A Prospectively Validated Clinical Risk Score Accurately Predicts Pancreatic Fistula after Pancreatoduodenectomy

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BACKGROUND: Clinically relevant postoperative pancreatic fistulas (CR-POPF) are serious inherent risks of pancreatic resection. Preoperative CR-POPF risk assessment is currently inadequate and rarely disqualifies patients who need resection. The best evaluation of risk occurs intraoperatively, and should guide fistula prevention and response measures thereafter. We sought to develop a risk prediction tool for CR-POPF that features intraoperative assessment and reveals associated clinical and economic significance.

STUDY DESIGN: Based on International Study Group of Pancreatic Fistula classification, recognized risk factors for CR-POPF (small duct, soft pancreas, high-risk pathology, excessive blood loss) were evaluated during pancreaticoduodenectomy. An optimal risk score range model, selected from 3 different constructs, was first derived ($n = 233$) and then validated prospectively ($n = 212$). Clinical and economic outcomes were evaluated across 4 ranges of scores (negligible risk, 0 points; low risk, 1 to 2; intermediate risk, 3 to 6; high risk, 7 to 10).

RESULTS: Clinically relevant postoperative pancreatic fistulas occurred in 13% of patients. The incidence was greatest with excessive blood loss. Duct size <5 mm was associated with increased fistula rates that rose with even smaller ducts. These factors, together with soft pancreatic parenchyma and certain disease pathologies, afforded a highly predictive 10-point Fistula Risk Score. Risk scores strongly correlated with fistula development ($p < 0.001$). Notably, patients with scores of 0 points never developed a CR-POPF, while fistulas occurred in all patients with scores of 9 or 10. Other clinical and economic outcomes segregated by risk profile across the 4 risk strata.

CONCLUSIONS: A simple 10-point Fistula Risk Score derived during pancreaticoduodenectomy accurately predicts subsequent CR-POPF. It can be readily learned and broadly deployed. This prediction tool can help surgeons anticipate, identify, and manage this ominous complication from the outset. (J Am Coll Surg 2013;216:1–14. © 2013 by the American College of Surgeons)

CME questions for this article available at http://jacscme.facs.org

Disclosure Information: Authors have nothing to disclose. Timothy J Eberlein, Editor-in-Chief, has nothing to disclose.

Presented at the American College of Surgeons 97th Annual Clinical Congress, San Francisco, CA, October 2011.

Received July 16, 2012; Revised September 5, 2012; Accepted September 5, 2012.

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Despite advancements in operative technique and improvements in postoperative outcomes, pancreatic fistula is widely considered to be the most common and troublesome complication after pancreatic resection. It represents the factor most often linked with postoperative mortality, certain complications such as delayed gastric emptying, longer hospital stays, readmissions, and increased costs. Furthermore, it frequently delays timely delivery of adjuvant therapies, and reduces overall patient survival.[1-7] Placement of pancreatic duct stents, the use of somatostatin analogs[8] or adhesive sealants, or modifications in reconstruction technique have done little to change the incidence or alter the impact of postoperative pancreatic fistulas (POPF).

The emergence of the International Study Group on Pancreatic Fistula (ISGPF) classification scheme established a universal and practical definition of POPF.[9] This

ISSN 1072-7515/12/$36.00
http://dx.doi.org/10.1016/j.jamcollsurg.2012.09.002

Abbreviations and Acronyms

AUC = area under the curve
CR-POPF = clinically relevant postoperative pancreatic fistula
ISGPF = International Study Group on Pancreatic Fistula
OR = odds ratio
PD = pancreatoduodenectomy
POPF = postoperative pancreatic fistula

consequently inspired further interest in prediction, prevention, and management of fistulas.[10-12] Recently, we described predictive factors for POPF after pancreatoduodenectomy (PD) within the framework of the ISGPF classification scheme.[13] Pancreatic duct size smaller than 3 mm; soft pancreatic parenchyma; ampullary, duodenal, cystic, or islet cell pathology; and intraoperative blood loss more than 1,000 mL were associated with increased risk of developing a clinically relevant pancreatic fistula (CR-POPF). These findings also revealed the additive effect of these risk factors and their negative impact on clinical and economic outcomes. Patients with more accrued risk factors (0 to 4) suffer more complications, have longer hospital stays, and incur greater hospital costs.[13] Intraoperative risk assessment appears to be critical. Preoperative risk stratification alone is inadequate, rarely disqualifies patients who require resection, infrequently alters the postoperative course, and is seldom used or widely applied.[14]

