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Sequential Drain Amylase to Guide Drain Removal Following Pancreatectomy

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Abstract

Background—Although used as criterion for early drain removal, postoperative day (POD) 1 drain fluid amylase (DFA) ≤ 5000 U/L has low negative predictive value for clinically relevant postoperative pancreatic fistula (CR-POPF). It was hypothesized that POD3 DFA ≤ 350 could provide further information to guide early drain removal.

Methods—Data from a pancreas surgery consortium database for pancreatoduodenectomy and distal pancreatectomy patients were analyzed retrospectively. Those patients without drains or POD 1 and 3 DFA data were excluded. Patients with POD1 DFA ≤ 5000 were divided into groups based on POD3 DFA: Group A (≤ 350) and Group B (> 350). Operative characteristics and 60-day outcomes were compared using chi-square test.

Results—Among 687 patients in the database, all data were available for 380. Fifty-five (14.5%) had a POD1 DFA > 5000. Among 325 with POD1 DFA ≤ 5000, 254 (78.2%) were in Group A and 71 (21.8%) in Group B. Complications (35 (49.3%) vs 87 (34.4%); p = 0.021) and CR-POPF (13 (18.3%) vs 10 (3.9%); p < 0.001) were more frequent in Group B.

Conclusions—In patients with POD1 DFA ≤ 5000, POD3 DFA ≤ 350 may be a practical test to guide safe early drain removal. Further prospective testing may be useful.

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Introduction

Many surgeons use intraperitoneal drains after pancreatectomy to allow for early identification, and mitigation, of complications associated with clinically relevant postoperative pancreatic fistulae (CR-POPF). However, it has been suggested that leaving drains in patients at lower risk of developing CR-POPF can be detrimental.[1] Bassi and colleagues demonstrated that early drain removal improved outcomes in patients with a postoperative day 1 drain fluid amylase (POD1 DFA) ≤ 5000 U/L.[2] They randomized low risk patients into early (POD3) and late (≥ POD5) drain removal. Early drain removal was associated with lower rates of pancreatic fistula, abdominal complications, and a shorter length of stay (LOS).[1]

Patients with a POD1 DFA > 5000 U/L have a 70% incidence of CR-POPF.[3, 4] However, POD1 DFA ≤ 5000 U/L does not reliably predict the absence of CR-POPF.[3] Previous reports have identified a POD1 DFA cutoff of < 90 U/L as having the highest negative predictive value (98.2%) for pancreatic fistula.[5] This uncertainty has discouraged some surgeons from removing drains early in the postoperative course. A meta-analysis by Giglio et al. included 13 studies (n = 4416 patients) with the aim of defining the accuracy of drain amylase values in predicting postoperative pancreatic fistula (POPF).[3] The authors determined that the probability of developing a CR-POPF if POD1 drain amylase is < 100 U/L is 3%. However, only 34% of patients had a POD1 drain amylase < 100 U/L. The authors suggested that a cut-off value of 350 U/L may be more clinically useful since 50% of patients were found to have values in this range and the incidence of CR-POPF was only 4%.

In addition to POD1, a second analysis of DFA later in the postoperative course may add additional useful data to predict an evolving or subsequent CR-POPF. Partelli et al. demonstrated that POD5 DFA > 200 U/L had a sensitivity of 90% and a specificity of 83% in predicting POPF.[4] Okano and colleagues calculated drain amylase output as the product of DFA concentration and the volume of fluid. The ratio of POD3/POD1 drain amylase output was lower in those patients that did not develop a CR-POPF.[6]

It is important to note that drains were not removed on POD1 in the only randomized prospective trial of early drain removal.[1] Drains were removed on POD3-5 if additional criteria were met. If the appearance of the drain fluid suggested a pancreatic fistula, early post-pancreatectomy hemorrhage, or bile leak, the drain was left in place. In addition, abdominal ultrasound was performed on POD3 and, if this showed a fluid collection > 5 cm, the drain was left in place. Presumably, the reason for this additional scrutiny was that, as patients resume oral intake in the first few days after surgery, a POPF may become evident. A simple, inexpensive, clinically predictive test to reassess the risk of subsequent CR-POPF on POD3 would be useful in directing drain removal, since visual appearance of the drain may not be a reliable way to assess risk and use of abdominal ultrasound for every patient is likely not economically or logistically feasible.

