Surgery 165 (2019) 315–322

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Validation of day 1 drain fluid amylase level for prediction of clinically relevant fistula after distal pancreatectomy using the NSQIP database

Fady Daniel, MD[a,1], Hani Tamim, PhD[b,1], Mohammad Hosni, MD[a], Feras Ibrahim, MD[a], Aurelie Mailhac, MSc[b], Faek Jamali, MD, FACS[c,*]

[a] Department of Internal Medicine, Gastroenterology and Hepatology Division, American University of Beirut Medical Center, Beirut, Lebanon
[b] Biostatistics Unit, Clinical Research Institute, American University of Beirut Medical Center, Beirut, Lebanon
[c] Department of Surgery, American University of Beirut Medical Center, Beirut, Lebanon

ARTICLE INFO

Article history:
Accepted 25 July 2018
Available online 7 November 2018

ABSTRACT

Background: The role of postoperative day 1 drain fluid amylase level in predicting clinically relevant postoperative pancreatic fistula is under investigation. In a previous multicenter study conducted on 338 patients undergoing distal pancreatectomy, day 1 drain fluid amylase level has been correlated to the development of a clinically relevant pancreatic fistula and an amylase value of 2,000 U/L was found to be most predictive of the development of clinically relevant postoperative pancreatic fistula. Our objective was to validate the previously established cutoff level for drain fluid amylase on postoperative day 1 after distal pancreatectomy as a predictor for clinically relevant postoperative pancreatic fistula using a different patient population from the National Surgery Quality Improvement Program database.
Methods: We studied all patients undergoing distal pancreatectomy from the National Surgery Quality Improvement Program pancreatectomy specific participant use file from 2014 to 2016. We applied the day 1 drain fluid amylase level of 2,000 U/L cutoff to divide patients into 2 groups and compared clinical outcomes in both groups. Among patients with a day 1 drain fluid amylase level < 2,000 U/L, we compared the patient characteristics of those who developed a clinically relevant postoperative pancreatic fistula to those who did not. Finally, to independently validate the previously defined day 1 drain fluid amylase level, we proceeded to determine the optimal cutoff value of day 1 drain fluid amylase level, which can be used as a predictor for the development of clinically relevant postoperative pancreatic fistula after distal pancreatectomy using a receiving operating characteristic curve.
Results: A total of 1,007 patients underwent distal pancreatectomy. The mean day 1 drain fluid amylase level was 4,290.04 ± 8,492.35 U/L. Clinically relevant postoperative pancreatic fistula occurred in 203 patients (20.2%). Using bivariate analysis, patients with day 1 drain fluid amylase level ≥ 2,000 U/L were more likely to develop clinically relevant postoperative pancreatic fistula (32.5% vs 11.25%, $P < .0001$), to have a higher mean number of days before drain removal (8.83 vs 5.59, $P < .0001$), to have a drain 30 days postoperatively (12.59% vs 3.63%, $P < .0001$), and to undergo percutaneous drainage (13.75% vs 9.69%, $P = .04$). Among patients with a day 1 drain fluid amylase level < 2,000 U/L, 11% of patients went on to develop a clinically relevant postoperative pancreatic fistula. Analysis of this subgroup of patients did not identify any discernable preoperative characteristics that were predictive of this complication. Application of maximal Youden index calculated the day 1 drain fluid amylase level value at 2,000 U/L with a sensitivity of 67.98% and a specificity of 63.81% for clinically relevant postoperative pancreatic fistula, with a positive predictive value of 32.17%, a negative predictive value of 88.75%, and a Youden index of 0.32.
Conclusion: Using a different population of patients and a different data set as well as an independent analysis, we successfully validated a day 1 drain fluid amylase level of 2,000 U/L as striking the best balance in terms of sensitivity and specificity for the detection of clinically relevant postoperative pancreatic

* Reprint requests: Faek Jamali, MD, FACS, Department of Surgery American University of Beirut Medical Center, Cairo Street, Hamra 72020 Beirut, Lebanon.
E-mail addresses: faekjamali@gmail.com, fj03@aub.edu.lb (F. Jamali).
[1] Both authors contributed equally to this paper.

https://doi.org/10.1016/j.surg.2018.07.030

fistula. The identified cutoff might be employed in the design of a trial of early drain removal in patients undergoing distal pancreatectomy.

Introduction

Distal pancreatectomy (DP) is defined as the resection of that portion of the pancreas extending to the midline and not including the duodenum and the distal bile duct.[1] Clinically relevant postoperative pancreatic fistula (CR-POPF) remains the Achilles heel of this operation because it occurs in 5% to 10% of patients, reaching 22% in some series,[2,3] and contributes significantly to perioperative morbidity. Pancreatic fistulas can lead to sepsis and hemorrhage if they are not adequately drained externally and have been associated with prolonged hospitalization and mortality in 20% to 40% of cases.[2] Several risk factors have been associated with CR-POPF after pancreatic resection, including high body mass index, a soft pancreas, a narrow pancreatic duct, increased intraoperative blood loss, prolonged operative time, and drain amylase >4,000 U/L on postoperative day 1.[2,4-7] However, most of the available evidence on the topic was derived from data on patients undergoing pancreaticoduodenectomy. Because CR-POPF after DP has a different cause and clinical manifestation, specific studies are needed to guide surgeons regarding the true incidence of pancreatic fistula and its optimal management.

