Using NSQIP data to determine when drains can be safely remove after pancreaticoduodenectomy

Laura Nicolais
Maine Medical Center
Abdimajid Mohamed BS
Tufts University
Timothy L. Fitzgerald (tlfitzgera@mmc.org)
Maine Medical Center

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Abstract

Purpose: Prior retrospective studies demonstrate the need for drainage after pancreatoduodenectomy. Early drain removal is a key component of most ERAS pathways; however, little consensus on timing and cutoff for amylase analysis exists. This study aimed to identify the ideal combination of postoperative day and drain amylase level for safe drain removal.

Methods: This retrospective cohort study used the NSQIP database to study outcomes of pancreatoduodenectomy patients.

Results: 7,583 patients underwent pancreatoduodenectomy with drain placement. 1,458 (19%) had a clinically relavent postoperative pancreatic fistula (CR-POPF). Of those, 7% had their highest drain amylase on day 1, compared to 29% and 64% on day 3-5 and 5, respectively ($p < 0.001$). An amylase level >300 U/L corresponded to a 46% chance of CR-POPF compared to 4.9% with amylase <300 U/L ($p < 0.001$). Drain amylase >5000 U/L, corresponded to 71.2% chance of CR-POPF compared to 11.2% with amylase <5000 U/L ($p < 0.001$). Compared to >5000 U/L, an amylase cutoff of >300 U/L had a lower specificity on day 1 (93%, CI: 0.92, 0.93) and further decreases on postoperative day 3-5 (81%, CI: 0.79-0.98). The sensitivity of a cutoff >300 U/L was superior: 24% (CI: 0.19-0.29) on postoperative day 1 but increased significantly to 72% (CI: 0.67-0.76) on postoperative days 3-5.

Conclusions: Current recommendations utilizing 5000 U/L will miss 6% of patients with CR-POPF. We recommend checking drain amylase on postoperative day three and to use 300 U/L as a cutoff for early drain removal protocols.

Introduction

The indication for pancreaticoduodenectomy (PD) includes both malignant and benign pancreatic pathologies. Although improvements in perioperative care have reduced the morbidity and mortality associated with this procedure, morbidity rates remain high and are estimated between 27–60 percent [1–3]. One of the most common and potentially devastating postoperative complications is a pancreatic fistula [4–6]. It occurs after 13–25% of cases and is associated with increased rates of sepsis, hemorrhage, length of stay, health care cost, and death [4, 7–9]. Given the potential significant impact of a pancreatic fistula, many investigators have focused on optimizing safe ways to prevent and monitor for this complication.

At many institutions, drain placement in the pancreatic operative bed is routine practice;[10] however, there is debate regarding the use of drains and the optimal protocol for their removal[9–16]. The most recent pancreaticoduodenectomy specific guidelines from the European ERAS Society, recommend routine use of perianastomotic drains with early drain removal on postoperative day three if the amylase level is < 5000 U/L on day one [17]. Postoperative day one drain fluid amylase has demonstrated predictive value for clinically relavant postoperative pancreatic fistula (CR-POPF) in multiple retrospective and prospective studies [10, 12–14, 18–21]. In contrast, other research suggests obtaining amylase levels

on postoperative day three may be superior [22, 23]. The clinical significance of elevated amylase levels on postoperative day one versus day three is unclear. It appears, in these prior publications, day for amylase screening was chosen arbitrarily.

It is equally unclear which cutoff for drain amylase ideally predicts the risk for clinically relevant postoperative pancreatic fistula (CR-POPF). The International Study Group on Pancreatic Fistula defined a CR-POPF as any drain output with an amylase level > 3 times the upper limit of normal serum amylase [24]. Studies vary significantly on the optimal amylase level to best predict CR-POPF, ranging from 100–5000 U/L without consensus [5, 13, 18, 25–27]. One metanalysis reviewed 13 studies and identified a postoperative day one drain amylase of < 100 U/L to be associated with a 3% rate of CR-POPF [27]. The authors noted only 34% of patients met this criterion and therefore suggest an amylase of < 350 U/L, representing 50% of patients, as a more clinically relevant cutoff. Finally, a study by Maggino et al. identified 2000 U/L as the ideal postoperative day one drain amylase cutoff for identifying CR-POPF [18].

