Prediction and consequences of postoperative pancreatitis after pancreaticoduodenectomy

Akseli Bonsdorff1, Ilkka Helanterä2, Timo Tarvainen1, Jukka Sirén1, Arto Kokkola1 and Ville Sallinen1,2,*

1Gastroenterological Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
2Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland
*Correspondence to: Ville Sallinen, Gastroenterological Surgery/Transplantation and Liver Surgery, Helsinki University Hospital and University of Helsinki, Haartmaninkatu 4, 00029 Helsinki, Finland (e-mail: ville.sallinen@helsinki.fi)

Abstract

**Background:** Recent studies have suggested postoperative acute pancreatitis (POAP) as a serious complication after pancreaticoduodenectomy (PD) and have speculated on its possible role in the pathogenesis of postoperative pancreatic fistula (POPF).

This study aimed to assess the impact of POAP on post-PD outcomes and fistula risk score (FRS) performance in predicting POAP.

**Methods:** All PDs at Helsinki University Hospital between 2013 and 2020 were analysed. POAP was defined as a plasma amylase activity greater than the normal upper limit on postoperative day (POD) 1 and stratified as clinically relevant (CR)-POAP once C-reactive protein (CRP) reached or exceeded 180 mg/l, and non-CR-POAP once CRP was less than 180 mg/l on POD 2. The Comprehensive Complication Index (CCI) was used to assess total postoperative morbidity. Different FRSs were assessed using receiver operating characteristic curves.

**Results:** Of the 508 patients included, POAP occurred in 202 (39.8 per cent) patients, of whom 91 (17.9 per cent) had CR-POAP. The incidence of CR-POPF was 12.6 per cent (64 patients). Patients with non-CR-POAP had a similar morbidity to patients with no POAP (median CCI score 22.6; 24.2; P = 0.142), while CCI score was significantly higher (37.2) in patients with CR-POAP (P < 0.001). CR-POAP was associated with increased rates of CR-POPF, delayed gastric emptying, haemorrhage, and bile leak, while non-CR-POAP was associated only with CR-POPF. Ninety-day mortality was 1.6 per cent, 0.9 per cent, and 3.3 per cent in patients with no-POAP, non-CR-POAP, and CR-POAP, respectively. Updated alternative FRS showed the best performance in predicting CR-POAP (area under the curve 0.834).

**Conclusion:** CR-POAP was associated with a higher CCI score, suggesting CR-POAP as a distinct entity from non-CR-POAP. FRSs can be used to assess the risk of CR-POAP.

Introduction

Postoperative acute pancreatitis (POAP) after pancreaticoduodenectomy (PD) has recently been a topic of eager discussion among pancreatic surgeons. Characterized by postoperative plasma hyperamylasaemia, POAP is considered the manifestation of an acute inflammatory process of the pancreatic remnant, possibly due to local hypoperfusion or pancreatic microtrauma during the surgical procedure. POAP has been speculated to have a detrimental effect on the healing of pancreatic anastomosis, potentially triggering more severe morbidity, including the pathogenesis of postoperative pancreatic fistula (POPF).

While some studies confirmed the association of POAP with worse postoperative outcomes, the lack of a uniform definition has prevented POAP from being demonstrated as a specific postoperative complication rather than just a biochemical manifestation of POPF. Connor’s definition for POAP is the most widely used and considers a cutoff for serum pancreatic enzymes greater than the upper limit of normal eventually combined with an increase in C-reactive protein (CRP) to characterize clinically relevant (CR)-POAP. The threshold for plasma enzymes of revised Atlanta criteria has also been used in the recent literature, as some studies have questioned Connor’s definition for including many patients without clinical signs of pancreatitis, thereby losing specificity. However, most have primarily focused on POAP, while CR-POAP, potentially with higher specificity, has been less thoroughly investigated.

