



Original research

Can early serum lipase measurement be routinely implemented to rule out clinically significant pancreatic fistula after pancreaticoduodenectomy?



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ABSTRACT

Introduction: Postoperative pancreatic fistula (POPF) is the most significant cause of morbidity and mortality after pancreaticoduodenectomy (PD). We evaluated the role of postoperative serum lipase concentration in ruling out POPF in the immediate post-operative period.

Materials and methods: We retrospectively analysed 98 consecutive PD performed between January 2009 and December 2014, investigating the correlation between postoperative day 1 (POD1) serum lipase concentration and POPF development.

Results: 29 patients (29.5%) developed POPF [grade A, 17 (17.3%); grade B, 8 (8.1%); grade C, 4 (4%)]. A receiver operating characteristic (ROC) analysis was conducted to determine the threshold value of POD1 serum lipase associated with clinically significant POPF (AUC = 0.76, 95% CI 0.64–0.86, P = 0.01). Such threshold was ≤ 44.5 U/L and its sensitivity and specificity were 92% and 66%, respectively. The positive and negative predictive values (PPV, NPV) were 31% and 98%, respectively.

Conclusion: Early routinely measurement of serum lipase proved to be helpful in ruling out clinically relevant POPF (CR-POPF). In our cohort, a POD1 cut-off of ≤ 44.5 U/L allowed early and accurate identification of patients with low probability to develop clinically significant POPF, who can eventually be selected for enhanced post-operative recovery with significant clinical and economic benefits.

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1. Introduction

POPF remains the most common and difficult complication following PD. Failure in early detection may delay proper treatment and carries the substantial risk of a fatal outcome. In-hospital mortality has significantly dropped below 5% over the last four decades, whereas the morbidity rate after PD remains high, in the range of 30%–65% [1,2]. Postoperative PD morbidities are mostly related to the development of a pancreatic fistula.

In the absence of effective strategies to reduce the incidence of

POPF, it seems crucial to identify the risk factors. Recent studies have revealed some of the features associated with pancreatic anastomotic failure, including soft pancreatic texture, small pancreatic duct, perioperative haemorrhage (PPH), high body mass index (BMI), coronary artery disease, advanced age (>70 years), duration of jaundice and elevated serum amylase on POD1 ([3–8]). Timely identification of patients at risk for POPF after PD may eventually allow physicians to apply strict preventive measures and to prompt specific treatments in an effort to contain the related morbidities. On the other hand, knowing with a reasonable probability that the patient will not develop a CR-POPF may have a positive impact in terms of enhancing the postoperative recovery. Serum amylase obtained in the first few days after PD is becoming increasingly important to stratify patients on the basis of their likelihood of developing POPF [9,10]. However, growing evidence supports the superiority of lipase over amylase for the diagnosis of pancreatic gland disruption [11]. Considering these findings we

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hypothesised that serum lipase may be a better marker in the setting of POPF than serum amylase.

The purpose of the current study was to correlate serum lipase concentration on POD1 and the probability of POPF development after PD.

2. Materials and methods

A retrospective review of 98 PD performed between January 2009 and December 2014 at our surgical division was carried out. In 85 out of 98 cases POD1 lipase were available for statistical analysis. The patient data were extracted from a dedicated database. Both pancreaticojejunostomy (PJ) and pancreaticogastrostomy (PG) were performed to restore pancreato-digestive continuity. The decision to perform a PG or a PJ was made intraoperatively by the attending surgeon according to his practice. The PJ was carried out as a single-layer full-thickness anastomosis with interrupted absorbable monofilament sutures anchoring the duct over a silastic tutor with few stitches. The PG consisted of two-layer full-thickness interrupted sutures, and it was fashioned through a supplementary anterior gastrotomy.

Two closed-suction drains were generally placed anteriorly and posteriorly to the pancreatic anastomosis. A nasogastric tube was left in place. The patients were admitted to the surgical ICU ward according to the institutional protocol. Locally advanced neoplasms encasing the superior mesenteric vein or the portal vein required resection of the involved segment and a vascular reconstruction. A standard lymphadenectomy, defined as the removal of N1 lymph nodes according to the TNM-UICC 2002 classification, was routinely performed. All patients were began somatostatin analogue prophylaxis on the day of surgery and continued for a total of 5 days, and they received total parenteral nutrition (TPN) until they were able to tolerate a solid diet. Serum lipase was measured on POD1, and amylase level in the drain fluid was determined on POD3 and thereafter. Serum amylase is no longer analysed in our laboratory as of 2011, hence, only serum lipase was investigated for the diagnosis of POPF.

POPF was defined using the current classification provided by the International Study Group of Pancreatic Fistula (ISGPF: grade A, B, C) [12]. Therefore, POPF was defined as any measurable drainage from an operatively placed drain on or after POD3 demonstrating amylase levels greater than three times the upper limit of the normal serum amylase level. POPF of Grade B and C were considered clinically significant.

