ORIGINAL ARTICLE

Factors Predictive of Reoperation After Pancreaticoduodenectomy for Pancreatic Cancer

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Abstract

While mortality is low, morbidity remains high for patients undergoing pancreas resections, especially for those who return to the operating room (RTOR). The aim of this study is to identify risk factors for RTOR following pancreaticoduodenectomy (PD) for ductal adenocarcinoma. Logistic regression models were constructed using the 2014 and 2015 National Surgical Quality Improvement Program (NSQIP) Pancreas Targeted database. Preoperative and procedure-related risk factors predictive of RTOR for patients undergoing either classic or pylorus-preserving pancreaticoduodenectomy for pancreatic ductal adenocarcinoma (PDAC) were identified. A total of 1736 patients were included. Multivariable analysis of patients undergoing classic PD demonstrated that an abnormally low preoperative WBC count was significantly associated with RTOR (OR 2.78, 95% CI 1.27–6.06, $p = 0.010$). For patients who underwent pylorus-preserving PD, the wound classification (OR 3.99, 95% CI 1.75–9.11, $p = 0.001$) and arterial resection (OR 26.3, 95% CI 7.96–87.20, $p < 0.001$) were associated with a higher rate of RTOR. When analyzing both approaches (classic and pylorus-preserving PD) together, only isolated arterial (OR 9.98, 95% CI 3.81–26.18, $p < 0.001$) and isolated venous (OR 1.79, 95% CI 1.05–3.05, $p = 0.032$) resections were independently associated with RTOR. The results of our study demonstrate that few factors are predictive of RTOR. Knowledge of these few variables in combination with a focus on the components of medical care in the immediate postoperative period may help identify individuals at risk for RTOR and improve patient care.

Keywords Pancreatic cancer · Reoperation · Morbidity · Mortality

Introduction

For patients with pancreas cancer, surgical resection remains the only potentially curative approach [1, 2].

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Pancreaticoduodenectomy (PD) is often performed for cancer in or near the head of the pancreas and remains one of the most common surgical procedures performed for pancreas cancer. Historically, perioperative mortality following PD was as high as 40%; however, in contemporary surgical practices, perioperative mortality rates of 2–3% are attainable if performed at centers with higher surgical volume [3–5]. Although PD is now considered a safe surgical procedure, the associated morbidity continues to remain as high as 60% [3–8].

In order to facilitate reduction in morbidity associated with pancreas resection, recent research efforts have led to the construction of nomograms and models predictive of specific postoperative complications including postoperative pancreatic fistula (POPF), surgical site infection, and mortality [9–12]. Models such as these allow providers to estimate an individual patient's risk for postoperative complications and tailor preoperative counseling accordingly. These models also serve as a foundation upon which to investigate potential risk-reduction interventions in patients found to be at high-risk for a particular complication.

In contemporary surgical practice of minimal mortality but high morbidity, some patients develop a complication that necessitates further intervention. These complications range from bleeding, draining collections or abscesses, obstruction, and anastomotic leaks. Although interventional radiology can address some of these and subvert the need, few patients still need to return to the operating room (RTOR).

While models have been developed to risk stratify patients for some complications following PD, to the best of our knowledge, we are not aware of any model to predict RTOR. The aim of this study was to identify preoperative and perioperative factors predictive of RTOR following PD for malignancy.

Methods

Data Source

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) Pancreas Targeted database prospectively collects data from patients undergoing surgical procedures of the pancreas and was first made available in 2014. This database is distinguished from the ACS-NSQIP Adult Participant Use Files by its inclusion of variables particularly relevant to pancreas surgery including pancreas duct diameter, gland texture, tumor stage, and nodal stage, to name a few. These data are collected by trained Surgical Clinical Reviewers who are regularly audited for accuracy and are a representative of surgical procedures performed from over 100 participating hospitals, with the majority located in the USA.