There is little consistency in data to support the recommended timing and cutoff for drain amylase analysis. Therefore, using the NSQIP database, this study aimed to identify the ideal combination of postoperative day and drain amylase level for safe drain removal.

Materials And Methods

Study Design and Data Collection:

This study is a retrospective cohort study utilizing the National Surgical Quality Improvement Program (NSQIP) database from 2015–2018. The NSQIP database is a prospectively collected database with over 1,000,000 cases submitted from over 700 sites every year [28]. This study included all patients who underwent pancreaticoduodenectomy (PD) (CPT 48153 and 48154) with drain placement. Subjects with missing data were excluded. This study was approved by the IRB at our institution.

Those included were divied into two groups: those with a CR-POPF (Grade B and Grade C fistula) and those without CR-POPF. We then utilized the International Study Group (ISGPS) definition for grading a clinically relevant postoperative pancreatic fistula (CR-POPF) [24]. ISGPS defines a CR-POPF as any fistula that results in a drain output of any measurable volume of fluid with amylase level greater than three times the upper institutional normal serum amylase level, associated with a clinically relevant development/condition related directly to the POPF. Examples include prolongation of hospital or ICU stay, need for therapeutic inteventions to manage the fistula or postoperative organ failure. Only subjects with a biochemical leak and grade B or grade C fistula were defined as having CR-POPF.

The assessment utilized two factors: postoperative day and amylase level. We created three groups based on the post operative day of highest amylase: 1, 3–5, or > 5. Based on the literature, we defined drain amylase cutoffs of 300 U/L and 5000 U/L.[17, 24]

Outcome:

The primary outcomes were specificity, sensitive and negative predictive value (NPV) for all combinations of postoperative day and drain amylase cutoff.

Statistical Analysis:

Statistical analysis utilized R software. When assessing differences between patients with CR-POPF and those without, univariate analysis was conducted using Pearsons Chi-squared test for categorical variables and 2-sample T-test for continuous variables. Significance was defined at $p < .05$ for all tests. Further analysis for sensitivity, specificity and negative predictive value (NPV) were performed for all combinations of postoperative day (i.e 1, 3–5, 5) and drain amylase cutoff (i.e. 300 or 5000 U/L).

Results

A total of 7,544 patients who underwent pancreaticoduodenectomy (PD) met inclusion criteria. Table 1 reviews the demographics of the study groups. In these cohorts, 1,458 (19%) had CR-POPF and 6,086 (81%) had no CR-POPF. Patients were similar in ASA class ($p = 0.14$) only. Patient groups differed by age ($p = 0.012$), sex ($p < 0.001$), BMI ($p < 0.001$), race ($p < 0.001$), pancreatic duct size ($p < 0.001$) and gland texture ($p < 0.001$). Men had a higher rate of CR-POPF (21% vs. 16.5%, $p < 0.001$) as did those with smaller duct size (< 3 mm, 25.5% vs. 3-6mm, 16.8% vs. >3mm, 11.1%) and softer pancreatic texture (soft, 30.3% vs. intermediate, 13.5% vs. hard, 8.6%). Those with CR-POPF had a higher average BMI (28.5 vs. 27.0).