This study offers a new and convenient scoring tool to predict CR-POPF. It is derived from intraoperative assessment, has been tested against high volumes of PD in a pancreatic surgical practice, and displays excellent discrimination. Ultimately, a patient's "fistula risk profile" might direct their clinical management and prevent, or mitigate, untoward outcomes.

METHODS

Data collection

Under IRB approval, clinical and economic outcomes data were obtained and analyzed prospectively for patients who underwent pancreatoduodenectomy at Beth Israel Deaconess Medical Center between January 2002 and May 2011. Three surgeons (MPC, TSK, and CMV) performed 445 pancreatoduodenectomies for a full spectrum of both malignant and benign conditions; enumerations and details of specific pathology, surgical techniques, and other practice parameters have been described elsewhere.[10,13] In brief, duct-to-mucosa pancreaticojejunostomy was the preferred reconstruction, with only 4 pancreaticogastrostomies in the series. Prophylactic octreotide was administered in roughly 50% of cases, and pancreatico-jejunal anastomotic stents (predominantly short, internal silicone elastomer tubes) were used in just 60 cases. Similarly, sealants were virtually never used (<1%). Pancreatic duct diameter was acquired intraoperatively using a ruler. Gland texture was intraoperatively determined by the operating surgeon as either firm or soft, and was not correlated to any histologic analysis. A single drain (#19 Blake) was placed under bulb suction adjacent to the pancreatico-jejunal anastomosis and measured for amylase activity after the initiation of soft food (usually on postoperative day 6).

Data on preoperative, intraoperative, and postoperative care were collected and maintained on a secure database. Preoperative parameters include patient demographics, presenting symptoms, laboratory tests, previous imaging studies, and preoperative therapies. Intraoperative parameters included total blood loss, operative time, fluids given, blood transfusions, diameter of the main pancreatic duct, and texture of the gland, as well as the use of drains, stents, fibrin sealants, or somatostatin analogues. Postoperative events and clinical outcomes were recorded and included therapeutic and diagnostic procedures, nutritional support, laboratory and imaging studies, recovery of gastrointestinal function, incidence, type and severity of complications, ICU transfers and duration, initial hospital duration, discharge disposition, and any hospital readmissions or reoperations within 90 days. Mortality was defined as death during the initial hospitalization or within 30 days of hospital discharge, or death due to any surgical complication at any point in time. All economic data were collected and analyzed using Casemix TSI.

Overview

Fistulas were classified according to the ISGPF classification scheme.[9] This scheme was used to differentiate CR-POPF from transient, asymptomatic biochemical fistulas. The latter have been shown to have no adverse clinical or economic impact on patient recovery.[10] Risk factors for CR-POPF were identified in an initial group of 233 patients who underwent PD between January 2002, and February 2007 (cohort 1).[13] From this, 3 candidate models for prediction of CR-POPF were developed. These 3 clinical scoring models were then examined prospectively and judged for accuracy in a separate collection of 212 patients who underwent PD between March 2007 and May 2011 (cohort 2). Logistic regression and receiver operating characteristic (ROC) analyses were performed among patients in cohort 2 for model discrimination, and to delineate the most accurate of the 3 candidate models. The accepted model was then scrutinized in order to uncover

effective strategies for managing patients with varying risk for CR-POPF development.