Study Population

Patients who underwent either classic (CPT 48150) or pylorus-preserving (CPT 48153) PD for pancreas malignancy (ICD-9 code of 157.0–9) were queried for years 2014 and 2015 in the ACS-NSQIP Pancreas Targeted database. Patients were excluded if (1) they had a histologic diagnosis other than pancreatic adenocarcinoma as obtained from the variable named "PAN_MALIG_HISTOLOGIC," (2) the pancreas duct size or texture was unknown, or (3) cases were classified as emergent.

Variables Examined

For analyses, patients were grouped according to RTOR status. Patient demographics including age, gender, race, BMI, smoking status, and medical diagnoses prior to surgery (diabetes, hypertension, jaundice, etc.) were collected in addition to preoperative laboratory values and perioperative factors (operative time, tumor/nodal stage, gland texture, duct size,

etc.). Postoperative outcomes were analyzed and stratified according to RTOR status. Operating room time was analyzed by quartile. American Society of Anesthesiologists (ASA) scores were reported as either ≤ 3 or ≥ 4. Perioperative mortality was defined as deceased at discharge.

Statistical Analysis

Statistical analyses were carried out using SAS software v9.3 (SAS Institute Inc., Cary, NC, USA) with p values less than 0.05 considered significant. Central tendencies were reported as either mean or median ± standard deviation, and data were compared descriptively by RTOR status. Student's t tests were used to analyze continuous variables whereas chi-square tests and Fisher's exact tests were used to analyze categorical data where appropriate. Logistic regression with Firth's penalized maximum likelihood estimation was used for the multivariable analysis. After fitting the full model, backward variable selection was employed to remove variables that were no longer significant at $\alpha = 0.10$. To be included for initial multivariable analysis, variables were required to have a p value less than 0.05 in the univariate analysis. To be retained in the model, the p value must have been less than 0.10.

Results

Cohort Characteristics

For patients who underwent either a classic ($N = 921$) or pylorus-preserving ($N = 815$) PD, the mean age and BMI were 65.9 ± 9.9 years and 26.8 ± 5.5, respectively. For all patients, 52% were male and 83% were Caucasian. A slight majority (61%) were jaundiced prior to surgery, and some patients received neoadjuvant chemotherapy (28%) or radiation therapy (14%). Hypertension (54%) and diabetes (29%) were the most common comorbidities. Median serum albumin (g/dL), bilirubin (mg/dL), hematocrit (%), platelet (10^9/L), and sodium (mmol/L) were 3.7 ± 0.6, 2.2 ± 3.1, 36.9 ± 4.8, 259.7 ± 99.9, and 138.4 ± 3.3, respectively, for the entire cohort.