Table 1
Demographics of all patients, by occurrence of CR-POPF

	Overall (N = 7,544)	**CR-POPF (N = 1458)**	**No CR-POPF (N = 6,086)**	**P-value**
Age (mean)	65.0	64.3	65.2	0.012
Sex				< 0.001
Female	3,396 (45%)	560 (16.5%)	2,836 (83.5%)	
Male	4,148 (55%)	898 (21.6%)	3,250 (78.4%)	
Race				< 0.001
White	5,692 (75%)	1,050 (18.4%)	4,642 (81.6%)	
Black	562 (7.4%)	87 (615.5%)	475 (84.5%)	
Other	343 (4.5%)	78 (22.7%)	265 (77.3%)	
Unknown	947 (13%)	243 (25.7%)	704 (74.3%)	
BMI (mean)	27.3	28.5	27.0	< 0.001
ASA Classification				0.14
Class 1–2	1,763 (23.4%)	362 (20.5%)	1,401 (79.5%)	
Class 3–4	5,769 (76%)	1,092 (18.9%)	4,677 (81.1%)	
Class 5	2 (< 0.1%)	1 (50%)	1 (50%)	
Not specified	8 (0.1%)	1 (12.5%)	7 (87.5%)	
Pancreas Duct Size				< 0.001
< 3 mm	2,025 (27%)	522 (25.8%)	1,503 (74.2%)	
3–6 mm	2,964 (39%)	499 (16.8%)	2,465 (83.2%)	
> 3 mm	910 (12%)	101 (11.1%)	809 (88.9%)	
Unknown	1,645 (22%)	336 (20.4%)	1,309 (79.6%)	
Pancreas Gland Texture				< 0.001
Soft	2,687 (36%)	811 (30.2%)	1,876 (69.8%)	
Intermediate	599 (7.9%)	81 (13.5%)	518 (86.5%)	
Hard	2,391 (32%)	205 (8.6%)	2,186 (91.4%)	
Unknown	1,867 (25%)	361 (19.3%)	1,505 (80.6%)	

Table 2 demonstrates data about subgroup analysis. There was a trend towards increased CR-POPF when measuring drain amylase on a later postoperative day. Of those with CR-POPF, 7% had their highest measured drain amylase on day 1, compared to 29% on day 3–5 and 64% on day 5 ($p < 0.001$). For analysis of drain fluid amylase cutoffs, 2,614 patients had an amylase level > 300 U/L. Of those with an amylase level > 300 U/L, 46% had CR-POPF compared to 4.9% for those with drain amylase < 300 U/L ($p < 0.001$). In contrast, 1,014 patients had drain amylase > 5000 U/L. For those with drain amylase > 5000 U/L, 71.2% had a CR-POPF compared to 11.2% of those with drain amylase < 5000 U/L ($p < 0.001$).

Table 2
Postoperative day and amylase cutoffs, by CR-POPF

	Overall (N = 7,544)	**CR-POPF (N = 1,458)**	**No CR-POPF (N = 6,086)**	**P-value**
Post-operative day				< 0.001
1	975 (13%)	99 (10.2%)	876 (89.8%)	
3–5	3,416 (46%)	422 (12.4%)	2,994 (87.6%)	
5	3,102 (41%)	935 (30.1%)	2,167 (69.9%)	
Unknown	51	2 (3.9%)	49 (96.1%)	
Amylase Cutoff (U/L)				< 0.001
< 300	4,741 (64%)	232 (4.9%)	4,509 (95.1%)	
> 300	2,614 (36%)	1,203 (46%)	1,411 (54%)	< 0.001
< 5000	6,341 (86%)	713 (11.2%)	5,628 (88.8%)	
> 5000	1,014 (14%)	722 (71.2%)	292 (28.8%)	

Table 3 reviews the test characteristics for each combination of postoperative day and drain fluid amylase levels. The highest specificity (98%) corresponds with the higher drain amylase level of > 5000 U/L for both postoperative day 1 and days 3–5. The sensitivity of an amylase > 5000 U/L is relatively low on postoperative day 1 (6%) but increases to 23% on postoperative days 3–5.

