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TITOLO DELLA TESI DI DOTTORATO

Post-operative acute pancreatitis after major pancreatic resections: from a clinical insight to an International Study Group of Pancreatic Surgery research project

S.S.D. MED/18

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Summary

Starting from an insight that emerged in the daily clinical practice, postoperative acute pancreatitis has become an increasingly recognized complication after major pancreatic resections, but its incidence and clinical impact, and even its existence quickly became a matter of debate.

The aim of the project was to observe, describe, analyze, and eventually develop a universally accepted definition for standardized reporting and outcome comparison. The phenomenon was initially observed and described on a retrospectively collected series of consecutive major pancreatic resection. Results were then reproduced and confirmed on a prospectively collected series of patients. At this point, a comprehensive systematic review of the literature of post-operative acute pancreatitis and post-operative hyperamylasemia was carried out to obtain a complete picture of the available evidence. The phenomenon was deeply analyzed using the prospective series to identify specific characteristics able to give a unique definition. All data collected were shared among the members of the International Study Group of Pancreatic Surgery and, eventually, a universally accepted definition of post-pancreatectomy acute pancreatitis was reached.

The whole project is developed in a series of six papers published on surgical journals from 2018 to 2021.

In the final paper, 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 to be clinically relevant to the patient.

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.

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Clinical implications of intraoperative fluid therapy in pancreatic surgery

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ABSTRACT

Background

Recent studies have suggested that intraoperative fluid overload is associated with a worse outcome after major abdominal surgery. However, evidence in the field of pancreatic surgery is still not consistent. The aim of this study was to evaluate whether intraoperative fluid management could affect the outcome of a major pancreatic resection.

Methods

Prospective analysis of 350 major pancreatic resections performed in 2016 at the Department of General and Pancreatic Surgery – The Pancreas Institute, University of Verona Hospital Trust. Patients were dichotomized according to intraoperative fluid volume administration (near-zero vs. liberal fluid balance) and matched using propensity score. Intraoperative fluid administration was then correlated to the postoperative outcome.

Results

Liberal fluid balance was associated with an increased rate of Clavien-Dindo ≥ IIIB both after pancreaticoduodenectomy (60.3 vs. 30.2%, $p< 0.01$) and distal pancreatectomy (50 vs. 27.1%, $p= 0.03$). In case of pancreaticoduodenectomy, liberal fluid balance was also associated with an increased rate of pancreatic fistula (33.3 vs. 19.9%, $p= 0.05$), but when considering patients with soft remnants, an increase rate of pancreatic fistula (52.8% vs. 23%, $p= 0.03$) was indeed associated with the near-zero fluid balance.

Conclusion

Considering all pancreatic resections, a liberal fluid balance is associated with an increased rate of postoperative morbidity. However, in the case of PD with a soft pancreas, a NZF balance could lead to pancreatic stump ischemia

and anastomotic failure. Intraoperative fluid management should be managed according to patient's pancreas-specific risk factors.

INTRODUCTION

Despite an international agreement regarding the surgical technique and outcome metrics in the field of pancreatic surgery[1,2], there are no current standard guidelines that provide recommendations regarding intraoperative fluid administration. The only evidence in this regard pertains to the application of enhanced recovery after surgery protocols derived from colorectal procedures[4]. Indeed, the choice of the intraoperative fluid amount is mostly dependent on the anesthesiologist's judgment and may considerably change between different institutions. Recent studies have suggested that the amount of fluid administered intraoperatively affects the surgical outcome[5,6] and may be procedure-dependent[7,8]. Intraoperative hypovolemia is a well-recognized risk factor for adverse effects[8]. Conversely, excessive fluid administration can impair pulmonary, cardiac, and gastrointestinal (GI) functions[9], eventually contributing to postoperative complications and a prolonged length of hospital stay (LHS)[4]. Therefore, defining the optimal strategy for intraoperative fluid administration in major abdominal surgery remains a relevant clinical issue.

Among elective abdominal surgical procedures, pancreatic resections still have the highest morbidity rate[10,11]. With the improvements in perioperative care and patient selection for surgery, mortality has markedly decreased to 2% at high volume centers[12]. Conversely, the incidence of complications still remains high, and there is only a small amount of evidence on the potential implications of intraoperative fluid administration in this regard. Available studies report controversial results. Some studies support restrictive fluid management as potentially associated with a reduced rate of complications, faster return of GI function, and shorter hospital stay[13–16]. However, other studies did not reveal any difference in postoperative outcomes by comparing restrictive vs. liberal intraoperative fluid management[17,18].

The aim of the present study is to assess the role of intra-operative fluid management in affecting postoperative outcome after major pancreatic resections at a high-volume center.

METHODS

The study is consistent with the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and was approved by the Institutional review board (N° 1101CESC – University of Verona Hospital Ethical Committee). Written informed consent for data retrieval was obtained from all patients. Data of patients who consecutively underwent a major pancreatic resection were prospectively collected and retrospectively analyzed. The surgical procedures included pancreaticoduodenectomy (PD) and distal pancreatectomy (DP). All of the procedures were performed between January and December 2016 at the Department of General and Pancreatic Surgery – The Pancreas Institute, University of Verona Hospital Trust. Clinical variables, including age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) grade, neoadjuvant therapy and estimated blood loss (EBL), were evaluated. The operative details and histological findings, type of surgery, operative time, need for vascular resection and pancreatic Fistula Risk Score (FRS)[19] in PD were also retrieved.

Intraoperative fluids were defined as all types of crystalloids and blood products that were intravenously administered in the operating theater from the beginning to the end of the surgical procedure. No specific institutional protocols for intraoperative fluid management for major pancreatic surgery were available during the study period, however, perioperative management was compliant with ERAS recommendations[3]. To evaluate the effect of intraoperative fluid management on the postoperative outcome, two different groups of patients were identified: the “near-zero fluid” (NZF) balance group and the liberal fluid balance group (LF). According to the ERAS protocols[4], the NZF balance attempts to maintain the central euvolemia while minimizing excess salt and water.

A balanced salt crystalloid solution was administered at a dose of 1 ml per kilogram of body weight per hour until the end of surgery to replace insensible perspiration. Also urine output was replaced with balanced crystalloids according to a 1:1 ratio. Blood loss was also replaced, and, in presence of evidence of hypovolemia, a fluid challenge was performed using small crystalloid boluses to test volume responsiveness. Blood products were not used to manage discrepancies in hemodynamic control. Blood transfusions were considered only after reaching the hemoglobin threshold of 7g/dL for healthy patients or 10g/dL for patients with history of ischemic cardiac disease according to the institutional protocol. The expected amount of fluids needed for the NZF balance was estimated from anesthesiology records and compared to the observed one that was recorded at the end of the procedure. If the expected was similar to the observed fluid balance, patients were included in the

NZF group. Otherwise, if the observed was greater than the expected fluid balance, patients were included in the LF group. When assigning patients to the NZF or LF balance groups, an arbitrary tolerance of ±10% was applied to the total amount of fluids administered intraoperatively. Maintenance fluids (Elettrol Reid Iii, Fresenius Kabi Italia Srl, Verona, Italy), small crystalloid boluses used to maintain blood pressure and active diuresis, packed red blood cells (PRBC) and fresh frozen plasma (FFP) were included in the fluid balance assessment.

The specific surgical procedures have been previously described by the group[20,21]. Post-operative morbidity was defined according to the International Study Group for Pancreatic Surgery (ISGPS) definitions of postoperative pancreatic fistula (POPF)[2], as well as delayed gastric emptying (DGE)[22] and post-pancreatectomy hemorrhage (PPH)[23]. Postoperative Acute Pancreatitis (POAP) was defined as an elevation of serum amylase count above the upper normal limit on post-operative day (POD) 0 or 1 as proposed by Connor[24]. Abdominal abscess was defined as a fluid collection within the abdominal cavity with radiological or clinical signs of infection. Sepsis was defined according to the 2016 updated criteria[25]. Intensive care unit (ICU) stay was considered an unplanned post-operative need for intensive care. Mortality was defined as the 90-day mortality.

The severity of surgical complications was determined using the Clavien–Dindo classification system[26]. The primary outcome of the study was the occurrence of a surgical complication scored as Clavien-Dindo equal or more than grade IIIB considering all pancreatic resections. The secondary outcome was the occurrence of pancreatic-surgery specific morbidity according to the specific pancreatic procedures.

More difficult procedures potentially require aggressive hydration to manage hemodynamic instability and usually are associated with higher morbidity rates. To eliminate this potential source of bias, patients undergoing PD or DP were matched in a 1:1 proportion according to operative time considered as an indirect measure of the complexity of the procedure.

The matching process was carried out using the propensity score with a caliper of 0.1. For univariate comparisons, Chi-square or Fisher's exact tests were used to evaluate categorical variables. The Bonferroni method was applied to correct p-values for multiple testing. Continuous variables were analyzed using Student's t-test or the Mann-Whitney test when appropriate. Stepwise backward logistic regression analysis identified covariates that were associated with the incidence of Clavien-Dindo IIIB morbidity. Variables were assessed for multicollinearity and removed from the model when necessary. All tests were 2-tailed. P-values < 0.05 were considered to be statistically significant. Statistical analysis was performed with SPSS software (SPSS, Inc., version 20 for Macintosh, IBM, Chicago, Il).

RESULTS

During the study period, 350 major pancreatic resections were performed, including 209 (59.7%) PD, 104 (29.7%) DP and 37 (10.6%) TP. Due to the small sample size, patients who underwent TP were excluded retrieving a final population of 313 patients. After stratifying for intraoperative fluid regimen and applying the propensity score, two 1:1 matched populations of 126 PDs and 96 DPs were obtained.

The demographic and patients' characteristics, both for the unmatched and for the matched populations, are reported in Table 1. After applying the propensity score matching, there were no differences between patients undergoing PD treated with NZF or LF approach. Considering patients undergoing DP, instead, those treated with NZF have a significantly lower body weight.

Table 2 provides the post-operative surgical outcomes of the two matched cohorts stratified according to intraoperative fluid management. Median intraoperative fluid infusion rate of patients undergoing PD was 7 mL/Kg/h (2 – 12) for the NZF group and 9 mL/Kg/h (4 – 29) for the LF group. For patients undergoing DP it was 6 mL/Kg/h (3 – 9) and 8mL/kg/h (2 – 16) for patients belonging to the NZF or LF balance group respectively. For patients undergoing PD, the use of a NZF balance was associated with a significantly increased rate of POAP, whereas LF balance was associated with an increased rate of POPF and with a two-fold increased rate of morbidity classified as Clavien-Dindo ≥ IIIB. Also for patients undergoing DP (n= 96), the use of a LF balance was associated with about a two-fold increased rate of Clavien-Dindo ≥ IIIB morbidity.

Since NZF balance was associated with an increased rate of POAP and POAP has been described as the expression of pancreatic stump ischemic damage[24], the hypothesis of intraoperative pancreatic stump hypoperfusion possibly related to the NZF balance[27] was tested by calling out from the matched population only patients with a soft pancreatic remnant (n= 62) that are usually more prone to develop POAP according to previous reports[24,28,29]. In this population the increased incidence of POAP with the use of NZF was even more pronounced (91.7 vs. 65.4%, p= 0.02). Moreover, unlike in the overall population, where LF was associated with an increased rate of POPF, for these patients the use of a NZF balance was associated with an increased rate of POPF (52.8% vs. 23%, p= 0.03).

Table 3 shows the results of both univariate and multivariate analysis of predictors of Clavien-Dindo ≥ IIIB morbidity. For patients undergoing PD, a LF balance, operating room (OR) time and fistula risk score were predictors of Clavien-Dindo ≥ IIIB morbidity at univariate analysis, but only LF balance was confirmed as an independent predictor. For patients undergoing DP, age, BMI and a LF balance were predictors of the main outcome, but only BMI and LF fluid balance were confirmed as independent predictors.

DISCUSSION

The post-operative outcome of pancreatic surgery has been radically improved in the last few decades, mainly via centralization of patients in high-volume centers[12]. Moreover, standardization of surgical procedures and outcome metrics have played a significant role in achieving these results. However, intraoperative fluid management in pancreatic surgery has not yet been standardized and still remains a controversial topic as several studies have demonstrated that the different strategies can affect the postoperative outcome[4–6,8]. The present prospective study demonstrated that, considering both PD and DP, liberal fluid management is associated with an increased risk of severe post-operative surgical complications classified as Clavien-Dindo equal or more than grade IIIB, namely those requiring intervention under general anesthesia. In addition, in patients undergoing PD, LF balance is associated with an increased rate of POPF. However, considering only the population of patients at high risk for POAP, results are completely reversed as, in these patients, NZF is associated with an increased rate of POPF.

High-level evidence is available in the literature that shows an improvement of the post-operative outcome avoiding a liberal fluid management strategy during a major abdominal procedure[5,8]. However, this knowledge is derived from colorectal surgery, and there are controversial results regarding the potential role of intraoperative fluids on the outcomes of pancreatic surgery. Recent randomized clinical trials in this regard have suffered from differences in the metrics used to define fluid regimen, making data comparison difficult. For example, only five studies used weight-based fluid regimens for comparisons[30–35]. As in our series, only one other study[33] considered both PD and DP, but failed to identify a significant relationship between intraoperative fluid management and the surgical outcome. Among those focused on PD, only Eng et al.[30] showed that larger volumes of intraoperative fluids were associated with a worse overall perioperative outcome. Once these data were eventually merged in the two meta-analyses[35,36], both failed to depict significant differences in surgical outcome when comparing liberal and near-zero fluid regimens.

Unlike the available evidence in pancreatic surgery, our results appeared to be more consistent with that retrieved from colorectal surgery and reported in the ERAS protocols[4]. We found that liberal fluid management could be detrimental considering both pancreatic head and left-sided resections, as it is associated with an increased rate of severe surgical complications. According to the results reported for the unmatched cohort, fluid management seems to be affected by confounding factors. In particular, during difficult procedures it is hard to maintain a near-zero fluid balance due to the complex blood pressure control. To reduce this potential source of bias, which would have consequently associated more complex procedures managed with LF to an increased rate of morbidity, the propensity score method was used to match patients according to the complexity of their procedure as expressed by the OR time.

An insightful sub-analysis of the present study is in regard to PD alone. We reported an increased rate of POPF after a liberal fluid policy, reaffirming the relationship between fluid overload and anastomotic failure. Excessive fluid administration leads to decreased tissue oxygenation and edema[9]. However, this hypothesis does completely not apply for POPF as pancreaticojejunostomy is a completely different anastomosis. Indeed, liberal fluid management could cause mucosal edema and swelling of the afferent jejunal loop, but a restrictive regimen could induce prolonged ischemia of the pancreatic stump. This is the reason why, considering only patients at high risk for POAP, that has been reported to be related to pancreatic stump hypoperfusion and ischemia[24,37], results are completely reversed, and a near-zero fluid balance becomes associated with an increased rate of POPF.

A potential explanation is that pancreatic tissue might react even to transient hypo-perfusion, as it occurs during surgery, with a consequent acute inflammatory response and stump necrosis. In the case of hypo-perfusion, pancreatic histological changes have been reported to occur within a few minutes of ischemia[27]. Post-operative acute pancreatitis after PD has recently been reported to be a clinical manifestation of this mechanism, which could eventually lead to POPF[24]. Considering patients with a normal soft pancreatic remnant, this study reports a significantly increased incidence of both POAP and POPF using the NZF balance.

Despite the prospective design of the study, there are several limitations. Even if propensity score may have reduced potential sources of bias, the variability in the choice of fluid regimen limits inferences regarding factors that could have determined the rate of administered fluids even if the dichotomization into two groups was carried out using ERAS recommendations. Available dedicated hemodynamics monitoring devices were not used as they are not included in the usual clinical practice at our institution. Two other potential sources of bias should also be highlighted: vasopressors affect perfusion, but their use was limited to selected cases; postoperative fluids may also affect hemodynamics in the early post-operative course. Data about post-operative fluids were also collected and analyzed, however, data are not presented since the effect of post-operative fluids is beyond the scope of this paper and severely affected by post-operative complications.

Moreover, due to the limited sample size, this study did not report data regarding total pancreatectomy. Thus, further studies are needed to confirm the implications of intraoperative fluid regimens in pancreatic surgery after risk stratification for complications. The ERAS protocols suggest a new concept of providing individualized fluid management based on surgical and patient risk factors[4]. A near-zero fluid balance could be safely applied in patients with limited individual risk or in those who are undergoing low risk procedures. Conversely, in high-risk surgery or in the case of high-risk patients, goal-directed fluid management is recommended to improve the stroke volume and optimize hemodynamics. Previous studies[15,16], however, have assessed the role of goal directed fluid management in pancreatic surgery without revealing substantial differences in post-operative outcomes, maybe due to an ineffective selection of patients who could benefit more from this kind of management. Beyond confirming the detrimental role of liberal fluid regimens, the present study reveals that the surgical risk associated with PD could be insidiously increased in the case of healthy patients with a soft pancreatic remnant who are managed with a near-zero fluid balance. The evidence supports the importance of a tailored intraoperative fluid management, not necessarily goal directed, that combines the extension of the surgical procedure, patient's risk factors and pancreatic-surgery specific features.

CONCLUSIONS

Intraoperative fluid management is associated with an increased rate of Clavien-Dindo ≥ IIIB complications both after PD and DP. In case of PD, a liberal fluid balance is associated with an increased rate of POPF, but when considering patients with soft pancreatic remnants, results are reversed and an increase rate of POPF is associated with a near-zero fluid balance. Further studies are needed to explore the effect of fluid management strategies on postoperative outcomes using patient, procedural, and pancreatic surgery-specific metrics.

REFERENCES

1. Bassi C, Andrianello S. Identifying key outcome metrics in pancreatic surgery, and how to optimally achieve them. *HPB*. 2017 Mar;19(3):178-181
2. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. 2017;161:584–591.
3. Lassen K, Coolsen MME, Slim K, et al. Guidelines for Perioperative Care for Pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society Recommendations. World J Surg. 2013 Feb;37(2):240-58.
4. Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). *Can J Anaesth*. 2015;62:158–168.
5. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238:641–8.
6. Nisanevich V, Felsenstein I, Almogy G, et al. Effect of Intraoperative Fluid Management on Outcome after Intraabdominal Surgery. *Anesthesiology*. 2005;103:25–32.
7. Holte K, Klarskov B, Christensen DS, et al. Liberal versus restrictive fluid administration to improve recovery after laparoscopic cholecystectomy: a randomized, double-blind study. *Ann Surg*. 2004;240:892–9.
8. Lobo DN, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: A randomised controlled trial. *Lancet*. 2002;359:1812–1818.
9. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. *British Journal of Anaesthesia*. 2002;89:622–632.
10. Harnoss JC, Ulrich AB, Harnoss JM, et al. Use and results of consensus definitions in pancreatic surgery: a systematic review.

Surgery. 2014;155:47–57.

11. McMillan MT, Allegrini V, Asbun HJ, et al. Incorporation of Procedure-specific Risk Into the ACS-NSQIP Surgical Risk Calculator Improves the Prediction of Morbidity and Mortality After Pancreatoduodenectomy. *Ann Surg*. 2017;265:978–986.

12. Finks JF, Osborne NH, Birkmeyer JD. Trends in hospital volume and operative mortality for high-risk surgery. *N Engl J Med*. 2011;364:2128–2137.

13. Weinberg L, Wong D, Karalapillai D, et al. The impact of fluid intervention on complications and length of hospital stay after pancreaticoduodenectomy (Whipple's procedure). *BMC Anesthesiol*. 2014;14:35.

14. Behman R, Hanna S, Coburn N, et al. Impact of fluid resuscitation on major adverse events following pancreaticoduodenectomy. *Am J Surg*. 2015;210:896–903.

15. Kratz T, Simon C, Fendrich V, et al. Implementation and effects of pulse-contour- automated SVV/CI guided goal directed fluid therapy algorithm for the routine management of pancreatic surgery patients. *Technol Health Care. 2016 Nov 14;24(6):899-907.*

16. Weinberg L, Ianno D, Churilov L, et al. Restrictive intraoperative fluid optimisation algorithm improves outcomes in patients undergoing pancreaticoduodenectomy: A prospective multicentre randomized controlled trial. *PLoS One. 2017 Sep 7;12(9):e0183313.*

17. Lindenblatt N, Park S, Alsfasser G, et al. [Intraoperative fluid management in pancreatic resections--the surgeon's view]. *Zentralbl Chir*. 2008;133:168–75.

18. Melis M, Marcon F, Masi A, et al. Effect of intra-operative fluid volume on peri-operative outcomes after pancreaticoduodenectomy for pancreatic adenocarcinoma. *J Surg Oncol*. 2012;105:81–84.

19. Callery MP, Pratt WB, Kent TS, et al. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg*. 2013;216:1–14.

20. Bassi C, Falconi M, Molinari E, et al. Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: Results of a prospective randomized trial. *Surgery*. 2003;134:766–771.

21. Melotti G, Butturini G, Piccoli M, et al. Laparoscopic distal pancreatectomy: results on a consecutive series of 58 patients. *Ann Surg*. 2007;246:77–82.

22. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007 Nov;142(5):761-8.

23. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): An International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery. 2007 Jul;142(1):20-5.

24. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. *HPB*

(Oxford). 2016;18:642–651.

25. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis for the third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA - J Am Med Assoc*. 2016;315:762–774.

26. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. *Ann Surg*. 2004;240:205–213.

27. Cuthbertson CM, Christophi C. Disturbances of the microcirculation in acute pancreatitis. *Br J Surg*. 2006;93:518–530.

28. Palani Velu LK, Chandrabalan V V., Jabbar S, et al. Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. *HPB*. 2014;16:610–619.

29. Palani Velu LK, McKay CJ, Carter CR, et al. Serum amylase and C-reactive protein in risk stratification of pancreas-specific complications after pancreaticoduodenectomy. *Br J Surg*. 2016;103:553–563.

30. Eng OS, Goswami J, Moore D, et al. Intraoperative fluid administration is associated with perioperative outcomes in pancreaticoduodenectomy: a single center retrospective analysis. *J Surg Oncol*. 2013;108:242–247.

31. Van Samkar G, Eshuis WJ, Bennink RJ, et al. Intraoperative fluid restriction in pancreatic surgery: A double blinded randomised controlled trial. *PLoS One*. 2015 Oct 14;10(10):e0140294

32. Wang S, Wang X, Dai H, et al. The Effect of Intraoperative Fluid Volume Administration on Pancreatic Fistulas after Pancreaticoduodenectomy. *J Investig Surg*. 2014;27:88–94.

33. Grant F, Brennan MF, Allen PJ, et al. Prospective Randomized Controlled Trial of Liberal Vs Restricted Perioperative Fluid Management in Patients Undergoing Pancreatectomy. *Ann Surg*. 2016;264:591–598.

34. Han IW, Kim H, Heo J, et al. Excess intraoperative fluid volume administration is associated with pancreatic fistula after pancreaticoduodenectomy. *Medicine (Baltimore)*. 2017;96:e6893.

35. Huang Y, Chua TC, Gill AJ, et al. Impact of perioperative fluid administration on early outcomes after pancreatoduodenectomy: A meta-analysis. *Pancreatology*. 2017;17:334–341.

36. Wang GS, Dong M, Sheng WW, et al. [Preoperative restricted versus liberal fluid administration on perioperative safety for pancreatic surgery: a Meta-analysis]. *Zhonghua Wai Ke Za Zhi*. 2017;55:618–625.

37. Strasberg SM, Drebin JA, Mokadam NA, Green DW JK, JP E. Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. *J Am Coll Surg*. 2002;194:746–758.