Univariate Analyses and Postoperative Outcomes

Of the 1736 patients, 75 (4.3%) required RTOR with intra-abdominal surgery accounting for 63% ($N = 47$) of cases. The most common procedures performed at reoperation were exploratory laparotomy ($N = 21$), wound debridement ($N = 7$), central line placement and/or removal ($N = 6$), blood vessel repair or ligation ($N = 5$), and endoscopic gastrostomy tube placement ($N = 5$) (Fig. 1). For cases with specific indications documented, reoperative procedures were most frequently performed for bleeding ($N = 12$), infection ($N = 9$), peritonitis
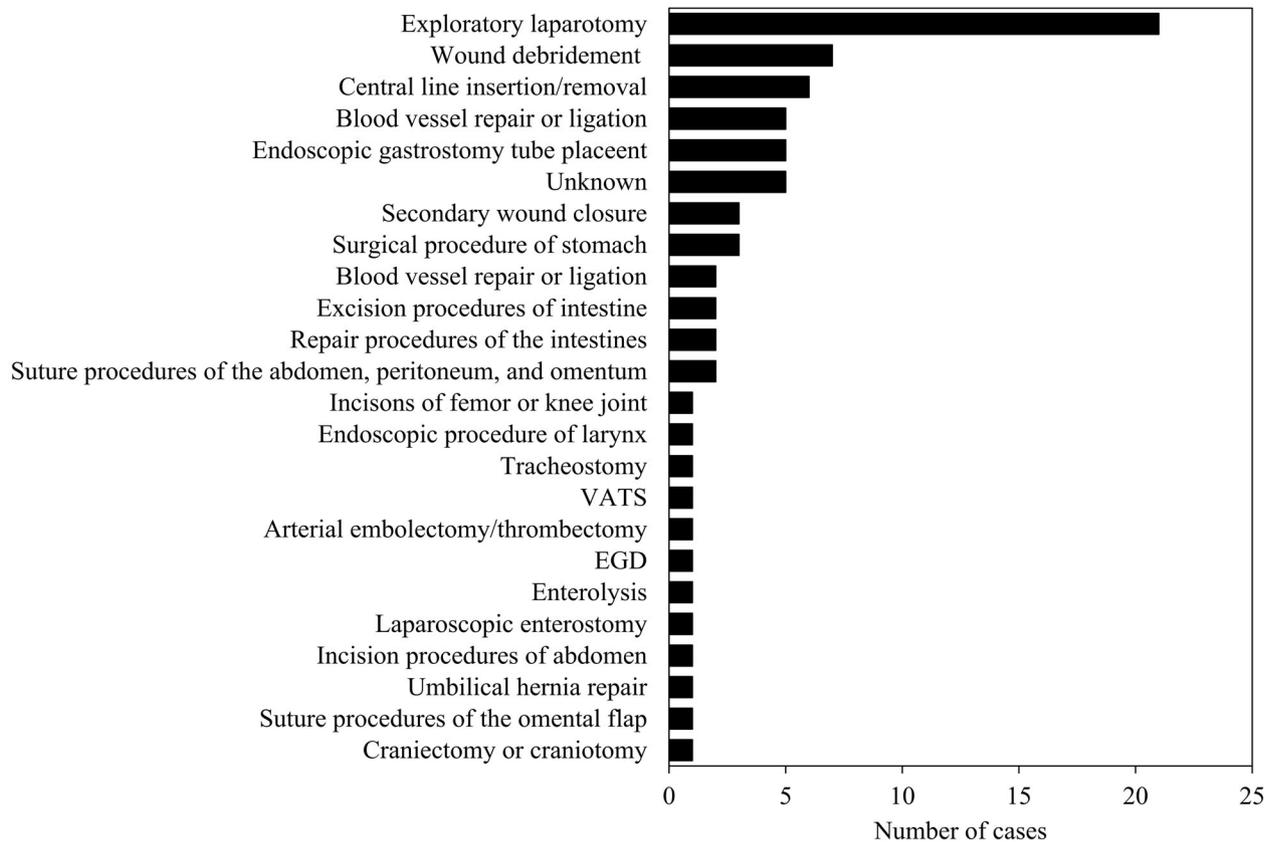
Reoperation procedures

Fig. 1 Figure depicting the types of procedures performed in all 75 patients who required reoperation

($N = 4$), wound disruption ($N = 4$), and vascular occlusion and/or insufficiency ($N = 3$) (Fig. 2).

For both classic and pylorus-preserving PD, the proportion of patients who required RTOR did not significantly differ with respect to age, gender, race, BMI, preoperative jaundice, administration of neoadjuvant chemotherapy, or radiation therapy (all $p > 0.05$). Similarly, smoking status, ASA score, and preoperative comorbidities did not significantly influence the rate of RTOR (all $p > 0.05$) (Supplemental Table 1). Preoperative labs were not associated with RTOR for patients who underwent pylorus-preserving PD; however, abnormal WBC and platelets counts were associated with higher rates of RTOR in patients who underwent classic PD on univariate analysis (Supplemental Table 2). With regard to perioperative factors, univariate analysis of both procedures combined demonstrated that isolated arterial vascular reconstruction was associated with a 26.1% risk of requiring RTOR. This was significantly higher than patients who did not require any vascular reconstruction (3.6%), required isolated vein reconstruction (6.1%), or required combined venous and arterial vascular reconstruction (4.3%) (Table 1). Univariate analysis of