It was hypothesized that a supplemental analysis of DFA on POD3 could add to the value of POD1 DFA in providing a clinically useful and more reliable method to predict which patients will not develop a CR-POPF. The cut-off of 350 U/L was selected based on the meta-analysis by Giglio et al.[3] Data from a prospectively maintained consortium database were reviewed retrospectively to determine the association of DFA on POD1 and POD3 with postoperative outcomes.

Methods

Analyzed data were reviewed retrospectively from a prospectively maintained Pancreas Surgery Registry including three high-volume academic pancreas centers. After obtaining informed consent, data were entered prospectively into the database by trained data analysts under the supervision of the surgeons. All data were backed up by source documents and the accuracy of data entered to the electronic database was periodically reviewed and verified by the coordinating center (Baylor College of Medicine).[7] Permission for this study was obtained from an Institutional Review Board (H-38662).

Although patients who underwent pancreatoduodenectomy (PD) or distal pancreatectomy (DP) were included, outcomes for these two different operations were analyzed separately. Patients without intraperitoneal drains and without POD1 and 3 DFA data were excluded from the study. Patients with POD1 DFA ≤ 5000 U/L were divided into two groups based on their POD3 DFA concentration: Group A (≤ 350 U/L) and Group B (> 350 U/L). The measurement of DFA on POD1 and POD3 is part of the institutional protocol. In patients with multiple drains the highest DFA concentration from any drain was used. Drain removal was recorded as the date on which the last drain was removed.

Baseline demographics and comorbidities such as body mass index (BMI), hypertension, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, diabetes, chronic pancreatitis, renal insufficiency, and smoking history were obtained from the database. Perioperative characteristics included pancreatic texture, pancreatic duct size, anastomotic technique, pathologic diagnosis, estimated blood loss (EBL), transfusion requirement, American Society of Anesthesiologists (ASA) score, and length of procedure. Complications within 60 days of surgery were recorded and graded using the Accordion Severity Grading for Surgical Complications,[8] and the International Study Group of Pancreatic Fistula (ISGPF) and the International Study Group of Pancreatic Surgery (ISGPS) definitions[9–10] for pancreatic fistula and delayed gastric emptying (DGE). A detailed definition of complications has been previously reported.[8] Patients were followed for mortality for 90 days after surgery. The primary outcome of interest was CR-POPF. Chi-square or Fisher's exact tests, when appropriate, were used to analyze categorical variables. Student's t-test or Mann-Whitney tests were used to evaluate continuous variables. Simple logistic regression analysis was employed to evaluate the ability of POD1 DFA and POD1 in combination with POD3 DFA to predict the absence of CR-POPF. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS v24 (IBM Corp. Armonk NY, USA).

Results

Among 687 patients who underwent PD or DP, 380 had intraperitoneal drains placed at the time of surgery and had both POD1 and POD3 DFA data available. Fifty-five patients identified with a POD1 DFA > 5000 U/L were analyzed separately. Among the remaining 325 patients with POD1 DFA ≤ 5000 U/L, 254 patients (78.2%) had a POD3 DFA ≤ 350 U/L (Group A) and 71 patients (21.8%) had a POD3 DFA > 350 U/L (Group B) (Figure 1). 241 (74.2%) patients underwent PD and 84 (25.8%) underwent DP. The overall rate of CR-POPF among patients with POD1 DFA ≤ 5000 U/L was 7.1%.

