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Preoperative risk evaluation for pancreatic fistula after pancreaticoduodenectomy

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Abstract

Background: Pancreatic fistula remains common, with limited ability to risk stratify patients preoperatively. The objective of this study was to identify risk factors for clinically-relevant postoperative pancreatic fistula (CR-POPF) that are routinely available in the preoperative setting.

Methods: Preoperatively available variables for all pancreaticoduodenectomies from 2014–2017 were examined using a national clinical registry. The cohort was separated into risk factor identification and internal validation subgroups.

Results: Among 15 033 pancreaticoduodenectomies, the CR-POPF rate was 16.7%. CR-POPF was more likely in patients that were male (odds ratio [OR], 1.51), obese (body mass index [BMI] > 30, OR, 1.97), had minimal preoperative weight loss (OR, 1.25), had a nondilated pancreatic duct (OR, 1.81), did not have diabetes, (OR, 1.80), did not receive neoadjuvant therapy (OR, 1.78), had no evidence of biliary obstruction (OR, 1.18), or had nonadenocarcinoma pathology (OR, 1.96; all $P < 0.01$). Patients with three or fewer risk factors had a CR-POPF rate of 7.1%, while those with six or more risk factors had a CR-POPF rate of 26.3% ($P < 0.001$).

Conclusion: Preoperative CR-POPF risk evaluation could be a useful tool in patient counseling and surgical planning, and risk may allow for more well-informed decisions regarding perioperative management, including enhanced recovery protocols and use of somatostatin analogs.

Keywords

pancreatic fistula; pancreatic surgery; pancreaticoduodenectomy; Whipple procedure

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

1 | INTRODUCTION

Pancreatic fistula is a significant cause of morbidity and mortality after pancreaticoduodenectomy, with clinical impact ranging from simple changes in drain management to abscess formation, sepsis, and death.^{1–4} This variation in clinical severity led to the International Study Group on Pancreatic Fistula (ISGPF) to develop a standardized grading system for pancreatic fistulae, which subcategorizes the fistula into either Grade A, B, or C. Grade A fistulae are essentially subclinical and were recently reclassified as biochemical leaks, while grades B and C fistulae have significant downstream effects and together can be considered clinically-relevant postoperative pancreatic fistula (CR-POPF).^{5,6} These definitions have been validated and are well accepted in clinical practice.^{7,9}

Significant efforts have been aimed at identifying risk factors that predict CR-POPF formation. The most well-validated predictive model is the fistula risk score (FRS), which uses pancreatic duct diameter, gland texture, intraoperative blood loss, and pathology to stratify patient risk.^{10–12} Other clinical risk scores have helped to explore additional predictive domains and simplify scoring without sacrificing predictive capabilities.^{13,14} Efforts at developing preoperative risk evaluation tools have been limited to small, single-institution studies or did not demonstrate significant discrimination in identifying clinically significant fistulae.^{15,16}

While the FRS and its derivatives are effective and well-validated tools for predicting CR-POPF, these existing risk schemes require intraoperative details, such as pancreatic gland texture and blood loss. The inclusion of post hoc information inherently limits the utility of these risk schemes in preoperative counseling, clinical decision-making, risk stratification, and early modification of perioperative pathways. In addition, attempts to model fistula risk while incorporating both preoperative and intraoperative variables may make it more difficult to identify preoperative surrogates for fistula risk, as more accurate intraoperative predictors (e.g., gland texture) will dominate predictive models. The objectives of this study were to (1) identify risk factors for CR-POPF after pancreaticoduodenectomy that could be identified preoperatively and (2) validate identified risk factors in a separate cohort

