Original Study

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Diagnostic Accuracy of Lipase as Early Predictor of Postoperative Pancreatic Fistula: Results from the LIPADRAIN study

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Objective: To evaluate the diagnostic accuracy of drain fluid lipase as an early predictor of postoperative pancreatic fistula and establish the most appropriate day for their measure.

Background: Clinically relevant postoperative pancreatic fistula remains a potentially life-threatening complication after pancreatic surgery. Early detection strategies remain key to reduce both the incidence and the burden of pancreatic fistula.

Methods: The LIPAse DRAIN (LIPADRAIN) study is a multicenter, prospective diagnostic study conducted in 7 tertiary university hospitals. Drain fluid values to detect clinically relevant postoperative pancreatic fistula from postoperative day 1 to postoperative day 6 were evaluated using receiver operating characteristic curve analysis. A biomarker was considered to be relevant for clinical use if its area under the curve (AUC) was greater than 0.75.

Results: Of the 625 patients included in the analysis, clinically relevant postoperative pancreatic fistula occurred in 203 (32%) patients. On postoperative days 3 and 4, drain fluid lipase was a reliable biomarker to detect clinically relevant postoperative pancreatic fistula (AUC: 0.761; 95% confidence interval [CI]: 0.761–0.799 and AUC: 0.784; 95% CI: 0.743–0.821, respectively). On postoperative day 3, with a threshold of 299 units/L, drain fluid lipase yielded a negative predictive value of 51%, sensitivity of 78%, and specificity of 63% for the detection of clinically relevant postoperative pancreatic fistula.

Conclusions: In this multicenter prospective study, drain fluid lipase is a reliable biomarker at postoperative days 3 and 4 for the diagnosis of clinically relevant postoperative pancreatic fistula after pancreatic surgery and should be systematically measured on postoperative day 3.

Keywords: Clinically relevant postoperative pancreatic fistula, Drain fluid lipase, Drain fluid amylase

INTRODUCTION

Pancreatectomy remains the mainstay in the management of both malignant and benign pancreatic tumors. Postoperative outcomes are classically associated with significant morbidity and mortality mostly due to the occurrence of clinically relevant postoperative pancreatic fistula (CR-POPF).[1,2] According to the updated consensus definition from the International Study Group on Pancreatic Fistula, CR-POPF occurs in 15% to 29% regardless of the type of resection.[3–5] To date, there is no standard strategy to prevent POPF and current strategies rely on mitigation.[6] Pancreatic juice leakage from the pancreatic anastomosis or the pancreatic stump containing mostly lipolytic and also proteolytic enzymes can lead to severe complications, especially postpancreatectomy hemorrhage, which stands as the first cause of failure-to-rescue and death after pancreatectomy.[7,8] Such consequences lead surgeons to place drains during pancreatic surgeries. Indeed, drains allow early detection and mitigation strategies that are paramount to reduce both the incidence and the burden of POPF. Regarding early detection, dynamic drain fluid amylase (DFA) level monitoring stands as the most widely used tool to guide postoperative

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drain management.[9,10] Previous studies have focused on lipase, which is now the biological reference assay for the diagnosis of acute pancreatitis due to its high specificity and its ability to capture the pancreas exocrine function.[11–17] These studies suggested a potentially more accurate sensitivity of drain fluid lipase (DFL) to diagnose CR-POPF as compared to DFA but lacked statistical power and adequate prospective design.

The LIPAse DRAIN (LIPADRAIN) study was designed to evaluate the diagnostic performances of DFL as an early predictor of CR-POPF and establish the most appropriate day for their measure.

METHODS

Design and Study Population

LIPADRAIN was a prospective observational diagnostic study conducted in 8 surgical departments of 7 tertiary university hospitals in France from May 2016 to August 2020. The trial was initiated by the investigators and supported by the University Hospital of Dijon and by a grant from the French Ministry of Health, France. The study was approved by the ethics committee "CPP Est 1" and the Agence Nationale de Sécrutié du Médicament and funded by a grant from the French Ministry of Health (PHRCI 2015;15-043) and the French National Research Agency under the program Investissements d'Avenir (ANR-11-LABX-0021 [LipSTIC Labex]). None of the trial funders had any role in the design or running of the trial, the analysis of the data, or the preparation of the article. Patients were eligible if they met the following criteria: age of 18 years or older, a scheduled pancreatic resection, and a health insurance cover. Patients with total pancreatectomy, under wardship, or pregnant woman and breastfeeding woman were excluded. Written informed consent was obtained from all patients before inclusion.