After DP, the majority of surgeons place routinely closed suction drains to help manage a prospective pancreatic fistula in the hope of converting the leak to a controlled fistula.[8] The International Study Group on Pancreatic Fistulas suggest that the drain effluent amylase level should be routinely analyzed to determine if a pancreatic leak is present.[9-11] As a result, CR-POPF has now been redefined as a drain output of any measurable volume of fluid with an amylase level >3 times the upper limit of institutional normal serum amylase activity, associated with a clinically relevant development or condition related directly to the postoperative pancreatic fistula.[11] Several studies have evaluated the measurement of drain fluid amylase on postoperative day 1 (DFA1) and its ability to predict pancreatic leak as well as guide drain management.[8,12,13] These studies have suggested that a low DFA1 is associated with a low rate of pancreatic fistula and could be used as a guide for early removal of the drain.[8,12,13]

A recent multi-institutional study conducted on 338 patients who underwent DP investigated the relationship between DFA1 and CR-POPF after DP and identified a DFA1 of 2,000 U/L as the optimal value for prediction of CR-POPF.[14] Our aim in this study was to validate these results in a different patient population and a larger database by using the pancreatectomy participant use file (PUF) in the American College of Surgeons National Surgery Quality Improvement Program (ACS-NSQIP) database.

Materials and methods

Data acquisition and patients

The ACS-NSQIP database is a prospective validated outcomes registry designed to provide feedback to member hospitals about 30-day risk-adjusted surgical morbidity and mortality and includes anonymized data for patients' demographic characteristics, functional statuses, admission sources, preoperative risk factors, laboratory data, perioperative variables, and 30-day postoperative outcomes for patients undergoing major surgery in more than 500 participating non-Veterans' Affairs administration hospitals.[15,16] The ACS-NSQIP methodology has previously been described in detail.[17]

For this study, we used the ACS-NSQIP procedure targeted PUF from 2014 to 2016 and extracted all distal pancreatectomy (DP) procedures using current procedural terminology (CPT) 48140, 48145, and 48146. Only patients who had a DFA1 recorded were included in the analysis. According to the NSQIP regulations, all patients who were less than 18 years of age, assigned with American Society of Anesthesiologists score of 6 (brain-death organ donors), underwent hyperthermic intraperitoneal chemotherapy, presented for transplant procedure, or underwent DP because of an occurrence or complication before the procedure or trauma cases[17,18] were excluded.

Definitions and outcomes

The primary outcome in this study was the development of a pancreatic fistula after DP. A pancreatic fistula is defined in the NSQIP as follows:

1. If the surgeon gave the clinical diagnosis along with one of the following: Patient was on nothing by mouth/total parenteral nutrition, drain continued for more than 7 days, percutaneous drainage was performed, reoperation was performed, or a spontaneous wound drainage occurred.
2. Persistent drainage along with one of the following: Patient was on nothing by mouth/total parenteral nutrition, drain continued for more than 7 days, percutaneous drainage performed, or reoperation was performed.

The highest DFA1 was recorded and analyzed. All relevant demographic and clinical data, such as age, sex, and race, along with pancreatic duct size, gland texture, histologic subtype, and type of surgery were included in the analysis.

Analysis

Clinical variables of patients undergoing DP with a recorded DFA1 were analyzed. To evaluate the validity of the previously identified DFA1 of 2,000 U/L, we used it to divide the NSQIP population into 2 groups and compared the clinical outcomes across these 2 groups especially as they pertain to the development of a pancreatic fistula and the duration of drain placement.

Among patients with a DFA1 of < 2,000 U/L, we identified 11% of patients who went on to develop a CR-POPF. We performed an analysis of all the preoperative patient characteristics for the population of patients with a DFA1 < 2,000 U/L, comparing those who developed a CR-POPF versus those who did not to identify if there were any unique characteristics or predictive risk factors for these patients to develop a CR-POPF despite a DFA1 < 2,000 U/L.

Furthermore, to independently validate the previously defined DFA1 level, we proceeded to determine the optimal cutoff value of DFA1 level, which can be used as a predictor for the development of CR-POPF after DP using a receiving operating characteristic curve. The area under the curve was calculated to evaluate the overall prognostic performance of the DFA1 level in the NSQIP population.