Table 3
Test characteristics for all combinations of postoperative day and amylase cutoff

	Sensitivity (CI)	Specificity (CI)	Negative Predictive Value (CI)
POD1, Amylase > 300	0.24 (CI 0.19–0.29)	0.93 (CI 0.92–0.93)	0.95 (CI 0.94–0.96)
POD 1, Amylase > 5000	0.06 (CI .04-.08)	0.98 (CI 0.98–0.99)	0.88 (CI 0.87–0.89)
POD 3–5, Amylase > 300	0.72 (CI 0.67–0.76)	0.81 (CI 0.79–0.83)	0.94 (CI 0.93–0.95)
POD 3–5, Amylase > 5000	0.23 (CI 0.20–0.27)	0.98 (CI 0.97–0.98)	0.86 (CI 0.85–0.88)

Compared to > 5000 U/L, an amylase cutoff of > 300 U/L had a lower specificity on day one (93%, CI: 0.92, 0.93) and further decreases on postoperative day 3–5 (81%, CI: 0.79–0.98). The sensitivity of a cutoff > 300 U/L was superior. This sensitivity was 24% (CI: 0.19–0.29) on postoperative day 1 but increased significantly to 72% (CI: 0.67–0.76) on postoperative days 3–5. The negative predictive value was highest for drain amylase > 300 U/L (95% on postoperative day 1 and 94% on postoperative day 3–5) when compared to an amylase > 5000 U/L (88% on day 1 and 86% on day 3–5).

Discussion

This study aimed to identify the ideal combination of drain amylase cutoff and postoperative day on which to test drain amylase. Despite a large volume of published literature addressing this question, there is no clear consensus. We found that testing on postoperative day 3–5 and using an amylase cutoff of 300 U/L, is the most internally valid combination. This screening provides the best overall combination of sensitivity, specificity, and NPV. Further, those with a drain amylase level above either cutoff, 300 U/L or 5000 U/L, were significantly more likely to have a CR-POPF. Interestingly, using a cutoff of > 5000 U/L, missed approximately 6% of the CR-POPF that would have been identified using a cutoff of > 300 U/L.

Data supporting drain placement after pancreaticoduodenectomy is conflicting. Two randomized, controlled trials argue against the use of routine drainage [11, 16]. Unfortunately, these studies did have limitations. One included patients undergoing pancretectomy and thus was not limited to pancreaticoduodenectomies while the second had a high number of protocol violations, i.e. drains placed in the nondrain group. In contrast, a third randomized trial enrolling patients from multiple centers across the United States was terminated early secondary to increased mortality in the no drain group [9]. In a subsequent planned *a priori* subset analysis, the investigators noted the increased mortality was confined to high-risk patients [29]. Based on this data, routine drain placement remains standard care for most patients.

Given the potential downsides of prolonged or unnecessary drainage, optimal drain management is imperative after pancreaticoduodenectomy. Prolonged drainage may result in increased rates of infection and anastomotic dehiscence; however, removing a drain too early, risks an undrained pancreatic leak [9, 30]. Current guidelines from the European and American ERAS Societies recommend removal on postoperative day three if drain amylase level is < 5000 U/L on day one [17]. These recommendations are derived from prospective and retrospective trials. Bassie et al. conducted a randomized controlled study of 114 patients reporting decreased CR-POPF with early drain removal on day three versus day five [12]. Ven Fong found drain amylase levels on day one were predictive of CR- POPF [13].

Although several investigators report similar predictive values for postoperative day one amylase levels, most guidelines recommend removal of drains on postoperative day three [21]. There is no clear data to support why testing and removal are separated by two days. We found of those who developed CR-POPF, more patients had their highest amylase measurement further from surgery. In those who did not develop a CR-POPF, we see a progressive decrease in risk on later days. Nissen et al. found this same temporal trend [26]. These data suggest that measuring drain amylase earlier may lead to overlooking some patients with CR-POPF. In contrast, a meta-analysis with pooled results from 10 trials compared testing on day one and three [31]. Testing on postoperative day one had higher sensitivity, specificity and AUC compared to day 3 (sensitivity 81%, specifivity 87%, AUC 0.89 vs. sensitivity 56%, specificity 79%, AUC .67). This clearly opposes our results; however, of the 10 studies included all were single institutions (N = 65–471) with the exception of one multicenter study (N = 1,239). In contrast, Lee et al. reported drain amylase on postoperative day three as the superior predictor of CR-POPF (AUC 0.89, CI: 0.82–0.96), when compared to day one (AUC 0.78, CI: 0.69–0.87) or 5 (AUC 0.76, CI: 0.66–0.85) [22]. These findings are consistent with our sensitivity calculations which reflect increased sensitivity for levels reported on postoperative day three.

