative acute pancreatitis (POAP) – as a distinct complication faced challenges. Surgeons have long noticed increased circulating pancreatic enzyme activity in the immediate postoperative period. Studies addressing these increases, termed postoperative serum hyperamylasemia (POH), have lacked standardization in both metrics and definitions. The clinical relevance of POH has also been a subject of controversy. Despite the differences, the collected evidence suggested that early POH might manifest as the biochemical representation of a local inflammatory/ischemic process in the pancreatic remnant, namely PPAP, potentially triggering postoperative morbidity. A wide range of incidence of PPAP was reported, due to the lack of uniformity in definitions and terminology across studies exploring this topic. Standardized criteria reveald a consistent incidence of PPAP, emphasizing the need for universal terminology.

Chapter 2 - Early and sustained elevation in serum pancreatic amylase activity: a novel predictor of morbidity after pancreatic surgery[2]

Variability in defining POH prompted a trend analysis of serum pancreatic amylase activity (spAMY) following partial pancreatic resections. Identifying patterns correlated with varying morbidity degrees, with sustained spAMY increase on POD 1+2 strongly linked to severe complications. Clinical practice adoption of dynamic spAMY evaluation, particularly on POD 1+2, emerged as an early predictor of overall and severe morbidity, influencing subsequent clinical management. For these patients, a reevaluation of enhanced recovery after surgery paradigms and drainage management protocols could be necessary. In contrast, patients with spAMY values within or below the reference range, indicating a low risk of subsequent morbidity, could benefit from enhanced recoveries and early hospital discharges. This approach not only laid the foundation for a new definition of POH but also set the stage for the standardized biochemical characterization of PPAP.

Chapter 3 - Post-pancreatectomy acute pancreatitis (PPAP): definition and grading from the International Study Group for Pancreatic Surgery (ISGPS)[3]

The lack of a universally accepted definition for PPAP has impeded objective comparisons of surgical experiences related to this complication. The ISGPS dedicated significant efforts to formulate a PPAP definition and grading system, integrating biochemical, radiologic, and clinical features. This initiative resulted in a universal definition for PPAP and a classification system based on clinical impact, introducing two severity grades beyond the biochemical evidence of POH. Establishing a consensus definition and grading system served as a foundational step for the systematic evaluation and classification of PPAP worldwide, opening new perspectives for identifying diagnostic and prognostic criteria for PPAP. It will also provide help in recognizing all complications associated with this condition and exploring potential treatments.

Notwithstanding a universal definition, many questions remain unanswered. What is the pathophysiological mechanism of PPAP? How relevant is the finding of POH per se? Is PPAP really a self-standing complication or rather a risk factor for a postoperative pancreatic fistula (POPF), and, on the same line, is it the POH-PPAP that instigates poor outcomes, or does it act through its association with POPF? How can PPAP be prevented/mitigated? And finally—and perhaps most importantly—how might its diagnosis change patient management?

Chapter 4 - Hyperspectral imaging in pancreatic surgery: Variations of parenchymal parameters related to postoperative pancreatic fistula risk after pancreatoduodenectomy[Unpubliched]

The application of hyperspectral imaging (HSI), an emerging non-invasive, intraoperative hybrid imaging modality that combines optical imaging and spectroscopy, allowed to visualize changes in intraoperative hemodynamic parameters of the remnant pancreatic parenchyma in patients undergoing pancreatoduodenectomy. The HSI camera used a push-broom scanning mechanism with a complementary metal oxide semiconductor (CMOS) image sensor, capable of capturing HS images in approximately 7 to 8 seconds with a spatial resolution of 640 by 476 pixels. Its spectral range was 500 to 1000 nm (ultraviolet to near-infrared) using 100 spectral bins uniformly sampled in 5 nm increments. Consequently, each HSI dimension was 640 by 476 by 100 (two spatial and one spectral dimension, named hypercube). The system has preset algorithms to calculate different tissue parameters, each calculated individually from different spectra parts. Included parameters were the oxygen saturation index (StO2%), accounting for the superficial microcirculation up to a depth of 1 mm; near-infrared (NIR) perfusion index reflecting deeper layers within the NIR spectrum with a penetration depth of 4 to 6 mm; the tissue water index (TWI) and organ hemoglobin index (OHI), which accounts for water and hemoglobin content in the observed region of interest.

Despite its potential, extensive integration of this technology into clinical practice remains distant. HSI's application in exploring intraoperative mechanisms associated with pancreas-specific complications shows promise, but its incorporation into predictive models and practical validation requires substantial further progress.

Chapter 5 - Acute pancreatitis following Pancreatoduodenectomy: a prospective study of diffusion-weighted magnetic resonance imaging, serum biomarkers, and clinical features[4]

Evidence was presented to draw parallels and contrasts between PPAP and its medical counterpart, acute pancreatitis. Although specific magnetic resonance imaging (MRI) sequences demonstrated the ability to detect initial pancreatic parenchymal changes in the early postoperative period, their practical implementation in clinical practice proved challenging. IVIM-MRI sequences, while promising, faced limitations in immediate postoperative use due to long acquisition times and the demanding nature of multiple breath-hold sequences, limiting their application in large scale. Furthermore, macroscopic radiologic changes consistent with PPAP were identifiable only in later computed tomography (CT) imaging. While simultaneous measurement of serum lipase and pancreatic amylase revealed sustained elevation in patients with macroscopic radiological features of PPAP, it did not offer additional value. The study underscores the clinical significance of C-reactive protein (CRP) associated with POH as a reliable indicator for early patient stratification, potentially influencing the level of care.

Chapter 6 - Postoperative serum hyperamylasemia (POH) predicts additional morbidity after pancreatoduodenectomy: It is not all about pancreatic fistula[5]

The clinical impact and sequelae associated with POH-PPAP have been also investigated and shown to contribute to the development of other complications, especially POPF. Contrary to the commonly-held belief, POH-PPAP has also relevant postoperative clinical implications independent of POPF occurrence, confirming the definite separation between POH-PPAP and POPF while corroborating their interplay. Interestingly, developing POH with POPF leads to a impressive early onset of higher postoperative burdens. Therefore the presence of POH could be considered crucial for early risk stratification. Given the rapid evolution that may occur, the presence of POH can represent the counterpart of the "*golden hour*" in trauma, in which prompt measures can potentially prevent poor outcomes after pancreaticoduodenectomy.

Chapter 7 - Postoperative serum hyperamylasemia (POH) adds sequential value to the Fistula Risk Score (FRS) in predicting pancreatic fistula after pancreatoduodenectomy[6]

Facing this evidence, an innovative early, dynamic, postoperative framework for POPF forecasting has been investigated. Early postoperative biologic markers (i.e., POH, drain fluid amylase, CRP) could guide postoperative management in a step-by-step approach during the first days after surgical resection. Recently, a "time-zero" concept of the pathophysiology of fistulas has been proposed, and a given anastomosis cannot leak unless or until it has been constructed. However, several subsequent temporal checkpoints can be identified, and the present POPF prediction process of using one fixed intraoperative risk assessment – such as the FRS- can be more valuably converted into a dynamic forecasting system. The risk of developing a POPF indeed changes over time, and all available prognostic elements, like POH, drain fluid amylase and CRP, should be dynamically applied during the early postoperative course to target recovery, plan additional preventive strategies and exert early management. Through this, surgeons could potentially convert from a passive "wait and see" mindset to a more active philosophy of surveillance and proactive intervention.

Chapter 8 - No role for protease inhibitors as a mitigation strategy for postpancreatectomy acute pancreatitis (PPAP): propensity score matching analysis[7]

POH may serve a dual role—it acts both as a preclinical condition and as a potential therapeutic window before the onset of overt PPAP morbidity. As a result, specific therapeutic strategies for PPAP have been investigated, confirming the challenges in improving outcomes. Specifically, the role of protease inhibitors seems ineffective in preventing a PPAP after a pancreatoduodenectomy once a POH has occurred. The delayed administration of protease inhibitors after the initiation of pancreatic inflammatory processes might be a factor contributing to the absence of retrieved effects. On the contrary, investigating the proactive use ofprotease inhibitors during surgery for patients deemed at high risk for POH, possibly in conjunction with other mitigation strategies, could prove more effective in influencing the occurrence of POH-PPAP. Further studies are needed to achieve benchmarks for treating PPAP.

Many grey areas persist to date, offering room for discussion and improvement. This doctoral thesis aims to provide a platform from which to move these questions forward.

Chapter 1 - Post-operative hyperamylasemia (POH) and acute pancreatitis after pancreatoduodenectomy (POAP): state of the art and systematic review

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Surgery 2021;169:377–38, doi: 10.1016/j.surg.2020.04.062.

ABSTRACT

Background

Post-operative hyperamylasemia (POH) is a frequent finding after pancreatoduodenectomy (PD), but its incidence and clinical implications have not yet been analyzed systematically. The aim of this review is to reappraise the concept of POH, including its definition, interpretation, and correlation, with post-operative acute pancreatitis (POAP).

Methods

Online databases were used to search all available relevant literature published through June 2019. The following search terms were used: “pancreaticoduodenectomy”, “amylase”, and “pancreatitis”. Surgical series reporting data on POH or POAP were selected and screened.

Results

Among 379 screened studies, 39 papers were included and comprised data from a total of 9,220 patients. POH was rarely defined in most of these series, and serum amylase values were measured at different cut-off levels and reported on different postoperative days (PODs). The actual levels of serum amylase activity and the representative cut-off levels required to reach a diagnosis of POAP were markedly greater on the first PODs and tended to decrease over time. Most studies analyzing POH focused on its correlation with post-operative pancreatic fistula (POPF) and other morbidities. The incidence of POAP varied markedly between studies, with its definition completely lacking in 40% of the analyzed papers. A soft pancreatic parenchyma, small pancreatic duct, and pathology differing from cancer or chronic pancreatitis were all predisposing factors to the development of POH.

Conclusions

POH has been proposed as the biochemical expression of pancreatic parenchymal injury related to localized ischemia and inflammation of the pancreatic stump. Such phenomena, analogous to those associated with acute pancreatitis, could perhaps be renamed as POAP from a clinical standpoint. Patients with POAP experienced an increased rate of all post-operative complications, particularly POPF. Taken together, the discrepancies among previous studies of POH and POAP outlined in the present review, may provide a basis for stronger evidence necessary for the development of universally accepted definitions for POH and POAP.

INTRODUCTION

Increased serum levels of pancreatic enzymes can be detected frequently via laboratory tests on the first few days after a pancreatic resection. An increase in serum pancreatic amylase levels is an established biochemical marker for the diagnosis of acute pancreatitis in a non-surgical setting, as defined by the revised Atlanta classification of acute pancreatitis[8]. In contrast, the meaning and importance of a similar increase in serum amylase activity after pancreatic surgery remains both unknown and controversial. The reported rate of post-operative hyperamylasemia (POH) after pancreatic resection is highly variable between centers. These differences, however, may be related to variability in the corresponding definitions of POH and the cut-offs values used in the various definitions of POH[9–18]. Moreover, the importance of POH from a clinical standpoint remains a matter of debate. In most reports[9,16–18], POH has been associated with post-operative pancreatic fistula (POPF). Nevertheless, the mechanism that links POH with POPF is still unclear. Most of the literature has suggested that this increase in serum amylase level is secondary to anastomotic leakage of pancreatic amylase from the pancreatico-enteric anastomoses with a subsequent systemic reabsorption via the peritoneum[16]; however, when the timing of the serum profiles of POH was analyzed, this increase was found to be very early postoperatively and not compatible with the reabsorption from the peritoneum of pancreatic exocrine secretions[11]. Other studies have theorized that this phenomenon may result from an "backflow" of amylase into blood vessels due to increased pressure in the local pancreatic parenchyma due to postoperative peripancreatic abscess[19]. The differentiation of these possibilities is difficult, and no validated or accepted explanation has been demonstrated.

When not associated with a POPF, POH has been considered as a potential marker of pancreatic trauma related to the mechanical injury to the pancreatic parenchyma induced by the operative procedure[18]. Despite all patients experiencing similar operative trauma during the pancreatectomies, not all patients subsequently develop an increase in serum amylase postoperatively. Hence, this proposed mechanism of surgery-induced mechanical injury does not completely explain this phenomenon.

In other surgical series[9,17,18,20,21], POH has been reported to be a clinically important biochemical marker of complications after pancreatoduodenectomy (PD). Furthermore, POH has been associated with an increased rate of POPF as well as other postoperative complications, such as intra-abdominal abscess, delayed gastric emptying (DGE)[22], and readmission to a critical care environment[17,20,23]. Given these premises, POH appears to not be merely a biochemical, post-operative finding, but may also be an independent predictor of post-operative morbidity[9,23]. Despite these previous findings, POH is still considered as only an indirect sign of POPF, because the mechanism that leads to the increase in serum amylase activity after a pancreatic resection and how it may further increase the risk of morbidity remains unknown.

Recently, POH has been proposed as the biochemical expression of a post-operative acute pancreatitis (POAP) caused by proposed mechanisms such as ischemia of the pancreatic-stump associated with local inflammation (pancreatitis)[23,24]. In terms of being analogous to pancreatitis, a local ischemic process occurring in the area of the pancreatic anastomosis has been suggested to induce POH, and the resultant "pancreatitis" may exacerbate systemic inflammatory responses to major abdominal surgery, leading to a cascade of systemic and local effects, including, but not limited to POPF[18].

Currently the literature is varied on the existence of POAP, and this topic remains controversial not only in the incidence of POAP but also in terms of the clinical relevance of POH. Therefore, the aim of the present review is to reappraise the concept of POH and POAP in the current scientific literature, including its definition, interpretation in a clinical context, and the association of POH with POAP and POPF.

METHODS

Search methods

An electronic, systematic, and complete literature review was carried out in compliance with the PRISMA[25] guidelines. The literature review was conducted using MEDLINE (PubMed), Embase, and the Cochrane Clinical Trials Registry and included all available, relevant literature published through June 2019. Titles, abstracts, and full-text articles were screened independently by two authors (EB and SA). All the references of the included studies were checked to identify additional missed papers. The following search terms were used: “Pancreaticoduodenectomy”, “amylase”, and “pancreatitis”. The full search strategy for MEDLINE is included in Appendix 1.

Eligibility criteria

Inclusion criteria were as follows: operative series reporting data about POH or acute pancreatitis developing after pancreatoduodenectomy (POAP), and articles in English with available full text for complete review. Studies that provided information on post-operative ranges of serum amylase activities and/or those reporting cut-off levels in an attempt to define POH were included irrespective of whether they were retrospective, prospective, or randomized control trials. Only studies that defined POPF according to the 2005[26] ISGPS statement or the 2016[27] updated version have been included. Case reports, case series, systematic reviews, editorials, and clinical guidelines were excluded as were unpublished works. Operative series of pediatric patients, papers that did not include an abstract written in English, and studies not involving humans were also excluded.

Data collection and analysis

Two authors extracted data independently from the included studies. Any uncertainties about including the researched papers in the review were resolved by consensus and, if necessary, by a third reviewer (GM) and examination of the full text. The following data were extracted from each of the included studies: first author; year of publication; study period; study design (prospective or retrospective cohort studies, randomized controlled trials); type of operation; total number of patients; overall incidence of POPF according to the old or to the updated ISGPS definition and grading system[26,27]; threshold used to define POH; post-operative day of assessment of serum amylase activity; sensitivity; specificity; area under the curve (AUC) of serum amylase cut-off to predict POPF; postoperative range and average serum amylase values; proportion of patients with POH; risk factors for POH; incidence of post-operative complications in the POH population; and the definition used for POAP.

Because serum amylase values were reported on different postoperative days and were measured at different cut-off levels or ranges, these data were not suitable for meta-analyses or meta-regressions. For the same reason, because the aim of the present review was to reappraise the concept of POH after pancreatoduodenectomy and not to define the diagnostic accuracy of post-operative serum amylase values, the results of the review are reported in the form of a narrative synthesis.

All identified studies were divided into the following three groups: those reporting a cut-off value of serum amylase to characterize POH; those reporting the range of serum amylase values postoperatively; and a group of studies in which POH was used as the diagnostic criterion for POAP. The analysis was extended eventually to all studies reporting POAP as a post-operative complication. The quality of included studies was assessed by using the Quality Assessment of Diagnostic Accuracy Studies[28] (QUADAS -2) criteria, which comprises four domains. According to the QUADAS-2 tool, most of the reviewed papers showed an unclear or high risk of bias and serious concerns regarding applicability and heterogeneity. Despite our inability to perform a true meta-analysis, we decided to review all relevant evidence as a systematic review to show the spectrum of such reports of POH and POAP to expose the controversies involved as well as investigate possible reasons for this heterogeneity of results, hoping that this review would stimulate and support a call for more formal studies of POH and POAP with consistent objective criteria.

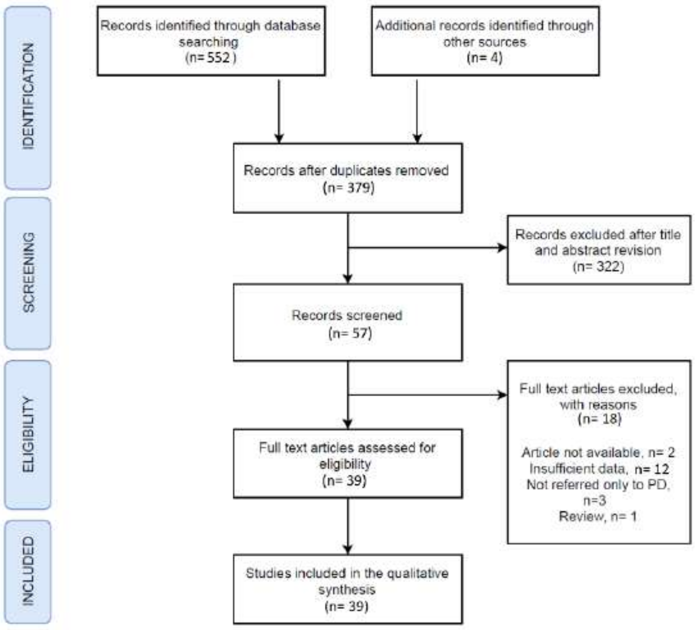

Figure 1: Flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

RESULTS

A total of 379 studies were identified after removing duplicates. Figure 1 shows the PRISMA[25] compliant flow-chart of the process of paper selection. Subsequently, 322 studies were discarded because they did not meet the inclusion criteria after reviewing the title or the abstract. The full text of each of the remaining 57 articles was examined in more detail leading to the exclusion of an additional 18 studies. Ultimately, 39 reports were included in this review, which comprised data from a total of 9,220 patients. In accordance with the aforementioned method for reporting data on POH or POAP, these included studies were divided into three different groups.

Studies reporting amylase cut-offs for the definition of POH

Eighteen studies[9–16,18–20,23,29–34] reported a cut-off value of postoperative serum amylase activity to define POH (Table 1). Ten studies were retrospective[9,12,13,16,18,20,23,30,31,34], six were prospective[10,11,15,19,29,33], and two were randomized clinical trials (RCT)[14,32]. The reported cut-off values of serum amylase activity varied from 38.5 U/l[13] to more than 400 U/l[20]; all used the common International Units for quantitating activity, though some reports may have had different upper limits of normal in their laboratory, which we could not control for. Most of the studies[9,11,12,14–16,19,20,23,29,31–34] assessed serum amylase values on the first post-operative day. Six studies measured amylase activity on POD 0 (the day of operation) [9,17,18,23,32,34], three on POD 2[15,20,32] , two on POD 3[13,32], and three studies on POD 4[10,30,33]; no studies reported values on the days after POD 4.

Several studies[9–11,13,15,16,18] used a receiving operating characteristic (ROC) curve to assess the association between POH and POPF. The area under the curve (AUC) for serum amylase activity differed between the included studies. The AUC value was less when calculated from the POD 3 onward, ranging between 0.59[30] to 0.68[13], as compared to the AUC calculated on the first 2 PODs[9,11,12,15,16,18,23] when the values were in the range of 0.75[9,12] to 0.88[15]. Similarly, the amylase cut off was greater on the first PODs and tended to decrease over time. Therefore, the amylase cut-off ranged from 127 U/L[18] to 177 U/L[15] on POD 0 and 1 and decreased to a range of 38.5[13] to 44.2 U/L[10] on POD 3 and 4. Based on the chosen cut-off value, the incidence of what the authors claimed to be POH varied from 8.4%[14] to 64%[11], with a median value of 30%. Six studies[10,11,14,16,20,23] analyzed different cut-off values of POH to identify the most appropriate value to predict POPF. POPF was observed with an incidence ranging from 14%[20] to 44%[17] in patients presenting with POH. In multivariate models, all studies except for one[14] reported that POH was statistically significantly associated with an increased rate of POPF, with an odds ratio (OR) or relative risk (RR) ranging between 1[10] to 16.9[15].

Seven studies[9,11,17,18,20,23,34] also reported an association between POH and postoperative morbidity other than POPF (primarily DGE and abdominal abscess) (Table 1). Only the study by Kawai et al.[33] did not find a relationship between POH and post-operative infection. Four studies[9,18,23,34] evaluated risk factors for POH and reported an association of increased serum amylase values and an increased incidence of POH in high-risk pancreatic remnants characterized by a soft pancreatic parenchyma and a small pancreatic duct[9,11,23]. Two studies[11,34] found the presence of pre-operative cardiac comorbidity as a risk factor for POH. One study[23] also identified exocrine insufficiency, neoadjuvant therapy, and an additional resection of the pancreatic-stump margin as factors protective of POH. Three

Table I

Studies reporting postoperative serum amylase cutoffs for the definition of POH and the correlation of POH with POPF. Receiver operating characteristic analysis, demonstrating the predictive ability of serum amylase activity for POPF were reported. POH was considered as a serum amylase value exceeding the cutoff; the association of POH with other morbidity and risk factors for POH were also reported.

Author (Journal)	Publication date	Setting	Study interval	No. of patients	POPF* incidence (2005†)	Cut off AMY U/L	POD AMY	AUC	Sen %	Spec %	POH n/%	Risk factors for POH	Percent POH associated with POPF	POH association with morbidity
Birgin E (*HPB [Oxford]*)[27]	2019	Retrospective	2009 –2015	190	1%‡	115	0–1	–	–	–	100/53	Cardiac morbidity Soft pancreas texture Small MPD Non-PDAC pathology	0% (*P* = .1)	Intra-abdominal collections Interventional drain placement DGE
Chen CB (*The American Surgeon*)[2]	2018	Retrospective	2009 –2014	524	8.8% (15%)	165	0–1	0.75	70	72	180/34	No DM Soft pancreas texture Small MPD Non-PDAC pathology	–20% (*P* = .001)* –31% (*P* = .001)†	DGE Intra-abdominal abscess Cardiac Pulmonary Wound infection Urinary tract infection
Bannone E (*Annals of Surgery*)[16]	2018	Retrospective	2016 –2017	292	22.2%	52	0–1	0.79	90.7	54.2	163/55.8	No DM Soft pancreas texture Small MPD Non-PDAC pathology Exocrine insufficiency No neo-adj therapy	36.2% (*P* < .01) OR 3.84 (*P* = .02)	Clavien Dindo >IIIb PPH Chyle leaks Abdominal abscesses Pulmonary Cardiac Relaparotomy ICU stay
						156	0	0.68	77.7	71	–	–	–	–
Jin S (*World J Gastroenterology*)[3]	2017	Prospective	2011– 2015	83	24% (33.7%)	44.2	4	0.78	78.6	70.9	–	–	–	–
						100		–	42.9	55				
						140		–	–	–	–	–	OR 1.009 (*P* = .05)	–
Author (Journal)	Pub. date	Setting	Study interval	No. of patients	POPF* incidence (2005†)	Cutoff AMY U/L	POD AMY	AUC	Sen %	Spec %	POH n/%	Risk factors for POH	POH association with POPF	POH association with morbidity
Kühlbrey CM (*Journal of Gastrointestinal Surgery*)[4]	2017	Prospective	2001 –2014	739	21.7%	>53	1	–	–	–	471/64	Non-PDAC or chronic pancreatitis pathology No preoperative biliary drainage PG Coronary heart disease	–	–
						54–158	1	–	–	–	126/22		16%	–
						>159	1	0.79	–	–	200/36		38%	Later drains removal
Partelli S (*HPB [Oxford]*)[5]	2017	Retrospective	2013 –2015	463	14%	100	1	0.75	–	–	–	–	OR 6.97 (*P* < .001)	–
Kinaci E (*Hepatobiliary & Pancreatic Diseases International*)[6]	2016	Retrospective	2006 –2015	107	23.5% (36.5%)	38.5	3	0.68	71	68	–	–	–	–
McMillan MT (*Journal of the American College of Surgeons*)[7]	2015	RCT	2008 –2009	106	29.2% (33%)	–	–	0.66	–	–	–	–	–	–
						95	1	–	38	78	22/21	(Only moderate/high-risk FRS patients considered)	50% *P* = .11	–
						130	1	–	31	78	20/19		45% *P* = .34	–
						140	1	–	31	78	20/19		45% *P* = .34	–
						195	1	–	28	86	15/14		53% *P* = .12	–
						292	1	–	21	94	9/8.4		66% *P* = .06	–
Jin S (*Medicine [Baltimore]*)[22]	2015	Prospective	2012 –2014	61	27.8 (34%)	140	1	–	76.2	55	–	–	OR 3.91 *P* = .024	–
Ansorge C (*The British Journal of Surgery*)[8]	2014	Prospective	2008 –2012	315	18.7% (24.1%)	177	1	0.86	82	76	–	–	OR 13.67, (6.46 –28.94)	–
						98	2	0.88	78	81	–	–	OR 16.97, (8.33 –34.59)	–
Palani Velu LK (*HPB [Oxford]*)[11]	2014	Retrospective	2008 –2013	185	23.2% (34.6%)	127	0	0.79	91.7	72.7	80/43	Soft pancreatic texture Small MPD		
Cloyd JM (*Journal of Gastrointestinal Surgery*)[9]	2014	Retrospective	2006 –2011	176	14.3% (18.5 %)	140	1	0.78	81.5	55.5	–	–	OR 4.49 (1.47 –13.74) (*P* < .01)	–
						200	1	–	74	65	–	–	OR 5.4 (2.1–13.9)	–
						260		–	62	75	–	–	OR 5.3 (2.2–12.8)	–
						292	1	–	63	79	–	–	OR 6.7 (2.7–16.6)	–
Kosaka H (*Journal of Hepatobiliary-Pancreatic Sciences*)[23]	2014	Retrospective	2009 –2012	100	32% (47%)	94.5	4	0.59	39	84	–	–	–	–
Okabayashi T (*Hepatogastroenterology*)[24]	2009	Retrospective	1999 –2007	100	(18%)	194	1	–	–	–	–	–	OR 2.0 (1.1–3.9) (*P* = .019)	–
Uemura K (*Journal of Surgical Oncology*)[25]	2008	RCT	2004 –2006	40	0% (7.5%)	300	0–1 –2–3	–	–	–	11/27.5 (overall) 2/8 (ulinastatin group) 9/36 (placebo group)	–	–	–
Okabayashi T (*Journal of Hepatobiliary Pancreatic Surgery*)[12]	2007	Prospective	1991 –2006	50	(28%)	195	1	–	71.4	69.4	–	–	OR 2.4 (1.0–5.7) (*P* = .01)	–
Author (Journal)	Pub. date	Setting	Study interval	No. of patients	POPF* incidence (2005†)	Cutoff AMY U/L	POD AMY	AUC	Sen %	Spec %	POH n/%	Risk factors for POH	POH association with POPF	POH association with morbidity
Winter JM (*Journal of the American College of Surgeons*)[13]	2007	Retrospective	1982 –2007	2,894	(9.4%)	292	1–2	–	–	–	–	–	OR = 2.0 (*P* = .01)	Overall Morbidity Abdominal abscess: DGE
						<100	1–2	–	–	–	1,181/51	–	4%	–
						100–399	1–2	–	–	–	727/31	–	14% OR = 4.3 (*P* < .001)	–
						>400	1–2	–	–	–	415/18	–	20% OR = 6.8 (*P* < .001)	–
Kawai M (*Annals of Surgery*)[26]	2006	Prospective	2002 –2004	104	9.6 (13.4)	150	1	–	–	–	–	–	–	Intra-abdominal infection: 6.9% (*P* = .4)
						>150	1	–	–	–	–	–	–	Intra-abdominal infection: 17% (*P* = .4)
						150	4	–	–	–	–	–	–	Intra-abdominal infection: 21.3% (*P* = .8)
						150	4	–	–	–	–	–	–	Intra-abdominal infection: 2.7% (*P* = .8)

A dash "–" was added for "unavailable" data.

AMY, serum amylase; *ADJ*, adjuvant; *BMI*, body mass index; *CRP*, C-reactive protein; *DM*, diabetes; *ICU*, intensive care unit; *MPD*, main pancreatic duct; *OR*, odds ratio; *PG*, pancreogastrostomy; *PPH*, postpancreatectomy hemorrhage; *Sen*, sensitivity; *Spec*, specificity.

* POPF definition: Bassi et al.[20]

† POPF definition: Bassi et al.[19]

‡ POPF without POAP: Birgin et al.[27]

studies claimed that a postoperative values of serum amylase activity below the normal range had a high negative predictive value for POPF, even in patients with other risk factors for POPF, such as a soft pancreatic parenchyma and a small pancreatic duct[9,11,23].

Studies reporting a range of serum amylase values

Twenty-one studies[10,12–16,18,19,23,29,30,35–44] reported a post-operative range of serum amylase activity (Table 2). Fourteen studies were retrospective[12,13,16,18,23,30,31,35,36,39–42,44], five were prospective[10,15,29,38,43], and two were RCTs[14,37].

Four studies[12,35,39,40] reported the overall median and range of serum amylase levels after pancreatoduodenectomy irrespective of any postoperative complications. Fifteen studies compared post-operative serum amylase values in patients with and without POPF; however, six of these studies[16,29,31,36,37,43] were performed before the 2016 revision of the POPF definition[27], so they also included Grade A POPFs (so called biochemical leaks) in the POPF group. The remainder of studies considered only Grades B and C POPFs (the clinically relevant POPFs) in the POPF group[10,13–15,18,35,40,41,44]. One study compared post-operative serum amylase ranges between patients with a clinically relevant POPF and those with a biochemical leak, showing statistically significantly greater values in the former group[39].

The incidence of POPF ranged between 7.6%[36,38] and 34.7%[40], with a median incidence of 18.7%. Most of these studies reported the median serum amylase value with its range, except for three studies[14,16,41], in which only the median value was mentioned. Five studies reported average serum amylase levels[31,36,37,42,43]. Mean and median post-operative serum amylase values varied dramatically between studies, and ranges were also highly variable and wide. The serologic assessments of "amylase activity" were performed on different PODs across these studies. Serum amylase levels were markedly greater on the first 2 PODs, in both patients with and without a POPF[10,13,15,16,18,29,31,35–37,39,41] when compared to values on subsequent PODs[13,15,30,40]. POPF groups showed an increased median amylase value compared to that of patients without a POPF. Most of the studies reported that the serum amylase level differed statistically significantly between the two groups[10,15,16,18,19,29,35,37,39,41,44]. This trend was not confirmed in three studies in which the median serum amylase values were not different between POPF and non-POPF patients. Only one study by Kinaci et al.[13] found a separate, statistically significant difference when considering different PODs, reporting that serum amylase correlated with POPF on POD 3 but not on POD 1. Three studies examined the influence of the texture of the pancreatic parenchyma on the level of postoperative serum amylase values. Palani Velu et al.[18] reported that serum amylase on POD 0 was increased in 64.8% of patients with a soft pancreatic parenchyma compared to only 21.4% of patients with a hard pancreatic parenchyma. The pancreatic pathology that was not pancreatic ductal adenocarcinoma (PDAC) was also found to be independently associated with an increase in serum amylase

Table II
Studies reporting a range of postoperative serum amylase values. Ranges of postoperative serum amylase activity were compared among patients with or without POPF. Overall ranges of postoperative serum amylase activity (or average serum amylase levels) and risk factors for POH were reported if outlined.

Author (Journal)	Publication date	Setting	Study interval	No. of patients	POPF* incidence (2005†)	Median AMY value (range) U/L	POD AMY	AMY POPF (range/SD) U/L	AMY BL (range/SD) U/L	AMY NO POPF (range/SD) U/L	P value	Risk factors for POH
Nahm CB (*HPB (Oxford)*)[37]	2018	Retrospective	2016–2017	35	22%	100	0–1	55 (10–914)	–	101 (24–573)	.014	High acinar score
Hanaki T (*Surgery Today*)[32]	2018	Retrospective	2012–2015	75	25.3%	1,179 (12–3,953)	1	507 (75–3,953)	219 (12–2,342)	–	.002	Soft pancreas texture
Bannone E (*Annals of Surgery*)[16]	2018	Retrospective	2016–2017	292	22.2%	–	0	–	–	–	–	AMY POAP POS: 114 (53–934) AMY POAP NEG: 11 (0–52)
							1	–	–	–	–	-AMY POAP POS: 186 (53-973) -AMY POAP NEG: 7 (0-46)
Jin S (*World Jour Gastroenterology*)[3]	2017	Prospective	2011–2015	83	24% (33.7%)	–	1	379.5 (157.5, 627.5)	–	124.0 (80.0, 165.0)	< .001	–
							4	30.0 (30.0, 50.0)		61.5 (45.5, 150.0)	< .001	–
Partelli S (*HPB (Oxford)*)[5]	2017	Retrospective	2013–2015	463	14%	58 (0–2,379)	1	–	–	–	–	–
Furukawa K (*Pancreas*)[13]	2016	Retrospective	2012–2015	46	34.7%	50 (4–239)	3	67.8 (16.8, 118.8)	68.6 (5.5, 131.7)		.96	–
Kinaci E (*Hepatobiliary & Pancreatic Diseases International*)[6]	2016	Retrospective	2006–2015	107	23.5% (36.5%)	–	1	251 (61–795)	155 (33–660)		.118	–
							3	70 (9–145)	30 (6–452)		.018	
McMillan MT (*Journal of the American College of Surgeons*)[7]	2015	RCT	2008–2009	106	29.2% (33%)	–	1	84	76		.32	(Only moderate/high-risk FRS patients considered)
Jin S (*Medicine (Baltimore)*)[22]	2015	Prospective	2012–2014	61	27.8/(34%)	–	1	380 (155.5–665)		127 (80–300)	.003	–
Fujiwara Y (*Anticancer Research*)[34]	2015	Retrospective	2000–2013	247	17.4% (21.4%)	439.5	1	529.8		420.4	.025	–
Rudis J (*Rozhledy V Chirurgii*)[28]	2014	Retrospective	2007–2011	160	8.75% (only GRADE C POPF*)	141 (58–529)	0	386 (58–529)	–	98 (58–235)	–	
Ansorge C (*The British Journal of Surgery*)[8]	2014	Prospective	2008–2012	315	18.7% (24.1%)	–	1	382 (199–601)	53 (16–175)		< .001	–
							2	246 (111–393)	25 (10–73)		< .001	–
							3	81 (36–111)	13 (7–33)		< .001	–
Palani Velu LK (*HPB (Oxford)*)[11]	2014	Retrospective	2008–2013	185	23.2% (34.6%)	–	0	217 (19–1,833)	92 (19–906)		< .001	Soft pancreatic texture Small MPD Non-PDAC or chronic pancreatitis pathology BMI of ≥25 kg/m²
Cloyd JM (*Journal of Gastrointestinal Surgery*)[9]	2014	Retrospective	2006–2011	176	14.3% (18.5 %)	–	1	659.0		246	< .001	–
Kosaka H (*Journal of Hepatobiliary Pancreatic Sciences*)[15]	2014	Retrospective	2009–2012	100	32% (47%)	–	4	86.6 (72–101,3)	56.9 (50–62)	–	–	–
Hiyoshi M (*World Journal of Surgery*)[35]	2013	Retrospective	2002–2010	176	17.1 % (39.3 %)	–	1–5	157.9 ± 96.3	160.5 ± 137.8		.92	–
El Nakeeb A (*World Journal of Surgery*)[29]	2013	Retrospective	2001–2012	471	7.6% (12.1 %)	–	1	341.45 ± 402.15		250.17 ± 331.17	.058	–
						–	5	286.66 ± 266.79		225.54 ± 289.58	0.13	–
Ansorge C (*The British Journal of Surgery*)[30]	2012	Prospective	2007–2010	48	14.5%	118.8 ± 194	1	306.4 ± 350	–	84.7 ± 130.5	–	–
						70 ± 118	2	143.5 ± 167		57.6 ± 106.4	–	–
Bassi C (*Annals of Surgery*)[20]	2010	RCT	2008–2009	114	13.1%	–	1	208.0 (40–670)		80.0 (4–733)	.001	–
Okabayashi T (*Journal of Hepatobiliary Pancreatic Surgery*)[12]	2007	Retrospective	1991–2006	50	(28%)	–	1	1,255 ± 2,454		210 ± 271	.01	–
Räty S (*Journal of Gastrointestinal Surgery*)[21]	2006	Prospective	2004–2006	39	7.6 (15.3)	–	4–6	–		–	–	AMY POAP POS: 747 ± 197 AMY POAP NEG: 121 ± 42 (P = .01) AMY DGE POS: 715 ± 205 AMY DGE NEG: 153 ± 70 (P = .02)

A dash indicates data not available.
AMY, serum amylase; *BL*, biochemical leak; *BMI*, body mass index; *MPD*, main pancreatic duct; *NEG*, negative; *POS*, positive; *RCT*, randomized controlled trial.
* POPF definition: Bassi et al.[20]
† POPF definition: Bassi et al.[19]

levels on POD 0. Hanaki et al.[39] also reported that serum amylase levels on POD 1 were statistically significantly greater in the group with a soft pancreatic texture. Nahm et al.[44] showed that a high acinar score (a measure of acinar cell density at the surgical margin of the pancreatic remnant) also correlated with an increase in serum amylase activity on POD 1 ($p < 0.001$). McMillan et al.[14] showed that serum amylase activity measured on POD 1 positively correlated with the Fistula Risk Score (FRS)[45] (a function of the texture of the pancreatic parenchyma, the size of the pancreatic duct, the pancreatic pathology for which the operation is being done, and the intraoperative blood loss); however, comparisons of median values across the risk zones of the FRS did not differ. Two studies investigated serum amylase levels in patients with presumed POAP[23,38]. Although the definitions of POAP did not match in the two studies, both reported statistically significantly increased serum amylase activity in patients with POAP when compared to the levels in patients without complications. Räty et al.[38] also identified a similar serum amylase increase in patients suffering from DGE[22].

Studies reporting POAP among post-operative complications

Twenty-two studies[10,11,18,23,29,32,34–38,44,46–55] reported POAP as a complication after pancreatic surgery (Table 3). Eleven studies were retrospective[18,23,34–36,44,47,48,51,52,54], eight studies were prospective[10,11,29,38,46,49,53,55] and three were RCTs[32,37,50]. The rates of POAP were highly variable, ranging from 0.7%[52] to more than 57%[44]. These differences were related to the variability of the definitions used in each study. In many reports, a definition was missing[10,36,49,50,54,55], while in others it was reported as an arbitrary generic increase in serum pancreatic enzymes[47,52]. The definition of the revised Atlanta consensus classification for acute pancreatitis[8] of greater than 3 times the upper limit of normal was used to define POAP in five studies[11,18,29,37,53], while two studies only used urine trypsinogen levels to define POAP[32,48]. Only three studies reported a specific cut-off value to define the occurrence of POAP[23,34,44]; however, even if the cut off was always defined as a serum amylase greater than the upper limit of the normal range, the cut offs varied among studies, because the upper limits of the normal range differed across centers. Six studies[29,35,37,38,51,53] used computed tomography to diagnose or confirm the occurrence of POAP. There was no agreement for the POD at which POAP was to be defined. Most studies did not report this POD[18,29,35,36,46,49,50,52,54,55]. When mentioned, POD 2 was the most frequently indicated day[29,37,38,47,48,53]. Indeed, POAP was the specific aim of only seven studies reported in this review[11,23,32,34,35,38,44].

The assessment of POAP had some similarities and differences across these studies. Kühlbrey et al.[11] defined POAP, in analogy to pancreatitis, as a local inflammatory process occurring in the area of the pancreatic anastomosis after pancreatic resection that could lead to increased systemic amylase concentrations and subsequently impair healing of the pancreatic anastomosis. Räty et al[38] suggested that POAP could start either postoperatively or during the operation immediately after the transection of the pancreas, with the release of multiple local and systemic mediators of inflammation. In this study, patients with POAP showed an increase incidence of coronary artery disease in their medical histories. The authors suggested ischemic factors, hyperlipidemia, and/or decreased glucose tolerance as proposed mechanisms underlying POAP. Our previous report[23] indicated POAP as a possible clinical and biochemical manifestation of intraoperative ischemic damage of the pancreatic stump that may eventually lead to anastomotic leakage, explained by an element of pancreatic stump necrosis. Moreover, due to the association between POAP and other additional morbidities, POAP has been identified as a specific complication after pancreatic surgery. Uemura et al.[32] reported that POAP was a consequence of direct trauma to the pancreatic parenchyma during a

Table III
Studies reporting POAP among postoperative complications. The definition of POAP used in each study was reported if outlined.