Preoperative risk scores, such as Fistula Risk Score (FRS), have been formulated for predicting CR-POPF but never assessed for POAP prediction. Single studies have demonstrated non-dilated main pancreatic duct and high acinar cell density at the resection line to be significant risk factors for POPF, and Partelli et al. have shown that FRS correlates positively with acinar cell density.

This study aimed to validate the effect of CR-POAP on postoperative outcomes after PD by applying the Comprehensive Complication Index (CCI) to compare individual outcomes. In addition, CR-POAP risk factors were investigated to assess the ability of previously validated risk scores to predict the occurrence of CR-POAP.

Methods

**Patient inclusion and data collection**

This study was approved by our institutional research committee (Helsinki University Hospital/115/2020). Data from all patients undergoing PD from 1 January 2013 to 30 October 2020 were...
retrospectively collected and analysed. All procedures were carried out at the Helsinki University Hospital, an academic teaching hospital functioning as a secondary and tertiary referral centre. Collected data included demographics, operative details, postoperative data, tumour histology, and follow-up. The last date of follow-up was defined as any contact with health care. Preoperative comorbidities were recorded and rated according to the Charlson Comorbidity Index19.

Operative details
Both Whipple and pylorus-preserving PDs were included in the study. Pancreasticojejunostomy was performed in a duct-to-mucosa fashion with two-layered anastomosis in all patients. Two intra-abdominal passive 24 Fr drains were always placed, and drain removal was based on low output and drain fluid amylase activity at postoperative days (POD) 1 to 3. The perioperative administration of somatostatin analogue, mainly pasireotide, up to POD 6 was used selectively for patients with a high-risk pancreas (soft texture and non-dilated main pancreatic duct). In addition, some of the patients were included between 2016 and 2018 in a randomized controlled trial comparing perioperative hydrocortisone to pasireotide20.

Postoperative data
All postoperative complications up to POD 30 were collected and classified according to the Clavien-Dindo classification (CD)21. Cumulative postoperative morbidity was assessed using the CD-based CCI18. PD-specific complications, including POPF22, postpancreatectomy haemorrhage23, delayed gastric emptying24, chyle leak25, and bile leak26, were defined according to the International Study Group for Pancreatic Surgery (ISGPS) and the International Study Group of Liver Surgery guidelines. Length of stay was defined as the POD on which patient was discharged after the index operation. Readmission was defined as a new hospital admission before POD 30. Mortality was considered to be postoperative if occurring before POD 90. A CCI score of 33.7 or more (which equals the total cumulative morbidity of one reoperation under general anaesthesia) was used to define patients with high postoperative morbidity, and a CCI score less than 12.3 (which results from two CD I complications) was used to define patients with low morbidity.

Laboratory variables included plasma amylase, drain fluid amylase, and plasma CRP. Owing to the lack of a widely accepted definition for POAP, Connor’s definition of plasma amylase activity greater than the upper limit of normal (ULN) was applied, and a POD2 CRP level of 180 mg/l or greater was used for defining CR-POAP1. Owing to the mutual inclusivity of POAP and CR-POAP, different FRS were applied. The original FRS27, alternative-FRS14, and updated alternative-FRS15 were included. According to pancreatic texture, tumour histology, main pancreatic duct diameter, and intraoperative blood loss, FRS rates patients on a scale from 0 to 10, where higher grades represent higher risks for POPF. The alternative-FRS considers the pancreatic texture, main pancreatic duct diameter, and BMI, while the Updated alternative-FRS adds the effect of sex to the alternative-FRS. Also, a recent risk stratification matrix for POPF, based solely on pancreatic texture and main pancreatic duct diameter, from ISGPS was included for validation and POAP risk assessment28.