TABLES

Table 1 - Patient characteristics stratified by intraoperative fluid regimens									
Pancreaticoduodenectomy									
		Before matching				After matching			
		Overall (n= 209)	NZF (n= 63)	LF (n= 146)	*p*	*Overall (n= 126)*	*NZF (n= 63)*	*LF (n= 63)*	*p*
Age (median, range)		65 (24 – 85)	63 (24 – 81)	66 (30 – 85)	0.4	65 (24 – 85)	63 (24 – 81)	67 (30 – 85)	0.1
Gender	Male	123 (58.9%)	36 (57.1%)	87 (59.6%)	0.7	77 (61.1%)	36 (57.1%)	41 (65.1%)	0.4
	Female	86 (41.1%)	27 (42.9%)	59 (40.4%)		49 (38.9%)	27 (42.9%)	22 (34.9%)	
BMI (Kg/m^2, mean, SD)		24.68 ±3.82	25.14 ±3.73	24.47 ±3.85	0.1	24.74 ±3.68	25.14 ±3.7	24.3 ±3.6	0.1
Weight (Kg, mean, SD)		71.2 ±13.6	72.7 ±13	70.5 ±13.8	0.2	72 ±13.8	72.7 ±13	71.6 ±14.7	0.4
ASA score	1	11 (5.3%)	4 (6.3%)	7 (4.8%)	0.7	5 (4%)	4 (6.3%)	1 (1.6%)	0.2
	2	153 (73.2%)	47 (74.6%)	106 (72.6%)		91 (72.2%)	47 (74.6%)	44 (69.8%)	
	3	45 (21.5%)	12 (19%)	33 (22.6%)		30 (23.8%)	12 (19%)	18 (28.6%)	
Neoadjuvant therapy		51 (24.4%)	12 (19%)	39 (26.7%)	0.2	32 (25.4%)	12 (19%)	20 (31.7%)	0.1
Vascular resection		35 (16.7%)	5 (7.9%)	30 (20.5%)	0.02	18 (14.2%)	13 (10.3%)	5 (7.9%)	0.07
Operative time (min, mean, SD)		390 ±111	472 ±73	355 ±106	< 0.01	357 ±87	362 ±73	349 ±116	0.1
EBL (mL, mean, SD)		423 ±208	392 ±132	437 ±232	0.7	415 ±193	392 ±132	437 ±237	0.6
Intraoperative transfusions		23 (11%)	4 (6.3%)	19 (13%)	0.2	11 (8.7%)	4 (6.3%)	7 (11.1%)	0.5
Intraoperative crystalloids (mL, median, range)		3700 (2000 – 7000)	2500 (2000 – 3900)	3800 (2500 – 7000)	< 0.01	3600 (2000 – 7000)	2500 (2000 – 3900)	3700 (2800 – 7000)	< 0.01
FRS risk category	Negligible	15 (7.2%)	5 (7.9%)	10 (6.8%)	0.8	11 (8.7%)	5 (7.9%)	6 (9.5%)	0.7
	Low	71 (34%)	19 (30.2%)	52 (35.6%)		43 (34.1%)	19 (39.2%)	24 (38.1%)	
	Intermediate	107 (51.2%)	35 (55.6%)	72 (49.3%)		65 (51.6%)	35 (55.6%)	30 (47.6%)	

	High	16 (7.7%)	4 (6.3%)	12 (8.2%)		7 (5.6%)	4 (6.3%)	3 (4.8%)	
Distal pancreatectomy									
		Before matching				After matching			
		Overall (n= 104)	NZF (n= 48)	LF (n= 56)	*p*	*Overall (n= 96)*	*NZF (n= 48)*	*LF (n=48)*	*p*
Age (median, range)		58 (16 – 86)	56 (16 – 83)	60 (22 – 86)	0.3	58 (16 – 83)	56 (16 – 83)	61 (30 – 80)	0.7
Gender	Male	48 (46.2%)	22 (45.8%)	26 (46.4%)	1	42 (44.4%)	22 (45.8%)	20 (42.4%)	0.8
	Female	56 (53.8%)	26 (54.2%)	30 (53.6%)		54 (55.6%)	26 (54.2%)	28 (57.6%)	
BMI (Kg/m^2, mean, SD)		24.85 ±3.7	25.33 ±3.6	24.43 ±3.9	0.2	24.64 ±3.64	25.33 ±3.6	23.63 ±3.51	0.06
Weight (Kg, mean, SD)		69.9 ±12.8	72.5 ±11.9	67.7 ±13.2	0.07	69.7 ±12.78	72.5 ±11.9	65.7 ±13	0.01
ASA score	1	10 (9.6%)	5 (10.4%)	5 (8.9%)	0.7	10 (11.1%)	5 (10.4%)	6 (12.1%)	0.8
	2	79 (76%)	35 (72.9%)	44 (78.6%)		71 (74.1%)	35 (72.9%)	36 (75.8%)	
	3	15 (14.4%)	8 (16.7%)	7 (12.5%)		14 (14.8%)	8 (16.7%)	6 (12.1%)	
Neoadjuvant therapy		14 (13.5%)	8 (16.7%)	6 (10.7%)	0.4	13 (13.6%)	8 (16.7%)	4 (9.1%)	0.5
Vascular resection		11 (10.6%)	4 (8.3%)	7 (12.5%)	0.5	8 (8.6%)	4 (8.3%)	4 (9.1%)	1
Operative time (min, mean, SD)		367 ±156	432 ±176	311 ±111	< 0.01	410 ±150	432 ±176	377 ±92	0.1
EBL (mL, mean, SD)		304 ±79	232 ±133	366 ±65	0.7	289 ±191	232 ±133	372 ±151	0.3
Intraoperative transfusions		9 (8.7%)	3 (6.3%)	6 (10.7%)	0.5	8 (8.6%)	3 (6.3%)	6 (12.1%)	0.4
Intraoperative crystalloids (mL, median, range)		2800 (1500 – 7000)	2200 (1500 – 4800)	2900 (1900 – 7000)	< 0.01	2800 (1500 – 7000)	2750 (1600 – 4800)	2900 (1500 – 7000)	< 0.01

ASA: American society of anesthesiology; BMI: body mass index; EBL: estimated blood loss; FRS: fistula risk score.

Table 2 - *Post-operative outcomes of all major pancreatic resections stratified by intraoperative fluid regimens and type of surgery*
Pancreaticoduodenectomy

		Overall (n= 126)	LF (n= 63)	NZF (n= 63)	p
Abdominal abscess		39 (31%)	15 (23.8%)	24 (38.1%)	0.1
PPH		13 (10.3%)	6 (9.5%)	7 (11.1%)	1
PPH grade	A	2 (15.4%)	1 (16.7%)	1 (14.3%)	0.9
	B	6 (46.2%)	3 (50%)	3 (42.9%)	
	C	5 (38.5%)	2 (33.3%)	3 (42.9%)	
DGE		15 (11.9%)	8 (12.7%)	7 (11.1%)	1
DGE grade	A	2 (13.3%)	1 (12.5%)	1 (14.3%)	0.9
	B	6 (40%)	3 (37.5%)	3 (42.9%)	
	C	7 (46.7%)	4 (50%)	3 (42.9%)	
POPF		50 (23.9%)	21 (33.3%)	29 (19.9%)	0.05
POPF grade	B	35 (16.7%)	16 (25.4%)	19 (13%)	0.07
	C	15 (7.2%)	5 (7.9%)	10 (6.8%)	
Biliary fistula		15 (7.2%)	4 (6.3%)	11 (7.5%)	1
POAP		65 (51.6%)	25 (39.7%)	40 (63.5%)	0.01
Sepsis		11 (8.7%)	5 (7.9%)	6 (9.5%)	1
Relaparotomy		13 (10.3%)	7 (11.1%)	6 (9.5%)	1
ICU stay		14 (11.1%)	9 (14.3%)	5 (7.9%)	0.3
LHS (median, range)		9 (3 – 108)	9 (6 – 96)	10 (3 – 108)	0.2
Mortality (in-hospital)		5 (4%)	2 (3.2%)	3 (2.8%)	1
Readmission (30-days)		6 (4.8%)	4 (6.3%)	2 (3.2%)	0.6
Clavien-Dindo ≥ IIIB		57 (45.2%)	38 (60.3%)	19 (30.2%)	<0.01
Distal pancreatectomy					

		Overall (n= 96)	LF (n= 48)	NZF (n= 48)	p
Abdominal abscess		34 (35.4%	14 (29.2%)	20 (41.7%)	0.2
PPH		8 (8.3%)	3 (6.2%)	5 (10.4%)	0.7
PPH grade	A	3 (37.5%)	2 (66.7%)	1 (20%)	0.2
	B	2 (25%)	1 (33.3%)	1 (20%)	
	C	3 (37.5%)	0	3 (60%)	
DGE		1 81%)	1 (2.1%)	0	1
DGE grade	A	1 (100%)	0	0	/
	B	0	0	0	
	C	0	0	0	
POPF		21 (21.9%)	11 (22.9%)	10 (20.8%)	1
POPF grade	B	19 (19.8%)	10 (20.8%)	9 (18.8%)	0.9
	C	2 (2.1%)	1 (2.1%)	1 (2.1%)	
Post-operative acute pancreatitis		58 (60.4%)	25 (52.1%)	33 (68.8%)	0.1
Sepsis		4 (4.2%)	1 (2.1%)	3 (6.3%)	0.6
Relaparotomy		8 (8.3%)	3 (6.3%)	5 (10.4%)	0.7
ICU stay		8 (8.3%)	2 (4.2%)	6 (12.5%)	0.2
LHS (median, range)		9 (5 – 71)	8 (5 – 71)	9 (6 – 42)	0.08
Mortality (in-hospital)		2 (2.1%)	0	2 (4.2%)	0.4
Readmission (30-days)		3 (3.1%)	3 (6.3%)	0	0.2
Clavien-Dindo ≥ IIIB		37 (28.5%)	24 (50%)	13 (27.1%)	0.03

DGE: delayed gastric emptying; ICU: intensive care unit; LHS: length of hospital stay; POPF: postoperative pancreatic fistula; PPH: post-pancreatectomy hemorrhage.

Table 3 - Univariate and multivariate analysis of predictors of Clavien-Dindo ≥ IIIB morbidity

Pancreaticoduodenectomy						
	Univariate			Multivariate		
	CD ≥IIIB					
	No (n=69)	Yes (n= 57)	p	OR	CI 95%	p
Age (median, range)	64 (30 – 83)	66 (24 – 85)	0.7			
BMI (Kg/m2, mean, SD)	25.02± 3.68	24.41± 3.69	0.4			
Neoadjuvant therapy	17 (24.6%)	15 (26.3%)	0.8			
ASA ≥ 3	15 (26.3%)	15 (21.7%)	0.6			
Diabetes	11 (25.9%)	14 (24.6%)	0.2			
Liberal intraoperative fluid management	25 (36.2%)	38 (66.7%)	< 0.01	2.75	1.16 – 6.50	0.02
EBL (mL, mean, SD)	408± 224	423± 147	0.1			
Operative time (min, mean, SD)	435± 105	381± 119	0.02	1.02	0.99 – 1.05	0.9
Vascular resection	8 (11.6%)	12 (21.1%)	0.2			
FRS(median, range)	3 (0 – 7)	4 (0 – 8)	0.02	1.64	0.78 – 1.99	0.8

Distal pancreatectomy						
	Univariate			Multivariate		
	CD ≥IIIB					
	No (n= 59)	Yes (n= 37)	p	OR	CI 95%	p
Age (median, range)	57 (27 – 83)	65 (16 – 86)	0.02	1.01	0.98 – 1.04	0.2
BMI (Kg/m2, mean, SD)	23.69± 3.72	25.1± 3.69	0.02	1.3	0.89 – 1.56	0.03
Neoadjuvant therapy	7 (11.9%)	6 (16.2%)	0.5			
ASA ≥ 3	8 (13.6%)	5 (13.5%)	1			
Diabetes	8 (13.6%)	6 (16.2%)	0.7			
Liberal intraoperative fluid management	35 (59.3%)	13 (35.1%)	0.03	2.42	1.001 – 5.87	0.05
EBL (mL, mean, SD)	295± 173	303± 311	0.07			
Operative time (min, mean, SD)	393± 175	371± 96	0.8			
Vascular resection	5 (8.5%)	5 (13.5%)	0.5			

ASA: American society of anesthesiology; BMI: body mass index; EBL: estimated blood loss; FRS: fistula risk score.

II

Postoperative acute pancreatitis following pancreaticoduodenectomy: a determinant of fistula potentially driven by the intraoperative fluid management

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ABSTRACT

Objective

Aim of the study is to characterize post-operative acute pancreatitis (POAP).

Summary Background Data

A standardized definition of POAP after pancreaticoduodenectomy (PD) has been recently proposed, but specific studies are lacking.

Methods

The patients were extracted from the prospective database of The Pancreas Institute of Verona. POAP was defined as an elevation of the serum pancreatic amylase levels above the upper limit of normal (52 U/L) on post-operative day (POD) 0 or 1. The endpoints included defining the incidence and predictors of POAP and investigating the association of POAP with post-operative pancreatic fistula (POPF).

Results

The study population consisted of 292 patients who underwent PD. The POAP and POPF rates were 55.8% and 22.3%, respectively. POAP was an independent predictor of POPF (OR 3.8), with a 92% sensitivity and 53.7% specificity (AUC 0.79). Pre-operative exocrine insufficiency (OR 0.39), neoadjuvant therapy (OR 0.29) additional resection of the pancreatic stump margin (OR 0.25), soft pancreatic texture (OR 4.38) and Main Pancreatic Duct (MPD) diameter ≤3 mm (OR 2.86) were independent predictors of POAP. In high-risk patients, an intra-operative fluid administration of ≤3 ml/kg/h was associated with an increased incidence of POAP (24.6 vs. 0%, p =0.04) and POPF (27.6 vs. 11.4%, p =0.05).

Conclusion

This study represents the first clinical application of the only available definition of POAP as a specific complication of pancreatic surgery. POAP is associated with an increased occurrence of POPF and overall morbidity and could potentially be avoided through a specific intra-operative fluid regimen in high-risk pancreas.

INTRODUCTION

Postoperative pancreatic fistula (POPF) remains the major determinant of morbidity and mortality after pancreaticoduodenectomy (PD)[1]. Over the past few decades, several attempts have been made to understand the underlying etiology of the breakdown of pancreatic anastomosis, with the goal of preventing its occurrence[2,3]. However, POPF seems to be a multifactorial event in which surgical techniques, anatomical factors, and infections all play major roles [1,3]. As described for other surgical procedures [4–7], changes in blood supply and drainage that potentially lead to tissue ischemia and anastomotic failure may also play a role in POPF [8,9]. Nevertheless, when POPF was first defined [10], the possibility that POPF may result from ischemic damage of the pancreatic remnant was not considered. Signs of pancreatic necrosis can usually be observed by radiological imaging only more than 72 hours [11–13] after the onset; however, an increase in serum amylase levels may represent the earliest sign of postoperative acute pancreatitis (POAP) [14–17]. Although POAP has been rarely reported as a separate pancreatic complication after PD [17], it is most frequently considered to be only an indirect sign of POPF [18–20].

Recent evidence has suggested that the pathophysiology of a significant proportion of POPF cases that occur after PD are due to POAP [21]. However, a universally accepted definition of POAP after major pancreatic resections has not yet been established, resulting in a gap in pancreatic surgery outcome metrics, leading to difficulties in data comparisons. POAP may represent another pancreatic surgery-specific complication, such as POPF, post-pancreatectomy hemorrhage (PPH), and delayed gastric emptying (DGE)[22,23], that requires proper assessment and strategic planning for prevention and treatment. Consequently, specific management of POAP could potentially reduce the incidence of POPF.

Despite the lack of specific studies, a standardized definition was recently proposed by Connor[21] that still requires application in a proper clinical setting. The aims of the present study were to characterize POAP according to the definition provided by Connor in the clinical setting of a high-volume center and to explore potential triggers.

METHODS

The study was approved by the institutional review board (N° 1101CESC, University of Verona Hospital Ethical Committee). The study was consistent with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations. Data from all patients who consecutively underwent pancreaticoduodenectomy (PD) from January 2016 to August 2017 were prospectively collected and retrospectively analyzed. All procedures were carried out at the Department of General and Pancreatic Surgery at The Pancreas Institute of the University of Verona Hospital Trust. The demographic data, operative details, including the amount of intraoperative fluid administration, postoperative data, and pathologic features were recorded.

Both pylorus-preserving and Whipple PDs with either pancreatojejunostomy (PJ) or pancreaticogastrostomy (PG) were performed. The operative and surgical drain placement procedures have been previously described by our group[24,25]. Postoperative morbidity was defined according to ISGPS definitions of postoperative pancreatic fistula (POPF)[26], delayed gastric emptying (DGE)[23], post-pancreatectomy hemorrhage (PPH)[22], and chyle leak[27]. 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[28]. Cardiac morbidity was defined as acute myocardial infarction or severe arrhythmia. Wound infection was defined according to the Centers for Disease Control and Prevention criteria[29]. The unplanned need for intensive care was defined as intensive care unit (ICU) stay. Mortality was defined as postoperative death occurring within 90 days of index surgery. The severity of complications was determined using the Clavien–Dindo classification system[30]. The risk of POPF was assessed according to the Fistula Risk Score (FRS) [31]. Morbidity was defined as any complication occurring within 30 days from index surgery. Readmission was defined as a new hospital admission after discharge within 30 days from index surgery.

Due to the absence of a widely accepted definition, POAP was defined according to Connor's definition [21] as an elevation in serum pancreatic amylase above the upper limit of normal on postoperative day (POD) 0 or 1. At our institution, the upper limit of normal for serum pancreatic amylase is 52 U/L. Serum pancreatic amylase was systematically measured two hours after surgery on POD0, POD1, and POD2 according to our institutional policy. No additional radiological or laboratory studies were required for the diagnosis. No specific protocols for the treatment of POAP were followed during the study period because none are available. Neither steroids nor somatostatin analogs were used in the perioperative period.

The primary endpoint of the study was the incidence of POAP, as defined by Connor [21]. The secondary endpoints were to identify the possible predictors of POAP and to investigate the association between POAP and POPF.

Moreover, to test the hypothesis of pancreatic remnant hypoperfusion and ischemia leading to POAP, we assessed the effect of intraoperative fluid management as an additional endpoint. This outcome was assessed by identifying two different groups of patients: a "near-zero fluid" (NZF) balance group and a liberal fluid (LF) balance group. According to ERAS protocols[32], NZF balance attempts to maintain the central euvolemia with a 1:1 replacement of blood lost and urine output, in addition to a maintenance infusion, to replace insensible perspiration in the case of open abdominal surgery. The expected amount of fluids needed for NZF balance was estimated from anesthesiology records and compared to the observed one, recorded at the end of the procedure. If the expected value was similar to the observed fluid balance, patients were included in the NZF group. Otherwise, if the observed was greater than the expected fluid balance, patients were included in the LF group. Maintenance fluids, small crystalloid boluses used to maintain blood pressure and active diuresis, packed red blood cells (PRBC), and fresh frozen plasma (FFP) were included in the fluid balance assessment.

For univariate comparisons, the chi-square test or Fisher's exact test were used to evaluate the categorical variables. The continuous variables were analyzed using Student's t-test or the Mann-Whitney test when appropriate. A receiver operating characteristic (ROC) curve was used to assess the association between serum amylase levels on PODs 0 and 1 and POPF occurrence. A stepwise backward logistic regression analysis was conducted to identify covariates associated with the incidence of POAP and POPF. The variables were assessed for multicollinearity and removed from the model when necessary. All tests were 2-tailed. A P value <0.05 was considered to be statistically significant. The statistical analysis was performed with SPSS software (SPSS Inc., version 20 for Macintosh, IBM, Chicago, IL, USA).

RESULTS

Incidence of POAP after PD

The study population consisted of 292 consecutive patients who underwent PD. The majority of patients were male (56.8%) with a median age of 65 years (24-87 years). According to Connor's definition[21], POAP occurred in 55.8% of patients and was classified as clinically relevant (C-reactive protein on POD2 ≥ 180 mg/L) in 52.7% (n= 86) of cases. Preoperative serum pancreatic amylase was above the upper normal level in 5.1% (n= 15) of cases. Only 8 (4.9%) patients developing POAP presented a preoperative amylase value above the upper limit of normal. Because Connor's definition was functional to POPF prediction, several ROC curves were plotted to assess the relationship between postoperative serum amylase values and POPF. The area under the curve (AUC) for serum amylase was 0.79 on POD 0 and 0.80 on POD 1. With the cut-off value of 52 U/L, POAP showed a 90.7% sensitivity, 54.2% specificity, 36.2% positive predictive value, 95.3% negative predictive value, and 62.3% accuracy in predicting the occurrence of POPF. By increasing the threshold to three times the upper limit of normal to mimic the criterion of the revised Atlanta classification for acute pancreatitis [11], the diagnostic performance of the test showed a 77.7% sensitivity, 71% specificity, 53.8% positive predictive value, 88.2% negative predictive value, and 73.3% accuracy. The AUC values of Connor's definition and of the Revised Atlanta Classification for acute pancreatitis were 0.78 and 0.68, respectively (Supplementary Figure 1).

Table 1 characterizes the postoperative outcome of patients developing POAP. Patients who developed POAP experienced a significantly increased rate of severe postoperative surgical morbidity scored as Clavien–Dindo ≥IIIB, including more cases of overall and grade C POPF, overall and grade C PPH, chyle leaks, abdominal abscesses, postoperative pneumonia, cardiac morbidity, relaparotomy, and ICU stays. Moreover, they also experienced a higher 90-day postoperative mortality rate. To analyze the clinical burden produced by POAP on the postoperative course, we conducted univariate and multivariate analyses of Clavien–Dindo ≥IIIB morbidity (Table 2). Independent from other complications, particularly POPF, POAP was an independent predictor of Clavien–Dindo ≥IIIB morbidity.

Analysis of risk factors for POAP

Table 3 reports the univariate and multivariate analyses of possible predictors of POAP. Due to multicollinearity of the main pancreatic duct diameter and stump texture, FRS risk zones were excluded from the model. Exocrine insufficiency, neoadjuvant therapy, additional resection of the pancreatic stump margin, small main pancreatic duct, and soft texture were defined as independent predictors of POAP. The AUC of the model was 0.87. Possible predictors of intraoperative pancreatic stump ischemia, such as operative time, estimated blood loss (EBL), and intraoperative fluid balance, were associated with POAP in the univariate analysis. Patients at high risk for POAP (n= 89, 30.5%), defined as those who were not treated with neoadjuvant therapy and had a main pancreatic duct ≤3 mm, soft pancreatic texture, and no additional transection margin resection or preoperative exocrine insufficiency, were then isolated and analyzed. Of these, 40 (44.9%) were treated with intraoperative NZF management. In patients at high risk for POAP, NZF management was associated with a higher rate of POAP (24.6 vs. 0%, $p < 0.01$) and POPF (27.6 vs. 11.4%, $p = 0.05$) than LF management.

Association between POAP and POPF

The overall POPF rate was 22.2%. Almost all patients who eventually developed POPF (n =58/65; 90.7%) presented POAP. Table 4 shows the univariate and multivariate analyses of the predictors of POPF. A BMI >25 kg/m^2, a soft pancreatic texture, a main pancreatic duct diameter ≤3 mm, and the occurrence of POAP were independent predictors of POPF. The AUC of the model was 0.84.

Table 5 shows the effect of POAP on patient outcomes when occurring alone or with POPF compared to no development of either POAP or POPF. Patients who developed POPF in association with POAP, compared with patients who developed POAP alone, experienced a significantly increased rate of Clavien–Dindo ≥IIIB morbidity, grade C PPH, DGE, abscesses, biliary fistulas, wound infections, and relaparotomy. Moreover, they required more frequent ICU admissions and hospital readmissions after discharge and experienced a significantly higher 90-day mortality rate. Comparing patients who did not develop POAP or POPF to those who developed POAP alone, the latter category showed a significantly increased rate of abdominal abscesses and chyle leak. A comparison with the group of patients who developed POPF but not POAP was not carried out due to the small sample size (n= 6).

DISCUSSION

Recent literature has shown an interest in post-pancreaticoduodenectomy acute pancreatitis. Rather than just a collateral manifestation of a POPF, POAP seems to be the specific cause of a significant proportion of pancreatic anastomotic failures [21], but its actual incidence and clinical impact has never been clearly defined. Therefore, the definition and standardization of reporting, as well as the identification of POAP risk factors, may positively affect postoperative morbidity.

This retrospective study suggests that, according to the only available definition [21], POAP is a specific clinical entity that is closely associated with POPF. Despite the need for further investigations on pancreatic anatomy and intraoperative hemodynamics [33,34], POAP may be a clinical manifestation of intraoperative ischemic damage of the pancreatic stump that eventually leads to anastomotic leakage.

Most of the trials exploring POAP [14,18,20,35–37] suffered from differences in metrics and definitions that led to difficulties in data comparison. The majority of these trials used the revised Atlanta classification for acute pancreatitis [11] to define POAP. However, clinical and radiological criteria of the revised Atlanta classification may not be adequate for the assessment of POAP after pancreatic surgery, because the clinical picture is hidden by postoperative analgesia and the morphological changes evident on cross-sectional imaging can usually only be detected after at least 72 hours[12]. The definition proposed by Connor [21] is based on biochemical evidence of pancreatic stump damage: an elevation in serum amylase levels above the upper limit of normal on POD0 or POD1. The serum amylase cut-off was lower than the one traditionally used to diagnose acute pancreatitis [11] because Kühlbrey reported a relevant incidence of POPF even in patients with postoperative serum amylase levels under the threshold of three times the upper limit of normal [14]. Such a low threshold explains why the rate of POAP does not necessarily equal that of POPF and in fact is usually higher. Although only a few reports have considered the predictive value of serum amylase on surgical outcomes after PD, they all identified postoperative hyperamylasemia as a risk factor for POPF [14,19,20,36,38]. This biochemical evidence suggests that POAP is induced intraoperatively and the resulting anastomotic dehiscence in several cases can be explained by pancreatic stump necrosis [21].

Intraoperative pancreatic ischemia is due to different factors, including anatomical features [39], vascularization, and intraoperative hemodynamics [40]. Some studies [39,40] have reported a vascular watershed in the neck of the pancreas that may result in stump ischemia at the level of the transection margin, eventually leading to necrosis and anastomotic dehiscence [40]. From our data, we can also speculate that, due to this vascular watershed, extending the resection to a more distal portion of the pancreatic stump could improve the blood supply of pancreatic anastomosis. The viability of the pancreatic stump has already been assessed using infrared scanning after the injection of indocyanine green dye. This method may be able to identify the ischemic segment needing further resection, avoiding ischemia and subsequent anastomotic failure[41,42].

A novel finding of the present series was the identification of risk factors for POAP. Additional resection of the pancreatic stump margin, preoperative exocrine insufficiency, neoadjuvant therapy, soft pancreatic texture, and an MPD diameter ≤3 mm were independent predictors of POAP. Neoadjuvant therapy allows changes in normal pancreatic tissue to progress to obstructive chronic pancreatitis and may cause inflow disturbances and prolonged circulation within the organ [40]. By contrast, normal pancreatic tissue appears to be extremely susceptible to ischemia, and even transient hypoperfusion can lead to pancreatic necrosis[39]. To avoid hypovolemia and hypoperfusion, a proper intraoperative fluid therapy is crucial. According to ERAS protocol [32], restrictive intraoperative fluid management is associated with an improved surgical outcome after abdominal procedures. However, this study highlighted that, in patients with a soft pancreatic remnant, a restrictive fluid balance is associated with a significantly increased risk of POAP and POPF. In these patients, tailored intraoperative fluid management could potentially minimize the risk of POAP and subsequently the incidence of POPF. Moreover, due to the high negative predictive value for POPF, a low serum amylase value on POD0/1 can identify patients at low risk for POPF who may benefit from an enhanced postoperative recovery program.