patients in the pylorus-preserving PD cohort demonstrated that arterial vascular reconstruction (46.2%) and placement of an operative drain (4.5%) were both associated with higher rates of RTOR compared to patients who did not require vascular reconstruction (3.4%) or had an operative drain placed at the time of surgery (0%). Additionally, patients who required RTOR tended to have drain amylase value peak after postoperative day 4 compared to postoperative days 1–4 for both procedures combined (7.5% vs. 3.5%) and for patients in the classic PD cohort (8.5% vs. 2.6%). In the pylorus-preserving PD cohort, we found that higher drain amylase values after postoperative day one were also associated with RTOR (7.5% vs. 3.5%). Importantly, we did not find that tumor stage, nodal stage, pancreas duct diameter, gland texture, or operative time to be significantly associated with RTOR status when procedures were analyzed individually or combined (all $p > 0.05$) (Table 1).

Patients who required RTOR had universally poorer outcomes. Analysis of both procedures combined revealed that perioperative mortality rate was higher in patients who required RTOR (29.0% vs. 3.9%) (Table 2). These patients were
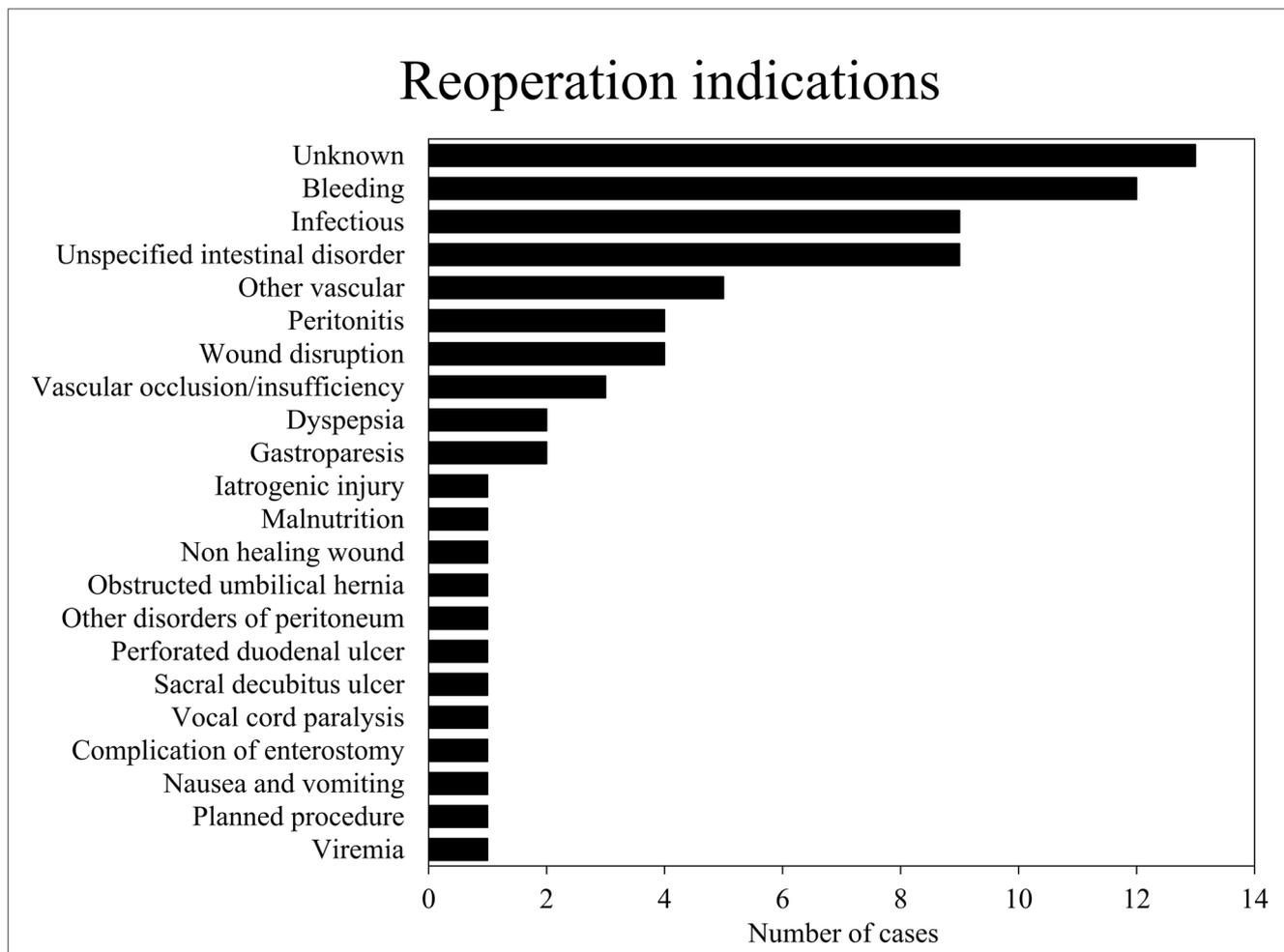
Fig. 2 Figure depicting the indication for reoperation in all 75 patients who required reoperation