2 | METHODS

2.1 | Data set and study design

The 2014–2017 American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Pancreatectomy Procedure Targeted Data File was the primary data set for this retrospective cohort study. Details of the ACS NSQIP are thoroughly described elsewhere.^{17,18} Briefly, the ACS NSQIP is a routinely audited, prospective, multi-institutional, risk-adjusted outcomes program that uses trained reviewers to collect data on more than 150 variables including preoperative risk factors, intraoperative variables, and postoperative 30-day outcomes. Beginning in 2014, ACS NSQIP hospitals could participate in a “pancreas targeted” program that required abstraction of additional variables following pancreatectomy. Pancreaticoduodenectomy cases were identified by CPT® code (48150, 48152, 48153, or 48154), as previously described in ACS NSQIP studies.¹³ Missing data

were imputed using maximum likelihood.¹⁹ The Northwestern IRB deemed this study exempt from review because it used pre-existing, deidentified data.

2.2 | Outcome variable

The primary outcome variable was CR-POPF, defined based on 2016 ISGPF definitions.⁶ A patient was determined to have a POPF if they had a drain amylase >300 or a clinically identified pancreatic fistula based on the ACS NSQIP fistula variable. The ACS NSQIP fistula definition includes the presence of drain >7 days, spontaneous wound drainage, percutaneous drainage, or reoperation.¹⁸ All patients with a class B or C fistula were classified as having a CR-POPF. Patients who had a pancreatic fistula were considered to have a CR-POPF if a drain was present for more than 21 days, hospital length of stay was at least 14 days, or if the patient experienced deep or organ space surgical site infection, postoperative percutaneous drain placement, reoperation, sepsis, shock, or systemic organ failure (respiratory, renal, or multisystem).

2.3 | Covariates

While all ACS NSQIP variables are abstracted retrospectively and postoperatively, only variables that could conceivably be determined before the index operation were included in the development of the risk scheme. These included patient characteristics, medical history, and laboratory values. Candidate variables were chosen based on clinical relevance in pancreatic surgery. Body mass index (BMI) was split into a categorical variable using common clinical cutoffs (<18.5 is underweight 18.5–24.9 is normal, 25–29.9 is overweight, 30 is obese).²⁰ Evidence of biliary obstruction was created as a composite variable and was considered present if the patient had preoperative jaundice, hyperbilirubinemia (>1.2mg/dL), or if a preoperative biliary stent was placed. Pancreatic ducts were considered normal if <3 mm or dilated if >3 mm. Pancreatic duct size in the ACS NSQIP database is measured through a combination of preoperative, intraoperative, and pathologic data available to reviewers, but was considered for utilization as a variable in the risk stratification scheme because of the demonstrated ability of preoperative imaging to accurately diagnose a dilated pancreatic duct and the correlation between pancreatic duct diameter on preoperative imaging and intraoperative risk assessments.^{21–23} Duct size was dichotomized to reflect practical clinical judgements regarding duct size (i.e., dilated or not dilated) to reflect real-life clinical practice and to facilitate the ease of use. Neoadjuvant radiation and chemotherapy were investigated separately in bivariate analysis, with the final exposure variable used in modeling being receipt of any neoadjuvant therapy (chemotherapy, radiation, or chemoradiation) due to the infrequency of radiation therapy alone (<1% of the cohort).

2.4 | Statistical analysis

The cohort was randomly split into derivation (66.6%) and validation (33.3%) cohorts. Characteristics of the cohorts were compared with ensure adequate randomization. Significant associations between CR-POPF and preoperative variables were examined using chi-square tests adjusted for patients clustering within hospitals. Preoperative laboratory values were dichotomized based on clinical guidelines and analyzed categorically. Variables with a P value <0.05 were included in a multivariable logistic regression model that

accounted for patients clustered within hospitals. A backward elimination process was then used, with any variables with nonsignificant P values ($P > 0.05$) being removed from the model. Potential effect modification was explored through serial addition and removal of multiplicative interaction terms. Model calibration was assessed using Hosmer-Lemeshow goodness of fit test, with $P > 0.05$ indicating adequate calibration. Finally, internal validation of predicted fistula risk was performed by calculating the risk of CR-POPF in the validation cohort and examining the predicted fistula rates to the actual fistula rates.