Classification of pancreatic fistula

The severity of pancreatic fistula was judged according to the ISGPF classification scheme.[9] According to this system, pancreatic fistula is defined as any appreciable drainage from an operatively placed drain (or a subsequently placed percutaneous drain) with an amylase content greater than 3 times the upper limit of normal serum amylase level measured on, or after, postoperative day 3. At our institution, this involves amylase-rich effluents that exceed 300 IU/L. Those below are designated in the "no fistula" group. Finally, severity of pancreatic fistula is determined based on 10 clinical criteria and then stratified into 3 levels of impact on the patient: grades A, B, and C. As emphasized elsewhere, this classification can be accurately assigned only after the clinical course has reached its completion.[9,15]

To summarize, grade A fistulas are transient, asymptomatic biochemical fistulas, defined by only elevated drain amylase levels. Grade B fistulas are clinically apparent, symptomatic fistulas that require diagnostic evaluation and therapeutic intervention. Finally, grade C fistulas render patients in critical condition, with sepsis and/or organ dysfunction. They require more significant interventions, usually in an intensive care setting, or surgical re-exploration for definitive management. Those who die as a result of the pancreatic fistula are appropriately assigned to this severe grade of fistula. As developed in previous studies, grades B and C are considered clinically relevant postoperative pancreatic fistulas (CR-POPF) based on their clinical effects and need for therapeutic intervention.[9,10,12]

Risk factors for pancreatic fistula

Distinct risk factors for CR-POPF after PD have been described.[13] First, a univariate analysis was performed to examine the relationship between each preoperative and intraoperative variable in our database and the outcomes of CR-POPF. Eighteen preoperative variables including age, sex, body mass index, biochemical markers, and the presence of comorbid conditions were studied. Another 24 intraoperative variables were examined, including operative time, blood loss, gland texture, pancreatic duct size, intraoperative transfusion, anastomotic technique, administration of octreotide, and the use of pancreatic duct stents, to list a few. Variables with $p < 0.10$ were retained for entry in a multivariate analysis. Variables were entered alone, and then in a stepwise fashion using a $p < 0.10$ for entry, and <0.05 for inclusion. Variables that independently predicted CR-POPF became candidates for the Fistula Risk Score (FRS), paying attention to developing a practical clinical scoring system with reasonable predictive power.

Fistula Risk Score

Derivation of Fistula Risk Score

We began in February 2007 by analyzing the incremental impact of the 4 significant risk factors for pancreatic fistula in 233 consecutive patients in cohort 1. Three separate scoring models were developed and examined for accuracy. The first (model I) assigned a single point for each of the 4 risk factors. In model II, points were weighted according to the magnitude of the β-coefficients from the regression equation for each parameter. In model III, points were similarly weighted, but were further modified in order to develop a more utilitarian application, which could facilitate recall for the operating surgeon. For categorical variables, we assigned points according to the severity of the risk parameter; for continuous variables, we constructed intervals such that each incremental increase of 1 point would reflect the attendant increased likelihood of developing a CR-POPF.

Internal validation of Fistula Risk Score

Internal validation of our model was performed prospectively, with data accrued beginning in March 2007. Each of the 3 models was examined in the 212 consecutive patients of cohort 2 using logistic regression analysis. Additionally, as a measure of model discrimination, receiver operating characteristic curves were plotted and the 3 models were compared on the basis of the area under the curve (AUC). The candidate model associated with the highest AUC was selected as the final Fistula Risk Score model. This model was then assessed for clinical and economic outcomes, with a particular concentration on the incidence and impact of CR-POPF.

Statistical analysis

Statistical computations were performed using Statistical Package for the Social Sciences 16.0 for Windows (SPSS, Inc) and STATA.8.2 for Windows (StataCorp LP). Factors associated with postoperative morbidity were calculated based on cross-tabulations using chi-square statistic and the Pearson correlation test, as described above. Categorical variables were compared using binomial or multinomial logistic regression to correlate clinical and economic outcomes with physiologic risk grades and operative severity classes. Continuous variables were compared using analysis of variance (ANOVA), Student's *t*-tests for independent variables,

and simple linear regression when appropriate. Statistical significance was accepted at $p < 0.050$.