also more likely to have a length of stay (LOS) > 10 days (8.5% vs. 2.3%) and develop POPF (9.3% vs. 3.8%) or delayed gastric emptying (11.5% vs. 3.1%) (Table 2). For patients in the pylorus-preserving PD cohort, those requiring RTOR had higher risk of perioperative mortality (31.3% vs. 3.4%), LOS > 10 days (7.7 vs. 2.3%), POPF (11.5% vs. 3.0%), and delayed gastric emptying (9.5% vs. 3.0%) (all $p < 0.05$) (Table 2). Similarly, patients in the classic PD cohort who underwent RTOR had higher risk of mortality (26.7% vs. 4.3%), LOS > 10 days (9.2% vs. 2.4%), delayed gastric emptying (13.6% vs. 3.3%), and more often required additional percutaneous drainage procedures (9.8% vs. 4.2%) (all $p < 0.05$) (Table 2).

Multivariable Modeling

Multivariable analyses demonstrated that preoperative WBC count, wound class, and vascular resection were factors independently associated with RTOR. For patients undergoing classic PD, an abnormally low preoperative WBC count was significantly associated with RTOR (OR 2.78, 95% CI 1.27–

6.06, $p = 0.010$) (C-statistic 0.585). For patients who underwent pylorus-preserving PD, a wound class of "contaminated" was higher risk of RTOR (OR 3.99, 95% CI 1.75–9.11, $p = 0.001$) compared to "clean/contaminated" cases whereas arterial vascular resection, as opposed to no vascular resection, was also higher risk (OR 26.3, 95% CI 7.96–87.20, $p < 0.001$) (C-statistic 0.679). When combining both classic and pylorus-preserving PD, only isolated arterial (OR 9.98, 95% CI 3.81–26.18, $p < 0.001$) and isolated venous (OR 1.79, 95% CI 1.05–3.05, $p = 0.032$) vascular resections, as compared to no vascular resection, were independently associated with RTOR (C-statistic 0.583) (Table 3).

Discussion

We have performed an analysis of patients undergoing PD using a large national clinical database and have determined that only preoperative WBC count, wound class, and vascular resection were independently associated with needing to RTOR in patients undergoing pancreas resection for cancer.