In a nonsurgical setting, the occurrence of acute pancreatitis can be easily diagnosed by biochemical and clinical pictures. This condition can completely resolve without leaving sequelae, or it can lead to additional morbidities, such as walled-off necrosis, abscesses, bleedings, pseudocysts, and organ failure[11]. POAP represents a specific complication after pancreatic surgery and has well-defined biochemical features as acute pancreatitis. However, its clinical picture is invariably covered by the postoperative analgesia. Moreover, POAP can quickly resolve or determine other postoperative complications, such as POPF, abdominal abscesses, PPH, infectious complications, re-laparotomy, and even death. However, the low serum amylase cut-off value does not allow for staging of the actual clinical burden of POAP, as different degrees of severity are probably included within the same definition. In this regard, a universally accepted definition associated with a clinically validated grading system of severity is needed to define appropriate management and compare results.

The major limitation of the current study was its retrospective design. Moreover, the patients were not stratified according to preoperative features and different surgical techniques to avoid low statistical power and clinical utility of the results.

CONCLUSION

The present paper represents the first application in a clinical setting of the current definition of POAP based on serum amylase levels at either POD0 or POD1 after PD. Rather than representing just a collateral finding of POPF, POAP may be the biochemical manifestation of intraoperative ischemic damage of the pancreatic stump that eventually leads to pancreatic anastomotic leakage. Patients with POAP had an increased rate of other additional severe complications and postoperative death. Individualized intraoperative fluid management for patients with high-risk pancreatic complications could potentially reduce the occurrence of POAP.

REFERENCES

1. Pulvirenti A, Marchegiani G, Pea A et al. Clinical Implications of the 2016 International Study Group on Pancreatic Surgery Definition and Grading of Postoperative Pancreatic Fistula on 775 Consecutive Pancreatic Resections. Ann Surg 2017 (Epub Ahead of Print)

2. Harnoss JC, Ulrich AB, Harnoss JM et al. Use and results of consensus definitions in pancreatic surgery: a systematic review. Surgery 2014;155(1):47–57.

3. McMillan MT, Vollmer CM, Asbun HJ et al. The Characterization and Prediction of ISGPF Grade C Fistulas Following Pancreatoduodenectomy. J Gastrointest Surg 2016;20(2):262–76.

4. Boyle NH, Manifold D, Jordan MH, Mason RC. Intraoperative assessment of colonic perfusion using scanning laser Doppler flowmetry during colonic resection. J Am Coll Surg 2000;191(5):504–10.

5. Boni L, David G, Dionigi G, Rausei S, Cassinotti E, Fingerhut A. Indocyanine green-enhanced fluorescence to assess bowel perfusion during laparoscopic colorectal resection. Surg Endosc 2016;30(7):2736–42.

6. Zehetner J, Demeester SR, Alicuben ET et al. Intraoperative Assessment of Perfusion of the Gastric Graft and Correlation With Anastomotic Leaks After Esophagectomy. Ann Surg 2015;262(1):74–8.

7. Jafari MD, Wexner SD, Martz JE et al. Perfusion assessment in laparoscopic left-sided/anterior resection (PILLAR II): a multi-institutional study. J Am Coll Surg 2015;220(1):82–92.e1.

8. Rudis J, Ryska M. Pancreatic leakage and acute postoperative pancreatitis after proximal pancreatoduodenectomy. Rozhl V Chir Mesic Ceskoslov Chir Spol 2014;93(7):380–5.

9. Ryska M, Rudis J. Pancreatic fistula and postoperative pancreatitis after pancreatoduodenectomy for pancreatic cancer. Hepatobiliary Surg Nutr 2014;3(5):268–75.

10. Bassi C, Dervenis C, Butturini G et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 2005;138(1):8–13.

11. Banks PA, Bollen TL, Dervenis C et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62(1):102–11.

12. Bollen TL, Singh VK, Maurer R et al. A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. Am J Gastroenterol 2012;107(4):612–9.

13. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology 1990;174(2):331–6.

14. Kühlbrey CM, Samiei N, Sick O, Makowiec F, Hopt UT, Wittel UA. Pancreatitis After Pancreatoduodenectomy Predicts Clinically Relevant Postoperative Pancreatic Fistula. J Gastrointest Surg 2017;21(2):330–8.

15. Räty S, Sand J, Lantto E, Nordback I. Postoperative acute pancreatitis as a major determinant of postoperative delayed gastric emptying after pancreaticoduodenectomy. J Gastrointest Surg 2006;10(8):1131–9.

16. Carter AE. Post-operative pancreatitis. Postgrad Med J 1956;32(367):248–58.

17. Kriger AG, Kubishkin VA, Karmazanovskiĭ GG et al. The postoperative pancreatitis after the pancreatic surgery. Khirurgiia (Sofiia) 2012;(4):14–9.

18. Jin S, Shi X-J, Wang S-Y et al. Drainage fluid and serum amylase levels accurately predict development of postoperative pancreatic fistula. World J Gastroenterol 2017;23(34):6357–64.

19. Palani Velu LK, Chandrabalan V V., Jabbar S et al. Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. HPB 2014;16(7):610–9.

20. Palani Velu LK, McKay CJ, Carter CR, McMillan DC, Jamieson NB, Dickson EJ. Serum amylase and C-reactive protein in risk stratification of pancreas-specific complications after pancreaticoduodenectomy. Br J Surg 2016;103(5):553–63.

21. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. HPB (Oxford) 2016;18(8):642–51.

22. Wente MN, Veit JA, Bassi C et al. Postpancreatectomy hemorrhage (PPH): An International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142(1):20–5.

23. Wente MN, Bassi C, Dervenis C et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2007 Nov;142(5):761-8.

24. Bassi C, Falconi M, Molinari E et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. Ann Surg 2005;242(6):767–71

25. Bassi C, Molinari E, Malleo G et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. Ann Surg 2010;252(2):207–14.

26. Bassi C, Marchegiani G, Dervenis C et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 2017;161(3):584–91.

27. Besselink MG, van Rijssen LB, Bassi C et al. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. 2017 Feb;161(2):365-372.

28. Seymour CW, Liu VX, Iwashyna TJ et al. Assessment of clinical criteria for sepsis for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 2016;315(8):762–74.

29. Condon R, Sherertz R, Gaynes RP et al. CDC Definitions of Nosocomial Surgical Site Infections, 1992: A Modification of CDC Definitions of Surgical Wound Infections. Infect Control Hosp Epidemiol 1992;13(10):606–8.

30. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications. A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. Ann Surg 2004;240(2):205–13.

31. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. J Am Coll Surg 2013;216(1):1–14.

32. Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). Can J Anaesth 2015;62(2):158–68.

33. Cuthbertson CM, Christophi C. Disturbances of the microcirculation in acute pancreatitis. Br J Surg 2006;93(5):518–30.

34. Strasberg SM, McNevin MS. Results of a technique of pancreaticojejunostomy that optimizes blood supply to the pancreas. J Am Coll Surg 1998;187(6):591–6.

35. Räty S, Sand J, Nordback I. Detection of postoperative pancreatitis after pancreatic surgery by urine trypsinogen strip test. Br J Surg 2007;94(1):64–9.

36. Cloyd JM, Kastenberg ZJ, Visser BC, Poultsides GA, Norton JA. Postoperative serum amylase predicts pancreatic fistula formation following pancreaticoduodenectomy. J Gastrointest Surg 2014;18(2):348–53.

37. Dalla Valle R, De Bellis M, Pedrazzi G et al. Can early serum lipase measurement be routinely implemented to rule out clinically significant pancreatic fistula after pancreaticoduodenectomy? Int J Surg 2015;21 Suppl 1:S50-54.

38. Okabayashi T, Maeda H, Nishimori I, Sugimoto T, Ikeno T, Hanazaki K. Pancreatic fistula formation after pancreaticooduodenectomy; for prevention of this deep surgical site infection after pancreatic surgery. Hepatogastroenterology 2009;56(90):519–23.

39. Cuthbertson CM, Christophi C. Disturbances of the microcirculation in acute pancreatitis. Br. J. Surg.2006;93(5):518–30.

40. Sugimoto M, Takahashi S, Kobayashi T et al. Pancreatic perfusion data and post-pancreaticoduodenectomy outcomes. J Surg Res 2015;194(2):441–9.

41. Strasberg SM, Drebin JA, Mokadam NA, Green DW JK. Prospective trial of a blood supply-based technique of pancreaticojejunostomy: effect on anastomotic failure in the Whipple procedure. J Am Coll Surg 2002;194:746–758.

42. Subar D, Pietrasz D, Fuks D, Gayet B. A novel technique for reducing pancreatic fistulas after pancreaticojejunostomy. J Surg Case Reports 2015;2015(7).

TABLES

Table 1 - Postoperative outcomes stratified by the occurrence of POAP (serum pancreatic amylase > 52 U/L on POD0 or 1)				
		POAP		
		No (n =129)	Yes (n =163)	p
Clavien-Dindo ≥IIIB		5 (3.8%)	23 (14.1%)	<0.01
POPF		6 (4.7%)	59 (36.2%)	<0.01
	B	4 (4.1%)	46 (35.4%)	<0.01
	C	2 (2.4%)	13 (10.3%)	
PPH		8 (6.2%)	21 (12.9%)	0.04
	A	1 (12.5%)	3 (14.3%)	<0.01
	B	6 (75%)	11 (52.4%)	
	C	1 (12.5%)	7 (33.3%)	
DGE		16 (12.4%)	22 (13.5%)	0.8
	A	3 (18.8%)	0	0.08
	B	7 (43.8%)	12 (54.5%)	
	C	6 (37.5%)	10 (45.5%)	
Abscess		17 (13.2%)	75 (46%)	<0.01
Chyle leak		1 (0.8%)	9 (5.5%)	0.03
Biliary fistula		4 (3.1%)	11 (6.7%)	0.2
Sepsis		8 (6.2%)	26 (16%)	0.01
Pneumonia		14 (10.9%)	38 (23.3%)	<0.01
Cardiac morbidity		4 (3.1%)	18 (11%)	0.02
Wound infection		13 (10.1%)	28 (17.2%)	0.08
Relaparotomy		5 (3.9%)	20 (12.3%)	0.01
ICU stay		7 (5.4%)	19 (11.7%)	0.04
Mortality at 90 days		2 (1.6%)	11 (6.7%)	0.03
Readmission		3 (2.3%)	11 (6.7%)	0.06
Serum pancreatic amylase (U/L, median, range)	POD0	11 (0 – 52)	114 (53 – 934)	< 0.01
	POD1	7 (0 – 46)	186 (53 – 973)	< 0.01
Drain amylase (U/L, median, range)	POD1	164 (20 – 7500)	3042 (101 – 7500)	< 0.01
	POD5	22 (13 – 7500)	163 (10 – 7500)	0.1
C-reactive protein (mg/L, median, range)	POD1	88 (8 – 253)	101 (3 – 316)	0.07
	POD2	152 (26 – 359)	220 (32 – 297)	< 0.01
	POD3	122 (20 – 443)	219 (40 – 507)	< 0.01

Abbreviations: Post-Operative Acute Pancreatitis (POAP); Post-Operative Pancreatic Fistula (POPF); Post-pancreatectomy Hemorrhage (PPH); Delayed gastric emptying (DGE), Intensive Care Unit (ICU)

Table 2 - Univariate and Multivariate predictors of Clavien-Dindo ≥IIIB morbidity						
	Univariate CLAVIEN-DINDO ≥IIIB			Multivariate		
	No (n =255)	Yes (n =37)	p	OR	CI95%	P
POPF	44 (17.3%)	21 (56.8%)	<0.01	1.64	1.01 – 3.70	0.04
PPH	7 (2.7%)	22 (59.5%)	<0.01	68.56	18.44 – 259.96	<0.01
DGE	31 (12.2%)	7 (18.9%)	0.2			
Abscess	65 (25.5%)	27 (73%)	<0.01	2.53	0.65 – 9.82	0.1
Chyle leak	10 (3.9%)	0	1			
Biliary fistula	10 (3.9%)	5 (13.5%)	0.02	0.92	0.08 – 9.98	0.9
Sepsis	18 (7.1%)	16 (43.2%)	<0.01	3.99	1.10 – 14.47	0.03
Pneumonia	35 (13.7%)	17 (45.9%)	<0.01	4.34	1.37 – 13.76	0.01
Cardiac morbidity	9 (3.5%)	13 (35.1%)	<0.01	5.88	1.27 – 27.12	0.01
Wound infection	32 (12.5%)	9 (24.3%)	0.07			
POAP	133 (52.2%)	30 (81.1%)	<0.01	2.45	1.68 – 8.84	0.05

Abbreviations: Post-Operative Pancreatic Fistula (POPF); Post Pancreatectomy Hemorrhage (PPH); Delayed gastric emptying (DGE), Post-Operative Acute Pancreatitis (POAP)

Table 3 – Univariate and multivariate analysis of predictors of POAP after PD

		Univariate Analysis POAP			Multivariate Analysis		
		No (n =129)	**Yes (n =163)**	**P**	**OR**	**CI95%**	**p**
Sex	Male	76 (58.9%)	90 (55.2%)	0.5			
	Female	53 (41.1%)	73 (44.8%)				
Age (median, range)		65 (36 – 83)	63 (24 – 87)	0.9			
BMI (median, range, kg/m^2)		23.8 (16 – 37)	24.2 (16 – 39)	0.2			
Smoker		36 (27.9%)	40 (24.5%)	0.7			
Alcohol abuse		13 (10.1%)	9 (5.5%)	0.3			
Chronic pancreatitis		7 (5.4%)	5 (3.1%)	0.3			
Exocrine insufficiency		29 (29.6%)	8 (7.2%)	<0.01	0.39	0.13 – 0.87	0.02
Diabetic		33 (25.6%)	18 (11%)	<0.01	0.49	0.18 – 1.33	0.1
Neoadjuvant therapy		55 (42.6%)	20 (12.3%)	<0.01	0.29	0.11 – 0.87	0.01
ASA	1	5 (3.9%)	9 (5.5%)	0.3			
	2	96 (74.4%)	115 (70.6%)				
	3	28 (21.7%)	39 (23.9%)				
Vascular resection		28 (21.7%)	16 (9.8%)	<0.01	1.21	0.44 – 3.2	0.7
Transection margin enlargement		20 (15.5%)	5 (3.1%)	<0.01	0.25	0.05 – 0.98	0.05
MPD ≤3mm		33 (25.6%)	106 (65%)	<0.01	2.86	1.60 – 5.10	<0.01
Texture	Hard	101 (78.3%)	42 (25.8%)	<0.01	1		
	Soft	28 (21.7%)	121 (74.2%)		4.38	1.91 – 10.05	<0.01
EBL (mL, median, range)		400 (50 – 1500)	400 (50 -1500)	0.2			
OR time (min, median, range)		401 (122 – 660)	397 (163 – 632)	0.9			
Intraoperative near-zero fluid balance		31 (24%)	58 (35.5%)	0.04	1.98	0.98 – 3.35	0.3
FRS risk zones	Negligible	25 (19.4%)	5 (3.1%)	<0.01	/		
	Low	62 (48.1%)	29 (17.8%)				
	Intermediate	40 (31%)	107 (65.6%)				
	High	2 (1.6%)	22 (13.5%)				
Pathology	PDAC	105 (80.9%)	81 (49.1%)	<0.01	1		
	NET	4 (3.5%)	16 (10.1%)		1.38	0.25 – 7.61	0.7
	Cystic	9 (7%)	17 (10.7%)		1.97	0.58 – 6.7	0.2
	Other	11 (8.7%)	49 (30.2%)		1.36	0.52 – 3.52	0.5

Abbreviations: Post-Operative Acute Pancreatitis (POAP); Body Mass Index (BMI); American Society of Anesthesiologists (ASA); Main pancreatic duct (MPD); Estimated Blood Loss (EBL); operating room (OR); Fistula Risk Score (FRS); Pancreatic ductal adenocarcinoma (PDAC); Neuroendocrine Tumor (NET).

Table 4 – Univariate and multivariate analysis of predictors of POPF after PD

		Univariate Analysis POPF			Multivariate Analysis		
		No (n =227)	**Yes (n =65)**	**p**	**OR**	**CI95%**	**p**
BMI >25 kg/m^2		78 (34.4%)	38 (58.5%)	<0.01	2.33	1.11 – 4.88	0.02
Exocrine insufficiency		32 (20.1%)	5 (10%)	0.07			
Diabetic		47 (20.7%)	4 (6.2%)	<0.01	0.70	0.18 – 2.75	0.6
Neoadjuvant therapy		70 (30.8%)	5 (7.7%)	<0.01	0.76	0.20 – 2.93	0.7
ASA	1	11 (4.8%)	3 (4.6%)	0.8			
	2	162 (71.4%)	49 (75.4%)				
	3	54 (23.8%)	13 (20%)				
Vascular resection		39 (17.2%)	5 (7.7%)	0.03	1.28	0.33 – 4.96	0.7
Transection margin enlargement		24 (10.6%)	1 (1.5%)	0.01	0.41	0.03 – 4.97	0.4
MPD ≤3mm		64 (39.3%)	52 (80%)	<0.01	2.30	1.09 – 5.35	0.05
Texture	Hard	138 (60.8%)	5 (7.7%)	<0.01	1	ref	
	Soft	89 (39.2%)	60 (92.3%)		6.92	2.24 – 21.33	<0.01
EBL (mL, median, range)		400 (50 – 1500)	400 (100 – 1500)	0.2			
OR time (min, median, range)		405 (105 – 660)	405 (170 – 632)	0.9			
Intraoperative near-zero fluid balance		66 (29.5%)	23 (35.4%)	0.2			
Pathology*	PDAC, chronic pancreatitis	154 (67.8%)	27 (41.5%)	<0.01	1	ref	
	NET, Cystic, other	73 (32.2%)	38 (58.5%)		1.32	0.61 – 2.89	0.4

POAP	104 (45.8%)	59 (90.8%)	<0.01	3.84	1.23 – 11.93	0.02

Abbreviations: Pancreaticoduodenectomy (PD); Post-Operative Pancreatic Fistula (POPF); Post-Operative Acute Pancreatitis (POAP); Body Mass Index (BMI); American Society of Anesthesiologists (ASA); Main pancreatic duct (MPD); Estimated Blood Loss (EBL); operating room (OR); Pancreatic ductal adenocarcinoma (PDAC); Neuroendocrine Tumor (NET);
* the variable pathology has been divided in high (NET, cystic, other) and low risk for POPF diagnosis (PDAC, chronic pancreatitis) according to the FRS.

Table 5 - Postoperative outcomes stratified by POAP occurrence in patients developing POPF

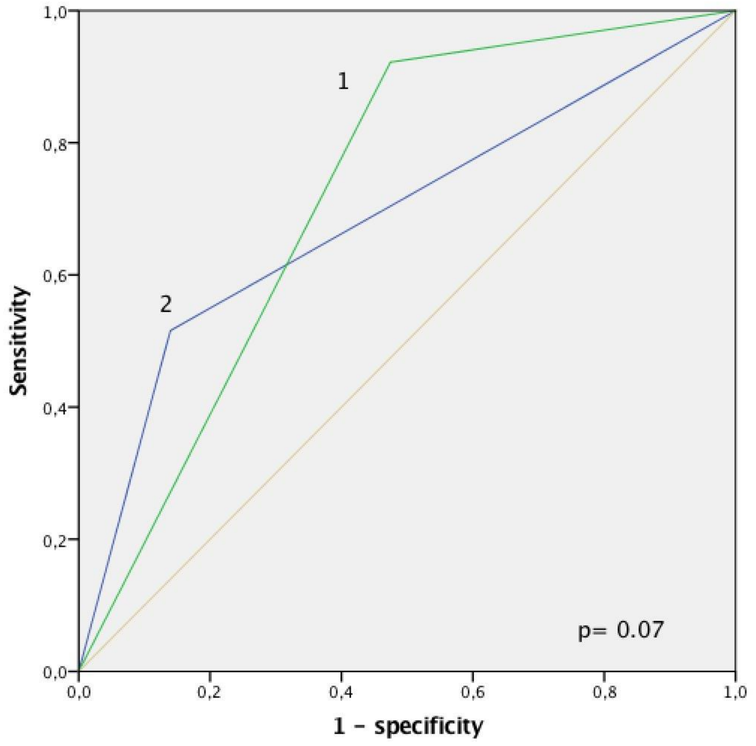
	Without POAP or POPF (n =123)	**POAP alone (n =104)**	**POPF+POAP (n =59)**	**P**
Clavien-Dindo ≥IIIB	5 (4.1%)	11 (10.6%)	16 (36.4%)	0.07* <0.01#
PPH	7 (5.7%)	6 (5.8%)	15 (25.4%)	1* <0.01#
A	1 (14.2%)	1 (16.7%)	2 (13.3%)	1* <0.01#
B	6 (85.7%)	5 (83.3%)	6 (40%)	
C	0	0	7 (46.7%)	
DGE	13 (10.6%)	10 (9.6%)	12 (20.3%)	0.8* 0.03#
A	3 (23.0%)	0	0	0.8* 0.01#
B	7 (53.8%)	9 (90%)	3 (25%)	
C	3 (23.0%)	1 (10%)	9 (75%)	
Abscess	11 (8.9%)	23 (22.1%)	52 (88.1%)	<0.01* <0.01#
Chyle leak	0	5 (4.8%)	4 (6.8%)	0.01* 0.6#
Biliary fistula	4 (3.3%)	3 (2.9%)	8 (13.6%)	1* 0.01#
Sepsis	5 (4.1%)	7 (6.7%)	19 (32.2%)	0.3* <0.01#
Pneumonia	11 (8.9%)	17 (16.3%)	21 (35.6%)	0.1* 0.02#
Cardiac morbidity	4 (3.3%)	8 (7.7%)	10 (16.9%)	0.1* 0.05#
Wound infection	12 (9.8%)	9 (8.7%)	19 (32.2%)	0.8* <0.01#
Relaparotomy	3 (2.4%)	6 (5.8%)	14 (23.7%)	0.3* <0.01#
ICU stay	4 (3.3%)	5 (4.8%)	14 (23.7%)	0.7* <0.01#
Mortality at 90 days	2 (1.6%)	5 (4.8%)	6 (10.2%)	0.2* 0.05#
Readmission	2 (1.6%)	5 (4.8%)	6 (10.2%)	0.2* 0.05#

**p value for POAP alone* vs. *without POAP or POPF. # p value for POAP alone* vs. *POPF+POAP*

Abbreviations: Post-Operative Acute Pancreatitis (POAP); Post-Operative Pancreatic Fistula (POPF); Post-pancreatectomy Hemorrhage (PPH); Delayed gastric emptying (DGE), Intensive Care Unit (ICU)

FIGURES' LEGENDS

Supplementary Figure 1 – ROC curves evaluating the diagnostic performance of serum pancreatic amylase value in predicting POPF according to different thresholds: > upper limit of normal (1) and > three times the upper limit of normal (2). The difference was not statistically significant.



III

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

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ABSTRACT

Background

Post-operative hyperamylasemia (POH) is a frequent finding after pancreaticoduodenectomy (PD), but its incidence and clinical implications have not been systematically analyzed yet. 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 including all the available literature published up to June 2019 were used. The following search terms were used: "Pancreaticoduodenectomy", "amylase", "pancreatitis". Surgical series reporting data about POH or POAP were selected and screened.

Results

From 379 studies, 39 papers were included considering 9220 patients. POH was rarely defined and serum amylase values were measured at different cut-off levels and reported on different postoperative days (PODs). Serum amylase levels and cut-off used were markedly higher in the first PODs and tended to decrease over times. The majority of the studies analyzing POH reported its correlation with post-operative pancreatic fistula (POPF) and other morbidity. The rate of POAP was markedly variable between studies, with its definition completely lacking in 40% of papers. Soft pancreatic parenchyma, small pancreatic duct, and pathology differing from cancer or chronic pancreatitis were all factors predisposing to POH development.

Conclusions

POH has been proposed as the biochemical expression of a pancreatic stump ischemia and local inflammation. Such phenomenon, in analogy to acute pancreatitis, could be renamed as POAP from the clinical standpoint.

Patients with POAP experienced an increase rate of all post-operative complications, particularly POPF. No universally accepted definitions for POH or POAP are currently used in the literature. Heterogeneity and variability on POH/POAP evidence call for further studies after a universally accepted definition and grading.

INTRODUCTION

Elevated pancreatic enzymes can frequently be detected at laboratory tests on the first days after pancreatic resections. An increase in serum pancreatic amylase level is an established biochemical marker for the diagnosis of acute pancreatitis in a non-surgical setting according to the Atlanta consensus[1], however the meaning of a similar increase after pancreatic surgery is still not defined.

The reported rate of post-operative hyperamylasemia (POH) after pancreatic resection is highly variable between centers, however these differences could be related to the variability of the definitions and cut-off used[2–11].

Moreover, also the meaning attributed to POH is still a matter of debate. In most reports[2,9–11], 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 emphasized that an increase in serum amylase level can be related to the release of pancreatic enzymes through an incontinent anastomosis with a subsequent systemic reabsorption[9]. However, when the timing of serum pancreatic enzyme elevation profiles was analyzed, its increment was found to be precocious and incompatible with the reabsorption of the pancreatic juice from the peritoneum[4]. Other studies theorized that it may result from an amylase backflow in blood vessels due to an increase pressure in the pancreatic tissue exerted by collections[12], but no evidences have been reported in this matter.