RESULTS

Overview

Overall, 93 of 445 patients suffered pancreatic fistula, as defined by ISGPF criteria, for an incidence of 20.9%. Transient, asymptomatic biochemical fistulas (ie, grade A) occurred in 8% of all patients (38% of all POPFs); CR-POPF (ie, grades B and C) represented 13% of all patients. Grade B fistulas were the most common fistula type (n = 50), comprising 54% of all POPF; a grade C fistula was a rare occurrence, manifesting in only 8 patients (9% of all POPF). Antibiotics were administered for fistula management in 10% of patients (n = 45); supplemental nutrition was initiated for 4% (n = 18); percutaneous drainage was infrequently used (2.5%). There were 22 readmissions (4.9%) and 11 reoperations (2.5%). Only 1 death was directly attributable to pancreatic fistulas. The median stay for all patients having PD was 8 days. Consistent with our previous work, escalations in fistula severity were associated with more nonfistulous complications (grade A, 26%; B, 84%; C, 88%, $p < 0.001$), increased ICU use (grade A, 0%, B, 14%, C, 50%, $p < 0.001$), progressively longer median hospital stays (grade A, 8 days; B, 10 days; C, 18 days, $p < 0.001$), and greater hospital costs (grade A, $18,545; B, $27,575; C, $39,118, $p < 0.001$). Other postoperative outcomes for each fistula grade resemble those previously described.[6,10]

Risk factors for clinically relevant fistulas

Logistic regression analysis was performed retrospectively for cohort 1.[13] Fifty-eight of 233 patients suffered a POPF, for an incidence of 24.7%. Transient, asymptomatic grade A fistulas occurred in 12%, while clinically relevant grade B and C fistulas also appeared in 12% of patients. There were 9 readmissions (3.8%), 5 reoperations (2.1%), and no deaths.

Univariate analysis of 18 preoperative and 24 intraoperative variables demonstrated that among this cohort, patient age, patient acuity (as measured by the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity [POSSUM] score), the use of a single-layer anastomosis, the texture of the pancreatic remnant, type of pathology, diameter of the pancreatic duct, and the amount of intraoperative blood loss were associated with CR-POPF. Yet on multivariate analysis, only soft pancreatic parenchyma; the presence of ampullary, duodenal, cystic, or islet cell pathology; a pancreatic duct diameter measuring 3 mm or smaller; and intraoperative blood loss in excess of 1,000 mL were significant.

Table 1. Multivariable Analysis of Risk Factors for Clinically Relevant Postoperative Pancreatic Fistula Derived from Cohort 1 (n = 233; January 2002 to February 2007)

Parameter	Odds ratio	95% CI	p Value
Gland texture			0.007
Firm	1.00		
Soft	5.02	1.97–12.81	
Pathology			<0.001
Adenocarcinoma or pancreatitis	1.00		
Ampullary, duodenal, cystic, islet cell	2.98	1.36–6.54	
Pancreatic duct diameter, mm			0.002
≥5	1.00	—	
4	1.76	1.23–2.52	
3	3.11	1.52–6.35	
2	5.48	1.88–15.98	
≤1	9.66	2.32–40.26	
Intraoperative blood loss, mL			0.024
≤400	1.00	—	
401–700	1.59	1.06–2.36	
701–1,000	2.51	1.13–5.59	
>1,000	3.99	1.20–13.21	

Independent logistic regression analysis of each of the 4 specific risk factors (Table 1) revealed that patients with pancreatic duct diameters measuring 3 mm or smaller (odds ratio [OR] 2.78, 95% CI 1.22 to 6.35, $p = 0.015$), or those with ampullary, duodenal, cystic, or islet cell pathology (OR 2.98, 95% CI 1.36 to 6.54, $p = 0.007$) were nearly 3 times as likely to develop CR-POPF when compared with patients with ducts larger than or equal to 4 mm, and those with pancreatic adenocarcinoma or chronic pancreatitis, respectively. Soft pancreatic parenchyma resulted in a 5-fold increase in the likelihood of developing CR-POPF (OR 5.02, 95% CI 1.97 to 12.81, $p < 0.001$). However, intraoperative blood loss in excess of 1,000 mL had the most significant impact, predisposing patients to nearly a 6-fold increase in fistula development (OR 5.60, 95% CI 1.65 to 18.98, $p = 0.006$).