The preoperative factors recorded included: age, gender, BMI, comorbidities such as hypertension and diabetes mellitus, smoking habit, alcohol consumption, tumour pathology, serum bilirubin, serum creatinine, international normalised ratio (INR) and albumin. Abdominal CT scans were pre-operatively reviewed by the radiologist and the surgeon and the size of the lesion and the Wirsung diameter was calculated.

The intraoperative data included the duration of surgery and the type of pancreato-digestive anastomosis. The outcome data included: serum lipase on POD1, occurrence of POPF and additional complications [Delay gastric emptying (DGE), biliary fistula, intra-abdominal collections, acute pancreatitis, bleeding, sepsis, deep venous thrombosis, pulmonary complications].

Mortality was recorded at 30 days. In addition, the patients were split into two cohorts: one included patients who did not develop POPF or who developed exclusively a grade A POPF, and the other included patients with a CR-POPF (grade B and C). The serum lipase levels were empirically chosen, and the sensitivity, specificity, PPV and NPV were calculated to identify the optimal threshold for determining the prognostic significance. ROC analysis was employed to measure the prognostic performance of serum lipase.

3. Statistical analysis

The categorical variables were described in terms of frequencies and percentages. For continuous variables, the mean, standard deviation, standard error, median and range were reported. Categorical variables were compared using the chi-squared test and the Fisher's exact test, and the Mann–Whitney U-test and Student's t test were used to compare continuous variables when applicable. To identify the optimum threshold value of serum lipase on POD1 to rule out CR-POPF, ROC analysis was performed. The area under the curve (AUC) is a measure of the diagnostic accuracy of a test: an AUC value of >0.50 indicates the discriminatory ability of a test to significantly differentiate between positive and negative outcomes with regard to the classification variable (in this case, grades B or C POPF).

A logistic regression analysis was calculated to obtain odds ratios (ORs) and 95% confidence intervals (CIs) and to explore the association between the perioperative clinicopathological factors. A multivariate binary logistic regression analysis was performed on the main variables and, in particular, on the variables that produced significant results in the univariate analysis ($P < 0.05$). A P -value <0.05 was considered statistically significant. The entire statistical analysis was performed using SPSS[®], version 20.0 (IBM, Armonk, New York, USA).

4. Results

The cohort was composed of 55 males (56.1%) and 43 females (43.9%) with a mean age of 67.1 years and a mean BMI of 24.4. The most common reason for surgery was pancreatic adenocarcinoma (81.4%). The demographic, operative, pathological and treatment characteristics of the cohort are summarised in Table 1 (continuous variables) and Table 2 (categorical variables).

The overall complication rate was 60.2%. The rate of complications of Clavien–Dindo Grade IIIa and above was 23.4%. In total, 29 (29.5%) of the 98 patients developed a POPF: 17 (17.3%) had grade A, 8 (8.1%) had grade B, and 4 (4%) had grade C. The rate of CR-POPF was 12.2%. Table 3 shows that POPF was significantly associated with intra-abdominal collections, and CR-POPF was also strongly correlated with acute pancreatitis, DGE, and pulmonary complications. Re-laparotomy was required in 3 patients with grade C fistula to either control the source of sepsis or to manage the haemorrhage. The 30-day surgical mortality was 2% ($n = 2$). One death occurred as a consequence of refractory PPH, and the other was a result of small bowel ischemia following a vascular reconstruction on POD1. The length of stay was longer in the group that developed POPF (30.7 ± 31.4 days vs. 21.3 ± 17.5 days), and was strongly associated with the development of a CR-POPF ($P = 0.002$). The median postoperative hospital stay of all PD patients was 18 days (range: 18.9–29.3 days) (IQR 25%–75% 12–28).

Of 98 consecutive PD cases, the serum lipase was evaluated on POD1 for 85 (86.7%). Patients with POPF had a mean serum lipase on POD1 of 126.7 ± 108.4 U/L compared to 43.3 ± 64 U/L in patients who did not develop POPF ($P < 0.001$). Table 5 presents the mean levels of serum lipase on POD1 in patients with each grade of POPF.

Fig. 1 graphically represents the differences in the serum lipase concentrations on POD1 between the cohort with no POPF or grade A POPF and the cohort with grade B/C POPF.

Different serum lipase levels were empirically tested in several samples to maximise the sensitivity for predicting the development of POPF without sacrificing specificity. The ROC analysis demonstrated a good fit with an AUC of 0.76 (Fig. 2).

A serum lipase of 44.5 U/L on POD1 was chosen as the discriminatory threshold, as the sensitivity and specificity were 92% and 66%, respectively, with a PPV and NPV of 31% and 98% (Fig. 2).

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