Among the 55 patients with POD1 DFA > 5000 U/L, 43 (78.2%) underwent PD and 12 (21.8%) underwent DP. Overall, the median POD1 DFA was 9729 U/L (7330 – 13,108 U/L) and median POD3 DFA was 1009 U/L (594 – 3076 U/L). The overall rate of fistula of any grade was 85.4% while the rate of CR-POPF was 34.5%. The date of drain removal was available for 45 (81.8%) patients in this group. All patients had their intraperitoneal drains removed after POD5 (median POD16, IQR POD8-POD29). Among the 43 patients who underwent PD, 41(95.3%) had soft gland texture and 37.2% developed a CR-POPF.

Table 1 displays the baseline characteristics of the study population with POD1 DFA ≤ 5000 U/L. There was no significant difference in age, gender, ethnicity, race, or distribution of comorbidities between Group A (POD3 DFA ≤ 350 U/L) and Group B (POD3 DFA > 350 U/L). There was a difference in the initial diagnosis between the two groups but only in patients who underwent PD. Patients in Group B had smaller pancreatic duct diameters, were more likely to have soft gland texture, less frequently had a diagnosis of pancreatic adenocarcinoma or pancreatitis on final pathology, and had an increased LOS when compared with patients in Group A (Table 1). Additionally, there were more ASA class 4 patients in Group B. When subset analysis was performed based on procedure type, these differences persisted in patients undergoing PD but not DP.

Morbidity was greater in Group B. Complications of any grade were more frequent (35 (49.3%) vs 87 (34.3%), $p = 0.021$). CR-POPF, the main outcome variable of interest, was more frequent in Group B (13 (18.3%) vs 10 (3.9%), $p < 0.001$). The difference in other specific complications did not reach significance. The differences in overall complication rate and CR-POPF persisted in patients undergoing PD but not DP (Table 2).

Data on the timing of drain removal were available for 189 (74.4%) patients in Group A and 45 (63.3%) in Group B. In both groups, most patients had their drains removed late, after POD5 (54.5% of patients in Group A and 91.1% in Group B (Figure 2)). The median POD of drain removal in Group A was POD6 (4–13) while it was POD11 (7–20) in Group B. When the patients in Group A were divided into subgroups according to timing of drain removal (early removal: ≤ POD5, late removal: after POD5), morbidity was greater in the late drain removal group (Table 3). This difference persisted in subgroup analysis of those patients in Group A that did not develop CR-POPF (45 (47.9%) vs 23 (28.8%), $p = 0.013$).

POD1 DFA alone significantly predicted the absence of CR-POPF. When compared to this test, combining POD1 DFA ≤ 5000 U/L and POD3 DFA ≤ 350 U/L, had a higher odds ratio for predicting no CR-POPF. This persisted when the tests were used to evaluate the absence of CR-POPF in PD and DP.

Discussion

CR-POPF remains a major concern for pancreatic surgeons. In patients at low risk of a pancreatic fistula, increased complications have been reported when removal of drains is delayed.[1, 11–20] Many surgeons continue to place intraperitoneal drains at the time of surgery because these have proven critical in mitigating pancreatic fistulae and associated complications. In a randomized controlled trial, Bassi and colleagues showed delayed drain removal in patients at low risk of pancreatic fistula was associated with an increased rate of pancreatic fistulae and abdominal complications when compared with early drain removal.[1] In this study, late removal was defined as after POD5. Kawai and colleagues also demonstrated increased fistula rates and intra-abdominal infections with late removal of drains when compared with early removal.[19] In this study, late drain removal was defined as after POD8. In a Cochrane review, Peng et al. demonstrated that late drain removal was associated with higher rates of postoperative complications.[15] These studies favor an early drain removal strategy to mitigate postoperative complications in patients at low risk of developing CR-POPF. Complete elimination of drains, particularly in the setting of pancreatoduodenectomy, is not advisable based on available evidence. Mortality has been shown to increase fourfold in patients undergoing PD without intraperitoneal drains placed at the time of surgery.[20] Placement of a drain at the time of resection and early drain removal in selected patients at low risk for CR-POPF is an alternative approach. This strategy may improve outcomes by having a drain already in place to mitigate a pancreatic fistula if one develops, and having the drain removed early (on or before POD5) to eliminate any potential harm caused by a drain in patients who do not develop a fistula. Thus, a simple, inexpensive, clinically useful objective test in the early postoperative period to assess the risk of subsequent CR-POPF would be useful.