Deeper analysis reflects the incremental impacts of narrowing of the pancreatic duct diameter or escalating intraoperative blood loss. First, each 1-mm decrease in the diameter of the pancreatic duct—from a baseline of 5 mm—resulted in a 76% increase in the odds of developing CR-POPF (OR 1.76, 95% CI 1.23 to 2.52, $p = 0.002$). A pancreatic duct diameter measuring 5 mm was considered a reasonable baseline because it represents the diameter most commonly encountered

(median duct diameter in the series, 5 mm) and has been referred to as the normal diameter of the main pancreatic duct in the literature.[16,17] Similarly, each unit of blood loss, measured in 300-mL increments, beyond a standard 400 mL, predisposed patients to roughly a 60% increase in fistula development (OR 1.59, 95% CI 1.06 to 2.36, $p = 0.024$). This standard estimate of 400 mL is also a reasonable baseline because it approximates our median blood loss (350 mL) and is consistent with other current published benchmarks.[18] Similarly, an increment of 300 mL provides an acceptable estimate for blood loss because it represents the approximate amount of blood volume replaced by a single unit of packed red blood cells.

All patients in the series ($n = 445$) were examined to assess the frequency of each risk factor. A total of 297 patients (67%) had at least 1 risk factor; more than one-third (38%) of them had multiple risk factors: 100 had 2, 64 had 3, and 7 had all 4 factors. The most common characteristic was a soft pancreatic parenchyma (present 49% of the time; $n = 219$), followed by ampullary, duodenal, cystic, or islet cell pathology (39%; $n = 172$,) and pancreatic duct size $\leq$3 mm (28%; $n = 124$). Intraoperative blood loss exceeding 1,000 mL was a rare event, occurring in only 20 patients (4.5%).

Fistula Risk Score models

Model I

In February 2007, we developed 3 separate models based on the 4 previously recognized risk factors, and examined their accuracy in predicting CR-POPFs among patients in cohort 1. The first model simply assigned a single point for each of the 4 risk factors. Therefore, patients who lack all 4 risk factors had 0 points, while those with all 4 risk factors accumulated 4 points. This "balanced" approach obviously ignored the incremental influences of any given risk factor, as well as the relative influences between risk factors.

Model II

In the second model, points were weighted according to the magnitude of the β-coefficients from the regression equation for each of the 4 parameters. For example, patients with a soft gland had nearly a 5-fold increase in the odds of developing CR-POPF, when compared with patients with firm glands (Table 1). So, 5 points were awarded for a soft gland, and 1 point was awarded for a firm gland. Patients harboring ampullary, duodenal, cystic, or islet cell tumors were predisposed to nearly a 3-fold increase in CR-POPF, and accordingly had 3 points assigned; those with pancreatic adenocarcinoma or pancreatitis were allocated only 1 point.

In contrast to model I, pancreatic duct diameter and intraoperative blood loss were analyzed as continuous variables, rather than dichotomized categorical variables. As previously demonstrated, each 1-mm decrease in the diameter of the pancreatic duct resulted in a 76% increase in the odds of developing a CR-POPF. When compared with the most commonly encountered 5-mm pancreatic duct, these odds rose in a stepwise fashion as the size of the duct further narrowed, from 3-fold (OR 3.11) for 3-mm ducts, to nearly 10-fold for 1-mm ducts (OR 9.66). Based on the respective odds ratios, 10 points were allocated to those patients with 1-mm ducts, 6 points for 2-mm ducts, 3 points for 3-mm ducts, 2 points for 4-mm ducts, and only 1 point for 5-mm ducts.