Table 1 Perioperative variables

	Percent of patients requiring RTOR		
	Pylorus-preserving Whipple	Classic Whipple	Both combined
Wound class			
1-Clean	0.0%*	0.0%	0.0%
2-Clean/contaminated	3.3%*	5.1%	4.3%
3-Contaminated	10.1%*	3.2%	5.7%
4-Dirty/infected	0.0%*	3.2%	1.6%
Operative time (minutes)			
1st quartile	2.4%	4.1%	3.1%
2nd quartile	3.9%	3.2%	3.6%
3rd quartile	4.2%	3.9%	4.0%
4th quartile	6.0%	6.9%	6.6%
Biliary stent			
None	3.4%	4.4%	3.9%
Stent	4.0%	4.8%	4.4%
Operative approach			
Open (planned)	3.9%	5.0%	4.4%
Other	5.7%	2.0%	3.0%
Pancreatic duct size			
< 3 mm	2.9%	4.0%	3.5%
3–6 mm	3.4%	5.3%	4.4%
> 6 mm	6.8%	3.7%	5.0%
Gland texture			
Hard	3.7%	4.7%	4.3%
Intermediate	4.8%	6.2%	5.5%
Soft	4.0%	3.9%	3.9%
Pancreatic reconstruction			
Not performed	0.0%	0.0%	0.0%
Pancreaticogastrostomy or pancreaticojejunostomy	3.9%	4.7%	4.3%
Gastrojejunostomy or duodenojejunostomy			
Antecolic	3.4%	4.4%	4.0%
Retrocolic	4.1%	5.0%	4.6%
Operatively placed drain(s)			
No	0.0%*	6.8%	3.6%
Yes	4.5%*	4.4%	4.4%
Vascular resection			
Artery	46.2%*	0.0%	26.1%*
Not performed	3.4%*	3.7%	3.6%*
Vein	2.9%*	8.4%	6.1%*
Vein and artery	0.0%*	5.9%	4.3%*
POD no. 1 highest drain amylase (IU)			
≤ 100	6.7%	4.2%	5.2%
> 100	8.5%	4.5%	6.0%
POD nos. 2–30 highest drain amylase (IU)			
≤ 30	3.5%*	4.8%	4.2%
> 30	7.5%*	3.7%	5.3%
Number of days with highest amylase level after surgery			
≤ 4	4.8%	2.6%*	3.5%*
> 4	6.4%	8.5%*	7.5%*

Table 1 (continued)

	Percent of patients requiring RTOR		
	Pylorus-preserving Whipple	Classic Whipple	Both combined
Number of days for last pancreatic drain removal after surgery			
≤ 4	2.1%	3.2%	2.8%
> 4	4.6%	4.2%	4.4%
T (tumor) stage			
T1	1.7%	4.1%	2.8%
T2	8.8%	7.5%	8.1%
T3	3.9%	4.2%	4.1%
N (node) stage			
N0	3.6%	5.4%	4.5%
N1	4.2%	4.4%	4.3%
M (metastases) stage			
No	3.0%	4.6%	3.8%
Yes	8.3%	0.0%	4.0%

$*p < 0.05$

Additionally, we have reported outcomes for patients who required RTOR and demonstrate that they experience much higher rates of morbidity and mortality.

The need to RTOR after surgery is relatively uncommon; however, the associated morbidity and mortality are significant, especially after pancreas resection. We have demonstrated that patients who require RTOR have a mortality rate nearly eight-fold higher than patients who do not RTOR. There are some important points to take from this study. First, we determined that an abnormal WBC count is independently associated with

RTOR. This may be reflective of the physiological response to neoadjuvant chemotherapy or malnutrition, both of which could potentially worsen operative outcomes. Second, we identified factors relevant to surgical technique that are associated with RTOR, namely, the need to perform vascular resection and wound class. It is likely that patients who require vascular reconstruction undergo surgeries that are technically more complicated. Additionally, we found that contaminated wounds were at higher risk of RTOR. The clinical significance of this is unclear as we included only elective PDs in which most

Table 2 Postoperative outcomes

	Percent of patients requiring RTOR		
	Pylorus-preserving Whipple	Classic Whipple	Both combined
Discharged deceased			
No	3.4%*	4.3%*	3.9%*
Yes	31.3%*	26.7%*	29.0%*
Hospital length of stay			
≤ 10 days	2.3%*	2.4%*	2.3%*
> 10 days	7.7%*	9.2%*	8.5%*
Postoperative pancreatic fistula			
No	3.0%*	4.5%	3.8%*
Yes	11.5%*	7.1%	9.3%*
Delayed gastric emptying			
No	3.0%*	3.3%*	3.1%*
Yes	9.5%*	13.6%*	11.5%*
Percutaneous drainage			
No	4.0%	4.2%*	4.1%
Yes	3.7%	9.8%*	7.4%