Table 1
Demographic and clinical characteristics of the study set

	All (N = *1007*)
Age	60.44 ± 14.42
Sex, female	550 (54.6)
Race, white	832 (88.8)
Disseminated cancer	63 (6.3)
Steroid use for chronic condition	44 (4.4)
Bleeding disorders	31 (3.1)
ASA classification	
I, II	323 (32.2)
III, IV	679 (67.8)
Chemotherapy within 90 days	146 (14.6)
Radiation therapy within 90 days	68 (6.8)
Operative approach	
Laparoscopic	294 (29.2)
Laparoscopic w/ open assist	92 (9.1)
Open (planned)	437 (43.4)
Robotic	102 (10.1)
Other	82 (8.2)
Pancreatic Duct Size*	
<3 mm	150 (60.0)
3–6 mm	56 (22.4)
>6 mm	44 (17.6)
Pancreatic gland texture*	
Soft	266 (57.3)
Intermediate	39 (8.4)
Hard	159 (34.3)
Drain still present at POD 30	75 (7.4)
Pancreatic fistula	203 (20.2)
Delayed gastric emptying	35 (3.5)
Percutaneous drainage	115 (11.4)
If malignant disease, indicate histologic subtype	
Pancreatic adenocarcinoma	284 (51.1)
Neuroendocrine nonfunctioning	127 (22.8)
Neuroendocrine functioning	49 (8.8)
IPMN, invasive	28 (5.0)
Cystadenocarcinoma	2 (0.4)
Other type	66 (11.9)
If benign disease, indicate histologic subtype	
Chronic pancreatitis	109 (21.4)
IPMN, noninvasive	105 (20.6)
Mucinous cystic neoplasm	94 (18.5)
Serous cystadenoma	52 (10.2)
Neuroendocrine w/ no metastases	48 (9.4)
Solid pseudopapillary neoplasm	16 (3.1)
Other	85 (16.7)
Duration of total hospital stay	6.77 ± 5.83
Highest drain amylase (IU) POD 1	4,290.04 ± 8,492.35
No. of days for last pancreatic drain removal after surgery	6.92 ± 6.06

* Indicates factors with missing data.
ASA, American Society of Anesthesiologists; *IPMN*, intraductal papillary-mucinous neoplasm of the pancreas; *POD*, postoperative day.

Ethical consideration

This study was designated exempt from review by the Institutional Review Board at the American University of Beirut Medical Center because the ACS-NSQIP PUF database is deidentified, publicly available, and Health Insurance Portability and Accountability Act compliant.

Results

Between 2014 and 2016, 1,012 patients who underwent DP and had a valid DFA1 were enrolled in the pancreatectomy PUF file and subject to this analysis (Table 1). Women and whites constituted most of the studied population with 54.6% and 88.8%, respectively. The average age was 60.41 ± 14.42. Minimally invasive distal pancreatectomy procedures (lap assisted, laparoscopic, and robotic) were slightly more common than their open counterpart, 48.4% vs 43.6%. Pancreatic adenocarcinoma and neuroendocrine tumors accounted for the majority of the malignant indications (73.9%), whereas chronic pancreatitis was the most common benign pancreatic pathologic condition (21.4%). A total of 57.3% of patients were described as having a soft pancreas and 60% had a pancreatic duct size of <3 mm. CR-POPF occurred in 203 patients (20.2%). It was managed by percutaneous drainage in 115 cases (11.4%). The average of the highest DFA1 was 4,290.04 ± 8,492.35 U/L. The average length of hospital stay was 6.77 ± 5.83 days. The pancreatic drain was kept for an average of 6.92 ± 6.06 days with only 75 patients (7.4%) having a pancreatic drain present at postoperative day 30.

The mean DFA1 level in patients who did not develop a CR-POPF was 3,164.10 ± 6,225.70 U/L, which is significantly different from those who developed a CR-POPF, with a mean of 8,882.10 ± 13,395.00 U/L ($P < .0001$). Similarly, the mean number of days the drain was kept in place after the operation was significantly higher in the patients who developed CR-POPF with 14.52 ± 7.77 compared with 5.58 ± 4.54 days ($P < .0001$).

Table 2
Development of CR-POPF at DFA1 cutoff level of 2,000 U/L

	Amylase		
	<2,000 U/L (n = *578)*	*≥2,000 U/L* (n = *429)*	P
Age	61.67 ± 14.24	58.69 ± 14.5	.0012
Sex, female	312 (53.98)	238 (55.48)	.65
Race, white	478 (89.01)	354 (88.5)	.83
Disseminated cancer	40 (6.92)	23 (5.36)	.36
Steroid use for chronic condition	25 (4.33)	19 (4.43)	1
Operative approach			
Laparoscopic	142 (24.57)	152 (35.43)	
Laparoscopic with open assist	42 (7.27)	50 (11.66)	
Open (planned)	287 (49.65)	150 (34.97)	
Robotic	64 (11.07)	38 (8.86)	
Pancreatic gland texture			
Soft	141 (54.65)	125 (60.68)	.41
Intermediate	24 (9.3)	15 (7.28)	
Hard	93 (36.05)	66 (32.05)	
Drain still present at POD 30	21 (3.63)	54 (12.59)	<.0001
Pancreatic fistula	65 (11.25)	138 (32.17)	<.0001
Percutaneous drainage	56 (9.69)	59 (13.75)	.04
Duration of total hospital stay	7.03 ± 6.67	6.43 ± 4.44	.11
No. of days for last pancreatic drain removal after surgery	5.59 ± 4.75	8.83 ± 7.14	<.0001
Highest drain amylase (IU) POD 1	624.07 ± 574.12	9,229.3 ± 1,1246	<.0001

POD, postoperative day.