A similar allocation was used for intraoperative blood loss. Each 300-mL loss of blood predisposed patients to roughly a 60% increase in fistula development. Accordingly, when compared with patients whose blood loss was at or below benchmark standards for pancreatic resection—400 mL, according to previous reports[18,19]—the likelihood of fistula development escalated for each additional unit of blood loss, measured in 300-mL increments: 60% (OR 1.59) for blood loss between 401 and 700 mL; 3-fold (OR 2.51) for blood loss between 701 and 1,000 mL; and 4-fold (OR 3.99) for blood loss in excess of 1,000 mL. So 4 points were allocated to those patients with blood loss greater than 1,000 mL, 3 points for ranges between 701 and 1,000 mL, 2 points for ranges between 401 and 700 mL, and only 1 point for blood loss less than or equal to 400 mL.

Therefore, for model II, patients were assigned between 4 and 22 points, with those patients lacking all 4 risk factors having 4 points, and those having extreme elements of all 4 risk factors accumulating 22 points.

Model III

The third model resembled model II, but was designed to be more practical (Table 2). Modifications were made in order to simplify its use, and to facilitate recall for the operating surgeon. For categorical variables, points were assigned based on the magnitude of the β-coefficients from the regression equation for each parameter, but adjusted to reflect the severity of each risk parameter. For example, a single point was awarded for ampullary, duodenal, cystic, or islet cell pathology, while 2 points were awarded for a soft pancreatic parenchyma. This adjustment reflects the ratio of the respective β-coefficients for each parameter (ie, 2 times greater for a soft pancreatic parenchyma). No points were allocated to patients with pancreatic adenocarcinoma or chronic pancreatitis, or to those with firm pancreatic parenchyma.

Table 2. Fistula Risk Score for Prediction of Clinically Relevant Pancreatic Fistula after Pancreatoduodenectomy (Model III)

Risk factor	Parameter	Points*
Gland texture	Firm	0
	Soft	2
Pathology	Pancreatic adenocarcinoma or pancreatitis	0
	Ampullary, duodenal, cystic, islet cell	1
Pancreatic duct diameter, mm	≥5	0
	4	1
	3	2
	2	3
	≤1	4
Intraoperative blood loss, mL	≤400	0
	401–700	1
	701–1,000	2
	>1,000	3

*Total 0 to 10 points.

Additional adjustments were made for the continuous variables in the model (the pancreatic duct diameter and the amount of intraoperative blood loss). The size of the intervals for each continuous variable was selected such that a 1-point increase would produce an equivalent increase in the odds of developing CR-POPF. Therefore, those points allocated for the pancreatic duct diameter increased by 1 as the diameter narrowed from 5 mm to 1 mm: 0 points for a 5-mm or greater duct diameter, up to 4 points for a 1-mm duct. Similarly, for blood loss, 0 points were awarded for intraoperative blood loss at or below 400 mL and ranged to 3 points for blood loss exceeding 1,000 mL. Overall, for model III, patients were awarded between 0 and 10 points, reflecting greater simplicity.

Internal validation of the Fistula Risk Score models

Next, internal validation of the clinical scoring models was performed prospectively beginning in March 2007 and concluding in May 2011 (cohort 2). Outcomes for the 212 consecutive patients who underwent pancreatoduodenectomy during this period resemble those of cohort 1, although there was a general trend toward improved performance. Overall, 16.5% of patients suffered any ISGPF degree of a POPF. Transient, asymptomatic grade A fistulas occurred less frequently (3%); clinically relevant grade B and C fistulas still represented 13% of all patients. There were 13 readmissions (6.1%), 6 reoperations (2.8%), and only 1 death (which was directly attributable to a pancreatic fistula). Pearson's goodness-of-fit test showed no significant differences between cohorts 1 and 2 in regard to the incidence of CR-POPF ($p = 0.514$), as well as all other clinical and economic outcomes.