Odds ratios greater than 1.0 indicate increased likelihood of developing a CR-POPF, and confidence intervals are reported to the 95% level of significance. Tests of significance were 2-sided with P values considered significant at the 0.05 level. Statistical analyses were performed using Stata v15.1 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Characteristics of derivation and validation cohorts

Of 15 224 patients undergoing pancreaticoduodenectomy, 114 patients had unknown POPF status and 77 patients had unknown cancer patients: treatment status and were excluded. The final cohort included 15 033 10 022 in the derivation cohort and 5011 in the validation cohort. Patient characteristics were not different between derivation and validation cohorts (Table 1).

3.2 | Candidate variable analysis in derivation cohort

The overall rate of POPF was 23.5%, and the rate of CR-POPF was 16.7%. Patient factors associated with CR-POPF on bivariate analysis included male sex (18.9% vs 13.8% for female; $P = 0.003$), diabetic status (17.4% for nondiabetic patients, 17.8% for noninsulin-dependent diabetic patients, and 10.3% for insulin-dependent diabetic patients; $P = 0.023$), higher BMI (10.6% for BMI < 18.5, 12.0% for BMI 18.5–24.9, 17.1% for BMI 25–29.9, 22.5% for BMI > 30; $P < 0.001$), and less than 10% preoperative weight loss (17.4% vs 11.9% for weight loss > 10%; $P = 0.022$). Disease-related factors associated with development of CR-POPF included histologic diagnosis (11.9% for pancreatic adenocarcinoma, 26.5% for nonadenocarcinoma malignancies, and 19.3% for other indications; $P < 0.001$), normal pancreatic duct diameter (23.5% vs 12.5% for dilated; $P < 0.001$), lack of preoperative biliary obstruction (19.8% vs 14.5% for patients with biliary obstruction; $P = 0.003$), and lack of neoadjuvant therapy (18.4% vs 8.6% for patients receiving neoadjuvant therapy; $P < 0.001$). Factors not associated with CR-POPF included age, race, smoking status, and preoperative albumin levels (Table 2).

3.3 | Multivariable models

The final multivariable model contained eight variables; sex, diabetic status, BMI, preoperative weight loss, biliary obstruction, histology, duct size, and neoadjuvant therapy status. All variables maintained statistical significant on multivariable modeling (Table 3).

3.4 | Escalating fistula rates with risk factor exposure

Adequate patient distribution was observed with regard to risk factor prevalence, with 2088 patients (20.8%) having three or fewer risk factors, 4709 (47.0%) having four or five risk factors, and 3225 (32.2%) having six or more risk factors in the derivation cohort. Escalating fistula rates were observed with increasing preoperative risk factors, with a 7.1% fistula rate with three or fewer risk factors, 14.0% with four or five, and 26.3% with six or more risk factors ($P < 0.001$, Figure 1).

A similar distribution of risk factors was observed in the validation cohort, with 1066 patients (21.3%) having three or fewer risk factors, 2295 (45.8%) having four or five risk factors, and 1650 (32.9%) having six or more risk factors. There was a similar stepwise increase in the rate of CR-POPF with increasing risk factors, ranging from 6.7% with fewer than three risk factors to 27.1% with six or more risk factors ($P < 0.001$, Figure 1).

4 | DISCUSSION

In this study, we identified several variables available in the preoperative setting that allow for early stratification of risk of CR-high risk for CR-POPF development after pancreaticoduodenectomy. To our knowledge, this is the most comprehensive attempt to date to identify patients at high risk for CR-POPF before surgery. Focusing the risk analysis on only preoperative variables affords the surgeon the opportunity to have a reproducible estimate of the CR-POPF risk before performing surgery.