Using DFA1 > 2000 U/L as a cutoff

To validate previous studies that suggested DFA1 of more than 2,000 U/L as a cutoff, we divided our population into 2 different groups based on their DFA1 levels (Table 2). Using bivariate analysis, patients with DFA1 levels ≥ 2,000 U/L were more likely to develop CR-POPF (32.17% vs 11.25%, $P < .0001$), to have a higher mean number of days before drain removal (8.83 vs 5.59, $P < .0001$), to have a drain 30 days postoperatively (12.59% vs 3.63%, $P < .0001$), and to undergo percutaneous drainage (13.75% vs 9.69%, $P = .04$). There was no significant difference regarding sex, race, disseminated cancer, steroid use for chronic condition, and history of bleeding disorder between the 2 groups (Table 2).

Comparing patients with DFA1 < 2,000 U/L who developed a CR-POPF versus those who did not

There were overall no statistically significant differences in overall preoperative risk factors between the group of patients with a DFA1 < 2,000 U/L who developed a CR-POPF and those who did not (Table 3). Operative time was noted to be significantly longer in the subgroup of patients who developed a pancreatic fistula. The main significant postoperative differences were the presence of delayed gastric emptying, requirement for percutaneous drainage, and higher percentage of patients who kept their drains for longer than 30 days among those who developed a leak. Duration of stay was also significantly longer in patients who developed a pancreatic fistula.

Derivation of the cutoff of DFA1 for CR-POPF prediction

We defined sensitivity as the fraction of the occurrence and specificity as the fraction of the absence of CR-POPF after DP that could be correctly identified by the method. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) along with Youden's index of various cutoffs for DFA1 were tested, as summarized in Table 4.

This analysis found a statistically significant area under the curve of 0.703 with a standard error of 0.021 and $P < .0001$ (95% confidence interval 0.662–0.744) (Fig. 1). The subsequent application of maximal Youden index calculated the DFA1 level value at

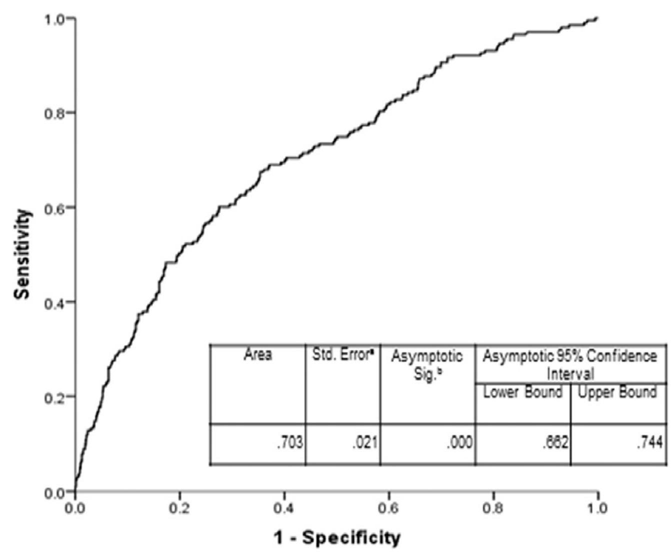

Fig. 1. Receiver operating characteristic curve of postoperative day 1 drain fluid amylase levels.

2,000 U/L with a sensitivity of 67.98% and a specificity of 63.81% for CR-POPF, with PPV and NPV of 32.17% and 88.75%, respectively, and a Youden index of 0.32. Notably, it split the study population equally, because 57.1% of the patients had a DFA1 < 2,000 U/L.

Discussion

Pancreatic fistula is the most common complication after DP, occurring in 3% to 26% of cases.[1, 19-21] Several studies have targeted this problem and tried to identify risk factors for the development of CR-POPF after DP. So far, the most significant indicator seems to be DFA1 level, and previously described cutoff levels, above which patients are more likely to develop CR-POPF, range between 90 and 5,000.[14,22-24] Most previous studies have derived their results based on a small number of cases, which may explain also the wide range of the proposed DFA1 cutoff levels. The largest multicenter study on this topic, by Maggino et al.,[14] investigated

Table 3
Comparison between patients with DFA1 < 2,000 U/L who developed CR-POPF versus those who did not