Study Conduct

Consecutive patients were screened from the operating room planning by a surgeon helped by a clinical research technician. If the patient was eligible, the surgeon presented the study to him the day before surgery and the patient was included after written consent.

Surgical approach, pylorus preservation and the type of reconstruction after pancreatoduodenectomy (PD), lymphadenectomy extent, and the use of falciform ligament or omentoplasty for vascular stump coverage were left at the discretion of each center. Similarly, the number and positioning of abdominal drains, the use of transanastomotic pancreatic stenting, oral feeding policy, and the use of somatostatin analogs were performed according to usual practices.

After surgery, serum levels of amylase, lipase, and C-reactive protein and drain fluid levels of amylase and lipase were systematically measured on postoperative day (POD) 1, 3, 4, and 6. Lipase and amylase assays were centralized at the biochemistry laboratory of Dijon University Hospital and measured at the end of the study blinded to clinical data.

Lipase and amylase activities were quantified on an Atellica analyzer with dedicated reagents (Siemens, Courbevoie, France). C-reactiv protein was determined by immunonephelometry.

Abdominal drains were systematically kept in place until POD 3. Drains removal was then based on POD 3 DFA levels, fistula risk score, and/or clinical evolution. POPF risk was assessed using the fistula risk score.[18] During the hospitalization, patients were examined by the surgeon daily. Postoperative abdominal computed tomography (CT) was performed in case of clinical worsening or routinely between POD 5 to 7 in patients who underwent vascular reconstruction. Patients were seen in the outpatient clinic within 6 weeks after surgery.

Outcomes

The primary outcome of LIPADRAIN was the accuracy of DFL to detect CR-POPF within 30 days following surgery. Clinically relevant (CR)-POPF (grade B-C) was defined in accordance with the updated 2016 International Study Group on Pancreatic Fistula consensus guidelines[3] and reported by surgical attending physicians blinded to drain amylase and lipase measurements. Secondary outcomes were the choice of the best timing to measure DFL and its kinetics.

Statistical Analysis

In a previous pilot study,[11] the area under the curve (AUC) of the receiver operating characteristic (ROC) curve of the value of lipase for the diagnosis of CR-POPF was 0.86 at POD 4. To show a diagnostic accuracy of lipase greater than 75% (minimum accuracy recommended for clinical use of a biomarker) with an expected AUC of 0.85 for DFL, a 10% fistula (B/C) prevalence, a significance level (alpha) of 0.025, and 80% statistical power, the sample size required 610 patients. To counterbalance patients with secondary exclusion criteria (total pancreatectomy or recused pancreatectomy), 770 patients were included.

Patients with biochemical leak and patients without fistula were gathered in the no CR-POPF group and patients with grade B-C POPF in the CR-POPF group. Categorical data were expressed with percentage frequencies and were compared with Fisher exact tests or χ^2 tests. Continuous outcomes were expressed as numbers, medians with interquartile range, and compared using the Wilcoxon test. The area under the ROC curves (AUC) was calculated for DFL and DFA levels on POD 1, 3, 4, and 6 as predictors of CR-POPF. A biomarker was considered to be relevant for clinical use if its AUC was greater than 0.75. Finally, a cutoff that prioritized sensitivity was chosen for each biomarker. AUC was compared with the Delong test.

A significance level of $P < 0.05$ was used, and the analysis was conducted using R software version 4.1.0 (R Core Team), Vienna, Austria.

RESULTS

Study Population

Over the study period, a total of 768 patients were considered for inclusion, of whom 143 patients (18.6%) were excluded. Details on patient inclusion are provided in Figure 1. The final study cohort comprised of 625 patients who underwent partial pancreatectomy, including 420 PD (67%) and 174 distal pancreatectomy (28%). Preoperative characteristics are displayed in Supplemental Table 1; see http://links.lww.com/AOSO/A405. The main indication for partial pancreatectomy was pancreatic adenocarcinoma (n = 259, 41%). Intraoperative characteristics are listed in Supplemental Table 1; see http://links.lww.com/AOSO/A405.