The relationship between CR-POPF and each model was examined by performing logistic regression analysis among patients in cohort 2. For all 3 approaches, as the model score escalated, the incidence of CR-POPF increased significantly ($p < 0.001$). Additionally, the AUC statistic was calculated in order to optimize the threshold level within each model, and this also served as a measure of model discrimination. Model III had the best performance, as reflected by the highest AUC (0.942); model II (0.938) and model I (0.936) were only slightly less accurate. Therefore, model III serves as the final proposed Fistula Risk Score (Table 2).

Under this selected model, the incidence and impact of CR-POPFs were analyzed among all patients (Fig. 1). The total score—from 0 to 10—was highly predictive of fistula development ($p < 0.001$). No patients with a total score of 0 points ($n = 73$; 16%) developed a CR-POPF. In contrast, nearly all patients with scores exceeding 7 points had CR-POPF. This threshold of 7 points, albeit a rare occurrence (3%), was selected on the basis of the calculated AUC statistic. Four risk strata were assigned according to the total score: negligible risk (0 points), low risk (1 to 2 points), intermediate risk (3 to 6 points), and high risk (7 to 10 points).

Further analysis revealed several interesting trends in quality outcomes and resource use. Clinical and economic outcomes segregated by score—as risk profile accrued, patients required more invasive interventions, remained hospitalized longer, and incurred greater hospital costs (Table 3). As anticipated, no patient assigned the distinction of negligible risk required either percutaneous drainage or reoperation for management of pancreatic fistula. Similarly, only 1 patient deemed low risk (1%) required percutaneous drainage for fistula, and none underwent reoperation. In contrast, these interventions (more so percutaneous drainage) were both used to control and treat CR-POPF among intermediate risk patients. Finally, among high risk patients, reoperation for fistula was a more common management strategy (25%), particularly relative to the other risk profiles.

Furthermore, when applied to all patients in the series, as risk profile accrued, not only did the overall incidence of POPF rise, but these fistulas were more likely to be of the clinically relevant type, as opposed to biochemical fistulas (Fig. 2). More specifically, low risk patients were least likely to develop CR-POPFs, compared with biochemical fistula (1:2 odds). In contrast, high risk patients almost always manifest CR-POPFs when fistulas occur (6:1 odds). These

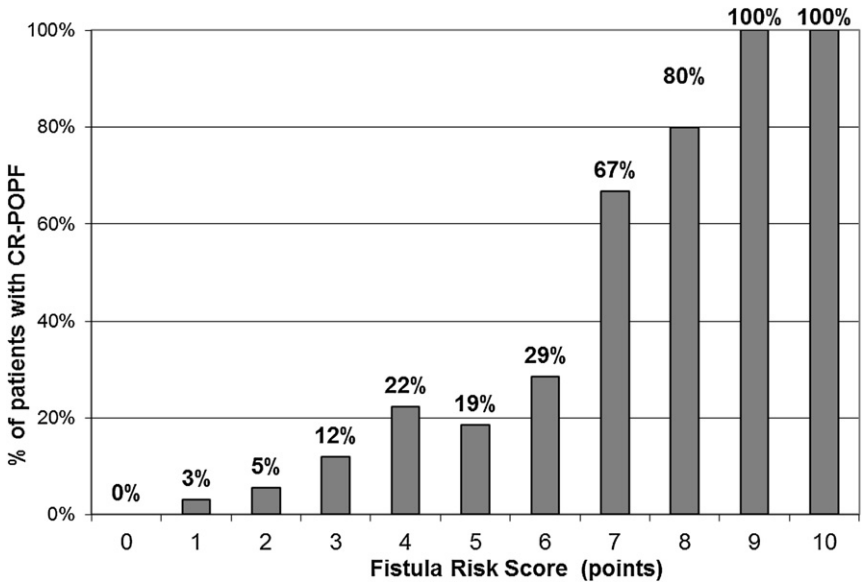

Figure 1. Clinically relevant postoperative pancreatic fistula (CR-POPF) in relation to the Fistula Risk Score in all patients (n = 445; January 2002, to May 2011).