	Pancreatic fistula		
	No N = *513*	*Yes* N = *65*	P
Sex, female	278 (54.2)	34 (52.3)	.77
Race, white	423 (88.9)	55 (90.2)	.76
Diabetes mellitus with oral agents or insulin	129 (25.2)	17 (26.2)	.86
Current smoker within 1 y	101 (19.7)	15 (23.1)	.52
Dyspnea	30 (5.9)	7 (10.8)	.17
History of severe COPD	23 (4.5)	6 (9.2)	.12
Hypertension requiring medication	260 (50.7)	34 (52.3)	.80
Disseminated cancer	36 (7.0)	4 (6.2)	1.00
Steroid use for chronic condition	23 (4.5)	2 (3.1)	1.00
>10% loss body weight in last 6 months	35 (6.8)	5 (7.7)	.79
Bleeding disorders	18 (3.5)	0 (0.0)	.25
Transfusion >4 units PRBCs in 72 h before surgery	6 (1.2)	0 (0.0)	1.00
Wound classification			.34
Clean	40 (7.8)	2 (3.1)	
Clean/contaminated	414 (80.7)	55 (84.6)	
Contaminated	47 (9.2)	5 (7.7)	
Dirty/infected	12 (2.3)	3 (4.6)	
ASA classification			.62
I	3 (0.6)	0 (0.0)	
II	134 (26.2)	13 (20.3)	
III	338 (66.1)	48 (75.0)	
IV	36 (7.1)	3 (4.7)	
Chemotherapy within 90 days	92 (18.1)	14 (21.5)	.50
Radiation therapy within 90 days	48 (9.5)	6 (9.2)	.95
Days from hospital admission to operation	35 (6.8)	2 (3.1)	.42
Elective surgery	486 (94.7)	63 (96.9)	.76
Preoperative obstructive Jaundice	4 (0.8)	1 (1.5)	.45
Preoperative biliary stent	10 (2.1)	3 (5.2)	.17
Chemotherapy within 90 days	92 (18.1)	14 (21.5)	.50
Radiotherapy within 90 days	48 (9.5)	6 (9.2)	.95
Operative approach			.81
Laparoscopic	130 (25.3)	12 (18.5)	
Laparoscopic with open assist	36 (7.0)	6 (9.2)	
Laparoscopic with unplanned conversion to open	34 (6.6)	4 (6.2)	
Open (planned)	253 (49.3)	34 (52.3)	
Robotic	55 (10.7)	9 (13.9)	
Robotic with open assist	2 (0.4)	0 (0.0)	
Robotic with unplanned conversion to open	3 (0.6)	0 (0.0)	
Pancreatic duct size			.67
<3 mm	68 (54.8)	10 (55.6)	
3–6 mm	37 (29.8)	4 (22.2)	
>6 mm	19 (15.3)	4 (22.2)	
Pancreatic gland texture			.62
Soft	127 (54.3)	14 (58.3)	
Intermediate	21 (9.0)	3 (12.5)	
Hard	86 (36.7)	7 (29.2)	
Pancreatic reconstruction	3 (0.6)	1 (1.6)	.38
Gastrojejunostomy or duodenojejunostomy	3 (1.2)	1 (3.5)	.36
Drain type			.39
Biliary anastomosis	1 (0.5)	0 (0.0)	
Pancreatic & biliary anastomosis	3 (1.3)	1 (3.8)	
Pancreatic anastomosis	33 (14.7)	2 (7.7)	
Pancreatic parenchyma	187 (83.5)	23 (88.5)	
Vascular resection	46 (9.0)	12 (18.7)	.01
Drain still present at POD 30	8 (1.6)	13 (20.0)	<.0001
Delayed gastric emptying	7 (1.9)	9 (13.9)	<.0001
Percutaneous drainage	32 (6.2)	24 (36.9)	<.0001
If malignant disease, indicate histologic subtype			.76
IPMN, invasive	14 (4.8)	2 (5.4)	
Neuroendocrine functioning	16 (5.4)	3 (8.1)	
Neuroendocrine nonfunctioning	50 (17.0)	4 (10.8)	
Other type	34 (11.5)	3 (8.1)	
Pancreatic adenocarcinoma	181 (61.4)	25 (67.6)	
T (tumor) stage			.51
T0	4 (1.4)	0 (0.0)	
T1	44 (15.8)	10 (28.6)	
T2	64 (23.0)	7 (20.0)	
T3	158 (56.8)	17 (48.6)	
T4	5 (1.8)	1 (2.9)	
Tis	1 (0.4)	0 (0.0)	
Tx	2 (0.7)	0 (0.0)	

(*continued on next page*)

Table 3 (*continued*)