When not deemed as a sign of POPF, POH has been considered as a potential marker of surgical trauma[11]. POH may reflect a mechanical damage of the pancreatic parenchyma induced by the surgical procedure, however, despite all patients experienced the surgical trauma during pancreatectomy, not all of them subsequently showed an increase in serum amylases, than this mechanism can not completely explain the phenomenon.

In other surgical series[2,10,11,13,14], POH is reported to be a significant biochemical marker of complications after pancreaticoduodenectomy (PD). It was associated with an increased rate of POPF but also other surgical complications such as intra-abdominal abscess, delayed gastric emptying (DGE)[15] and readmission to a critical care environment[10,13,16]. Given these premises, POH appears to be not merely a biochemical post-surgical finding, but rather, an independent predictor of post-operative morbidity[2,16]. Despite these evidences, POH is still considered only an indirect sign of POPF because the mechanism that leads to the rise of serum amylases after a pancreatic resection and how it can cause further morbidity is still not known.

Recently, POH has been proposed as the biochemical expression of a post-operative acute pancreatitis (POAP) caused by pancreatic stump ischemia and local inflammation[16,17]. In analogy to pancreatitis, a local ischemic process occurring in the area of the pancreatic anastomosis could induce POH and the subsequent pancreatitis may exacerbate the systemic inflammatory response to major abdominal surgery, leading to a cascade of systemic and local effects, including, but not limited to POPF[11].

Currently the literature appears to be varied and controversial in defining POH therefore, the aim of this review is to reappraise the concept of POH in the current scientific literature including its definition, interpretation in the clinical context and correlation with post-operative acute pancreatitis (POAP).

METHODS

An electronic, systematic and complete research was carried out in compliance with the PRISMA[18] guidelines.

Search methods

The research was conducted using the MEDLINE (PubMed), Embase and the Cochrane Clinical Trials Registry including all the available literature published up to June 2019. Titles, abstracts and full-text articles were screened independently by two authors. All the references of the included studies were checked to identify additional missed papers. The following search terms were used: “Pancreaticoduodenectomy”, “amylase”, “pancreatitis”. The full search strategy for MEDLINE is included in Appendix 1.

Eligibility criteria

Inclusion criteria were as follows: surgical series reporting data about POH or acute pancreatitis after pancreaticoduodenectomy, articles in English with available full text for complete review. Studies that provided information on post-operative serum amylase cut-off or serum amylase range were both included irrespective of whether they were retrospective, prospective or randomized control trials. Case reports, case series, systematic reviews, editorials and clinical guidelines were excluded, as well as unpublished works. Surgical series of pediatric patients, the absence of an abstract in English language and studies not involving humans were also excluded.

Data collection and analysis

Two authors independently extracted data from the included studies. Any uncertainties about entering the review were resolved by consensus and, if necessary, by a third reviewer and examination of the full text. The following data were extracted from the included studies: first author, year of publication, study period, study design (prospective or retrospective cohort studies; randomized controlled trials), type of surgery, total number of participants, overall incidence of POPF[19], threshold used to define POH, post-operative day for serum amylase assessment, sensibility, specificity, area under the curve (AUC) of serum amylase cut-off to predict POPF, postoperative serum amylase range and average, proportion of participants with POH, POH risk factors, incidence of POPF and other post-operative complications in POH population, definition used for POAP.

Serum amylase values were reported on different postoperative days and measured at different cut-off levels or ranges resulting in inconsistent data not suitable for meta-analyses or meta- regressions.

For the same reason, since the aim of the study is to reappraise the concept of POH after pancreaticoduodenectomy and not to define the diagnostic accuracy of post-operative serum amylase, the results of the review are reported in the form of a narrative synthesis.

All identified studies were divided into three main groups: those reporting a cut-off of serum amylase value to characterize POH; those reporting a range of serum amylase; and a third group of studies in which POH was used as a diagnostic criterion for POAP. The analysis is eventually extended to all the studies reporting POAP as a post-operative complication. The quality of included studies was assessed by using the Quality Assessment of Diagnostic Accuracy Studies[20] (QUADAS -2) criteria which comprises 4 domains. According to the QUADAS-2 tool, most of the revised papers showed an unclear or high risk of bias and concerns on applicability. Although we preferred to review all relevant evidence and then investigate possible reasons for heterogeneity.

RESULTS

Figure 1 shows the PRISMA compliant flow-chart of the process of papers selection.

A total of 379 studies were identified after removing duplicates. 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. This led to the exclusion of additionally 18 studies. Eventually, 39 papers were included in this systematic review, with a total of 9220 patients. In accordance with the method of reporting data about POH or POAP, these studies were divided into three different groups.

Studies reporting the amylase cut-off

Eighteen studies[2–9,11–13,16,21–26] reported a post-operative serum amylase cut-off value to define POH (Table 1). Ten studies were retrospectives[2,5,6,9,11,13,16,22,23,26], six were prospectives[3,4,8,12,21,25], and two were randomized clinical trials (RCT)[7,24]. The reported serum amylase cut-off values varied from 38.5 U/l[6] to more than 400 U/l[13]. Most of the studies[2,4,5,7–9,12,13,16,21,23–26] assessed serum amylase value on the first post-operative day. Six studies measured it on POD 0[2,10,11,16,24,26], three on POD 2[8,13,24] and two on POD 3[6,24]. Three studies measured the value of amylase on POD 4[3,22,25], however no one reported values determined on the days following POD 4.

Several studies[2–4,6,8,9,11] used a receiving operating characteristic (ROC) curve to assess the association between POH and POPF. The area under the curve (AUC) for serum amylase differed between the studies. Its value was lower when calculated from the third POD onwards, ranging between 0.59[22] to 0.68[6]; compared to the AUC calculated on the first PODs[2,4,5,8,9,11,16] when the values were in the range of 0.75 to 0.86. Similarly, the amylase cut off was higher on the first post-operatives days and tended to decrease over times. Therefore the amylase cut-off ranges from 127 U/L[11] to 177 U/L[8] on POD 0-1 and decreases to 38.5[6]- 44.2 U/L[3] on POD 3-4. Based on the chosen cut-off value the POH incidence varied from 8.4%[7] to 64%[4], with a median value of 30%. Six studies[3,4,7,9,13,16] analyzed different cut-off values of POH to identify the best in predicting POPF. POPF was observed with an incidence ranging from 14%[13] to 44%[10] in those patients presenting with POH. In multivariate models POH was significantly associated to an increased rate of POPF with an odds ratio (OR) or relative risk (RR) ranging between 1[3] to 16.9[8]. Only one study failed to identify a serum amylase cut-off able to predict POPF[7].

Eight studies[2,4,10,11,13,16,26] also reported the association between POH and surgical morbidity other than POPF, mainly DGE and abdominal abscess (see Table 1). Only the study by Kawai et al.[25] did not find a relationship between POH and post-operative infections. Four studies[2,11,16,26] evaluated POH risk factors and reported elevated serum amylase values and an increased incidence of POH in high risk pancreatic remnant. Two studies[4,26] found the presence of pre-operative cardiac comorbidity as a risk factor for POH. One study[16] also identified exocrine insufficiency, neoadjuvant therapy, and an additional resection of the pancreatic stump margin as POH protective factors. Three studies revealed that a low serum amylase values have a high negative predictive value for POPF even in patients with a high-risk pancreatic stump, namely those with a soft pancreatic parenchyma and a small main pancreatic duct [2,4,16].

Studies reporting a range of serum amylase

Twenty-one studies[3,5–9,11,12,16,21,22,27–36] reported a post-operative serum amylase range (Table 2). Fourteen studies were retrospectives[5,6,9,11,16,22,23,27,28,31–34,36], five were prospectives[3,8,21,30,35], and two were RCTs[7,29].

Four studies[5,27,31,32] reported the overall median and range of serum amylase after pancreaticoduodenectomy irrespective of the developed complications. Fifthteen[3,6–9,11,12,21,27–29,32–34,36] studies compared post-operative serum amylase values in patients with and without POPF. Six studies[9,21,23,28,29,35] however, since were performed before the revision of POPF definition, have included in the POPF group also those with grade A POPF. The remainder considered only B-C POPF grades between POPF group[3,6–8,11,27,32,33,36]. One study compared post-operative serum amylase range between patients with a clinically relevant POPF and those with a biochemical leak, showing significantly higher values in the first group[31].

POPF incidence ranged between 7.6%[28,30] and 34.7%[32], with a median incidence of 18.7%. Most of these studies reported the median serum amylase value with its range, except three[7,9,9], in which only the median value was mentioned. Six studies reported serum amylase average[23,28,29,34,35].

Mean and median of post-operative serum amylase values vary dramatically between studies, and ranges were all wide. The serological assessment was performed on different PODs. Serum amylase level was markedly higher in the first PODs, in both patients with and without POPF[3,6,8,9,11,21,23,27–29,31,33] when compared to values resulted from the ensuing PODs[6,8,22,32]. POPF groups showed an increased median amylase value compared to patients without POPF. Most of the studies reported that the serum amylase level differed significantly between the two groups[3,8,9,11,12,21,27,29,31,33,36]. This trend has not been confirmed by three studies in which the median serum amylase values were not significantly different between POPF and non-POPF patients. Only one study found a separate statistical significance when considering different PODs: Kinaci et al.[6] reported that serum amylase on POD 3 showed a significant correlation with POPF, although serum amylase on POD 1 did not effectively predict POPF. Three studies examined the influence of pancreatic parenchyma on the level of serum amylase. Palani Velu et al.[11] reported that serum amylase on POD 0 was elevated in 21.4% of patients with a hard pancreatic remnant compared with 64.8% of patients with a soft pancreatic remnant. Non-PDAC pathology were also found to be independently associated with raised POD 0 serum amylase. Hanaki et al.[31] also reported that serum amylase levels were significantly higher in the group with a soft pancreatic texture. Nahm et al.[36] showed that a high acinar score of the pancreatic stump also correlated significantly with an elevation of day 1 serum amylase ($p < 0.001$). Mc Millan et al.[7] showed that serum amylase measured on POD 1 positively correlated with the Fistula Risk Score (FRS); however comparisons of median values across FRS risk zones were non-significant. Two studies investigated the behavior of serum amylase in patients with POAP[16,30]. Both reported a significantly increase serum amylase activity in patients with POAP when compared to those without the complication. Räty et al.[30] also identified a similar serum amylase increase in patients suffering from DGE[15].

Studies reporting POAP between post-operative complications

Twenty-two studies[3,4,11,16,21,24,26–30,36–46] reported the post-operative pancreatitis as a complication after pancreatic surgery (Table 3). Eleven studies were retrospectives[11,16,26–28,36,38,39,42,43,45], seven studies were prospectives[3,4,21,30,37,40,44,46] and three were RCTs[24,29,41]. The POAP rate was highly variable ranging from 1,5%[28,45] to more than 57%[36]. These differences were related to the variability of the definitions used. In many reports the definition was missing[3,28,40,41,45,46], in others it was reported as a generic elevation of serum pancreatic enzymes[38,43]. The Atlanta consensus definition for acute pancreatitis[1] was used to define POAP in five studies[4,11,21,29,44], while two studies only used urine trypsinogen to define POAP[24,39]. Only three studies reported a specific cut-off value to define the POAP occurrence[16,26,36]; however even if the cut off was always defined as a serum amylase greater than the upper limit of normal, the cut off varied between the studies as the upper limit differed between centers. Six studies[21,27,29,30,42,44] used the CT scan to diagnose or to confirm the occurrence of POAP. There was no agreement for the post-operative day on which POAP has to be defined. Most studies did not reported it[11,21,27,28,37,40,41,43,45,46] while, when mentioned, POD 2 was the most frequently indicated[21,29,30,38,39,44].

POAP was the specific aim of only seven studies reported in this review[4,16,24,26,27,30,36].

The assessment of POAP had some similarities and differences between these studies. Kühlbrey et al.[4] defined POAP, in analogy to pancreatitis, a local inflammatory process occurring in the area of the pancreatic anastomosis after pancreatic resection that could induce increased systemic amylase concentration and could subsequently impaired the healing of the pancreatic anastomosis. Räty et al[30]. assessed that POAP started postoperatively, or during the operation right after the transection of the pancreas, with the release of multiple local and systemic mediators of inflammation. In this study patients with postoperative pancreatitis showed an increase incidence of coronary artery disease in the medical history. The authors suggested ischemic factors or hyperlipidemia or decreased glucose tolerance as the mechanism behind POAP. Our previous report[16] indicated POAP a possible clinical and biochemical manifestation of an intraoperative ischemic damage of the pancreatic stump that may eventually lead to the anastomotic leakage, explained by a 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.[24] reported that POAP was a consequence of the direct trauma to the pancreatic parenchyma during pancreaticoduodenectomy. Similarly Addeo et al.[38] related the occurrence of POAP to fractures induced by the sutures to the pancreas. Laaninen et al.[39] combined the two theories and reported that a pancreatic tissue ischemia or damage to the pancreas itself, such as resection of the pancreas and the suturing of pancreaticojejunal anastomosis, can initiate a widespread inflammation with an uncontrollable activation of trypsin and other digestive enzymes. Rudis and Ryska[27] analyzed only patients with grade C POPF. In all these patients the macroscopic findings during surgical revision were indicative of POAP with development of POPF. Autopsy, however, revealed POAP in 57% of cases. In the misdiagnosed cases, the authors attributed the superficial pancreatic necrosis to the digestion of tissue by POPF. They did not also consider the necrosis of the pancreatic stump as POAP and attributed it to a surgical technical error. Differently Palani Velu et al.[11] identified 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 the burden of POAP instead of its physiopathology. Nahm et al.[36] demonstrated that the biochemical evidence of POAP precedes the development of POPF. Nevertheless, the causation of POPF by POAP has not been established. Specifically, it was not clear 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) is associated with the development of both. Birgin et al.[26] determined C-Reactive Protein cut-off values that discriminate the clinically relevant POAP cases. They changed however the POPF definition, restricting it to patients with high drain amylase values but normal serum amylase ranges.

DISCUSSION

The present study provides a systematic view about POH and POAP after pancreaticoduodenectomy. Several studies report data about this topic, however, these evidences completely lack in standardization, metrics and definitions.

POH is rarely defined in almost all reports and the threshold used is rarely specified in methods. Among the studies that reported a serum amylase cutoff to define POH, almost none surprisingly provided the same serum amylase value[4,7,12]. Similarly, there is no agreement about the POD on which serum amylase should be assessed in order to establish the occurrence of POH[3,6,8,10]. Despite this extreme variability, POH does not seem to be such a rare event and its incidence can reaches up to 64% of cases[4]. Moreover, some characteristics of POH seems to emerge. The absolute value of serum amylase was higher on the first PODs and decreases with the time after surgery[6,8,11,22]. This indicates that POH is an early event after PD and the amylase concentrations may return to normal despite the development of further complications. It is maybe for this behavior that POH was steadily considered a so frequent and fleeting post-operative condition that its clinical interpretation was not deeply investigated.

The majority of the studies analyzing POH reported its correlation with POPF[2,4,5,7–13,16,27]. Even if the association between POH and POPF has been widely reported[2,4,7,9,10,13,16,36], several papers suggest that not all patients developing POH subsequently develop a POPF[2,4,10,16]. Reported serum amylase ranges had frequently overlapped between patients who developed POPF and those who did not experience the complication. Serum amylase values were therefore not always able to completely discriminate between the two groups[6,11,27,29,32]. Until now, most of available reports focused on the low diagnostic accuracy of serum amylase in predicting POPF, considering POH only a secondary diagnostic test or an indirect sign for POPF. Maybe the emphasis should be moved to the pathophysiology of this condition and POH might no longer be considered only the serological evidence of POPF. POH has been confirmed to be also strongly associated to an increased rate of postoperative complications other than POPF, especially DGE and abdominal abscesses[2,10,11,13,16]. Given these evidences POH seems to be the biochemical marker of an early pathological event able to trigger several post-operative morbidities, including POPF, but not confined to it.

Nevertheless, the pathological mechanism underling POH remains unclear due to the limited possibility of investigating specific changes in pancreatic parenchyma occurring in the early post-operative period. In a non-surgical setting, acute pancreatitis[1] is characterized by an increase in serum amylase concentration and the ability to induce further morbidity. Likewise, a similar pathological mechanism, characterized by serum hyperamylasemia and subsequent complications, could affect the post-surgical course.

Also POAP has been reported by many studies, however both nomenclature and definitions are confusing and frequently missing[37,40,45,46].

Although the different interpretations between reports, some aspects belonging to POAP and its relationship with POH could be highlighted. POAP is an early event after surgery[4,16,36], it induces an increased systemic serum amylase concentration[16,21,44] and it is able to maintain systemic and local alterations that may lead to the onset of other post-operative complications[4,11,16,26,30,39]. Pathologic changes that occur in acute pancreatitis could be extended to POAP, representing a continuum between inflammation and necrosis[1,39].

However, considering only the serum amylase value, this does not allow for staging of the actual clinical burden of POAP, as different degrees of severity are probably included. In nonsurgical settings, the occurrence of acute pancreatitis can completely resolve without leaving sequelae, or it can lead to dramatic scenarios. Mild pictures of POAP tend to self-limit in the first post-operative days. Others are able to determine further abdominal complications up to rare cases of extensive necrosis and anastomotic disruption as reported in series considering surgical revisions for grade C POPF[27,47].

POH as well as POAP have often been interpreted as an expression of surgical damage only[24,38]. Nevertheless, since it does not occur in all patients undergoing PD, this explanation seems to be reductive. Surgical trauma however, intended as a series of events that occur during surgery, ranging from manipulation, mobilization and alteration of blood supply, certainly play a fundamental role in POAP[16]. Within this background, POH should be considered as a biomarker for the detection of POAP and their risk factors shared[2,4,11,16].

A soft pancreatic parenchyma and a small pancreatic duct size as well as non-PDAC pathology predisposed patients to develop higher serum amylase levels postoperatively. Conversely, exocrine insufficiency, neoadjuvant therapy, and an additional resection of the pancreatic stump margin have been interestingly highlighted as factors linked to a reduce occurrence of POH and POAP[2,4,11,16,31].

Patients presenting with these risk factors may be more prone to develop a postoperative inflammation-ischemia cascade within the pancreatic parenchyma. This condition must be called POAP, a pancreas-specific complication able to produce additional morbidity such as POPF, DGE and abdominal abscesses[2,11,13,16].

POPF was largely investigated and treated when it had already occurred[19]. POAP has been highlighted as one of its possible cause and it is almost unexplored[16]. Shifting the focus, from treatment to POPF prevention, new therapeutic and diagnostic scenarios open. Since POH seems to be an early serological marker of POAP, its correct interpretation would allow a very precocious therapeutic intervention, aimed at the prevention or attenuation of other post-operative complications, especially POPF.

The local inflammatory/ischemic process characterizing POAP and occurring in the area of the pancreatic stump could subsequently impaired the healing of the pancreatic anastomosis, leading to POPF[4,16]. Moreover this cascade occurs more frequently in high-risk patients, having a soft and fatty pancreas and narrow pancreatic duct[36,39]. These patients still experience dramatics post-operative scenarios related to POPF occurrence[48]. The correct definition of POAP and its diagnostic assessment could lead to a better therapeutic strategy in order to reduce the incidence or the burden of POPF especially in these critical patients.

The present review has several limitations. Firstly, 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[2,9,11,23,38]. Exclusion of these studies would have produced however a consistent selection bias. Moreover, most of the studies did not report the reference interval or the definition used both for POH and POAP[3,28,40,41,45,46]. This significant heterogeneity between the studies made it impossible to perform a meta-analysis or a meta-regression. Anyway, one of the aims of the present review was to highlight this extreme variability and gap of evidence about POH/POAP.

New studies focusing on the relationship between POH and POAP and its pathophysiology are mandatory. In the light of these evidences, it should be crucial to reach a shared definition of POH/POAP. This review must be intended as the basis that is necessary for further studies and for a shared ad universally accepted definition of POH/POAP which should be referred to an International Study Group for Pancreatic Surgery position paper. Providing a definition for POH/POAP is beyond the scope of the present paper and it would likely be lost in the bulk of evidence available about this topic. Whatever the shared definition will be, it must include a biochemical diagnosis of POAP based on a serum amylase or lipase or urinary trypsinogen assessment at a specific time point; a morphological correlation through 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 the comparison between centers on surgical techniques, and on possible therapeutic strategies.

CONCLUSION

This review failed to find a shared and clear definition for both POH and POAP. POH is a frequent serological finding after PD, however, at present, no definition or agreed threshold is available. POH has been proposed as the biochemical expression of a pancreatic stump ischemia and local inflammation, that in analogy to acute pancreatitis, was renamed as POAP. Patients with POAP experienced an increase rate of all post-operative complications, among which POPF. A specific definition of POAP, universally accepted and recognized, is still missing. This new topic is worthy of investigation since it would open up to new therapeutic strategies and prevention of morbidity after PD.

REFERENCES

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111. doi:10.1136/gutjnl-2012-302779

2. Chen CB, McCall NS, Pucci MJ, et al. The Combination of Pancreas Texture and Postoperative Serum Amylase in Predicting Pancreatic Fistula Risk. *Am Surg*. 2018;84(6):889-896.

3. Jin S, Shi X-J, Wang S-Y, et al. Drainage fluid and serum amylase levels accurately predict development of postoperative pancreatic fistula. *World J Gastroenterol*. 2017;23(34):6357-6364. doi:10.3748/wjg.v23.i34.6357

4. Kühlbrey CM, Samiei N, Sick O, Makowiec F, Hopt UT, Wittel UA. Pancreatitis After Pancreatoduodenectomy Predicts Clinically Relevant Postoperative Pancreatic Fistula. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2017;21(2):330-338. doi:10.1007/s11605-016-3305-x

5. Partelli S, Pecorelli N, Muffatti F, et al. Early Postoperative Prediction of Clinically Relevant Pancreatic Fistula after Pancreaticoduodenectomy: usefulness of C-reactive Protein. *HPB*. 2017;19(7):580-586. doi:10.1016/j.hpb.2017.03.001

6. Kinaci E, Sevinc MM, Ozakay A, Bayrak S, Cakar E, Sari S. Intraoperative acidosis is a new predictor for postoperative pancreatic fistula after pancreaticoduodenectomy. *Hepatobiliary Pancreat Dis Int HBPD INT*. 2016;15(3):302-309.

7. McMillan MT, Malleo G, Bassi C, et al. Drain Management after Pancreatoduodenectomy: Reappraisal of a Prospective Randomized Trial Using Risk Stratification. *J Am Coll Surg*. 2015;221(4):798-809. doi:10.1016/j.jamcollsurg.2015.07.005

8. Ansorge C, Nordin JZ, Lundell L, et al. Diagnostic value of abdominal drainage in individual risk assessment of pancreatic fistula following pancreaticoduodenectomy. *Br J Surg*. 2014;101(2):100-108. doi:10.1002/bjs.9362

9. Cloyd JM, Kastenberg ZJ, Visser BC, Poultsides GA, Norton JA. Postoperative serum amylase predicts pancreatic fistula formation following pancreaticoduodenectomy. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2014;18(2):348-353. doi:10.1007/s11605-013-2293-3

10. Palani Velu LK, McKay CJ, Carter CR, McMillan DC, Jamieson NB, Dickson EJ. Serum amylase and C-reactive protein in risk stratification of pancreas-specific complications after pancreaticoduodenectomy. *Br J Surg*. 2016;103(5):553-563. doi:10.1002/bjs.10098

11. Palani Velu LK, Chandrabalan VV, Jabbar S, et al. Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. *HPB*. 2014;16(7):610-619. doi:10.1111/hpb.12184

12. Okabayashi T, Kobayashi M, Nishimori I, Sugimoto T, Onishi S, Hanazaki K. Risk factors, predictors and prevention of pancreatic fistula formation after pancreatoduodenectomy. *J Hepatobiliary Pancreat Surg*. 2007;14(6):557-563. doi:10.1007/s00534-007-1242-5

13. Winter JM, Cameron JL, Yeo CJ, et al. Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy. *J Am Coll Surg*. 2007;204(5):1029-1036; discussion 1037-1038. doi:10.1016/j.jamcollsurg.2007.01.026

14. Gebauer F, Kloth K, Tachezy M, et al. Options and limitations in applying the fistula classification by the International Study Group for Pancreatic Fistula. *Ann Surg*. 2012;256(1):130-138. doi:10.1097/SLA.0b013e31824f24e4

15. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. 2007;142(5):761-768. doi:10.1016/j.surg.2007.05.005

16. Bannone E, Andrianello S, Marchegiani G, et al. Postoperative Acute Pancreatitis Following Pancreaticoduodenectomy: A Determinant of Fistula Potentially Driven by the Intraoperative Fluid Management. *Ann Surg*. July 2018. doi:10.1097/SLA.0000000000002900

17. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. *HPB*. 2016;18(8):642-651. doi:10.1016/j.hpb.2016.05.006

18. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1. doi:10.1186/2046-4053-4-1

19. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. 2017;161(3):584-591. doi:10.1016/j.surg.2016.11.014

20. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536. doi:10.7326/0003-4819-155-8-201110180-00009

21. Jin S, Shi X-J, Sun X-D, et al. The gastric/pancreatic amylase ratio predicts postoperative pancreatic fistula with high sensitivity and specificity. *Medicine (Baltimore)*. 2015;94(3):e339. doi:10.1097/MD.0000000000000339

22. Kosaka H, Kuroda N, Suzumura K, Asano Y, Okada T, Fujimoto J. Multivariate logistic regression analysis for prediction of clinically relevant pancreatic fistula in the early phase after pancreaticoduodenectomy. *J Hepato-Biliary-Pancreat Sci*. 2014;21(2):128-133. doi:10.1002/jhbp.11

23. Okabayashi T, Maeda H, Nishimori I, Sugimoto T, Ikeno T, Hanazaki K. Pancreatic fistula formation after pancreaticooduodenectomy; for prevention of this deep surgical site infection after pancreatic surgery. *Hepatogastroenterology*. 2009;56(90):519-523.