Statistics
Continuous variables are reported as median and interquartile range (i.q.r.), and categorical variables as frequencies and proportions (per cent). Differences between continuous variables were assessed using the Mann–Whitney U test; for categorical variables, differences were assessed using Fisher’s exact test or the χ² test. Receiver operating characteristic (ROC) curves were used to analyse the association of FRS and the occurrence of CR-POAP and CR-POPF, and the association of plasma amylase values and morbidity. Logistic binary regression was performed to assess the potential risk factors for CR-POAP. Fisher’s exact test was used to assess associations in univariable analysis. An unadjusted two-sided P value of less than 0.10 was required for inclusion in the multivariable analysis, and a two-sided P value of less than 0.05 in multivariable analysis was used to identify independent risk factors. In general, a two-sided P value of less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS 27.0 software (SPSS 27.0 for Macintosh, IBM, Armonk, NY, USA).

Results
Patient demographics
A total of 614 patients underwent PD during the study period. After excluding patients with missing POD 1 plasma amylase and POD 2 CRP values, a total of 508 (82.7 per cent) patients were included in the analyses. Basic demographics are reported in Table 1.

Incidence and outcomes of POAP and CR-POAP
Different cutoffs were investigated for POD1 plasma amylase in predicting CR-POPF and a CCI-score of 33.7 or more. The area under the curve (AUC) value for POD 1 plasma amylase was 0.86 for predicting CR-POPF and 0.65 for a CCI of 33.7 or more. Connor’s POAP had AUC values of 0.79 for CR-POPF and 0.61 for a CCI of 33.7 or more. A cutoff of 1.5 times the ULN for plasma amylase performed the best with AUC values of 0.80 and 0.62. Given the slightest difference from Connor’s cutoff, further analyses maintained Connor’s definition (Fig. S1).

POAP occurred in 202 (39.8 per cent) patients: 91 with CR-POAP (17.9 per cent, or 45.0 per cent of patients with POPF) and 111 with non-CR-POAP (21.9 per cent, or 55.0 per cent of patients with POAP). CR-POPF occurred in 64 (12.6 per cent) patients. The median CCI score of the whole cohort was 24.2 (i.q.r. 15.0 to 34.6).

Postoperative outcomes stratified by the occurrence of CR-POAP are reported in Table 2. CCI score was significantly higher in patients with CR-POAP compared with non-CR-POAP (37.2 versus 24.2; P < 0.001) or no-POAP patients (37.2 versus 22.6; P < 0.001). No difference in CCI score was highlighted between non-CR-POAP and no-POAP groups (24.2 versus 22.6; P = 0.142). All clinically relevant complications—except for chyle leak—occurred significantly more in patients with CR-POAP than those with non-CR-POAP or no-POAP (Table 2). Only six (6.6 per cent) patients with CR-POAP had a low postoperative morbidity (CCI score < 12.3) (Table 2). The rate of POPF (any grade) and CR-POPF progressively increased from no-POAP patients to the non-CR-POAP and up to the CR-POAP group: 6.2 per cent versus...
Table 1 Patient demographics, perioperative data, and pathology of 508 patients undergoing pancreaticoduodenectomy