	Pancreatic fistula		
	No N = *513*	*Yes* N = *65*	P
N (node) stage			.74
N0	166 (60.1)	20 (58.8)	
N1	101 (36.6)	12 (35.3)	
Nx	9 (3.3)	2 (5.9)	
M (metastases) stage			.49
M0/Mx	206 (90.7)	24 (85.7)	
M1	21 (9.3)	4 (14.3)	
If benign disease, indicate histologic subtype			.94
Chronic pancreatitis	66 (26.8)	9 (26.5)	
IPMN, noninvasive	49 (19.9)	7 (20.6)	
Mucinous cystic neoplasm	36 (14.6)	5 (14.7)	
Neuroendocrine with no metastases	21 (8.5)	1 (2.9)	
Other	44 (17.9)	7 (20.6)	
Serous cystadenoma	27 (11.0)	5 (14.7)	
Solid pseudopapillary neoplasm	3 (1.2)	0 (0.0)	
If benign, tumor size			.15
<2 cm	38 (25.2)	9 (45.0)	
2–5 cm	82 (54.3)	9 (45.0)	
>5 cm	31 (20.5)	2 (10.0)	
Age	61.72 ± 14.26	61.26 ± 14.21	.81
BMI	27.89 ± 6.23	28.52 ± 6.36	.45
Preoperative serum sodium	139.18 ± 3.04	139.54 ± 3.30	.38
Preoperative BUN	15.42 ± 6.91	14.53 ± 4.97	.21
Preoperative serum creatinine	0.94 ± 0.82	0.82 ± 0.20	.01
Preoperative serum albumin	4.02 ± 0.53	4.01 ± 0.48	.88
Preoperative total bilirubin	0.53 ± 0.31	0.51 ± 0.26	.65
Preoperative AST	24.57 ± 16.27	24.44 ± 10.97	.94
Preoperative alkaline phosphatase	87.36 ± 48.06	85.61 ± 26.58	.68
Preoperative hematocrit	38.75 ± 5.41	39.23 ± 4.13	.41
Preoperative platelet count	229.21 ± 100.27	240.84 ± 95.07	.38
Total operation time	245.24 ± 106.98	285.48 ± 117.27	.004
Duration of total hospital stay	6.71 ± 6.31	9.52 ± 8.66	.01
Highest drain amylase			
POD 2–POD 30 (IU)	483.81 ± 1901.9	18,999 ± 30,523	<.0001
No. of days with highest amylase			
Level after surgery	2.65 ± 2.14	8.44 ± 7.58	<.0001
No. of days for last pancreatic drain removal after surgery	5.02 ± 3.72	11.73 ± 8.66	<.0001
Highest drain amylase (IU) POD 1	616.84 ± 579.69	681.14 ± 528.80	.39

ASA, American Society of Anesthesiologists; *AST*, aspartate aminotransferase; *BMI*, body mass index; *BUN*, blood urea nitrogen; *COPD*, chronic obstructive pulmonary disease; *IPMN*, intraductal papillary-mucinous neoplasm of the pancreas; *MIS*, minimally invasive surgery; *POD*, postoperative day; *PRBC*, packed red blood cells.

Table 4
Analyzing different cutoff values, using sensitivity, specificity, negative predictive value, positive predictive value, and Youden index

Amylase cutoff	*Sensitivity*	*Specificity*	*Youden index*	*Positive predictive value*	*Negative predictive value*
500	84.73 (78.87–89.24)	34.95 (31.67–38.37)	0.20	24.75 (21.62–28.16)	90.06 (86.06–93.05)
1000	75.86 (69.27–81.45)	47.39 (43.90–50.91)	0.23	26.69 (23.16–30.53)	88.60 (85.12–91.37)
1500	71.43 (64.60–77.42)	56.09 (52.58–59.55)	0.27	29.12 (25.20–33.36)	88.60 (85.44–91.17)
2000	67.98 (61.02–74.24)	63.81 (60.36–67.12)	0.32	32.17 (27.81–36.85)	88.75 (85.82–91.16)
2500	60.59 (53.48–67.29)	70.27 (66.96–73.39)	0.31	33.98 (29.16–39.14)	87.60 (84.74–89.99)
3000	57.14 (50.02–63.99)	73.88 (70.67–76.86)	0.31	35.58 (30.43–41.08)	87.22 (84.43–89.59)
3500	55.17 (48.05–62.09)	75.62 (72.47–78.52)	0.31	36.36 (31.03–42.04)	86.98 (84.21–89.34)
4000	52.22 (45.12–59.22)	78.98 (75.96–81.71)	0.30	38.54 (32.81–44.60)	86.75 (84.03–89.08)
4500	48.28 (41.26–55.36)	81.59 (78.70–84.18)	0.30	39.84 (33.73–46.27)	86.20 (83.50–88.53)
5000	46.30 (39.34–53.41)	83.08 (80.27–85.57)	0.29	40.87 (34.51–47.54)	85.97 (83.28–88.30)

338 patients with DP and proposed 2,000 U/L as an optimal cutoff value in predicting CR-POPF and used a validation set of another 166 patients to validate their results.[14] Our data using the NSQIP targeted pancreatectomy PUF data set from 2014–2016 included more than 1,000 patients who underwent DP; all of them had a valid DFA1, which therefore would represent the largest study population of DP focusing on a specific DFA1 cutoff value. Compared with the validation set used by Maggino et al.,[14] our data are more complete. Only 166 patients (50%) of the validation set used by Maggino et al.[14] had DFA1 recorded. Moreover, out of the 166 patients, 71.7% of the patients had DFA1 < 2,000 U/L, thus splitting the validation set unevenly.