Postoperative Outcomes

In-hospital: 25 patients (4%) died and 119 (19%) had severe morbidity (Supplemental Table 1; see http://links.lww.com/AOSO/A405). CR-POPF and grade B-C postpancreatectomy hemorrhage rates were (n = 203) 32% and (n = 16) 3%, respectively, whereas 112 patients (18%) experienced delayed gastric emptying. Overall, 65 patients required reintervention (10%). Median hospital stay was 16 days (interquartile range, 11–23) and the overall readmission rate at 30 days was 13% (n = 79).

Drain Fluid Lipase/Amylase Performance for Early CR-POPF Diagnosis

Median levels of lipase activity measured in the abdominal drain on POD 1, 3, 4, and 6 were significantly higher in patients who

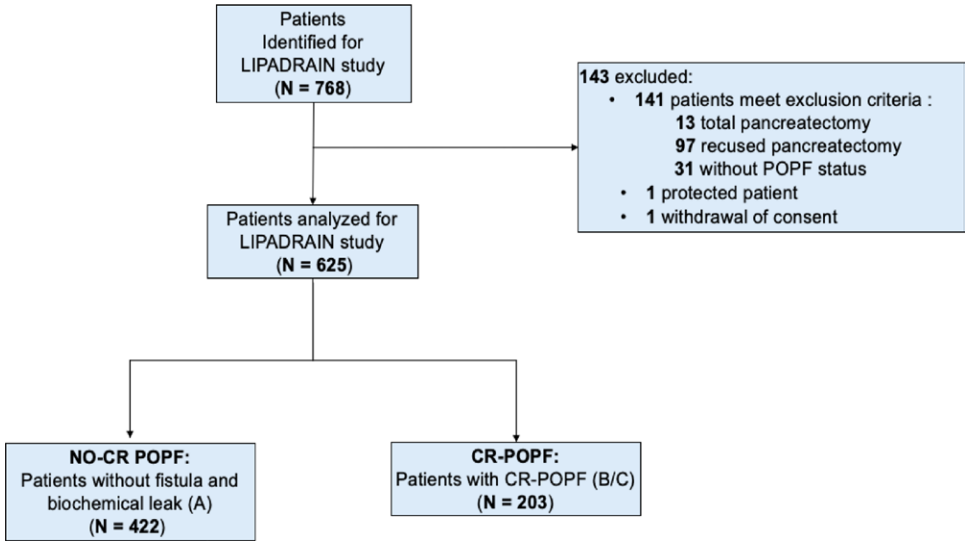

FIGURE 1. LIPADRAIN study flowchart. Selection of patient included in the analyses.