| n (%) or median (i.q.r.) |
|-------------------------|
| Age (years)             | 68 (61–73) |
| Sex ratio (M : F)       | 277 : 231 (54.5 : 45.5) |
| BMI (kg/m²)             | 25.5 (23.0–28.1) |
| Charlson Comorbidity -index | 2 (2–3) |
| Comorbidities           |            |
| MI                      | 35 (6.9) |
| CHF                     | 24 (4.7) |
| Peripheral vascular disease | 30 (5.9) |
| CVA or TIA              | 25 (4.9) |
| Hemiplegia              | 1 (0.2) |
| Dementia                | 5 (1.0) |
| COPD                    | 68 (13.4) |
| Connective tissue disease | 14 (2.8) |
| Peptic ulcer disease    | 5 (1.0) |
| DM without end-organ complications | 122 (24.0) |
| DM with end-organ complications | 6 (1.2) |
| Moderate-to-severe CKD  | 15 (3.0) |
| Liver disease           | 7 (1.4) |
| Leukaemia               | 2 (0.4) |
| Lymphoma                | 6 (1.2) |
| Preoperative medication |            |
| Anticoagulation         | 61 (12.0) |
| Immunosuppression       | 9 (1.8) |
| Corticosteroid          | 26 (5.1) |
| Preoperative ERCP      | 368 (72.4) |
| Neoadjuvant therapy     | 106 (20.9) |
| Venous resection        | 126 (24.8) |
| Arterial resection      | 15 (3.0) |
| Pancreatic texture      |            |
| Soft                    | 259 (51.0) |
| Non-soft                | 249 (49.0) |
| Main pancreatic duct diameter (mm)* | 265 (52.2) |
| >3                      |            |
| ≤3                      | 242 (47.8) |
| Estimated blood loss (ml) | 650 (400–1100) |
| Pathology               |            |
| PDAC                    | 269 (53.0) |
| Ampullary adenocarcinoma | 52 (10.2) |
| Cholangiocarcinoma      | 46 (9.1) |
| Neuroendocrine tumour   | 22 (4.3) |
| IPMN                    | 21 (4.1) |
| Duodenal adenocarcinoma | 16 (3.1) |
| Other                   | 82 (16.1) |

*Data not available on all patients: BMI available in 507/508 patients; main pancreatic duct diameter available in 507/508 patients. i.q.r., interquartile range; M, male; F, female; MI, myocardial infarction; CHF, congestive heart failure; CVA, cerebrovascular accident; TIA, transient ischaemic attack; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CKD, chronic kidney disease; ERCP, endoscopic retrograde cholangiopancreatography; PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal papillary mucinous neoplasm.

CR-POAP had a 39.1 per cent PPV, 79.7 per cent accuracy in predicting a CCI of 33.7 or more, and 63.6 per cent accuracy in predicting a CCI of 33.7 or more, and 28.7 per cent PPV, 98.0 per cent NPV, 90.7 per cent sensitivity, 67.6 per cent specificity, and 70.5 per cent accuracy in predicting CR-POPF.

In patients with an elevated POD 2 CRP, the possible increased value of POAP diagnosis in predicting morbidity is reported in Table 3. CCI score was significantly higher in patients with CR-POAP compared with patients with no POAP but a CRP of 180 or more on POD2 (n = 75; CCI 37.2 versus 29.6 (P < 0.001)). The PPV of an exclusively elevated CRP on POD 2 in predicting a CCI of 33.7 or more was 27.0 per cent versus 61.5 per cent of CR-POAP. Multivariable analysis on predictors of a CCI of 33.7 or more identified CR-POAP (odds ratio (o.r.) 2.9, 95 per cent confidence interval (c.i.) 1.57 to 5.35), CR-POPF (o.r. 3.81, 95 per cent c.i. 1.93 to 7.55), and BMI (o.r. 1.07 per unit of increase, 95 per cent c.i. 1.02 to 1.13) as independent risk factors of high postoperative morbidity (Table S1).

**Prediction of CR-POAP**

Uni- and multivariable analyses investigating predictors of CR-POAP are reported in Table 4. In a multivariable model, male sex (o.r. 2.47), soft pancreatic texture (o.r. 7.11), BMI (o.r. 1.14 for one unit increase), and main pancreatic duct diameter (o.r. 0.78 for one unit increase) were deemed independent risk factors for CR-POAP. A model containing all the independent risk factors had an AUC value of 0.866 (95 per cent c.i. 0.830 to 0.902) in predicting CR-POAP.

ROC curves assessing the diagnostic performance of different FRS for predicting CR-POPF are displayed in Fig. 1. The updated alternative-FRS showed the highest AUC value (0.819), followed by the alternative-FRS (0.805), the novel ISGPS POPF risk stratification (0.787), and the original FRS (0.763).