24. Uemura K, Murakami Y, Hayashidani Y, et al. Randomized clinical trial to assess the efficacy of ulinastatin for postoperative pancreatitis following pancreaticoduodenectomy. *J Surg Oncol*. 2008;98(5):309-313. doi:10.1002/jso.21098

25. Kawai M, Tani M, Terasawa H, et al. Early removal of prophylactic drains reduces the risk of intra-abdominal infections in patients with pancreatic head resection: prospective study for 104 consecutive patients. *Ann Surg*. 2006;244(1):1-7. doi:10.1097/01.sla.0000218077.14035.a6

26. Birgin E, Reeg A, Téoule P, et al. Early postoperative pancreatitis following pancreaticoduodenectomy: what is clinically relevant postoperative pancreatitis? *HPB*. 2019;21(8):972-980. doi:10.1016/j.hpb.2018.11.006

27. Rudis J, Ryska M. Pancreatic leakage and acute postoperative pancreatitis after proximal pancreatoduodenectomy. *Rozhl V Chir Mesicnik Ceskoslovenske Chir Spolecnosti*. 2014;93(7):380-385.

28. El Nakeeb A, Salah T, Sultan A, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience). *World J Surg*. 2013;37(6):1405-1418. doi:10.1007/s00268-013-1998-5

29. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg*. 2010;252(2):207-214. doi:10.1097/SLA.0b013e3181e61e88

30. Räty S, Sand J, Lantto E, Nordback I. Postoperative acute pancreatitis as a major determinant of postoperative delayed gastric emptying after pancreaticoduodenectomy. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2006;10(8):1131-1139. doi:10.1016/j.gassur.2006.05.012

31. Hanaki T, Uejima C, Amisaki M, et al. The attenuation value of preoperative computed tomography as a novel predictor for pancreatic fistula after pancreaticoduodenectomy. *Surg Today*. 2018;48(6):598-608. doi:10.1007/s00595-018-1626-y

32. Furukawa K, Gocho T, Shirai Y, et al. The Decline of Amylase Level of Pancreatic Juice After Pancreaticoduodenectomy Predicts Postoperative Pancreatic Fistula. *Pancreas*. 2016;45(10):1474-1477. doi:10.1097/MPA.0000000000000691

33. Fujiwara Y, Shiba H, Shirai Y, et al. Perioperative serum albumin correlates with postoperative pancreatic fistula after pancreaticoduodenectomy. *Anticancer Res*. 2015;35(1):499-503.

34. Hiyoshi M, Chijiiwa K, Fujii Y, Imamura N, Nagano M, Ohuchida J. Usefulness of drain amylase, serum C-reactive protein levels and body temperature to predict postoperative pancreatic fistula after pancreaticoduodenectomy. *World J Surg*. 2013;37(10):2436-2442. doi:10.1007/s00268-013-2149-8

35. Ansorge C, Regner S, Segersvärd R, Strömmer L. Early intraperitoneal metabolic changes and protease activation as indicators of pancreatic fistula after pancreaticoduodenectomy. *Br J Surg*. 2012;99(1):104-111. doi:10.1002/bjs.7730

36. Nahm CB, Brown KM, Townend PJ, et al. Acinar cell density at the pancreatic resection margin is associated with post-pancreatectomy pancreatitis and the development of postoperative pancreatic fistula. *HPB*. 2018;20(5):432-440. doi:10.1016/j.hpb.2017.11.003

37. Malleo G, Salvia R, Butturini G, et al. Is routine imaging necessary after pancreatic resection? An appraisal of postoperative ultrasonography for the detection of pancreatic fistula. *Pancreas*. 2014;43(2):319-323. doi:10.1097/MPA.0000000000000029

38. Addeo P, Rosso E, Fuchshuber P, et al. Double purse-string telescoped pancreaticogastrostomy: an expedient, safe, and easy technique. *J Am Coll Surg*. 2013;216(3):e27-33. doi:10.1016/j.jamcollsurg.2012.11.010

39. Laaninen M, Bläuer M, Vasama K, et al. The risk for immediate postoperative complications after pancreaticoduodenectomy is increased by high frequency of acinar cells and decreased by prevalent fibrosis of the cut edge of pancreas. *Pancreas*. 2012;41(6):957-961. doi:10.1097/MPA.0b013e3182480b81

40. Okano K, Kakinoki K, Suto H, et al. Persisting ratio of total amylase output in drain fluid can predict postoperative clinical pancreatic fistula. *J Hepato-Biliary-Pancreat Sci*. 2011;18(6):815-820. doi:10.1007/s00534-011-0393-6

41. Pessaux P, Sauvanet A, Mariette C, et al. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. *Ann Surg*. 2011;253(5):879-885. doi:10.1097/SLA.0b013e31821219af

42. Bruno O, Brancatelli G, Sauvanet A, Vullierme MP, Barrau V, Vilgrain V. Utility of CT in the diagnosis of pancreatic fistula after pancreaticoduodenectomy in patients with soft pancreas. *AJR Am J Roentgenol*. 2009;193(3):W175-180. doi:10.2214/AJR.08.1800

43. Barreto G, D'Souza MA, Shukla PJ, Shrikhande SV. The gray zone between postpancreaticoduodenectomy collections and pancreatic fistula. *Pancreas*. 2008;37(4):422-425. doi:10.1097/MPA.0b013e318175ddd0

44. Molinari E, Bassi C, Salvia R, et al. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. *Ann Surg*. 2007;246(2):281-287. doi:10.1097/SLA.0b013e3180caa42f

45. Lermite E, Pessaux P, Brehant O, et al. Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. *J Am Coll Surg*. 2007;204(4):588-596. doi:10.1016/j.jamcollsurg.2007.01.018

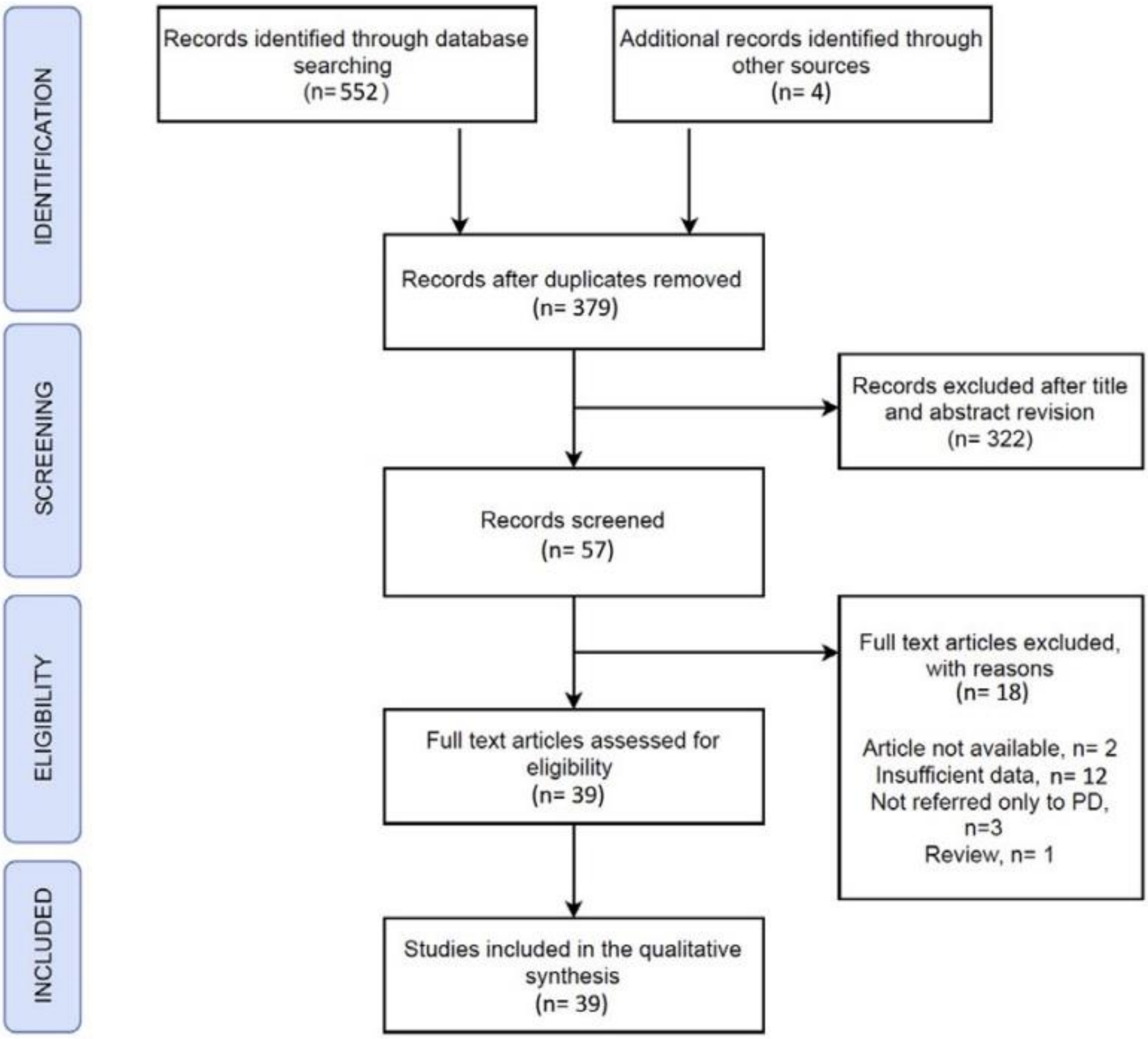
46. Matsusue S, Takeda H, Nakamura Y, Nishimura S, Koizumi S. A prospective analysis of the factors influencing pancreaticojejunostomy performed using a single method, in 100 consecutive pancreaticoduodenectomies. *Surg Today*. 1998;28(7):719-726. doi:10.1007/BF02484618

47. Globke B, Timmermann L, Klein F, et al. Postoperative acute necrotizing pancreatitis of the pancreatic remnant (POANP): a new definition of severe pancreatitis following pancreaticoduodenectomy. *HPB*. August 2019. doi:10.1016/j.hpb.2019.07.016

48. McMillan MT, Vollmer CM, Asbun HJ, et al. The Characterization and Prediction of ISGPF Grade C Fistulas Following Pancreatoduodenectomy. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2016;20(2):262-276. doi:10.1007/s11605-015-2884-2

FIGURES

Figure 1 - The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.



IV

Characterization of postoperative acute pancreatitis (POAP) after distal pancreatectomies

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ABSTRACT

Background

Postoperative acute pancreatitis (POAP) has recently been reported as a specific complication after pancreaticoduodenectomies (PDs). The aim of this study was to characterize POAP after distal pancreatectomies (DPs).

Methods

Outcomes of 368 patients who underwent DPs from January 2016 to December 2019 were retrospectively analyzed. POAP was defined as an elevation of serum amylase above the normal upper limit on postoperative days 0–2. We assessed the incidence of POAP after DPs and examined possible predictors and relationships of POAP with postoperative pancreatic fistula (POPF).

Results

POAP and POPF rates were 67.9% and 28.8%, respectively. Patients who developed POAP experienced a significantly increased rate of severe morbidity (18.4 vs. 9.3%, p=0.030). Neoadjuvant therapy (OR 0.28; 0.09–0.85, p= 0.025), age ≥ 65 years (OR 0.34; 0.13–0.85, p= 0.020), duct size (OR 0.02; 0.002–0.47, p= 0.013), pancreatic thickness (OR 3.4; 1.29–8.9, p= 0.013), resection at the body-tail level (OR 4.3; 1.15–23.19, p= 0.041), and neuroendocrine histology (OR 1.14; 1.06–3.90, p= 0.013) were independent predictors of POAP. Furthermore, POAP was an independent predictor of POPF (OR 5.8; 2.27–15.20, p < 0.001). POPF occurred in 37% of patients who developed POAP. Patients developing POAP alone showed a significantly increased rate of biochemical leakage and bacterial contamination in drainage cultures.

Conclusion

POAP is a frequent event after DP and, despite its close association with POPF, evidently represents a separate phenomenon . A universally accepted definition of POAP that applies to all types of pancreatic resections is needed, as it may identify patients at higher risk for additional morbidity immediately after surgery.

INTRODUCTION

Many surgeons are familiar with a potential postoperative inflammatory process of the remaining pancreatic parenchyma associated with increased postoperative morbidity after major pancreatic resections, but little evidence supports its existence and underlying mechanisms. Nevertheless, the concept of postoperative acute pancreatitis (POAP) has recently gained popularity in the literature regarding pancreatic surgery[1–6].

POAP has been described as a local inflammatory/ischemic process of the pancreatic parenchyma, characterized by an increased systemic serum amylase concentration[1,7,8], that might impair the healing process of pancreatic anastomosis[1,5,6], exacerbate systemic inflammatory responses to major abdominal surgery[9,10], and trigger several postoperative complications including postoperative pancreatic fistula (POPF)[1,5,7,11].

This topic might have significant implications in surgical outcomes, because POAP may represent the earliest adverse event after surgery and its proper management may help to circumvent further morbidity. However, the absence of a widely accepted definition of POAP limits the acquisition of a sufficient level of evidence necessary to fully understand and describe POAP. The most recent and structured definition available is that proposed by Connor et al.[2]. A handful of articles have explored the reliability of this definition after pancreaticoduodenectomies (PDs)[1,11–13], highlighting a close relationship between POAP and severe morbidity, including POPF. At present, no evidence on the potential implications of POAP after distal pancreatectomies (DPs) is available[6].

Such as after pancreatic head resections, POPF represents the greatest contributor to major morbidity and mortality[14,15] associated with DPs, and its prevention remains a challenge[16]. Although POPF occurs more frequently after DP, it incurs a lower complication burden[17]. Age, body mass index (BMI), estimated blood loss, operative time, and hypoalbuminemia have been identified as independent predictors of POPF after DP[18–20], but the variability in the reported results has not yet allowed for the creation of a reliable POPF prediction model as the fistula risk score for PDs[21]. Despite the bulk of available data, POPF after DP remains poorly understood, suggesting the presence of unmeasured factors. Given the close relationship between POAP and postoperative morbidity highlighted after pancreatic head resections, similar results may be achieved by exploring this process in the context of DPs. Hence, the purpose of this study was to define the incidence and characterization of POAP after DP and to identify predictive factors and potential relationships regarding the development of POPF.

METHODS

This study was approved by the institutional review board (Ethics Committee of the Provinces of Verona and Rovigo, approval number 1101CESC) and was consistent with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) recommendations.

Inclusion and exclusion criteria

Patients who consecutively underwent DPs from January 2016 to December 2019—in the Department of General and Pancreatic Surgery at The Pancreas Institute of the University of Verona Hospital Trust—were considered eligible for participation in this study. Data were extracted from a prospectively collected database and were retrospectively analyzed. Patients with missing data on postoperative serum amylase values were excluded (n = 36).

Data collection

Clinical and pathological variables included demographic data, operative details, postoperative data, and pathological features. Preoperative characteristics included age, sex, BMI (kg/m^2), neoadjuvant therapy, the need for preoperative pancreatic enzyme replacement therapy (PERT), and preoperative serum pancreas-specific amylase values and serum albumin values. According to our institutional protocols, serum pancreas-specific amylase values were routinely assessed on POD0 two hours after the end of the surgical procedure, at

7 a.m. on postoperative day (POD) 1 and 2 if normal and, if altered, on all subsequent PODs until normalization.

Intraoperative data that were collected consisted of the type of approach (minimally invasive, either laparoscopic and robot-assisted, or open DP), spleen preservation (either according to the Kimura[22] or Warshaw[23] technique), vascular resection, estimated blood loss (EBL), and pancreatic stump management. The surgical techniques that we used for open and minimally invasive DPs have already been described elsewhere by our group[24,25]. DPs were classified according to the level of the transection line as follows: “formal” in the case of a transection at the pancreatic neck; “extended” in the case of a transection at the level of the gastroduodenal artery (GDA); and “parenchyma-sparing” in the case of a transection at the left of the portal-vein axis at the level of the pancreatic body-tail.

Pancreatic texture was not recorded because of the absence of standardization and reporting for minimally invasive cases. The main pancreatic duct diameter was measured via preoperative computer tomography (CT) scans at the level of the planned transection, and the pancreatic thickness was intraoperatively measured with a caliber at the pancreatic transection line. The pancreatic stump area was calculated by approximating the shape of an ellipse, the major and minor axes of which were retrieved from pathological reports.

Operative procedures

Pancreatic stump management included the use of a scalpel, mechanical stapler, or ultrasonic devices. When the pancreas was cut with a scalpel, it was followed by selective suturing of the main pancreatic duct followed by sewing over the pancreatic stump with interrupted sutures. In the case of a staple closure, triple-row stapling was reinforced with a polyglycolic-acid felt (NEOVEIL Endo GIA Reinforced Reload with Tri-Staple Technology 60 mm, COVIDIEN, North Haven, CT, USA). A purple (3 mm) or black (4 mm) cartridge was used at the surgeon’s discretion. Both a stepwise parenchymal-flattening technique and a prolonged peri-firing compression were subsequently executed[26]. When the pancreas was transected using an ultrasonic dissector (HARMONIC, Johnson & Johnson Medical, Ethicon, Tokyo, Japan), the dissector was used at the lowest vibration level for the full duration of the pancreatic dissection.

Outcome metrics

Postoperative morbidity was defined according to the international study group for pancreatic surgery (ISGPS) definitions of POPF[27], delayed gastric emptying (DGE)[28], postpancreatectomy hemorrhage (PPH)[29], and chyle leakage[30]. The updated definition of POPF was retrospectively applied to all cases operated in 2016. An 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[31]. Cardiac morbidity was defined as acute myocardial infarction or severe arrhythmia. Wound infection was defined according to the Centers for Disease Control and Prevention criteria[32]. The severity of complications was determined using the Clavien–Dindo classification system[33]. Morbidity was defined as any complication occurring within 30 days from the indexed surgery date. Readmission was defined as a new hospital admission after discharge within 30 days from the indexed surgery date. Mortality was defined as postoperative death occurring within 30 days of the indexed surgery date.

The primary endpoint of the study was POAP after DPs. Owing to the absence of a widely accepted definition, POAP was defined according to the definition proposed by Connor[2] as an elevation in serum pancreatic amylase activity above the upper limit of normal (ULN) on POD 0–2. Predicted severity was based on C-reactive protein (CRP), and clinically relevant POAP (CR-POAP) was defined as a CRP $\geq$ 180 mg/L on POD2. At our institution, the ULN for serum pancreatic amylase activity was 52 U/L at the time of the completion of our present study. No additional radiological or laboratory studies were required for the diagnosis of POAP. No specific protocols for the treatment of POAP were followed during the study period because there have been no previous studies that have supported evidence-based specific treatments. Prophylactic steroids or somatostatin analogs were not used.

The primary objective of this study was to assess the incidence of POAP after DPs. Secondary objectives were to describe the postoperative course of patients developing POAP, to evaluate potential predictors of POAP, and to compare them to potential predictors of POPF. Ultimately, the relationship between POAP and POPF was explored by analyzing the postoperative course of patients according to the combination of these two complications.

Statistical analysis

Continuous variables are reported as the mean and standard deviation or median and interquartile range when appropriate. Differences between groups were assessed by Chi-square tests, Fisher's exact tests, or Mann-Whitney U tests. Correlations between continuous variables were assessed using Pearson's or Spearman's correlation tests when appropriate. A stepwise backward logistic regression analysis was conducted to identify covariates associated with the incidence of POAP and POPF. The variables were assessed for multicollinearity and were removed from the model when necessary. A receiver operating characteristic (ROC) curve was used to assess the association between different serum pancreatic amylase thresholds and severe postoperative surgical morbidity scored as Clavien–Dindo ≥ III.

All of the tests were two-tailed. A two-sided P value of less than 0.05 was considered to be statistically significant. Statistical analyses were carried out via SPSS software (version 20 for Mac, IBM, Chicago; Illinois).

RESULTS

A total of 368 patients were included in the present analysis. Overall baselines, operative characteristics, and postoperative outcomes are listed in Table 1. The mean age was 59 (±14) years, and most patients were female (57.3%). The most common indication was pancreatic ductal adenocarcinoma (PDAC) (40.2%), followed by cystic neoplasms (28.0%) and neuroendocrine tumors (25.5%). A minimally invasive approach was preferred in 34.3% of patients. The POPF rate was 28.8%, whereas severe postoperative complications (Clavien–Dindo ≥ III) occurred in 15.5% of patients. The 30-day overall mortality rate was 0.3% (n= 1).

Incidence of POAP and association with postoperative morbidity

The overall POAP incidence after DP was 67.9% (n= 250), whereas CR-POAP occurred in 45.1% (n= 166) of cases. Table 2 characterizes postoperative outcomes of patients according to POAP occurrences. Patients developing POAP experienced a significantly increased rate of severe postoperative surgical morbidity scored as Clavien–Dindo ≥III, as well as an increased rate of POPF, PPH, abdominal abscesses, sepsis, and relaparotomy. Patients with POAP were significantly more frequently discharged maintaining the surgical drainage in place and more frequently presented with bacterial contamination, including multi-drug-resistant (MDR) bacteria at drainage cultures. Patients who developed POAP also showed a significantly increased value of drainage fluid amylase on POD1, as well as CRP on POD2 and POD3. There was only a poor correlation between POD1 serum pancreatic amylase and drainage fluid amylase ($r = 0.269$, $p < 0.001$).

ROC curves were plotted to test the ability of POAP in predicting severe morbidity (Clavien–Dindo ≥III). The area under the curve (AUC) for POAP was 0.57, which exhibited an 81% sensitivity, 34% specificity, 18% positive predictive value (PPV), and 91% negative predictive value (NPV). The AUC for CR-POAP was 0.62, which exhibited a 66% sensitivity, 59% specificity, 90% NPV, and 23% PPV. By increasing the serum pancreatic amylase threshold above x3 ULN per the revised Atlanta criteria[34] for acute pancreatitis, the AUC was 0.59, with a 28% sensitivity, 90% specificity, 87% NPV, and 35% PPV.

Determinants of POAP and its association with POPF

Table 3 shows the univariate and multivariable analyses of the potential predictors of POPF. Only the occurrence of POAP, an “extended” DP, increased EBL, and increased operative time were independent predictors of POPF. The AUC of the model was 0.81.

Table 4 shows how the postoperative course changed according to the possible combinations of POAP and POPF. Among patients presenting POAP (n= 250), 93 (37.2%) cases developed POPF. Considering only those with CR-POAP (n= 166), POPF occurred in 72 (43.3%) cases. Comparing patients who did not develop POAP or POPF to those who developed POAP alone (n = 157), the latter category showed only a significantly increased rate of biochemical leakage and bacterial contamination in drainage cultures.

Patients who developed POPF, with or without POAP, experienced a significantly increased rate of Clavien–Dindo ≥ III morbidity, PPH, DGE, abscesses, sepsis, cardiac morbidity, pneumonia, bacterial infections in drainage cultures, and relaparotomy. Moreover, they required more frequent ICU admissions and hospital readmissions after discharge. Almost no difference was noted in the incidence of major complications in patients with POPF in terms of whether or not they were associated with POAP.

Table 5 reports the univariate and multivariable analyses of possible predictors of POAP. In terms of the multivariable analysis, parenchyma-sparing DP, pancreatic thickness, and neuroendocrine histology at final the pathology were independent risk factors of POAP. In contrast, neoadjuvant therapy, being older than 65 years, and a dilated main pancreatic duct were independently associated with a reduced risk of POAP. The AUC of the model was 0.82. There was no matching by comparing POAP to POPF predictive factors.

DISCUSSION

This retrospective study revealed that postoperative hyperamylasemia (POH), consistent with the only available definition of POAP, was extremely frequent after DPs. Patients who developed POAP had a worse postoperative course, as they presented a significantly higher incidence of severe complications, including POPF. However, developing POAP alone was not associated with relevant changes in postoperative burden, as only an increased incidence of biochemical leakage and bacterial contamination in drainage cultures were found. Previous studies have thoroughly investigated the relationship between POAP and POPF and their associated risk factors. While our present POPF determinants were in line with those reported in the literature[18–20], those related to the development of POAP were different and crucially linked to the presence of a healthy pancreatic parenchyma, namely, in terms of an increased thickness and a preserved functionality.

In recent years, there has been a growing interest around the concept of POAP after major pancreatic resections, in the context of it potentially representing an ischemic-inflammatory process of the pancreatic stump area that is able to induce additional morbidity, including POPF[1,2,12]. Most previous studies have only focused on PDs[1–6], where evidence on DPs has relied on only a single previous study[6]. POAP has been identified as one of the strongest independent predictors of POPF. Such a close cause-effect relationship may suggest that these entities are part of a single process. However, cases of POPF without POAP exist and determinants of the two entities do not completely overlap. Even when considering patients suffering from CR-POAP, where POAP should result in clinically relevant changes of the postoperative course by definition, more than half of these patients do not develop POPF or other severe complications. This evidence disproves the assumption expressed in other previous studies that all patients with CR-POAP can be classified as CR-POPF[12] and supports the need to consider POAP and POPF as separate entities. Furthermore, this evidence suggests that POAP may represent a stand-alone complication and may not merely be a sign of mechanical surgical damage or serologic evidence of pancreatic leakage. In the timeline of postoperative complications, POAP appears early, starting during or shortly after surgery. POAP may subsequently alter the healing process or the mechanical stability of the pancreatic stump, possibly representing a root mechanism behind POPF occurrence.