Several reports have been published that propose guidelines for drain management based on drain fluid characteristics, including POD1 DFA and fluid color/appearance, as well as fistula risk scores that incorporate patient-specific intraoperative characteristics, including gland texture, duct size, EBL, and pathology.[2, 21] Early removal of drains may be safe in selected patients at low risk of fistula. In this study, we evaluated the ability of POD3 DFA $\leq$ 350, in combination with POD1 DFA $\leq$ 5000, as a tool to identify which patients will not develop a CR-POPF after pancreatectomy. Complications and CR-POPF were more frequent in those patients with POD3 DFA > 350. These patients also had smaller pancreatic ducts, softer pancreatic texture, and pathological diagnoses that are usually correlated with softer gland texture. These factors have been associated with higher rates of pancreatic fistula.[11–13] The combination of POD1 and POD3 DFA may be a simple and clinically useful method to identify which patients will not develop a CR-POPF and guide safe early drain removal.

Although the combination of POD1 $\leq$ 5000 and POD3 $\leq$ 350 DFA was highly sensitive in predicting subsequent CR-POPF, the results must be carefully interpreted. A limitation of this retrospective study is that the parameters for drain removal were not controlled. In addition to DFA, the color or volume of drain output, the surgeon's concern about the pancreatojejunostomy, pancreatic transection margin, or other factors may have influenced decisions about the timing of drain removal.

The timing of drain removal itself may have been an additional confounding factor. To address this, we looked at timing of drain removal in both study groups. Only four patients in group B (POD3 DFA > 350 U/L) had drains removed early. In a subset analysis of group A (POD3 DFA ≤ 350 U/L) late drain removal (which we defined as after POD5) was associated with increased overall morbidity but not with a statistically significant higher rate of CR-POPF. Although this data does not prove causality, it is consistent with previous reports that have found increased complications with prolonged drain placement after pancreatectomy.[2, 12–18]

When PD and DP subgroups were analyzed separately, overall morbidity and rate of CR-POPF was higher in patients with POD3 DFA > 350 U/L only in patients undergoing PD. Our study may have been underpowered to detect a difference after DP. However, due to the different complication profiles of PD and DP it is important to avoid a combined analysis of their outcomes.

This study demonstrated that after pancreatectomy, patients at lower risk of CR-POPF (POD1 DFA ≤ 5000 U/L) can be further sub-stratified for risk using POD3 DFA ≤ 350. The first screen (POD1 DFA) identified about 14% of patients undergoing pancreatectomy that would be screened out as high risk for fistula and thus not eligible for early drain removal. Using a second screen of POD3 DFA identified an additional 19% at increased risk, thus about 1/3 of the patients undergoing pancreatic resection would be screened out of the safe early drain removal group. Our data suggests that POD3 DFA may be an additional clinically useful guide for surgeons considering early drain removal. However, to prove the value of this approach, a randomized prospective trial would be required.

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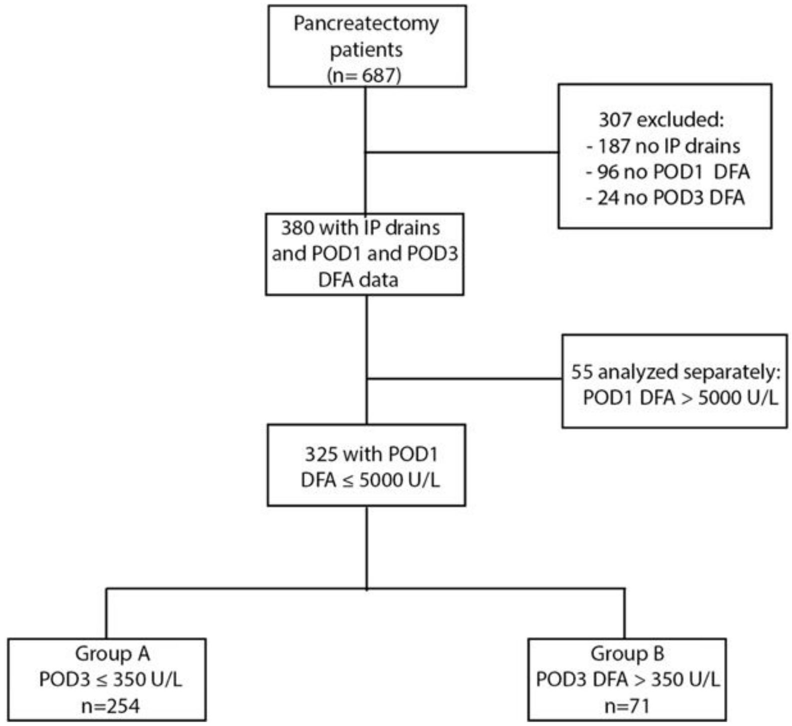