Similar curves were plotted for predicting CR-POAP and are reported in Fig. 2. All risk scores performed better in predicting CR-POAP than CR-POPF. The updated alternative-FRS showed the best performance in predicting CR-POAP, with the highest AUC value of 0.834.

**Discussion**

CR-POAP carries serious risks for subsequent morbidity, as it has been associated with significantly more cumulative postoperative complications than non-CR-POAP or no POAP at all. These translate into a longer initial hospital stay, while patients with non-CR-POAP had a similar length of stay than those with no POAP. Multivariable analysis determined CR-POAP to be an independent risk factor for high postoperative morbidity (CCI 33.7 or more), regardless of the occurrence of CR-POPF.

Interestingly, previously established risk scores for CR-POPF seemed to predict CR-POAP with even higher accuracy. The updated alternative-FRS, which considers pancreatic texture, main pancreatic duct diameter, sex, and BMI, showed the best performance in predicting CR-POAP.

POAP is still a controversial topic. The lack of a validated uniform definition and variability in metrics between previous studies have limited the production of high-quality evidence and meta-analyses. For these reasons, this study focused on finding and validating risk factors for POAP defined according to the most frequently applied definition proposed by Connor. A considerable limitation of Connor’s definition is the low specificity for detecting complicated postoperative courses. The occurrence of Connor’s POAP has been reported to be high, ranging from 39.8 per cent in this study cohort to as high as 64 per cent.
confirming that POAP frequently occurs after PD, and a proportion of patients do not evolve towards more severe clinical states.

An elevation of CRP over 180 mg/l on POD 2 was therefore included to characterize clinically relevant POAP with significantly better PPV, specificity, and accuracy than Connor’s POAP in predicting complications. The clinical relevance of POAP based on alterations in the clinical course, mirroring the ISGPF classification of CR-POPF, was also proposed, but an early biochemical alteration in inflammatory markers may be crucial for risk stratification already on POD 2. CR-POAP seems to identify patients at high risk for further morbidity, who could be the target of therapeutic strategies, such as continuing pasireotide administration and maintaining intra-abdominal drains.

Most of the previous studies have focused mainly on the incidence and outcomes of POAP, while the few evaluating CR-POAP applied inconsistent definitions. Loos et al. reported that a POD 2 CRP value greater than 135 mg/l along with a POD1 plasma amylase value of three times the ULN was predictive of postoperative pancreatitis verified at CT. Instead of a POD 2 assessment as proposed by Connor, Ikenaga et al. used POD3 CRP values to define CR-POAP, showing its association with postoperative complications, especially CR-POPF.

### Table 3 The increased value of postoperative acute pancreatitis (POAP) diagnosis on patients with postoperative day (POD) 2 C-reactive protein (CRP) of 180 mg/l or higher

| POD 2 CRP ≥ 180 mg/l | CR-POAP (n = 91) | P value |
|----------------------|------------------|--------|
| Normal amylase (n = 75) | 29.6 (20.9–37.2) | 37.2 (30.8–47.6) | <0.001 |
| Drain fluid amylase (U/l) | 48 (16–190) | 1300 (390–3300) | <0.001 |
| Length of stay (days) | 11 (8–14) | 13 (9–18) | 0.005 |
| CCI score ≥ 33.7 | 20 (27.0) | 56 (61.5) | <0.001 |
| POPF, grades BL, B, and C | 13 (17.3) | 70 (76.9) | <0.001 |
| CR-POPF | 4 (5.3) | 46 (50.5) | <0.001 |

Data are median (interquartile range) or n (%). *Equals the total cumulative morbidity of one reoperation under general anaesthesia (i.e. equal to high postoperative morbidity). †Equals the total cumulative morbidity of two Clavien-Dindo I complications (i.e. equal to low postoperative morbidity).
The FRS was established in 2013 to predict CR-POPF, and updated versions have been published and validated since then. The updated alternative FRS is the most recent and achieved the best prediction of CR-POPF in this study. Interestingly, all the risk scores predicted CR-POAP better than CR-POPF, including the updated alternative FRS, which showed the best predicting performance for CR-POAP. As the risk factors of CR-POAP and CR-POPF overlap, we can speculate that these two entities eventually share the same origin. Whether it is pancreatitis that precedes fistula or a currently unknown entity that precedes them both cannot be inferred from this study. However, well-established FRS can be used to predict CR-POAP accurately, without the need for additional specific risk scores.

