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Removal of Drains after Pancreaticoduodenectomy: Optimizing Timing and Amylase Level

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1. Abstract

1.1. Background: Early drain removal after pancreatoduodenectomy is a key component of most ERAS pathways. However, recommendations regarding the timing of removal and cutoff level for amylase vary.

1.2. Methods: This report includes all patients in the NSQIP database undergoing a pancreatoduodenectomy from 2015-2018. Two groups, significant pancreatic leak vs. no significant leak, are compared. The univariate analysis utilized Pearson's chi-squared and T-test, and significance is defined at $p < .05$.

1.3. Results: 7,583 patients underwent pancreatoduodenectomy with drain placement; 1,458 (19%) had a clinically relevant postoperative pancreatic fistula (CR-POPF). Of those, 7% had their highest drain amylase on day 1, compared to 29% and 64% on days 3-5 and > 5 ($p < 0.001$). An amylase level >300 U/L on any day 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 on any day, corresponded to 71.2% chance of CR-POPF compared to 11.2% with amylase <5000 U/L ($p < 0.001$). An amylase cutoff of >300 U/L on day one had a specificity of 93%, decreasing to 81% postoperative days 3-5. The sensitivity of a cutoff >300 U/L was 24% on postoperative day one and increased to 72% on postoperative days 3-5.

1.4. Conclusion: Current recommendations utilizing 5000 U/L will not identify an additional 6.2% of patients with CR-POPF compared to 300 U/L. Based on the data above, surgeons should consider checking drain amylase on postoperative day three and using 300 U/L as a cutoff for drain removal protocols.

2. Introduction

The indication for pancreaticoduodenectomy (PD) includes malignant and benign pancreatic pathologies. Although improvements in perioperative care have reduced the morbidity and mortality associated with this procedure, morbidity rates remain high at about 23% [1]. A pancreatic fistula is one of the most common and potentially devastating postoperative complications [2-4]. It occurs after 13-25% of cases and is associated with increased rates of sepsis, hemorrhage, length of stay, health care cost, and death [2, 5-7]. Given the potentially significant impact of a pancreatic fistula, many investigators have focused on preventing and mitigating this complication. Drain placement in the pancreatic operative bed is routine at many institutions [8]. However, there is debate regarding the use of drains and the optimal protocol for their removal [7-14]. Pancreaticoduodenectomy-specific guidelines from the European ERAS Society recommend removing drains on postoperative day three if the amylase level is < 5000 U/L on the first day [15]. Postoperative day one drain fluid amylase has demonstrated predictive value for clinically relevant postoperative pancreatic fistula (CR-POPF) in multiple retrospective and prospective studies [8, 10-12, 16-19]. In contrast, other research suggests obtaining amylase levels on postoperative day three may be superior [20, 21]. The clinical significance of elevated amylase levels on postoperative day one versus three is unclear. In these prior publications, the day for amylase screening is 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 recommends an amylase level >3 times normal as the cutoff [24]. However, studies vary significantly on the optimal amylase level to best predict CR-POPF, ranging from 100-5000 U/L [3, 11, 16, 22-24]. For example, one meta-analysis reviewed 13 studies and identified a postoperative day-one drain amylase of <100 U/L associated with a 3% rate of CR-POPF [24]. However, the authors noted that only 34% of patients met this criterion, suggesting 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 determining CR-POPF [16]. There is little consistency in data to support the recommended timing and cutoff for drain amylase analysis. Therefore, using the National Surgical Quality Improvement Program (NSQIP) database, this study aimed to identify the ideal combination of postoperative day and drain amylase level for safe drain removal.

3. Materials and Methods

3.1. 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 with drain placement who underwent pancreaticoduodenectomy (PD) (Current Procedural Terminology code 48153 and 48154). Subjects with missing data are excluded. The institutional IRB approved this study. Those included were divided into CR-POPF (Grade B and Grade C fistula) and no CR-POPF. We then utilized the International Study Group (ISGPS) definition for grading a clinically relevant postoperative pancreatic fistula (CR-POPF) [25]. ISGPS defines a CR-POPF as any fistula with amylase level > 3 times normal serum associated with a clinically relevant complication. Examples include prolonged hospital or ICU stay, the need for therapeutic interventions to manage the fistula, or postoperative organ failure.This manuscript defines grade B or grade C fistula as CR-POPF. Grade B or grade C fistula was defined using NSQIP data elements. These data elements included amylase level > three times normal and drain continued >7 days, percutaneous drainage, Grade B POPF present, Grade C POPF present, spontaneous wound drainage, persistent drainage with NPO-TPN, or persistent drainage with reoperation. The remaining patients were defined as having no CR-POPF. This group included the following NSQIP data elements: Pancreatic Fistula- No and Biochemical Leak only. To assess drain removal, we examined NSQIP data point DRAINREMOVAL (Number of Days for Last Pancreatic Drain Removal after Surgery). The assessment utilized two factors: postoperative day and amylase level. We created three groups based on the postoperative day of highest amylase: 1, 3-5, or > 5. Based on the literature, we chose drain amylase cutoffs of 300 U/L and 5000 U/L, as they are the most commonly cited levels in ERAS pathways [15, 25].