Author (Journal)	Pub. date	Setting	Study interval	No. of patients	POAP definition used	Patients with POAP (*n*/%)	POD POAP
Birgin E (*HPB [Oxford]*)[27]	2018	Retrospective	2009–2015	190	At least 1 of the following criteria: Urinary trypsinogen-2 levels >50 μg/L Serum amylase (>150 U/L)/lipase (> 393 U/L)	100/53	0–1
Nahm CB (*HPB [Oxford]*)[37]	2018	Retrospective	2016–2017	35	At least 1 of the following criteria: Urinary trypsinogen-2 levels >50 μg/L Serum amylase (>100 U/L)/lipase (>78 U/L)	20/57	0–1
Bannone E (*Annals of Surgery*)[16]	2018	Retrospective	2016–2017	292	Serum pancreatic amylase >upper limit of normal (52 U/L)	163/55.8	0–1
Jin S (*World Journal Gastroenterology*)[3]	2017	Prospective	2011–2015	83	No definition	1/2.5	Not reported
Kühlbrey CM (*Journal of Gastrointestinal Surgery*)[4]	2017	Prospective	2001–2014	739	Serum pancreatic amylase >159 U/L (Atlanta criteria*)	256/35	1
Jin S (*Medicine [Baltimore]*)[22]	2015	Prospective	2012–2014	61	Serum amylase >3 times the maximum normal value (Atlanta criteria*) Confirmed by CT scan	1/2	2
Malleo G (*Pancreas*)[39]	2014	Prospective	2009–2010	173	No definition	24/13.9	Not reported
Rudis J (*Rozhledy V Chirurgii*)[28]	2014	Retrospective	2007–2011	160	Only in grade C POPF† patients: CT scan (on POD 5) Relaparotomy evaluation Autopsy	14/100% of grade C POPF† (relaparotomy evaluation) 4/57% of grade C POPF† (at autopsy histology)	Not reported
Palani Velu LK (*HPB [Oxford]*)[11]	2014	Retrospective	2008–2013	185	Serum amylase ≥300 IU/L (Atlanta criteria*)	Not reported	Not reported
El Nakeeb A (*World Journal of Surgery*)[29]	2013	Retrospective	2001–2012	471	No definition	7/1.5	Not reported
Addeo P (*Journal of the American College of Surgeons*)[40]	2013	Retrospective	2010–2012	50	Elevated serum lipases and drain amylases	3/6	1–2
Laaninen M (*Pancreas*)[41]	2012	Retrospective	2007–2009	40	Positive urine trypsinogen test	9/29 Patients with >40% acini in pancreatic stump: 6/50 Patients with <40% acini in pancreatic stump: 3/11	2
Okano K (*Journal of Hepatobiliary Pancreatic Sciences*)[42]	2011	Prospective	2007–2010	54	No definition	1/2.6	Not reported
Pessaux P (*Annals of Surgery*)[43]	2011	RCT	2006–2009	158	No definition	4/2.5 Without external pancreatic stent group: 1/1.2 External pancreatic stent group: 3/3.9 ($P = .28$)	Not reported
Bassi C (*Annals of Surgery*)[30]	2010	RCT	2008–2009	114	Serum amylase >3 times the maximum normal value (Atlanta criteria*) confirmed by CT scan or clinical course	Early drain removal group: 4/7 Late drain removal group: 6/10.5 ($P = .741$)	2
Bruno O (*American Journal of Roentgenology*)[44]	2009	Retrospective	2005–2009	50	CT scan (only soft pancreas texture)	8/16	7
Barreto G (*Pancreas*)[45]	2008	Retrospective	2003–2007	149	High serum amylase and lipase with delayed abdominal collection	1/0.7	Not reported
Uemura K (*Journal of Surgical Oncology*)[25]	2008	RCT	2004–2006	40	Elevation of urine trypsinogen-2 >50 mg/L	5/12.5	1–3
Molinari E (*Annals of Surgery*)[46]	2007	Prospective	2005–2006	137	Serum amylase >3 times the maximum normal value (Atlanta criteria*) confirmed by CT scan or clinical course	19/13.6	2
Lermite E (*Journal of the American College of Surgeons*)[47]	2007	Retrospective	1996–2005	131	No definition	2/1.5	Not reported
Räty S (*Journal of Gastrointestinal Surgery*)[31]	2006	Prospective	2004–2006	39	CT scan	10/25.6	2–5
Matsusue S (*Surgery Today*)[48]	1998	Prospective	1981–1996	100	No definition	1/1	Not reported

CT, computer tomography; *RCT*, randomized controlled trial.
* Atlanta criteria: Banks et al.[1]
† POPF definition: Bassi et al.[19]

pancreatoduodenectomy. Similarly, Addeo et al.[47] related the occurrence of POAP to fractures induced by the surgical sutures to the pancreas. Laaninen et al.[48] combined the two theories and reported that pancreatic tissue ischemia or damage to the pancreas itself, such as resection of the pancreas and the suturing of pancreatico-jejunal anastomosis, can initiate local or widespread inflammation with an uncontrolled activation of trypsin and other digestive enzymes. Rudis and Ryska[35] analyzed patients deceased after developing Grade C POPFs; in all these patients, the macroscopic findings during operative revision were indicative of POAP with subsequent development of POPF. Autopsy, however, revealed POAP with diffuse necrosis in only 57% of cases. In all other cases, the authors attributed the presence of superficial pancreatic necrosis to the digestion of tissues by the POPF. They did not consider necrosis of the pancreatic stump as POAP and attributed the pancreatic leak to an error in the surgical technique. In contrast, Palani Velu et al.[18] proposed POAP as a localized necrotizing pancreatitis able to increase the post-operative systemic inflammatory insult, and POH as a marker of surgical trauma to a functioning pancreas. Two studies, in light of the previous considerations, have better investigated the timing and burden of POAP instead of its physiopathology. Nahm et al.[44] defined POAP as an increase in serum amylase activity greater than normal and demonstrated that the biochemical evidence of POAP preceded the development of POPF. Nevertheless, the causation of POPF by POAP has still not been established. Specifically, it remains unclear whether an initial "leak" of pancreatic fluid leads to the development of POAP, if POAP is at least responsible for the development of POPF or if some external factor (e.g., pancreatic ischemia/inflammation) is associated with the development of both of these phenomena. Birgin et al.[34] determined cut-off values of C-reactive-protein that discriminated clinically relevant POAP cases in patients with presumed POAP; however, these authors used a different definition of POPF, restricting it to patients with high-drain amylase values but normal serum amylase ranges.

DISCUSSION

The present study provided a systematic review of evidence regarding POH and POAP after pancreatoduodenectomy. Several studies have addressed this topic, but findings lack standardization in terms of both metrics and definitions. POH often was not even defined in many of the included reports, and the threshold of serum amylase activity used to make the diagnosis of POH was rarely specified in a consistent, objective fashion. Among the studies that reported a serum amylase cutoff to define POH, no consistent or agreed-on value was used across the studies, making comparison of studies difficult at best[11,14,19]. Similarly, there was no agreement about the POD at which serum amylase should be assessed in order to establish the occurrence of POH[10,13,15,17]. Despite this extreme variability, POH does not seem to be merely a rare event, because, depending on its definition, its prevalence can reach as great as 64% of assessed cases[11]. Moreover, some characteristics of POH have emerged from review of these many studies. The absolute value of serum amylase was greater on the first PODs and decreased with time postoperatively and was often not measured after POD 4[13,15,18,30]. These findings indicate that POH is an early event after PD and that amylase concentrations may return to normal despite the development of further complications. This pattern of POH may partially account for why POH has consistently been considered as a frequent but fleeting and unimportant postoperative condition in some studies, for which its clinical interpretation has still not been deeply investigated and its clinical relevance not yet accepted universally among pancreatic surgeons.

The majority of the studies analyzing POH have focused on its correlation with POPF[9,11,12,14–20,23,35]. Even if the association between POH and POPF has been widely reported[9,11,14,16,17,20,23,44], several papers suggest that not all patients developing POH subsequently have or develop POPF[9,11,17,23]. The reported ranges of postoperative serum amylase activity frequently overlapped between patients who did and who did not develop a POPF or other postoperative complications. Serum amylase values are therefore not always able to confidently or completely discriminate between the two groups[13,18,35,37,40]. At present, most of the available reports have focused on the low diagnostic accuracy of postoperative levels of serum amylase in predicting POPF or have considered POH as only a secondary diagnostic test or an indirect sign of POPF. Hence, perhaps the emphasis should be moved to the pathophysiology of this condition so that POH may no longer be considered only the serologic evidence of POPF. POH has, however, been confirmed in some studies to be associated with an increased rate of postoperative complications other than POPF, especially DGE and abdominal abscesses[9,17,18,20,23]. Given these findings, POH may represent a biochemical marker of an early pathologic event able to be associated with or even to trigger several post-operative morbidities, including but not confined to POPF.

Nevertheless, the pathologic mechanism underling POH remains unclear due to the limited possibility of investigating specific changes in the pancreatic parenchyma occurring in the early post-operative period. In a non-surgical setting, acute pancreatitis[8] is characterized by an increase in serum amylase activity and the ability to induce further morbidity. Likewise, a similar pathologic mechanism characterized by serum hyperamylasemia and subsequent complications could affect the post-surgical course. The topic of POAP has also been reported by many studies, especially with POH. Unfortunately, both the nomenclature and objective evidence-based definitions of POAP have been either inconsistent, poorly defined, or actually missing[46,49,54,55].

Although there have been different interpretations between reports, some aspects belonging to POAP and its relationship with POH have been highlighted. POAP, at least as it has been defined, appears to be an early event after pancreatoduodenectomy[11,23,44], as it induces or at least is associated with an increased systemic serum amylase concentration[23,29,53], and it appears to be associated (or causes) systemic and local alterations that may lead to the onset of other post-operative complications[11,18,23,34,38,48]. Pathologic changes that occur in acute pancreatitis may be also attributed to POAP, representing a continuum between inflammation and necrosis[8,48].

The conundrum of POAP, as defined only by the serum amylase value, does not allow for staging of the actual morphology or clinical burden of POAP, because different degrees of severity are likely included within the same term. In nonsurgical settings, the occurrence of acute pancreatitis can resolve completely without any clinical sequelae, or it can lead to dramatic morbidity related to necrotizing pancreatitis. Mild symptoms consistent with POAP could be self-limiting within the first PODs. Other studies, however, highlighted the association of POAP with further abdominal complications up to severe cases of rare but extensive pancreatic necrosis and anastomotic disruption, as reported in series considering surgical revisions for Grade C POPF[35,56].

POH and POAP have often been interpreted as an expression of operative injury during the pancreatic resection[32,47]. Nevertheless, since these complications do not occur in all patients undergoing PD, this explanation, may be insufficient and potentially misleading. Operative trauma, however, is a series of events that occur during the pancreatic resection —ranging from manipulation, mobilization, alterations in blood supply, and transection of the parenchyma— and may play a fundamental role in the development of POAP[23]. Within this framework, POH may represent a biomarker for the detection of POAP and can share its risk factors[9,11,18,23].

A soft pancreatic parenchyma, a small pancreatic duct, as well as non-PDAC pathology, all appear to predispose patients to develop greater serum amylase levels postoperatively. Conversely, exocrine insufficiency, neoadjuvant therapy, and an additional resection of the pancreatic stump margin interestingly have been highlighted as factors protective of POH and POAP[9,11,18,23,39]. Patients presenting with the aforementioned risk factors may be more prone to develop the postoperative cascade of ischemia/inflammation within the pancreatic parenchyma, which interestingly may actually be localized to the area of pancreatic stump and not generalized to the entire pancreas as with medical acute pancreatitis. Moreover, the presence of this condition, should therefore be referred to as POAP, because it is a pancreas-specific complication able to produce additional morbidity, such as POPF, DGE, and abdominal abscesses[9,18,20,23].

POPF has largely been investigated and treated after it has already occurred[27]. Recently POAP has been identified as the underlying cause of POPF, but it has been mostly unexplored[23]. Shifting the focus from the treatment to the prevention of POPFs, new therapeutic and diagnostic scenarios may be available. Because POH seems to represent an early serologic marker of POAP, its recognition and interpretation might allow for a promising early therapeutic intervention aimed at the prevention or mitigation of other post-operative complications, especially POPF.

The local ischemic/inflammatory process of POAP occurring in the area of the pancreatic stump may subsequently impair the healing of the pancreatic anastomosis, and thereby lead to POPF[11,23]. Moreover, this cascade appears to occur more frequently in high-risk patients who have a soft and fatty pancreas, a small pancreatic duct and a pancreatic pathology different form PDAC[44,48]. These patients still experience dramatic post-operative scenarios related to POPF occurrence[57]. The acceptance of a universal definition of POAP and its diagnostic assessment may lead to a better understanding and acceptance of POAP as a distinct entity, and thus a therapeutic strategy to decrease the incidence or the burden of POPF, especially in these critical patients.

The present review has many limitations related to the literature from which this study originates. First, the included studies have several methodological deficiencies. POH was the endpoint of a limited number of reports, and it was almost always reported as a collateral finding[9,16,18,31,47]. Nevertheless, exclusion of these studies would have produced a consistent selection bias. Second, most of the studies did not report the reference interval or the definition used for both POH and POAP[10,36,49,50,54,55]. This substantial heterogeneity among the included studies made it impossible to perform a meta-analysis or a meta-regression. Regardless, one of the aims of the present review was to highlight this extreme variability and gap of evidence regarding this concept of POH and POAP.

New studies focusing on the presence and the relationship between POH and POAP as well as its pathophysiology are mandatory. Considering the inconsistencies in the methodologies and definitions of these previous findings, it is crucial that a shared and universally accepted definition of POH/POAP should be established and referred to, possibly as an ISGPS statement. Define POH/POAP is beyond the scope of this review because the definition should be based on stronger evidence than that currently available in the literature. Whatever the shared definition will be, it should consider the following: a biochemical diagnosis of POAP based on a serum amylase, lipase, or urinary trypsinogen assessment at specific time points; an attempt at morphologic correlation via cross-sectional imaging; and a severity stratification on the basis of clinical relevance. An accurate definition and grading of POAP will allow the stratification of patients both for clinical care and for the reporting of clinical research. An aligned terminology will also allow for comparisons among centers and different operative techniques, as well as for assessing the efficacies of different therapeutic strategies.

CONCLUSION

An increase, albeit mild, in the perioperative and postoperative serum amylase activity is a relatively frequent serologic finding after PD. At present, however, no definition or agreed threshold for the diagnosis of POH is available. POH has been proposed to represent the biochemical expression of pancreatic stump ischemia and local inflammation and, based on its analogous features to those of acute pancreatitis, was named as POAP. This designation and its presence is very controversial amongst pancreatic surgeons. Patients with POAP appear to experience an increased rate of all post-operative complications, including POPF. Taken together, the conclusions of the present review provide an argument and a basis to obtain stronger evidence in order to provide a specific, universally accepted and recognized definitions of POH/POAP, which may subsequently better enable the discovery and development of novel therapeutic strategies and aid in the prevention of morbidity after PD.

Chapter 2 - Early and sustained elevation in serum pancreatic amylase activity: a novel predictor of morbidity after pancreatic surgery

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Annals of Surgery 277(1):p e126-e135, January 2023, doi:10.1097/SLA.0000000000004921

ABSTRACT

Objective

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

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.

INTRODUCTION

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[8]. Currently, the meaning and implications of an increase in serum pancreatic enzymes after partial pancreatic resections is a matter of vibrant debate[9,18,23]. 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[1]. By contrast, several studies have already described the possible prognostic implications of a postoperative increase in serum pancreatic enzymes for short-term outcomes[23,56,58–60]. Recently, the utility of postoperative serum pancreatic enzymes has been reappraised following the observation of postoperative hyperamylasemia (POH) in the absence of any clinically relevant change in the postoperative course[61,62]. However, almost all previous studies have assessed the prognostic value of serum pancreatic enzymes based on a single postoperative measurement[1,34,59], 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 pancreaticoduodenectomy (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.

Pancreatic amylase measurement and classification

According to the institutional protocols, serum pancreatic amylase (spAMY) activity is routinely assessed 2 h 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 10–52 U/L.

Six patterns of post-operative amylase have been identified based on the spAMY standard range: (I) spAMY values less than the lower limit of normal (LLN) at all post-operative measurements; (II) spAMY values within the reference range (WRR) at all post-operative measurements. Patients with post-operative increased spAMY values greater than the upper limit of normal (ULN) are divided according to four observed categories: (III) a single post-operative spAMY value greater than the ULN (spAMY > 52 U/l in a single post-operative measurement regardless of whether it was recorded on POD 0, 1, or 2); post-operative spAMY values greater than the ULN in two 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 upper limit of normal (> 52 U/L), and more than 3 times the upper limit (> 156 U/L, Atlanta criteria for acute pancreatitis[8]).

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 [EBL], and operative time) were retrieved. The surgical technique for PD and DP has been described elsewhere by our group[63–66].

Both pylorus-preserving and Whipple PDs with either pancreatojejunostomy 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[67] or Warshaw[68] 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 (MPD) 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 transanastomotic 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)[69]. 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[53,70].

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[1,62,69], 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 (ISGPS) definitions of POPF[27], delayed gastric emptying (DGE)[22], postpancreatectomy hemorrhage (PPH)[71], and chyle leak[72]. 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[73]. 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 90-days postoperatively. The severity of complications was assessed according to the Clavien–Dindo (CD) classification system[74]. Due to the existence of different etiologies, postoperative complications are likely to have different patterns of onset (early or late), as previously reported[71,75]. 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 retrieved. The analysis was focused on complications graded as CD ≥ II[74], namely a complication requiring a relevant change in the post-operative course, and on severe complications graded as CD ≥ III[74].

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's t-test when appropriate. Categorical variables are reported as frequencies, and differences were assessed through the chi-square test or Fisher's exact test where appropriate. Correlations between spAMY and DFA values were assessed using Pearson's or Spearman's 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 two-sided P-value < 0.05 was considered statistically significant. Statistical analyses were performed 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.

Table 1. Patients characteristics and post-operative outcomes of the overall population and stratified according to the type of surgery.

		Overall (n= 983)	**PD (n= 720)**	**DP (n= 263)**
Age *(years, median, IQR)*		64 (55-71)	65 (56-72)	61 (49-70)
Gender	*Male*	519 (52.8%)	406 (56.4%)	113 (43%)
	Female	464 (47.2%)	314 (43.6%)	150 (57%)
BMI (Kg/m2, 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%)

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

Postoperative spAMY patterns

The six post-operative 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 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 post-operative CD ≥ II morbidity for the six 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.

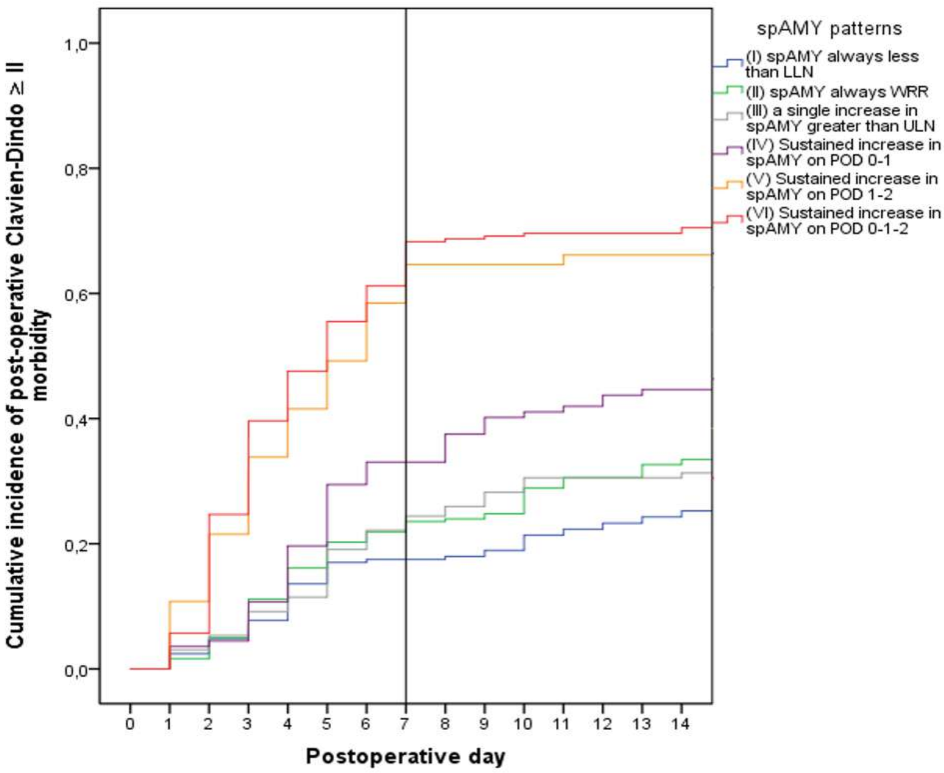

Figure 1: The Kaplan–Meier curves for the cumulative incidence of post-operative Clavien-Dindo ≥ II morbidity in different spAMY patterns.

Abbreviations: spAMY: pancreatic serum amylases. POD: post-operative day. CD: Clavien Dindo Score. WRR: within the reference range; LLN: lower limit of normal; ULN: upper limit of normal.

Table 2: Cumulative incidence of post-operative Clavien-Dindo ≥ II morbidity in the different spAMY patterns.

<table>
<tr><th></th><th>Population (overall n= 983)</th><th>Cumulative incidence of CD ≥ II morbidity by POD 7</th><th colspan="5">P value</th></tr>
<tr><td>(I) spAMY always less than LLN (n= 206) (< 10 U/l)</td><td>21%</td><td>17.4%</td><td rowspan="2">0.095</td><td></td><td rowspan="2"></td><td rowspan="3"></td><td rowspan="4"></td></tr>
<tr><td>(II) spAMY always WRR (n= 242) (10-52 U/L)</td><td>24.6%</td><td>23.5%</td><td rowspan="2">0.93</td></tr>
<tr><td>(III) A single increase in spAMY greater than ULN (n= 131) (>52 U/L on POD0/POD1/POD2) ł</td><td>13.3%</td><td>24.4%</td><td rowspan="4"></td><td rowspan="2">0.024</td></tr>
<tr><td>(IV) Sustained increase in spAMY on POD 0-1 (n= 112) (>52 U/L on POD 0+1)*</td><td>11.4%</td><td>33%</td><td rowspan="3"></td><td rowspan="2">0.002</td></tr>
<tr><td>(V) Sustained increase in spAMY on POD 1-2 (n= 65) (>52 U/L on POD 1+2)</td><td>6.6%</td><td>64.6%</td><td rowspan="2"></td><td rowspan="2">0.54</td></tr>
<tr><td>(VI) Sustained increase in spAMY on POD 0-1-2 (n= 227) (>52 U/L on POD 0+1+2)</td><td>23.1%</td><td>68.2%</td><td></td></tr>
</table>

Abbreviations: *spAMY: pancreatic serum amylases. POD: post-operative day. CD: Clavien Dindo Score. WRR: within the reference range; LLN: lower limit of normal, ULN: upper limit of normal.*

ł: 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 x 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.

Three spAMY patterns were eventually defined (Figure 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 pre-operative 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).

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****
POPF *(total n.)*		52 (9%)	33 (29.5%)	**<0.001**	140 (47.9%)	**0.001**
Grade	*BL*	23 (4%)	16 (14.3%)		31 (10.6%)	
	B	48 (8.3%)	31 (27.7%)	**<0.001**	107 (36.6%)	**<0.001**
	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%)		14 (4.8%)	
	B	11 (1.9%)	3 (2.7%)	0.407	26 (8.9%)	**0.001**
	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%)		8 (2.7%)	
	B	32 (5.5%)	11 (9.8%)	**0.015**	26 (8.9%)	0.11
	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 *(days, 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 II (≤ 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 vs 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 vs Sustained increase in spAMY activity greater than the ULN including on POD 1 + 2

Abbreviations: spAMY: serum pancreatic amylases, LLN: lower limit of normal, WRR: within the reference range, ULN: upper limit of normal, POD: post-operative day, POPF: post-operative pancreatic fistula, BL: Biochemical leak, PPH: post pancreatectomy hemorrhage, DGE: delayed gastric emptying, ICU: intensive care unit, LOS: length of hospital stay.

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 post-operative 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. There was a poor correlation between POD1 spAMY and POD 1 DFA (r = 0.001, P = 0.967).

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 53–156 U/l on POD 1 + 2 (#3a), 34.6% had one 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, while greater spAMY values (#3c) were significantly more frequent after PD. Further stratified sub-analysis 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 (Figure 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). In the multivariable model for DP patients, preoperative diabetes (OR 0.19, CI 95% 0.058 – 0.681; 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).

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/m², 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**
Fistula Risk Score *(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
Blood Loss *(mL, median, IQR)*		400 (200-600)	435 (262-645)	400 (200-600)	0.34
POPF *(total n.)*		30 (35.3%)	48 (48%)	62 (57.9%)	**0.008**
Grade	*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

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

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.

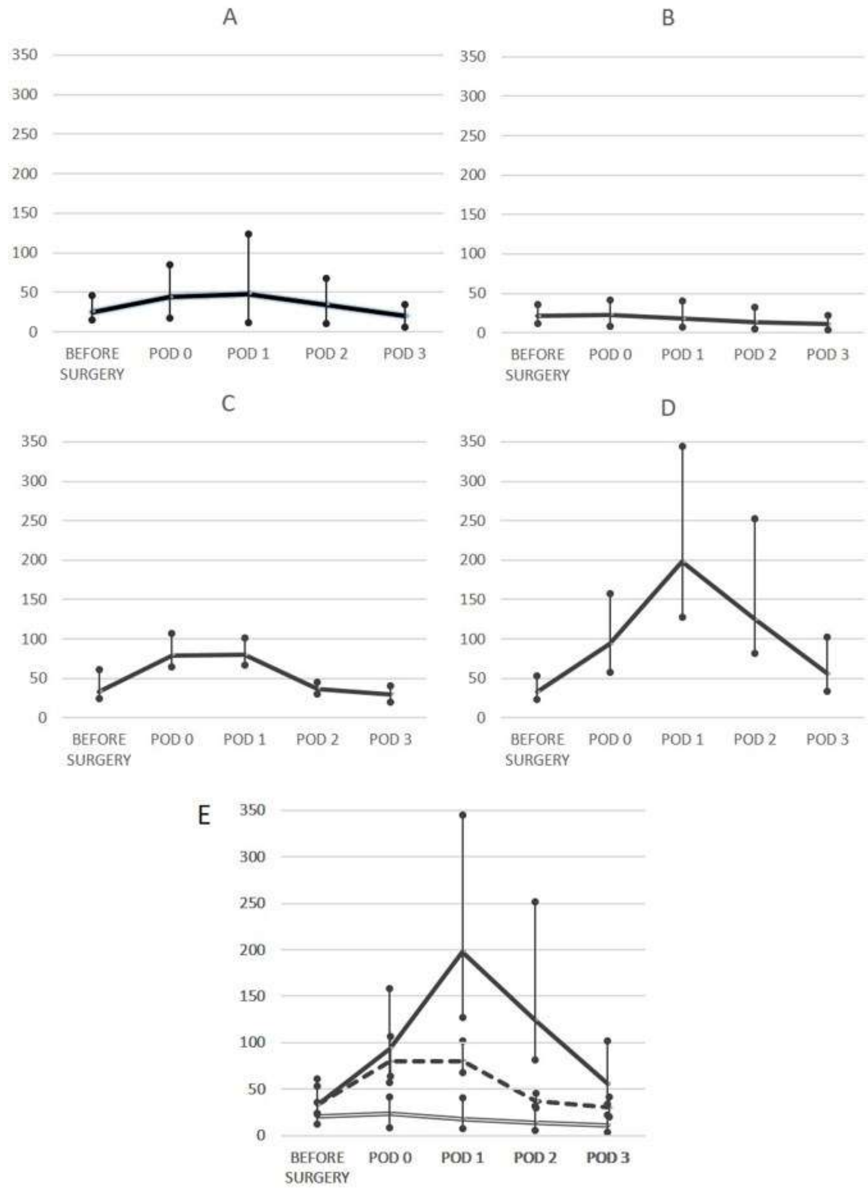

Figure 2: Analysis of perioperative spAMY levels [before surgery, and postoperatively on the day of surgery (POD 0), and thereafter (POD 1-3)]. (A) All patients; (B) Pattern #1 (spAMY values always less than the LLN/spAMY values always WRR/a single increase in spAMY activity greater than the ULN); (C) 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.

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 postoperative hyperamylasemia (POH) in recent years[23,59,60,76,77], the characterization of this phenomenon and its possible prognostic role remains largely unknown, mainly because POH typically occurs early after surgery[58,62]. 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 acute pancreatitis[23,59–62,62,77,78]. While POH has been investigated as a punctual increase in pancreatic amylase activity[9,23,59], 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[59,60].

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 upper limit of normal 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[79] and the increased burden of PD compared to DP[80]. 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[81]. By contrast, patients with increased spAMY activity, even under the threshold of 3 times the upper limit of normal 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.

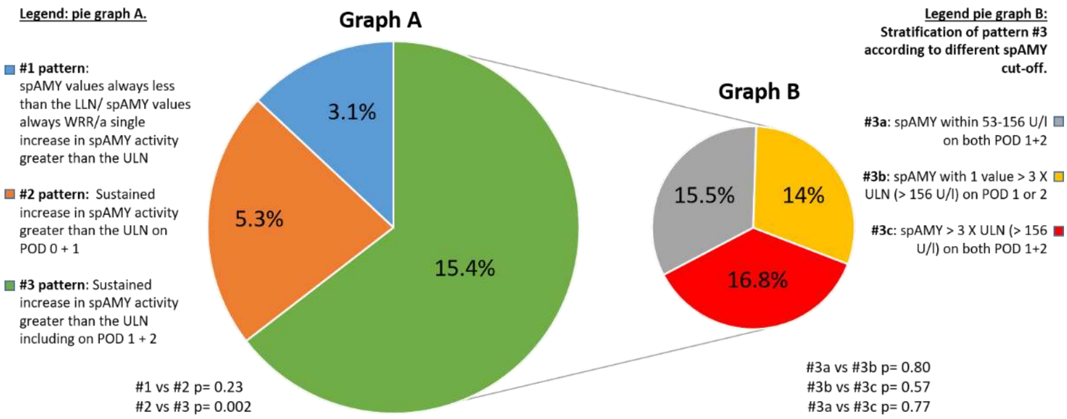

Figure 3: Incidence of post-operative Clavien-Dindo ≥ III morbidity within POD 7 in different spAMY patterns (pie graph A). Pattern #3, representing the group with the highest incidence of early severe complications has also been stratified according to different spAMY cut-offs (pie graph B).

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[69,82]. 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[78,82–84], they may alter the clinical outcome, eventually lowering the risk of postoperative complications. Facing this challenge, the risk for early postoperative complications could be re-adjusted 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[85] and drainage management protocols[37,70] 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[16] or of surgical mechanical trauma[18]; however, POH has been recently interpreted as a marker of an acute inflammatory process of the pancreatic remnant[1,58,60]. In a non-surgical context injuries to the pancreatic parenchyma may lead to premature activation of pancreatic enzymes and a subsequent increase in serum levels[8]. 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[86,87]. 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 acute pancreatitis process.

This study adds solid evidence to the increasing literature investigating POH and its clinical significance[1,56,59]. The correlation between spAMY trends and postoperative morbidity can serve as a biochemical characterization of post pancreatectomy acute pancreatitis. 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 intra-operative 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 single center, with homogeneity among surgical approaches and postoperative management. Thus, different reference ranges or pancreatic enzymes (e.g., lipase) may have been evaluated, potentially leading to different results.

CONCLUSION

A sustained rise in postoperative spAMY activity greater than the upper limit of normal, 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 post pancreatectomy acute pancreatitis and could prompt further appraisal of systematic measures to ultimately improve the clinical pathway of the early postoperative course.

Chapter 3 - Post-pancreatectomy acute pancreatitis (PPAP): definition and grading from the International Study Group for Pancreatic Surgery (ISGPS)

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Annals of Surgery 2022 Apr 1; 275: 663–672, doi: 10.1097/SLA.0000000000005226

ABSTRACT

Objective

The International Study Group for Pancreatic Surgery (ISGPS) aimed to develop a universally accepted definition for post-pancreatectomy acute pancreatitis (PPAP) for standardized reporting and outcome comparison.

Background Data

PPAP is an increasingly recognized complication after partial pancreatic resections, but its incidence and clinical impact, and even its existence are variable because an internationally accepted consensus definition and grading system are lacking.

Methods

The ISGPS developed a consensus definition and grading of PPAP with its members following an evidence review and after a series of discussions and multiple revisions from April 2020 to May 2021.

Results

We defined PPAP as an acute inflammatory condition of the pancreatic remnant beginning within the first three postoperative days following a partial pancreatic resection. The diagnosis requires (1) a sustained postoperative serum hyperamylasemia (POH) greater than the institutional upper limit of normal for at least the first 48 hours postoperatively; (2) associated with clinically relevant features; and (3) radiologic alterations consistent with PPAP. Three different PPAP grades were defined based on the clinical impact: (1) grade POH, biochemical changes only; (2) grade B, mild or moderate complications; and (3) grade C, severe life-threatening complications.

Conclusions

The present definition and grading scale of PPAP, based on biochemical, radiologic, and clinical criteria, are instrumental for a better understanding of PPAP and the spectrum of postoperative complications related to this emerging entity. The current terminology will serve as a reference point for standard assessment and lend itself to developing specific treatments and prevention strategies.

INTRODUCTION

The occurrence of an acute inflammatory process of the pancreatic parenchyma after pancreatic resections has been reported[55,88,89], but the existence of clinically evident post-pancreatectomy acute pancreatitis (PPAP) as a distinct complication has been challenged or, at least, considered to be a rare event[16,18,19,36,54]. Recently, emerging evidence defines PPAP as a local inflammatory/ischemic process of the pancreatic remnant, occurring more frequently than previously thought, which is able to trigger further postoperative morbidity[1,11,44,56,58–60,76,77,90,91].

A series of events related to operative trauma, ranging from manipulation, mobilization, alteration of blood supply, and/or stasis of pancreatic juice, appear to play a fundamental role in the etiology of PPAP[1,58]. These pathophysiological events may trigger a series of cascading events causing acinar cell disruption, intracellular activation of proteolytic enzymes, pancreatic parenchymal edema, and peripancreatic inflammation, leading to local and/or systemic effects[92]. PPAP may impair the healing of the pancreatic remnant and/or anastomosis with the subsequent development of a postoperative pancreatic fistula (POPF)[26]. However, even in the absence of POPF, it may also lead to other abdominal and systemic complications, such as organ space infection/intra-abdominal abscess[93], hemorrhage, the systemic inflammatory response syndrome (SIRS), and systemic sepsis[59,62,77,91].

According to this hypothesis, PPAP is initiated very early in the perioperative period, with a widely ranging incidence from 1%[36,54] to 67%[62]. This inordinate range of occurrence is due directly to a distinct lack of uniformity in definitions and terminology.

Notably, however, when more standardized criteria have been used, the incidence of PPAP is reported more uniformly[34,44,59,60,90,91]. Different reports have based their definitions of PPAP on the biochemical and radiologic criteria of the revised Atlanta classification for acute pancreatitis (AP)[8], both together[29,37,53,59,76,77] or individually[11,18,38,51]. In 2016, Connor et al.[58] presented the first attempt to define PPAP specifically. The definition of PPAP was based only on biochemical evidence, using any serum pancreatic enzyme level greater than the upper limit of normal, rather than the threshold of greater than 3X the upper limit of normal used by the revised Atlanta classification[8]. Subsequent studies using the Conor definition of PPAP resulted in conflicting findings[59,61,77,91]. Differences in the incidence of PPAP were also reported between partial pancreatoduodenectomy[59,60,94] and distal (left-sided) pancreatectomy[60,62]. Not all patients with increased serum pancreatic enzyme activity have shown radiologic alterations or indeed postoperative morbidity related to an acute pancreatitis process, precluding a reliable grading system of the severity of PPAP [59,61].

Given these limits, a universally accepted definition of PPAP was lacking in the pancreatic surgical literature[1,59,91], leading to the inability to objectively compare the experience with different pancreatic resections, operative techniques, and perioperative treatments inhibiting the exploration of potential variance across different centers.

Faced with heterogeneity in study definitions and outcomes, the need for a shared and universally accepted terminology was required before further clarification of the prevalence and importance of this entity could be delineated[59,77,90,91]. Previously, the International Study Group for Pancreatic Surgery (ISGPS) introduced several globally accepted consensus definitions and grading systems for the most common complications after pancreatic surgery[22,27,71,72]. These systems have been well-accepted, widely cited, and broadly adopted in the literature, allowing for paramount and accurate comparisons of outcomes across all clinicians caring for post pancreatectomy patients. Based on the knowledge acquired thus far, the present consensus paper aimed to provide a universal and objective consensus definition and grading system for PPAP after partial pancreatic resection.

METHODS

An extensive and systematic search for acute pancreatitis after pancreatic resection was conducted on all published articles of interest in this context on PubMed and Embase. A systematic review on the same topic has already been published in July 2020[1]. An update of this search was then carried out up to April 2021 to supplement that particular review with several newly published studies. The following search terms were used: “acute pancreatitis,” “postoperative acute pancreatitis,” “postoperative pancreatitis,” and “postoperative hyperamylasemia”. A non-MeSH search also was performed. All obtained results were analyzed, and a manual inspection of the cited references was also performed to find any other related articles. Studies of any design specifically investigating acute pancreatitis after pancreatic resection were included. The language of the selected papers was limited to English with available full text for complete review. Case reports were excluded.

An Aristotelian system of logic development was used to achieve a consensus that was consistent with the scientific evidence. A task force of the ISGPS was nominated to provide a first, tentative draft. A subsequent internal analysis of the institutional experiences of the ISGPS members was also carried out to corroborate or refute the results claimed in the literature. Several virtual meetings were scheduled among the task force to discuss the manuscript drafts. The initial proposal of the definition and grading system of PPAP was circulated to all participants for comments and approval. Multiple revised drafts were circulated through electronic mail for critical analysis and further modifications. Numerous revisions were circulated, commented upon, and edited electronically from April 2020 to May 2021 by all the contributing members of the ISGPS who participated in this study. Eventually, a consensus was achieved across all members and approved for publication.

RESULTS

A total of 26 studies[10,18,29,34–38,44,46,49,51,53,54,59–62,76,77,90,91,94–97] have already reported PPAP as a complication after pancreatic resections. The rates of PPAP were highly variable because the diagnostic criteria either lacked any reliable standards or differed tremendously depending on the reports[10,36,46,49,50,54].

Terminology

Although many papers refer to this complication as “postoperative acute pancreatitis –POAP” [1,59,60,62,77,78,90,91,98], the terminology chosen and that will be maintained in this report is “post-pancreatectomy acute pancreatitis”, to specify that acute pancreatitis occurs after pancreatic resections, and to differentiate it from acute pancreatitis observed after other operations[99–101]. Moreover, the term “acute” describes the early occurrence of this complication and differentiates it from a chronic or late-onset obstructive pancreatitis related to an anastomotic stricture or other forms of pancreatic duct obstruction[102,103].

Previous attempts at a definition of PPAP: The biochemical evidence

In some of the reported literature attempting to define PPAP, the diagnostic criteria outlined by the revised Atlanta classification[8] were used[18,29,37,53,59,76,77,91,94] because of the belief that this well-accepted definition could be applied in the postoperative period. It was instinctive to draw similarities between PPAP and the more common and better-understood etiologies and findings of other types of AP. Because the clinical picture of PPAP might be obscured by postoperative analgesia, biochemical and radiologic criteria were included in the definition but not pain. The increase in serum levels of pancreatic enzymes appears to be the easiest, most accessible, and biologically intuitive indicator of PPAP, and indeed has been used as a single criterion for diagnosis in several reports[18,94]. All studies used the more common International Units for quantitating enzyme activity, although some reports may have used different upper limits of normality in their laboratory for which we could not control. Nevertheless, the meaning and the implications of an increased value of serum pancreatic enzyme activity alone have been interpreted historically in different ways[1,9,18].

The first structured definition of PPAP as proposed by Connor et al.[58] was based only on the assumed biochemical evidence of pancreatic inflammation – namely an increase in serum pancreatic enzymes levels to greater than the upper limit of normal at a single assessment time point on a postoperative day (POD) 0 or 1. In addition, urinary trypsinogen-2 (U-TRP2) on POD 1 – 2 was considered in the definition mentioned above. Due to the widespread familiarity and access to serum amylase values, most studies used elevated serum total amylase activity or its pancreatic isoform as the criterion for the diagnosis[34,44,59,60,77,90,91]. Reports investigating the prognostic implications of the Connor definition invariably identify a significant association between an increase in serum amylase activity, even under the threshold of 3-times the upper limits of normal[11], and an increase in postoperative morbidity[9,34,44,59,60,62,77,90,91]. This association appeared strengthened when serum pancreatic enzymes activity was combined with increased values of serum C-reactive protein (CRP >180 mg/dl on POD 2). However, such a condition defined as "clinically relevant" by Connor et al.[58] did not always result in clinically relevant changes to the expected postoperative course[60,62].

Some reports have demonstrated a temporal trend of serum amylase activity in the initial postoperative period[35,59,95]. Patients with a PPAP process have frequently shown a peak of serum amylase activity on POD 1 that might progressively decrease to normal values from POD 3 onward[59]. The comprehensive investigation of the serum amylase time trends highlighted that the presence of a single altered serum amylase value was not associated with increased morbidity. By contrast, patients with an early and sustained increase in serum amylase activity ─ even under the threshold of 3-times the upper limit of normal ─ were found to be twice as likely to develop early postoperative complications[96].