The present study has some limitations in addition to its observational nature. Data on plasma amylase and CRP levels were missing in approximately 15 per cent of patients, and were consequently excluded from analyses, questioning whether the final cohort reflects the entire population. In addition, it might

### Table 4 Results of univariable and multivariable analyses on predictors for clinically relevant postoperative acute pancreatitis (CR-POAP) in 508 patients undergoing pancreaticoduodenectomy

| Continuous variables | Univariable analysis of risk factors for CR-POAP | Multivariable analysis of risk factors for CR-POAP |
|----------------------|-----------------------------------------------|-----------------------------------------------|
|                      | CR-POAP (n = 91) | No CR-POAP (n = 417) | P value | 95% c.i. | P value |
| Age (years)          | 67 (58–74)      | 66 (61–73)          | 0.498   |          |        |
| BMI (kg/m²)          | 26.93 (24.90–29.64) | 25.24 (22.53–27.47) | < 0.001 | 1.14    | 1.07–1.22 < 0.001 |
|                      | Unit of increase: 1 kg/m² |
| Charlson index       | 3 (2–4)         | 2 (2–3)            | 0.224   |          |        |
| Estimated blood loss (ml) | 600 (450–1000) | 700 (400–1200)     | 0.573   |          |        |
| Main pancreatic duct diameter (mm) | 2 (2–3)     | 4 (3–6)            | < 0.001 | 0.78    | 0.66–0.93 0.006 |
|                      | Unit of increase: 1 mm |
| Categorical variables |                                            |                                            |
| Sex                  | Male 63 (69.2)  | 214 (51.3)         | 0.002   | 2.47    | 1.37–4.43 0.003 |
|                      | Female 28 (30.8) | 203 (48.7)         | Ref.    |          |        |
| Neoadjuvant therapy  | 6 (6.6)         | 100 (24.0)        | < 0.001 | 0.65    | 0.23–1.82 0.414 |
| Preoperative ERCP    | 60 (65.9)       | 308 (74.0)        | 0.121   |          |        |
| Venous resection     | 7 (7.7)         | 119 (28.5)        | < 0.001 | 2.28    | 0.88–5.91 0.091 |
| Soft pancreatic texture | 85 (93.4)   | 174 (41.7)        | < 0.001 | 7.11    | 2.70–18.71 < 0.001 |
| Tumour histology     | PDAC 21 (23.1)  | 248 (59.8)        | < 0.001 | 1.03    | 0.39–2.70 0.954 |
|                      | IPMN or MCN 5 (5.5) | 30 (7.2)        | 0.655   |          |        |
| Extrapancreatic malignancies | 39 (42.9) | 75 (45.3)        | < 0.001 | 2.31    | 0.93–5.73 0.071 |
| Other                | 22 (24.1)       | 46 (11.0)         | < 0.001 | 1.85    | 0.69–4.95 0.223 |
|                      |                 |                   |         |         |        |

Data are median (interquartile range) or n (%). o.r., odds ratio; c.i., confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; PDAC, pancreatic ductal adenocarcinoma; IPMN, intraductal mucinous papillary neoplasm; MCN, mucinous cystic neoplasm; NET, neuroendocrine tumour; CA, carcinoma.