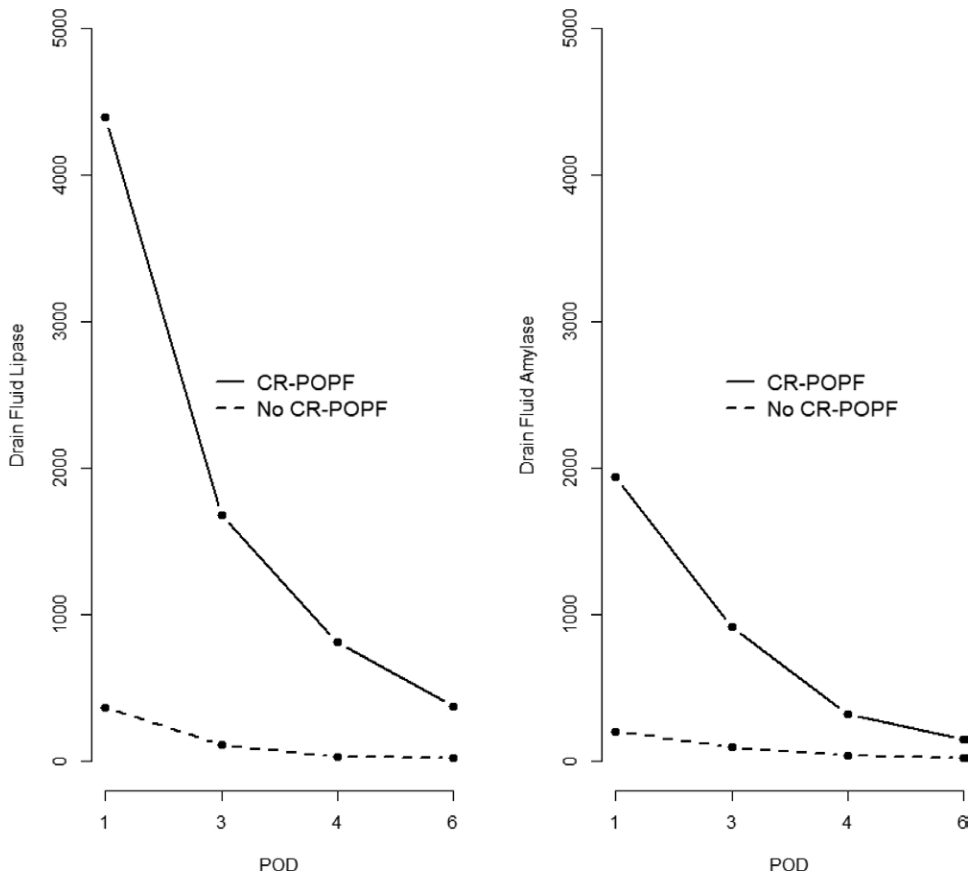

FIGURE 2. Daily median levels of DFL and DFA (IU/L) according to the presence or absence of CR-POPF.

developed CR-POPF. The kinetics of DFL and DFA in patients who developed CR-POPF decreased systematically after POD 1 to return to low levels at POD 6 (Fig. 2).

ROC curve analysis showed that DFL level on POD 4 and 3 yielded the best diagnosis performance for CR-POPF (AUC: 0.784, 95% confidence interval [CI]: 0.743–0.821, and AUC: 0.761, 95% CI: 0.716–0.799, respectively) despite the absence of significant difference between POD 3, 4, and 6 (Fig. 3). With a threshold of 299 IU/L, DFL yielded a negative predictive value of 51%, sensitivity of 78%, and specificity of 63% for the detection of CR-POPF on POD 3. With a threshold of 10 IU/L, DFL yielded a negative predictive value of 66%, sensitivity of 99%, and specificity of 15% for the detection of CR-POPF on POD 3.

Regarding amylase, ROC curve analysis showed that DFA level on POD 3 and 4 yielded the best predictive performance for CR-POPF (AUC: 0.777, 95% CI: 0.737–0.816 and AUC: 0.784, 95% CI: 0.743–0.823, respectively) (Fig. 4). With a