Numerous reports have examined potential drain amylase cutoff levels. Results range from 100–5000 U/L thus leaving a question of which cuttoff is ideal [5, 13, 18, 25–27, 32, 33]. These studies were performed with smaller sample sizes relative to our study and most were performed at single institutions. Ven Fong et al. included 126 patients and reported 600 U/L afforded the best accuracy (86%), sensitivity (93%) and specificity (79%) [13]. This level was further validated in a subsequent second cohort of 369 patients. Using similar study designs Sutcliffe et al., Maggino et al., and Kawai et al. recommended cutoffs of 350 U/L, 2,000 U/L and 4,000 U/L, respectively [18, 32, 33]. Based on our analysis, we conclude that a cutoff of > 300 U/L allowed for a lower rate of missed CR-POPF when compared to a cutoff of > 5000 U/L; 4.9% of those with an amylase < 300 U/L experienced a CR-POPF compared to 11.2% with amylase < 5000 U/L. Our data is advantaged by a large sample size across a variety of practice settings.

Based upon our data, we identified postoperative day 3–5 with a drain amylase level of > 300 U/L to be the combination with the most internal validity. This combination is associated with a high sensitivity (72%), high specificity (81%), and high NPV (94%). Although all other combinations had a higher specificity, ranging from 93–98%, we accepted a slightly lower specificity and placed more importance on sensitivity to ensure that no CR-POPF is missed. A retrospective study by Mannen et al., evaluated 57

patients who underwent pancreaticoduodenectomy and reported similar findings [23]. The authors reported amylase levels of > 500 U/L on day three were associated with sensitivity and specificity of 83% and 79%, respectively.

This study is not without its limitations. First, inherent in all retrospective studies is an inability to validate the variables used to create this model. For example, we are unable to go back and confirm that each patient included did in fact have an amylase measured on every postoperative day. Second, we used a range for postoperative 3–5 which in practice is not normally seen. With current recommendations, early drain removal on postoperative 3 will occur in most cases. The use of this range makes our results less generalizable in the current practice climate. Finally, when interpreting results of diagnostic accuracy that are dependent on prevalence, such as negative predictive value, not generalizable to beyond the study population. However, with the use of a large national database such as NSQIP, this is less of a concern.

Conclusions

In conclusion, pancreatic fistulas are a dreaded post-pancreaticoduodenectomy complication and are associated with poor outcomes including death. Because of this, routine drain placement is currently recommended yet, ideal timing of drain amylase testing and drain removal have yet to be clearly defined. The current recommendation leaves a large gap of time between the amylase measurement on day one and drain removal on day three. Our data shows that peak amylase levels increase each day and thus measuring on day 1 could increase the risk of missing a potential fistula. Further, the current recommended cutoff of 5000 U/L also risks missing 6% of patients with CR-POPF. We recommend checking drain amylase on postoperative day three and to use 300 U/L as a cutoff for early drain removal protocols. However, the patients overall clinical picture should be considered when making the final decision to pursue early drain removal.

Declarations

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Authors contibutions:

Laura Nicolais MD

Contributions: Analysis and interpretation of data, drafting manuscript, critical revision of manuscript

Abdimajid Mohamed BS:

Contributions: Acquisition of data, analysis and interpretation of data, critical revision of manuscript

Corresponding author:

Timothy L. Fitzgerald, MD

Contributions: Study concept and deisgn, analysis and interpretation of data, critical revision of manuscript

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