The radiologic evidence

Apart from biochemical findings, the existence of PPAP has also been demonstrated through pancreatic parenchymal abnormalities observed on cross-sectional imaging[35,38,51,59,77]. Radiologic features of PPAP include but are not limited to interstitial parenchymal edema, peripancreatic fluid collections, and peripancreatic and parenchymal necrosis[59,61,77] (Figure 1). Thus, the classical features of PPAP involve changes in the

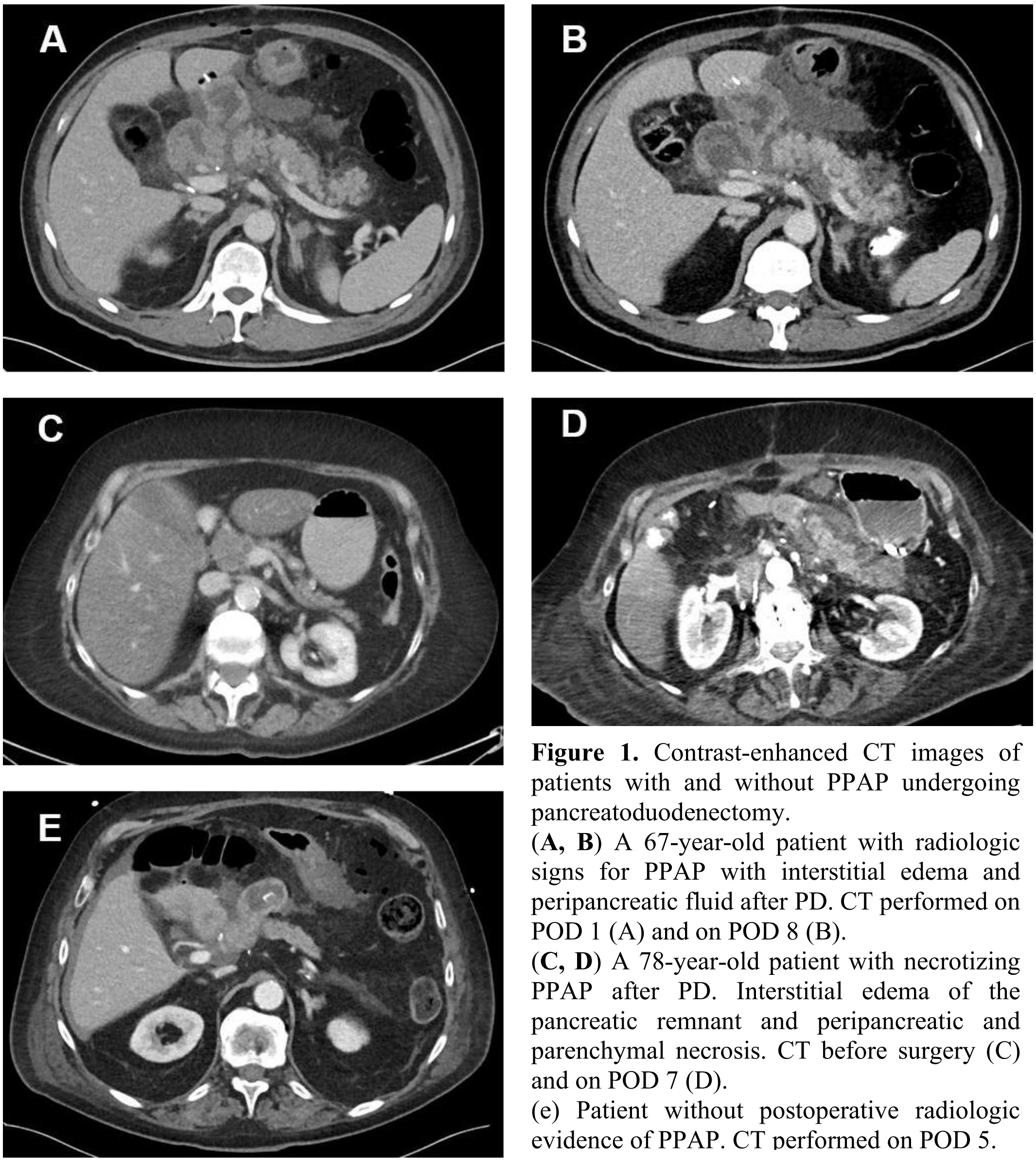

Figure 1. Contrast-enhanced CT images of patients with and without PPAP undergoing pancreatoduodenectomy.
(**A, B**) A 67-year-old patient with radiologic signs for PPAP with interstitial edema and peripancreatic fluid after PD. CT performed on POD 1 (A) and on POD 8 (B).
(**C, D**) A 78-year-old patient with necrotizing PPAP after PD. Interstitial edema of the pancreatic remnant and peripancreatic and parenchymal necrosis. CT before surgery (C) and on POD 7 (D).
(e) Patient without postoperative radiologic evidence of PPAP. CT performed on POD 5.

(Images by courtesy of Markus W. Büchler MD, Heidelberg, Germany.
Abbreviations: CT: computed tomography; PPAP: post-pancreatectomy acute pancreatitis; POD: postoperative day, PD: pancreatoduodenectomy).

pancreatic remnant with surrounding fat stranding and/or peri-remnant fluid collections arranged not primarily at the level of the pancreatico-enteric anastomosis but especially along the pancreatic remnant[52]. Differences in the reported rates of "radiologic PPAP" may exist for several reasons. First, postoperative computed tomography (CT) was not performed in all patients believed to have (or not have) PPAP due to the retrospective design of most series, and the grading system used to score the severity of PPAP was not always reported[29,38,51,53,61]. When mentioned, the Modified CT Severity Index[104] for AP was the most frequently reported method[59,61,77]. Moreover, there was no consensus on the appropriate timing of axial imaging, which differed between studies. Thus, the ability to see evidence of pancreatic inflammation on CTs varied tremendously. These differences may eventually result in misleading interpretations because of underestimating the actual degree of parenchymal involvement and the inability to assess the complications related to PPAP reliably[55]. One publication has claimed that abnormalities can be seen as early as POD 2[38], while another maintained that radiologic signs of PPAP (confirmed at pathology) could not be detected before POD 5[35]. Recent publications included in their analyses a wide timeframe[59] for the performance of CT and demonstrated rates twice as high as those that used a shorter interval[77]. Nevertheless, different degrees of radiologic severity of PPAP were documented, ranging from mild pancreatic abnormalities to severe, albeit rare, parenchymal necrosis. Patients with radiologic evidence for PPAP were associated with increased postoperative morbidity[59]. All radiographic abnormalities consistent with PPAP were detected almost exclusively (99%[59]) in patients with serum amylase values greater than the upper limits of normal[59,61,77]; 15% of patients with radiologic signs of PPAP after partial pancreatoduodenectomy had serum amylase values greater than the upper limit of normal but less than the Atlanta criteria[8] on POD 1. Notably, 85% of this cohort showed a serum amylase activity >3-times the normal limits on POD 1[59].

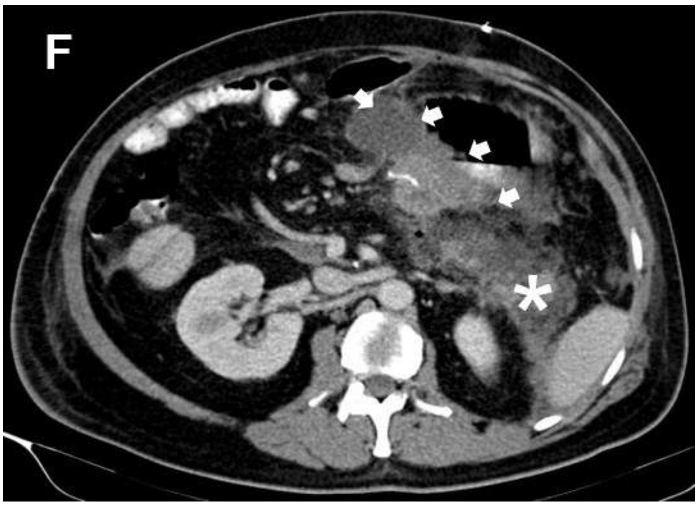

Figure 2. Contrast-enhanced CT image of necrotizing PPAP after pancreatoduodenectomy.

(F) Patient with necrosis of the pancreatic remnant (asterisk), peripancreatic necrosis, and peripancreatic collection (white arrows).

(Image by courtesy of Savio Barreto MD, Flinders Medical Centre, Australia; Abbreviations: CT: computed tomography; PPAP: post-pancreatectomy acute pancreatitis).

The pathologic evidence

The presence of an ischemic/inflammatory process of the pancreatic remnant was suggested as the etiology in several pathologic reports, particularly in series considering operative revisions for Grade C POPF[35,56,92]. These patients indeed represent the most severe and rare scenarios of PPAP (Figure 2). The pathologic findings indicative of PPAP included in such cases acute necrotizing pancreatitis in 41-57% of surgical specimens of completion pancreatectomies for grade-C POPF[35,56].

The clinical evidence

Most series evaluating postoperative hyperamylasemia and PPAP showed an association of these conditions with increases in major postoperative morbidity[60,77,91,96], and some series have documented PPAP associated with a greater perioperative mortality[61,91]. Most studies analyzing biochemical and radiologic findings of PPAP focused on its correlation with POPF[18,20,59,60,76,77,90,91,94], and many have identified PPAP as an independent predictor of POPF[18,29,60,76,77,91]. Considering differences in the applied definitions and the intrinsic diversity in management among different centers, the reported association of PPAP and POPF has ranged from 25% to 41% ($p < 0.05$)[18,59,60,76,77,90,91,94]. However, PPAP was also associated with an increased incidence of several postoperative complications other than POPF. These include post-pancreatectomy hemorrhage (PPH)[71], organ space infection/intra-abdominal abscess[93] formation, delayed gastric emptying (DGE)[20], sepsis, and relaparotomy. Considering possible reporting biases, as rarely those particular complications were the main outcomes of such studies, organ space infection/intra-abdominal abscess in patients with PPAP ranged from 12% to 46%, with statistically significant differences in all studies reporting them[18,34,60,90,91]. Still, patients experiencing PPAP without POPF showed significantly increased rates of organ space infection/intra-abdominal abscess[91]. Others found PPAP being associated with delayed gastric emptying[96,105], while many studies did not report significant differences[60,91]. Few reports reported PPH amongst postoperative morbidity[18,61,76,91,97]. Nevertheless, when PPH was specifically investigated in patients suffering from PPAP, it has been noted that only half of clinically relevant PPH occurred with a concomitant POPF[76]. This latter category more often required surgical revision than patients with PPAP alone[76]. Reoperation is reported in 6% to 29% of cases of PPAP[18,59,76,90,91], with increased rates of completion pancreatectomy[35,56,61,76], and need for intensive care[61,91]. Since PPAP is an early event, a stronger association between PPAP and additional early complications has been demonstrated, thus resulting in a change in postoperative management as early as the initial postoperative period[96].

Distal (left-sided) pancreatectomy

The evidence of PPAP after distal pancreatectomy still is limited[60–62,94,96]. According to the best evidence acquired so far, PPAP has been reported as a severe but less frequent complication than after partial pancreatoduodenectomy[61]. A radiologically confirmed PPAP (Figure 3) has been associated with increased overall morbidity, especially with severe pancreas-specific complications, but not increased mortality after left resections[61].

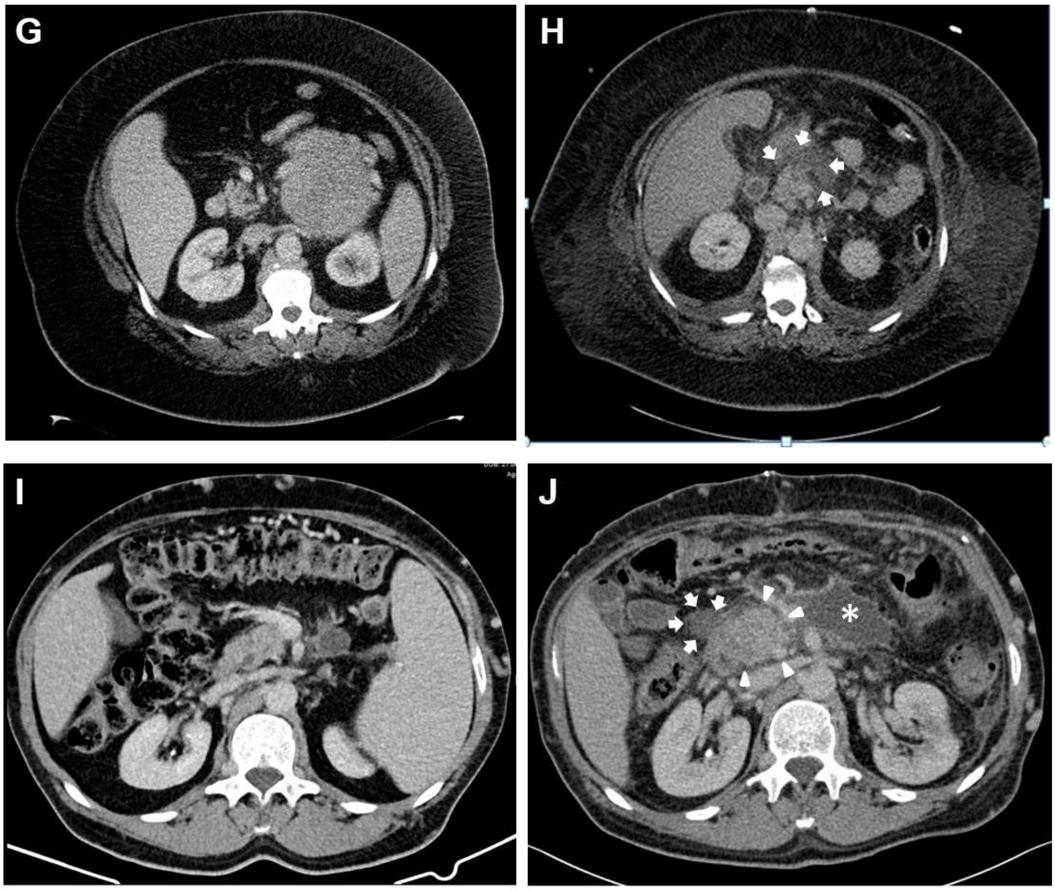

Figure 3. Comparison of preoperative (g, i) and postoperative (H, J) contrast-enhanced CT images of patients with PPAP undergoing distal pancreatectomy.
(H) Patient with radiologic signs of PPAP with interstitial edema and peripancreatic fluid.
(J) Patient with necrotizing PPAP with interstitial edema of the pancreas (white arrow heads), peripancreatic necrosis (white arrows), and a peripancreatic fluid collection (asterisk).
(Images by courtesy of Markus W. Büchler MD, Heidelberg, Germany. Abbreviations: CT: computed tomography; PPAP: post-pancreatectomy acute pancreatitis).

The ISGPS consensus definition and grading of PPAP

The ISGPS defines PPAP as an acute inflammatory condition of the pancreatic remnant occurring in the setting of a partial pancreatic resection and initiated early in the perioperative period within the first 3 postoperative days. This pathophysiologic process can present various degrees of severity and several local and systemic complications, resulting in a deviation from the expected postoperative course.

A sustained increase in serum amylase activity greater than the specific institutional upper limit of normal, which persists within at least the first 48 hours postoperatively, is necessary for the diagnosis. To be defined as PPAP, however, this condition needs to be confirmed by cross-sectional imaging and, as is the case for other ISGPS definitions, to be clinically relevant to the patient. Whenever only postoperative hyperamylasemia (POH) is found, which does not negatively alter the patient's clinical recovery, PPAP should not be reported. This is analogous to the nomenclature of "biochemical leak" in the previously established POPF definition framework[27]. Table 1 summarizes the main features of the PPAP diagnostic criteria. Figure 4 displays the sequential PPAP grading system. Like previous ISGPS classification systems, the grade of severity may be defined after the *complete* course of the PPAP event has evolved, and its ultimate effect on the outcome can be assessed.

Table 1. The ISGPS classification and grading of PPAP.

	Biochemical features	**Radiologic features*[X]**	**Grade**	**Clinical impact**
PPAP Post-pancreatectomy acute pancreatitis	Sustained (that persists within at least 48 hours) serum amylase[#] activity > the Institutional upper limit of normal	Yes	**GRADE B**	Mild or moderate complications that require: - Acute medical treatment (e.g. antibiotics, steroids, supplementary nutritional support), - Interventional radiology and / or endoscopic-guided drainage and/or angiographic procedures.
		Yes	**GRADE C**	Severe life-threatening complications that lead to: persistent organ failure (of at least 48 hours), possibly leading to intensive care admission; surgical intervention; or death.

[#]future studies may validate the importance of serum lipase.

*: Radiologic (contrast-enhanced computed tomography scan / magnetic resonance imaging) features consistent with PPAP might include: diffuse (or localized) inflammatory enlargement of the pancreatic remnant (interstitial parenchymal edema), inflammatory changes of the peripancreatic fat, intra and/or peripancreatic fluid collections, parenchymal and/or peripancreatic necrosis.

[X]:Mortele KJ, Wiesner W, Intriere L, et al. A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. AJR Am J Roentgenol. 2004;183:1261–1265

1) *POH (Postoperative Hyperamylasemia*)

As only biochemical evidence, POH had, by definition, no clinically relevant impact. Notably, POH did not result in any deviation in the normal postoperative recovery course and, therefore, did not warrant systematic radiologic evaluation.

2) Grade B PPAP

This grade refers to a distinctly defined PPAP which involved: 1) a sustained increase in serum amylase activity greater than the institutional upper limit of normal, that has persisted within at least the first 48 hours postoperatively, 2) the association with a clinically relevant downturn in the patient's condition, and 3) radiologic "abnormalities" consistent with PPAP. These include diffuse (or localized) inflammatory enlargement of the pancreatic remnant (interstitial parenchymal edema), inflammatory changes of the peripancreatic fat, intra and/or peripancreatic fluid collections, parenchymal and/or peripancreatic necrosis[104].

A grade B PPAP includes all cases associated with local and systemic complications of intermediate severity, attributable to its presence. PPAP associated morbidity includes, but is not confined to, POPF[27] and may occur even in its absence. The early postoperative period could be characterized by a combination of features of the systemic inflammatory response syndrome and abdominal complications, most worryingly organ space infection/intra-abdominal abscess[93], PPH[71], and POPF[27]. Grade B PPAP has required a change in the management of the expected postoperative recovery course, including specific pharmacologic (e.g., antibiotics, supplementary nutritional support), endoscopic, or interventional radiologic treatments that are specifically invoked for the management of the PPAP and its sequelae, and not for other complications *per se* (i.e., urinary tract infection, pneumonia, etc.).

3) Grade C PPAP

Whenever a grade B PPAP leads to persistent organ failure (defined as either single or multiple organ failure for at least 48 hours)[106,107], the PPAP severity is elevated to a grade C. This tier includes severe but rare cases of extensive pancreatic necrosis that may lead to dramatic clinical scenarios, including pancreatic anastomotic disruption (when performed)[35,56]. A stay in an intensive care unit (ICU) may be necessary to treat potentially life-threatening illnesses secondary to PPAP-related morbidity. Reoperation also shifts grade B PPAP to Grade C PPAP when performed to treat complications triggered by its occurrence, especially severe PPH[71] or grade C POPF[108]. This latter scenario is associated with the highest mortality rate.

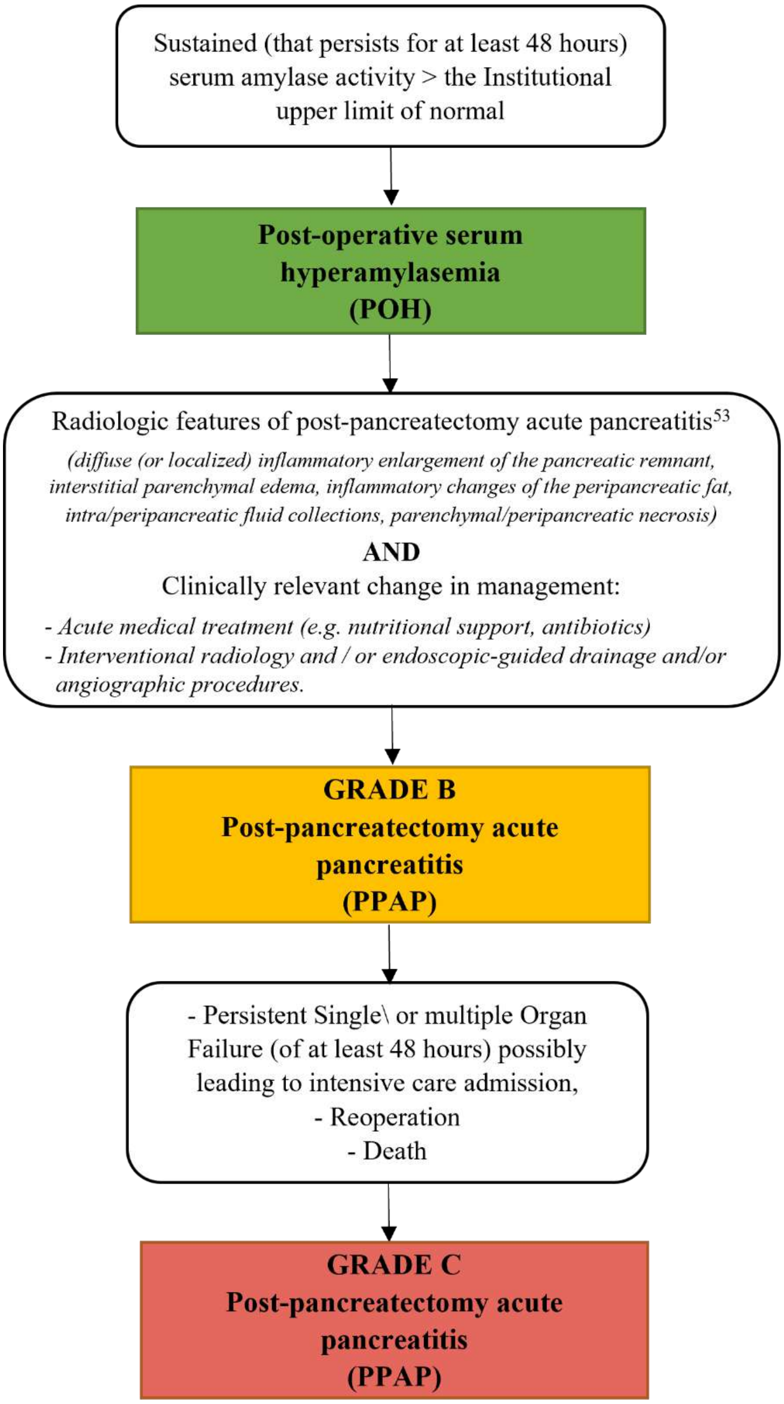

Figure 4. Flow chart for POH and PPAP grade definition.
(Abbreviations: POH, Postoperative Serum Hyperamylasemia; PPAP, Post - Pancreatectomy Acute Pancreatitis).

[104]. Mortele KJ, Wiesner W, Intriere L, et al. A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. AJR Am J Roentgenol. 2004;183:1261–1265.

DISCUSSION

The present ISGPS consensus statement provides a conceptual framework and definition for post-pancreatectomy acute pancreatitis (PPAP), which incorporates biochemical, morphologic, and clinical criteria encountered specifically during the postoperative setting. Faced with the lack of uniformity on reporting PPAP, such a universal definition creates the basis to permit the assessment of treatments to either prevent or manage complications, to compare the incidence and the outcomes between centers, and to facilitate new multicentric studies that will confirm and/or improve the classification model.

In developing the classification system, consideration was given to each possible criterion previously evaluated in the reported literature as thoroughly as possible. The choice of the ideal biochemical criterion (the threshold for serum amylase activity) led to the greatest controversy and discussion. Because increases in serum amylase values are relatively common in the initial postoperative period, traditionally, amylase activity has been considered only an indirect sign of POPF or a minor postoperative epiphenomenon, with its actual clinical relevance early postoperative clinical setting questioned[16,18]. Conversely, recent evidence suggests that an early increase above normal in serum amylase values, even if not greater than three times the upper limits of normal, may represent the biochemical evidence of a postoperative inflammatory condition of the remnant pancreatic parenchyma[29,37,53,59,76,77,92]. The threshold in serum amylase we choose to accept is less than the traditionally used for acute pancreatitis (AP) because increased postoperative morbidity and radiologic findings consistent with PPAP have been reported even in patients with increased postoperative serum amylase levels under the threshold of three-times the upper limits of normal[34,59,61,91,94,96,96]. Furthermore, patients with PPAP have a reduced volume of pancreatic parenchyma in the range of 30-50% after partial pancreatectomy. Obstructive pancreatitis and chemotherapy-induced fibrosis are frequent changes reported in patients undergoing pancreatic surgery, possibly resulting in lower pancreatic enzyme values during a postoperative acute inflammatory process[109].

Substantial concerns regarding serum amylase activity measured only on POD 1 emerged because this time point was not highly specific, and other potential causes may contribute to such a biochemical finding[59,60,65]. This concern of the ISGPS has led to the suspicion that a single threshold value for serum amylase activity does not correctly depict an abnormality in the postoperative context. By contrast, the dynamic appraisal of the temporal trend in serum amylase values has revealed the highest peak on POD 1 and a subsequent, gradual decrease from POD 2 to normalization on POD 3-5[1,59]. This temporal trend in serum amylase activity appears even more striking in patients with radiologic features of PPAP[59,61]. Moreover, recent evidence has highlighted that the presence of a single altered serum amylase value is not associated with increased postoperative complications. In contrast, its sustained increase is associated with greater overall, as well as severe early morbidity[96]. Therefore, the presence of a sustained postoperative hyperamylasemia (POH) as measured on at least two consecutive days in the first 48 hours after surgery may allow the clinician to more accurately identify those with a pancreatic inflammatory process, possibly excluding those with single and nonspecific increases in serum amylase levels[96].To date, most of the papers published on PPAP have taken into account serum amylase activity[18,59–61,77,91,94,96]. For this reason, the current definition suggests this criterion for the POH definition. Nevertheless, some papers have also reported serum lipase as a diagnostic parameter[34,56,110]. As serum amylase may not be routinely available at all centers, serum lipase may be considered, but further detailed evaluations are requested.

Because PPAP is a perioperative phenomenon identified by early routine laboratory test abnormalities that can subsequently evolve to definite morbidity, the word "initiation" was adopted in the consensus definition, and POD 3 was eventually targeted as relevant. The presence of a sustained POH that became clinically relevant, showing morphologic alterations on cross-sectional imaging, thereby acquired the features of a distinct postoperative complication, namely PPAP. As with acute pancreatitis, serum amylase activity can decrease before developing related complications, so serum amylase activity alone is therefore not suitable in staging the actual clinical burden of PPAP[60–62]. Just as amylase-rich fluid in drains does not properly define POPF alone, POH does not equal PPAP. Still, increased blood amylase levels reveal a prognostic implication, and patients presenting early with POH should be monitored closely compared to those without increased serum amylase levels.

Some centers have used elevated serum CRP levels for the prediction of PPAP severity[58,65,77]. Although higher CRP values are associated with increased morbidity, this is not a constant occurrence. CRP is a well-known prognostic marker but is not diagnostic or predictive of any specific condition[111]. Although the use of elevated serum CRP values has not been considered in this ISGPS definition of PPAP, it remains an important prognostic factor that could be regarded in a *prospective* management assessment. By contrast, the actual grading of PPAP is defined post hoc, determined only after the clinical course is completed.

Specific knowledge about the pathogenesis of PPAP is limited[92,112], and most assumptions are inferred from studies of AP[58,113]. Many of the pre- and intra-operative factors leading to pancreatic tissue inflammation/necrosis have been highlighted, and all refer to a normal and functional pancreatic parenchyma[44,48,62,77,91,114]. Nevertheless, factors involved in the occurrence of the worst clinical scenarios are still unknown[98]. Future studies addressing this topic would provide crucial guidance.

Because PPAP is an early event in the postoperative course, its prompt diagnosis and treatment might decrease the occurrence or the burden of subsequent morbidity, including local and systemic complications[65,91]. PPAP is frequently associated with early complications and rapidly evolving scenarios, especially in the most severe cases[96]. The early phase may manifest as the systemic inflammatory response syndrome (SIRS). Moreover, PPAP increases the risk for pancreas-specific complications, particularly POPF. PPAP has been identified as one of the strongest independent predictors of POPF. Such a close relationship had suggested that these entities are constantly part of a single process; however, cases of POPF without PPAP exist and vice-versa, therefore confirming only the coexistence of such different complications. As a result, three possible scenarios can be outlined: (1) PPAP exclusively, (2) POPF exclusively, and (3) PPAP and POPF occurring at the same time leading to a challenging diagnosis and possibly a mutual interaction more adversely affecting the clinical outcome than either alone[35,96,115].

Indeed, PPAP may also lead to other local complications especially peripancreatic collections[62,91] and PPH[76]. All patients developing severe morbidity showed concurrent complications[74]. Similarly, rare but extreme cases of post-pancreatectomy necrotizing pancreatitis[35,56,59,61] result in a complex clinical scenario, in which the highest degree of simultaneous complications (e.g., grade C PPAP, grade C POPF, grade C PPH, sepsis, and organ failure) determines the patient's outcome. Going forward, the early recognition of this process could influence clinical practice so that pathways of enhanced recovery after surgery (ERAS)[85], mitigation strategies[116], and protocols for management of the drains[37,70] might eventually be re-designed in these patients[65,70,84]. PPAP includes an extended spectrum of manifestations which one could speculate may eventually be related to the extent of involvement of the pancreatic parenchyma. PPAP may involve the pancreatic parenchyma predominately at the transection site or extend beyond that to the entire pancreatic remnant. Differences between partial pancreatoduodenectomy and distal (left-sided) pancreatectomy have been highlighted regarding PPAP[60,61,84]. Different anatomical and surgical features and the different postoperative burden between these two procedures might represent paramount factors. Future studies comparing the incidence, severity, and behavior of PPAP in different types of resections should be informative[98].

No study has yet defined or suggested any specific treatment or mitigation strategy for PPAP after pancreatic resection. A shared definition is necessary to design randomized controlled studies addressing specific treatments targeting PPAP, with the potential aim at reducing major morbidity after pancreatic surgery. In this context, facing the previous internationally accepted frameworks and definitions, the pancreas-specific morbidity (i.e., POPF, PPH, DGE, chyle leak) also if related to PPAP occurrence, should still be classified, reported, and approached following the previous ISGPS statements[22,27,71,72].

The first cross-sectional imaging evaluation should be performed in situations where there is a deteriorating clinical picture, usually between POD 5 and POD 15, in order to determine whether this is due to PPAP. Radiological examination is also required for other specific complications such as early PPH. Outside the proposed range of time, clinicians should be aware that the acquired images could be biased because the PPAP process may be at its very early or later phases, i.e., at the point of not being able to characterize the condition as PPAP properly. Moreover, a self-limiting process may show no radiologic alterations when already resolved [8,117]. The evidence acquired so far has adopted the Modified CT Severity Index[104] for acute pancreatitis, which currently appears to be the most reliable tool for evaluating the radiologic evidence of PPAP. Yet, no correlation between radiologic score and clinical severity has been investigated so far[59,61,77]. As with AP, the local findings are in continuous evolution, but their extent up to the point of pancreatic necrosis may not correlate directly with the early severity of clinical picture[8]. As recognition of and experience with PPAP grows, it may be necessary to revise the radiographic assessment and reporting of this clinical entity in the near future.

Subsequent events in the course of PPAP might alter its staging. For this reason, the final grading as already uniformly applied for other ISGPS definitions should be deferred until the complication has run its entire course. Many of these are properly accrued and recorded out to the point of 90-days postoperatively. Therefore, the ISGPS grading of PPAP refers to a retrospective assessment of the severity of the complication and not to a prospective treatment proposal. This consensus statement has limitations, which are essentially the consequence of the somewhat imperfect data available. Although we fully acknowledge the existing knowledge gaps, faced with the increasing literature growing on this topic, a universally accepted and shared definition is deemed necessary to foster prospective, comparable, and systematic studies on this topic[115]. Prospective cohort studies will be necessary to validate this definition. Therefore, using this ISGPS statement to standardize metrics, namely, by systematically measuring serum pancreatic enzymes in the first postoperative days and performing radiologic examinations at specific time points, the validity and the accuracy of such a definition will be tested.

The ISGPS maintains that the practice of sharing and comparing the outcomes of different surgical series using this definition and grading system of PPAP will provide great value. The presence of a consensus definition and grading system will serve as a foundation to open new perspectives in identifying diagnostic and prognostic criteria for PPAP and recognizing all the complications associated with this condition. Hopefully, treatments to decrease the occurrence or the burden of complications related directly to PPAP will then be established. The interchangeability of the enzymes will be determined from future studies exploring the role of serum lipase. Additional pre- and intra-operative data,[44,62,78,90] as well as other post-operative parameters[58], biochemical markers (e.g. CRP, serum lipase activity, U-TRP2[32,34,44,48,95]), and specific radiologic scores, will undoubtedly lead to better clarity this entity.

Chapter 4 - Hyperspectral imaging in pancreatic surgery: Variations of parenchymal parameters related to postoperative pancreatic fistula risk after pancreatoduodenectomy

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Unpubliched data

ABSTRACT

Introduction:

Intraoperative hemodynamic changes may be critical in developing pancreas-specific morbidity. However no evidence currently exists to support this hypothesis. Hyperspectral imaging (HSI) can quantify intraoperative hemodynamic parameters.

Aim:

To assess pancreatic HSI parameters over a pancreatoduodenectomy (PD) and their association with postoperative complications (e.g., postoperative pancreatic fistula – POPF, and postoperative serum hyperamylasemia - POH).

Methods:

Consecutive patients undergoing PD from 2020 to 2021 were included (n=66). HS images were captured at multiple standard surgical time points (T0-5). Oxygen saturation (StO2%), organ hemoglobin index (OHI), tissue water index (TWI), and near-infrared perfusion (NIR) were retrieved by means of an HSI camera (range: 500-995 nm) at different pancreatic sites: (1) body, (2) transected part (i.e., the isthmic area), and (3) head.

Results:

StO2%, NIR, and TWI decreased over time in all pancreatic segments compared to baseline (T5<T0, p<0.05). OHI significantly increased in all pancreatic sites, with a sharp peak during retroportal lamina dissection (T4>T0, p<0.05). Higher OHI values at the pancreatic body (OR 1.92, CI 1.03-3.55, p=0.038) and transected part (OR 2.01, CI 1.00-4.03, p=0.049) were risk factors for POPF development. Higher NIR at the transected part (OR 0.22, CI 0.11-0.41, p<0.001) and body (OR 0.18, CI 0.09-0.34, p<0.001), and higher TWI at the transected part (OR 0.18, CI 0.07-0.45, p<0.001) and body (OR 0.35, CI 0.17-0.70, p=0.003) were protective for POH occurrence.

Conclusion:

HSI can visualize changes in hemodynamic parameters of the remnant pancreatic parenchyma during a PD. Besides well-recognized pancreatic risk factors, HSI hemodynamic parameters were associated with POPF and POH occurrence. Such results may help to understand their pathogenesis and direct future research agendas.

INTRODUCTION

Pancreatoduodenectomy (PD) is a complex surgical procedure associated with considerable morbidity[66]. Specifically, postoperative pancreatic fistula (POPF) still represent the most harmful complication after PD, being the main catalyst for more detrimental postoperative outcomes[108,118]. Despite several surgical and perioperative management improvements, POPF rates remain high (up to 20%), even in high-volume centers worldwide[119].

Identifying risk factors and implementing preventative measures for POPF have been the focus of significant research over the last decades[120]. However, the exact mechanisms and pathophysiology of POPF are still poorly understood[121]. Notably, the intraoperative setting during which surgical trauma occurs has seldom been investigated, although considered the beginning - by definition - of the sequence of events leading from the initial surgical insult to the clinically relevant event. Indeed, whether the anastomotic construction poses the time zero in fistula physiology for PD, potential intraoperative drivers acting upon innate pancreatic and patient characteristics may influence the success of the anastomosis during the whole intraoperative period.

Recent studies have suggested intraoperative pancreatic manipulation, impaired blood supply, and pancreatic stump hypoperfusion to be critical in developing an inflammatory process of the pancreatic remnant[1,58,122,123], namely postpancreatectomy acute pancreatitis (PPAP), considered a key pathway leading to POPF[3]. However, physiological dynamic parameters of pancreatic tissue, such as perfusion, oxygenation, and water content, are yet to be untangled, and the ischemic cause of such pancreas-specific complications remains largely speculative.

Previous series have attempted to assess pancreatic perfusion based on fluorescence imaging, Doppler ultrasound, spectroscopy, or the surgeons' visual perception[122,124,125]. However, the need for exogenous dye, costs, and lack of standardized results have limited their implementation in clinical practice. Hyperspectral imaging (HSI) is an emerging non-invasive, non-ionizing, intraoperative hybrid imaging modality that combines optical imaging and spectroscopy to provide quantifiable diagnostic information on tissue perfusion and composition[126,127]. Given the potential of HSI to investigate and detect multiple biological phenomena, its intraoperative application could hypothetically provide early critical information on pancreatic tissue hemodynamics; however, its feasibility and benefits have never been tested in pancreatic surgery[128–130].

This study aims to assess HSI parameters of the pancreatic parenchyma over a pancreatoduodenectomy procedure and to evaluate whether pancreatic oxygenation, perfusion, water, and hemoglobin content might be associated with the occurrence of pancreas-specific complications.

METHODS

This prospective, single-centre, observational cohort study was approved by the local ethics committee (Comitato Etico delle Province di Verona e Rovigo, approval number 2758 CESC) and performed according to the Declaration of Helsinki and to the STrengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations[131].

Participants

Consecutive patients who were candidates for elective pancreatoduodenectomy (PD) at the Department of General and Pancreatic Surgery of the University of Verona (Italy) were prospectively included starting from September 2020 until June 2021 (n=66). All eligible patients provided written informed consent at the time of hospital admission.

Hyperspectral imaging

This study used a commercially available HSI camera (TIVITA®, Diaspective Vision GmbH, Germany), certified for contact-free intraoperative use in humans. The HSI camera used a push-broom scanning mechanism with a complementary metal oxide semiconductor (CMOS) image sensor, capable of capturing HS images in approximately 7 to 8 seconds with a spatial resolution of 640 by 476 pixels. Its spectral range was 500 to 1000 nm (ultraviolet to near-infrared) using 100 spectral bins uniformly sampled in 5 nm increments. Consequently, each HSI dimension was 640 by 476 by 100 (two spatial and one spectral dimension, named hypercube). Each image was taken at the camera's optimal focal distance (40-50 cm), designed to ensure sterility over the surgical field. The operating room lights were turned off during each acquisition to prevent illumination artifacts, and calibrated illumination was provided by the camera's 6-bulb 20 W Osram Halospot 70 Halogen lamp. Numerical values stored in the hypercube represented reflectance values at every pixel and each of the 100 wavelengths. The TIVITA® system has preset algorithms to calculate different tissue parameters, each calculated individually from different spectra parts. Included parameters were the oxygen saturation index (StO2%), accounting for the superficial microcirculation up to a depth of 1 mm; near-infrared (NIR) perfusion index reflecting deeper layers within the NIR spectrum with a penetration depth of 4 to 6 mm; the tissue water index (TWI) and organ hemoglobin index (OHI), which accounts for water and hemoglobin content in the observed region of interest. Besides indexes, the device manufacturer's software also produced a pseudo-color (RGB) image derived from each hypercube, subsequently used for annotations.

Image annotation

After image acquisition, each RGB image associated with each HSI acquisition was labeled by an experienced surgeon. Each image of the pancreas was annotated using three fixed different categories corresponding to three pancreatic sites (Figure 1):

(1) Body (corresponding to the pancreatic body/tail).

(2) Transected part (i.e., the isthmic pancreatic area where the pancreatic head is sharply transected from the pancreatic body, and

(3) Head (corresponding to the pancreatic head),

Regions in the image where the annotating surgeon could not confidently identify the tissue type, as well as surgical instruments or sutures, were not included. This mitigated the problem of extracting values using incorrect or highly uncertain annotations[132]. All annotations were performed using open-source image manipulator software (GIMP, GNU Image Manipulation Program, version 2.10). An annotation layer was associated with each tissue category, and the annotating surgeon manually demarcated regions in the image corresponding to the tissue category using GIMP's polygon selection tool. Final HSI tissue parameters (StO2, NIR, OHI, and TWI) were calculated as a median of all pixels in the specific area.

Surgical procedure and HSI acquisition time point

All pancreatic resections were performed according to previously described institutional techniques using an open approach[64,66]. HS images were captured during a pancreatoduodenectomy at multiple specific and critical time points (Figure 1). Specifically, the first picture was acquired at the beginning of the surgical procedure after midline laparotomy and gastrocolic ligament opening (time point 0 - T0) and before performing any invasive maneuver, possibly altering the pancreatic parenchyma characteristics (Figure 1). Further images were acquired 2 minutes after crucial standard surgical steps, namely division of Henle's trunk (time point 1 - T1), gastroduodenal artery division (time point 2 – T2), pancreatic hemostatic stitches, usually placed at the superior and inferior pancreatic margin before pancreas division (time point 3 – T3), and retroportal lamina dissection (time point 4 – T4). The last time point (time point 5 – T5) differed according to the pancreatic sites, namely after pancreaticojejunostomy fashioning for (2) the transected part and (1) body of the pancreas, and to the resected specimen for the pancreatic (3) head. The pancreatic head, being progressively devascularized during PD in order to be resected, was included as a reference for progressive ischemia.

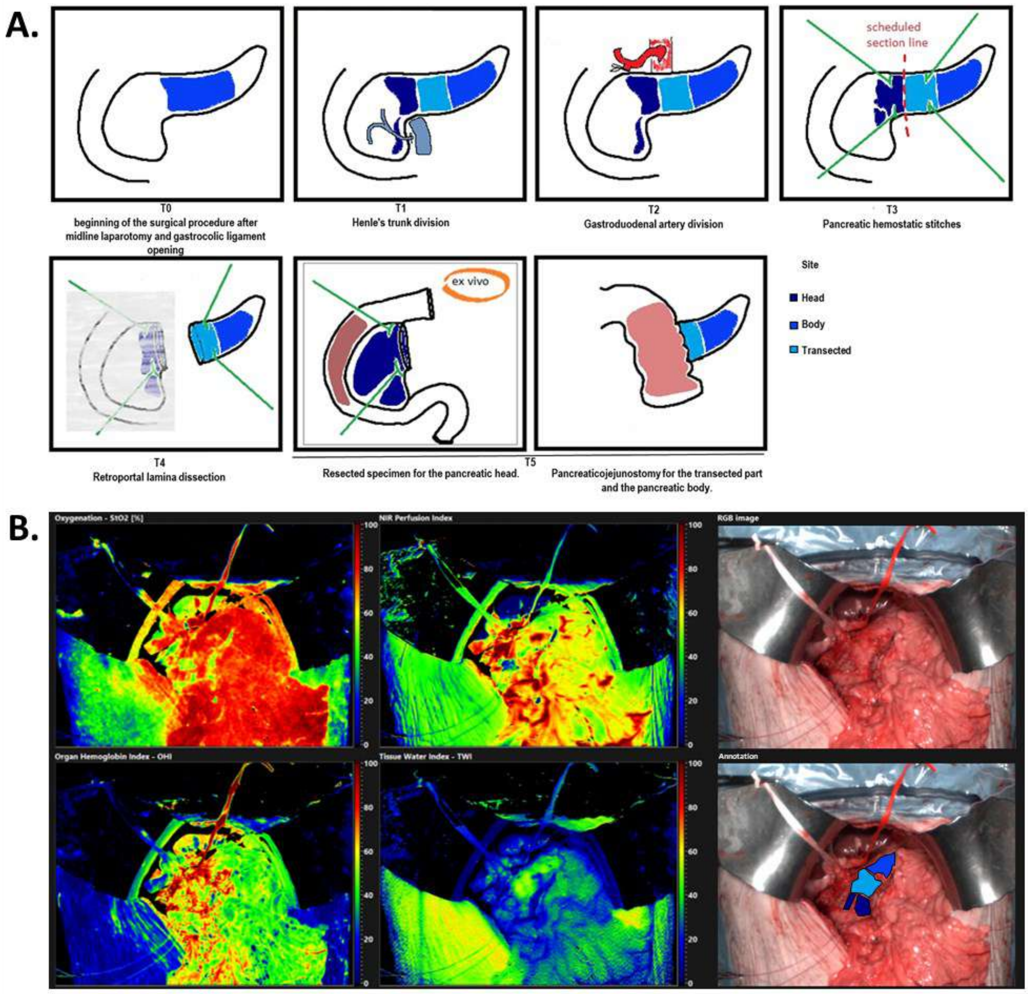

Figure 1. A - Graphical representation of the HSI acquisition time points and annotations of the different pancreatic segments at each time points. B – Example of the photos acquired with the hyperspectral camera. In oreder of appearance in the first two column: oxygen saturation index (StO2%); near-infrared (NIR) perfusion index; organ hemoglobin index (OHI) and tissue water index (TWI). In the third column: the pseudo-color RGB (Red-Green-Blue) images, and its annotation.