The advantages of preoperative risk estimation are numerous. While it is unlikely to modify a surgeon's decision to recommend surgery, it could better inform the surgical risk discussion and facilitate shared decision-making for patients undergoing pancreaticoduodenectomy. The utility of rigorous preoperative risk estimation has been demonstrated in many surgical fields, notably including the ACS Surgical Risk Calculator.^{24,25} The ability to more accurately discuss CR-POPF risk can benefit patients by helping to set postoperative expectations and provide tangible numbers for informed discussions. Identification of these preoperative risk variables gives an evidence-based structure to the sometimes overwhelming discussion of the risks of pancreaticoduodenectomy.

Preoperative risk assessment can also potentially demonstrate value by allowing for selective employment of enhanced recovery pathways and perioperative protocols. There is growing interest in the implementation of enhanced recovery pathways for patients undergoing pancreatic resection, which often include preoperative steps.²⁶ Identification of CR-POPF risk can help providers determine which patients are most likely to benefit from enhanced recovery protocols, and conversely, identify high-risk patients who should be placed on modified pathways or excluded entirely. One example of a related application involves administration of pasireotide, a somatostatin analog that has been shown to significantly reduce the rate of pancreatic fistula.²⁷ While pasireotide has been shown to be cost effective or cost neutral when used in all patients, studies demonstrate improved cost-effectiveness with selective usage.^{28–31} Pasireotide administration protocols often require preoperative or early intraoperative dosing, and a preoperative CR-POPF risk estimation could allow surgeons to better select which patients will benefit from pasireotide well before the day of

surgery. Future studies are needed to determine the utility of preoperative risk evaluation in the context of pasireotide use, as the use of somatostatin analogs is not currently abstracted in ACS NSQIP.

A further utility of this study is best understood when contextualizing the results with existing, validated risk scores. Previous studies have attempted to develop formal risk scores for preoperative fistula risk stratification, but these have been limited in terms of performance, usability, and the robustness of the data underlying score derivation.^{15,16} Because preoperative risk evaluation is unlikely to change the overall decision to perform a resection of a pancreatic tumor, we focused on identifying novel risk factors to aid clinicians in risk evaluation and discussion preoperatively rather than the development of a formal risk score for stratification. More formal risk stratification using the best possible information (e.g., gland texture) in the form of either the FRS or alternative FRS can then be utilized to guide postoperative decisions, such as drain management. Overall, preoperative risk evaluation can serve as a complement to other validated risk stratification schemas, such as the FRS and alternative FRS. Future work could aim to prospectively evaluate the variables identified in this study in conjunction with intraoperative variables to identify synergistic results and optimize final risk stratification.

This study has several limitations. It is notable that several of the identified risk factors may be associated with the development of pancreatic adenocarcinoma, including diabetic status and use of neoadjuvant therapy. It is possible that these variables are not directly related to CR-POPF, but instead act through an intermediate variable, such as gland texture (e.g., neoadjuvant therapy or diabetes lead to firm gland texture, and in turn lower CR-POPF rate). As such, these variables may be preoperative surrogates for more traditional fistula risk variables. However, we believe that the exact causal mechanism of any observed associations in this study are secondary considerations and do not detract from the predictive capacity of the risk scheme. It should be noted that all included variables had independent effects in adjusted models without significant statistical interaction, indicating additive risks at the patient level regardless of the underlying mechanism. In addition, while internal validation strongly implies the associations are robust, further external validation would be optimal before clinical implementation. Finally, as described in Section 2, the ACS NSQIP variable used for pancreatic duct diameter is determined by the clinical reviewer using a combination of preoperative, intraoperative, and pathologic information. Duct diameter for this study was intentionally stratified at 3 mm to approximate the “normal vs dilated” pancreatic duct that is routinely determined on preoperative imaging in real-life clinical practice and has been demonstrated to be a reliable estimate of intraoperative findings in multiple studies.^{21,23} Future iterations and/or external validations could include pancreatic duct diameter as measured on preoperative imaging to verify this assumption.