The FRS was established in 2013 to predict CR-POPF, and updated versions have been published and validated since then. The updated alternative FRS is the most recent and achieved the best prediction of CR-POPF in this study. Interestingly, all the risk scores predicted CR-POAP better than CR-POPF, including the updated alternative FRS, which showed the best predicting performance for CR-POAP. As the risk factors of CR-POAP and CR-POPF overlap, we can speculate that these two entities eventually share the same origin. Whether it is pancreatitis that precedes fistula or a currently unknown entity that precedes them both cannot be inferred from this study. However, well-established FRS can be used to predict CR-POAP accurately, without the need for additional specific risk scores.

The present study has some limitations in addition to its observational nature. Data on plasma amylase and CRP levels were missing in approximately 15 per cent of patients, and were consequently excluded from analyses, questioning whether the final cohort reflects the entire population. In addition, it might
be argued that defining CR-POAP with CRP levels is disingenuous as such an increase may result from the expected inflammatory process. However, POD 2 is early enough to have reasonable clinical applicability as most severe complications occur later in the postoperative period. Postoperative CT would have been of high utility in confirming the diagnosis of POAP, but as radiological imaging is performed only when deemed necessary, a large proportion of this cohort had not undergone a postoperative CT. Owing to the retrospective nature of the study, misclassification bias during the collection and classification of complications is possible.

A recent consensus definition for post-pancreatectomy acute pancreatitis was released by the ISGPS. Postoperative pancreatitis is defined as an acute inflammatory condition of the pancreatic remnant and the diagnosis is based on sustained elevation in plasma amylase levels (at least 48 hours postoperatively) with associated alterations in clinical course, and radiological alterations, such as parenchymal oedema or peripancreatic fluid collections. As stated previously, the lack of radiological images for many of the patients in this study cohort make it impossible to validate the new definition. This study points out that the inclusion of CRP in the new definition could be of use. Future studies might use CR-POAP as an outcome or investigate the inclusion of CRP in the newly proposed definition. CR-POAP shares most of the risk factors associated with CR-POPF, and, as an independent complication, CR-POAP may promote its onset. The updated alternative-FRS can be used to predict CR-POAP accurately.

**Supplementary material**

Supplementary material is available at BJS Open online.

**References**

1. Connor S. Defining post-operative pancreatitis as a new pancreatic specific complication following pancreatic resection. *HPB* 2016;18:642–651.
2. Bannone E, Andrianello S, Marchegiani G, Masini G, Malleo G, Bassi C et al. Postoperative acute pancreatitis following pancreaticoduodenectomy: a determinant of fistula potentially driven by the intraoperative fluid management. *Ann Surg* 2018;268:815–822.
3. Nahm CB, Brown KM, Townend PJ, Colvin E, Howell VM, Gill AJ 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;20:432–440.
4. Kühbrey CM, Samiei N, Sick O, Makowiec F, Hopt UT, Wittel UA. Pancreatitis after pancreateoduodenectomy predicts clinically relevant postoperative pancreatic fistula. *J Gastrointest Surg* 2017;21:330–338.
5. Bannone E, Andrianello S, Marchegiani G, Malleo G, Paiella S, Salvia R et al. Postoperative hyperamylasemia (POH) and acute pancreatitis after pancreatectoduodenectomy (POAP): state of the art and systematic review. *Surgery* 2021;169:377–387.
6. 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 pancreatectoduodenectomy. *Br J Surg* 2016;103:553–563.
7. Cloyd JM, Kastenberg ZJ, Visser BC, Poultsides GA, Norton JA. Postoperative serum amylase predicts pancreatic fistula formation following pancreatectoduodenectomy. *J Gastroint Surg* 2014;18:348–353.
8. Gasteiger S, Prirnaves F, Göbel G, Braunwarth E, Cardini B, Maglione M 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.

---

**Funding**

Academy of Finland, Finska Läkarësällskapet and Helsinki University Hospital research funds.

**Disclosure.** The authors declare no conflict of interest.

**Data availability statement**

Collected data will not be made available as the study permissions do not permit the sharing of individual patient data.
9. Ikenaga N, Ohtsuka T, Nakata K, Watanabe Y, Mori Y, Nakamura M. Clinical significance of postoperative acute pancreatitis after pancreaticoduodenectomy and distal pancreatectomy. Surgery 2021;169:732–737.

10. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102–111.

11. Loos M, Strobel O, Dietrich M, Mehrabi A, Ramouz A, Al-saeedi M et al. Hyperamylasemia and acute pancreatitis after pancreaticoduodenectomy: two different entities. Surgery 2021; 169:369–376.

12. Partelli S, Tamburrino D, Andreasi V, Mazzocato S, Crippa S, Perretti E et al. Implications of increased serum amylase after pancreaticoduodenectomy: toward a better definition of clinically relevant postoperative acute pancreatitis. HPB 2020; 22:1645–1653.

13. Miller BC, Christe JD, Behrman SW, Callery MP, Drebbin JA, Kent TS et al. Assessing the impact of a fistula after a pancreaticoduodenectomy using the post-operative morbidity index. HPB 2013; 15:781–788.

14. Mungroop TH, Van Rijsen LB, Van Klaveren D, Smits FJ, Van Woerden V, Linnemann RJ et al. Alternative fistula risk score for pancreaticoduodenectomy (a-FRS): design and international external validation. Ann Surg 2019;269:937–943.

15. Mungroop TH, Klompmaker S, Wellner UF, Steyerberg EW, Coratti A, D’Hondt M et al. Updated alternative fistula risk score (ua-FRS) to include minimally invasive pancreaticoduodenectomy: pan-European validation. Ann Surg 2021;273:334–340.

16. Partelli S, Tamburrino D, Crippa S, Facci E, Zardini C, Falconi M. Evaluation of a predictive model for pancreatic fistula based on amylase value in drains after pancreatic resection. Am J Surg 2014;208:634–639.

17. Chen H, Wang W, Ying X, Deng X, Peng C, Cheng D et al. Predictive factors for postoperative pancreatitis after pancreaticoduodenectomy: a single-center retrospective analysis of 1465 patients: predictors of postoperative pancreatitis. Pancreatology 2020;20:211–216.

18. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1–7.

19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic variables in longitudinal studies: development. J Chronic Dis 1987;40:373–383.

20. Tarvainen T, Sirén J, Kokkolaa A, Salinen V. Effect of hydrocortisone vs pasireotide on pancreatic surgery complications in patients with high risk of pancreatic fistula: a randomized clinical trial. JAMA Surg 2020;155:291–298.

21. Dindo D, Demartines N, Clavien PA. 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.

22. Bassi C, Marchegiani G, Dervenis C, Sarr M, Abu Hilal M, Adham M 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, Veit JA, Bassi C, Dervenis C, Fingerhut A, Gouma DJ et al. Postpancreatectomy hemorrhage (PPH)—an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20–25.

24. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR 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.

25. Besselink MG, van Rijsen LB, Bassi C, Dervenis C, Montorsi M, Adham M 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. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149:680–688.

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

28. Schuh F, Mihaljevic AL, Probst P, Trudeau MT, Muller PC, Marchegiani G et al. A simple classification of pancreatic duct size and texture predicts postoperative pancreatic fistula: a classification of the International Study Group of Pancreatic Surgery (ISGPS). Ann Surg 2021. [Epub ahead of print].

29. Birgin E, Reeg A, Teoule P, Rahbari NN, Post S, Reissfelder C et al. Early postoperative pancreatitis following pancreaticoduodenectomy: what is clinically relevant postoperative pancreatitis? HPB 2019;21:972–980.

30. Marchegiani G, Barreto SG, Bannone E, Sarr M, Vollmer CM, Connor S et al. Postpancreatectomy acute pancreatitis (PPAP): definition and grading from the International Study Group for Pancreatic Surgery (ISGPS). Ann Surg 2021; DOI: 10.1097/SLA.0000000000005226 [Epub ahead of print].