3.2. Statistical Analysis

Statistical analysis utilized R software. When assessing differences between patients with CR-POPF and those without, univariate analysis was conducted using Pearson's Chi-squared test for categorical variables and a 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) was performed for all combinations of the postoperative day (i.e., 1, 3-5, > 5) and drain amylase cutoff (i.e., 300 or 5000 U/L).

4. Results

Seven thousand five hundred forty-four patients who underwent pancreaticoduodenectomy (PD) met the 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 2) outlines the subgroup analysis of those with CR-POPF; 7% had their highest measured drain amylase on day 1, compared to 29% on days 3-5 and 64% on day> 5 ($p < 0.001$). Two thousand six hundred fourteen 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 3) reviews the test characteristics for each combination of postoperative day and drain fluid amylase level. As expected, specificity is higher with a more strict cutoff and lower with a more lenient cutoff. The highest specificity (98%) corresponds with a drain amylase level of >5000 U/L for postoperative days one and 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.

Compared to >5000 U/L, an amylase cutoff of >300 U/L (as would be expected) 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). However, the sensitivity of a cutoff >300 U/L was superior. This sensitivity was 24% (CI: 0.19-0.29) on postoperative day one but increased significantly to 72% (CI: 0.67-0.76) on postoperative days 3-5. As expected, the negative predictive value was highest for drain amylase >300 U/L (95% on postoperative day 1 and 94% on a postoperative day 3-5) when compared to an amylase >5000 U/L (88% on day 1 and 86% on day 3-5). The AUC for an amylase cutoff of 300 was 0.86 for day one and 0.83 for days 3-5 (Figure 1).

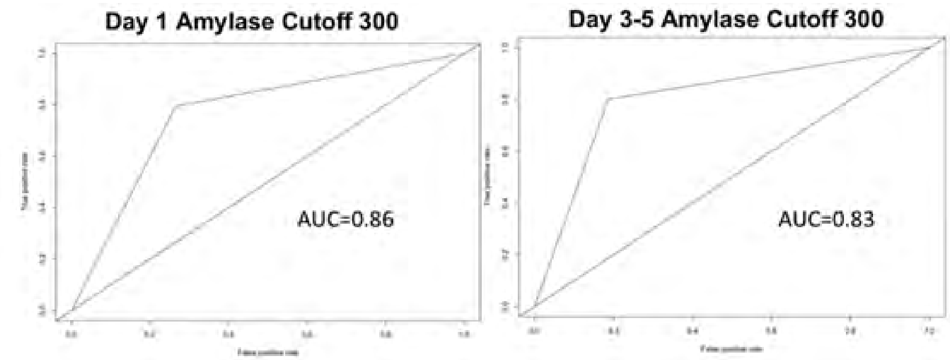

Figure 1: Area Under the Curve for Amylase level < 300.

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	64.3	65.2	0.012
Sex				
Female	3,396 (45%)	560 (16.5%/38.4%)	2,836 (83.5%/46.6%)	< 0.001
Male	4,148 (55%)	898 (21.6%/61.6%)	3,250 (78.4%/53.4%)	
Race				
White	5,692 (75%)	1,050 (18.4%/72.0%)	4,642 (81.6%/76.3%)	< 0.001
Black	562 (7.4%)	87 (15.5%/6.0%)	475 (84.5%/7.8%)	
Other	343 (4.5%)	78 (22.7%/5.3%)	265 (77.3%/4.4%)	
Unknown	947 (13%)	243 (25.7%/16.7%)	704 (74.3%/11.6%)	
BMI (mean)	27.3	28.5	27	< 0.001
ASA Classification				
Class 1-2	1,763 (23.4%)	362 (20.5%/24.8%)	1,401 (79.5%/23.0%)	0.14
Class 3-4	5,769 (76%)	1,092 (18.9%/74.9%)	4,677 (81.1%/76.8%)	
Class 5	2 (< 0.1%)	1 (50%//0/0.1%)	1 (50%/0.0%)	
Not specified	8 (0.1%)	1 (12.5%/0.1%)	7 (87.5%/1.1%)	
Pancreas Duct Size				`
<3 mm	2,025 (27%)	522 (25.8%/35.8%)	1,503 (74.2%/24.7%)	
3-6 mm	2,964 (39%)	499 (16.8%/34.2%)	2,465 (83.2%/40.5%)	
>3 mm	910 (12%)	101 (11.1%/6.9%)	809 (88.9%/13.3%)	
Unknown	1,645 (22%)	336 (20.4%/23.0%)	1,309 (79.6%/21.5%)	
Pancreas Gland Texture				
Soft	2,687 (36%)	811 (30.2%/55.6%)	1,876 (69.8%/30.8%)	< 0.001
Intermediate	599 (7.9%)	81 (13.5%/5.6%)	518 (86.5%/8.5%)	
Hard	2,391 (32%)	205 (8.6%/14.0%)	2,186 (91.4%/35.9%)	
Unknown	1,867 (25%)	361 (19.3%/24.8%)	1,505 (80.6%/24.7%)	