Figure 1. Patient Selection

Flowchart illustrating patient selection strategy.

IP: intraperitoneal, POD: postoperative day, DFA: drain fluid amylase

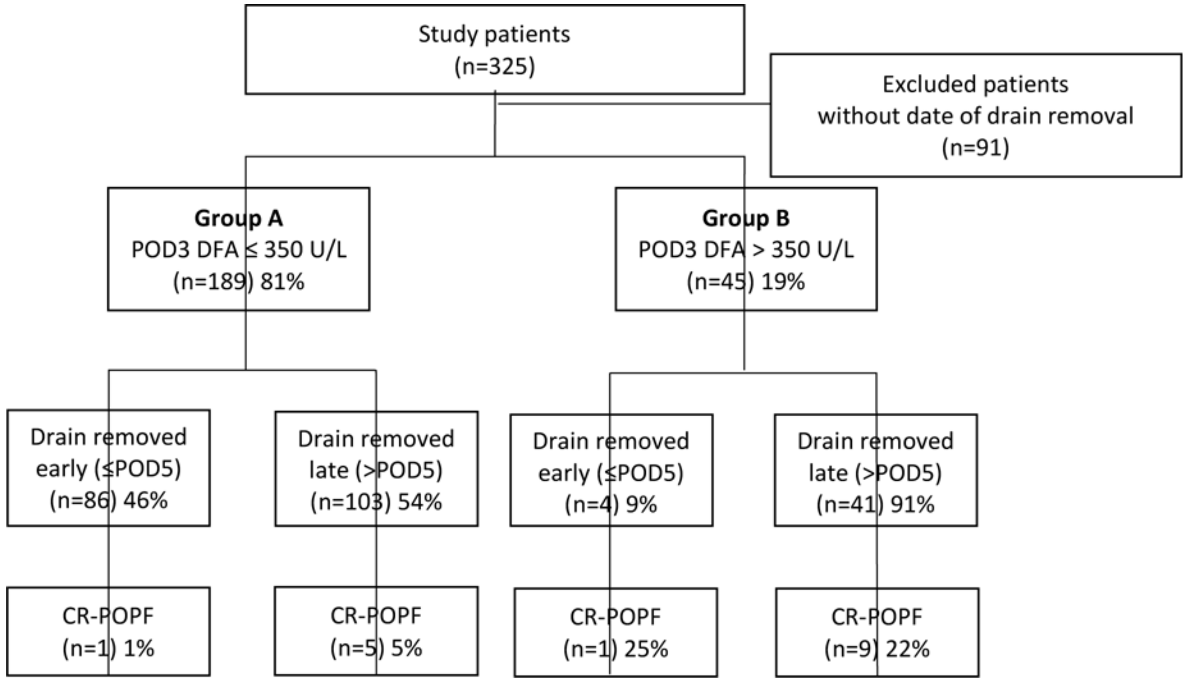

Figure 2. Timing of Drain Removal in Group A and Group B

Figure shows timing of drain removal for Group A and Group B patients as well as the rates of CR-POPF with early and late drain removal in each group.