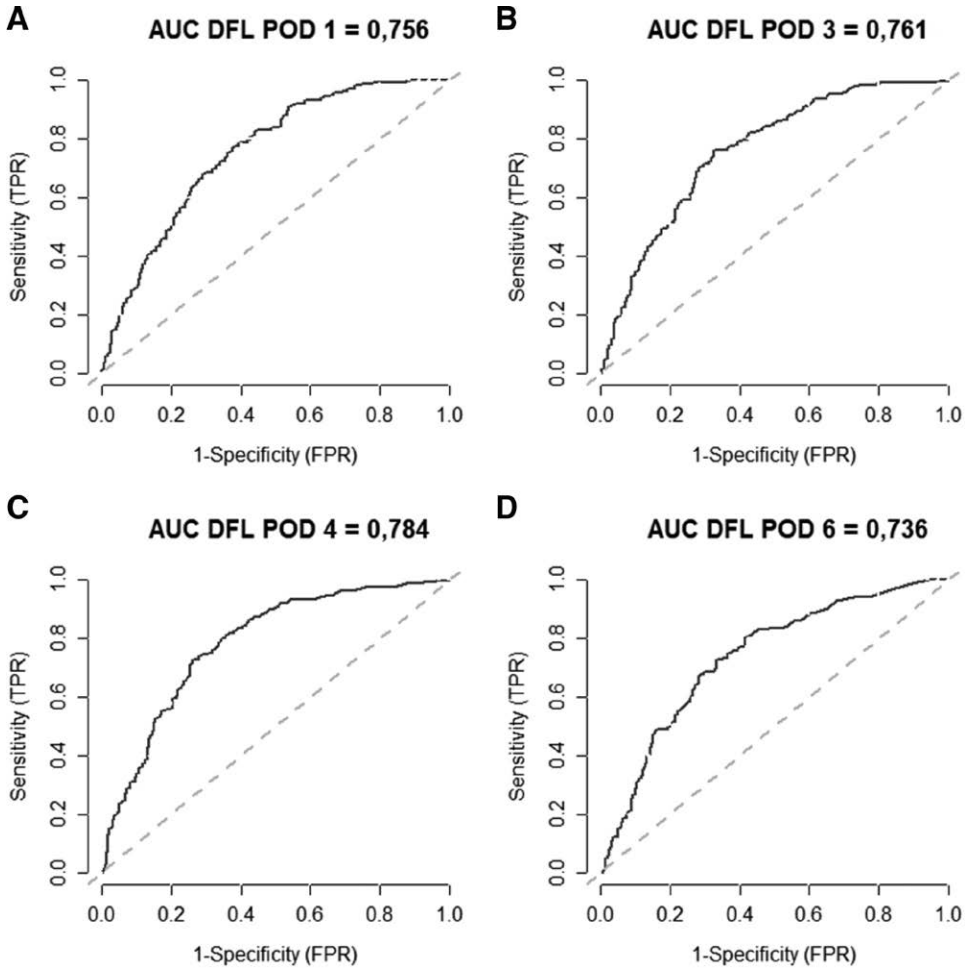

FIGURE 3. Outcomes from ROC curve analysis for drain fluid lipase. A, Receiver operating characteristic (ROC) curves for levels of drain fluid lipase at POD 1 (area under the curve [AUC] 0·756 [95% confidence interval: 0·714–0·797]), (B) at POD 3 (AUC: 0·761 [0·716–0·799]), (C) at POD 4 (AUC: 0·784 [0·743 to 0·821]), and (D) at POD 6 (AUC: 0·736 [0·693–0·778]). CR-POPF was the outcome variable.

cutoff of 296 IU/L, DFA yielded a negative predictive value of 47%, sensitivity of 74%, and specificity of 69% for the diagnosis of CR-POPF on POD 3.

There was no difference in predictive performance between DFL and DFA, whether on postoperative days 1, 3, 4, or 6 ($p>0.05$).

DISCUSSION

As the most dreaded complication after partial pancreatectomy, POPF occurrence and burden have been largely reported in the literature. In the current multicenter prospective study, the rates of mortality and CR-POPF were consistent with the existing literature.[1,4,19] In this setting, early POPF detection using drain fluid enzyme levels stands as the cornerstone of POPF mitigation strategies, especially in high-risk patients has been established as the standard of care.[20] To our knowledge, LIPADRAIN study is the largest prospective study using centralized dosage to identify DFL and DFA accuracy for early diagnosis of CR-POPF.

Focusing on CR-POPF detection, based on the consensus definition from the ISGPS, DFA is classically considered as the reference assay.[3] Yet, reasons why DFA was identified as the gold standard assay for POPF over DFL remain unclear.[21] Indeed, DFL has been previously reported as a biomarker of POPF with various cutoff values ranging from 500 to 1000 IU/L.[11] Further, another publication has suggested that DFL could be more sensitive than DFA for diagnosing CR-POPF.[13] The current study showed that both DFL and DFA allowed early POPF diagnosis. Indeed, both POD 3 DFL and DFA had an AUC of over 0.750. Similar performances were observed on POD 4. Nevertheless, instead of POD 4, POD 3 remains more relevant to allow POPF diagnosis as early as possible.

Conversely, serum lipase stands as the assay of reference for acute pancreatitis diagnosis.[22,23] Considering that post-pancreatectomy acute pancreatitis is now well-defined and acknowledged as increasing both the risk and the burden of POPF, monitoring serum lipase postoperatively would be warranted.[24,25] Still, whether monitoring serum lipase instead of serum amylase remains to be ascertained. Nevertheless, pairing serum lipase and DFL analysis would allow a cost-effective detection of both POPF and POAP relying only on lipase levels.

Monitoring drain fluid at different postoperative time points remains of paramount importance in the modern era of dynamic drain management and enhanced recovery programs.[10,20,26,27] Still, regarding drain fluid value kinetics, DFL and DFA in patients who developed CR-POPF decreased after POD 1 to return to low levels upon POD 6. Such an observation questions the relevance of repeating drain fluid analysis in patients with positive DFL on POD 3. Instead, in those patients, postoperative standardized monitoring protocols should be followed, including systematic abdominal CT in case of unexpected clinical or biological evolution to decrease the risk of failure-to-rescue. Additionally, any perianastomotic fluid collection should be drained and the instauration of broad-spectrum antibiotics should be discussed.

Several limitations must be addressed. First, CR-POPF is classically determined post hoc once the clinical course is completed.