Clinical data

Demographics, intraoperative data, and postoperative outcomes were collected. Preoperative characteristics included age (years), gender, BMI [kg/m^2], comorbidities, and neoadjuvant therapy use.

Intraoperative variables included pancreatic texture (based on the manual palpation of experienced pancreatic surgeons), pancreatic duct diameter (measured using a sterile disposable ruler), pathology (considering histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis as having a "high-risk pathology"), and estimated blood loss (EBL)[133]. Notably, these variables are included in the Fistula Risk Score (FRS)[69], widely used as a predictive score for POPF and recently emerged as a suitable tool for predicting postoperative serum hyperamylasemia (POH), the biochemical diagnostic criteria for PPAP[6]. Externalized pancreatic stents (PankreaPlus polyvinyl catheter; Peter Pflugbeil Gmbh Medizinische Instrumente) were used as a specific mitigation strategy in all patients at high risk for POPF and in selected cases when the risk was estimated as moderate according to FRS[69]. Neither sealants nor patches were used in any circumstance, nor were prophylactic octreotide or steroids ever administered as mitigation strategies. Surgical drains were placed in all patients apart from those deemed at low and negligible risk according to FRS[69], unless for other surgical reasons (e.g., high-risk hepaticojejunostomy, vascular resections). A previously published protocol was used for drain management with a selective placement and early removal policy[134,135].

Outcome metrics

The primary endpoint was to assess changes in HSI parameters of the pancreatic parenchyma over a stratified pancreatoduodenectomy procedure according to specific pancreatic sites.

The secondary endpoints were to assess the impact of intraoperative HIS parameters on surgical outcomes and to evaluate whether HSI parameters at specific pancreatic sites might be associated with the occurrence of pancreas-specific complications, including POPF and POH. PPAP[3], postpancreatectomy hemorrhage (PPH)[136], and delayed gastric emptying (DGE)[137] were not considered due to the extremely low incidence (n<10 events) recorded in this series that prevented reliable analysis.

Pancreas-specific morbidity, such as POPF, PPH, DGE, and POH-PPAP, were defined according to the International Study Group for Pancreatic Surgery (ISGPS)[3,118,136,137]. POH was characterized by a sustained increase in serum amylase activity greater than the institutional upper limit of normal (standard range: 10–52 U/L), persisting within at least the first 48 hours postoperatively (POD 1-2). Postoperative complications were scored according to the Clavien-Dindo classification[74] over the course of 90 days. Only an unplanned need for intensive care was defined as an intensive care unit (ICU) stay. Mortality was defined as postoperative death recorded up to 90 days postoperatively.

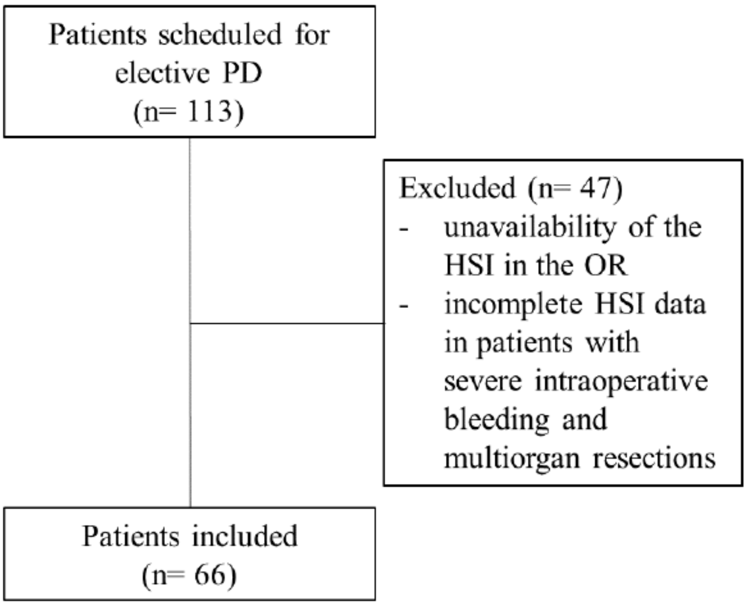

Figure 2: Strobe flowchart.

Statistical analysis

Continuous variables are expressed as medians and interquartile range (IQR) and compared with the Mann-Whitney *U* test. Categorical variables are presented as absolute numbers with percentages, and associations were tested using the chi-square test or Fisher's exact test. The issue of unmeasured values in some covariates (due to a reasonably "missing at random" (MAR) mechanism[138]) was handled by using the multiple imputation method, and final estimates of the coefficients and standard errors were obtained by pooling model results on ten imputed datasets[139]. A linear mixed model (estimated using REML and nloptwrap optimizer) was used to analyze HSI indexes (StO2, NIR, OHI, and TWI) with time. The model included patients as a random effect, while the model's intercept corresponded to time = T0. Standardized parameters were obtained by fitting the model on a standardized version of the dataset. Results were reported as 95% Confidence Intervals (CIs) and p-values, computed using a Wald t-distribution approximation. Univariable and multivariable logistic regression (variables with $p<0.05$ at the univariable analysis were included in the multivariable model) were used to identify independently associated factors with pancreas-specific complications (i.e., POPF and POH). To account for the HSI indexes' variance over time, HSI indexes were entered in the model as a sum of all time point values, assuming a linear relationship between endpoints and time. These results were presented as odds ratio (OR) and 95% confidence interval (CI). All these analyses were repeated for each pancreatic tissue category remaining after the surgical procedure, namely (2) transected part and (3) body. All statistical tests were two-tailed, and a 5% significance level was adopted. For analysis of repeated measures, a Benjamini-Hochberg correction was applied. All analyses were computed using the open-source R software (v4.0.2).

RESULTS:

A total of 66 PDs were included in the analysis as reported in Figure 2. Overall demographic, surgical, HSI, and outcome variables were displayed in Table 1. Figure 3 displayed variations of HSI parameters along the surgical procedure stratified according to pancreatic sites.

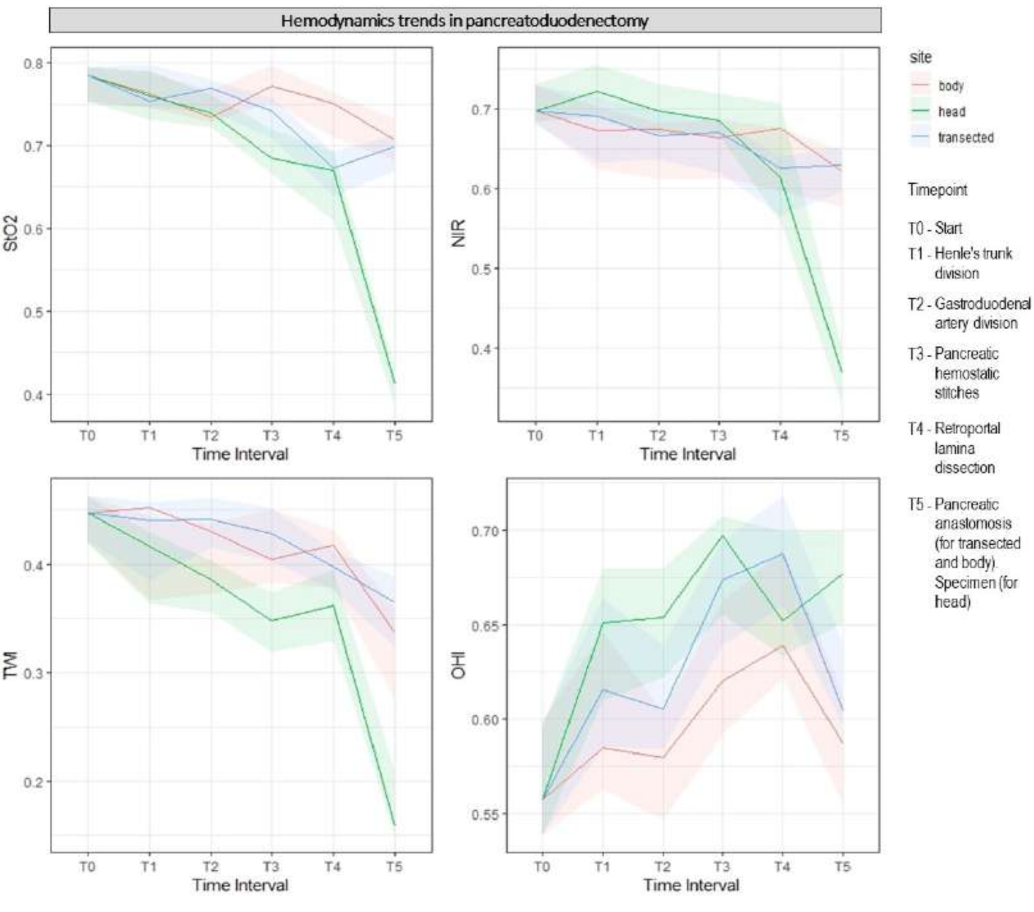

Figure 3. Overall trends of HSI indexes during a PD in the different pancratic sites.

Table 1 – Patients characteristics		Overall (n= 66)
Sex	Male	35 (52%)
	Female	31 (47%)
Age (years, median, IQR)		66 (60-72)
BMI (, Kg/m^2, median, IQR)		24 (21 - 26)
Smoker		17 (25.8%)
Alcohol abuse		3 (4.5%)
Diabetes		13 (19.7%)
Neoadjuvant therapy		34 (51.5%)
Pancreatic gland texture	Soft	32 (48.5%)
	Hard	34 (51.5%)
FRS zones	Negligible (0)	3 (4.5%)
	Low (1 -2)	15 (22.7%)
	Moderate (3-6)	40 (60.6%)
	High (7-10)	8 (12.1%)
EBL (mL, median, IQR)		500 (372 - 925)
Main pancreatic duct diameter (mm, median, IQR)		4 (3-5)
Operative time (min, median, IQR)		391 (307 - 494)
Vascular resection		9 (13.6%)
Pancreatic transanastomotic stent		19 (28.8%)
High-risk pathological diagnosis		24 (36.4%)
POH		19 (28.8%)
CR-PPAP (BC grades)		4 (6%)
Biochemical leak		6 (9.1%)
CR-POPF (total, n.)		10 (15.2%)
grade	B	9 (13.6%)
	C	1 (1.5%)
Organ space infection		16 (24.2%)
CR-PPH (BC grades)		3 (4.5%)
CR-DGE (BC grades)		4 (6%)
Mortality		2 (3%)
LHS (days, median, IQR)		10 (7 – 16)
Clavien Dindo Classification	Uneventful	29 (43.9%)
	I	6 (9.1%)
	II	20 (30.3%)
	IIIa	3 (4.5%)
	≥ III b	8 (12.1%)

Abbreviations: BMI: body mass index, EBL: estimated blood loss, FRS: fistula risk score, POPF: Postoperative Pancreatic Fistula; PPH: post pancreatectomy hemorrhage, DGE: delayed gastric emptying, LHS: length of hospital stay, ICU: intensive care unit; POD: postoperative day, IQR: interquartile range, High-risk pathological diagnosis: histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis,
POH: Postoperative serum hyperamylasemia [serum amylase activity greater than the institutional upper limit of normal (52 U/l), persisting within at least the first 48 hours postoperatively (postoperative day – POD– 1 and 2)].

The variance of HSI indexes in the pancreatic body during PD

StO2. Compared to T0, StO2 decreased significantly at T4 (beta = -0.06, 95% CI [-0.11, -0.02], p = 0.005) and T5 (beta = -0.09, 95% CI [-0.14, -0.05], p<.001, Std. beta = -0.55).

The models showed 38% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 3%.

NIR. NIR perfusion of the pancreatic body decreased significantly at T5 (beta = -0.06, 95% CI [-0.10, -0.02], p = 0.004, Std. beta = -0.33). The models showed 56% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) <1%.

OHI. The effect of time on OHI was statistically significant at several time points. Compared to starting levels (T0), OHI significantly increased at T1 (beta = 0.07, 95% CI [0.04, 0.11], p<.001, Std. beta = 0.54), T3 (beta = 0.09, 95% CI [0.05, 0.12], p<.001, Std. beta = 0.66), T4 (beta = 0.11, 95% CI [0.07, 0.14], p<.001, Std. beta = 0.79), and T5 (beta = 0.05, 95% CI [0.01, 0.08], p = 0.007, Std. beta = 0.35). The models showed 47% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 7%.

TWI. Time does not affect TWI over most time points. TWI showed alternate trends over the procedure but significantly decreased at T5 compared to T0 (beta = -0.04, 95% CI [-0.08, -4.56e-03], p = 0.027; Std. beta = -0.32). The models showed 30% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 3%.

The variance of HSI indexes in the transected pancreas during PD

During the PD procedure, there was a significant effect of time on all HSI indexes estimated in the transected pancreas (pancreatic stump).

StO2. StO2 of the transected pancreas significantly decreased at T1 (beta = -0.08, 95% CI [-0.12, -0.03], p = 0.001; Std. beta = -0.47), T3 (beta = -0.08, 95% CI [-0.13, -0.04], p<.001; Std. beta = -0.50), T4 (beta = -0.09, 95% CI [-0.13, -0.04], p<.001; Std. beta = -0.53), and T5 (beta = -0.08, 95% CI [-0.13, -0.03], p< .001; Std. beta = -0.49) compared to baseline values (T0). The models showed 33% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 4%.

NIR. The effect of time on NIR in the transected pancreas was statistically significant and negative at T4 (beta = -0.07, 95% CI [-0.11, -0.03], p<.001; Std. beta = -0.44), and T5 (beta = -0.07, 95% CI [-0.11, -0.03], p<.001; Std. beta = -0.47). The models showed 49% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 3%.

OHI. Compared to baseline, OHI significantly increased at T3 (beta = 0.09, 95% CI [0.06, 0.12], p<.001; Std. beta = 0.77), T4 (beta = 0.10, 95% CI [0.07, 0.13], p<.001; Std.

beta = 0.79), and T5 (beta = 0.03, 95% CI [1.38e-03, 0.06], p = 0.040; Std. beta = 0.26). The models showed 50% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 9%.

TWI: TWI significantly varied in the transected pancreas with a fluctuating trend. The effect of time on TWI was statistically significant and positive at T1 (beta = 0.03, 95% CI [1.93e-04, 0.06], p = 0.049; Std. beta = 0.28) while negative at T5 (beta = -0.06, 95% CI [-0.09, -0.03], p<.001; Std. beta = -0.51). The models showed 36% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 7%.

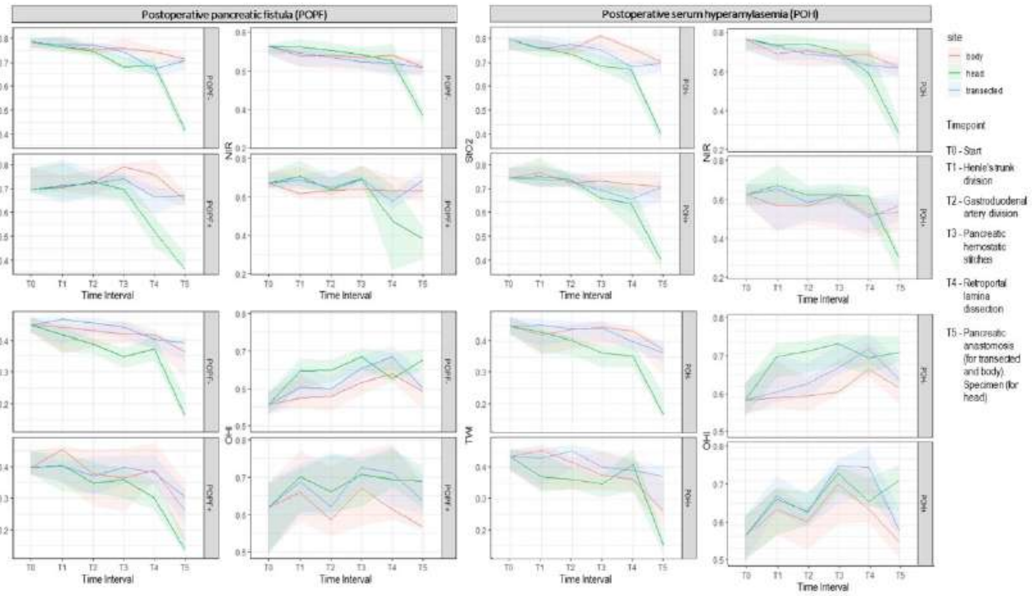

Figure 4. Trends of HSI indexes during a PD in the different pancratic sites stratified according to Postopertive pancreatic fistula (POPF) and postoperative hyperamylasemia (POH) occurrence.

The variance of HSI indexes in the pancreatic head during PD

StO2. StO2 decreased progressively and significantly from T1 (beta = -0.06, 95% CI [-0.10, -0.03], p<0.001) to T5 (beta = -0.29, 95% CI [-0.33, -0.26], p<0.001). The models showed 57% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 39%.

NIR. NIR perfusion decreased significantly at T5 (beta = -0.25, 95% CI [-0.29, -0.21], p< 0.001). The models showed 56% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 32%.

OHI. Compared to starting levels (T0), OHI significantly increased from T2 (beta = 0.07, 95% CI [0.05, 0.10], p<0.001) to T5 (beta = 0.09, 95% CI [0.06, 0.12], p<0.001), through T3 (beta = 0.09, 95% CI [0.06, 0.12], t(388) = 6.25, p<0.001) and T4 (beta = 0.09, 95% CI

[0.06, 0.12], p<0.001). The models showed 38% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 12%.

TWI. TWI showed alternate trends but, compared to T0, significantly decreased at T2 (beta = -0.04, 95% CI [-0.07, -7.61e-04], p = 0.045) and T5 (beta = -0.20, 95% CI [-0.24, -0.16], p<0.001). The models showed 44% of total explanatory power (conditional R2), and the part related to the fixed effects alone (marginal R2) was 27%.

Model results, stratified according to each parameter, including intercepts, and the effect of time at each time point, are reported in supplementary Tables 1, 2, and 3.

Table 2 – Univariate and multivariate analysis of predictors of POPF during a pancreaticoduodenectomy.

	Univariable Analysis POPF			Multivariable Analysis		
	OR	**CI 95%**	**P value**	**OR**	**CI 95%**	**P value**
Pancreatic body[1]						
StO2	0.41	0.22-0.75	0.004	0.64	0.32-1.29	0.211
NIR	0.90	0.59-1.40	0.618		-	
TWI	0.54	0.29-0.98	0.041	0.64	0.32-1.29	0.215
OHI	1.92	1.16-3.14	0.010	1.92	1.03-3.55	**0.038**
Sex (male)	1.15	0.66-2.00	0.610		-	
BMI	1.10	1.03-1.17	0.006	1.10	1.02-1.19	**0.013**
Texture (soft)	5.33	2.82-10.85	<0.001	3.98	1.90-8.83	**<0.001**
High-risk pathological diagnosis	3.17	1.81-5.63	<0.001	2.19	1.11-4.38	**0.025**
MPD diameter	0.79	0.66-0.93	0.006	0.96	0.80-1.15	0.687
Transected pancreas[2]						
StO2	0.78	0.45-1.37	0.386		-	
NIR	1.24	0.78-2.08,	0.381		-	
TWI	0.25	0.12-0.50	0.001	0.21	0.08-0.49	**<0.001**
OHI	2.38	1.35-4.23	0.003	2.01	1.00-4.03,	**0.049**
Sex (male)	1.15	0.66-2.00	0.610		-	
BMI	1.10	1.03-1.17	0.006	1.10	1.02-1.18	**0.014**
Texture (soft)	5.33	2.82-10.85	<0.001	5.15	2.37-12.01	**0.001**
High-risk pathological diagnosis	3.17	1.81-5.63	<0.001	1.89	0.92-3.90	0.084
MPD diameter	0.79	0.66-0.93	0.006	0.96	0.79-1.14	0.625

[1]. AIC = 299.1, C-statistic = 0.777, H&L = Chi-sq(8) 49.55 (p<0.001)
[2]. AIC = 286.2, C-statistic = 0.786, H&L = Chi-sq(8) 83.47 (p<0.001)

Abbreviations: POPF: Postoperative Pancreatic Fistula; StO2%: saturation of oxygen; NIR: near-infrared perfusion index; OHI: total hemoglobin index; TWI: tissue water index.

Predictors of POPF: HSI indexes and other variables

POPF occurred in 10 patients (15.2%). Of the POPF patients, nine (13.6%) had grade B, and one (1.5%) had grade C. Table 2 shows the results of univariate and multivariable analyses of the predictors of POPF stratified according to pancreatic sites including both HSI variables and known POPF risk factors. At multivariable analysis, higher OHI values at the pancreatic body (OR 1.92, CI 1.03-3.55, p = 0.038) and at the transected pancreatic stump (OR 2.01, CI 1.00-4.03, p = 0.049) resulted as risk factors for POPF development, while higher TWI values (OR 0.21, CI 0.08-0.49, p<0.001) were protective only in the transected pancreas (Figure 4). In addition, higher BMI and soft pancreatic texture were confirmed independent risk factors for POPF at both sites.

Table 3 – Univariate and multivariate analysis of predictors of POH during a pancreaticoduodenectomy.

	Univariable Analysis POH			Multivariable Analysis		
	OR	**CI 95%**	**P value**	**OR**	**CI 95%**	**P value**
Pancreatic body[1]						
StO2	1.72	1.06-2.84	0.032	1.17	0.55-2.57	0.689
NIR	0.10	0.06-0.17	<0.001	0.18	0.09-0.34	**<0.001**
TWI	0.39	0.24-0.63	<0.001	0.35	0.17-0.70	**0.003**
OHI	0.69	0.43-1.06	0.100		**-**	
Sex (male)	1.02	0.66-1.58	0.919		-	
BMI	1.05	0.99-1.11	0.074		**-**	
Texture (soft)	6.62	4.02-11.23	<0.001	2.23	1.08-4.68	**0.032**
High risk pathological diagnosis	10.36	6.32-17.39	<0.001	5.97	3.20-11.41	**0.001**
MPD diameter	0.59	0.50-0.69	<0.001	0.66	0.53-0.82	**<0.001**
Transected pancreas[2]						
StO2	1.58	1.00-2.54	0.054		-	
NIR	0.11	0.06-0.18	<0.001	0.22	0.11-0.41	**<0.001**
TWI	0.49	0.28-0.86	0.012	0.18	0.07-0.45	**<0.001**
OHI	0.53	0.32-0.85	0.110		**-**	
Sex (male)	1.02	0.66-1.58	0.919		-	
BMI	1.05	0.99-1.11	0.074		**-**	
Texture (soft)	6.62	4.02-11.23	<0.001	2.74	1.27-6.10	**0.011**
High risk pathological diagnosis	10.36	6.32-17.39	<0.001	6.24	3.29-12.14	**<0.001**
MPD diameter	0.59	0.50-0.69	<0.001	0.60	0.47-0.75	**<0.001**

[1]. AIC = 288.1, C-statistic = 0.891, H&L = Chi-sq(8) 26.80 (p=0.001)
[2]. AIC = 279.3, C-statistic = 0.903, H&L = Chi-sq(8) 67.88 (p<0.001)

Abbreviations: POH: Postoperative serum hyperamylasemia; StO2%: saturation of oxygen; NIR: near-infrared perfusion index; OHI: total hemoglobin index; TWI: tissue water index.

Predictors of POH: HSI indexes and other variables

A total of 19 patients (28.8%) developed POH, and four subsequently progressed towards a clinically relevant PPAP (6%). As reported in Table 3, at multivariable analysis, higher NIR values at the transected pancreas (OR 0.22, CI 0.11-0.41, $p<0.001$) and at the pancreatic body (OR 0.18, CI 0.09-0.34, $p<0.001$), as well as higher TWI values at the transected pancreas (OR 0.18, CI 0.07-0.45, $p<0.001$) and at the pancreatic body (OR 0.35, CI 0.17-0.70, $p = 0.003$) were protective for POH occurrence (Figure 4). In addition, a smaller main pancreatic duct diameter, soft pancreatic texture, and high-risk pathological diagnoses were also confirmed as independent predictors of POH.

DISCUSSION

This study first explored quantifiable changes in physiological dynamic parameters of pancreatic tissue during a pancreatoduodenectomy using hyperspectral imaging (HSI). The entire pancreatic parenchyma showed significant changes in HSI hemodynamic parameters during the surgical procedure. Specifically, pancreatic oxygenation (StO2), perfusion (NIR), and water content (TWI) tended to decrease over time, while hemoglobin content (OHI) showed the opposite behavior, with a significant increase. In this scenario, besides markers of normal pancreatic parenchyma, HSI hemodynamic parameters were associated with POPF and POH occurrence. Such results may help to understand their genesis and direct future mitigation strategies.

Prevention of postoperative pancreatic morbidity has been a central topic of discussion in recent decades[31,120,140]. Several interacting parameters have been associated with postpancreatectomy morbidity[69,141,142]. Their coding into valid clinical risk scores and subsequent application have led to significant improvements in the care of postpancreatoduodenectomy patients but have failed to decisively drop the incidence of pancreas-specific complications[108,119]. These challenges suggest unexamined mechanisms are involved in the progression from risk factors to clinical events[6, 24]. Specifically, there is a growing trend of thought that changes in intraoperative hemodynamic parameters of the remnant pancreatic parenchyma, including perfusion, congestion, and hydration, could well influence or be the first signs of dire postoperative outcomes[58,122,124,143].

This study first investigates and quantifies the trend of hemodynamic parameters within the pancreatic parenchyma during a whole PD procedure using a promising non-invasive intraoperative optical technology such as HSI. This analysis offers new perspectives by showing how pancreatic hemodynamic parameters change during the surgical procedure, providing valuable food for thought.

The time-trend analysis evinced an overall decrease in pancreatic perfusion parameters (StO2 and NIR) throughout the entire PD procedure, together with a sharp increase in pancreatic hemoglobin content (OHI), peaking during retroportal lamina dissection. Although this trend is not unexpected for the pancreatic head, which undergoes a gradual vascular deprivation during a PD, it obtains valuable information for the remnant pancreatic parenchyma. Comparing these results with previous experimental models of venous and arterial occlusion[144,145], such changes in HSI parameters could be consistent with venous parenchymal congestion, even though there is no clear evidence excluding a mixed model in which arterial ischemia is also present. Hemoglobin levels increase significantly when arterial inflow is still present; however, venous outflow is precluded or limited. Notably, oxygenation (StO2 and NIR) also decreases to a lower plateau during venous congestion. These results can be critical and potentially practice-changing, but validation studies are required before modifying surgical plans. Indeed, although this study provides initial insight into critical time points during a PD, the hemodynamic repercussions of pancreatic vascular manipulation or different surgical techniques are still largely unexplored. The timing and type of intraoperative intervention or surgical approaches may be debated and should ideally be tested within the constraints of randomized trials.

Additionally, despite being significant, less than 10% of surgical time points alone explained the variance in HSI parameters in the remnant pancreas. Accordingly, while an overall trend was highlighted, significant heterogeneity between patients was observed, suggesting unmeasured factors were relevant in intraoperative hemodynamic changes. Due to the limited sample size, the temporal trend analysis was not further stratified, and future analyses should evaluate the influence of preoperative predictors on HSI parameter trends.

Although other unmeasured factors besides surgical steps could affect variations in physiological dynamic pancreatic parameters, the question remains whether these hemodynamic changes are associated with poor postoperative outcomes or act through association with other pancreatic-specific predictors. Indeed, recent studies have labeled hemodynamic changes as grounds for developing an acute inflammatory process of the pancreatic remnant, namely PPAP[3], considered a critical pathway underlying POPF[146,147]. In addition, postoperative serum hyperamylasemia (POH) has been identified as the first biochemical expression of such processes and one of the earliest alterations associated with worse postoperative outcomes[5]. Predictors of POH and POPF were therefore assessed, including both HSI parameters and known risk factors for these complications. This study confirms previous independent predictors of both POH and POPF mostly related to a functioning pancreatic parenchyma[6,69,70,119]. In addition to previous literature, some HSI parameters have emerged as POH and POPF risk factors. Higher tissue hemoglobin content at the pancreatic body and transected pancreatic stump resulted as risk factors for POPF development, while a higher tissue water index was protective in the transected pancreas.

Likewise, higher tissue water content and NIR perfusion at the pancreatic stump and body were protective against POH occurrence, confirming that adequate inflow, outflow, and hydration are critical to maintaining pancreatic tissue homeostasis. These results can help explain the physiopathology behind such pancreas-specific complications and eventually identify situations where changes in HSI parameters may have a synergistic effect on other endogenous risk factors. Still, those results should be considered carefully due to the technical limitations of intraoperative HSI data retrieval and the limited sample size of POH and POPF populations that may have artificially inflated performance statistics and prevented the detection of predictive cut-offs. Indeed, the performed regression accounted for the variance of HSI parameters over time, as it is becoming evident that it is not necessarily the absolute values of oxygenation, hemoglobin or water content assessed at a single intraoperative time point, but rather their kinetic trends that can help guide fistula or POH prognostication.

Facing such evidence, identifying patients with known prognostic factors susceptible to intraoperative variations of hemodynamic parameters could become crucial to apply or withhold individual mitigation strategies but require further investigations. Hemodynamic changes of the pancreatic parenchyma that begin during the surgical procedure, before the manifestation of early postoperative serological changes, symptoms, or clinically relevant complications, could eventually be considered "preclinical morbidity." Consequently, they may represent an early indicator of the surgical burden that can enhance validated intraoperative risk stratification scores[69,140,148] to set appropriate management strategies and targeted monitoring before subsequent clinical morbidity occurs. As the field is now embracing a dynamic model[6,149] in predicting postoperative morbidity, even if this study considers only the snapshot of the surgical procedure, the intraoperative setting can provide many "real-time" insights into the potential of anastomotic failure besides HSI hemodynamic parameters, including blood loss, tissue integrity, and confidence with the construction of the pancreatic anastomosis[143,150–152]. Further studies are necessary to validate if HSI parameters could implement morbidity forecasting.

Still, whether HSI parameters could be fully modifiable or rather partially fixed procedure-related risk factors is yet to be assessed. Indeed, changes in hemodynamic parameters involved the entire pancreatic remnant, questioning whether an ideal pancreatic transection line could be retrieved. Interestingly, proper pancreatic hydration seems to play a major role, also representing one of the more accessible manipulable parameters. However, this finding does not promote unregulated fluid overload but otherwise confirms previous evidence for balanced fluid therapy algorithms to maintain proper parenchyma hydration[78,123,153,154]. In this context, HSI might be a non-invasive useful extension for intraoperative monitoring that can be furthered in the perioperative period, as previously reported[155].

This study has several limitations. Despite the prospective nature of this study, the limited sample size has precluded a further stratified analysis of HSI parameter trends to identify possible predictors. However, based on the assessment of HSI parameters on clinical effects, it was found that the pancreatic gland is susceptible to both biological modifiers and hemodynamic parameters, suggesting a new avenue for translational research into the underlying mechanisms of pancreas-specific complications.

Moreover, large variability was observed in the retrieved HSI indexes among the included patients. Besides pancreatic, patient, and procedure-related characteristics, HSI technical issues should be reported as plausible explanations. These involved uncertain annotations, residual ambient light, and motion artifacts[132]. Notably, data quality is critical in implementing optical imaging technologies in surgical practice[156]. Different pancreatic segments are difficult to annotate as they are rarely clearly delineated and often hidden under adjacent tissues, surgical instrumentation, or intraoperative abdominal fluids. To minimize these biases, HS images were acquired and annotated using a standard methodology and adhering to regular intraoperative protocols. With technological advances, future series should validate the findings of the present analysis by including patients from multiple centers performing different intraoperative protocols and using different HSI acquisition systems. While being a limitation of this study, the need for larger cohorts highlights the difficulties of acquiring, storing, and analyzing HSI data[157]. However, differently from other intraoperative techniques (i.e., NIR fluorescence[124]), HSI allowed for quantifiable and reproducible assessments of hemodynamic parameters. Indeed, *in vivo* remission spectrometry cannot provide the actual tissue hemoglobin concentration or the exact perfusion, but provided surrogate indexes. However, the accuracy of HIS indexes to quantify perfusion variation within the gastrointestinal tract has been previously validated with *in vivo* experiments using robust biomarkers[144,145,158]. Optical imaging technologies, especially HSI, being contactless and non-invasive have minimal impact on the surgical workflow; however, in critical intraoperative conditions, multiple HSI acquisitions are not negligible. For this reason, images at all time points were not captured from patients with severe intraoperative bleeding or multiorgan resections, then further excluded. Consequently, the final cohort may not be fully representative of the entire population of patients undergoing pancreatoduodenectomy.

CONCLUSION

This is the first study using HSI to visualize changes in hemodynamic parameters of the remnant pancreatic parenchyma in patients undergoing pancreatoduodenectomy. Besides well-recognized inherent pancreatic risk factors, variations in HSI hemodynamic parameters were associated with POPF and POH occurrence.

Future studies should be directed towards investigating the interplay between variations in HSI hemodynamic parameters and morbidity occurrence to guide surgical techniques and target tailored mitigation strategies.

Chapter 5 - Acute pancreatitis following Pancreatoduodenectomy: a prospective study of diffusion-weighted magnetic resonance imaging, serum biomarkers, and clinical features

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Accepted manuscript Surgery 2023.

ABSTRACT

Background

Postpancreatectomy acute pancreatitis (PPAP) is challenging to diagnose and poorly characterized in its early phases, yet it represents the ideal target for novel therapeutic opportunities possibly gleaned from medical acute pancreatitis (AP). This study aims to systematically investigate early radiologic, biochemical, and clinical features of PPAP.

Methods

Prospective observational study of patients undergoing pancreatoduodenectomy from September 2019 to January 2021. Diffusion-weighted magnetic resonance imaging (DW-MRI) was performed on postoperative day (POD) 3. Serum pancreatic amylase and lipase were assessed daily until POD 5. Postoperative serum hyperamylasemia (POH) and PPAP were defined based on the International Study Group for Pancreatic Surgery (ISGPS) definition.

Results

A total of 65 patients were enrolled according to the sample size calculation. Patients with POH and PPAP had significantly lower apparent diffusion coefficient (ADC) values at DW-MRI but no macroscopic features consistent with acute pancreatitis (AP). Subsequently, 21 patients (32.3%) underwent computed tomography imaging for clinical worsening, and six had radiologic features of AP. All these latter patients had POH and worse outcomes, characterized by local (postoperative pancreatic fistula: 83%) and systemic morbidity (Sepsis: 66.7%). The POH incidence was 21.5% (n=14), while PPAP occurred in 6 patients (9.2%), with 4 grade B (6.1%) and 2 grade C (3%).

Conclusions

PPAP is characterized by early serum hyperamylasemia and hyperlipasemia. Although pancreatic changes may appear at POD3 DW-MRI, its standard use has no impact on postoperative management. Macroscopic radiologic features appear later and correlate with worse clinical scenarios. This paper paves the ground for the inclusion of PPAP in the spectrum of AP, promoting the transfer of treatment strategies for AP into managing PPAP.

INTRODUCTION

Acute Pancreatitis (AP) is a potentially lethal disease characterized by local injury and potentially systemic morbidity[8]. In recent years, an acute inflammatory process of the pancreatic parenchyma has also been described as occurring after pancreatic surgery and named Postpancreatectomy Acute Pancreatitis (PPAP)[3].

Although the actual incidence of PPAP is yet to be elucidated, its occurrence can critically impact outcomes after pancreatoduodenectomy[3,159]. AP and PPAP share pathological findings on a continuum between parenchymal inflammation and necrosis[3,8], but PPAP may display features different from AP due to peculiar parenchyma involvement and aetiology[159]. Facing this background, the definition of PPAP has been only recently outlined by the International Study Group for Pancreatic Surgery (ISGPS), differing slightly from the Revised Atlanta Criteria definition of AP[3,8]. Although diagnosing PPAP can be challenging, it can be crucial to avoid additional morbidity[96,160]. However, due to the early onset in the perioperative period, the actual spectrum of its early phases has not been systematically explored yet. Moreover, the recent ISGPS definition has left some unsolved issues, including the need to investigate the role of lipases as a diagnostic criterion, the actual spectrum of PPAP complications, the proper timing for postoperative radiological evaluation, and the preferred imaging modality for PPAP assessment.

Magnetic Resonance Imaging (MRI) has been proven to accurately and simultaneously depict earlier morphologic abnormalities of pancreatic duct and parenchyma during AP[161,162]. In particular, diffusion-weighted (DW) sequences are reported to be highly sensitive to interstitial oedema[163]. Since the pathophysiological mechanisms possibly leading to PPAP include microvascular impairment induced by surgical trauma as a critical event[113], perfusion alterations and changes in capillary permeability may significantly impact the early stages of the disease[113]. Intravoxel incoherent motion (IVIM) MRI sequences have also recently emerged as a key tool to provide quantitative estimates of physiological parameters associated with perfusion and permeability in vivo[164,165], and therefore it could be applied for this purpose even after pancreatoduodenectomy. Given the peculiar post-surgical context and aetiology of PPAP, MRI imaging with specific sequences could hypothetically provide early critical information to enable proactive interventions; however, its feasibility and benefits have never been tested in the postoperative period to date.

This study aims to characterize the new ISGPS definition of PPAP by investigating its early radiologic, biochemical, and clinical spectrum of either local or systemic changes associated.

METHODS

Study design

This is a single-centre prospective observational pilot study. It was approved by the Ethics Committee (Comitato Etico delle Province di Verona e Rovigo (approval number 2130CESC-10/04/2019), registered at ClinicalTrial.gov (NCT04917172), and designed in accordance with the Declaration of Helsinki, and the Strengthening the Reporting of Observational Studies in Epidemiology Statement (STROBE) guidelines[131].

Sample size calculation

Sample size has been assessed on pancreatic apparent diffusion coefficient (ADC) values at MRI, yet no previous studies have ever applied a DW-MRI after pancreatectomy to detect an acute pancreatitis process. In a study on AP, the mean ADC in the AP group was reported to be equal to 1.32×10^{-3} $mm^2/sec \pm 0.13$; whereas it was 1.77×10^{-3} mm^2/sec $\pm$ 0.32 in the normal pancreas[165]. Based on previous reports on POH-PPAP, showing an incidence of around 30%[96,160], the enrollment ratio was defined accordingly. A sample of 24 patients has been estimated to provide the study with at least 85% power at a two-sided alpha level of 5%. Given the different context, precisely the postoperative one, an interim analysis was planned and conducted when results were available for half of the planned maximum to verify the appropriateness of the sample size[166]. Since the retrieved ADC data differed from the literature, a sample size re-estimation was performed to maintain the trial power at 85%[167], and 65 patients were finally required, expecting a 10% dropout rate (e.g., inability to perform all MRI sequences).

Inclusion and exclusion criteria

Adult patients scheduled for pancreatoduodenectomy (PD) at the Department of General and Pancreatic Surgery, The Pancreas Institute, University of Verona Hospital

Trust, were screened for inclusion from September 2019 to January 2021. All eligible patients provided written informed consent at hospital admission.

Exclusion criteria included:

- preoperative serum pancreatic amylase (10-52 U/l) or lipase activity (10-60 U/l) greater than the upper limit of normal at routinary preoperative blood tests;
- chronic use of steroids;
- inability to perform MRI (e.g., claustrophobia, presence of non-MRI-compatible metal implants, adverse reaction to contrast agents);
- need to extend the resection to the pancreatic body for any reason[123];

All pancreatic resections, including pylorus-preserving and Whipple pancreaticoduodenectomies, were carried out according to the Institutional standards with a pancreatojejunostomy reconstruction and an open approach. No prophylactic octreotide or steroids were administrated.

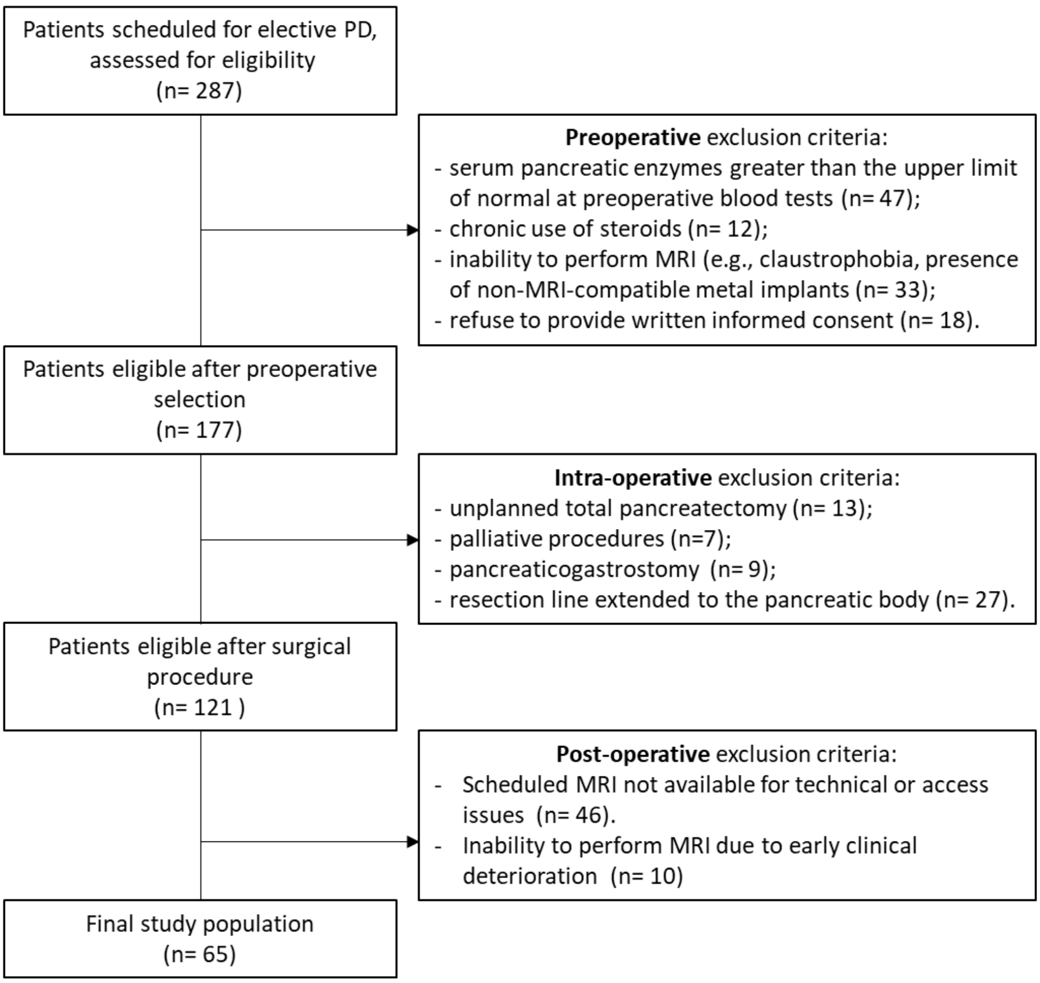


Figure 1: STROBE compliant flowchart of the study

Data collection

Demographics, operative details, and postoperative data were prospectively collected from medical records and included radiologic, biochemical, and clinical data. The details about clinical definitions, methodology and indications of imaging procedures, and laboratory determinations are available in supplemental tables 1, 2, and 3.