5 | CONCLUSION

Risk of CR-POPF development after pancreaticoduodenectomy can be evaluated using variables that can be readily and accurately assessed in the preoperative setting including sex, diabetic status, BMI, pathology, evidence of biliary obstruction, pancreatic duct size, and receipt of neoadjuvant therapy. Early risk evaluation could potentially aid patient

informed consent, guide clinical decision-making in areas, such as neoadjuvant therapy, assist with selection of patients for perioperative risk reduction protocols, including somatostatin analog usage, and serve as a valuable complement to current risk scores.

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Abbreviations:

ACSNSQIP	American College of Surgeons National Surgical Quality Improvement Program
CR-POPF	clinically-relevant postoperative pancreatic fistula
FRS	fistula risk score
ISGPF	International Study Group on Pancreatic Fistula

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FIGURE 1.

CR-POPF rates based on preoperative risk factors in derivation and validation cohorts. Rate of CR-POPF based on number of risk factors in both derivation and validation cohort.

Fistula rates in the derivation cohort were 7.1% with three or fewer risk factors, 14.0% with four or five, and 26.3% with six or more risk factors. Fistula rates in the validation cohort ranged from 6.7% with fewer than three risk factors to 27.1% with six or more risk factors.

CR-POPF, clinically-relevant postoperative pancreatic fistula

TABLE 1

Overall cohort characteristics and characteristics of derivation and validation groups

Characteristic	Overall N = 15 033	Derivation N = 10 022	Validation N = 5011	P value*
Age, y				0.933
Mean ± standard deviation	65.2 ± 11.6	65.2 ± 11.6	62.2 ± 11.6	
Range	18–100	18–100	18–96	
Sex, %				0.945
Male	53.8	53.8	53.9	
Female	46.2	46.2	46.1	
Year, %				0.836
2014	20.5	20.7	20.1	
2015	24.5	24.5	24.5	
2016	26.9	26.8	27.2	
2017	28.1	28.0	28.1	
Race, %				0.422
Nonhispanic white	73.3	73.5	72.8	
Nonhispanic black	7.6	7.5	8.0	
Hispanic	4.6	4.4	5.0	
Other	4.2	4.2	4.1	
Unknown	10.3	10.4	10.1	
BMI				0.421
<18.5	2.8	2.7	2.8	
18.5–24.9	35.6	35.2	36.4	
25–29.9	35.6	36.0	34.7	
30	26.1	26.1	26.1	
Neoadjuvant treatment, %				0.906
Received	18.6	18.6	18.6	
Not received	81.4	81.4	81.4	
POPF (%)				0.068
Yes	23.5	23.0	23.4	
No	76.5	77.0	75.6	

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Characteristic	Overall N = 15 033	Derivation N = 10 022	Validation N = 5011	P value*
CR-POPF (%)				0.440
Yes	16.7	16.5	17.0	
No	83.3	83.5	83.0	

Abbreviations: BMI, Body mass index; CR-POPF, clinically-relevant postoperative pancreatic fistula.

* Cluster-adjusted Chi-square test of association.

TABLE 2

Bivariate analysis of candidate preoperative predictive variables in derivation cohort (N = 10 022)

Characteristic	With CR-POPF		P value *
	N	%	
Age, y			0.503
<65	714	16.5	
65–74	620	17.8	
75	324	14.9	
Sex			0.003
Male	1021	18.9	
Female	637	13.8	
Year			0.847
2014	340	16.4	
2015	440	17.9	
2016	430	16.0	
2017	448	16.0	
Race			0.053
Nonhispanic white	1141	15.5	
Nonhispanic black	104	13.9	
Hispanic	98	22.2	
Other	75	17.6	
Unknown	240	23.1	
Diabetes			0.023
No	1299	17.4	
NIDDM	227	17.8	
IDDM	132	10.3	
Smoker			0.413
No	1385	16.9	
Yes	273	15.0	
Functional status			0.446
Independent	1639	16.5	
Dependent	19	24.1	
COPD			0.497
No	1576	16.4	
Yes	82	19.4	
HTN			0.223
No	718	15.4	
Yes	940	17.5	
CHF			0.788
No	1651	16.5	
Yes	7	20.6	
BMI, kg/m ²			<0.001