Using the DFA1 of 2,000 U/L as a cutoff, as suggested by Maggino et al.,[14] we confirmed that patients presenting with a DFA1 level > 2,000 U/L have a significantly higher chance of developing CR-POPF. In our study population 65 patients (11.25%) with DFA1 level < 2,000 U/L developed CR-POPF compared with 138 of those who had DFA1 ≥ 2,000 U/L (32.17%). In our data set a DFA1 of 2,000 U/L had the highest sensitivity and specificity (67.98% and 63.81%, respectively) for the detection of CR-POPF. Moreover, it has a high NPV of 88.7, making it easier to identify patients with low risk of developing CR-POPF. A total of 57.1% of patients had DFA1 < 2,000 U/L, making them potentially suitable for early drain removal and possible accelerated postoperative recovery pathways. Despite this statistically significant result, we understand the clinical management of patients with DP still represents a complex challenge and clinical decisions of early drain removal mat not be solely based on DFA1 level values. If all patients with DFA1 < 2,000 U/L were assumed to be safe from developing a CR-POPF and had their drain removed, 65 patients would have been misleadingly classified because these patients would have had their drain removed and still developed a CR-POPF. Although by applying this cutoff level of 2,000 U/L, we would be able to reduce the cases where the drain is kept to 42.9% of all patients who had DP ($n = 434$), we would be achieving this reduction at the cost of 65 patients (6.4%) who would have their drain removed and still develop CR-POPF. Indeed, this illustrates the fact that DFA1 is a modest predictor of CR-POPF with a maximum positive predictive value of 40%, irrespective of cutoff used. On the other hand, its NPV is not significantly compromised by increasing cutoff levels.

To further validate the previously determined cutoff DFA1 level, we conducted a sensitivity analysis of the DFA1 using Youden index and receiving operating characteristic analysis. Although DFA1 = 2,000 U/L meets the selection criteria of ideal balance between sensitivity and specificity, lowering the DFA1 cutoff value may be more relevant clinically. As a matter of fact and as demonstrated in Table 3, the lower the DFA1 level, the higher the sensitivity for the detection of CR-POPF. If we use a DFA1 of 500 U/L, the sensitivity reaches almost 85% and the NPV is >90%, which may be a more clinically relevant target to guide actual decision making such as early drain removal, accelerated recovery pathways, and early discharge planning, because this will permit an unnecessary prolonged drainage that might itself increase postoperative morbidity.[25,26] This increased sensitivity comes at the expense of lower specificity, which has little impact on actual clinical decision-making.

The routine use of drains after distal pancreatectomy and its potential impact on postoperative outcomes as well as incidence of pancreatic fistula remains in itself a subject of intense debate. Despite significant evidence from randomized controlled trials indicating the lack of benefit of routine intraperitoneal drainage after distal pancreatectomy,[27,28] the practice of placing drains in the postoperative period remains very common in surgical practice today. Reasons for the continued routine use of drains after pancreatic surgery are many and include lack of awareness, lack of trust in the strength of the data, and surgeon habit. When drains are placed postoperatively, there is currently little guidance regarding the optimal timing for their removal. The use of a DFA1 level of 2,000 U/L as an outline in this and other studies may help guide early drain removal.

In addition to its retrospective nature, one of the limitations of the study is that it employed a different definition of CR-POPF than that in the multicenter trial. The definition of CR-POPF in the NSQIP database is based on surgeon's judgment along with more than 1 week of persistent drainage, total parenteral nutrition use, or percutaneous drainage requirement. Maggino et al.[14] used a more stringent definition in accordance with the 2016 International Study Group of Pancreatic Fistula consensus definition.[14] Nevertheless, the prevalence of CR-POPF was the same (20.6%) in both of our development cohorts. The 2,000 U/L DFA1 cutoff still remained the best significant statistical compromise in our study. Giglio et al.[29] have suggested in their meta-analysis adopting 2 cutoff values, the lower to improve sensitivity (rule-out value) and the higher to improve the specificity (rule-in value).

In conclusion, we have effectively validated the DFA1 amylase level of 2,000 in patients undergoing DP using the NSQIP database population. The study results are strengthened by the strict data collection methodology of the ACS-NSQIP database and its large number of patients with complete data available for analysis. This study represents the largest population study to date on the subject. A DFA1 level of 2,000 U/L strikes the best balance in terms of sensitivity and specificity for the detection of CR-POPF. In the model we presented, the analysis was based on finding the best combination of sensitivity, specificity, NPV, and PPV. The identified cutoff may be used in the design of a trial of early drain removal in patients undergoing DP.