Although several technical aspects have been correlated with the risk for POPF after DP[19,35–39], none of the pancreatic stump closure techniques were found to predict POAP in the present series. Moreover, Kühlbrey et al.[6] found that the use of pancreatojejunostomy to cover the pancreatic stump after DP did not affect the occurrence of POAP. This evidence emphasizes that POAP is not an expression of surgical mechanical trauma and that it is independent of the surgical technique that is applied. These data, together with those derived from animal models[1,40], support alternative mechanisms underlying POAP occurrence that deserve further investigations. The intraoperative ischemic damage leading to POAP may be related to anatomical and hemodynamic factors, and even the mobilization of the gland or transient perfusion disturbances may represent pivotal mechanisms involved in pancreatic parenchymal damage[1,40]. Few studies have analyzed the relationship between pancreatic transection lines and the viability of the remaining parenchyma[16]. Unlike the pancreatic head, the body-tail level is characterized by an abundant arterial anastomotic network and limited venous drainage[41]. In this study, a "parenchymal-sparing" resection was associated with a higher incidence of POAP. Based on our data, we speculate that pancreatic transection at the body-tail level may be associated with an increased incidence of POAP, given the susceptibility of the pancreatic parenchyma to both arterial and venous ischemia.

Other predictors of POAP deserve further inquiries. Young patients not receiving neoadjuvant treatments or those suffering from neuroendocrine tumors, with an increased pancreatic thickness and a small pancreatic duct, were more likely to develop POAP. All these characteristics typically represent a “normal” and functioning pancreatic parenchyma and have already been recognized as predictors of POAP after pancreatic head resections[1]. Again, this aspect highlights that normal pancreatic tissue is extremely susceptible even to temporary alterations in blood supply and intraoperative damage[40]. In contrast, neoadjuvant therapy, as well as PDAC pathology, induces changes in pancreatic tissue with increased fibrosis and in-flow disturbances[40].

In this study, POAP alone, intended as only postoperative serum hyperamylasemia (POH), did not cause any clinically relevant change in the postoperative course of DPs. This behavior resembles that of biochemical fistula and probably does not represent an actual complication and results only in a serum biochemical alteration. Such a low threshold for serum amylase values, as proposed by Connor, led many patients to be included among those developing POAP even if they did not show any clinically meaningful changes in their postoperative course. This finding raised doubts that POAP actually existed in these patients. Furthermore, less than half of the patients diagnosed with POAP subsequently developed POPF. Even considering cases defined as CR-POAP by Connor[2], in which serum amylase activity is combined to increase CRP, more than half of these patients do not subsequently develop POPF. This phenomenon suggests that this existing definition of CR-POAP is unable to identify a clinically relevant complication requiring a change in the management of the expected postoperative pathway. Using the definition of POAP by Connor[2] in the context of pancreatic head resections allowed our present study to appreciate the existence of POAP and how it affects the postoperative course, but ,dealing with DP, such definition raises several concerns. Current criteria do not apply uniformly to both PD and DP and do not allow for a reliable grading of POAP severity, making it difficult to differentiate patients with POH from those with a clinically relevant condition (e.g., POAP). The revised Atlanta consensus classification for acute pancreatitis[34] has been previously used to define POAP in the literature[6–8,42,43], but lowering the threshold of serum amylase to define POAP, as in the definition by Connor's[2], has allowed for a high sensitivity in identifying patients at risk for major complications. Unfortunately, in this context, there will be a large number of false-positive patients that will not experience any clinically relevant change in their postoperative course.

A major concern is indeed represented by the lack of a universally accepted definition of POAP. In the absence of objective findings, such as drainage fluid amylase for POPF, each definition is likely to be extremely weak since each is based only on the relationship between POAP and other complications, including pancreatic fistula. First of all, we need to demonstrate the existence of an ischemic/inflammatory process at the level of the pancreatic stump area after a major pancreatic resection. For this purpose, it is crucial to describe both the morphological and biochemical alterations of this process and the association between them. Studies providing data from cross-sectional imaging may be able to identify specific characteristics of the pancreatic stump area appearing in the earliest postoperative course that may be related to hypoperfusion, ischemia, and/or inflammation. Furthermore, biochemical markers will likely provide additional evidence. A single value of serum amylase does not seem to be adequate, and future studies should focus on further tests such as inflammatory markers and proteins related to pancreatic tissue damage, as well as their temporal trends. Only after obtaining such data, it will be possible to scale the burden of POAP by distinguishing POH without any clinical relevance from CR-POAP and its different grades of severity. Finally, the correct recognition of POAP as an early postoperative event, as well as the achievement of a shared definition, would allow the development of new treatments and prevention strategies.

Our present study had several limitations, including its retrospective design. Only patients with complete data were included, and we excluding those without multiple assessments of serum amylase activity after surgery. For this reason, our results may not be fully representative of the entire population of patients undergoing DPs. In addition, to better describe the impact of POAP after DPs, all types of surgery were considered in this study, including those associated with a known increase in postoperative complications such as "extended" DPs or multiorgan resections. Moreover, patients were not stratified according to preoperative features and different surgical techniques to avoid reducing the statistical power and clinical utility of our results. Finally, since a universally accepted definition of POAP is still not available, it is possible that the current definition is not appropriate to highlight significant differences between the included patients in our present study.

CONCLUSION

Our present study represents the first to investigate the incidence of POAP, its impact on the postoperative course, and its possible risk factors after DPs. We found that POAP was a frequent event after DPs, and although it was associated with an increased occurrence of POPF, we conclude that it should be considered as a separate entity. The current definition of POAP may still not be adequate to properly characterize POAP, and classifications of POAP severities are still needed. A new definition of POAP that uniformly applies to all major pancreatic resections could improve data reporting and comparisons, eventually leading to novel therapeutic scenarios.

REFERENCES

1. Bannone E, Andrianello S, Marchegiani G, et al. Postoperative Acute Pancreatitis Following Pancreaticoduodenectomy: A Determinant of Fistula Potentially Driven by the Intraoperative Fluid Management. *Ann Surg*. Published online July 12, 2018. doi:10.1097/SLA.0000000000002900

2. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. *HPB*. 2016;18(8):642-651. doi:10.1016/j.hpb.2016.05.006

3. Chen H, Wang W, Ying X, et al. Predictive factors for postoperative pancreatitis after pancreaticoduodenectomy: A single-center retrospective analysis of 1465 patients. *Pancreatol Off J Int Assoc Pancreatol IAP Al*. 2020;20(2):211-216. doi:10.1016/j.pan.2019.11.014

4. Globke B, Timmermann L, Klein F, et al. Postoperative acute necrotizing pancreatitis of the pancreatic remnant (POANP): a new definition of severe pancreatitis following pancreaticoduodenectomy. *HPB*. Published online August 17, 2019. doi:10.1016/j.hpb.2019.07.016

5. Nahm CB, Brown KM, Townend PJ, et al. Acinar cell density at the pancreatic resection margin is associated with post-pancreatectomy pancreatitis and the development of postoperative pancreatic fistula. *HPB*. 2018;20(5):432-440. doi:10.1016/j.hpb.2017.11.003

6. Kühlbrey CM, Samiei N, Sick O, Makowiec F, Hopt UT, Wittel UA. Pancreatitis After Pancreatoduodenectomy Predicts Clinically Relevant Postoperative Pancreatic Fistula. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2017;21(2):330-338. doi:10.1007/s11605-016-3305-x

7. Jin S, Shi X-J, Sun X-D, et al. The gastric/pancreatic amylase ratio predicts postoperative pancreatic fistula with high sensitivity and specificity. *Medicine (Baltimore)*. 2015;94(3):e339. doi:10.1097/MD.0000000000000339

8. Molinari E, Bassi C, Salvia R, et al. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. *Ann Surg*. 2007;246(2):281-287. doi:10.1097/SLA.0b013e3180caa42f

9. Laaninen M, Bläuer M, Vasama K, et al. The risk for immediate postoperative complications after pancreaticoduodenectomy is increased by high frequency of acinar cells and decreased by prevalent fibrosis of the cut edge of pancreas. *Pancreas*. 2012;41(6):957-961. doi:10.1097/MPA.0b013e3182480b81

10. Räty S, Sand J, Lantto E, Nordback I. Postoperative acute pancreatitis as a major determinant of postoperative delayed gastric emptying after pancreaticoduodenectomy. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2006;10(8):1131-1139. doi:10.1016/j.gassur.2006.05.012

11. Chen CB, McCall NS, Pucci MJ, et al. The Combination of Pancreas Texture and Postoperative Serum Amylase in Predicting Pancreatic Fistula Risk. *Am Surg*. 2018;84(6):889-896.

12. Birgin E, Reeg A, Téoule P, et al. Early postoperative pancreatitis following pancreaticoduodenectomy: what is clinically relevant postoperative pancreatitis? *HPB*. 2019;21(8):972-980. doi:10.1016/j.hpb.2018.11.006

13. Partelli S, Tamburrino D, Andreasi V, et al. Implications of increased serum amylase after pancreaticoduodenectomy: toward a better definition of clinically relevant postoperative acute pancreatitis. *HPB*. Published online April 11, 2020. doi:10.1016/j.hpb.2020.03.010

14. Lee MK, Lewis RS, Strasberg SM, et al. Defining the post-operative morbidity index for distal pancreatectomy. *HPB*. 2014;16(10):915-923. doi:10.1111/hpb.12293

15. Kelly KJ, Greenblatt DY, Wan Y, et al. Risk stratification for distal pancreatectomy utilizing ACS-NSQIP: preoperative factors predict morbidity and mortality. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2011;15(2):250-259, discussion 259-261. doi:10.1007/s11605-010-1390-9

16. Miao Y, Lu Z, Yeo CJ, et al. Management of the pancreatic transection plane after left (distal) pancreatectomy: Expert consensus guidelines by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. Published online April 2, 2020. doi:10.1016/j.surg.2020.02.018

17. McMillan MT, Christein JD, Callery MP, et al. Comparing the burden of pancreatic fistulas after pancreatoduodenectomy and distal pancreatectomy. *Surgery*. 2016;159(4):1013-1022. doi:10.1016/j.surg.2015.10.028

18. Goh BKP, Tan Y-M, Chung Y-FA, et al. Critical appraisal of 232 consecutive distal pancreatectomies with emphasis on risk factors, outcome, and management of the postoperative pancreatic fistula: a 21-year experience at a single institution. *Arch Surg Chic Ill 1960*. 2008;143(10):956-965. doi:10.1001/archsurg.143.10.956

19. Ferrone CR, Warshaw AL, Rattner DW, et al. Pancreatic fistula rates after 462 distal pancreatectomies: staplers do not decrease fistula rates. *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2008;12(10):1691-1697; discussion 1697-1698. doi:10.1007/s11605-008-0636-2

20. Ecker BL, McMillan MT, Allegrini V, et al. Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group. *Ann Surg*. 2019;269(1):143-149. doi:10.1097/SLA.0000000000002491

21. Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg*. 2013;216(1):1-14. doi:10.1016/j.jamcollsurg.2012.09.002

22. Kimura W, Yano M, Sugawara S, et al. Spleen-preserving distal pancreatectomy with conservation of the splenic artery and vein: techniques and its significance. *J Hepato-Biliary-Pancreat Sci*. 2010;17(6):813-823. doi:10.1007/s00534-009-0250-z

23. Warshaw AL. Conservation of the spleen with distal pancreatectomy. *Arch Surg Chic Ill 1960*. 1988;123(5):550-553. doi:10.1001/archsurg.1988.01400290032004

24. Butturini G, Damoli I, Crepaz L, et al. A prospective non-randomised single-center study comparing laparoscopic and robotic distal pancreatectomy. *Surg Endosc*. 2015;29(11):3163-3170. doi:10.1007/s00464-014-4043-3

25. Melotti G, Butturini G, Piccoli M, et al. Laparoscopic distal pancreatectomy: results on a consecutive series of 58 patients. *Ann Surg*. 2007;246(1):77-82. doi:10.1097/01.sla.0000258607.17194.2b

26. Nakamura M, Ueda J, Kohno H, et al. Prolonged peri-firing compression with a linear stapler prevents pancreatic fistula in laparoscopic distal pancreatectomy. *Surg Endosc*. 2011;25(3):867-871. doi:10.1007/s00464-010-1285-6

27. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. 2017;161(3):584-591. doi:10.1016/j.surg.2016.11.014

28. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. 2007;142(5):761-768. doi:10.1016/j.surg.2007.05.005

29. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery*. 2007;142(1):20-25. doi:10.1016/j.surg.2007.02.001

30. Besselink MG, van Rijssen LB, Bassi C, et al. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. *Surgery*. 2017;161(2):365-372. doi:10.1016/j.surg.2016.06.058

31. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):762-774. doi:10.1001/jama.2016.0288

32. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections. *Infect Control Hosp Epidemiol*. 1992;13(10):606-608.

33. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213.

34. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111. doi:10.1136/gutjnl-2012-302779

35. Carter TI, Fong ZV, Hyslop T, et al. A dual-institution randomized controlled trial of remnant closure after distal pancreatectomy: does the addition of a falciform patch and fibrin glue improve outcomes? *J Gastrointest Surg Off J Soc Surg Aliment Tract*. 2013;17(1):102-109. doi:10.1007/s11605-012-1963-x

36. Mita K, Ito H, Fukumoto M, et al. Pancreaticojejunostomy using a fibrin adhesive sealant (TachoComb) for the prevention of pancreatic fistula after pancreaticoduodenectomy. *Hepatogastroenterology*. 2011;58(105):187-191.

37. Diener MK, Seiler CM, Rossion I, et al. Efficacy of stapler versus hand-sewn closure after distal pancreatectomy (DISPACT):

a randomised, controlled multicentre trial. *Lancet*. 2011;377(9776):1514-1522. doi:10.1016/S0140-6736(11)60237-7

38. Okabayashi T, Hanazaki K, Nishimori I, et al. Pancreatic transection using a sharp hook-shaped ultrasonically activated scalpel. *Langenbecks Arch Surg*. 2008;393(6):1005-1008. doi:10.1007/s00423-007-0236-8

39. Pulvirenti A, Landoni L, Borin A, et al. Reinforced stapler versus ultrasonic dissector for pancreatic transection and stump closure for distal pancreatectomy: A propensity matched analysis. *Surgery*. 2019;166(3):271-276. doi:10.1016/j.surg.2019.02.016

40. Cuthbertson CM, Christophi C. Disturbances of the microcirculation in acute pancreatitis. *Br J Surg*. 2006;93(5):518-530. doi:10.1002/bjs.5316

41. Kulenović A, Sarač-Hadžihalilović A. INVESTIGATION OF VASCULARIZATION OF HUMAN PANCREAS USING METHOD OF SELECTIVE ARTERIOGRAPHY WITH INSIGHT INTO SIGNIFICANCE TO A SURGICAL APPROACH FOR THIS ORGAN. *Bosn J Basic Med Sci*. 2010;10(1):15-18.

42. Palani Velu LK, Chandrabalan VV, Jabbar S, et al. Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. *HPB*. 2014;16(7):610-619. doi:10.1111/hpb.12184

43. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg*. 2010;252(2):207-214. doi:10.1097/SLA.0b013e3181e61e88

TABLES

Table 1 – Patients characteristics (n= 368)		
Sex	**M**	157 (42.7%)
	F	211 (57.3%)
Age (mean, SD)		59 (14)
BMI (mean, SD, Kg/m²)		25 (4.2)
Smoker		90 (24.5%)
Alcohol abuse		25 (6.8%)
Preoperative PERT		41 (11.1%)
Diabetes		71 (19.3%)
Ischemic cardiac disease		31 (8.4%)
Hypertension		135 (36.7%)
COPD		12 (3.3%)
Chronic renal failure		9 (2.4%)
ASA score	**1**	33 (9%)
	2	282 (76.6%)
	3	53 (14.1%)
History of acute pancreatitis		41 (11.1%)
Preoperative albumin (g/L, mean, SD)		43.5 (3.6)
Preoperative MDR at rectal swab		19 (5.2%)
Neoadjuvant therapy		74 (20.1%)
Approach	**Open**	242 (65.8%)
	Laparoscopic	76 (20.7%)
	Robotic	50 (13.6%)
Surgery Type	**DP with splenectomy**	284 (77.2%)
	DP spleen-preserving	34 (9.2%)
	Extended DP	50 (13.6%)
OR time (min, mean, SD)		291 (95)
EBL (mL, median, IQR)		250 (250)
Vascular resection		35 (9.5%)
Multiorgan resection		29 (7.9%)
Transection line	**Formal**	233 (63.3%)
	Pancreas sparing (body- tail)	84 (22.8%)
	GDA level	51 (13.9%)
Tumor site	**Tail**	108 (29.3%)
	Body	219 (59.5%)
	Isthmus	41 (11.1%)
Transection technique	**Tri-staple**	226 (61.4%)
	Harmonic	121 (39.2%)
	Scalpel	21 (5.7%)
POPF		106 (28.8%)
grade	**BL**	56 (15.2%)
	B	95 (24.8%)
	C	11 (2.9%)
POAP		**250 (67.9%)**
CR- POAP		**166 (45.1%)**
Abscess		114 (31%)
PPH		51 (13.9%)
grade	**A**	9 (2.4%)
	B	32 (8.7%)
	C	11 (3%)
DGE		17 (4.6%)
grade	**A**	5 (1.4%)
	B	6 (1.6%)
	C	6 (1.6%)
Sepsis		50 (13.6%)
Pneumonia		73 (19.8%)
Cardiac morbidity		25 (6.8%)
Urinary tract infection		20 (5.4%)
Acute kidney failure		7 (1.9%)

SSI		10 (2.7%)
Relaparotomy		24 (6.5%)
Unplanned ICU stay		21 (5.7%)
Mortality		1 (0.3%)
LHS (days, median, IQR)		8 (6)
Readmission		34 (9.2%)
Discharge with drain		96 (26.1%)
Clavien-Dindo	**I**	50 (13.6%)
	II	123 (33.4%)
	IIIA	25 (6.8%)
	IIIB	13 (3.5%)
	IVA	10 (2.7%)
	IVB	8 (2.2%)
	V	1 (0.3%)
Clavien-Dindo ≥ III		57 (15.5%)
Pathology	**PDAC**	148 (40.2%)
	NET	94 (25.5%)
	Cystic	103 (28%)
	Other	23 (6.3%)

Table 2 - Postoperative outcomes stratified by POAP occurrence

		POAP		P
		No (n= 118)	**Yes (n= 250)**	
Clavien-Dindo ≥ III		11 (9.3%)	46 (18.4%)	**0.030**
POPF		13 (11%)	93 (37.2%)	**<0.001**
	BL	12 (10.2%)	44 (17.6%)	0.086
	B	13 (11%)	82 (32.8%)	0.352
	C	0	11 (4.4%)	
PPH		8 (6.8%)	43 (17.2%)	**0.006**
	A	1 (0.8%)	8 (3.2%)	0.542
	B	7 (5.9%)	25 (10%)	
	C	0	10 (4%)	
DGE		6 (5.1%)	11 (4.4%)	0.793
	A	3 (2.4%)	2 (1.1%)	0.323
	B	1 (0.8%)	5 (2.2%)	
	C	2 (1.6%)	4 (1.5%)	
Serum amylase (UI/L, median, IQR)	**POD0**	24 (14)	73 (57)	< 0.001
	POD1	29 (15)	99 (60)	< 0.001
	POD2	13 (17)	49 (55)	< 0.001
C-reactive protein (mg/L, median, IQR)	**POD1**	59 (27)	85 (61)	0.914
	POD2	140 (91)	223 (157)	0.034
	POD3	154 (92)	255 (157)	< 0.001
Drain fluid amylase (UI, median, IQR)	**POD1**	799 (1364)	2627 (5790)	< 0.001
Abscess		21 (17.8%)	93 (37.2%)	**< 0.001**
Sepsis		9 (7.6%)	41 (16.4%)	**0.023**
Pneumonia		20 (16.9%)	53 (21.2%)	0.401
Cardiac morbidity		12 (10.2%)	13 (5.2%)	0.118
Urinary tract infection		5 (4.2%)	15 (6%)	0.625
Acute renal failure		3 (2.5%)	4 (1.6%)	0.685
Wound infection		1 (0.8%)	9 (3.6%)	0.178
Relaparotomy		2 (1.7%)	22 (8.8%)	**0.011**
Unplanned ICU stay		3 (2.5%)	18 (7.2%)	0.092
Positive drain cultures		7 (5.9%)	65 (26%)	**< 0.001**
Positive drain cultures (MDR bacteria)		0	25 (10%)	**< 0.001**
Mortality		0	1 (0.4%)	1.000
Readmission		9 (7.6%)	25 (10%)	0.565
Discharged with drain		16 (13.6%)	80 (32%)	**< 0.001**

Table 3 – Univariate and multivariate analysis of predictors of POPF after DP							
		Univariate Analysis			Multivariate Analysis		
		POPF		P	OR	CI95%	p
		No (n= 262)	Yes (n= 106)				
Sex	**M**	112 (42.7%)	45 (42.5%)	1.000			
	F	150 (57.3%)	61 (57.5%)				
Age > 65 years		105 (40.1%)	39 (36.8%)	0.637			
BMI (Kg/m², mean, SD)		24.8 (4.3)	25.7 (3.9)	0.015	1.028	0.948 – 1.116	0.503
Smoker		63 (24%)	27 (25.5%)	0.790			
Alcohol abuse		17 (6.5%)	8 (7.5%)	0.819			
History of acute pancreatitis		31 (11.8%)	10 (9.4%)	0.586			
Preoperative PERT		30 (11.5%)	11 (10.4%)	0.856			
Diabetes		56 (21.4%)	15 (14.2%)	0.144			
Ischemic cardiac disease		24 (9.2%)	7 (6.6%)	0.536			
Hypertension		86 (32.8%)	49 (46.2%)	0.017	1.745	0.636 – 3.879	0.247
COPD		8 (3.1%)	4 (3.8%)	0.749			
Chronic renal failure		2 (0.8%)	7 (6.6%)	0.003	4.716	0.728 – 30.531	0.104
Preoperative MDR bacteria at rectal swab		12 (4.6%)	7 (6.6%)	0.441			
Neoadjuvant therapy		52 (19.8%)	22 (20.8%)	0.886			
ASA	**1**	24 (9.2%)	9 (8.5%)	0.205			
	2	194 (74%)	88 (83%)				
	3	44 (16.8%)	9 (8.5%)				
Preoperative albumin (g/L, mean, SD)		42.9 (3.7)	44.1 (3.1)	0.163			
Vascular resection		23 (8.8%)	12 (11.3%)	0.439			
Transection line	**Formal**	177 (67.6%)	56 (52.8%)	0.014	1	-	-
	Parenchyma sparing (body- tail)	56 (21.4%)	28 (26.4%)		0.535	0.169 – 1.691	0.287
	Extended (GDA level)	29 (11.1%)	22 (20.8%)		1.393	1.099 – 3.607	0.041
Transection technique	**Tri-stapler**	173 (66%)	53 (50%)	0.015	1	-	-
	Harmonic	75 (28.6%)	46 (43.4%)		2.615	0.716 – 9.547	0.146
	Scalpel	14 (5.3%)	7 (6.6%)		0.976	0.430 – 2.212	0.858
Approach	**Open**	179 (68.3%)	63 (59.4%)	0.115			
	Minimally invasive	83 (31.7%)	43 (40.6%)				
EBL (mL, median, IQR)		250 (250)	300 (325)	0.001	1.002	1.000 – 1.003	0.019
OR time (min, mean, SD)		269 (87)	323 (81)	< 0.001	1.004	1.002 – 1.011	0.023
Main duct diameter (mm, median, IQR)		2 (1)	2 (2)	0.069			
Pancreas thickness (mm, mean, SD)		16 (0.4)	17.5 (0.4)	0.001	1.594	0.753 – 3.371	0.223
Stump area (cm², mean, SD)		4.2 (1.8)	4.7 (2)	0.003			
Pathology	**PDAC**	115 (43.9%)	33 (31.3%)	0.081			
	NET	59 (22.5%)	35 (33%)				
	Cystic	73 (27.9%)	30 (28.3%)				
	Other	15 (5.7%)	8 (7.5%)				
POAP		157 (59.9%)	93 (87.7%)	< 0.001	5.898	2.278 – 15.209	< 0.001