Characteristic	With CR-POPF		P value*
	N	%	
<18.5	29	10.6	
18.5–24.9	422	12.0	
25–29.9	617	17.1	
30	590	22.5	
Weight loss			0.022
<10%	1472	17.4	
>10%	186	11.9	
Preoperative steroid use			0.329
No	1604	16.4	
Yes	54	22.0	
ASA			0.688
1–2	364	16.6	
3–5	1294	16.5	
Histology			<0.001
Pancreatic adenocarcinoma	659	11.9	
Nonadenocarcinoma malignancy	506	26.5	
Pancreatic duct size**			<0.001
Normal	571	23.5	
Dilated	675	12.5	
Unknown	412	18.8	
Biliary obstruction***			0.003
No	769	19.8	
Yes	889	14.5	
Neoadjuvant XRT			0.001
No	1618	17.4	
Yes	40	5.3	
Neoadjuvant chemo			<0.001
No	1501	18.3	
Yes	157	8.7	
Any neoadjuvant			<0.001
No	1498	18.4	
Yes	160	8.6	
Preoperative albumin			0.928
<3	162	16.6	
3	1496	16.5	

Abbreviations: BMI, Body mass index; CHF, congestive heart failure; CR-POPF, clinically-relevant postoperative pancreatic fistula; HTN, hypertension; IDDM, insulin-dependent diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus.

* Cluster-adjusted Chi-square test of association.

** Normal defined as <3 mm, dilated ≥ 3 mm.

*** Defined as presence of jaundice, hyperbilirubinemia (>1.2 mg/dL), or stent placement.

TABLE 3

Adjusted multivariable model *

Characteristic	Adjusted OR (95% CI)	P Value
Sex		
Female	1.0	Ref
Male	1.51 (1.35–1.68)	<0.001
Diabetes		
IDDM	1.0	Ref
NIDDM	1.75 (1.36–2.26)	<0.001
No diabetes	1.80 (1.44–2.25)	<0.001
BMI		
<18.5	1.03 (0.70–1.53)	0.884
18.5–24.9	1.0	Ref
25–30	1.40 (1.22–1.61)	<0.001
>30	1.97 (1.72–2.27)	<0.001
Preoperative weight loss		
>10%	1.0	Ref
<10%	1.25 (1.08–1.44)	0.003
Biliary obstruction **		
Present	1.0	Ref
Absent	1.18 (1.04–1.33)	0.009
Histology		
Pancreatic adenocarcinoma	1.0	Ref
Nonadenocarcinoma	1.96 (1.67–2.30)	<0.001
malignancy ***		
Other	1.35 (1.16–1.57)	<0.001
Pancreatic duct size, %		
Dilated (≥ 3 mm)	1.0	Ref
Normal (<3 mm)	1.81 (1.58–2.07)	<0.001
Any neoadjuvant therapy, %		
Received	1.0	Ref
Not received	1.78 (1.41–2.24)	<0.001

Abbreviations: BMI, Body mass index; CI, control interval; IDDM, insulin-dependent diabetes mellitus; NIDDM, noninsulin-dependent diabetes mellitus; OR, odds ratio.

* Multivariable logistic regression model with robust standard errors, adjusted for patient clustering at the hospital level. Unknown values treated as categorical variables.

** Defined as presence of jaundice, hyperbilirubinemia (>1.2 mg/dL), or stent placement.

*** Includes duodenal carcinoma, ampullary carcinoma, cholangiocarcinoma, neuroendocrine tumors.