Table 2: Risk for CR-POPR by Postoperative Day with Highest Amylase Level and Amylase Cutoff

	Overall (N = 7,544)	CR-POPF (N = 1,458)	No CR-POPF (N = 6,086)	P-value
Postoperative day with highest amylase level				
1	975 (13%)	99 (10.2%/6.8%)	876 (89.8%/14.4%)	< 0.001
03-May	3,416 (46%)	422 (12.4%/28.9%)	2,994 (87.6%/49.2%)	
5	3,102 (41%)	935 (30.1%/64.1%)	2,167 (69.9%/35.6%)	
Unknown	51	2 (3.9%/1.3%)	49 (96.1%/0.8%)	
Amylase Cutoff (U/L)				
< 300	4,741 (64%)	232 (4.9%/16.2%)	4,509 (95.1%/76.2%)	< 0.001
> 300	2,614 (36%)	1,203 (46%/83.8%)	1,411 (54%/23.8%)	
< 5000	6,341 (86%)	713 (11.2%/49.7%)	5,628 (88.8%//95.1%)	< 0.001
> 5000	1,014 (14%)	722 (71.2%/50.3%)	292 (28.8%/4.9%)	

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)

5. Discussion

This study aimed to identify the ideal 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 days 3-5 and using an amylase cutoff of 300 U/L is the most internally valid combination. This screening provides the best combination of sensitivity, specificity, and NPV. Using a cutoff of >5000 U/L missed approximately 6% of the CR-POPF compared to >300 U/L. Data support drain placement after pancreaticoduodenectomy [7, 9, 14]. ERAS protocols recognize the potential downsides of prolonged or unnecessary drainage. Therefore, defining optimal drain management is imperative. Prolonged drainage may result in increased rates of infection and anastomotic dehiscence. In contrast, removing a drain too early risks an undrained pancreatic leak [7, 26]. Current guidelines from the European and American ERAS Societies recommend removal on postoperative day three if the drain amylase level is <5000 U/L on day one [15]. These recommendations are derived from prospective and retrospective trials. Bassi et al. conducted a randomized controlled study of 114 patients reporting decreased CR-POPF with early drain removal on day three versus day five [10]. Similarly, using data from the NCDB, Xourafas found that amylase < 5,000 on day one favored drain early drain removal [27]. In contrast to the NCBD data presented in this study, the authors did not look at other amylase cutoffs or the timing of drain amylase. Ven Fong found that drain amylase levels on day one was predictive of CR- POPF [11].

Some guidelines recommend checking drain amylase on postoperative day three [19]. We found that more patients who developed CR-POPF had their highest amylase measurement after day one. Nissen et al. found this same temporal trend [23]. These data suggest that measuring drain amylase earlier may lead to overlooking some patients with CR-POPF. A meta-analysis with pooled results from 10 trials compared testing on days one and three [28]. Testing on a postoperative day one had higher sensitivity, specificity, and AUC compared to day 3 (sensitivity 81%, specificity 87%, AUC 0.89 vs. sensitivity 56%, specificity 79%, AUC .67). This opposes our results; however, of the ten studies included all were small, single-institution series (N= 65-471) except one. In contrast, Lee et al. reported drain amylase on a 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) [20]. Numerous reports have examined potential drain amylase cutoff levels. The recommended range varies from 100 to 5000 U/L, thus questioning which cutoff is ideal [3, 10, 16, 22-24, 29, 30]. These studies are single institutional with small sample sizes. Ven Fong et al. included 126 patients and reported 600 U/L afforded the best accuracy (86%), sensitivity (93%), and specificity (79%) [11]. This level was further validated in a 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 [26, 29, 30]. Based on our data, we recommend a cutoff of >300 U/L allowed for a lower rate of missed CR-POPF 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 recommendation favors a better NPV.

Based on our data, we identified postoperative days 3-5 with a drain amylase level of >300 U/L as the combination with the most internal validity. This combination is associated with 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 NPV. A retrospective study by Mannen et al. evaluated 57 patients who underwent pancreaticoduodenectomy and reported similar findings [21]. The authors reported amylase levels of >500 U/L on day three are 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. Second, we used a range for postoperative 3-5. Most current recommendations define early drain removal as postoperative three. Finally, we must acknowledge that the groups with and without CR-POPF are not balanced. However, our goal in this study was not to identify risk-associated CR-POPF but rather to define an ideal timing and cutoff for drain amylase for existing ERAS protocols. In conclusion, pancreatic fistulas are a dreaded pancreaticoduodenectomy complication and are associated with poor outcomes, including death. Because of this, routine drain placement is recommended. However, the ideal timing and cutoff levels for amylase have yet to be clearly defined. Based on the data presented above, we recommend checking drain amylase on postoperative day three and using 300 U/L as a cutoff.

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8. Conflict of Interest

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