References

1. Lillemoe KD, Kaushal S, Cameron JL, Sohn TA, Pitt HA, Yeo CJ. Distal pancreatectomy: indications and outcomes in 235 patients. *Ann Surg*. 1999;229:693–698 discussion 698-700.
2. Lai EC, Lau SH, Lau WY. Measures to prevent pancreatic fistula after pancreatoduodenectomy: a comprehensive review. *Arch Surg*. 2009;144:1074–1080.
3. Cullen JJ, Sarr MG, Ilstrup DM. Pancreatic anastomotic leak after pancreaticoduodenectomy: incidence, significance, and management. *Am J Surg*. 1994;168:295–298.
4. El Nakeeb A, Salah T, Sultan A, El Hemaly M, Askr W, Ezzat H, et al. Pancreatic anastomotic leakage after pancreaticoduodenectomy. Risk factors, clinical predictors, and management (single center experience). *World J Surg*. 2013;37:1405–1418.
5. Graham JA, Kayser R, Smirniotopoulos J, Nusbaum JD, Johnson LB. Probability prediction of a postoperative pancreatic fistula after a pancreaticoduodenectomy allows for more transparency with patients and can facilitate management of expectations. *J Surg Oncol*. 2013;108:137–138.
6. Yeh TS, Jan YY, Jeng LB, Hwang TL, Wang CS, Chen SC, et al. Pancreaticojejunal anastomotic leak after pancreaticoduodenectomy—multivariate analysis of perioperative risk factors. *J Surg Res*. 1997;67:119–125.
7. 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.
8. McMillan MT, Malleo G, Bassi C, Allegrini V, Casetti L, Drebin JA, et al. Multicenter, prospective trial of selective drain management for pancreatoduodenectomy using risk stratification. *Ann Surg*. 2017;265:1209–1218.
9. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. 2005;138:8–13.
10. Butturini G, Daskalaki D, Molinari E, Scopelliti F, Casarotto A, Bassi C. Pancreatic fistula: definition and current problems. *J Hepatobiliary Pancreat Surg*. 2008;15:247–251.
11. 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.
12. Israel JS, Rettammel RJ, Leverson GE, LR1 Hanks, CS1 Cho, Winslow ER, et al. Does postoperative drain amylase predict pancreatic fistula after pancreatectomy? *J Am Coll Surg*. 2014;218:978–987.
13. Lee CW, Pitt HA, Riall TS, Ronnekleiv-Kelly SS, Israel JS, Leverson GE, et al. Low drain fluid amylase predicts absence of pancreatic fistula following pancreatectomy. *J Gastrointest Surg*. 2014;18:1902–1910.
14. Maggino L, Malleo G, Bassi C, Allegrini V, Beane JD, Beckman RM, et al. Identification of an optimal cut-off for drain fluid amylase on postoperative day 1 for predicting clinically relevant fistula after distal pancreatectomy: a multi-institutional analysis and external validation. *Ann Surg*. 2017.
15. Khuri SF, Henderson WG, Daley J, Jonasson O, Jones RS, Jr CampbellDA, et al. The patient safety in surgery study: background, study design, and patient populations. *J Am Coll Surg*. 2007;204:1089–1102.
16. Fink AS, Campbell Jr DA, Mentzer Jr RM, Henderson WG, Daley J, Bannister J, et al. The National Surgical Quality Improvement Program in non-veterans administration hospitals: initial demonstration of feasibility. *Ann Surg*. 2002;236:344–353 discussion 353-4.
17. Shiloach M, Frencher SK, Steeger JE, Rowell KS, Bartzokis K, Tomeh MG, et al. Toward robust information: data quality and inter-rater reliability in the American College of Surgeons National Surgical Quality Improvement Program. *J Am Coll Surg*. 2010;210:6–16.
18. American College of Surgeons. User Guide for the 2016 ACS NSQIP Procedure Targeted Participant Use Data File (PUF). *Chicago (IL): American College of Surgeons*. 2017:1–83.
19. Fahy BN, Frey CF, Ho HS, et al. Morbidity, mortality, and technical factors of distal pancreatectomy. *Am J Surg*. 2002;183:237–241.
20. Bilimoria M, Cormier J, Mun Y, Lee JE, Evans DB, Pisters PW, et al. Pancreatic leak after left pancreatectomy is reduced following main pancreatic duct ligation. *Br J Surg*. 2003;90:190–196.
21. Pannegeon V, Pessaux P, Sauvanet A, Vullierme MP, Kianmanesh R, Belghiti J, et al. Pancreatic fistula after distal pancreatectomy: predictive risk factors and value of conservative treatment. *Arch Surg*. 2006;141:1071–1076 discussion 1076.
22. Molinari E, Bassi C, Salvia R, Butturini G, Crippa S, Talamini G, 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.

23. Nathan H, Cameron JL, Goodwin CR, Seth AK, Edil BH, Wolfgang CL, et al. Risk factors for pancreatic leak after distal pancreatectomy. *Ann Surg*. 2009;250:277–281.
24. Lee MK, Lewis RS, Strasberg SM, Hall BL, Allendorf JD, Beane JD, et al. Defining the postoperative morbidity index for distal pancreatectomy. *HPB (Oxford)*. 2014;16:915–923.
25. Kawai M, Tani M, Terasawa H, Ina S, Hirono S, Nishioka R, 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;244:1–7.
26. Bassi C, Molinari E, Malleo G, Crippa S, Butturini G, Salvia R, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg*. 2010;252:207–214.
27. Van Buren G, Bloomston M, Schmidt CR, Behrman SW, Zyromski NJ, Ball CG, et al. A prospective randomized multicenter trial of distal pancreatectomy with or without routine intraperitoneal drainage. *Ann Surg*. 2017;266:421–431.
28. Schorn S, Nitsche U, Demir IE, Scheufele F, Tieftrunk E, Schirren R, et al. The impact of surgically placed intraperitoneal drainage on morbidity and mortality after pancreas resection: a systematic review and meta-analysis. *Pancreatology*. 2018;18:334–345.
29. Giglio MC, Spalding DR, Giakoustidis A, Zarzavadjian Le Bian A, Jiao LR, Habib NA, et al. Meta-analysis of drain amylase content on postoperative day 1 as a predictor of pancreatic fistula following pancreatic resection. *Br J Surg*. 2016;103:328–336.