Table 4 - Postoperative outcomes stratified by POAP and POPF occurrence							
	POAP - POPF - (n= 105)	**POAP + POPF - (n= 157)**	**p***	**POAP - POPF + (n= 13)**	**p****	**POAP + POPF + (n= 93)**	**p*****
Clavien-Dindo ≥ III	4 (3.8%)	6 (3.8%)	1.000	7 (53.8%)	**< 0.001**	40 (43%)	0.556
BL	12 (11.4%)	44 (28%)	**0.001**	-	-	-	-
PPH	6 (5.7%)	15 (9.6%)	0.354	2 (15.4%)	0.622	28 (30.1%)	0.342
A	1 (1%)	6 (3.8%)	0.308	0	**0.008**	2 (2.2%)	0.563
B	5 (4.8%)	9 (5.7%)		2 (15.4%)		16 (17.2%)	
C	0	0		0		10 (10.8%)	
DGE	3 (2.9%)	3 (1.9%)	0.686	3 (23.1%)	**0.006**	8 (8.6%)	0.133
A	2 (1.9%)	1 (0.6%)	0.650	1 (7.7%)	**< 0.001**	1 (1.1%)	0.070
B	1 (1%)	1 (0.6%)		0		4 (4.3%)	
C	0	1 (0.6%)		2 (15.4%)		3 (3.2%)	
Abscess	14 (13.3%)	33 (21%)	0.139	7 (53.8%)	**0.014**	60 (64.5%)	0.543
Sepsis	16 (15.2%)	15 (9.6%)	0.759	4 (30.8%)	**0.003**	38 (40.9%)	0.764
Positive drain cultures	2 (1.9%)	14 (8.9%)	**0.032**	5 (38.5%)	**0.007**	51 (54.8%)	0.375
Positive drain cultures (MDR bacteria)	0	5 (3.2%)	0.085	0	1.000	20 (21.5%)	0.122
Pneumonia	16 (15.2%)	15 (9.6%)	0.176	4 (30.8%)	**0.042**	38 (40.9%)	0.559
Cardiac morbidity	8 (7.6%)	9 (5.7%)	0.612	4 (30.8%)	**0.010**	4 (4.3%)	0.008
Urinary tract infection	5 (4.8%)	7 (4.5%)	1.000	0	1.000	8 (8.6%)	0.592
Acute renal failure	2 (1.9%)	1 (0.6%)	0.566	1 (7.7%)	0.148	3 (3.2%)	0.412
SSI	1 (1%)	1 (0.6%)	1.000	0	1.000	8 (8.6%)	0.592
Relaparotomy	2 (1.9%)	4 (2.5%)	1.000	0	1.000	18 (19.4%)	0.119
Unplanned ICU stay	1 (1%)	3 (1.9%)	0.652	2 (15.4%)	**0.048**	15 (16.1%)	1.000
Readmission	4 (3.8%)	4 (2.5%)	0.717	5 (38.5%)	**< 0.001**	21 (22.6%)	0.299

* POAP-/POPF- vs. POAP+/POPF-
** POAP+/POPF- vs. POAP-/POPF+
*** POAP-/POPF+ vs. POAP+/POPF+

Table 5 – Univariate and multivariate analysis of predictors of POAP after DP							
		Univariate Analysis			Multivariate Analysis		
		POAP		P			
		No (n=118)	Yes (n= 250)		OR	CI95%	p
Sex	**M**	57 (48.3%)	100 (40%)	0.143			
	F	61 (51.7%)	150 (60%)				
Age > 65 years		66 (55.9%)	78 (31.2%)	**<0.001**	0.342	0.137 – 0.857	**0.022**
BMI > 25 Kg/m²		55 (46.6%)	121 (48.4%)	0.823			
Smoker		29 (24.6%)	61 (24.4%)	1.000			
Alcohol abuse		11 (9.3%)	14 (5.6%)	0.190			
History of acute pancreatitis		16 (13.6%)	25 (10%)	0.375			
Preoperative PERT		24 (20.3%)	17 (6.8%)	**< 0.001**	0.487	0.169 – 1.405	0.183
Diabetes		39 (33.1%)	32 (12.8%)	**< 0.001**	0.523	0.197 – 1.393	0.195
Ischemic cardiac disease		17 (14.4%)	14 (5.6%)	**0.008**	0.413	0.120 – 1.419	0.160
Hypertension		44 (37.3%)	91 (36.4%)	0.908			
COPD		6 (5.1%)	6 (2.4%)	0.211			
Chronic renal failure		0	9 (3.6%)	0.063			
Preoperative MDR bacteria at rectal swab		7 (5.9%)	12 (4.8%)	0.623			
Neoadjuvant therapy		39 (33.1%)	35 (14%)	**< 0.001**	0.284	0.095 – 0.854	**0.025**
ASA	**1**	4 (3.4%)	29 (11.6%)	**<0.001**	1	-	-
	2	86 (72.9%)	196 (78.4%)		1.818	0.367 – 8.996	0.464
	3	28 (23.7%)	25 (10%)		0.949	0.150 – 6.012	0.955
Preoperative albumin (g/L, mean, SD)		42.4 (3.6)	43.6 (3.5)	0.007	1.059	0.944 – 1.187	0.329
Vascular resection		15 (12.5%)	22 (8.3%)	0.197			
Transection line	**Formal**	88 (74.6%)	145 (58%)	**< 0.001**	1	-	-
	Parenchyma sparing (body- tail)	12 (10.2%)	72 (28.8%)		4.367	1.159 – 23.198	**0.041**
	Extended (GDA level)	18 (15.3%)	33 (13.2%)		1.464	0.498 – 4.303	0.488
Transection technique	**Tri-stapler**	71 (59.2%)	165 (62.3%)	0.480			
	Harmonic	40 (33.3%)	88 (33.2%)				
	Scalpel	9 (7.5%)	12 (4.5%)				
Approach	**Open**	97 (82.2%)	145 (58%)	**< 0.001**	1	-	-
	Minimally invasive	21 (17.8%)	105 (42%)		1.919	0.520 – 7.086	0.328
EBL (mL, median, IQR)		300 (300)	250 (250)	0.115			
OR time (min, mean, SD)		273 (94)	290 (85)	0.557			
Main duct diameter (mm, median, IQR)		2 (1)	1 (1)	**< 0.001**	0.029	0.002 – 0.474	**0.013**
Pancreas thickness (mm, mean, SD)		14.8 (4)	17.3 (4)	**< 0.001**	3.400	1.293 – 8.944	**0.013**
Stump area (cm², mean, SD)		3.70 (1.50)	4.75 (1.95)	**< 0.001**			
Pathology	**PDAC**	68 (57.6%)	80 (32%)	**< 0.001**	1	-	-
	NET	16 (13.6%)	78 (31.2%)		1.141	1.064 – 3.901	**0.013**
	Cystic	28 (23.7%)	75 (30%)		0.526	0.101 – 2.548	0.623
	Other	6 (5.1%)	17 (6.8%)		0.225	0.069 – 1.371	0.834

V

Early and Sustained Elevation in Serum Pancreatic Amylase Activity: A Novel Predictor of Morbidity after Pancreatic Surgery

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ABSTRACT

Objective

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

Summary Background Data

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

Methods

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

Results

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

Conclusions

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

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

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

METHODS

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

Inclusion and exclusion criteria

Patients who consecutively underwent 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 postoperative 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 (> 156U/L, Atlanta criteria for acute pancreatitis[1]).

Data collection

Demographics, operative details, postoperative data were collected from medical records. Preoperative characteristics (including age, sex, BMI [kg/m2], 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[13–16]. 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[17] or Warshaw[18] technique), the level of the transection line (transection at the left of the portal vein axis, at the level of the pancreatic body-tail, or at the pancreatic neck), and pancreatic stump management (with or without a triple row staple reinforced with a polyglycolic acid felt [NEOVEIL Endo GIA Reinforced Reload with Tri-Staple Technology 60 mm; COVIDIEN, North Haven, CT, USA]) was also retrieved. The pancreatic texture was only assessed for PD due to the absence of standardization and reporting for DP performed with the MIPS approach. The size of the main pancreatic duct (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)[19]. Drains were routinely placed during DP. In the case of drain placement, early removal on POD 3 was promoted on the basis of the POD 1 drain fluid amylase (DFA) value[20,21].

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

Outcome metrics

Postoperative morbidity was defined according to the International Study Group for Pancreatic Surgery (ISGPS) definitions of POPF[22], delayed gastric emptying (DGE)[23], postpancreatectomy hemorrhage (PPH)[24], and chyle leak[25]. The updated definition of POPF was retrospectively applied to all patients operated in 2016. Abdominal abscess was defined as fluid collection within the abdominal cavity with radiological or clinical signs of infection. Sepsis was defined according to the 2016 updated criteria[26]. Only an unplanned need for intensive care was defined as intensive care unit (ICU) stay. Mortality was defined as postoperative death recorded out to the point of 90-days postoperatively. The severity of complications was assessed according to the Clavien–Dindo (CD) classification system[27].

Due to the existence of different etiologies, postoperative complications are likely to have different patterns of onset (early or late), as previously reported[24,28]. Given the early onset of spAMY alteration, the association of spAMY with early postoperative morbidity was investigated. As it is not possible to objectively define a threshold to separate early from late complications, the time trend of morbidity was examined, and the time-to-complication occurrence retrieved. The analysis was focused on complications graded as CD ≥ II[27], namely a complication requiring a relevant change in the post-operative course, and on severe complications graded as CD ≥ III[27]. The primary objective of the study was to characterize the early postoperative spAMY trend after a partial pancreatic resection. As a secondary objective, the correlation between early spAMY patterns and postoperative morbidity was explored with the purpose of identifying clinically relevant spAMY trends. Eventually, predictors of the spAMY pattern associated with the worst postoperative outcome were explored.

Statistical analysis

Continuous variables are reported as the median and interquartile range. Differences were assessed with the Mann-Whitney or Student'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.

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 postoperative 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.

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). Comparing postoperative outcomes, the presence of a sustained increase in spAMY activity greater than the ULN including POD 1 + 2 (#3) appeared to have the worst postoperative outcome. Indeed, pattern #3 was associated with increased overall and severe (at least as CD ≥ III) early morbidity, overall and grade C POPF, overall and severe PPH, sepsis, relaparotomy, and ICU stay. Pattern #2 exhibited a greater postoperative burden than #1, with an increased rate of overall early postoperative complications, POPF, biochemical leak (BL), and DGE, but no significant difference in CD severe morbidity. Due to existing concerns regarding the mechanism underlying postoperative spAMY increases, the relationship between spAMY and DFA was also explored. As shown in Supplemental Figure A1 (Supplemental Digital Content 1, http://links.lww.com/SLA/D130), there was a poor correlation between POD1 spAMY and POD 1 DFA (r = 0.001, P = 0.967).

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 - Supplemental Digital Content 2, http://links.lww.com/SLA/D131). In the multivariable model for DP patients, preoperative diabetes (OR 0.19, CI 95% 0.058 – 0.681; P= 0.010) and neoadjuvant therapy (OR 0.22; CI 95% 0.062 – 0.789; P= 0.020) were confirmed as independent predictors (Supplemental Table A2 - Supplemental Digital Content 3, http://links.lww.com/SLA/D131).

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

DISCUSSION

To the best of our knowledge, this is the first study to characterize different patterns of postoperative spAMY activity after partial pancreatic resections. These spAMY trends are based on the presence of values above or below the normal range at multiple and sequential postoperative blood tests. We found that different patterns were associated with distinct rates of postoperative complications. Notably, a sustained increase in spAMY activity including POD 1 + 2 (pattern #3) was associated with the highest rate of overall and severe early postoperative complications. Despite ongoing debate regarding postoperative hyperamylasemia (POH) in recent years[2,8,9,29,30], the characterization of this phenomenon and its possible prognostic role remains largely unknown, mainly because POH typically occurs early after surgery[6,11]. Due to the temporary nature of POH, appropriate assessment and definition are often difficult and remain a matter of discussion. Such debate has recently seen a rise in popularity because POH has been increasingly considered as the main biochemical evidence of postoperative acute pancreatitis[2,8–11,11,30,31]. While POH has been investigated as a punctual increase in pancreatic amylase activity[2,4,8], the spAMY time trend has never been systematically evaluated. Interestingly, the present study highlighted that the presence of a single altered value of spAMY was not associated with increased morbidity. By contrast, patients with a sustained spAMY activity were found to be twice as likely to develop early complications. Based on these findings, a single postoperative serum pancreatic enzymatic assessment does not allow for proper scaling of the risk of postoperative morbidity. This finding could also explain why, despite a high sensitivity in predicting pancreatic specific complications, the specificity of spAMY reported by previous studies was relatively low[8,9]. The temporal course of postoperative morbidity was carefully analyzed to assess the association with different spAMY patterns. Most complications occurred within the first week after surgery, but the strongest correlation was observed with early complications occurring up to POD 7. Escalation to higher and sustained spAMY values was associated with increased overall and severe postoperative early morbidity. Patients with spAMY activity less than the LLN, and those presenting with a spAMY pattern both WRR and/or with a single increase of spAMY activity (pattern #1) showed a low likelihood of developing severe morbidity. Conversely, it was found that almost one-third of patients who presented with an increased spAMY activity on POD 0 + 1 (pattern #2) went on to develop early overall complications, although only approximately 5% were classified as severe. Given this short spAMY peak and the related intermediate burden, we could speculate that this latter pattern possibly represents the expression of a self-limiting process that does not proceed towards more severe morbidity.

Finally, patients showing a sustained spAMY activity including POD 1 + 2 (pattern #3) were found to have the highest postoperative incidence of overall (68%) and severe (15%) early morbidity. In addition, pancreas-specific complications such as POPF, PPH, and abdominal abscess are of increasing severity among different spAMY patterns. Particularly, with regard to pattern #3, spAMY values greater than 3 times the 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 POPF32 and the increased burden of PD compared to DP33. 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 mechanism34. 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. The analysis of risk factors for the pattern of spAMY associated with the worst postoperative outcome (pattern #3) revealed that this phenomenon, even with differences compared PD to DP, is essentially linked to the presence of a healthy pancreatic parenchyma, namely a soft pancreatic texture and preserved functionality. These results are in line with those of previous studies, and such features have been already included in prognostic scores[19,35]. Nevertheless, this study adds further evidence by introducing the concept of a "postoperative continuing reassessment for early morbidity" risk until POD 2. Given that the risk of postoperative complications changes over time, the risk estimation should equally be a dynamic process. Since prevention and mitigation strategies begin either before or during the surgical procedure on the basis of well-known risk scores[31,35–37], they may alter the clinical outcome, eventually lowering the risk of postoperative complications. Facing this challenge, the risk for early postoperative complications could be 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[38] and drainage management protocols[20,39] may need to be redefined. In contrast, patients with spAMY values within or less than the reference range, with a low risk of subsequent morbidity, could benefit from enhanced recoveries and early hospital discharges. Finally, but of outmost importance, the prognostic relevance of spAMY trends indicates the need to redefine POH. Historically, POH has been considered only as a consequence of POPF[40] or of surgical mechanical trauma[3]; however, POH has been recently interpreted as a marker of an acute inflammatory process of the pancreatic remnant[5,6,9]. In a non-surgical context injuries to the pancreatic parenchyma may lead to premature activation of pancreatic enzymes and a subsequent increase in serum levels1. The pathological mechanism has been related to the disruption of pancreatic cells or to an alteration of the normal exocytosis process, with the secretion of the zymogen contents at the basolateral side of the acinar cells[41,42]. However, as the spAMY has a half-life of approximately 10 hours, the persistence of increased values for 48 hours, may potentially be the expression of an ongoing release and hence an acute pancreatitis process.

This study adds solid evidence to the increasing literature investigating POH and its clinical significance[5,7,8]. The correlation between spAMY trends and postoperative morbidity can serve as a biochemical characterization of 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.

REFERENCES

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012 revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.
2. Bannone E, Andrianello S, Marchegiani G, et al. Postoperative Acute Pancreatitis Following Pancreaticoduodenectomy: A Determinant of Fistula Potentially Driven by the Intraoperative Fluid Management. *Ann Surg*. . Epub ahead of print July 12, 2018. DOI: 10.1097/SLA.0000000000002900.
3. Palani Velu LK, Chandrabalan VV, Jabbar S, et al. Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. *HPB (Oxford)*. 2014;16:610–619.
4. Chen CB, McCall NS, Pucci MJ, et al. The Combination of Pancreas Texture and Postoperative Serum Amylase in Predicting Pancreatic Fistula Risk. *Am Surg*. 2018;84:889–896.
5. Bannone E, Andrianello S, Marchegiani G, et al. Postoperative hyperamylasemia (POH) and acute pancreatitis after pancreatoduodenectomy (POAP): State of the art and systematic review. *Surgery*. . Epub ahead of print July 5, 2020. DOI:10.1016/j.surg.2020.04.062.
6. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. *HPB (Oxford)*. 2016;18:642–651.

7. Globke B, Timmermann L, Klein F, et al. Postoperative acute necrotizing pancreatitis ofthe pancreatic remnant (POANP): a new definition of severe pancreatitis following pancreaticoduodenectomy. *HPB (Oxford)*. . Epub ahead of print August 17, 2019. DOI: 10.1016/j.hpb.2019.07.016.

8. Loos M, Strobel O, Dietrich M, et al. Hyperamylasemia and acute pancreatitis after pancreatoduodenectomy: Two different entities. *Surgery*. . Epub ahead of print September 25, 2020. DOI: 10.1016/j.surg.2020.07.050.

9. Ikenaga N, Ohtsuka T, Nakata K, et al. Clinical significance of postoperative acutepancreatitis after pancreatoduodenectomy and distal pancreatectomy. *Surgery*. . Epub ahead of print September 4, 2020. DOI: 10.1016/j.surg.2020.06.040.

10. Loos M, Strobel O, Mehrabi A, et al. Postoperative acute pancreatitis is a serious butrare complication after distal pancreatectomy. *HPB*. . Epub ahead of print January 13, 2021. DOI: 10.1016/j.hpb.2021.01.004.

11. Andrianello S, Bannone E, Marchegiani G, et al. Characterization of postoperative acute pancreatitis (POAP) after distal pancreatectomy. *Surgery*. . Epub ahead of print October 23, 2020. DOI: 10.1016/j.surg.2020.09.008.

12. Birgin E, Reeg A, Téoule P, et al. Early postoperative pancreatitis followingpancreaticoduodenectomy: what is clinically relevant postoperative pancreatitis? *HPB (Oxford)*. 2019;21:972–980.

13. Butturini G, Damoli I, Crepaz L, et al. A prospective non-randomised single-center study comparing laparoscopic and robotic distal pancreatectomy. *Surg Endosc*. 2015;29:3163–3170.

14. Bassi C, Falconi M, Molinari E, et al. Reconstruction by pancreaticojejunostomy versus pancreaticogastrostomy following pancreatectomy: results of a comparative study. *Ann Surg*. 2005;242:767–771, discussion 771-773.

15. Andrianello S, Marchegiani G, Malleo G, et al. Pancreaticojejunostomy With Externalized Stent vs Pancreaticogastrostomy With Externalized Stent for Patients With High-Risk Pancreatic Anastomosis: A Single-Center, Phase 3, Randomized Clinical Trial. *JAMA Surg*. 2020;155:313–321.

16. Bassi C, Marchegiani G, Giuliani T, et al. Pancreatoduodenectomy at the Verona Pancreas Institute: the Evolution of Indications, Surgical Techniques and Outcomes: A Retrospective Analysis of 3000 Consecutive Cases. *Annals of Surgery*.;Publish Ahead of Print . Epub ahead of print January 22, 2021. DOI: 10.1097/SLA.0000000000004753.

17. Kimura W, Yano M, Sugawara S, et al. Spleen-preserving distal pancreatectomy withconservation of the splenic artery and vein: techniques and its significance. *J Hepatobiliary Pancreat Sci*. 2010;17:813–823.

18. Warshaw AL. Conservation of the spleen with distal pancreatectomy. *Arch Surg*. 1988;123:550–553.

19. Callery MP, Pratt WB, Kent TS, et al. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg*. 2013;216:1–14.

20. Salvia R, Marchegiani G, Andrianello S, et al. Redefining the Role of Drain Amylase Value for a Risk-Based Drain Management after Pancreaticoduodenectomy: Early Drain Removal Still Is Beneficial. *J Gastrointest Surg*. . Epub ahead of print June 3, 2020.DOI: 10.1007/s11605-020-04658-8.

21. Molinari E, Bassi C, Salvia R, et al. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. *Ann Surg*. 2007;246:281–287.

22. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. 2017;161:584–591.

23. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. 2007;142:761–768.

24. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery*. 2007;142:20–25.

25. Besselink MG, van Rijssen LB, Bassi C, et al. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. *Surgery*. 2017;161:365–372.

26. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315:762–774.

27. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.

28. Thompson JS, Baxter BT, Allison JG, et al. Temporal patterns of postoperative complications. *Arch Surg*. 2003;138:596–602; discussion 602-603.

29. Zimmitti G, Langella S, Sega V, et al. Serum amylase elevation following pancreatoduodenectomy with pancreatogastrostomy is strongly associated with major complications. *ANZ J Surg*. . Epub ahead of print October 5, 2020. DOI: 10.1111/ans.16282.

30. Partelli S, Tamburrino D, Andreasi V, et al. Implications of increased serum amylase after pancreaticoduodenectomy: toward a better definition of clinically relevant postoperative acute pancreatitis. *HPB (Oxford)*. . Epub ahead of print April 11, 2020. DOI: 10.1016/j.hpb.2020.03.010.

31. Andrianello S, Marchegiani G, Bannone E, et al. Clinical Implications of Intraoperative Fluid Therapy in Pancreatic Surgery. *J Gastrointest Surg*. . Epub ahead of print July 31, 2018. DOI: 10.1007/s11605-018-3887-6.

32. Pratt W, Maithel SK, Vanounou T, et al. Postoperative pancreatic fistulas are not equivalent after proximal, distal, and central pancreatectomy. *J Gastrointest Surg*. 2006;10:1264–1279.

33. McMillan MT, Christein JD, Callery MP, et al. Comparing the burden of pancreatic fistulas after pancreatoduodenectomy and distal pancreatectomy. *Surgery*. 2016;159:1013–1022.

34. Manenti A, Manco G, Farinetti A, et al. Acute pancreatitis after pancreatectomy: Inside the dilemma pancreatitis-pancreatic fistula. *Surgery*.;0 . Epub ahead of print November 13, 2020. DOI: 10.1016/j.surg.2020.10.011.

35. Ecker BL, McMillan MT, Allegrini V, et al. Risk Factors and Mitigation Strategies for Pancreatic Fistula After Distal Pancreatectomy: Analysis of 2026 Resections From the International, Multi-institutional Distal Pancreatectomy Study Group. *Ann Surg*. 2019;269:143–149.

36. Patel K, Teta A, Sukharamwala P, et al. External pancreatic duct stent reduces pancreatic fistula: a meta-analysis and systematic review. *Int J Surg*. 2014;12:827–832.

37. Andrianello S, Marchegiani G, Balduzzi A, et al. Pros and pitfalls of externalized transanastomotic

1. stent as a mitigation strategy of POPF: a prospective risk-stratified observational series. *HPB (Oxford)*. . Epub ahead of print November 19, 2020. DOI: 10.1016/j.hpb.2020.10.025.

38. Lassen K, Coolsen MME, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr*. 2012;31:817–830.

39. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg*. 2010;252:207–214.

40. Cloyd JM, Kastenberg ZJ, Visser BC, et al. Postoperative serum amylase predicts pancreatic fistula formation following pancreaticoduodenectomy. *J Gastrointest Surg*. 2014;18:348–353.

41. Frulloni L, Patrizi F, Bernardoni L, et al. Pancreatic Hyperenzymemia: Clinical Significance and Diagnostic Approach. *JOP Journal of the Pancreas*.;6 Available from: https://pancreas.imedpub.com/pancreatic-hyperenzymemia-clinical-significance-anddiagnostic-approach.php?aid=3082. 2005. Accessed February 24, 2021.

42. Scheele G, Adler G, Kern H. Exocytosis occurs at the lateral plasma membrane of the pancreatic acinar cell during supramaximal secretagogue stimulation. *Gastroenterology*.1987;92:345–353.

VI

Postpancreatectomy Acute Pancreatitis (PPAP):

Definition and Grading from the International Study Group for Pancreatic Surgery (ISGPS).

Marchegiani G, Barreto SG, Bannone E, Sarr M, Vollmer CM, Connor S, Falconi M, Besselink MG, Salvia R, Wolfgang CL, Zyromski NJ, Yeo CJ, Adham M, Siriwardena AK, Takaori K, Hilal MA, Loos M, Probst P, Hackert T, Strobel O, Busch ORC, Lillemoe KD, Miao Y, Halloran CM, Werner J, Friess H, Izbicki JR, Bockhorn M, Vashist YK, Conlon K, Passas I, Gianotti L, Del Chiaro M, Schulick RD, Montorsi M, Oláh A, Fusai GK, Serrablo A, Zerbi A, Fingerhut A, Andersson R, Padbury R, Dervenis C, Neoptolemos JP, Bassi C, Büchler MW, Shrikhande SV.

From the International Study Group for Pancreatic Surgery.

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.

Summary 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.

Discussion

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.

BACKGROUND

The occurrence of an acute inflammatory process of the pancreatic parenchyma after pancreatic resections has been reported[1–3], but the existence of clinically evident postpancreatectomy acute pancreatitis (PPAP) as a distinct complication has been challenged or, at least, considered to be a rare event[4–8]. 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[9–19]. 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[9,19]. 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[20]. PPAP may impair the healing of the pancreatic remnant and/or anastomosis with the subsequent development of a postoperative pancreatic fistula (POPF)[21]. 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[22], hemorrhage, the systemic inflammatory response syndrome (SIRS), and systemic sepsis[14,15,18,23]. According to this hypothesis, PPAP is initiated very early in the perioperative period, with a widely ranging incidence from 1%[7,8] to 67%[23]. 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[10,12,14,17,18,24]. Different reports have based their definitions of PPAP on the biochemical and radiologic criteria of the revised Atlanta classification for acute pancreatitis (AP)[25], both together[14–16,26–28] or individually[6,13,29,30]. In 2016, Connor et al.[9] 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[25]. Subsequent studies using the Conor definition of PPAP resulted in conflicting findings[14,15,18,31]. Differences in the incidence of PPAP were also reported between partial pancreatoduodenectomy[14,17,32] and distal (left-sided) pancreatectomy[17,23]. 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 [14,31]. Given these limits, a universally accepted definition of PPAP was lacking in the pancreatic surgical literature[14,18,19], 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[10,14,15,18]. 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[33–36]. 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 202019. 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[6–8,10,12,14–18,23,24,26–32,37–43] have already reported PPAP as a complication after pancreatic resections (Supplemental Table A1 - Supplemental Digital Content 1, http://links.lww.com/SLA/D460). The rates of PPAP were highly variable because the diagnostic criteria either lacked any reliable standards or differed tremendously depending on the reports[7,8,39–41,44].