Participants

Different patient groups were defined based on the ISGPS diagnostic criteria and the grading system of PPAP[3].

(1) Without PPAP or POH: Patients without sustained postoperative serum hyperamylasemia (POH) nor imaging consistent with AP.

(2) POH: a sustained postoperative serum hyperamylasemia not meeting the PPAP definition (neither clinically relevant nor consistent imaging)

(3) PPAP: requiring the fulfilment of three criteria:

- POH: a sustained postoperative serum hyperamylasemia, namely a sustained increase in serum amylase activity greater than the institutional upper limit of normal (52 U/L) persisting for at least the first 48 hours postoperatively (postoperative day -POD- 1 and 2);
- The presence of macroscopic radiologic features of AP at postoperative CT;
- The occurrence of clinically relevant complications.

PPAP severity was classified into grades B and C, with progressive clinical deterioration according to the ISGPS clinical criteria. The grading for each patient was determined only after a complete postoperative follow-up (up to 90 days) was accomplished[3].

(4) Macroscopic radiologic features of AP at CT: Imaging consistent with AP, independently from serum values or clinical condition.

Outcome measures

The primary outcome was the difference in ADC values at DW-MRI in the PPAP (3) and POH (2) groups compared to patients without PPAP or POH (1). Secondary outcomes included local and systemic inflammatory biochemical parameters, correlations between different serum pancreatic enzyme activities (pancreatic amylase and lipases), and the association between postoperative morbidity[22,27,71,74,93,168,169] and postoperative macroscopic radiologic features of AP. Finally, the PPAP incidence and grading were assessed.

Table 1. Patient's characteristics

Patient's characteristics		**Overall (n=65)**
Sex	Male	32 (49.2%)
	Female	33 (50.8%)
Age (years, median, IQR)		65 (58-72)
Body Mass Index (Kg/m^2, median, IQR)		23.7 (21.8-25.4)
Smoker n (%)		10 (15.4%)
Preoperative pancreatic enzyme replacement therapy n (%)		22 (33.8%)
Diabetes n (%)		15 (23.1%)
Pancreatic gland texture n (%)	Soft	32 (49.2%)
	Hard	33 (50.8%)
Estimated blood loss (mL, median, IQR)		500 (350-800)
Main pancreatic duct diameter (mm, median, IQR)		4 (3-5)
Operative time (min, median, IQR)		380 (309-480)
Pathology n (%)	Pancreatic ductal adenocarcinoma	43 (66.2%)
	Pancreatic neuroendocrine tumour	7 (10.8%)
	Cystic neoplasms	3 (4.6%)
	Ampullary carcinoma	4 (6.1%)
	Duodenal adenocarcinoma	2 (3%)
	Others	6 (9.3%)
POH n (%)	Considering serum pancreatic amylase activity (persisting 48h, POD 1-2)	20 (30.7%)
	Considering serum lipase activity (persisting 48h, POD 1-2)	22 (33.8%)
PPAP n (%)		6 (9.2%)
Grade n (%)	B	4 (6.1%)
	C	2 (3.1%)
Biochemical leak n (%)		4 (6.2%)
POPF n (%)		11 (16.9%)
Grade n (%)	B	10 (15.4%)
	C	1 (1.5%)
Abdominal Abscess n (%)		12 (18.5%)
Post pancreatectomy haemorrhage n (%)		8 (12.3%)
Delayed gastric emptying n (%)		9 (13.8%)
Surgical site infection n (%)		4 (6.2%)
Sepsis n (%)		12 (18.5%)
Pneumonia n (%)		8 (12.3%)
Respiratory Failure n (%)		4 (6.2%)
Cardiac Morbidity n (%)		5 (7.7%)
Acute kidney injury n (%)		3 (4.6%)
Relaparotomy n (%)		5 (7.7%)
Intensive care unit stay n (%)		4 (6.2%)
Mortality n (%)		1 (1.5%)
Length of hospital stay (days, median, IQR)		9 (7-18)
Clavien Dindo Classification n (%)	Uneventful	30 (46.2%)
	I	5 (7.7%)
	II	18 (27.7%)
	IIIa	2 (3.1%)
	≥ III b	10 (15.4%)

Abbreviations: PPAP: postpancreatectomy acute pancreatitis, POH: Postoperative serum hyper-amylasemia/lipasemia, POPF: postoperative pancreatic fistula, IQR: interquartile range. Pancreatic gland texture was defined based on the manual palpation of experienced pancreatic surgeons.

Statistical analysis

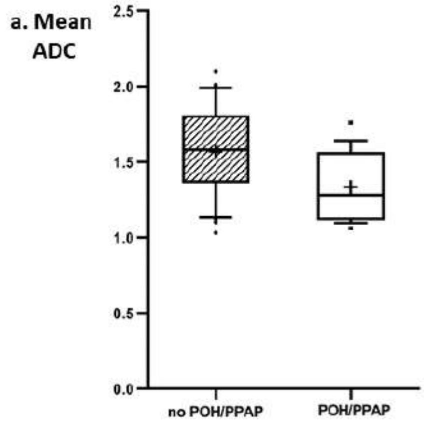
Categorical variables were reported as numbers with percentages and compared using the chi-square test or Fisher's exact test when appropriate. Continuous variables were presented as medians with interquartile ranges (IQR) or means with standard deviations, and differences were assessed with the Mann-Whitney U test in non-parametric distributions or the Student T-test in cases of normal distribution. Comparisons of continuous variables between multiple independent groups were performed using the Kruskal-Wallis analysis of variance in the non-parametric or ANOVA in the case of parametric distribution. Testing for normal distribution was performed using the Shapiro-Wilk test for normality. As serum pancreatic amylase and lipase activity markedly deviated from normality, the Friedman test was used to test the difference among repeated measures of serum pancreatic amylase and lipase over time, with a post hoc analysis of Wilcoxon signed-rank tests for pairwise comparisons. The intraindividual correlation between longitudinal assessment of serum pancreatic enzymes was examined using repeated measures correlation (R package *rmcorr*)[170]. The predictive power of the mean pancreatic stump ADC was assessed by calculating the area under the receiver-operator characteristic (ROC) curve analysis. All tests were two-tailed and a p value < 0.05 was considered significant, while for repeated measures analysis, a Holm-Sidak correction was applied. Statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, Version 22.0; I.B.M. Corp, Armonk, NY, USA) and R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

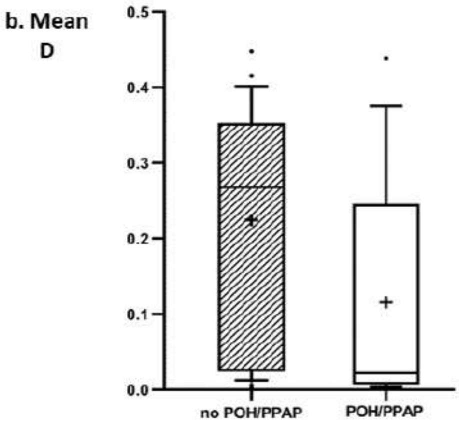
RESULTS

A total of 287 patients scheduled for elective PD were screened for eligibility. Of those, 65 patients were included. Figure 1 shows the STROBE-compliant study flow chart for patient enrolment. Baseline characteristics of the study population are reported in Table 1 and were comparable to the overall PD cohort over the same study period [5,6].

Radiologic data

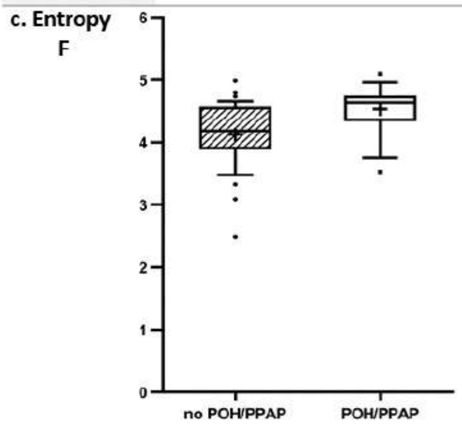
After retrospectively applying the ISGPS definition[3] at POD 3 DW-MRI, the mean pancreatic stump ADC was significantly lower in the PPAP (3) and POH (2) group (n=20) compared to patients without PPAP or POH (1) (n=45) (p =0.006), with a difference of 0.23 (95% CI, 0.08 to 0.38) between the two cohorts (Figure 2. a). The ROC curve for ADC values predicting POH-PPAP yielded an AUC of 0.74 (95% CI 0.60-0.84; p=0.001). An ADC value of 1.32 showed 63% sensitivity, 82% specificity, 59% positive predictive value, and 84% negative predictive value in predicting the occurrence of POH/PPAP. There was no significant difference in MRI parameters between patients with PPAP (3) and those with POH (2) (p=0.98); therefore, the analysis was not further stratified.

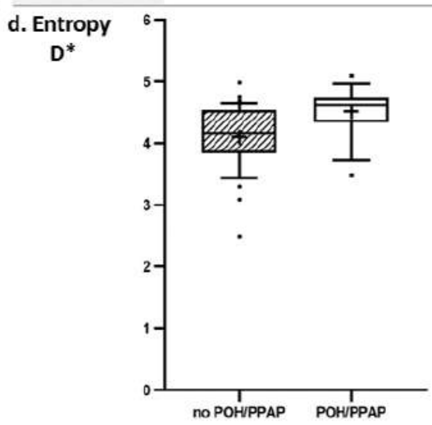




ADC	(1) Without PPAP or POH (n=45)	(4) PPAP and (2) POH (n=20)	p
Mean (SD) (× 10^{-3} mm^2/s)	1.56 (0.28)	1.33 (0.22)	**0.006**
Kurtosis (SE)	- 0.93 (0.74)	-1.2 (1.1)	
Skewness (SE)	-0.40 (0.37)	0.45 (0.5)	

D	(1) Without PPAP or POH (n=45)	(4) PPAP and (2) POH (n=20)	p
Mean (SD)#	0.22 (0.15)	0.11 (0.14)	**0.03**
Kurtosis (SE)	6.7 (2.9)	14.3 (7.6)	0.20
Skewness (SE)	1.3 (0.38)	2.7 (0.73)	**0.01**
Entropy (SE)	3.4 (0.17)	3.1 (0.37)	0.65





F	(1) Without PPAP or POH (n=45)	(4) PPAP and (2) POH (n=20)	p
Mean (SD)#	0.51 (0.06)	0. 49 (0.05)	0.44
Kurtosis (SE)	0.32 (0.21)	0.63 (0.22)	0.08
Skewness (SE)	0.04 (0.12)	0.29 (0.17)	0.18
Entropy (SE)	4.1 (0.08)	4.5 (0.10)	**0.004**

D*	(1) Without PPAP or POH (n=45)	(4) PPAP and (2) POH (n=20)	p
Mean (SD)#	0.33 (0.06)	0.34 (0.06)	0.88
Kurtosis (SE)	0.40 (0.28)	0.98 (0.68)	0.59
Skewness (SE)	-0.4 (0.11)	-0.02 (0.17)	0.91
Entropy (SE)	4.1 (0.08)	4.5 (0.10)	**0.003**

Figure 2: Box plot illustration and analysis of diffusion-weighted (DW) magnetic resonance imaging (MRI), including the apparent diffusion coefficient (ADC), the IVIM parameters (D, D* and F), and their histogram analysis. The lines in the box plot indicate the median value and the interquartile range (IQR); the cross indicates the mean value.

Considering IVIM parameters, the combined PPAP(3) and POH (2) group showed significantly lower average values of true diffusion coefficient (D) on IVIM acquisitions compared to patients without PPAP or POH (1) (Figure 2. b). Histogram analysis also revealed other significant factors, with most results related to the heterogeneity of perfusion parameters: D* and F (Figure 2. c-d). Figure 3 shows the radiological imaging of two patients with and without PPAP, respectively. No macroscopic features consistent with AP were identified at any MRI (supplementary table 4). A total of 21 patients subsequently underwent computed tomography (CT) imaging for clinical worsening (median POD 13.5, IQR 7-15), and 6 (28.6%) had macroscopic radiologic features of AP (4).

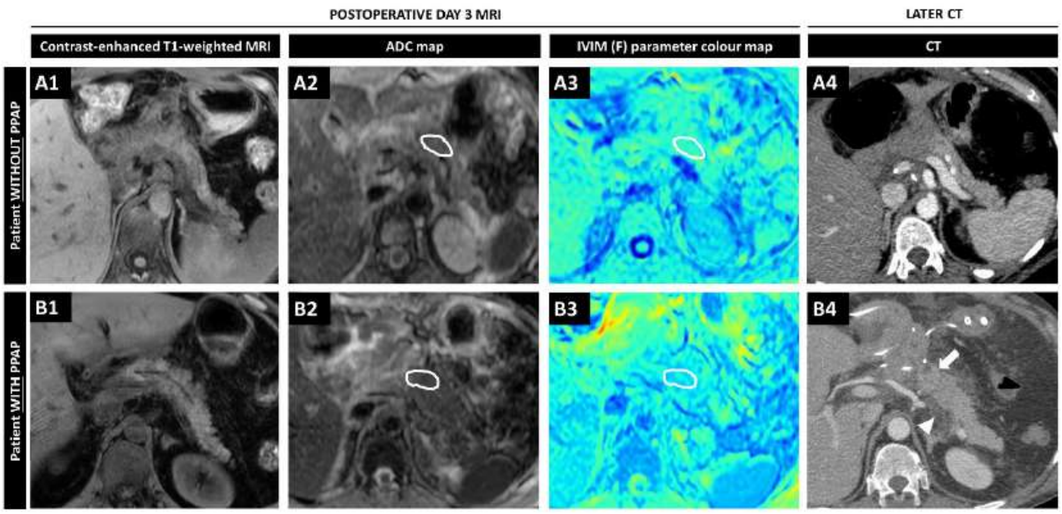


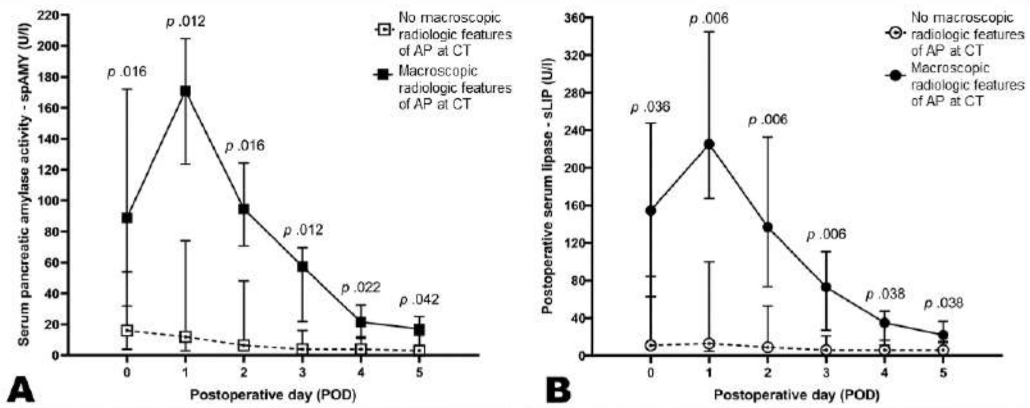
Figure 3: Contrast-enhanced T1-weighted MRI (1), ADC map (2), and IVIM (F) parameter colour map (3) with ROIs containing the pancreatic stump, and postoperative CT (4) images of patients without PPAP (A: Patient with an uneventful postoperative course and a CT scan performed on POD 8), and with PPAP (B: Patient with grade C PPAP. CT scan performed on POD 7 showing pancreatic parenchymal enlargement affecting the pancreatic stump and body [white arrow], with decreased attenuation and extensive stranding of retroperitoneal and intraperitoneal fat [white indicator]).

Biochemical data

Figure 4 shows the levels of local (serum pancreatic amylase [spAMY], serum pancreatic lipase [sLIP]) and systemic (C-reactive protein [CRP], white blood cells [WBC]) inflammatory markers over time.

In the overall population, the median values of spAMY and sLIP differed significantly between time points, with higher values in the early PODs and a subsequent gradual decrease to normal levels on POD 4-5 (Supplemental Figure 1). Up to 31 (47.6%) and 32 (49.2%), patients showed at least one altered spAMY and/or sLIP value, respectively. Of these, almost one-third had a peak of activity 2 to 24 hours after surgery. All patients with (4) macroscopic radiologic features of AP at CT (n=6) had persistent spAMY and sLIP

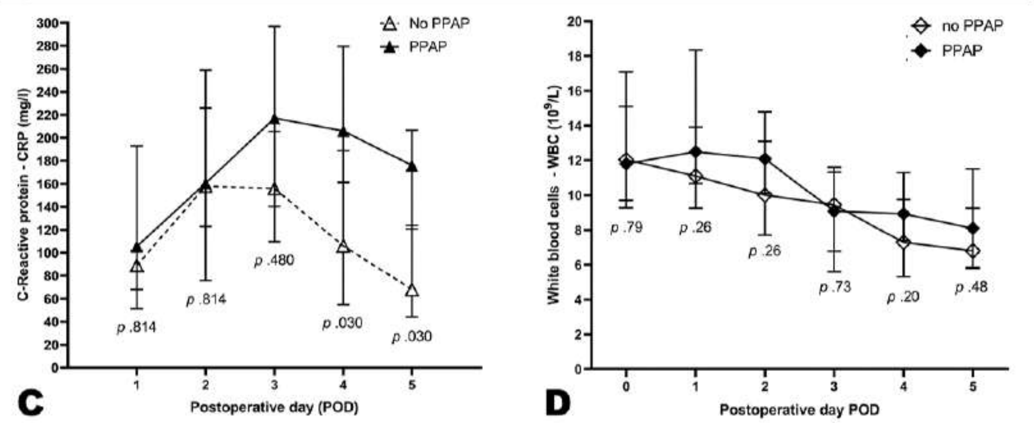
Local markers



		No macroscopic radiologic features of AP at CT	Macroscopic radiologic features of AP at CT
spAMY (U/l, median, IQR)	POD 0	16 (4-56)	89 (32-172)
	POD 1	12 (3-74)	171 (123.5-204.7)
	POD 2	6.5 (3-48)	94.5 (70.7-124.2)
	POD 3	4 (3-20.2)	57 (21.7-32.5)
	POD 4	4 (3-12.5)	21.5 (12-32.5)
	POD 5	3 (3-13)	17 (6.25-25)

		No macroscopic radiologic features of AP at CT	Macroscopic radiologic features of AP at CT
sLIP (U/l, median, IQR)	POD 0	11 (6-84.2)	154.5 (63-247.5)
	POD 1	13 (5-100)	225 (167.2-345)
	POD 2	9 (5-53)	137.5 (73.5-232.7)
	POD 3	6 (5-21)	73 (27-110.7)
	POD 4	6 (4-16.5)	35 (11.5-47.5)
	POD 5	6 (4-14)	22 (14-36.5)

Systemic markers



		No PPAP	PPAP
CRP (mg/l, median, IQR)	POD 1	89 (68-102)	105.5 (51.2-193.5)
	POD 2	158 (123-226)	160 (75.7-259)
	POD 3	156 (55-189)	217 (140.2-297.7)
	POD 4	106 (55-189)	206 (161.2-279.5)
	POD 5	68 (44-124)	176 (120.7-206)

		No PPAP	PPAP
WBC (10^9/l, median, IQR)	POD 1	11.1 (9.2-13.9)	12.5 (10.6-18.3)
	POD 2	10 (7.7-13.1)	12 (10.1-14.8)
	POD 3	9.4 (6.7-11.3)	9.0 (5.6-11-6)
	POD 4	8.9 (7.3-11.3)	8.9 (7.3-11.3)
	POD 5	6.6 (5.8-9.2)	8.1 (5.8-11-5)

Figure 4: Analysis of postoperative local and systemic serum inflammatory markers from the day of surgery (postoperative day - POD 0) to POD 5, stratified according to PPAP occurrence. (A) serum pancreatic amylase activity (U/l), (B) serum lipase activity (U/l), (C) serum C-reactive protein (mg/dl), and (D) white blood cells (109/l). A Holm-Sidak correction was applied to all p-values.

increases for up to 48 hours and beyond, namely POH (Fig. 4.a-b). Still, 14 (21.5%) patients without macroscopic radiologic features of AP at CT (n=59) showed POH, including postoperative serum hyper-amylasemia and hyper-lipasemia. Only 2 patients had sustained isolated hyperlipasemia without hyperamylasemia. Intraindividual correlation between longitudinal assessment of serum pancreatic enzymes showed a significant positive relationship between spAMY and sLIP activity: $r(65) = 0.84$, 95% CI [0.80, 0.87], $p < 0.001$. Also, a positive Urine trypsinogen- 2 (U-TRP 2) test (13 patients) was significantly associated with both postoperative hyperamylasemia and hyperlipasemia (n=10; 77%, p< 0.001). Once the PPAP definition[3] was retrospectively applied, no difference in the median spAMY and sLIP activity was found between the PPAP (3) and POH (2) groups (Table 2).

Table 2. Postoperative serum pancreatic enzymes activity stratified according to PPAP and POH occurrence

	(1) Without PPAP or POH (n= 45)	(2) POH (n= 14)	P*	(3) PPAP (n= 6)	P**
Serum pancreatic amylase (U/l)					
POD 0	6 (3-30)	70 (44-77.5)	<0.001	89 (32-172)	**0.41**
POD 1	5 (3-16)	254 (128-468)	<0.001	171 (123-205)	**0.43**
POD 2	4 (3-16)	145 (86-204)	<0.001	94 (71-124)	**0.21**
POD 3	3 (3-7)	39 (25-102)	<0.001	57 (22-69)	**1**
POD 4	3 (3-6)	39 (10-53)	<0.001	21 (12-32)	**0.46**
POD 5	3 (3-4.5)	32 (8-48)	<0.001	17 (6-25)	**0.24**
Serum lipase (U/l)					
POD 0	8 (5-26)	99 (81-162)	<0.001	154 (63-247)	**0.50**
POD 1	6.5 (5-31)	337 (129-593)	<0.001	225 (153-345)	**0.80**
POD 2	6 (4-11.7)	110 (66-256)	<0.001	130 (61-233)	**1**
POD 3	6 (4-9)	30 (14-108)	<0.001	53 (19-111)	**0.75**
POD 4	5 (4-8)	34 (11-54)	<0.001	15 (9-38)	**0.33**
POD 5	5 (4-8.5)	22 (8.5-55)	<0.001	22 (9-36.5)	**0.77**

* p-value for (1) without PPAP or POH vs (2) POH

** p-value for (2) POH vs (3) PPAP

Abbreviations: POH: postoperative serum hyperamylasemia; PPAP: postpancreatectomy acute pancreatitis; POD: postoperative day; IQR: interquartile range

There was a general increase in the systemic inflammatory markers after surgery, with an early elevation and decrease of WBC in all patients. (Figure 4.d). CRP showed otherwise a later peak (at 72 hours), with significant persistent altered values in PPAP (3) patients compared to those without PPAP (n=59) from POD 4 onwards (Figure 4. c).

Clinical data

Table 3 stratifies the postoperative outcomes according to the presence of POH (2) and PPAP (3), characterizing local and systemic complications associated with these scenarios. Notably, an increased rate of pancreas-specific complications, namely POPF, PPH, and organ space infections, as well as systemic dysfunctions, including sepsis, respiratory failure, cardiac morbidity, and acute kidney injury, characterized the PPAP scenario. POH

(2) was associated with an increased rate of PPH (21.4% vs 2.2% p= 0.038) compared to patients without PPAP or POH (1).

By applying the ISGPS grading system [3], PPAP (3) occurred in 9.2% (6 patients), eventually classified in 4 cases (6.1%) of grade B and 2 cases (3%) of grade C PPAP.

Table 3. Postoperative clinical sequelae stratified according to the presence of POH or PPAP.

		(1) Without PPAP or POH (n= 45)	(2) POH (n= 14)	(3) PPAP (n= 6)	p
Local complications					
POPF		5 (11.1%)	1 (7.1%)	5 (83.3%)	**<0.001**
grade	*BL*	1 (2.2%)	3 (21.4%)	0	**<0.001**
	B	5 (11.1%)	1 (7.1%)	4 (66.7%)	
	C	0	0	1 (16.7%)	
Organ space infections		5 (11.1%)	3 (21.4%)	4 (66.7%)	**0.006**
PPH		1 (2.2%)	3 (21.4%)	4 (66.7%)	**<0.001**
grade	*A*	0	1 (7.1%)	1 (16.7%)	**0.002**
	B	1 (2.2%)	2 (14.3%)	2 (33.3%)	
	C	0	0	1 (16.7%)	
Delayed gastric emptying (DGE)		6 (13.3%)	2 (14.3%)	1 (16.7%)	0.974
Surgical site infection (SSI)		1 (2.2%)	1 (7.1%)	2 (33.3%)	**0.022**
Systemic complications					
SIRS (≤ POD 3)		6 (13.3%)	3 (21.4%)	2 (33.3%)	0.292
Sepsis		5 (11.1%)	3 (21.4%)	4 (66.7%)	**0.006**
Pleural effusion		5 (11.1%)	2 (14.3%)	2 (33.3%)	0.342
Pneumonia		5 (11.1%)	1 (7.1%)	2 (33.3%)	0.253
Respiratory failure		2 (4.4%)	0	2 (33.3%)	**0.044**
Cardiac morbidity		1 (2.2%)	2 (14.3%)	2 (33.3%)	**0.019**
Acute kidney injury		0	1 (7.1%)	2 (33.3%)	**0.005**
Unplanned ICU stay		1 (2.2%)	1 (7.1%)	2 (33.3%)	**0.022**
Relaparotomy		1 (2.2%)	2 (14.3%)	2 (33.3%)	**0.019**
Discharge with drain		2 (4.4%)	3 (21.4%)	3 (50%)	**0.004**
Clavien Dindo Score ≥ grade IIIb		3 (6.7%)	3 (21.4%)	4 (66.7%)	**0.001**
LOS *(days)*		9 (7-13)	14 (9-18)	39 (26-57)	**0.001**
Mortality		1 (2.2%)	0	0	1

Results in total number (%) except for LOS: median (interquartile range). Abbreviations: POH: postoperative serum hyperamylasemia; PPAP: postpancreatectomy acute pancreatitis; POPF: postoperative pancreatic fistula; BL: Biochemical leak, PPH: post pancreatectomy haemorrhage, POD: postoperative day, ICU: Intensive care unit; LOS: length of hospital stay, SIRS: systemic inflammatory response syndrome

DISCUSSION

This study systematically defines the early features of postpancreatectomy acute pancreatitis. Patients with PPAP displayed lower pancreatic ADC values at DW-MRI, indicating restricted diffusion, local and systemic biochemical alterations, including increased serological inflammatory markers, and a more severe postoperative burden characterized by both pancreas-specific and systemic morbidity.

The damage to pancreatic tissues is already recognized among the possible etiologies of acute pancreatitis in a non-surgical setting. However, an acute inflammatory process of the pancreatic parenchyma after a partial pancreatic resection has been somehow neglected until very recent years. Some similarities between PPAP and the better-understood medical counterpart AP have already been explored[3,159]; thus, evidence acquired so far on PPAP primarily relied on series with mixed metrics[96,160]. Given the peculiar postoperative context of a reduced volume of pancreatic parenchyma, a raw pancreatic stump surface, and a pancreatico-enteric anastomosis, specific features of PPAP have eventually emerged[159] and prompted a distinct international definition[3]. The surgical community now faces diagnostic, terminology, and prognostic challenges addressed in the last decades for medical AP. Given the several advances made in understanding the pathophysiological mechanisms of AP, detecting potential targets for future therapeutic trials[171,172], acknowledging PPAP in a spectrum of AP within the pancreatic remnant raises significant chances for its prevention and treatment.

This paper primarily reports that early and specific MRI sequences can detect initial pancreatic parenchymal changes, even before macroscopic alterations become apparent. The diffusion of water seen at DW-MRI is inversely correlated with tissue cellularity and cell membrane integrity. At a cellular level, acute pancreatitis is characterized by infiltration of inflammatory cells, disturbances in microcirculation, and acinar cell damage, which potentially explain the lower ADC values observed in POH/PPAP patients in this study and in the literature regarding AP[165]. Also, microstructural properties of pancreatic tissues assessed through the IVIM sequences, which reflect the tissue diffusivity and microcapillary perfusion[164], showed higher heterogeneity of perfusion parameters (D* and F) in POH/PPAP patients. Still, those results should be considered carefully due to the technical limitations of early IVIM data retrieval as well as the substantial overlap of DWI values between POH and PPAP patients, preventing the detection of specific cut-offs able to dichotomize PPAP patients from the POH population.

Moreover, although MRI was recognized to be more sensitive than CT in visualizing early changes of AP[161,163], none of the POD3 MRIs showed early macroscopic features of an AP process, questioning the actual impact of such a policy, even on patients with early POH. Conversely, among patients that subsequently underwent CT imaging for clinical worsening, macroscopic AP features become apparent several days after the index surgery (in the range of 7-15 PODs), so later radiologic imaging, unlike earlier assessments, is critical for diagnosing and treating subsequent deteriorating clinical scenarios[162]. When images are taken outside this timeframe, clinicians should be aware that they could be biased because the PPAP process may be at its very early or later stages and, therefore, cannot be reliably characterized. The IVIM-MRI sequences seem to have limited application in the immediate postoperative period, as they require a long acquisition time (longer than 30 minutes), including multiple breath-hold sequences, which are demanding in ill patients with poor cooperation. Of note, more than 40% of the patients eligible for this analysis were unable to perform the POD 3 MRI due to clinical status and daily radiological service schedule overload. Additionally, IVIM data is not immediately available for radiologists and surgeons, and specially designed software has been developed for this purpose. Such limits and the relatively higher cost of MRI confirmed the limited practical feasibility of early IVIM-MRI in the immediate postoperative period.

The increase in serum levels of pancreatic enzymes is the earliest and most accessible marker of an incipient PPAP after partial pancreatectomy. In this study, all patients with macroscopic radiological features of AP at CT had a sustained increased serum enzyme activity for up to 48 hours of both serum lipase and pancreatic amylase - defined as POH (postoperative serum hyperlipasemia – hyperamylasemia)[96]. Therefore, no additional value of the simultaneous measurement of both enzymes has been identified. As serum amylase may not be routinely available at all centres, serum lipase may be considered within the same POH definition[3]. As described in AP, the degree of the elevation of serum pancreatic enzymes activities did not correlate with the severity of the disease[173], and approximately 20% of patients with POH did not subsequently develop radiologically confirmed PPAP, displaying indeed better clinical outcomes. Various prognostic models have been developed to predict the severity of medical AP early in the disease course, ranging from simple laboratory markers assessment to clinical scoring systems[174]. In this study, CRP persisted increased in patients with PPAP showing unfavourable courses; conversely, in line with the previous literature, a peak of serum CRP at 72 hours followed by a progressive decline to normal levels was associated with more favourable clinical outcomes[175]. Although further studies are needed, these promising results highlight the role of CRP, once associated with POH, as a reliable indicator for early patient stratification to select the appropriate level of care and prevent additional morbidity.

Almost 21.5% of the study population developed POH, while PPAP occurred in 9.2% of patients, eventually classified as 6.1% grade B and 3% grade C PPAP. To date, few reports[146,147,176] have validated the ISGPS definition of PPAP. All the reports indicated that grade C PPAP is rare, while POH and grade B PPAP showed the greatest discrepancy. Such variations may reflect different management strategies, attitudes toward postoperative imaging or the difficulty in evaluating PPAP radiologically, mainly when imaging is performed too early, as highlighted in this study. An ongoing prospective, multicenter, international validation study supervised by the ISGPS will provide further evidence.
Whether the association between PPAP and worst surgical outcomes is included in the definition itself, this study comprehensively characterized the nature of PPAP-associated morbidity, which involves both local and systemic complications, potentially requiring intensive care admission and reoperations. Interestingly, compared to patients without POH or PPAP, patients with POH displayed an increased rate of early and mild haemorrhages without evolving towards the most severe scenarios nor showing late pancreatic alterations at radiology[8,162]. Further studies on POH-PPAP will be critical to understanding the underlying mechanism by which complication burden increases and how to optimize management strategies in high-risk patients.

The surgical community is now facing the same challenges of its medical counterparts in dealing with the unique scenario of acute pancreatitis occurring after a partial pancreatic resection[171]. PPAP seems challenging to diagnose and argues for further studies on specific preventive strategies and additional early predictors to identify actual PPAP patients from the overall POH population. As a universally accepted definition was lacking, no standard therapeutic or mitigation strategies for POH/PPAP exist. Still, the evidence acquired on pathogenic pathways[171] and treatment strategies of AP[177] could be translated into the multidisciplinary management of PPAP.

The chance to diagnose complications occurring in the earliest phases of a post-surgical course may lead to a significant clinical benefit. Namely, it might impact the use of enhanced recovery protocols[85], new specific therapeutic agents, including a tailored fluid therapy with lactated Ringer's solution given its immunomodulatory properties[178], specific analgesics protocols to avoid potential detrimental effects of opioids (e.g., epidural versus intravenous)[179], and experimental studies on calcium signalling pathway possibly involved through intraoperative pancreatic manipulation (e.g., Piezo1)[172]. Clinically, future trials must inquire about the initial systemic management of PPAP, the timing and modality of oral intake and nutritional support[85], drainage management protocols[180], and systematic radiology assessment[181].

Forty years after its first definition[117] and 20 from the revision of Atlanta[8], the process of acute pancreatitis could include various subtypes based on etiological, biochemical, and prognostic factors. Together with spontaneous and post-endoscopic interventional procedures (i.e., endoscopic retrograde cholangiopancreatography), AP, after partial pancreatic resection, has now emerged as a distinct entity.

This study has limitations. First, patients unable to perform POD 3 MRI due to early clinical deterioration were excluded. For this reason, our results may not fully represent the entire PPAP population that more frequently showed early clinically relevant scenarios[5]. IVIM diffusion-weighted MRIs were acquired using a slice thickness of 5 mm; image misalignment with contrast-enhanced T1-weighted images of the pancreas used as anatomic reference (1 mm thick slices) may have been a source of variance and approximation of results. However, this limitation has been overcome by compensating misalignment through a rigid transformation using specific software. Moreover, DW-MRI was analyzed only postoperatively, without including individual before-after surgery variations. Future studies should assess the intra-individual variability of DW-MRI parameters. Finally, the ADC cut-off of 1.32 assessed on POD 3 should be further validated.

CT imaging was performed only for clinical worsening; indeed, we considered exposing patients to radiation without a clinical indication unethical.

Finally, patients with PPAP were limited in this series, preventing the use of multivariable analyses identifying PPAP risk factors. Such a low incidence may be related to the high rate of patients diagnosed with pancreatic ductal adenocarcinoma, a recognized protective factor for POH-PPAP. Further specific investigations on high-risk patient cohorts could lead to different results. However, the novelty and the significance of most of the results provided a solid ground for further prospective validation studies comparing centres, surgical approaches, and techniques.

CONCLUSION

Postpancreatectomy acute pancreatitis is characterized by specific radiologic, biochemical and clinical alterations. A persistently increased activity for up to 48 hours of serum lipase and pancreatic amylase is the earliest serological marker, though it lacks correlation with clinical severity. Once associated with POH, the persistence of CRP elevation after POD 3 predicts a worse postoperative outcome. Although pancreatic parenchymal changes related to an initial inflammatory phase may be apparent at early DW-MRI, its standard use has little, if no, impact on postoperative management at the expense of increased costs and patient discomfort. Macroscopic radiologic changes consistent with PPAP appear later in the postoperative period and are critical for diagnosing and treating subsequent deteriorating clinical scenarios. This paper paves the ground for including PPAP in the broader spectrum of acute pancreatitis definition, promoting future validation studies comparing institutional outcomes and treatment strategies.

Chapter 6 - Postoperative serum hyperamylasemia (POH) predicts additional morbidity after pancreatoduodenectomy: *It is not all about pancreatic fistula*

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Surgery. 2022 May 27; S0039-6060(22)00231-8, doi: 10.1016/j.surg.2022.04.003

ABSTRACT

Background

The association between postoperative serum hyperamylasaemia (POH) and morbidity has been hypothesized but rarely explored once occurring with or without (POH-exclusive) a combined postoperative pancreatic fistula (POPF).

Methods

Analysis of patients who consecutively underwent pancreaticoduodenectomy from 2016 to 2020. POH was defined as serum amylase activity greater than the institutional upper limit of normal (52 U/l), persisting within the first 48 hours postoperatively (postoperative day –POD– 1 and 2).

Results

Among 852 patients, 15.8% developed POH-exclusive. Compared to patients without POH or POPF (64.3%), they showed a significantly higher postoperative burden (Clavien-Dindo ≥ II: 52.6% vs. 30.8%) with increased rates of bacteraemia (12.6% vs 6%), pleural effusion (13.3% vs 5.3%), postpancreatectomy haemorrhage (13.3% vs 7.5%), PPAP (10.3% vs. 0%) and organ site infections (18.5% vs 10.9%), all $p < 0.05$. A total of 13.8% experienced POH with POPF leading to the worse outcome. The combined occurrence of POH with POPF led to a shorter median time to morbidity (3 PODs, 95% IC 2.2-3.7 vs. 6 PODs, 95% IC 4.2-8; $p <0.001$) than patients experiencing POPF-exclusive (5.9%). 46.6% of POH patients developed POPF. BMI (OR 1.1), male sex (OR 2.1), increased drain fluid amylase on POD 1 (OR 1.001), and increased C-reactive Protein (OR 1.01) were independent risk factors for POPF once POH has occurred.

Conclusions

POH has relevant postoperative clinical implications, independently from POPF occurrence. Developing POH with POPF leads to an earlier onset of higher postoperative burdens. Once POH is diagnosed, risk factors for additional POPF could identify patients who may benefit from additional surveillance, specific drains protocols, and preventive strategies.

INTRODUCTION

Postoperative serum hyperamylasemia (POH) is a status of persistently elevated serum amylase activity potentially associated with a worse postoperative outcome[9,59,77] as the biochemical expression of an acute inflammatory process of the pancreatic remnant[1,96]. POH has been recently considered a key diagnostic criterion for postpancreatectomy acute pancreatitis (PPAP) after a partial pancreatic resection[182], possibly leading to additional morbidity[23,58]. This includes but it is not limited to postoperative pancreatic fistula (POPF)[16,17,77,96]. POH and POPF have been historically considered a unique complication, but even after the advent of universally accepted, standardized definitions eventually dividing them, their actual relationship still is controversial[182].

POH and POPF may exist independently or occur together, with a potential detrimental effect on postoperative outcomes [9,11,17,23]. Although it is well reported that POPF is the most significant contributor to major morbidity and mortality after pancreatic surgery[108,183,184], whether the combined occurrence with POH significantly affects the postoperative course has not been explored. Moreover, the postoperative morbidity exclusively related to POH in the absence of POPF[23,62,76] is still unknown.

The present study aims to assess the association between POH and postoperative outcomes, focusing on exploring POH and POPF related morbidity once occurring alone or combined. In addition, possible risk factors of POPF occurrence in the POH population were investigated.

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 pancreaticoduodenectomy (PD) between January 2016 and December 2020 were 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 pancreatic amylase activity were excluded.

Data collection

Demographics, operative details, postoperative data were collected from medical records. Preoperative characteristics included age, sex, BMI [kg/m^2], comorbidities, and neoadjuvant therapy. Intraoperative data of vascular resections, estimated blood loss, and operative time were retrieved.

All pancreatic resections were carried out according to the Institutional standards via an open approach[64,66]. Both pylorus-preserving and Whipple PDs with either pancreatojejunostomy or pancreaticogastrostomy were included. No prophylactic octreotide or steroids were administrated. Gland texture was defined based on the manual palpation of experienced pancreatic surgeons, and the main pancreatic duct size was measured using a sterile disposable ruler. The Fistula Risk Score (FRS) was calculated for each patient[69]. According to our institutional standards, an externalized transanastomotic stent (PankreaPlus polyvinyl catheter; Peter Pflugbeil Gmbh Medizinische Instrumente) could be placed according to the operator's choice. Drains could be omitted in patients deemed at negligible/low risk for postoperative pancreatic fistula (POPF) according to the FRS[69]. Early removal on a postoperative day (POD) 3 was promoted in drain placement based on the POD 1 drain fluid amylase (DFA) value[53,70].

Patients' pathological reports were reviewed. Previous studies have highlighted histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis as a risk factor for several postoperative complications, including POH/PPAP and POPF[1,62,69]. Accordingly, those cases were defined as having a "high-risk pathological diagnosis."