POD: postoperative day, DFA: drain fluid amylase, CR-POPF: clinically relevant postoperative pancreatic fistula

Table 1

Demographics, Comorbid Conditions, and Perioperative Characteristics of 325 patients with POD1 DFA ≤ 5000 U/L

n (%) or Median (Interquartile Range)	PD (n=241)			DP (n=84)		
	Group A (n=190)	**Group B (n=51)**	**p-value**	**Group A (n=64)**	**Group B (n=20)**	**p-value**
Age	65 (57–72)	65 (58–72)	0.971	56 (46–69)	57 (44–66)	0.425
Gender						
Female	89(46.8%)	29(56.9%)	0.204	42(65.6%)	10(50.0%)	0.209
BMI	27 (22–30)	28 (24–31)	0.349	28 (23–31)	30 (27–34)	0.236
Comorbidities						
HTN	71(37.4%)	20(39.2%)	0.865	23(35.9%)	7(35.0%)	1.000
COPD	10(5.3%)	2(3.9%)	1.000	3(4.7%)	1(5.0%)	1.000
PVD	11(5.8%)	1(2.0%)	0.466	2(3.1%)	0	1.000
Chronic pancreatitis	31(16.3%)	4(7.8%)	0.124	5(7.8%)	2(10.0%)	0.627
Renal insufficiency	7(3.7%)	1(2.0%)	1.000	4(6.3%)	0	0.575
Diabetes	60(31.6%)	12(23.5%)	0.256	16(25.0%)	6(30.0%)	0.361
Diagnosis						
PDAC	93(48.9%)	8(15.7%)	<0.001	17(26.6%)	5(25.0%)	0.912
Cystic	20(10.5%)	17(33.3%)		26(40.6%)	11(55.0%)	
pNET	10(5.3%)	6(11.8%)		10(15.6%)	2(10.0%)	
Ampullary cancer	24(12.6%)	7(13.7%)		–	–	
Cholangiocarcinoma	4(2.1%)	2(3.9%)		–	–	
Pancreatitis	23(12.1%)	4(7.8%)		4(6.3%)	0	
Other cancer	5(2.6%)	1(2.0%)		3(4.7%)	1(5.0%)	
Other	11(5.8%)	6(11.8%)		3(4.7%)	1(5.0%)	
EBL (ml)	200 (55–365)	200 (100–300)	0.773	112 (45–300)	100 (26–412)	1.000
Transfusion	26(13.7%)	2(3.9%)	0.055	5(7.8%)	2(10.0%)	0.660

n (%) or Median (Interquartile Range)	PD (n=241)			DP (n=84)		
	Group A (n=190)	Group B (n=51)	p-value	Group A (n=64)	Group B (n=20)	p-value
Operative time (min)	442(384–519)	406(346–497)	0.041	260(207–326)	232(187–344)	0.506
Soft gland	72(37.9%)	41(80.4%)	<0.001	39(60.9%)	13(65.0%)	0.709
Pancreatic duct ≤ 3mm	29(15.3%)	15(29.4%)	0.018	32(50.0%)	10(50.0%)	0.569
LOS (days)	7(5–8)	7(6–10)	0.005	5(4–6)	5(4–6)	0.907
Readmission	39(21%)	13(25%)	0.374	12(18.8%)	4(20.0%)	0.726
Reoperation	3(2%)	1 (2%)	0.576	0	0	–
Operative mortality	3(3%)	1 (2%)	1.000	1(1.6%)	0	1.000

PD: pancreatoduodenectomy, DP: distal pancreatectomy, BMI: body mass index, HTN: hypertension, COPD: chronic obstructive pulmonary disease, PVD: peripheral vascular disease, PDAC: pancreatic adenocarcinoma, pNET: pancreatic neuroendocrine tumor, ASA: American Society of Anesthesiologists, EBL: estimated blood loss, LOS: Length of stay

There were no significant differences in race, ethnicity, smoking status, or American Society of Anesthesiologists (ASA) Class.