Terminology

Although many papers refer to this complication as “postoperative acute pancreatitis – POAP” [10,14,15,17–19,23,45,46], 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[47–49]. 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[50,51].

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[25] were used[6,14–16,18,26–28,32] 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[6,32]. 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[6,19,52]. The first structured definition of PPAP as proposed by Connor et al.[9] 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[10,12,14,15,17,18,24]. 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 normal13, and an increase in postoperative morbidity[10,12,14,15,17,18,23,24,52]. 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.[9] did not always result in clinically relevant changes to the expected postoperative course[17,23]. Some reports have demonstrated a temporal trend of serum amylase activity in the initial postoperative period[14,37,38]. 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[14]. 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[42].

The radiologic evidence

Apart from biochemical findings, the existence of PPAP has also been demonstrated through pancreatic parenchymal abnormalities observed on cross-sectional imaging[14,15,29,30,38]. Radiologic features of PPAP include but are not limited to interstitial parenchymal edema, peripancreatic fluid collections, and peripancreatic and parenchymal necrosis[14,15,31]. Thus, the classical features of PPAP involve changes in the 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[53]. 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[27–31]. When mentioned, the Modified CT Severity Index[54] for AP was the most frequently reported method[14,15,31]. 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[29], while another maintained that radiologic signs of PPAP (confirmed at pathology) could not be detected before POD 5[38]. Recent publications included in their analyses a wide timeframe[14] for the performance of CT and demonstrated rates twice as high as those that used a shorter interval[15]. 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[14]. All radiographic abnormalities consistent with PPAP were detected almost exclusively (99%[14]) in patients with serum amylase values greater than the upper limits of normal[14,15,31]; 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[25] on POD 1. Notably, 85% of this cohort showed a serum amylase activity >3-times the normal limits on POD 1[14].

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[11,20,38]. These patients indeed represent the most severe and rare scenarios of PPAP. 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[11,38].

The clinical evidence

Most series evaluating postoperative hyperamylasemia and PPAP showed an association of these conditions with increases in major postoperative morbidity[15,17,18,42], and some series have documented PPAP associated with a greater perioperative mortality[18,31]. Most studies analyzing biochemical and radiologic findings of PPAP focused on its correlation with POPF[6,10,14–18,32,55], and many have identified PPAP as an independent predictor of POPF[6,15–18,28]. 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% ($p < 0.05$)[6,10,14–18,32]. However, PPAP was also associated with an increased incidence of several postoperative complications other than POPF. These include post-pancreatectomy hemorrhage (PPH)[35], organ space infection/intra-abdominal abscess[22] formation, delayed gastric emptying (DGE)[55], 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[6,10,17,18,24]. Still, patients experiencing PPAP without POPF showed significantly increased rates of organ space infection/intra-abdominal abscess[18]. Others found PPAP being associated with delayed gastric emptying[42,56], while many studies did not report significant differences[17,18]. Few reports reported PPH amongst postoperative morbidity[6,16,18,31,43]. 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[16]. This latter category more often required surgical revision than patients with PPAP alone[16]. Reoperation is reported in 6% to 29% of cases of PPAP[6,10,14,16,18], with increased rates of completion pancreatectomy[11,16,31,38], and need for intensive care[18,31]. 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[42].

Distal (left-sided) pancreatectomy

The evidence of PPAP after distal pancreatectomy still is limited[17,23,31,32,42]. According to the best evidence acquired so far, PPAP has been reported as a severe but less frequent complication than after partial pancreatoduodenectomy[31]. A radiologically confirmed PPAP has been associated with increased overall morbidity, especially with severe pancreas-specific complications, but not increased mortality after left resections[31].

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[33]. Table 1 summarizes the main features of the PPAP diagnostic criteria. Figure 1 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.

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[54]. 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[33] 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/intraabdominal abscess[22], PPH[35], and POPF[33]. 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)[57,58], 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)[11,38]. 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[35] or grade C POPF[59]. This latter scenario is associated with the highest mortality rate.

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[4,6]. 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[14–16,20,26–28]. 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[14,18,24,31,32,42,42]. 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[60].

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[14,17,61]. 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[14,19]. This temporal trend in serum amylase activity appears even more striking in patients with radiologic features of PPAP[14,31]. 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[42]. 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[42].To date, most of the papers published on PPAP have taken into account serum amylase activity[6,14,15,17,18,31,32,42]. 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[11,24,62]. 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[17,23,31]. 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[9,15,61]. 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[63]. 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[20,64], and most assumptions are inferred from studies of AP[9,65]. 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[12,15,18,23,66,67]. Nevertheless, factors involved in the occurrence of the worst clinical scenarios are still unknown[45]. 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[18,61]. PPAP is frequently associated with early complications and rapidly evolving scenarios, especially in the most severe cases[42]. 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[38,42,68].

Indeed, PPAP may also lead to other local complications especially peripancreatic collections[18,23] and PPH[16]. All patients developing severe morbidity showed concurrent complications[69]. Similarly, rare but extreme cases of post-pancreatectomy necrotizing pancreatitis[11,14,31,38] 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)[70], mitigation strategies[71], and protocols for management of the drains[26,72] might eventually be re-designed in these patients[61,72,73]. 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[17,31,73]. 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[45]. 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[33–36].

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 [25,74]. The evidence acquired so far has adopted the Modified CT Severity Index[54] 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[14,15,31]. 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[25]. 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[68]. 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,[10,12,23,46] as well as other post-operative parameters[9], biochemical markers (e.g. CRP, serum lipase activity, UTRP2[12,24,37,66,75]), and specific radiologic scores, will undoubtedly lead to better clarity this entity.

REFERENCES

1. Bacchini I, Mantovani R, Viti M, et al. [Study of postoperative amylasemia. Its diagnostic value in postoperative acute pancreatitis (PAP)]. *Minerva Chir*. 1980;35:429–438.
2. Matsusue S, Takeda H, Nakamura Y, et al. A prospective analysis of the factors influencing pancreaticojejunostomy performed using a single method, in 100 consecutive pancreaticoduodenectomies. *Surg Today*. 1998;28:719–726.
3. Kelly TR, Troyer ML. Pancreatic Ducts and Postoperative Pancreatitis. *Arch Surg*. 1963;87:614–618.
4. Cloyd JM, Kastenberg ZJ, Visser BC, et al. Postoperative serum amylase predicts pancreatic fistula formation following pancreaticoduodenectomy. *J Gastrointest Surg*. 2014;18:348–353.
5. Okabayashi T, Kobayashi M, Nishimori I, et al. Risk factors, predictors and prevention of pancreatic fistula formation after pancreatoduodenectomy. *J Hepatobiliary Pancreat Surg*. 2007;14:557–563.
6. Palani Velu LK, Chandrabalan VV, Jabbar S, et al. Serum amylase on the night of surgery predicts clinically significant pancreatic fistula after pancreaticoduodenectomy. *HPB (Oxford)*. 2014;16:610–619.
7. Lermite E, Pessaux P, Brehant O, et al. Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. *J Am Coll Surg*. 2007;204:588–596.
8. El Nakeeb A, Salah T, Sultan A, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience). *World J Surg*. 2013;37:1405–1418.
9. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. *HPB (Oxford)*. 2016;18:642–651.
10. Chen H, Wang W, Ying X, et al. Predictive factors for postoperative pancreatitis after pancreaticoduodenectomy: A single-center retrospective analysis of 1465 patients. *Pancreatology*. 2020;20:211–216.
11. Globke B, Timmermann L, Klein F, et al. Postoperative acute necrotizing pancreatitis of the pancreatic remnant (POANP): a new definition of severe pancreatitis following pancreaticoduodenectomy. *HPB (Oxford)*. . Epub ahead of print August 17, 2019. DOI: 10.1016/j.hpb.2019.07.016.

12. Nahm CB, Brown KM, Townend PJ, et al. Acinar cell density at the pancreatic resection margin is associated with post-pancreatectomy pancreatitis and the development of postoperative pancreatic fistula. *HPB (Oxford)*. 2018;20:432–440.
13. Kühlbrey CM, Samiei N, Sick O, et al. Pancreatitis After Pancreatoduodenectomy Predicts Clinically Relevant Postoperative Pancreatic Fistula. *J Gastrointest Surg*. 2017;21:330–338.
14. Loos M, Strobel O, Dietrich M, et al. Hyperamylasemia and acute pancreatitis after pancreatoduodenectomy: Two different entities. *Surgery*. . Epub ahead of print September 25, 2020. DOI: 10.1016/j.surg.2020.07.050.
15. Partelli S, Tamburrino D, Andreasi V, et al. Implications of increased serum amylase after pancreaticoduodenectomy: toward a better definition of clinically relevant postoperative acute pancreatitis. *HPB (Oxford)*. . Epub ahead of print April 11, 2020. DOI: 10.1016/j.hpb.2020.03.010.
16. Zimmitti G, Langella S, Sega V, et al. Serum amylase elevation following pancreatoduodenectomy with pancreatogastrostomy is strongly associated with major complications. *ANZ J Surg*. . Epub ahead of print October 5, 2020. DOI: 10.1111/ans.16282.
17. Ikenaga N, Ohtsuka T, Nakata K, et al. Clinical significance of postoperative acute pancreatitis after pancreatoduodenectomy and distal pancreatectomy. *Surgery*. . Epub ahead of print September 4, 2020. DOI: 10.1016/j.surg.2020.06.040.
18. Bannone E, Andrianello S, Marchegiani G, et al. Postoperative Acute Pancreatitis Following Pancreaticoduodenectomy: A Determinant of Fistula Potentially Driven by the Intraoperative Fluid Management. *Ann Surg*. 2018;268:815–822.
19. Bannone E, Andrianello S, Marchegiani G, et al. Postoperative hyperamylasemia (POH) and acute pancreatitis after pancreatoduodenectomy (POAP): State of the art and systematic review. *Surgery*. . Epub ahead of print July 5, 2020. DOI: 10.1016/j.surg.2020.04.062.
20. Wüster C, Shi H, Kühlbrey CM, et al. Pancreatic Inflammation and Proenzyme Activation Are Associated With Clinically Relevant Postoperative Pancreatic Fistulas After Pancreas Resection. *Ann Surg*. 2020;272:863–870.
21. Bassi C, Dervenis C, Butturini G, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. 2005;138:8–13.
22. Borchardt RA, Tzizik D. Update on surgical site infections: The new CDC guidelines. *JAAPA*. 2018;31:52–54.
23. Andrianello S, Bannone E, Marchegiani G, et al. Characterization of postoperative acute pancreatitis (POAP) after distal pancreatectomy. *Surgery*. . Epub ahead of print October 23, 2020. DOI: 10.1016/j.surg.2020.09.008.
24. Birgin E, Reeg A, Téoule P, et al. Early postoperative pancreatitis following pancreaticoduodenectomy: what is clinically relevant postoperative pancreatitis? *HPB (Oxford)*. 2019;21:972–980.
25. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62:102–111.
26. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg*. 2010;252:207–214.
27. Molinari E, Bassi C, Salvia R, et al. Amylase value in drains after pancreatic resection as predictive factor of postoperative pancreatic fistula: results of a prospective study in 137 patients. *Ann Surg*. 2007;246:281–287.

28. Jin S, Shi X-J, Sun X-D, et al. The gastric/pancreatic amylase ratio predicts postoperative pancreatic fistula with high sensitivity and specificity. *Medicine (Baltimore)*. 2015;94:e339.

29. Räty S, Sand J, Lantto E, et al. Postoperative acute pancreatitis as a major determinant of postoperative delayed gastric emptying after pancreaticoduodenectomy. *J Gastrointest Surg*. 2006;10:1131–1139.

30. Bruno O, Brancatelli G, Sauvanet A, et al. Utility of CT in the diagnosis of pancreatic fistula after pancreaticoduodenectomy in patients with soft pancreas. *AJR Am J Roentgenol*. 2009;193:W175-180.

31. Loos M, Strobel O, Mehrabi A, et al. Postoperative acute pancreatitis is a serious but rare complication after distal pancreatectomy. *HPB*. . Epub ahead of print January 13, 2021. DOI: 10.1016/j.hpb.2021.01.004.

32. C. M. Kühlbrey, Samiei N, Sick O, et al. Pancreatitis After Pancreatoduodenectomy Predicts Clinically Relevant Postoperative Pancreatic Fistula. *J Gastrointest Surg*. 2017;21:330–338.

33. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. *Surgery*. 2017;161:584–591.

34. Besselink MG, van Rijssen LB, Bassi C, et al. Definition and classification of chyle leak after pancreatic operation: A consensus statement by the International Study Group on Pancreatic Surgery. *Surgery*. 2017;161:365–372.

35. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. *Surgery*. 2007;142:20–25.

36. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery*. 2007;142:761–768.

37. Räty S, Sand J, Nordback I. Detection of postoperative pancreatitis after pancreatic surgery by urine trypsinogen strip test. *Br J Surg*. 2007;94:64–69.

38. Rudis J, Ryska M. Pancreatic leakage and acute postoperative pancreatitis after proximal pancreatoduodenectomy. *Rozhl Chir*. 2014;93:380–385.

39. Jin S, Shi X-J, Wang S-Y, et al. Drainage fluid and serum amylase levels accurately predict development of postoperative pancreatic fistula. *World J Gastroenterol*. 2017;23:6357–6364.

40. Malleo G, Salvia R, Butturini G, et al. Is routine imaging necessary after pancreatic resection? An appraisal of postoperative ultrasonography for the detection of pancreatic fistula. *Pancreas*. 2014;43:319–323.

41. Okano K, Kakinoki K, Suto H, et al. Persisting ratio of total amylase output in drain fluid can predict postoperative clinical pancreatic fistula. *J Hepatobiliary Pancreat Sci*. 2011;18:815–820.

42. Bannone E, Marchegiani G, Balduzzi A, et al. Early and Sustained Elevation in Serum Pancreatic Amylase Activity: A Novel Predictor of Morbidity after Pancreatic Surgery. *Ann Surg*. . Epub ahead of print April 30, 2021. DOI: 10.1097/SLA.0000000000004921.

43. Yoo D, Park SY, Hwang DW, et al. Lack of Association between Postoperative Pancreatitis and Other Postoperative Complications Following Pancreaticoduodenectomy. *J Clin Med*.;10 . Epub ahead of print March 11, 2021. DOI: 10.3390/jcm10061179.

44. Pessaux P, Sauvanet A, Mariette C, et al. External pancreatic duct stent decreases pancreatic fistula rate after pancreaticoduodenectomy: prospective multicenter randomized trial. *Ann Surg*. 2011;253:879–885.

45. Zyromski NJ. Postpancreatectomy acute pancreatitis: Fact? Fiction? Functional definition and future. *Surgery*.;0 . Epub ahead of print November 23, 2020. DOI: 10.1016/j.surg.2020.10.023.

46. Andrianello S, Marchegiani G, Bannone E, et al. Clinical Implications of Intraoperative Fluid Therapy in Pancreatic Surgery. *J Gastrointest Surg*. . Epub ahead of print July 31, 2018. DOI: 10.1007/s11605-018-3887-6.

47. Svensson LG, Decker G, Kinsley RB. A prospective study of hyperamylasemia and pancreatitis after cardiopulmonary bypass. *Ann Thorac Surg*. 1985;39:409–411.

48. Feng F, Tan H, Li X, et al. Incidence and Risk Factors of Acute Pancreatitis After Scoliosis Surgery: A Prospective Study. *Spine (Phila Pa 1976)*. 2018;43:630–636.

49. Elgharably H, Gamaleldin M, Ayyat KS, et al. Serious Gastrointestinal Complications after Cardiac Surgery & Associated Mortality. *Ann Thorac Surg*. . Epub ahead of print November 17, 2020. DOI: 10.1016/j.athoracsur.2020.09.034.

50. Yen H-H, Ho T-W, Wu C-H, et al. Late acute pancreatitis after pancreaticoduodenectomy: incidence, outcome, and risk factors. *Journal of Hepato- Biliary-Pancreatic Sciences*. 2019;26:109–116.

51. Demirjian AN, Kent TS, Callery MP, et al. The inconsistent nature of symptomatic pancreatico-jejunostomy anastomotic strictures. *HPB*. 2010;12:482–487.

52. Chen CB, McCall NS, Pucci MJ, et al. The Combination of Pancreas Texture and Postoperative Serum Amylase in Predicting Pancreatic Fistula Risk. *Am Surg*. 2018;84:889–896.

53. Barreto G, D'Souza MA, Shukla PJ, et al. The gray zone between postpancreaticoduodenectomy collections and pancreatic fistula. *Pancreas*. 2008;37:422–425.

54. 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.

55. Winter JM, Cameron JL, Yeo CJ, et al. Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy. *J Am Coll Surg*. 2007;204:1029–1036; discussion 1037-1038.

56. Räty S, Sand J, Lantto E, et al. Postoperative acute pancreatitis as a major determinant of postoperative delayed gastric emptying after pancreaticoduodenectomy. *J Gastrointest Surg*. 2006;10:1131–1139.

57. Lambden S, Laterre PF, Levy MM, et al. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. *Crit Care*.;23 . Epub ahead of print November 27, 2019. DOI: 10.1186/s13054-019-2663-7.

58. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707–710.

59. Pulvirenti A, Marchegiani G, Pea A, et al. Clinical Implications of the 2016 International Study Group on Pancreatic Surgery Definition and Grading of Postoperative Pancreatic Fistula on 775 Consecutive Pancreatic Resections. *Ann Surg*. Epub ahead of print July 3, 2017. DOI: 10.1097/SLA.0000000000002362.

60. Hong W, Geng W, Chen B, et al. Predictors of acute pancreatitis with low elevation of serum amylase. *Therapeutics and Clinical Risk Management*. 2017;13:1577.

61. Andrianello S, Marchegiani G, Malleo G, et al. Pancreaticojejunostomy With Externalized Stent vs Pancreaticogastrostomy With Externalized Stent for Patients With High-Risk Pancreatic Anastomosis: A Single-Center, Phase 3, Randomized Clinical Trial. *JAMA Surg*. 2020;155:313–321.

62. Gasteiger S, Primavesi F, Göbel G, et al. Early Post-Operative Pancreatitis and Systemic Inflammatory Response Assessed by Serum Lipase and IL-6 Predict Pancreatic Fistula. *World J Surg*. 2020;44:4236–4244.

63. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. *Front Immunol*.;9 . Epub ahead of print April 13, 2018. DOI: 10.3389/fimmu.2018.00754.

64. Laaninen M, Bläuer M, Sand J, et al. Difference in Early Activation of NF-κB and MCP-1 in Acinar-Cell-Rich versus Fibrotic Human Pancreas Exposed to Surgical Trauma and Hypoxia. *Gastroenterol Res Pract*. 2014;2014:460363.

65. Cuthbertson CM, Christophi C. Disturbances of the microcirculation in acute pancreatitis. *Br J Surg*. 2006;93:518–530.

66. Laaninen M, Bläuer M, Vasama K, et al. The risk for immediate postoperative complications after pancreaticoduodenectomy is increased by high frequency of acinar cells and decreased by prevalent fibrosis of the cut edge of pancreas. *Pancreas*. 2012;41:957–961.

67. Partelli S, Andreasi V, Schiavo Lena M, et al. The role of acinar content at pancreatic resection margin in the development of postoperative pancreatic fistula and acute pancreatitis after pancreaticoduodenectomy. *Surgery*. . Epub ahead of print April 28, 2021. DOI: 10.1016/j.surg.2021.03.047.

68. Shrikhande SV. Invited commentary: Evolving landscape of postoperative hyperamylasemia, postoperative acute pancreatitis, and postoperative pancreatic fistula: Time for a unifying definition. *Surgery*. 2021;169:740–741.

69. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.

70. Lassen K, Coolsen MME, Slim K, et al. Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced Recovery After Surgery (ERAS®) Society recommendations. *Clin Nutr*. 2012;31:817–830.

71. Laukkarinen J. Commentary on: Postoperative acute pancreatitis. *Surgery*. 2021;169:742–743.

72. Salvia R, Marchegiani G, Andrianello S, et al. Redefining the Role of Drain Amylase Value for a Risk-Based Drain Management after Pancreaticoduodenectomy: Early Drain Removal Still Is Beneficial. *J Gastrointest Surg*. . Epub ahead of print June 3, 2020. DOI: 10.1007/s11605-020-04658-8.

73. Andrianello S, Marchegiani G, Balduzzi A, et al. Pros and pitfalls of externalized transanastomotic stent as a mitigation strategy of POPF: a prospective risk-stratified observational series. *HPB (Oxford)*. . Epub ahead of print November 19, 2020. DOI: 10.1016/j.hpb.2020.10.025.

74. Bradley EL. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg*. 1993;128:586–590.

75. Uemura K, Murakami Y, Hayashidani Y, et al. Randomized clinical trial to assess the efficacy of ulinastatin for postoperative pancreatitis following pancreaticoduodenectomy. *J Surg Oncol*. 2008;98:309–313.

TABLES

	Biochemical features	**Radiologic features*54**	**Grade**	**Clinical Impact**
PPAP Post pancreatectomy acute pancreatitis	Sustained (that persists for 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.

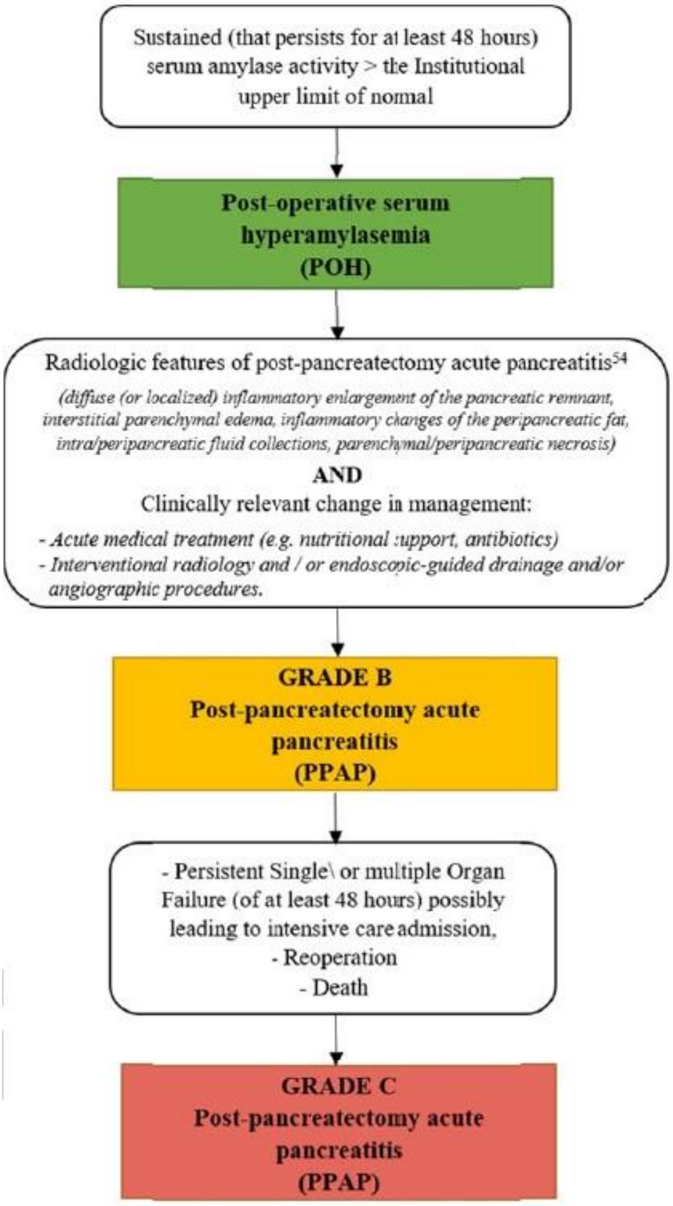
#future studies may validate the importance of serum lipase.

*: 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.

54. 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

FIGURES

Figure 1 – Flow chat for POH and PPAP grade definition. (Abbreviations: POH, postoperative serum hyperamylasemia, PPAP, post-pancreatectomy acute pancreatitis. 54 MOrtele KJ et al AJR Am J Roientgenol 2004; 183:1261 – 1265.


Sustained (that persists for at least 48 hours) serum amylase activity > the Institutional upper limit of normal
Post-operative serum hyperamylasemia (POH)
Radiologic features of post-pancreatectomy acute pancreatitis[54]
(diffuse (or localized) inflammatory enlargement of the pancreatic remnant, interstitial parenchymal edema, inflammatory changes of the peripancreatic fat, intra/peripancreatic fluid collections, parenchymal/peripancreatic necrosis)
AND
Clinically relevant change in management:
- Acute medical treatment (e.g. nutritional support, antibiotics)
- Interventional radiology and / or endoscopic-guided drainage and/or angiographic procedures.
GRADE B Post-pancreatectomy acute pancreatitis (PPAP)
- Persistent Single\ or multiple Organ Failure (of at least 48 hours) possibly leading to intensive care admission,
- Reoperation
- Death
GRADE C Post-pancreatectomy acute pancreatitis (PPAP)