Outcome metrics

POH was defined according to the International Study Group for Pancreatic Surgery (ISGPS) definition[182] as an elevation in serum pancreatic amylase activity greater than the institutional upper limit of normal, which persisted within at least the first 48 hours postoperatively (thus including POD 1 and 2). According to the institutional protocols, serum pancreatic amylase activity is routinely assessed 2 h after completing the surgical procedure (POD 0) and at 7 am on POD 1, 2, and 3. In case of altered values, the assessment is continued beyond POD 3 until normalization, but no standardized treatment is currently in use. The Institutional serum pancreatic amylase standard range is 10–52 U/L. Contrast-enhanced CT imaging was performed during the postoperative course when clinically required, facing worsening of the patient's clinical conditions, suspicious for abdominal complications. Accordingly, radiologic alterations were defined once a reduced enhancement of the pancreatic stump, swelling of the pancreatic parenchyma, and/or stranding of the peripancreatic adipose tissue were detected.

Postoperative morbidity was defined according to the ISGPS definitions of PPAP[182], POPF[27], delayed gastric emptying (DGE)[22], postpancreatectomy hemorrhage (PPH)[71], and chyle leak[72]. The updated definition of POPF was retrospectively applied to all patients operated in 2016. Organ space infections[93] were defined as fluid collections within the abdominal cavity with radiological or clinical signs of infection. The occurrence of acute myocardial infarction or severe arrhythmia has been considered cardiac morbidity[185]. Acute kidney injury (AKI) was determined according to 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[169]. 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 90-days postoperatively. The severity of complications was assessed according to the Clavien–Dindo (CD) classification system[74]. Given the early onset of POH in the postoperative period, the possible effect of POH on different morbidity distributions was investigated. The time-to-complication occurrence was retrieved for this purpose. The analysis focused on complications graded as CD ≥ II[74], a complication requiring a relevant change in the postoperative course, and severe complications graded as CD ≥ III[74].

Objectives

The association between POH and postoperative morbidity was explored by stratifying the study population according to POPF occurrence. As a result, four possible scenarios were outlined:

(1) Without POH or POPF,

(2) POH-exclusive,

(3) POH with POPF, and

(4) POPF-exclusive.

The primary objective of the study was the association between POH exclusive (2) and postoperative morbidity. As secondary objectives, the burden of the combined occurrence of POH with POPF (3) was explored. Finally, predictors of the POPF occurrence in the POH population were investigated.

Table 1 – Patients characteristics		**Overall (n= 852)**
Sex	*Male*	463 (54.3%)
	Female	389 (45.7%)
Age *(years, median, IQR)*		65 (56-72)
BMI *(Kg/m^2, median, IQR)*		24 (22-26)
Smoker		184 (21.6%)
Alcohol abuse		28 (3.3%)
Diabetes		170 (20%)
Neoadjuvant therapy		274 (32.2%)
Pancreatic gland texture	*Soft*	423 (49.6%)
	Hard	429 (50.4%)
FRS zones	*Low (0-2)*	283 (33.2%)
	Moderate (3-6)	441 (51.8%)
	High (7-10)	128 (15%)
Estimated Blood Loss *(mL, median, IQR)*		450 (300-701)
Main pancreatic duct diameter *(mm, median, IQR)*		4 (3-5)
Operative time *(min, median, IQR)*		408 (341-467)
Vascular resection		129 (15.1%)
Pancreatic transanastomotic stent		246 (28.9%)
High-risk pathological diagnosis		339 (39.8%)
POH		253 (29.7%)
Postpancreatectomy acute pancreatitis (PPAP)		64 (7.5%)
Biochemical leak		28 (3.3%)
POPF *(total, n.)*		169 (19.8%)
grade	*B*	136 (16%)
	C	33 (3.9%)
Organ space infection		201 (23.6%)
Post pancreatectomy hemorrhage (PPH)		110 (12.9%)
Delayed gastric emptying (DGE)		141 (16.5%)
Chyle leak		30 (3.5%)
Biliary fistula		54 (6.3%)
Bacteremia		135 (15.8%)
Pleural effusion		108 (12.7%)
Pneumonia		135 (15.8%)
Cardiac Morbidity		44 (5.2%)
Acute kidney injury		28 (3.3%)
Relaparotomy		70 (8.2%)
ICU stay		80 (9.4%)
Mortality		21 (2.5%)
Readmission		46 (5.4%)
Length of hospital stay *(days, median, IQR)*		9 (7-20)
Clavien Dindo Classification	Uneventful	376 (44.1%)
	I	71 (8.3%)
	II	261 (30.6%)
	IIIa	36 (4.2%)
	≥ III b	108 (12.7%)

Abbreviations: BMI body mass index, ASA American Society of Anesthesiologists, FRS: fistula risk score; POPF: Postoperative Pancreatic Fistula; ICU: intensive care unit, IQR: interquartile range. High-risk pathological diagnosis: histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis. POH: Post-Operative Hyperamylasemia [serum amylase activity greater than the institutional upper limit of normal (52 U/l), persisting within at least the first 48 hours postoperatively (postoperative day –POD– 1 and 2)].

Statistical analysis

Continuous variables are reported as the median and interquartile range. Differences were assessed with the Mann-Whitney or Student's t-test when appropriate. Categorical variables are reported as frequencies, and differences were evaluated by the chi-square test or Fisher's exact test where applicable. All tests were two-sided. The cumulative incidence functions for morbidity were plotted using the Kaplan–Meier method. The statistical significance of differences in morbidity occurrence was determined using the log-rank test with a Wilcoxon signed-rank test for pairwise post-hoc analysis for multiple comparisons. For post hoc, adjust p-value the Bonferroni's correction was applied. The analysis of predictors of POPF occurrence among the POH population was carried out using a standard logistic regression (enter method). The variables were assessed for multicollinearity and were removed from the model when necessary (e.g., PPAP, serum amylase activity). A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS software (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, NY).

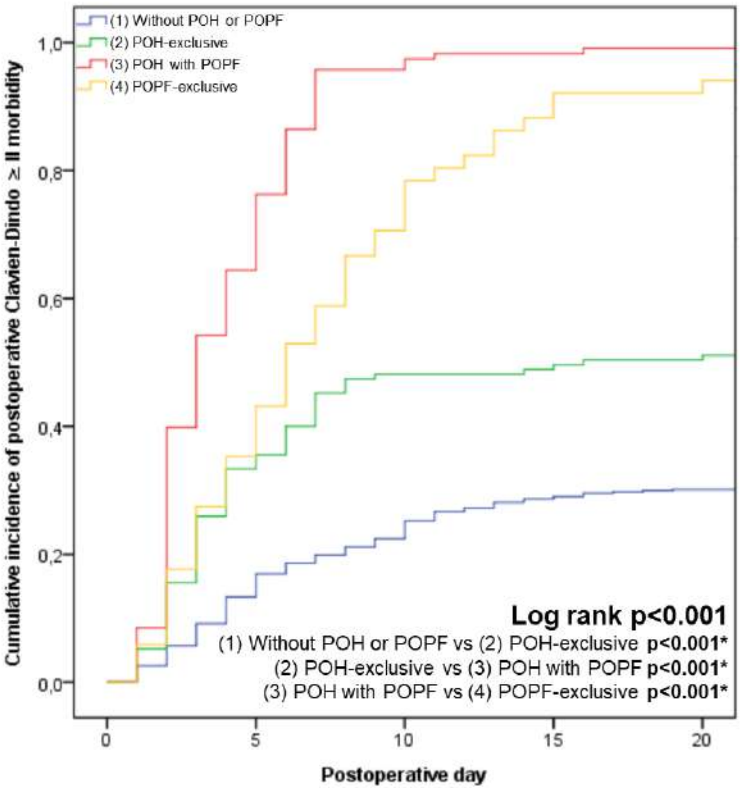

Figure 1: Kaplan Meir functions for the cumulative incidence of postoperative Clavien-Dindo ≥ II morbidity in the overall population stratified according to POH and POPF occurrence. As a result, four possible scenarios were outlined: (1) Without POH or POPF, (2) POH-exclusive, (3) POH with POPF, and (4) POPF-exclusive. (*) Adjusted p-value according to Bonferroni's correction. *Abbreviations: POH postoperative serum hyperamylasemia, POPF postoperative pancreatic fistula. POD: postoperative day. CD: Clavien Dindo Score.*

RESULTS

A total of 852 patients was included. Overall baseline, operative characteristics, and postoperative outcomes are listed in Table 1. The overall postoperative burden is displayed in Figure 1. The CD ≥ II morbidity distribution was highly discriminative between the four scenarios, reflecting the escalation in postoperative morbidity from patients (1) without POH or POPF (30.8%), (2) POH-exclusive (52.6%) to (3) POH with POPF (99.2%) and (4) POPF-exclusive (94.1%).

POH-exclusive (2)

POH-exclusive (2) occurred in 15.8% (n=135) of cases. Compared to patients (1) without POH or POPF (n= 548, 64.3%), POH-exclusive (2) patients experienced a significantly increased rate of bacteremia, pleural effusions, PPH, radiological alterations, and organ site infections. They had significantly longer hospital stays, higher readmission rates, and were more frequently discharged with onsite surgical drain. The (2) POH-exclusive scenario required significantly more antibiotic therapy, parenteral and enteral nutritional support (Table 2). Drain fluid amylase (DFA) on POD1 and CRP during the first three PODs were significantly increased in the (2) POH-exclusive scenario. While the overall postoperative burden was significantly higher in these patients, no difference in severe morbidity (CD ≥ III) was observed compared to patients (1) without POH or POPF, and almost one-third (34.1%, n=46) of (2) POH-exclusive patients had an uneventful postoperative course.

POH impact on POPF

While POPF-exclusive (4) occurred in 5.9% of cases, 118 patients (13.8%) experienced POH with POPF (3). Patients developing POPF experienced significantly higher morbidity and mortality than those without POH or POPF (1) and POH-exclusive (2) (Table 2).

Despite similar rates of postoperative morbidity, patients developing (3) POH with POPF had a significantly shorter median time interval to CD ≥ II morbidity than patients experiencing (4) POPF-exclusive (3 PODs, 95% IC 2.2-3.7 vs. 6 PODs, 95% IC 4.2-8; p <0.001; Figure 1).

With regards to the cumulative incidence of severe morbidity scored as CD ≥ III, POPF patients had the worse outcome (Figure 2). However, the difference between POH with POPF (3) and POPF-exclusive (4); and between POH-exclusive (2) and those without POH or POPF (1) remained not significant.

Table 2 - Postoperative outcomes stratified by POH and POPF occurrence after pancreaticoduodenectomy.

		(1) Without POH or POPF (n =548)	(2) POH-exclusive (n =135)	p*	(3) POH with POPF (n =118)	p**	(4) POPF-exclusive (n=51)	p***
Pancreas- specific complications other than POPF	PPH (Total, n)	41 (7.5%)	18 (13.3%)	**0.03**	37 (31.4%)	**0.001**	14 (27.5%)	0.61
	Grade A	11 (2%)	2 (1.5%)	**0.04**	0	**<0.001**	1 (2%)	0.45
	B	23 (4.2%)	11 (8.1%)		15 (12.7%)		6 (11.8%)	
	C	7 (1.3%)	5 (3.7%)		22 (18.6%)		7 (13.7%)	
	DGE	68 (12.4%)	21 (15.6%)	0.32	38 (32.2%)	**0.003**	14 (27.5%)	0.53
	Organ space infection	60 (10.9%)	25 (18.5%)	**0.02**	82 (69.5%)	**<0.001**	34 (66.7%)	0.71
	Chyle leak	11 (2%)	8 (5.9%)	**0.03**	10 (8.5%)	0.47	1 (2%)	0.17
	Biliary fistula	25 (4.6%)	3 (2.2%)	0.33	18 (15.3%)	**<0.001**	8 (15.7%)	0.94
	Radiologic alterations#	10 (1.8%)	19 (14%)	**<0.001**	50 (42.4%)	**<0.001**	4 (7.8%)	**<0.001**
	PPAP	0	14 (10.3%)	-	50 (42.4%)	**<0.001**	0	-
Systemic complications	Bacteremia	33 (6%)	17 (12.6%)	**0.01**	56 (47.5%)	**<0.001**	29 (56.9%)	0.26
	Pleural effusion	29 (5.3%)	18 (13.3%)	**0.002**	45 (38.1%)	**<0.001**	16 (31.4%)	0.48
	Pneumonia	51 (9.3%)	19 (14.1%)	0.11	44 (37.3%)	**<0.001**	21 (41.2%)	0.63
	Cardiac morbidity	16 (2.9%)	9 (6.7%)	0.06	16 (13.6%)	0.09	3 (5.9%)	0.14
	AKI	10 (1.8%)	5 (3.7%)	0.19	12 (10.2%)	**0.04**	1 (2%)	0.11
	ICU stay	17 (3.1%)	9 (6.7%)	0.07	36 (30.5%)	**<0.001**	18 (35.3%)	0.54
	Relaparotomy	18 (3.3%)	9 (6.7%)	0.08	30 (25.4%)	**<0.001**	13 (25.5%)	0.99
	Clavien Dindo ≥ II	169 (30.8%)	71 (52.6%)	**<0.001**	117 (99.2%)	**<0.001**	48 (94.1%)	0.73
	Clavien Dindo ≥ III	44 (8%)	15 (11.1%)	0.25	58 (49.2%)	**<0.001**	27 (52.9%)	0.65
	Mortality at 90 days	5 (0.9%)	1 (0.7%)	1	12 (10.2%)	**0.001**	3 (5.9%)	0.55
Other outcomes	Antibiotics	113 (20.6%)	51 (37.8%)	**<0.001**	104 (88.1%)	**<0.001**	46 (90.2%)	0.69
	Enteral nutrition	66 (12%)	41 (30.4%)	**<0.001**	90 (76.3%)	**<0.001**	37 (72.5%)	0.74
	Parenteral nutrition	81 (14.8%)	42 (31.4%)	**<0.001**	93 (78.8%)	**<0.001**	42 (82.4%)	0.59
	Discharge with drain	3 (0.5%)	7 (5.2%)	**0.001**	30 (25.4%)	**<0.001**	9 (17.6%)	0.27
	Drain removal (days, median, IQR)	3 (3-4)	5 (4-7)	**<0.001**	29 (21-41)	**<0.001**	26 (14-36)	0.18
	Readmission	18 (3.3%)	12 (8.9%)	**0.008**	14 (11.9%)	0.53	2 (3.9%)	0.15
	Length of hospital stay (days, median, IQR)	8 (6-11)	10 (8-14)	**<0.001**	32 (22-45)	**<0.001**	36 (26-61)	0.14

**p value for (1) without POH or POPF* vs. *(2) POH-exclusive.*
*** p value for (2) POH-exclusive vs. (3) POH with POPF*
**** p value for (3) POH with POPF* vs. *(4) POPF-exclusive*
 # Analysis of 400 patients with postoperative CT imaging.

Abbreviations: POH: Post-Operative Hyperamylasemia; PPAP: postpancreatectomy acute pancreatitis; POPF: Postoperative Pancreatic Fistula; PPH: post pancreatectomy hemorrhage, DGE: delayed gastric emptying, ICU: intensive care unit, AKI: Acute kidney injury, IQR: interquartile range.

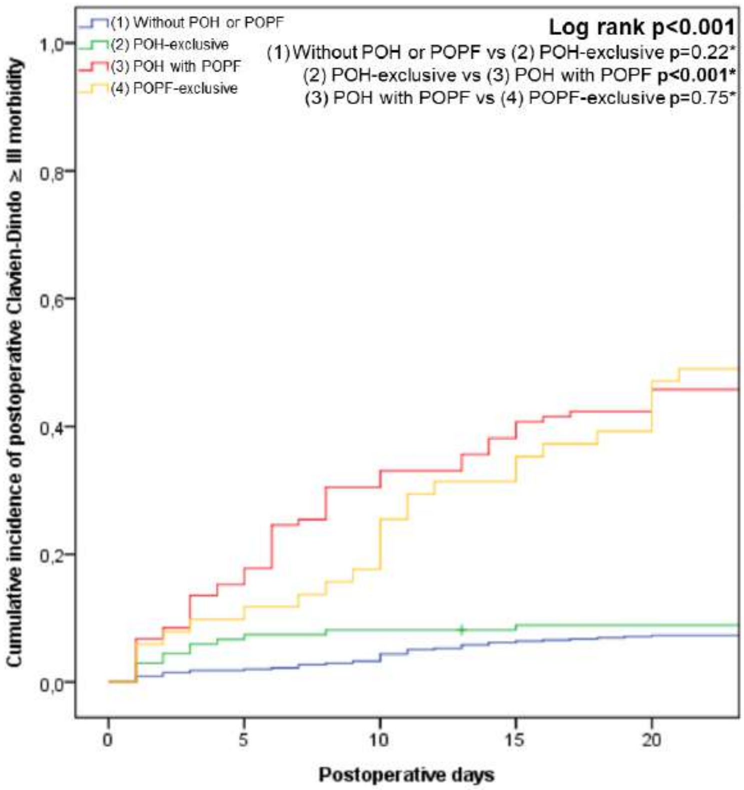

Figure 2: Kaplan Meir functions for the cumulative incidence of postoperative Clavien-Dindo ≥ III morbidity in the overall population stratified according to POH and POPF occurrence. As a result, four possible scenarios were outlined: (1) Without POH or POPF, (2) POH-exclusive, (3) POH with POPF, and (4) POPF-exclusive. (*) Adjusted p-value according to Bonferroni's correction.

Abbreviations: POH postoperative serum hyperamylasemia, POPF postoperative pancreatic fistula. POD: postoperative day. CD: Clavien Dindo Score.

Predictors of POH and POPF

Table 3 reports univariate analysis of pre- and intra- operative factors associated with each scenario. Compared to patients without POH or POPF (1), patients with POH-exclusive (2) were younger and showed lower preoperative diabetes, neoadjuvant therapy, and vascular resections. They also displayed a smaller pancreatic duct, soft pancreatic parenchyma, and high-risk pathological diagnosis. No differences were found between POH-exclusive (2) and POH with POPF scenarios (3).

Overall, 253 patients (29.7%) showed POH. They developed a POPF in 46.6 % of cases vs. 8.5% ($p < 0.001$) of those without POH eventually developing POPF. Predictors of clinically relevant POPF occurrence in the POH population were explored in Table 4. At multivariable analyses, BMI, male sex, higher POD 1 DFA, and POD 2 CRP values were independent risk factors of POPF occurrence once POH had occurred. The AUC of the model was 0.80 (IC95% 0.74 - 0.86).

Table 3 – Univariate Analysis of pre and intraoperative factors stratified by POH and POPF occurrence after pancreaticoduodenectomy

		(1) Without POH or POPF (n =548)	**(2) POH-exclusive (n =135)**	**p***	**(3) POH with POPF (n =118)**	**p****	**(4) POPF-exclusive (n=51)**	**p*****
Age (years)		66 (57-73)	63 (54-69)	**0.002**	65 (56-72)	0.11	67 (60-70)	0.52
BMI (kg/m2)		24 (22-26)	24 (21-26)	0.37	26 (23-28)	**<0.001**	25 (22-28)	0.14
Sex	Male	291 (53.1%)	61 (45.2%)	0.09	75 (63.6%)	0.004	36 (70.6%)	0.37
	Female	257(46.9%)	74 (54.8%)		43 (36.4%)		15 (29.4%)	
Smoke		129 (23.5%)	24 (17.8%)	0.15	23 (19.5%)	0.72	8 (15.7%)	0.66
Alcohol abuse		14 (2.6%)	3 (2.2%)	1	7 (5.9%)	0.19	4 (7.8%)	0.73
Diabetes		141 (25.7%)	12 (8.9%)	**<0.001**	11 (9.3%)	1	6 (11.8%)	0.62
Neoadjuvant therapy		216 (39.4%)	26 (19.3%)	**<0.001**	20 (16.9%)	0.63	12 (23.5%)	0.31
Vascular resection		106 (19.3%)	9 (6.7%)	**<0.001**	10 (8.5%)	0.58	4 (7.8%)	1
Texture	Soft	146 (26.6%)	119(88.1%)	**<0.001**	112(94.9%)	0.06	46 (90.2%)	0.31
	Hard	402 (73.4%)	16 (11.9%)		6 (5.1%)		5 (9.8%)	
FRS zones	Low (0-2)	268 (48.9%)	8 (5.9%)	**<0.001**	5 (4.2%)	0.08	2 (3.9%)	0.57
	Moderate (3-6)	244 (44.5%)	94 (69.6%)		69 (58.5%)		34 (66.7%)	
	High (7-10)	36 (6.6%)	33 (24.4%)		44 (37.3%)		15 (29.4%)	
High-risk pathological diagnosis		155 (28.3%)	83 (61.5%)	**<0.001**	79 (66.9%)	0.36	22 (42.1%)	**0.004**
Operative time (min)		410 (337-471)	386 (339-444)	**0.04**	425 (370-480)	**0.001**	410 (347-465)	0.12
Estimated Blood Loss (mL)		450 (300-701)	400 (250-600)	**0.003**	500 (350-711)	**0.002**	650 (400-900)	0.07
Main Duct diameter (mm)		5 (3-6)	3 (2-4)	**<0.001**	3 (2-4)	0.11	3 (2-4)	0.07
Transanastomotic stent		97 (17.7%)	59 (43.7%)	**<0.001**	54 (45.8%)	0.80	36 (70.6%)	**0.003**
Serum pancreatic amylase POD 1 (U/l)		9.5 (3-29)	224 (139-427)	**<0.001**	232 (155-371)	0.60	47 (28-52)	**<0.001**
Serum pancreatic amylase POD 2 (U/l)		7 (3-19)	143 (88-301)	**<0.001**	155 (96-307)	0.43	23 (18-38)	**<0.001**
DFA POD 1 (U/l)		48 (21-238)	1775 (759-3811)	**<0.001**	3304 (1416-7500)	**<0.001**	1032 (409-4118)	**<0.001**
CRP POD 1 (mg/dl)		88 (66-112)	89 (66-106)	0.83	104 (82-136)	**<0.001**	104 (76-125)	0.35
CRP POD 2 (mg/dl)		149 (103-207)	172 (129-234)	**<0.001**	261 (196-312)	**<0.001**	246 (189-319)	0.73
CRP POD 3 (mg/dl)		132 (77-197)	192 (135-250)	**<0.001**	288 (219-335)	**<0.001**	292 (184-338)	0.75

Continuous variables are reported as median and interquartile range.
**p value for POH-exclusive* vs. *without POH or POPF.*
*** p value for POH-exclusive vs. POH with POPF*
**** p value for POH with POPF* vs. *POPF-exclusive*

Abbreviations: POH: Postoperative Hyperamylasemia, POPF: Postoperative Pancreatic Fistula; BMI: Body Mass Index; FRS: Fistula risk score, DFA: Drain Fluid Amylase; POD: Postoperative day; CRP: C-Reactive protein, High-risk pathological diagnosis: histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis.

Table 4 - Multivariable Analysis for risk factors of clinically relevant POPF in the POH population (n=253).

	P value	**OR**	**IC 95%**
Age (years)	0.91	1.001	0.975-1.029
BMI (kg/m^2)	**0.015**	**1.117**	**1.022-1.220**
Sex (Male)	**0.030**	**2.073**	**1.072-4.009**
Diabetes	0.73	0.825	0.271-2.505
Neoadjuvant therapy	0.91	0.951	0.369-2.448
Soft pancreatic texture	0.33	1.810	0.544-6.020
High-risk pathological diagnosis	0.74	0.885	0.423-1.856
Operative time (min)	0.33	1.002	0.998-1.006
EBL (ml)	0.25	1.001	1.000-1.002
Main Duct diameter (mm)	0.66	0.957	0.781-1.172
DFA POD 1 (U/l)	**0.007**	**1.001**	**1.001-1.002**
CRP POD 2 (mg/dl)	**<0.001**	**1.010**	**1.006-1.015**

Abbreviations: BMI: body mass index; EBL: estimated blood loss, POD: postoperative day, DFA: drain fluid amylase, CRP: C-reactive protein, High-risk pathological diagnosis: histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis

DISCUSSION

This study demonstrates the detrimental effect of POH on pancreaticoduodenectomy outcomes. It depicts the progressive worsening of postoperative scenarios depending on the sequential presence of POH and POPF. The absence of POH or POPF (1) leads to the best outcomes. The addition of POH-exclusive (2) and the eventual development of POPF cause a significant clinical worsening, with a faster deterioration once POH and POPF (3) occur together. Stigmata of normal pancreatic parenchyma are present in both the POH-exclusive and POPF scenarios; however, independent predictors of POPF once POH occurred were found and could serve as targets to label individuals at higher risk of developing additional morbidity.

The sequence of events leading the initial surgical insult to poor postoperative outcomes after pancreaticoduodenectomy is still poorly understood yet vastly investigated in the literature[53,69,121,142,186,187]. In this study, patients with (2) POH-exclusive suffered more systemic and local complications than patients (1) without POH or POPF, including bacteremia, surgical site infections, PPAP and PPH. Such increased postoperative burden has translated into longer hospital stays, more antibiotics, and nutritional support treatments involving up to two-thirds of patients with (2) POH-exclusive, confirming that a spectrum of postoperative morbidity can occur in these patients, regardless of a POPF development. POH has been previously interpreted as a biochemical alteration concomitant to POPF[34,58]. The present findings suggest that POH could represent the biochemical expression of a broader and more complex process, eventually leading to various complications. Indeed, POH has been recently included as a major diagnostic criterion of a postpancreatectomy acute pancreatitis (PPAP)[182], and although only a laboratory abnormality by definition, its recognition and investigation may allow for an earlier therapeutic window in the immediate postoperative period[1,115,116]. However, the underlying mechanisms linking (2) POH exclusive to further morbidity are yet to be fully unravelled. Only 10% of (2) POH-exclusive patients evolved towards more severe sequelae and/or had a clinically relevant PPAP, and nearly 1/3 followed an uneventful clinical course. Therefore, the presence of POH per se does not equal an incipient major morbidity, and further studies are needed to understand the complex interplay of factors contributing to (2) POH-exclusive morbidity.

The relationship between POH and POPF plays a major role in the present study. Patients with POH are at higher risk for POPF development as half of them subsequently developed a leak of the pancreatic anastomosis [14,108,187]. Compared to the (2) POH-exclusive scenario, clinical outcomes worsened in an escalating fashion in patients eventually developing (3) POH with POPF, confirming POPF to be the main driver of severe morbidity and mortality after pancreaticoduodenectomy. Although the topic has already been explored in the literature[27,184], the clinical impact of a combined occurrence of (3) POH with POPF has been scarcely reported. Patients developing (3) POH with POPF showed a faster progression to additional clinically relevant scenarios than others, including those with (4) POPF-exclusive. Such a clinical deterioration occurred impressively early, on average, within the first three postoperative days. Still, the overall rates of postoperative morbidity did not significantly differ among POPF-related scenarios, suggesting, once again, that POPF is a multifactorial event. We could speculate that POH is the early serum marker of just one of many etiologic factors of POPF, namely PPAP[1,9,69,121], radiologically and clinically confirmed in approximately 40% of these patients. Finally, (4) POPF-exclusive patients had delayed relevant clinical pictures. We can speculate that such later onset is due to other known mechanisms (e.g., infections, alteration of the healing process) that eventually occur and affect the final outcome[121,186,188]. Still, 8% of these patients showed parenchymal and peripancreatic radiological changes, which confirmed the challenging differential diagnosis in postoperative imaging and the need for further studies.

These results can be clinically critical and potentially game-changing in clinical practice. Given the rapid evolution that may occur, the presence of POH can represent the counterpart of the "*golden hour*" in trauma[189], in which prompt measures can potentially prevent poor outcomes after pancreaticoduodenectomy. The underestimation of an incipient clinical worsening could be harmful, as well as an overestimation could lead to unnecessary costs and a waste of resources. Early efforts should be made to predict a potential subsequent clinical deterioration and decide whether a patient may benefit from target treatments. Although no evidence is available to date, the postoperative period offers a standardized setting - with a known time of onset and regular monitoring - potentially privileged to design future clinical trials testing new specific therapeutic agents and strategies. These may eventually include balanced but adequate fluid administration[178,190], tailored enhanced recovery pathways with new goals in oral intake and nutritional support[85], redesigned drains protocols, especially once mitigations strategies have been applied[70], and optionally completion pancreatectomy, facing the worst clinical scenarios[191]. This study highlighted BMI, male sex, increased drain fluid amylase on POD 1, and increased CRP values as independent risk factors for POPF once POH is ongoing. Such risk factors align with the previous pancreatic literature[12,17,53,69,70,148] but are evaluated in a new timeframe, namely that of the earliest postoperative period. The (2) POH-exclusive and the (3) POH with POPF populations were similarly associated with other already recognized risks factors related to functional pancreatic parenchyma (e.g., soft texture, small pancreatic duct)[1,23,69,152], and included in several risk scores proposed over the years[69,148]. Still, the need for further or different scores underlines that POPF is not captured by a static, omni-comprehensive, and punctual evaluation. The growing understanding of mechanisms contributing to POPF calls for its dynamic evaluation, in which variables should be ultimately considered in a sequential assessment starting in the preoperative screening and continuously reappraised until early postoperative[69,96,141].

Finally, but of the utmost importance, this study confirms a definite separation between POH and POPF while confirming their interplay, as recently outlined in an international statement that included POH among the diagnostic criterion of PPAP[182]. Although it may be argued as a limitation, this study deliberately did not focus on PPAP because it aimed to highlight early factors – such as POH – of clinical outcomes. Conversely, those results encourage further prospective studies targeting the POH-PPAP population for new preventive or therapeutic measures.

This study has limitations. Even if data were prospectively collected, patients without complete data on multiple postoperative assessments of serum amylase activity were excluded, and the final cohort may not be fully representative of the entire population of patients undergoing pancreaticoduodenectomy. An inherent drawback of this study is that only pancreaticoduodenectomies were included. Although with a different definition of POH, no clinically relevant change was previously reported in the postoperative course of distal pancreatectomy in the POH population[62].

CONCLUSION

Postoperative serum hyperamylasemia has relevant implications for the postoperative outcome of a pancreaticoduodenectomy, independently from POPF occurrence. Although separate entities, the POH population has 3 to 4 folds increased risk of POPF development, and patients developing POH with POPF have higher postoperative burdens with an earlier onset of clinically relevant scenarios.

Once a POH is diagnosed, several risk factors for POPF could identify patients who may benefit from additional surveillance and preventive strategies. Further studies are needed to explore the mechanisms behind the development of POH clinical sequelae, potentially identifying specific management strategies that could be early applied once POH occurs.

Chapter 7 - Postoperative serum hyperamylasemia (POH) adds sequential value to the Fistula Risk Score (FRS) in predicting pancreatic fistula after pancreatoduodenectomy

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Annals of Surgery, 2022 Jul 25; DOI: 10.1097/SLA.0000000000005629

ABSTRACT

Objective

To evaluate whether postoperative serum hyperamylasemia (POH), with drain fluid amylase (DFA) and C-reactive protein (CRP), improves the Fistula Risk Score (FRS) accuracy in assessing the risk of a postoperative pancreatic fistula (POPF).

Background Data:

The FRS predicts POPF occurrence using intraoperative predictors with good accuracy but intrinsic limits.

Methods

Outcomes of patients who underwent pancreaticoduodenectomies (PD) between 2016 and 2021 were evaluated across FRS risk zones and POH occurrence. POH consists of serum amylase activity greater than the upper limit of normal (52 U/l), persisting within the first 48 hours postoperatively (postoperative day –POD– 1 and 2).

Results

Out of 905 PDs, some FRS elements, namely soft pancreatic texture (OR 11.6), pancreatic duct diameter (OR 0.80), high-risk pathological diagnosis (OR 1.54), but not higher blood loss (OR 0.99), were associated with POH. POH was an independent predictor of POPF, which occurred in 46.8% of POH cases (p<0.001). Once POH occurs, POPF incidence rises from 3.8% to 42.9%, 22.9% to 41.7%, and 48.9% to 59.2% in patients intraoperatively classified at low, moderate and high FRS risk, respectively. The predictive ability of multivariable models adding POD 1 drain fluid amylase, POD 1-2 POH and POD 3 C-reactive protein to the FRS showed progressively and significantly higher accuracy

(AUC FRS=0.82, AUC FRS-DFA=0.85, AUC FRS-DFA-POH=0.87, AUC FRS-DFA-POH-CRP=0.90, DeLong always $p<0.05$).

Conclusions

POPF risk assessment should follow a dynamic process. The stepwise retrieval of early, postoperative biologic markers improves clinical risk stratification by increasing the granularity of POPF risk estimates and affords a possible therapeutic window before the actual morbidity of POPF occurs.

INTRODUCTION

Postoperative pancreatic fistula (POPF) still is the most harmful complication after a pancreaticoduodenectomy, playing the role of the major trigger of additional morbidity and mortality[108,118]. Accordingly, its early prediction represents a crucial step towards the goal of improving postoperative outcomes. The implementation of specific POPF risk scores in clinical practice has significantly modified management protocols[69,142,148,192]. In detail, the proficiency in foreseeing the occurrence and gravity of POPF has made it possible to selectively apply, or withhold, various mitigation strategies[69,84,140,151,193]. The Fistula Risk Score (FRS)[69] - including both endogenous and intraoperative variables assessed during the surgical procedure - is the most widely applied predictive score. When incorporated into daily practice, the FRS has proven to markedly improve outcomes by segregating patients into discrete classes receiving tailored treatments[119,194].

Still, POPF rates remain significant - as high as 20%[108] - even at high-volume centers applying FRS-driven protocols worldwide. Rather than depicting a major flaw of the score, such a relevant incidence of POPF might be explained by yet unexamined mechanisms of progression from risk factors to clinical events, as well as the intrinsic imperfection of embarking upon prediction assessment at a single time point as leaks manifest temporally over the course of the postoperative period.

To that end, recent literature has identified early postoperative variables associated with POPF, which may be biochemical signs of the biological response to surgical trauma based on the interaction of pre-existing and evolving factors[12,16,53]. Prior reports demonstrated drain fluid amylase (DFA) activity and serum C-reactive protein (CRP) strongly associated with pancreatic leakage[10,12,15,42,149]. Recently, postoperative serum hyperamylasemia (POH) has been identified as the biochemical expression of an acute inflammatory process of the pancreatic remnant and therefore has been included among diagnostic criteria for postpancreatectomy acute pancreatitis (PPAP)[182]. As one of the earliest biochemical alterations associated with worse postoperative outcomes, its identification opens a new diagnostic portal to the immediate postoperative period[1,115,116]. However, whether POH might improve the accuracy of POPF risk estimates has not yet been investigated.

This study aimed to assess the POPF incidence in patients undergoing a pancreatoduodenectomy (PD) stratified by FRS and POH. The primary endpoint explored the models' performance in appraising POPF hazard while considering the FRS alone or when augmented with early postoperative biologic markers (namely, POH, DFA and CRP). In addition, predictors of POH and POPF occurrence were evaluated.

METHODS

A prospectively maintained database included all consecutive patients who underwent a pancreaticoduodenectomy performed from January 2016 to May 2021 at the Department of General and Pancreatic Surgery—The Pancreas Institute, University of Verona Hospital Trust. The study was approved by the local ethics committee (Comitato Etico delle Province di Verona e Rovigo, approval number 1101CESC) and performed according to the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE).

Demographics, intraoperative data, and postoperative outcomes were collected. Preoperative characteristics included age, sex, BMI [kg/m^2], comorbidities, and neoadjuvant therapy use. All pancreatic resections were carried out according to previously described institutional techniques via an open approach[64,66]. Both pylorus-preserving and classical PDs with either pancreatojejunostomy or pancreaticogastrostomy were included.

The risk for pancreatic fistula was assessed according to the Fistula Risk Score (FRS)[69] by combining: (1) pancreatic texture (defined based on the manual palpation of experienced pancreatic surgeons), (2) pancreatic duct diameter (measured using a sterile disposable ruler), (3) pathology (considering histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis as having a "high-risk pathology"), and (4) estimated blood loss (EBL). The FRS values escalate in risk from zero to ten so that higher scores reflect higher risks for clinically-relevant POPF; accordingly, four risk zones have been defined; negligible risk (0 points), low risk (1–2 points), moderate risk (3–6 points), and high risk (7–10 points)[69].

Externalized pancreatic stents (PankreaPlus polyvinyl catheter; Peter Pflugbeil Gmbh Medizinische Instrumente) were employed as a specific mitigation strategy in all patients at high risk for POPF and in selected cases when the risk was estimated as moderate. Neither internal stents nor sealants, patches or Roux limbs were used in any circumstance, nor were prophylactic octreotide or steroids ever administrated as fistula mitigation strategies. According to our institutional policies, we followed an early drain removal and selective drain management protocol, as previously described[14,70]. Surgical drains were placed in all patients apart from those deemed at low and negligible risk according to FRS unless for other surgical reasons (e.g., high-risk hepaticojejunostomy, vascular or multiorgan resections). When drains were placed, early removal on postoperative day (POD) 3 was promoted based on the POD 1 drain fluid amylase (DFA) value < 5000 U/l[53,70] and without a new assessment in POD 3 if no sinister drain fluid appeared. Additional DFA values were recorded from POD 5 and/or thereafter if a drain was kept in place based upon initially high DFA levels or clinical indications to maintain the drain longer.

Outcome metrics

Postoperative complications were scored according to the Clavien-Dindo Classification[74] over the course of 90 days. Pancreas-specific morbidity, including postoperative pancreatic fistula (POPF)[118]; postpancreatectomy hemorrhage[136]; delayed gastric emptying[137]; chyle leak[195]; and PPAP[182], were defined according to the International Study Group for Pancreatic Surgery (ISGPS). POH was characterized by a sustained increase in serum amylase activity greater than the institutional upper limit of normal (standard range 10–52 U/L), persisting for at least the first 48 hours postoperatively (POD 1-2). According to our institutional protocols, serum pancreatic amylase activity is routinely assessed 2 hours after completing the surgical procedure (POD 0) and at 7 am from POD one to three, and, in case of altered values, beyond until normalization. No standardized treatment is currently applied in the setting of realizing POH. Postoperative protocols also included the routine measurement of serum inflammatory markers (C-reactive protein - CRP) in POD 1, 2, and 3. Organ space infections[93] were defined as fluid collections within the abdominal cavity with radiological or clinical signs of infection. Only an unplanned need for intensive care was defined as an intensive care unit (ICU) stay. Mortality was defined as postoperative death recorded out to the point of 90-days postoperatively.

The primary endpoints were to assess POPF incidence stratified by FRS and POH and, furthermore, the POPF forecasting capability of the FRS using models that included postoperative POH, DFA and CRP values. Finally, predictors of POH and POPF were investigated.

Table 1. Patients characteristics		**Overall (n= 905)**
Sex	Male	494 (54.6%)
Age (years, median, IQR)		66 (56-72)
Body Mass Index – BMI- (Kg/m^2, median, IQR)		24 (22-26.2)
Smoker		207 (22.9%)
Alcohol abuse		30 (3.3%)
Diabetes		176 (19.4%)
Neoadjuvant therapy		299 (33%)
High-risk pathological diagnosis		360 (39.8%)
Estimated Blood Loss – EBL - (mL, median, IQR)		450 (723)
Main pancreatic duct diameter (mm, median, IQR)		4 (3-5)
Pancreatic gland texture	Soft	456 (50.4%)
	Hard	449 (49.6%)
Fistula Risk Score (FRS)	0	63 (7%)
	1	121 (13.4%)
	2	113 (12.5%)
	3	151 (16.7%)
	4	109 (12%)
	5	119 (13.1%)
	6	96 (10.6%)
	7	71 (7.8%)
	8	45 (5%)
	9	13 (1.4%)
	10	4 (0.4%)
FRS zones	Negligible (0)	63 (7%)
	Low (1-2)	234 (25.9%)
	Moderate (3-6)	475 (52.5%)
	High (7-10)	133 (14.7%)
Operative time (min, median, IQR)		410 (343-472)
Pancreatic transanastomotic stent		344 (38%)
Serum amylase POD 0 (U/l, median, IQR)		31 (9-75)
Serum amylase POD 1 (U/l, median, IQR)		29.5 (6-135)
Serum amylase POD 2 (U/l, median, IQR)		19 (5-74.7)
Serum amylase POD 3 (U/l, median, IQR)		12 (4-30)
POH		265 (29.3%)
DFA POD 1 (U/l, median, IQR)		286 (33-1476)
C-reactive protein POD 2 (mg/dl, median, IQR)		171 (117-235)
C-reactive protein POD 3 (mg/dl, median, IQR)		164 (98-247)
Biochemical leak		28 (3.1%)
POPF (clinically relevant)		183 (20.2%)
POPF grade	B	148 (16,4%)
	C	36 (4%)
Postpancreatectomy acute pancreatitis		68 (7.5%)
Organ space infection		210 (23.2%)
Post pancreatectomy haemorrhage (PPH) (ABC grades)		120 (13.3%)
delayed gastric emptying (DGE)		151 (16.7%)
Chyle leak		31 (3.4%)
Relaparotomy		77 (8.5%)
Intensive care unite unplanned		83 (9.2%)
Mortality		24 (2.7%)
Drain removal (days, median, IQR)		7 (5-25)
Length of hospital stay (days, median, IQR)		9 (7-20)
Clavien Dindo Classification	Uneventful	391 (43.2%)
	I	76 (8.4%)
	II	283 (31.3%)
	IIIa	37 (4.1%)
	≥ III b	118 (13%)

Abbreviations: POPF: Postoperative Pancreatic Fistula; POD: postoperative day, IQR: interquartile range. High-risk pathological diagnosis: histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis.

Statistical analysis

Continuous variables are expressed as medians and interquartile range (IQR) and compared with the Mann-Whitney *U* test. Categorical variables are presented as absolute numbers with percentages, and associations were tested using the chi-square test or Fisher's exact test. A standard logistic regression (enter method) was performed to assess the potential risk factors for POH and POPF. The predictive power of POD 3 serum C-reactive protein was assessed by calculating the area under the receiver-operator characteristic (ROC) curve, and the retrieved cut-off of 200 mg/dl (sensibility= 77%; specificity= 73%) was considered for further analysis. The predictive probability of developing a POPF was calculated according to the FRS elements for each patient. Three other logistic regression models[196] were built, namely the FRS-DFA by adding POD 1 DFA > 5000 U/l, FRS-DFA-POH, by also adding POH, and FRS-DFA-POH-CRP, by adding POD 1 DFA (> 5000 U/l), POH and POD 3 CRP (> 200 mg/dl) to conventional FRS variables. The predictive abilities of those models were compared with the ROC method and expressed by the area under the ROC curve (AUC). The difference between the areas under the ROC curves was tested with the DeLong method, and Holm's correction was applied for multiple pairwise comparisons. Otherwise, a two-sided p-value of 0.05 was considered significant for each test. All statistical computations were performed with IBM SPSS (IBM SPSS Statistics for Windows, Version 22.0; IBM Corp, Armonk, NY).