Table 2

60-day Morbidity of 325 patients with POD1 DFA ≤ 5000 U/L n (%)

n (%)	Overall (n=325)			PD (n=241)			DP (n=84)		
	Group A (n=254)	**Group B (n=71)**	**p-value**	**Group A (n=190)**	**Group B (n=51)**	**p-value**	**Group A (n=64)**	**Group B (n=20)**	**p-value**
Patients with any complications	87(34.3%)	35(49.3%)	0.021	72(37.9%)	29(56.9%)	0.015	15(23.4%)	6(30.0%)	0.554
Gastrointestinal									
Fistula of any grade	25(19.8%)	60(84.5%)	<0.001	18(9.5%)	46(90.2%)	<0.001	7(10.9%)	14(70.0%)	<0.001
CRPOPF	10(3.9%)	13(18.3%)	<0.001	8(4.2%)	11(21.6%)	<0.001	2(3.1%)	2(10.0%)	0.200
Bile leak	2(0.8%)	2(2.8%)	0.197	2(1.1%)	2(3.9%)	0.203	0	0	–
Enteric leak	1(0.4%)	0	1.000	0	0	–	1(1.6%)	0	1.000
Chyle leak	7(2.8%)	1(1.4%)	1.000	5(2.6%)	1(2.0%)	1.000	2(3.1%)	0	1.000
DGE	31(12.2%)	13(18.3%)	0.105	26(13.7%)	13(25.5%)	0.035	5(7.8%)	0	0.607
SBO	2(0.8%)	1(1.4%)	0.462	1(0.5%)	1(2.0%)	0.336	1(1.6%)	0	1.000
Gastrointestinal bleeding	2(0.8%)	1(1.4%)	0.504	2(1.1%)	0	1.000	0	1(5.0%)	0.203
Postoperative hemorrhage	1(0.4%)	0	1.000	1(0.5%)	0	1.000	0	0	–
Infectious complications									
Seroma	1(0.4%)	2(2.8%)	0.106	1(0.5%)	1(2.0%)	0.365	0	1(5.0%)	0.203
Wound infection	16(6.3%)	3(4.2%)	0.773	14(7.4%)	3(5.9%)	1.000	2(3.1%)	0	1.000
Wound dehiscence	2(0.8%)	0	1.000	2(1.1%)	0	1.000	0	0	–
Intraabdominal abscess	15(5.9%)	4(5.6%)	1.000	11(5.8%)	3(5.9%)	1.000	4(6.3%)	1(5.0%)	1.000
UTI	14(5.5%)	2(2.8%)	0.539	11(5.8%)	1(2.0%)	0.467	3(4.7%)	1(5.0%)	1.000
Bacteremia/sepsis	3(1.2%)	0	1.000	2(1.1%)	0	1.000	1(1.6%)	0	1.000

CRPOPF: clinically relevant pancreatic fistula, DGE: delayed gastric emptying, SBO: small bowel obstruction, UTI; urinary tract infection

There were no significant differences in any of the following complications: acute respiratory distress syndrome, altered mental status, arrhythmia, central venous catheter infection, hepatic failure, myocardial infarction, pneumonia, renal failure, stroke, transient ischemic attack, or thromboembolism.

Table 3

Complications and Timing of Drain Removal

Group A Patients with Available Date of Drain Removal Data (n=189)			
n (%)	**Early Drain Removal (n=86)**	**Late Drain Removal (n=103)**	**p-value**
Any complications *	24 (27.9%)	51 (49.5%)	0.003
CR-POPF	1 (1.1%)	5 (4.8%)	0.225
Intra-abdominal abscess	2 (2.3%)	9 (8.7%)	0.114

Group B Patients with Available Date of Drain Removal Data (n=45)			
n (%)	**Early Drain Removal (n=4)**	**Late Drain Removal (n=43)**	**p-value**
Any complications *	1 (25.0%)	27 (62.7%)	0.286
CR-POPF	1 (25.0%)	9 (20.9%)	0.442
Intra-abdominal abscess	0	3 (6.9%)	1.000

*Excluding Grade A pancreatic fistula

CR-POPF: clinically relevant postoperative pancreatic fistula