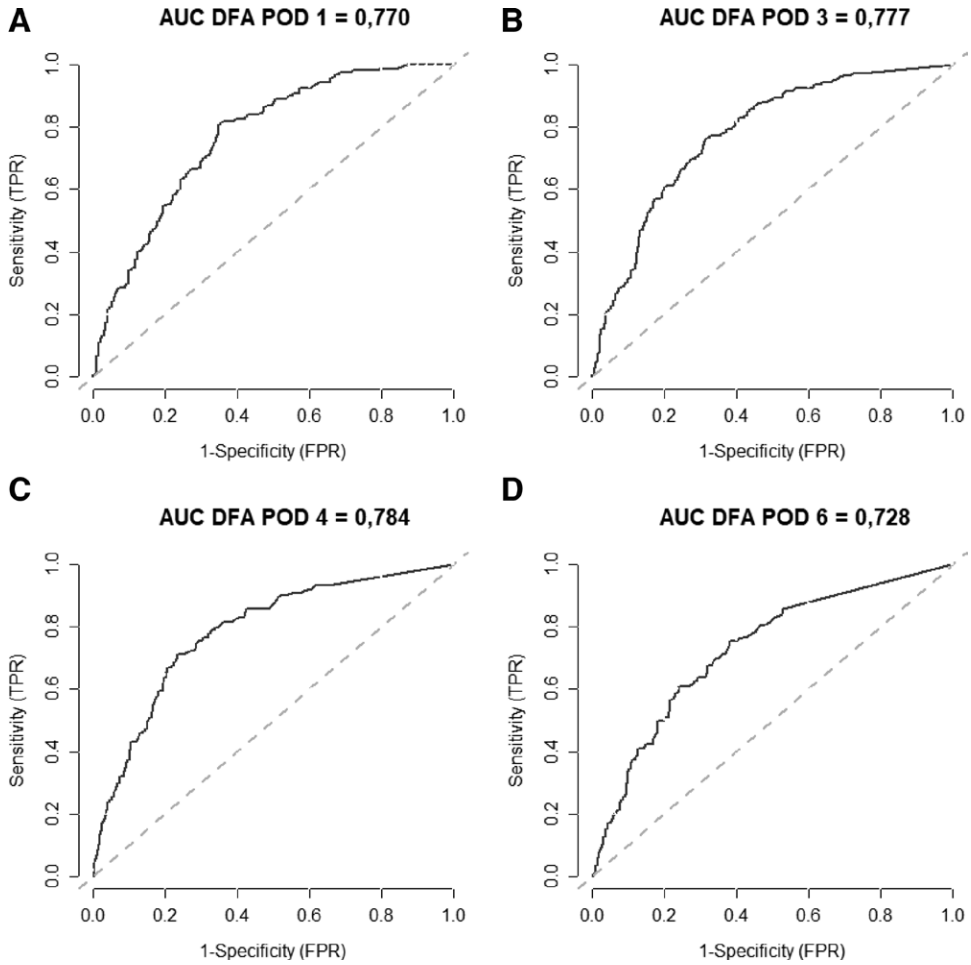

FIGURE 4. Outcomes from ROC curve analysis for drain fluid amylase. A, Receiver operating characteristic (ROC) curves for levels of drain fluid amylase at POD 1 (area under the curve [AUC]: 0·770 [95% confidence interval: 0·726–0·808]), (B) at POD 3 (AUC: 0·777 [0·737–0·816]), (C) at POD 4 (AUC: 0·784 [0·742–0·823]), and (D) at POD 6 (AUC: 0·728 [0·681–0·774]). CR-POPF was the outcome variable.

Despite its prospective design, POPF mitigation strategies and postoperative management including drain management and antibiotics in case of suspected POPF were not standardized among participating centers. This variation in management could have impacted the clinical evolution of POPF and the association between postoperative DFL levels and outcomes. Second, reported DFA cutoffs associated with CR-POPF in large series differed between distal pancreatectomy and PD [28,29] In the current series, cutoff values for DFL and DFA have been identified in the whole cohort including all types of pancreatectomies, mostly PD. Next studies will be designed to identify specific DFL cutoff values for any different type of pancreatectomy. Finally, cutoff values identified in the LIPADRAIN cohort would need external validation to strengthen their applicability in clinical practice. In this multicenter prospective study, DFL was identified as a reliable biomarker for predicting CR-POPF after pancreatectomy. DFL levels equal to or higher than 300 IU/L upon POD 3 should be considered for tailored drain management strategy after performing an abdominal CT even in asymptomatic patients.

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