RESULTS

A total of 905 PDs were included in the analysis. Of these, 29.3% (n= 265) developed POH and 20.2% (n= 183) POPF. Of the POPF patients, 148 (16.3%) had grade B, and 36 (3.9%) grade C. According to the FRS, the risk for POPF was negligible in 7% (n = 63), low in 25.9% (n = 234), moderate in 52.5% (n = 300), and high in 14.7% (n = 133) of patients. Overall demographic, surgical, and outcome variables are displayed in Table 1.

Predictors of POH: FRS elements and other variables

As reported in table 2, patients with POH were younger, had higher BMI, and had a lower rate of diabetes, neoadjuvant treatment, and vascular resections. Considering FRS elements, patients with POH displayed a smaller median MPD diameter, lower EBL, and higher rates of soft pancreatic texture and high-risk pathological diagnoses. Most FRS elements were confirmed as independent risk factors for POH at multivariable analysis, with the highest risk attributed to a soft pancreatic texture (OR 11.6), while EBL, older age and smoking resulted as protective factors (AUC of the model 0.85, 95% CI 0.82-0.87).

Table 2. Univariate and multivariable analysis of predictors of POH after PD

		Univariate Analysis			Multivariable Analysis		
		No POH (n=640)	**POH (n=265)**	**p**	**OR**	**95% CI**	**p**
Texture	Soft	215 (33.6%)	241 (90.9%)	<0.001	11.60	7.1-18.9	**<0.001**
	Hard	425 (66.4%)	24 (9.1%)			ref	
MPD (mm, median, IQR)		4 (3-6)	3 (2-4)	<0.001	0.80	0.73-0.89	**<0.001**
Pathological diagnosis	High risk	190 (29.7%)	170 (64.2%)	<0.001	1.54	1.03-2.31	**0.03**
	Low risk	450 (70.3%)	95 (35.8%)			ref	
EBL (ml, median, IQR)		485 (300-750)	450 (300-650)	0.014	0.99	0.98-0.99	**0.03**
FRS zones	Negligible (0)	63 (9.8%)	0	<0.001			
	Low (1-2)	220 (34.4%)	14 (5.3%)				
	Moderate (3-6)	300 (46.9%)	175 (66%)				
	High (7-10)	57 (8.9%)	76 (28.7%)				
OT (min, median, IQR)		410 (340-479)	405 (350-466)	0.73			
Vascular resection		115 (18%)	20 (7.5%)	<0.001	0.81	0.43-1.49	0.50
BMI (Kg/m^2, median, IQR)		24 (22-26)	24 (22-27)	0.015	1.04	0.9-1.10	0.07
Sex	Male	353 (55.2%)	141 (53.2%)	0.59			
	Female	287 (44.8%)	124 (46.8%)				
Diabetes		152 (23.8%)	24 (9.1%)	<0.001	0.69	0.39-1.2	0.19
Smoking history		158 (24.7%)	49 (18.5%)	0.04	0.64	0.42-0.99	**0.04**
Alcohol abuse		20 (3.1%)	10 (3.8%)	0.62			
Neoadjuvant		249 (38.9%)	50 (19.9%)	<0.001	0.82	0.51-1.31	0.41
Age (years, median, IQR)		66 (57-72)	64 (55-71)	0.010	0.98	0.96-0.99	**0.04**

Abbreviations: BMI body mass index, EBL: estimated blood loss, OT: operative time, MPD: main pancreatic duct, FRS: fistula risk score, IQR: interquartile range, POH: Postoperative serum hyperamylasemia [serum amylase activity greater than the institutional upper limit of normal (52 U/l), persisting within at least the first 48 hours postoperatively (postoperative day – POD– 1 and 2)].

Figure 1. a-b reports the POH incidence in relation to the FRS risk zones and individual FRS scores. Most POH patients segregated into moderate-high FRS zones (p<0.001). As the model score escalated, the incidence of POH increased significantly (p < 0.001) with an inversion point at FRS 5. Of the 63 patients (7%) with an FRS of 0 (negligible risk; FRS Scenario 1[140]), none developed a POH.

Predictors of POPF: FRS elements and other variables

Table 3 shows the results of univariate and multivariable analyses of the predictors of POPF after PD. Soft texture, MPD diameter, EBL, BMI, male sex, POD 1 DFA activity, POD 3 CRP values and POH were confirmed as independent predictors of POPF at the multivariable model (AUC 0.90; 95% CI 0.88-0.92). Increasing FRS scores correlated well

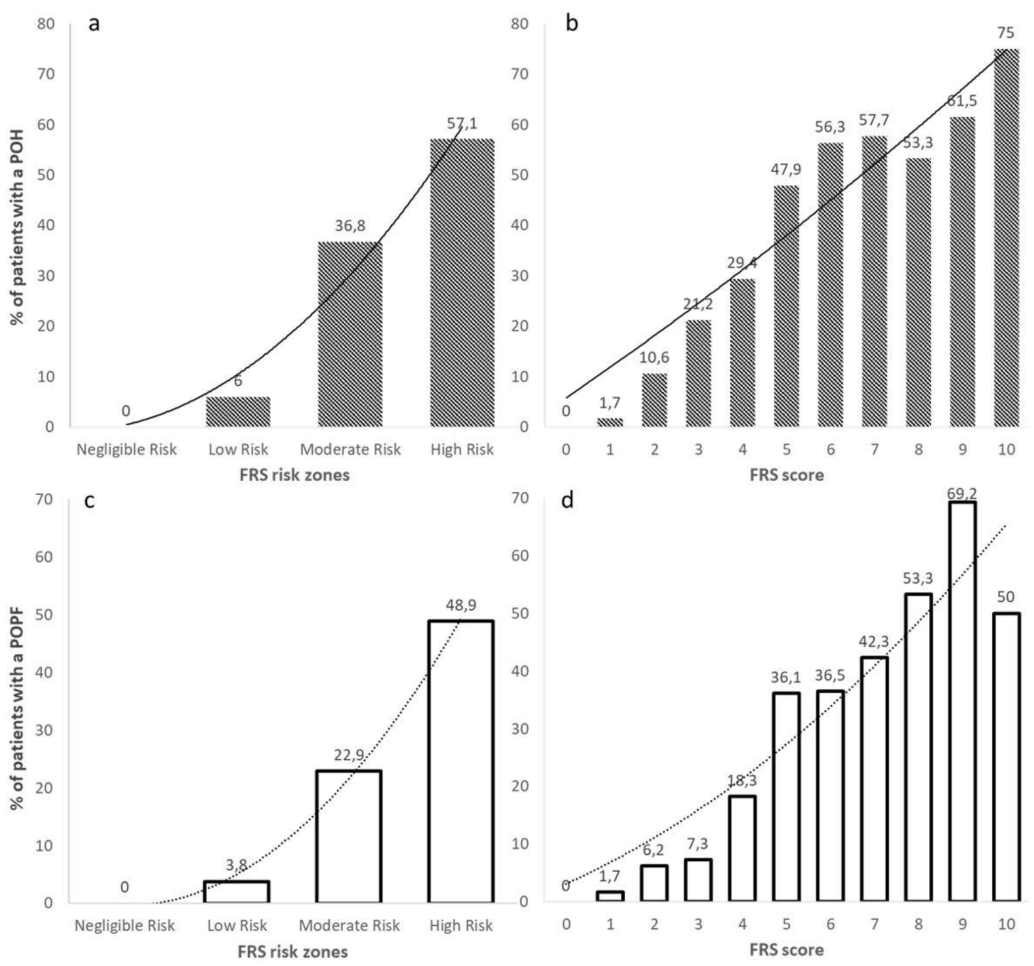


Figure 1: Bar graphs and trendline of postoperative serum hyperamylasemia (POH) occurrence according to the Fistula Risk Zones and Score (a,b). Bar graphs and trendline of postoperative pancreatic fistula (POPF) occurrence according to the Fistula Risk Zones and Score (c,d).

with POPF development ($p < 0.001$). When segregated by defined FRS risk zones, POPF occurred in 11 low-risk (3.8 %), 29 moderate-risk (22.9%), and 65 high-risk patients (48.9%), $p < 0.001$ (Figure 2). No POPF occurred within negligible risk (FRS 0) patients (Figure 1. c-d), while only one occurred in the drainless cohort (1.5%).

Correlation between POH and POPF after risk stratification

Patients with POH developed a POPF in 46.8% of cases vs 9.2% ($p < 0.001$) of those without POH. The increasing incidence of POPF moving along the FRS-risk zones was maintained in patients without POH, while in POH patients, the incidence of POPF was constantly >40% in all risk zones (except negligible, where POH did not occur – as above), including low-risk cases, with consequent loss of a linear correlation (Figure 2). POH was strongly associated with POPF regardless of mitigation strategies.

As the FRS model score escalated, the incidence of grade C POPF in the POH population showed an increasing trend, although not significant.

Table 3. Univariate and multivariable analysis of predictors of POPF after PD

		Univariate Analysis			Multivariable Analysis		
		No POPF (n=722)	**POPF (n=183)**	**p**	**OR**	**95% CI**	**p**
Texture	Soft	286 (39.6%)	170 (92.9%)	< 0.001	7.6	3.9-15.3	**< 0.001**
	Hard	436 (60.45)	13 (7.1%)			Ref.	
MPD (mm, median, IQR)		4 (3-5.2)	3 (2-4)	< 0.001	0.8	0.76-0.98	**0.03**
Pathological diagnosis	High risk	249 (34.5%)	111 (60.7%)	< 0.001	0.92	0.55-1.51	0.73
	Low risk	473 (65.5%)	72 (39.3%)			Ref.	
EBL (ml, median, IQR)		450 (300-701)	500 (390-800)	0.005	1.002	1.001-1.002	**0.005**
FRS zones	Negligible (0)	63 (8.7%)	0	< 0.001			
	Low (1-2)	225 (31.2%)	9 (4.9%)				
	Moderate (3-6)	366 (50.7%)	109 (59.6%)				
	High (7-10)	68 (9.4%)	65 (35.5%)				
Operative time (min, median, IQR)		405 (340-469)	425 (358-480)	0.03			
Vascular resection		117 (16.2%)	18 (9.8%)	0.03			
BMI (Kg/m^2, median, IQR)		24 (21.8-26)	25 (23-28)	< 0.001	1.11	1.04-1.18	**0.001**
Sex	Male	374 (51.8%)	120 (65.6%)	0.001	1.9	1.23-3.06	**0.004**
	Female	348 (48.2%)	63 (34.4%)			Ref.	
Diabetes		157 (21.7%)	19 (10.4%)	0.001	0.78	0.39-1.54	0.47
Smoke		170 (23.5%)	37 (20.2%)	0.33			
Neoadjuvant		261 (36.1%)	38 (20.8%)	< 0.001	0.94	0.52-1.69	0.84
Age (years, median, IQR)		65 (56-72)	66 (58-72)	0.54			
DFA (POD 1, U/L,median, IQR)		101 (21-721)	2354 (796-5510)	< 0.001	2.72	1.48-5.02	**0.001**
POH		141 (19.5%)	124 (67.8%)	< 0.001	3.11	1.94-4.99	**< 0.001**
CRP (POD 3, mg/dl, median, IQR)		145 (85-206)	286 (207-332)	< 0.001	7.04	4.29-11.57	**<0.001**

Abbreviations: BMI body mass index, EBL: estimated blood loss, OT: operative time, MPD: main pancreatic duct, FRS: fistula risk score, DFA: drain fluid amylase, POD: postoperative day, POPF: Postoperative Pancreatic Fistula; CRP: C-Reactive Protein, IQR: interquartile range,

POH: Postoperative serum hyperamylasemia [serum amylase activity greater than the institutional upper limit of normal (52 U/l), persisting within at least the first 48 hours postoperatively (postoperative day –POD– 1 and 2)].

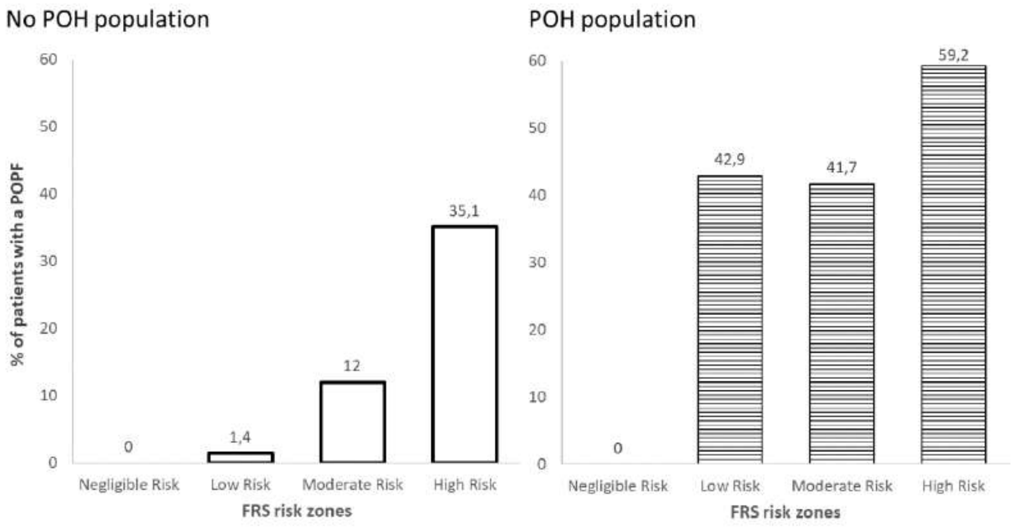


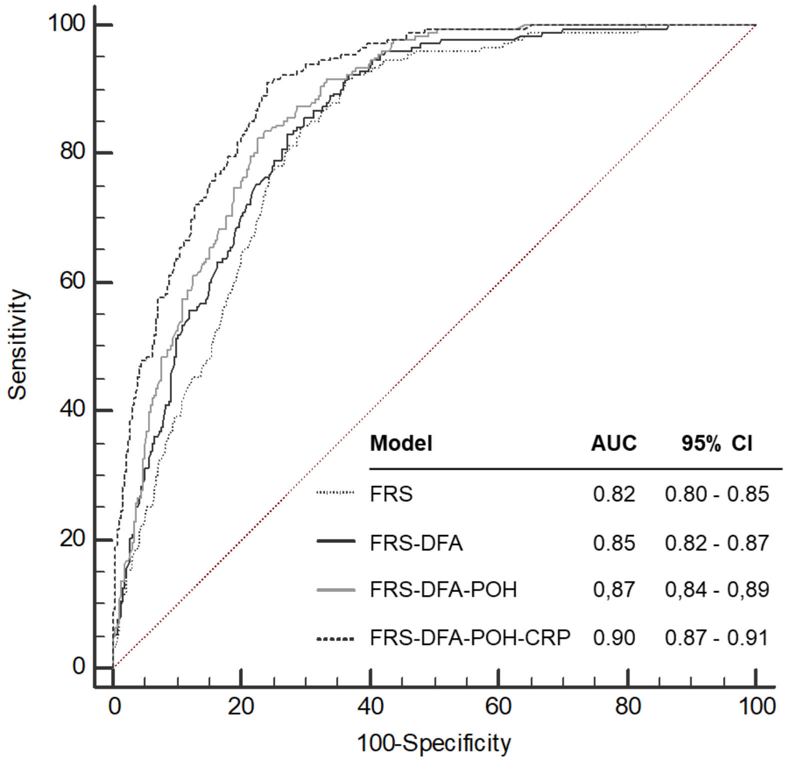
Figure 2: Bar graphs of postoperative pancreatic fistula (POPF) occurrence according to the Fistula Risk Zones stratified by postoperative serum hyperamylasemia (POH) occurrence.

Development of iterative risk modeling

To test the added value of early postoperative biochemical values to the initial risk stratification using the FRS, the predictive ability of the original FRS model and those sequentially, including POD 1 DFA, POD 1-2 POH and POD 3 CRP, were compared and displayed in Figure 3. The ROC curve for FRS alone yielded an AUC of 0.82 (95% CI 0.80-0.85). By adding POD 1 DFA (>5000 U/l) to the FRS (FRS-DFA), the ROC curve showed higher accuracy (AUC = 0.85, 95% CI 0.82-0.87). The difference between the two models was statistically significant (DeLong p = 0.002). A third model was developed, including POH (FRS-DFA-POH), with an accuracy significantly higher than the FRS-DFA version (DeLong p = 0.006) (AUC = 0.87, 95% CI 0.84-0.89). Finally, POD 3 CRP (>200 mg/dl) was also included (FRS-DFA-POH-CRP), showing a significant predictive improvement (AUC 0.90, 95% CI 0.87-0.91) over the FRS-DFA-POH model (DeLong p <0.001).

DISCUSSION

This study demonstrates that early and sequentially acquired postoperative biologic markers could improve appraising patients' specific pancreatic fistula hazard profiles, given the setting of risk stratification and mitigation strategies. Besides early, known parameters like drain fluid amylase and C-reactive protein, this study specifically highlighted the added value of postoperative serum hyperamylasemia (POH). Although most risk factors for both POH and POPF overlap and are already integrated into predictive tools like the Fistula Risk



Pairwise comparison of ROC curves:
FRS vs. FRS-DFA: De Long p=0.002*; FRS-DFA vs. FRS-DFA-POH: DeLong p = 0.006*;
FRS-DFA-POH vs. FRS-DFA-POH-CRP: DeLong p<0.001*
*statistically significant with Holm's correction.

Figure 3: Receiver operating characteristic (ROC) curves comparing different models for postoperative pancreatic fistula (POPF) risk assessment: original-FRS, FRS-DFA (including drain fluid amylase > 5000 UI assessed on POD 1), FRS-DFA-POH (including postoperative serum hyperamylasemia > 52 U/l at least on both POD 1 and 2) and FRS-DFA-POH-CRP (including serum C-reactive protein > 200 mg/dl assessed on POD 3), which shows the best accuracy. The difference between the areas under the ROC curves was tested with the DeLong method, and Holm's correction was applied for multiple pairwise comparisons. Data based on 837 patients with surgical drains.

Score (FRS)[69], the assessment of POH in the immediate postoperative period appears to further improve POPF risk assessment. This is particularly relevant in patients intraoperatively deemed at low to moderate risk, with POH being associated with a 2-10 fold added risk compared to baseline FRS estimates.

In recent decades, it has been gradually established how POPF prediction plays a significant role in managing pancreatic resections. Identified risk associations have eventually been incorporated into predictive scores[69,141,148,192]. The extensive implementation of forecasting tools in clinical practice has allowed the early appraisal of patients at higher risk for anastomotic leakage and has driven either the application or withholding of mitigation strategies with the potential to positively affect surgical outcomes[14,15,70,84]. However, the effective prediction of a pancreatic fistula remains a challenge, suggesting that several interacting biologic parameters could influence its occurrence[148,197,198].

This study, once again, confirms that the four elements of the FRS[69] are independent predictors of POPF and properly stratify patients into discrete classes of risk. In addition to previous validation literature, the FRS has hereby also emerged as a suitable tool for POH prediction. This can be explained by the mutual congruence of risk factors [1,9,96,142]. Of these, the soft pancreatic parenchyma still represents the most critical element. Hence, we could speculate that such a fragile pancreatic texture is more susceptible to surgical injury during both the operative dissection and anastomotic suturing[44,92], as well as being more vulnerable to physiologic stressors (e.g. hypotension). Moreover, the soft pancreas is typically associated with a non-dilatated main pancreatic duct, making it challenging to reconstruct and more likely to occlude[142], and it has a preserved exocrine function, resulting in a florid secretion of proteolytic enzymes[43]. Conversely, higher estimated blood loss, advanced age and smoking resulted as protective factors for POH, possibly representing indirect indicators of a firmer pancreas due to chronic pancreatitis or advanced malignancy requiring more complex surgical resections.

Although the FRS was able to stratify patients with an increased risk of developing POH, considerable inconsistency remained. Indeed, in patients with FRS 10 - the highest risk - POH does not seem to manifest in all cases. Additional hereditary factors, untested pathological mechanisms, and intraoperatively applied mitigation strategies might have influenced this inter-individual susceptibility.

Given the considerable overlap among known predictors, POH and POPF have been historically considered a unique, singular complication[20], and even after the advent of separate standardized definitions[118,182], their relationship is still controversial. Notably, POPF may occur without POH, but half of the POH population subsequently developed a POPF. Albeit confirming a definite separation between POH and POPF, this evidence highlights their strong interplay and suggests a possible evolution from risk factor exposure to POPF occurrence.

The mechanism through which the FRS elements promote a POPF has not been fully elucidated yet, but POH has been recently proposed as the earlier serum marker of one key pathway leading to POPF, namely postpancreatectomy acute pancreatitis (PPAP)[1,69,121]. In this context, since risk factors do not equal causative conditions, the predictive ability of a single intraoperative risk assessment has inherent limitations. In this scenario, POH might play a central role as it subsequently represents both a preclinical condition in response to the surgical trauma and a new possible therapeutic window before the actual morbidity of POPF becomes apparent. Indeed, once POH has occurred, the incidence of POPF was constantly increased by greater than 40% in most risk zones. This is particularly important for patients previously classified at low-moderate risk for POPF, with POPF incidence escalating up from 3.8% - 22.9% to 42.9% - 41.7%, respectively. Such a significant "stage migration" associated with POH makes its identification very valuable.

Recently, a "time-zero" concept of the pathophysiology of fistulas has been proposed. Namely, a given anastomosis cannot leak unless or until it has been constructed[199]. However, as developed in this paper, several subsequent temporal checkpoints can now be identified, and the present POPF prediction process of using one fixed risk assessment can now be more valuably converted into a dynamic forecasting system. The risk of developing a POPF indeed changes over time, and all available prognostic elements should be dynamically applied during the early postoperative course to target recovery, plan additional preventive strategies and exert early management.

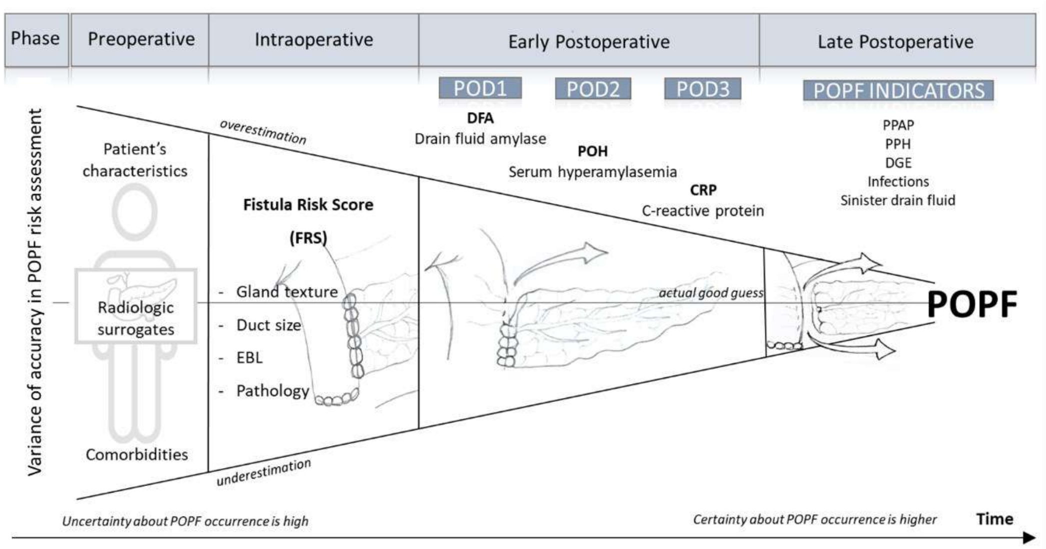


Figure 4: Dynamic risk assessment of postoperative pancreatic fistula (POPF) over time. The cone of uncertainty of POPF hazard estimation is reported on the horizontal axis from preoperative to postoperative time points, while the vertical axis reflects the variance of POPF estimation accuracy. The cone of uncertainty is a graphic depiction of the increasing accuracy of estimates as the details of an event become more known over time.
Abbreviations: DGE: delayed gastric emptying, EBL: estimated blood loss, POD: postoperative day, PPAP: post pancreatectomy acute pancreatitis, PPH: postpancreatectomy haemorrhage.

The practice-changing findings of the present paper are about the role of early postoperative biologic markers, as they add value to fistula risk assessment by the FRS (Figure 4). In the present analysis, the predictive ability of the multivariable model after adding early postoperative parameters like postoperative day 1 drain fluid amylase (DFA) activity (FRS-DFA) was higher than traditional metrics. Once POH (POD 2) was added, the accuracy of POPF risk assessment significantly increased, with yet the best prediction achieved by incorporating POD 3 C-reactive protein (FRS-DFA-POH-CRP).

The results of this framework have practical implications. Early biologic markers could guide postoperative management in a step-by-step approach during the first days after surgical resection[12]. Facing their strong association with POPF, fistula mitigation interventions and other management approaches may be actively and stepwise applied. These may be as simple as measuring drain fluid amylase on subsequent timepoint (POD 3-5) to enhance the identification of patients for safe early drain removal or committing to more prolonged drainage[200], as well as obtaining earlier imaging. Possibly this framework could select patients benefiting from more aggressive approaches. While still speculative, they could include instituting therapeutics like tailored fluid administration, nutritional support, and anti-inflammatory therapy. Of note, no standard therapeutic or mitigation strategies exist once POH has occurred, and future trials may explore new specific therapeutic targets[171]. Alternatively, comfort may be assured in those patients with low POPF risk through accelerated recovery programs and early discharge[85]. Notably, no patients in the FRS 0 class developed either a POH or POPF, confirming drainless policies and fast-track recovery are still reliable in these patients[201].

This study has limitations. Pancreatic texture, EBL assessment, and mitigation strategies application can be affected by the personal judgment of surgeons involved in the surgical procedure and may have altered the model accuracy. However, as a single-centre analysis, the application of standardized protocols may have limited this bias. Identifying a significant predictive value for CRP on POD 3 represents another limitation, as drains were mostly removed within POD 3 if POD 1 DFA was <5000 U/l without a new DFA assessment before removal. Moreover, the CRP cut-off of 200 mg/dl assessed on POD 3 should be further validated. Other series identified subsequent conditional DFA thresholds to enhance POPF prediction, but further analyses should evaluate their value once added to the present framework[70,200]. Moreover, although the first three postoperative days are an early postoperative timeframe, the earlier and more accurate the prediction of a fistula can be, the greater the benefits for patients. The intraoperative appraisal of these or new parameters may implement the current dynamic framework[124,202]. Ultimately, while considering the variation of POPF risk over time, this study voluntarily includes only early postoperative parameters (i.e. POH, DFA, CRP) appraised within the first three postoperative days - namely before a POPF can even be assigned by definition[118]. This analysis excluded the influence of other factors such as PPAP[182], drain contamination and infections[121] or PPH[136] that usually occur later temporally and could be considered POPF indicators. Further studies are needed to evaluate other functional parameters or their trends in an ongoing forecast of the risk and severity of POPF.

In conclusion, an accurate POPF risk assessment should follow a dynamic and iterative process using trusted data sources, ideally starting in the preoperative setting, continuing through the operative anastomotic creation, and continuously reappraised along the course of the postoperative period, when the regular acquisition on a daily basis of additive data can help recalibrate the risk assessment.

POH detection improves clinical risk stratification by increasing the granularity of POPF risk estimates when considered with validated predictive tools such as the Fistula Risk Score[140], drain fluid amylase activity and C-reactive protein. As biologic markers are an early postoperative signal in response to the surgical procedure, their stepwise assessment affords a possible therapeutic window before the actual morbidity of POPF occurs. Through this, surgeons could potentially convert from a passive "wait and see" mindset about fistula development to a more active philosophy of surveillance and proactive intervention. A more dynamic POPF forecasting method might guide clinical decision-making by allowing patients selection for adapted ERAS protocols[85], tailored drain removal or continuation, or future clinical trials of other putative fistula mitigation approaches.

Chapter 8 - No role for protease inhibitors as a mitigation strategy for postpancreatectomy acute pancreatitis (PPAP): propensity score matching analysis

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Pancreatology. 2023 Dec;23(8):904-910. doi: 10.1016/j.pan.2023.09.142.

ABSTRACT

Background:

While the use of protease inhibitor gabexate mesylate (GM) is still controversial in acute pancreatitis, it has never been tested for postpancreatectomy acute pancreatitis (PPAP). This study aims to assess the impact of GM on postoperative serum hyperamylasaemia (POH) or PPAP after pancreatoduodenectomy (PD).

Methods:

Consecutive patients developing POH after PD between 2016 and 2021 were included. According to GM administration, patients were divided into GM-treated and control (CTR) groups. GM was administered from postoperative day 1 to 3 in POH patients who underwent surgery before 2017. A 2:1 propensity matching was used to minimize the risk of bias.

Results:

Overall, 264 patients with POH were stratified in the GM (59 patients) and CTR (104 patients) cohorts, which showed balanced baseline characteristics after matching. No difference in postoperative complications was observed between the groups (all p> 0.05), except for PPAP occurrence, which was significantly higher in the GM group (37% vs. 22%, p= 0.037). A total of 45 patients (28%) evolved to PPAP. Comparing PPAP patients in the GM and CTR groups, no significant differences in POPF, relaparotomy, and mortality (all p> 0.09) were found. No difference in intravenous crystalloid administration was found in patients with PPAP, whether or not they developed major complications or pancreatic fistula (p> 0.05).

Conclusion:

Protease inhibitor seems ineffective in preventing a PPAP after PD once a POH has occurred. Further studies are needed to achieve benchmarks for treating PPAP and identify mitigation strategies to prevent the evolution of POH into additional morbidity.

INTRODUCTION

Post-pancreatectomy acute pancreatitis (PPAP) is a condition characterized by acute inflammation of the pancreatic parenchyma, possibly occurring after pancreatic resections and being able to trigger further and severe postoperative complications[3]. Postoperative serum hyperamylasemia (POH), sustained elevated within at least the first 48 h after surgery, is a key criterion for PPAP diagnosis but could also provide an early window of opportunity for treatment before subsequent clinically relevant morbidity has occurred[5].

To date, no pharmacological prophylaxis has been tested to prevent PPAP, though some existing drugs could be effective. These include protease inhibitors that primarily promote the inactivation of pancreatic enzymes [203] but have also shown additional effects, including modulating inflammation, immunity, and cell apoptosis [204]**.** Due to this rationale, protease inhibitors like gabexate mesylate (GM) have been previously suggested as beneficial drugs in acute pancreatitis (AP) [205] and may have a role in preventing PPAP.

Despite the promising experimental data supporting their use in AP [206,207], subsequent clinical trials reported contradictory results [208–214], whereas metanalyses identified heterogeneity in its use across studies leading to inconclusive and hardly comparable results that precluded its standard application in clinical practice [209,215–217]. Against these drawbacks, the perioperative period offers a standardized setting, with regular monitoring and systematic management, potentially privileged to evaluate these specific therapeutic agents. To date, however, no studies have verified the efficacy of GM in preventing PPAP.

This study aims to evaluate the possible impact of the intravenous administration of GM in affecting post-pancreatoduodenectomy outcomes in a high-risk cohort with early postoperative POH.

METHODS

This single-center, retrospective study was approved by the local ethics committee (Comitato Etico delle Province di Verona e Rovigo, approval number 1101CESC) and performed according to the Declaration of Helsinki and the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) [131].

Inclusion and exclusion criteria

All patients who experienced a sustained postoperative serum hyperamylasemia (POH), defined according to the ISGPS [3], have been retrieved from a prospectively maintained database, including all consecutive pancreatoduodenectomies (PD) performed from January 2016 to December 2021 at the Department of General and Pancreatic Surgery—The Pancreas Institute, University of Verona Hospital Trust.

Patients with incomplete data on postoperative serum pancreatic amylase activity or GM administration were excluded.

Procedures

All PDs were performed according to previously described institutional techniques via an open approach [64,66,218]. Externalized pancreatic stents (PankreaPlus polyvinyl catheter; Peter Pflugbeil Gmbh Medizinische Instrumente) were employed as a specific mitigation strategy in all patients at high risk for POPF and in selected cases when the risk was estimated as moderate according to Fistula Risk Score (FRS) [69]. Neither sealants nor patches were used in any circumstance, nor were prophylactic octreotide or steroids ever administrated as mitigation strategies. Surgical drains were placed in all patients apart from those deemed at low and negligible risk according to FRS [69], unless for other surgical reasons (e.g., high-risk hepaticojejunostomy, vascular resections). A previously published protocol was used for drain management with an early removal policy [134,135].

Data collection

Demographic, preoperative, and intraoperative data were collected. Preoperative data included: age, body mass index (BMI) [kg/m^2], and diabetes history. Intraoperative data encompassed operative time and pancreatic anastomosis type. The risk for pancreatic fistula [69] and POH [6] was assessed according to the FRS by combining: (1) pancreatic texture (defined based on the manual palpation of experienced pancreatic surgeons), (2) pancreatic duct diameter (measured using a sterile disposable ruler), (3) pathology (considering histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis as having a "high-risk pathology"), and (4) estimated blood loss (EBL) [133].

Study groups

Patients were categorized into two groups based on their treatment modality: one group received the gabexate mesylate treatment (GM), while the other group, referred to as the control group (CTL), did not receive GM infusion. At our Institution, GM was routinely administrated until 2017 in all patients presenting POH patients. After 2017, patients with POH did not receive standardized treatments other than intravenous fluid therapy as per their clinical condition.

For patients who received GM and presented with increased pancreas-specific serum amylase activity 48 hours after surgery, GM was administered intravenously from the postoperative day (POD) 1 and continued for at least 3 PODs. The GM dose administered was 1 g/day (Foy®; Dong-a Pharmaceutical, Seoul, Korea) diluted in 500 mL Ringer's solution and infused for 24 hours with a central venous line.

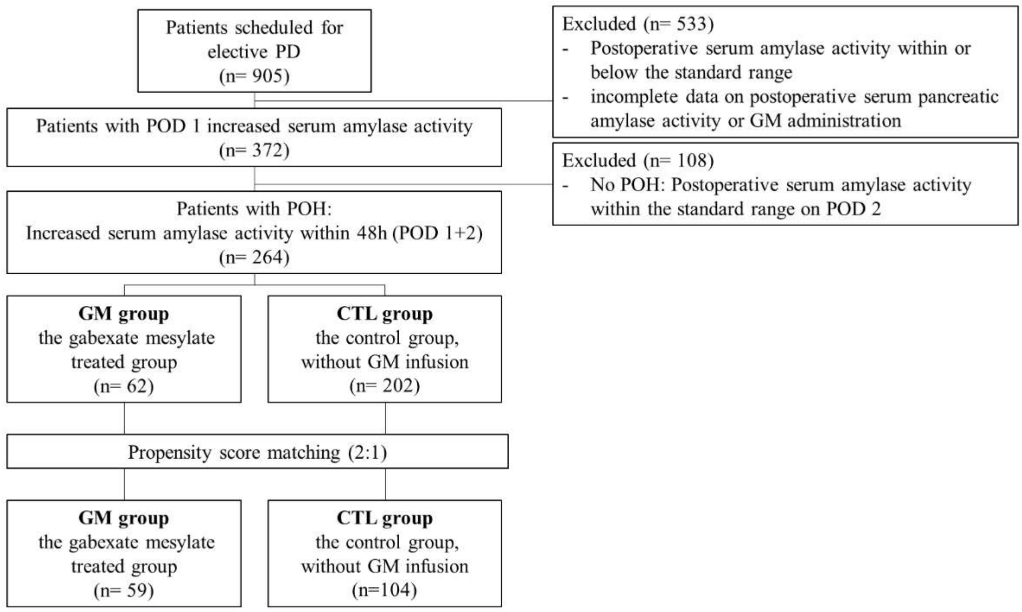

Figure 1: Strobe flowchart.

Outcomes metrics

The primary endpoint of the study was to assess the impact of GM treatment on patients with POH. Specifically, the incidence of postoperative pancreas-specific and severe complications was compared between the GM and the CTR group. The secondary endpoints were to assess the impact of GM treatment on patients with PPAP and to evaluate whether GM treatment might affect the occurrence of major postoperative complications in PPAP patients.

Pancreas-specific morbidity, including postoperative pancreatic fistula (POPF)[118]; post pancreatectomy hemorrhage [136]; delayed gastric emptying [137]; and PPAP [3], were defined according to the International Study Group for Pancreatic Surgery (ISGPS). POH was defined as an elevation in pancreas-specific serum amylase activity greater than the institutional upper limit of normal (standard range 10–52 U/L), which persisted within at least the first 48 hours postoperatively (thus including POD 1 and 2) [3].

Postoperative complications were scored according to the Clavien-Dindo Classification [74] over 90 days, defining major complications as a Clavien-Dindo grade of III or higher. Also, sepsis [219], relaparotomy, length of hospital stay (LOS), and postoperative intravenous crystalloid therapy (ml/kg/h) from POD 1 to 3 were retrieved from medical records. Only an unplanned need for intensive care was defined as an intensive care unit (ICU) stay. Mortality was defined as postoperative death recorded out to the point of 90 days postoperatively.

Statistical analysis

Continuous variables are expressed as medians and interquartile range (IQR) and compared with the Mann-Whitney U test. Categorical variables are presented as absolute numbers with percentages, and associations were tested using the chi-square test or Fisher's exact test.

Propensity score matching (PSM) was used to minimize bias between the GM and CTR groups [220]. As POPF is the major trigger of additional morbidity and mortality after pancreatoduodenectomy [108,118,120], patients were matched 2:1 (Control: Treatment) using propensity scores generated using a multivariable logistic regression model including known risk factors for POPF, like intraoperative blood loss, pancreatic texture, main pancreatic duct diameter, and diagnosis [69] to obtain two study groups with similar intraoperative risk factors for POPF. Notably, these variables are included in the FRS [69] , which have recently emerged as a suitable tool for POH prediction [6]. There were no patients with missing data in matching variables. Nearest-neighbour matching was performed with a caliper of 0.1 units of the pooled estimate of the common standard deviation of the logits of the propensity scores. The propensity-matched analysis was performed using the MatchIt package (Ho, Imai, King, & Stuart, 2011).

A two-sided p-value of 0.05 was considered significant for each test. All analyses were performed in R (R Foundation for Statistical Computing, Vienna, Austria).

Table 1. Demographic and clinical characteristics of patients who had POH following PD according to the treatment with GM in the matched and unmatched population according to FRS.

Variable	Unmatched Cohort				Matched Cohort			
	Overall N= 264[1]	**CTR** N=202[1]	**GM** N = 62[1]	**P value**[2]	**Overall** N=163[1]	**CTR** N=104[1]	**GM** N=59[1]	**P value**[3]
Gender				0.5				0.5
Female	124 (47%)	97 (48%)	27 (44%)		77 (47%)	51 (49%)	26 (44%)	
Male	140 (53%)	105 (52%)	35 (56%)		86 (53%)	53 (51%)	33 (56%)	
Age, yrs	64.0 (55.0-71.0)	64.5 (56.0-71.0)	62.5 (52.2-71.8)	0.3	64.0 (55.5-72.0)	65.0 (57.5-72.0)	63.0 (52.5-71.5)	0.2
BMI	25.0 (22.0-27.0)	24.5 (22.0-27.0)	25.0 (23.0-27.0)	0.7	25.0 (22.0-27.0)	24.0 (22.0-27.0)	25.0 (23.0-27.0)	0.3
Diabetes	24 (9.1%)	20 (9.9%)	4 (6.5%)	0.4	11 (6.7%)	8 (7.7%)	3 (5.1%)	0.7
Texture				0.4				>0.9
hard	24 (9.1%)	20 (9.9%)	4 (6.5%)		11 (6.7%)	7 (6.7%)	4 (6.8%)	
soft	240 (91%)	182 (90%)	58 (94%)		152 (93%)	97 (93%)	55 (93%)	
MPD diameter, mm	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.2	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.6
Estimated blood loss, ml	435.0 (300.0-642.5)	450.0 (300.0-713.8)	350.0 (200.0-500.0)	**<0.001**	399.0 (250.0-500.0)	394.5 (250.0-482.5)	400.0 (200.0-500.0)	0.7
Diagnosis				0.8				0.8
High risk	170 (64%)	131 (65%)	39 (63%)		107 (66%)	69 (66%)	38 (64%)	
Low risk	94 (36%)	71 (35%)	23 (37%)		56 (34%)	35 (34%)	21 (36%)	
Anastomosis				0.2				>0.9
PG	23 (8.7%)	20 (9.9%)	3 (4.8%)		10 (6.1%)	7 (6.7%)	3 (5.1%)	
PJ	241 (91%)	182 (90%)	59 (95%)		153 (94%)	97 (93%)	56 (95%)	
Operative time, min	405.0 (350.0-465.5)	408.0 (350.0-464.0)	401.0 (344.5-473.8)	>0.9	391.0 (342.0-460.0)	390.0 (342.5-446.2)	397.0 (349.0-477.5)	0.2
Pancreatic stent	182 (69%)	140 (69%)	42 (68%)	0.8	116 (71%)	77 (74%)	39 (66%)	0.3

[1] n (%); Median (25%-75%), [2] Pearson's Chi-squared test; Wilcoxon rank sum test,

[3] Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test

Abbreviations: BMI: body mass index, MPD: main pancreatic duct, PG: pancreatogastrostomy, PJ: pancreatojejunostomy.

RESULTS

Patient characteristics

A total of 264 patients with POH were included in the study and are reported in Figure 1. Baseline characteristics before propensity score matching were mostly comparable between the GM and CTL group (Table 1), except for the EBL, which was significantly higher in the CTR group (p <0.001) and the pancreas-specific amylase activity during the first three postoperative days, with higher average values in the GM-treated group (Supplementary Figure 1). Using PSM, 59 patients of the GM-treated group were matched to 104 patients from the CTR group, obtaining two balanced cohorts for all baseline variables, with the exception of the postoperative amylase serum.

Table 2: Postoperative outcomes comparing the GM and the CTR groups in the POH population after propensity score matching.