$*p < 0.05$

Table 3 Multivariable analysis of variables predictive of return to operating room

		OR	95% CI		*p* value
			Lower	Upper	
Classic pancreaticoduodenectomy (C-statistic 0.585)					
WBC	High abnormal vs. normal	1.77	0.76	4.11	0.183
	Low abnormal vs. normal	2.78	1.27	6.06	0.010
Pylorus-preserving pancreaticoduodenectomy (C-statistic 0.679)					
Wound class	Clean vs. clean/contaminated	2.32	0.11	50.50	0.592
	Contaminated vs. clean/contaminated	3.99	1.75	9.11	0.001
	Dirty/Infected vs. clean/contaminated	0.58	0.03	9.89	0.703
Vascular resection	Artery vs. none	26.3	7.96	87.20	< 0.001
	Vein vs. none	0.83	0.30	2.30	0.714
	Vein and artery vs. none	1.01	0.05	20.23	0.993
Combined (C-statistic 0.583)					
Vascular resection	Artery vs. none	9.98	3.81	26.18	< 0.001
	Vein vs. none	1.79	1.05	3.05	0.032
	Vein and artery vs. none	1.48	0.40	5.52	0.563

wounds are classified as clean/contaminated. For patients undergoing elective PD, contaminated cases would have included those with gross spillage of enteric contents, which may be indicative of less than optimal operative technique and serve as a nidus for infection. While factors known prior to surgery have been demonstrated to be predictive of individual complications following surgery such as POPF and mortality, we failed to demonstrate that patient characteristics and perioperative factors can comprehensively predict who is at high risk for RTOR [9, 13].

Identifying individuals at high risk for RTOR will allow for investigation of risk reduction interventions to lower RTOR rates and mitigate associated complications. The inability to predict RTOR using pre- and perioperative factors is significant and suggests that there are other factors present in the postoperative period that partly determine RTOR risk. For example, patients who undergo vascular reconstruction may benefit from avoidance of low flow states to ensure that important vascular structures (i.e., portal vein) remain patent and do not thrombose. While poor anastomotic technique may certainly contribute to the development of venous thrombosis, postoperative medical management of a patient's fluid status may also contribute to the avoidance or occurrence of such complications. The postoperative management of pancreas surgery patients varies, and many pancreas surgeons do not utilize enhanced recovery pathways which have been shown to reduce morbidity and readmission rates in surgical subspecialties such as colorectal and bariatric surgery [14–16].

This study has limitations which must be addressed. Aside from this being a retrospective analysis of prospectively collected data, we were unable to investigate the relationship between RTOR risk and medical management in the postoperative period. In clinical practice, the decision to RTOR is almost uniformly in response to a postoperative complication that requires definitive treatment. For patients undergoing PD, POPF is the most common serious complication that frequently alters the postoperative care plan; however, other complications can occur such as bleeding which may also require RTOR. In our study, we determined that the most common indications for RTOR were vascular catastrophes and source control for sepsis or infectious etiologies. The single most common procedure performed was also found to be exploratory laparotomy which is indicative of the severity of disease in these patients. Another limitation is that the threshold for needing to RTOR may differ among providers; however, we believe that our data are representative of "real-world" practice, even though some variation likely exists.

This data demonstrates that few factors are predictive of RTOR. However, this data will significantly improve patient discussions in the preoperative period and help set expectations prior to surgery. Future directions for research in this area could include investigating the relative risk of postoperative complications that lead to RTOR and investigating the effects of enhanced recovery pathways for patients undergoing pancreas resection on morbidity and mortality.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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