		Postoperative Treatment		
Variable	**Overall** N = 163[1]	**CTR** N = 104[1]	**GM** N = 59[1]	**p-value**[2]
PPAP	45 (28%)	23 (22%)	22 (37%)	**0.037**
CR-POPF	76 (47%)	46 (44%)	30 (51%)	0.4
POPF Grade				>0.9
Biochemical Leak	12 (14%)	8 (15%)	4 (12%)	
Grade B	59 (67%)	36 (67%)	23 (68%)	
Grade C	17 (19%)	10 (19%)	7 (21%)	
PPH	31 (19%)	18 (17%)	13 (22%)	0.5
PPH Grade				0.088
Grade A	1 (3.2%)	1 (5.6%)	0 (0%)	
Grade B	10 (32%)	8 (44%)	2 (15%)	
Grade C	20 (65%)	9 (50%)	11 (85%)	
DGE	37 (23%)	25 (24%)	12 (20%)	0.6
Percutaneous drain placement	13 (8.0%)	7 (6.7%)	6 (10%)	0.5
Sepsis	51 (31%)	35 (34%)	16 (27%)	0.4
Pneumonia	46 (28%)	27 (26%)	19 (32%)	0.4
Relaparotomy	26 (16%)	14 (13%)	12 (20%)	0.2
ICU admission	24 (15%)	15 (14%)	9 (15%)	0.9
LOS, days	15.0 (9.0-31.5)	14.5 (9.0-29.2)	15.0 (10.0-33.5)	0.7
POD drain removal	8.0 (5.0-27.8)	8.0 (5.0-27.0)	8.0 (5.0-31.5)	0.5
Discharged with drain	23 (14%)	17 (16%)	6 (10%)	0.3
30 days-Readmission	14 (8.6%)	8 (7.7%)	6 (10%)	0.6
Mortality	8 (4.9%)	5 (4.8%)	3 (5.1%)	>0.9
Clavien-Dindo ≥3	44 (27%)	25 (24%)	19 (32%)	0.3
Clavien-Dindo ≥2	123 (75%)	76 (73%)	47 (80%)	0.3

[1] n (%); Median (25%-75%), [2] Pearson's Chi-squared test; Fisher's exact test; Wilcoxon rank sum test

Abbreviations: PPAP postpancreatectomy acute pancreatitis, POPF: postoperative pancreatic fistula, PPH, postpancreatectomy hemorrhage, DGE: delayed gastric emptying, ICU: intensive care unit, LOS: length of hospital stay, POD: postoperative day.

However, in a specific univariate regression analysis such a variable was not associated with PPAP development. Therefore, a further matching to improve the balance between those two groups was waived (Table 1, Supplementary Table 1, Supplementary Figure 2).

Postoperative outcomes in the POH population.

Table 2 shows postoperative outcomes in the POH population stratified according to GM treatment after PSM. A higher rate of PPAP was observed in the GM compared to the CTR group (37% vs. 22%, p= 0.037). Other pancreas-specific complications, such as POPF, PPH, and DGE, were comparable between groups. Length of hospital stay (LOS), readmissions, and mortality were not significantly different.

Table 3: Postoperative outcomes in patients who developed PPAP (n= 45) comparing the GM and the CTR groups after propensity score matching.

Variable		Overall, N = 45[1]	Postoperative Treatment		p-value[2]
			CTR N = 23[1]	GM N = 22[1]	
PPAP		45 (100%)	23 (100%)	22 (100%)	
POPF		36 (80%)	18 (78%)	18 (82%)	>0.9
POPF grade	*BL*	1 (2.7%)	0 (0%)	1 (5.3%)	
	Grade B	30 (81%)	15 (83%)	15 (79%)	
	Grade C	6 (16%)	3 (17%)	3 (16%)	
PPH		10 (22%)	5 (22%)	5 (23%)	>0.9
PPH Grade	*Grade B*	2 (20%)	2 (40%)	0 (0%)	
	Grade C	8 (80%)	3 (60%)	5 (100%)	
Delayed gastric emptying		17 (38%)	11 (48%)	6 (27%)	0.2
Percutaneous drain placement		5 (11%)	2 (8.7%)	3 (14%)	0.7
Sepsis		20 (44%)	13 (57%)	7 (32%)	0.10
Pneumonia		20 (44%)	10 (43%)	10 (45%)	0.9
Relaparotomy		10 (22%)	5 (22%)	5 (23%)	>0.9
ICU unplanned		12 (27%)	6 (26%)	6 (27%)	>0.9
Length of hospital stay, *days*		32.0 (17.0-46.0)	39.0 (21.5-46.0)	25.5 (15.5-42.2)	0.2
POD drain removal		23.0 (8.0-38.0)	29.5 (10.0-42.8)	21.5 (7.0-36.5)	0.4
Discharged with drain		9 (20%)	6 (26%)	3 (14%)	0.5
30 days-Readmission		6 (13%)	4 (17%)	2 (9.1%)	0.7
Mortality		5 (11%)	3 (13%)	2 (9.1%)	>0.9
Clavien-Dindo ≥3		19 (42%)	10 (43%)	9 (41%)	0.9

[1] n (%); Median (25%-75%); [2] Fisher's exact test; Pearson's Chi-squared test; Wilcoxon rank sum test.

Abbreviations: PPAP postpancreatectomy acute pancreatitis, POPF: postoperative pancreatic fistula, BL: biochemical leak, PPH, postpancreatectomy hemorrhage, ICU: intensive care unit, POD: postoperative day.

Postoperative outcomes in the PPAP population.

Among the POH population, 45 matched patients (28%) evolved toward a PPAP. Of those, 22 were treated with GM. No significant differences were found in pancreas-specific and severe postoperative complications, relaparotomy, ICU, LOS, readmission, and mortality between groups (Table 3). No difference in intravenous crystalloid administration was found in patients with PPAP, whether or not developing either major complications (CD ≥3) or POPF (Supplementary Table 2).

DISCUSSION

In this large retrospective study investigating the impact of GM in patients presenting POH, gabexate mesylate (GM) did not show efficacy in preventing PPAP once a POH occurred after a pancreatoduodenectomy. Moreover, in patients further developing PPAP, GM failed to prevent the occurrence of additional pancreas-specific or other severe postoperative complications.

To the best of our knowledge, this is the first study to investigate a specific therapeutic strategy for PPAP. Only recently, PPAP has been defined as an acute inflammatory process of the pancreatic parenchyma, possibly occurring after partial pancreatic resections [3] and able to trigger further severe postoperative morbidity. There is a need for early recognition and treatment of this condition to prevent or mitigate subsequent complications [5]. Since PPAP is characterized -by definition- by early postoperative serum hyperamylasaemia (POH) persisting within 48 hours after surgery, a POH may represent the ultimate target to avoid subsequent detrimental outcomes [96]. A strength of this study was the inclusion of only this high-risk cohort of patients with early POH. Indeed, POH patients had a PPAP rate of 28% in this series, with almost 50% further developing severe complications.

To date, however, no pharmacological prophylaxis or treatments has been tested in the POH-PPAP population, although some existing drugs containing protease inhibitors may have the potential to prevent its progression or alleviate its course. Nevertheless, protease inhibitors, such as GM, have been discontinued in clinical practice as suggested by current guidelines [221,222]. Indeed, despite promising initial experimental evidence [207,215,223] and several clinical trials performed over the past 40 years [211,215,216,224–226], there is still no clear-cut proof whether they can alter the clinical course of acute pancreatitis [209,211,216] or PPAP.

This study highlighted no beneficial effect of GM on PPAP prevention once a POH has occurred. Instead, an increased rate of PPAP was observed in the GM group. However, this observation was not associated with a worse postoperative course, as complication rate, LOS, readmission, and mortality were similar as in those not receiving GM. This result should be eventually interpreted as the consequence of GM administration to patients who were clinically more critical, a state frequently associated with an incoming PPAP [5]. However, an unintended detrimental effect of GM on PPAP could not be excluded despite only speculated. Protease inhibitors (PIs) may worsen fat necrosis caused by lipases [227], as inhibiting proteases can increase lipase activity [228,229], a key factor in pancreatitis [230]. Additionally, GM may interfere with autophagy by inhibiting lysosomal proteases, which might hinder the autophagic flux and ultimately lead to other manners of cell death [231]. The detrimental effects of PIs such as GM on PPAP are likely complex and involve multiple biological pathways. Further research is needed to fully comprehend the mechanisms underlying these phenomena.

To minimize this selection bias and obtain a more accurate estimate of the effect of GM on PPAP-associated morbidity, we conducted a sub-analysis that included only patients who developed PPAP. Even in this subset, GM failed to prevent severe complications or mortality, which is consistent with previous literature on the use of GM for AP [209].

Notwithstanding the daunting results of the present series, some key issues should be thoughtfully considered in the overall scenario of GM administration for PPAP prevention. The apparent success of protease inhibitors in experimental pancreatitis [206,207] has already found difficulties in translating to clinical practice [217]. A deeper evaluation of animal and human studies' methodology, including this one, may reveal why GM has not fulfilled its promise. Reasons could be outlined for the mechanisms of action of this class of drugs. In vivo, GM has a biological half-life of less than one minute, and its complexes with trypsin dissociate rapidly [232]. Prior tests have shown that GM's small molecular weight, compared to other protease inhibitors, allows for better cell penetration and inhibition of both intracellular and extracellular trypsin [223]. Most of this data comes from animal studies where GM was administered prophylactically, and the pancreas was well perfused, with the drug available for intracellular targets even before the enzyme is activated [233]. However, it is currently unclear how the drug is distributed in the pancreas when inflammation has already set in. Therefore, we can speculate that the lack of differences between the two study groups in this analysis might be due to the late administration of the drug after a pancreatic inflammatory process has already begun, manifesting itself as POH. Moreover, it is unclear whether the drug has a similar distribution into the pancreas 1–2 days after a pancreatic resection and the onset of a pancreatitis process [215]. This is particularly significant given that postsurgical pancreatic ischemia is believed to be one of the main determinants of PPAP development [58]. This evidence, while representing a negative outcome of the study, suggests that alternative strategies are needed to investigate the role of GM as a POH-PPAP mitigation strategy.

Differently from its medical counterpart AP, the trigger initiating the inflammatory process can be precisely identified in the surgical procedure [58,234]. Recently, one of the most widely applied intraoperative predictive scores, namely the Fistula Risk Score (FRS) [69], has also emerged as a suitable tool for predicting POH [119,194]. Consequently, patients intraoperatively deemed at higher risk for POH might benefit from receiving GM through a prophylactic administration during the surgical procedure to prevent POH instead of PPAP. A new study investigating this timing of GM administration may be worthwhile, but the question remains whether it is worth the effort. Protease inhibitors might still have a role in a controlled surgical setting but ultimately in a multi-mitigation approach. Indeed, it is unrealistic that the attack of a single cascade could drastically halt the progression to postoperative morbidity, including PPAP. Further studies should address whether different and combined mitigation strategies [84,135,235,236], eventually including protease inhibitors, may influence POH-PPAP occurrence. In this regard, this study performed a sub-analysis evaluating postoperative intravenous fluid resuscitation.

Because no proven drug therapy for acute pancreatitis exists, several guidelines indicate that early treatment is primarily supportive [221]. Intravenous fluid balance is considered a critical component of initial therapy in AP [221] and standard postoperative management [153]. Recent studies highlighted that adverse postoperative outcomes are associated with both excessive intraoperative fluid administration and overly restrictive fluid regimens, resulting in an increased incidence of PPAP [78,123,237]. Similarly, in the context of acute medical pancreatitis, early aggressive fluid resuscitation was associated in a higher rate of fluid overload and no improvement in clinical outcomes [238,239]. This study found no differences in intravenous fluid resuscitation between patients with PPAP, regardless they eventually developed major complications or pancreatic fistula. These results cannot provide definitive answers, and fluid balance may have been overlooked as postoperative protocols are frequently highly standardized instead of goal directed. The impact of fluid therapy on PPAP should be confirmed in randomized, controlled trials comparing different volumes of perioperative intravenous fluids.

Several study limitations should be acknowledged. Given its retrospective nature, this study compared two cohorts of patients from different periods. Specifically, the cohort receiving the GM included patients up to 2017 since the GM was subsequently discontinued. Variations in management protocols may have altered the results. Furthermore, beyond the first three days of standard therapy, the duration of GM administration was not uniform among treated patients, as discontinuation was tailored based on clinical conditions and laboratory data at the discretion of the treating surgeon. Some strategies have been applied to overcome the intrinsic bias of retrospective studies. The study cohort consisted only of POH patients, and the two study groups were balanced through PSM for the main known risk factors (i.e., FRS[45]) to limit selection bias and possible confounding factors. Among the limitations, it's important to note that the two study groups were not matched for serum amylase activity, which was higher in the GM-treated group. However, serum amylase activity did not prove to be predictive of PPAP, confirming previous findings from both PPAP and medical acute pancreatitis (AP) studies. This evidence consistently demonstrates that the degree of increased serum pancreatic enzyme activity does not correlate with disease severity[4,173], making it a diagnostic rather than prognostic marker. We acknowledge that a randomized controlled trial would be a more appropriate scenario to test the effect of GM. However, a preliminary study exploring the potentials and pitfalls of GM administration after a PD in a retrospective fashion may lead the way for more consistent future prospective data.

In conclusion, GM does not prevent the occurrence of PPAP after PD once POH has occurred. Further studies are needed to explore specific management and preventive strategies to achieve benchmarks for treating a PPAP.

Summary

With the thesis "Translational research in Post-pancreatectomy Acute Pancreatitis: from intraoperative spectral imaging assistance to clinical treatment" we analyzed some of the pivotal aspects of the current definition, characterization, and future perspective of post-pancreatectomy acute pancreatitis. Evaluating data from multiple international high-volume institutions dealing with this new pancreas-specific morbidity, we provided clinically relevant information on commonly used biomarkers, diagnostic tools, and prognostic outcomes following pancreatic resections in patients eventually developing this complication. Also, we explored the role of new diagnostic techniques such as intraoperative hyperspectral imaging (HSI) and intravoxel incoherent motion-magnetic resonance imaging (IVIM-MRI), developed a new dynamic tool capable to predict postoperative morbidity, and finally explored possible treatment strategies to improve surgical outcomes.

Looking ahead, future goals involve advancing the research on post-pancreatectomy acute pancreatitis to enhance our understanding of this complex condition. Currently, the validation of the ISGPS definition and grading is underway, and I am leading the coordination of data collection across 17 high-volume pancreatic surgery centers worldwide. I am enthusiastic about exploring innovative approaches, including refining diagnostic tools, incorporating intraoperative optical imaging techniques for early detection, and enhancing predictive models through the integration of artificial intelligence.

This interdisciplinary Ph.D. journey, bridging clinical and technological research centers, has underscored the significance of combining clinical expertise with insights from engineers and data scientists. This collaboration is pivotal for the future of surgery, promising improved patient outcomes. As I transition to the next phase of my career, I envision spearheading multicenter projects to investigate potential therapeutic strategies for PPAP: Additionally, I aim to contribute to the systematic reporting of radiological findings, fostering collaboration not only among surgeons but also with gastroenterologists, radiologists, and other stakeholders in a multidisciplinary approach.

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Supplementary:

Chapter 2.

Supplemental Table A1– Univariate and Multivariable analysis of predictors of the pattern associated with the worst outcome: (#3) Sustained increase in spAMY activity greater than the ULN including on POD 1 + 2, after Pancreatoduodenectomy.

		#3: Sustained increase in spAMY activity greater than the ULN including on POD 1 + 2					
		Univariate analysis			**Multivariable analysis**		
		Yes (n= 222)	**No (n= 498)**	**p**	**OR**	**CI 95%**	**p**
Age (years, median, IQR)		64 (55-71)	66 (57-72)	0.051			
Sex	**M**	117 (52.7%)	289 (58%)	0.193			
	F	105 (47.3%)	209 (42%)				
BMI (Kg/m^2, median, IQR)		25 (23-27)	24 (22-26)	0.080			
Smoke		43 (19.4%)	125 (25.1%)	0.105			
Alcohol		9 (4.1%)	19 (3.8%)	0.838			
Diabetes		19 (8.6%)	118 (23.7%)	< 0.001	0.588	0.305 – 1.018	0.057
ASA score	**1**	5 (2.3%)	13 (2.6%)	0.818			
	2	170 (76.6%)	389 (78.1%)				
	3	47 (21.1%)	96 (13.3%)				
Neoadjuvant therapy		36 (16.2%)	158 (31.7%)	< 0.001	0.979	0.586 – 1.636	0.935
Vascular resection		17 (7.7%)	93 (18.7%)	< 0.001	0.773	0.403 – 1.482	0.773
Operative time (min, median, IQR)		410 (359 - 465)	420 (358-480)	0.338			
EBL (mL, median, IQR)		415 (300-642)	450 (300-700)	0.097			
Soft texture		201 (90.5%)	182 (36.5%)	< 0.001	8.890	5.286 – 14.951	**< 0.001**
High-risk pathological diagnosis		128 (57.7%)	132 (26.5%)	< 0.001	2.238	1.496 – 3.347	**< 0.001**
Main duct diameter (mm, median, IQR)		3 (2-4)	4 (3-6)	< 0.001	0.780	0.697 – 0.874	**< 0.001**

Abbreviations: spAMY: serum pancreatic amylases, POD: post-operative day, BMI: body mass index, ULN: upper limit of normal, ASA American Society of Anesthesiologists, EBL: estimated blood loss, High-risk pathological diagnosis: histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis, IQR: interquartile range .

Supplemental Table A2– Univariate and Multivariable analysis of predictors of the pattern associated with the worst outcome: (#3) Sustained increase in spAMY activity greater than the ULN including on POD 1 + 2, after Distal Pancreatectomy.

		#3: Sustained increase in spAMY activity greater than the ULN including on POD 1 + 2					
		Univariate analysis			**Multivariable analysis**		
		Yes (n= 70)	**No (n= 193)**	**p**	**OR**	**CI95%**	**p**
Age (years, median, IQ range)		60 (49-68)	62 (49-71)	0.210			
Sex	**M**	31 (44.3%)	82 (42.5%)	0.888			
	F	39 (55.7%)	111 (57.5%)				
BMI (Kg/m^2, median, IQ range)		24 (22-27)	25 (22-28)	0.088			
Smoke		18 (25.7%)	47 (24.4%)	0.872			
Alcohol		5 (7.1%)	17 (8.8%)	0.804			
Diabetes		3 (4.3%)	42 (21.8%)	< 0.001	0.198	0.058 – 0.681	**0.010**
ASA score	**1**	10 (14.3%)	15 (7.8%)	0.071			
	2	56 (80%)	151 (78.2%)				
	3	4 (5.7%)	27 (14%)				
Neoadjuvant therapy		3 (4.3%)	44 (22.8%)	< 0.001	0.221	0.062 – 0.789	**0.020**
Vascular resection		3 (4.3%)	18 (9.3%)	0.301			
Operative time (min, median, IQ range)		248 (220-334)	270 (209-355)	0.668			
EBL (mL, median, IQ range)		250 (150-350)	200 (150-400)	0.966			
Stump area (cm^2, median, IQ range		4.4 (3.5-5.3)	4 (2.9-5.4)	0.349			
Stump thickness (cm, median, IQ range)		1.5 (1.5-2)	1.5 (1.3-2)	0.116			
Transection at body-tail level		31 (44.3%)	44 (22.8%)	0.001	1.605	0.772 – 3.338	0.205
MIPS		40 (57.1%)	69 (35.8%)	0.003	1.268	0.628 – 2.561	0.509
Staple closure		41 (58.6%)	126 (65.3%)	0.385			
Spleen preserving		11 (15.7%)	19 (8.7%)	0.193			
High risk pathological diagnosis		53 (75.7%)	108 (56%)	0.004	1.093	0.525 – 2.274	0.812

Abbreviations: spAMY: serum pancreatic amylases, POD: post-operative day, ULN: upper limit of normal, BMI: body mass index, ASA American Society of Anesthesiologists, EBL: estimated blood loss, MIPS: minimally invasive pancreatic surgery, High-risk pathological diagnosis: histology other than pancreatic ductal adenocarcinoma or chronic pancreatitis, IQR: interquartile range.

Chapter 4

Supplementary Table 1.

Mixed-effects linear regression to estimate the variations of the hyperspectral indexes in the pancreatic body among different surgical timepoints. In this table, the reference level is timepoint 0 (intercept -T0), aptly the beginning of the surgical procedure after midline laparotomy and the gastrocolic ligament opening and before performing any invasive maneuver, possibly altering the pancreatic parenchyma characteristics.

Index	Time	beta	95% CI	t	df	p	conditional R2 *(model's total explanatory power)*	marginal R2 *(part related to the fixed effects alone)*
StO2%	(Intercept -T0)	0.76	0.72, 0.79	37.56	388	< .001	0.38	0.03
	T1	-0.04	-0.09, 7.23e-04	-1.93	388	0.054		
	T2	-0.04	-0.09, 9.55e-04	-1.92	388	0.055		
	T3	-0.03	-0.07, 0.02	-1.13	388	0.257		
	T4	-0.06	-0.11, -0.02	-2.83	388	0.005		
	T5	-0.09	-0.14, -0.05	-3.97	388	< .001		
NIR	(Intercept -T0)	0.69	0.65, 0.73	32.48	388	.001	0.56	<0.01
	T1	-0.02	-0.06, 0.02	-1.08	388	0.280		
	T2	-0.04	-0.08, 3.73e-03	-1.78	388	0.076		
	T3	-0.03	-0.07, 0.01	-1.42	388	0.156		
	T4	-0.04	-0.08, 2.98e-03	-1.82	388	0.070		
	T5	-0.06	-0.10, -0.02	-2.86	388	0.004		
OHI	(Intercept -T0)	0.59	0.56, 0.62	36.99	388	< .001	0.47	0.07
	T1	0.07	0.04, 0.11	4.23	388	< .001		
	T2	0.02	-0.01, 0.06	1.32	388	0.189		
	T3	0.09	0.05, 0.12	5.17	388	<.001		
	T4	0.11	0.07, 0.14	6.19	388	<.001		
	T5	0.05	0.01, 0.08	2.71	388	0.007		
TWI	(Intercept -T0)	0.46	0.43, 0.49	30.37	388	< .001	0.30	0.03
	T1	0.03	-9.72e-03, 0.06	1.43	388	0.153		
	T2	-0.01	-0.05, 0.02	-0.68	388	0.498		
	T3	0.02	-0.02, 0.05	0.94	388	0.348		
	T4	<0.01	-0.03, 0.04	0.04	388	0.966		
	T5	-0.04	-0.08, -4.56e-03	2.22	388	0.027		

Abbreviations: StO2%: saturation of oxygen; NIR: near-infrared perfusion index; OHI: total hemoglobin index; TWI: tissue water index.
T1: Henle's trunk division; T2: the gastroduodenal artery division; T3: pancreatic hemostatic stitches, usually placed at the superior and inferior pancreatic margin before pancreas division; T4: retroportal lamina dissection; T5: pancreatic anastomosis.

Supplementary Table 2.
Mixed-effects linear regression to estimate the variations of the hyperspectral indexes in the pancreatic body among different surgical timepoints. In this table, the reference level is timepoint 0 (intercept -T0), aptly the beginning of the surgical procedure after midline laparotomy and the gastrocolic ligament opening and before performing any invasive maneuver, possibly altering the pancreatic parenchyma characteristics.

Index	Time	beta	95% CI	t	df	p	conditional R2 *(model's total explanatory power)*	marginal R2 *(part related to the fixed effects alone)*
StO2%	(Intercept - T0)	0.74	0.70, 0.78	37.21	388	< .001	0.33	0.04
	T1	-0.08	-0.12, -0.03	-3.29	388	0.001		
	T2	-0.02	-0.06, 0.03	-0.76	388	0.447		
	T3	-0.08	-0.13, -0.04	-3.48	388	<.001		
	T4	-0.09	-0.13, -0.04	-3.73	388	<.001		
	T5	-0.08	-0.13, -0.03	-3.41	388	< .001		
NIR	(Intercept - T0)	0.69	0.65, 0.72	35.28	388	< .001	0.49	0.03
	T1	-0.02	-0.06, 0.01	-1.22	388	0.222		
	T2	-0.02	-0.06, 0.02	-1.14	388	0.254		
	T3	-0.03	-0.07, 0.01	-1.39	388	0.166		
	T4	-0.07	-0.11, -0.03	-3.52	388	<.001		
	T5	-0.07	-0.11, -0.03	-3.71	388	< .001		
OHI	(Intercept - T0)	0.57	0.54, 0.60	39.50	388	< .001	0.50	0.09
	T1	0.03	-2.20e-03, 0.06	1.82	388	0.069		
	T2	0.03	-4.31e-03, 0.06	1.68	388	0.093		
	T3	0.09	0.06, 0.12	6.19	388	<.001		
	T4	0.10	0.07, 0.13	6.39	388	<.001		
	T5	0.03	1.38e-03, 0.06	2.06	388	0.040		
TWI	(Intercept - T0)	0.46	1.93e-04, 0.06	34.54	388	< .001	0.36	0.07
	T1	0.03	0.07, 0.06	1.98	388	0.049		
	T2	8.34e-03	-0.02, 0.04	0.53	388	0.593		
	T3	0.02	-7.73e-03, 0.05	1.47	388	0.142		
	T4	-0.03	-0.06, 4.10e-03	1.70	388	0.089		
	T5	-0.06	-0.09, -0.03	-3.64	388	< .001		

Abbreviations: StO2%: saturation of oxygen; NIR: near-infrared perfusion index; OHI: total hemoglobin index; TWI: tissue water index.
T1: Henle's trunk division; T2: the gastroduodenal artery division; T3: pancreatic hemostatic stitches, usually placed at the superior and inferior pancreatic margin before pancreas division; T4: retroportal lamina dissection; T5: pancreatic anastomosis.

Supplementary Table 3.

Mixed-effects linear regression to estimate the variations of the hyperspectral indexes in the **pancreatic head** among different surgical timepoints. In this table, the reference level is timepoint 0, aptly the beginning of the surgical procedure after midline laparotomy and the gastrocolic ligament opening and before performing any invasive maneuver, possibly altering the pancreatic parenchyma characteristics.

Index	Time	beta	95% CI	t	df	p	conditional R2 *(model's total explanatory power)*	marginal R2 *(part related to the fixed effects alone)*
StO2%	(Intercept -T0)	0.75	0.72, 0.78	50.21	388	< .001	0.57	0.39
	T1	-0.06	-0.10, -0.03	-3.40	388	< .001		
	T2	-0.04	-0.08, -5.54e-03	-2.28	388	0.023		
	T3	-0.10	-0.13, -0.06	-5.63	388	< .001		
	T4	-0.16	-0.20, -0.13	-9.08	388	< .001		
	T5	-0.29	-0.33, -0.26	-16.49	388	< .001		
NIR	(Intercept -T0)	0.71	0.67, 0.74	38.65	388	< .001	0.56	0.32
	T1	0.03	-0.01, 0.07	1.39	388	0.166		
	T2	0.01	-0.03, 0.05	0.54	388	0.591		
	T3	0.02	-0.02, 0.06	1.08	388	0.282		
	T4	0.02	-0.02, 0.06	1.09	388	0.276		
	T5	-0.25	-0.29, -0.21	-12.13	388	< .001		
OHI	(Intercept -T0)	0.57	0.54, 0.59	45.74	388	< .001	0.38	0.12
	T1	0.03	-3.30e-03, 0.05	1.74	388	0.083		
	T2	0.07	0.05, 0.10	5.11	388	< .001		
	T3	0.09	0.06, 0.12	6.25	388	< .001		
	T4	0.09	0.06, 0.12	6.41	388	< .001		
	T5	0.09	0.06, 0.12	5.99	388	< .001		
TWI	(Intercept -T0)	0.45	0.42, 0.48	30.04	388	< .001	0.44	0.27
	T1	0.02	-0.02, 0.05	0.84	388	0.403		
	T2	-0.04	-0.07, -7.61e-04	-2.01	388	0.045		
	T3	-0.03	-0.07, 4.00e-03	-1.75	388	0.080		
	T4	0.02	-0.02, 0.05	0.84	388	0.403		
	T5	-0.20	-0.24, -0.16	-10.76	388	< .001		

Abbreviations: StO2%: saturation of oxygen; NIR: near-infrared perfusion index; OHI: total hemoglobin index; TWI: tissue water index.
T1: Henle's trunk division; T2: the gastroduodenal artery division; T3: pancreatic hemostatic stitches, usually placed at the superior and inferior pancreatic margin before pancreas division; T4: retroportal lamina dissection; T5: resected specimen.

Chapter 5

SUPPLEMENTAL TABLE 1. METHODS OF RADIOLOGIC DATA

Magnetic Resonance Imaging (MRI)	
Since the optimal timing for initial radiologic assessment is at least 72h after AP onset based on international guidelines[7], MRI studies were performed on a 1.5 T scanner (Ingenia, Philips, Eindhoven, The Netherlands) using a multi-channel phased-array torso coil on postoperative day 3 (72 h after the index surgery).	
MRI protocols consisted of a combination of:	- T1 and T2-weighted sequences, - a dynamic contrast-enhanced T1-weighted imaging after a bolus injection of 0.1 mmol/kg Gadoteridol (ProHance, Bracco, Milan, Italy) at a rate of 2 mL/sec, - a diffusion-weighted (DW) MRI sequence with multiple b-values.
Diffusion-weighted (DW) MRI sequences	
DW MRI exploits the motion of water molecules in biological tissues. DW data were quantitatively analyzed according to monoexponential and bi-exponential models.	
Monoexponential model:	The ADC was calculated as $\frac{S_b}{S_0} = e^{-b*ADC}$. Such formula can also be written as $\ln\left(\frac{S_b}{S_0}\right) = -b * ADC$, where $ln\left(\frac{S_b}{S_0}\right)$ is y, while b is x, obtaining $y = -ADC * x$, therefore defining ADC as the negative slope of the line. These formulas were applied twice to calculate ADC for small b-values (up to b boundary =150 s/mm²) than for high values of b. B boundary is the b-value from where the perfusion phenomenon is no longer evident, and diffusion gets involved.
Bi-exponential model:	The intravoxel incoherent motion (IVIM) theory was introduced by Le Bihan et al. [10,11], and it was used to measure tissue perfusion and tissue diffusivity effects separately, according to: $\frac{S_b}{S_0} = (1 - f_{IVIM}) * e^{-b*D} + f_{IVIM} * e^{-b*(D+D^*)}(1)$ Here, the f_{IVIM} gives the volume fraction of incoherently flowing blood in the tissue, also expressed as the perfusion fraction. S_b is the intensity of a voxel at the current b value, while S_0 is the intensity of the same voxel at b=0. D is the true diffusion coefficient (mm/s) that reflects the extravascular space where only diffusion effects occur, and D* is the perfusion-related diffusion coefficient (mm/s) as it reflects dephasing due to perfusion in capillaries. The f_{IVIM} was calculated using the relation: $f_{IVIM} = b_{boundary}(ADC_{0-b_{boundary}} + ADC_{b_{boundary}-800})$. Subsequently, D and D* were computed using the formula (1). In DWI acquisition sequences, the following values of b were used: [0 10 20 30 40 50 80 100 150 200 400 800].
Post-processing DW- IVIM- MRI	
The IVIM images were loaded into a post-processing workstation (Intel Core i7 and NVIDIA Geforce GTX GPU). The IVIM data were quantitatively extracted using in-house, specially designed software, implemented in Matlab (Natick, Massachusetts: The MathWorks Inc.). The software for visualization, regions of interest (ROI) contouring, and statistical analysis of the IVIM maps was realized through a Python implemented user interface. ROIs comprising the pancreatic stump were manually drawn on contrast-enhanced T1-weighted images of the pancreas (anatomic reference), excluding the main pancreatic duct when visible. The software automatically colocalized these ROIs on the corresponding sections of DW images at all b-values and performed the pixel-by-pixel data fitting. Then the average parametric values (normalized by scaling between 0 and 1) and their histogram analysis within the ROIs were obtained. Image misalignment between the IVIM MRIs and the T1-weighted pancreatic contrast images was compensated through a rigid transformation using Mevislab software (mevis Medical Solutions, Bremen, Germany).	
Computed tomography (CT) imaging	
Contrast-enhanced multidetector CT imaging was performed in the postoperative course when clinically required, facing worsening of the patient's clinical conditions, suspicious for abdominal complications.	
Radiologic PPAP assessment	
The presence of radiologic findings, consistent with PPAP, was evaluated in consensus by two board-certified radiologists (G.Z. and L.C.) at both MRI or subsequent CT examinations in a blinded manner.	

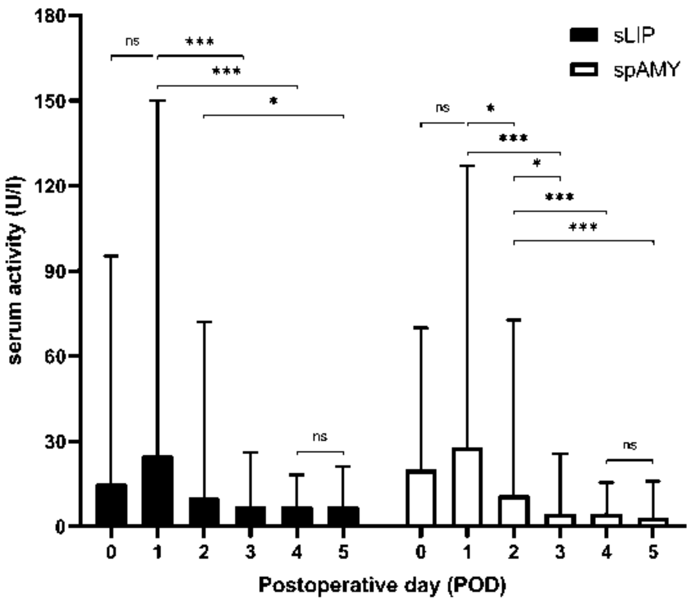
SUPPLEMENTAL TABLE 2. METHODS BIOCHEMICAL DATA

Blood tests:	
Laboratory blood tests were performed 2 hours after the surgical procedure (postoperative day – POD 0) and at 7 am from POD 1 to POD 5.	
Serum pancreatic amylase (spAMY) activity	standard range 10–52 U/l
Serum lipase (sLIP) activity	standard range 10–60 U/l
C-reactive protein (CRP)	standard <5 mg/l
Total white blood cells (WBC)	standard range 4.30-10.00 10^9/l
Urine tests:	
A urine trypsinogen strip test (Actim Pancreatitis ®; Medix Biochemica, Kauniainen, Finland) was used at POD 1 as a rapid test to detect the pancreatic enzyme trypsinogen-2 in urine (U–TRP2).	
***Methods*: This immunochromatography-based test was carried out by dipping the tip of the test strip into a urine sample. Trypsinogen-2 binds to monoclonal antibody-labelled blue latex particles, which migrate across a nitrocellulose membrane with a catching zone containing an antibody specific for an epitope on TRP2. A U-TRP2 concentration of more than 50 µg/l results in a blue line developing in this zone and was considered a positive result.**	

SUPPLEMENTAL TABLE 3. METHODS OF CLINICAL DATA

Local complications	
Postpancreatectomy acute pancreatitis (PPAP)	ISGPS definition [2]: Its radiological features were defined at CT once biochemical and clinical signs were present.
Postoperative serum hyperamylasemia – hyperlipasemia (POH)	ISGPS definition [2]: A sustained increase in serum pancreatic enzymes activity greater than the institutional upper limit of normal persisting for at least the first 48 hours postoperatively (postoperative day 1-2)
Postoperative pancreatic fistula (POPF)	ISGPS definition [16].
Postpancreatectomy hemorrhage (PPH)	ISGPS definition [17].
Delayed gastric emptying (DGE)	ISGPS definition [18].
Organ space infections	Defined as fluid collections within the abdominal cavity with radiological or clinical signs of infection [19].
Systemic complications	
Sepsis and the Systemic Inflammatory Response Syndrome (SIRS)	Defined according to the Sepsi-2 criteria [20] to investigate the pro-inflammatory host response associated with PPAP. Given the early onset of PPAP in the postoperative period, SIRS criteria were recorded until POD 3.
Cardiac morbidity	Defined as acute myocardial infarction or severe arrhythmia.
Acute kidney injury (AKI)	Once occurring from POD 3. Defined according to 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [21].
Intensive care unit (ICU) stay	Defined as an unplanned need for intensive care.
Mortality	Defined as death occurring up to 90-days postoperatively.
The severity of complications	Assessed according to the Clavien–Dindo (CD) classification system [22] at 90-days.

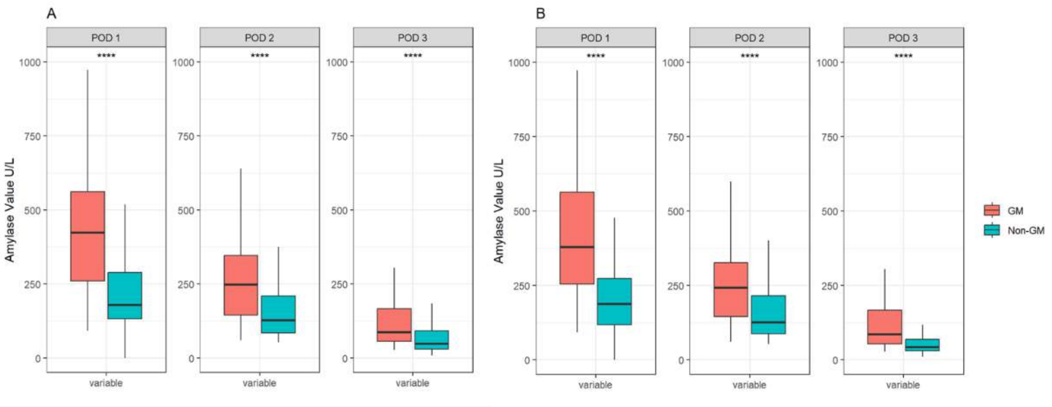
Suplementary Table 4. MRI findings in PPAP patients	
MRI findings (n,%)	**PPAP** **n=6**
Pancreatic anastomosis fluid	4 (66%)
Biliary anastomosis fluid	5 (83%)
Ascites	5 (83%)
Postoperative pancreatic fistula	3 (50%)
Biliary fistula	1 (17%)
Normal parenchymal thickness and signal intensity	3 (50%)
Thin and T1-hypointense parenchyma	2 (33%)
Dilated main pancreatic duct	1 (17%)



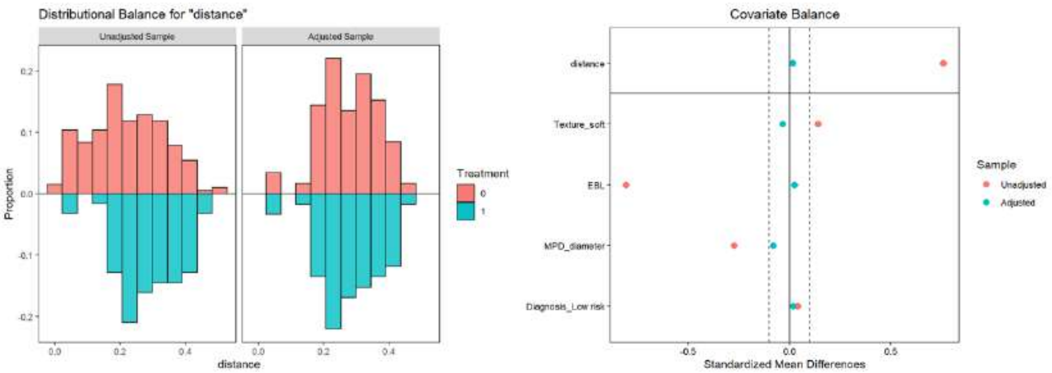
Supplemental Figure 1: Bar charts of the median (IQR) of pancreatic serum amylase activity (black) and serum lipase activity (grey) from the day of surgery (postoperative day - POD 0) to POD 5 in the overall study population. Median values of both serum enzyme activities differed significantly between time points with higher values in the early postoperative days (POD) and a gradual decrease (more rapid for pancreatic serum amylases than serum lipases) to normal levels on POD. 4-5. The Friedman test was used to test the difference among repeated measures over time, with a post hoc analysis of Wilcoxon signed-rank tests for pairwise comparisons. A Holm-Sidak correction was applied to all p-values. The resulting p-value less than 0.05 is flagged with one star (*), while once less than 0.001, it is flagged with three stars (**). Ns: no statistical significative.

Chapter 8

Supplementary Figure 1: Serum Amylase Values in GM and Non-GM group in Unmatched (A) and Matched (B) Cohort.



Supplementary Figure 2: A. Mirrored plot displaying the distributions of propensity scores before and after weighting adjustment. B. Covariate balance measured by standardized mean difference. The two dashed vertical lines indicate the threshold within which the balance is considered to be achieved. Abbreviations: EBL: estimated blood loss, MPD: main pancreatic duct.



Supplementary table 1: Univariable Regression Analysis for Risk Factors for PPAP (Unmatched Cohort)

Characteristic	**N**	**Event N**	**OR**	**95% CI**	**p-value**
Serum amylase POD1	263	67	1.00	1.00, 1.00	**0.12**
Serum amylase POD2	256	66	1.00	1.00, 1.00	**0.30**
Serum amylase POD3	199	52	1.00	1.00, 1.01	**0.080**

Abbreviations: OR = Odds Ratio, CI = Confidence Interval, POD: postoperative day

Supplementary Table 2: Difference in intravenous crystalloid administration on patients with PPAP developing major complications (CD ≥3) or POPF after propensity score matching.

Variable	**Clavien Dindo >=3**				**Pancreatic Fistula**			
	Overall, N = 45[1]	**No**, N = 26[1]	**Yes**, N = 19[1]	**p-value**[2]	**Overall**, N = 45[1]	**No**, N = 9[1]	**Yes**, N = 36[1]	**p-value**[2]
POD 1 ev fluids, ml/kg/die	36.0 (30.0-41.0)	38.0 (33.0-41.0)	35.0 (28.0-40.0)	0.4	36.0 (30.0-41.0)	38.0 (34.5-39.0)	36.0 (30.0-41.0)	>0.9
POD 2 ev fluids, ml/kg/die	36.0 (29.8-43.2)	36.0 (28.0-39.0)	36.0 (30.0-45.0)	0.4	36.0 (29.8-43.2)	38.0 (30.0-44.0)	36.0 (29.0-42.0)	0.4
POD 3 ev fluids, ml/kg/die	30.0 (21.0-39.0)	30.0 (23.0-41.0)	28.0 (20.5-36.0)	0.3	30.0 (21.0-39.0)	30.0 (25.0-39.0)	30.0 (21.0-38.5)	>0.9

[1] Median (25%-75%)

[2] Wilcoxon rank sum test