CR-POPFs drove clinical outcomes and ultimately determined management practices and resource use (Table 4). Increased Fistula Risk Score, however, did not have any significant impact on the incidence of other nonfistulous complications or rates of hospital readmission, although there was a general trend toward worse outcomes with higher scores.

Fiscal analysis demonstrates that the economic burden of a high-risk profile equates to a 6-day increase in hospital stay, and an approximate $22,000 cost increase

Table 3. Risk Stratification Based on the Fistula Risk Score for Patients in Cohort 2 (n = 212, March 2007 to May 2011)

	Risk profile (model score)				
Variable	**Negligible risk (0 points)**	**Low risk (1–2 points)**	**Intermediate risk (3–6 points)**	**High risk (7–10 points)**	**p Value**
Patients, n (% of overall)	45 (21)	87 (41)	72 (34)	8 (4)	—
Risk factors					
Soft gland texture	—	30 (34)	67 (93)	8 (100)	<0.001
Ampullary, duodenal, cystic, islet cell	—	24 (28)	55 (76)	7 (88)	<0.001
Pancreatic duct diameter ≤3 mm	—	10 (12)	60 (83)	8 (100)	<0.001
Intraoperative blood loss >1,000 mL	—	2 (2)	4 (6)	1 (12)	0.166
Any fistula, n (%)	—	7 (8)	20 (28)	8 (100)	<0.001
ISGPF classification, n (%)					<0.001
No fistula	45 (100)	80 (92)	52 (72)	—	
Grade A	—	2 (2)	4 (6)	1 (12)	
Grade B	—	5 (6)	13 (18)	5 (63)	
Grade C	—	—	3 (4)	2 (25)	
Clinically relevant fistulas, n (%)	—	5 (6)	16 (22)	7 (88)	<0.001
Nonfistulous complications, n (%)	22 (49)	40 (46)	35 (39)	6 (75)	0.480
Hospital duration, d, median					0.010
Index	8	8	8	14	
Total	8	8	9	20	
Total hospital costs, median, $	21,874	22,674	23,329	43,489	0.026
Cost increase (beyond "negligible risk"), $	—	800	1,455	21,615	—

ISGPF, International Study Group on Pancreatic Fistula.

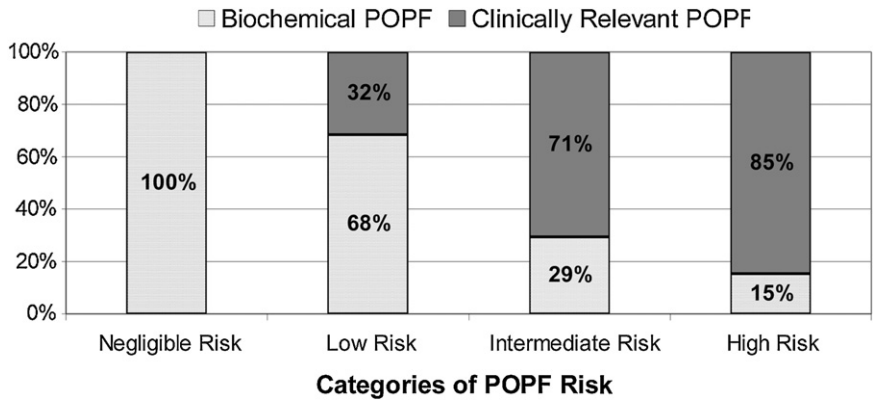

Figure 2. Character of pancreatic fistula according to the Fistula Risk Score among patients with pancreatic fistula (n = 93) after all pancreatoduodenectomies performed between January 2002 and May 2011 (n = 445). POPF, postoperative pancreatic fistula.

(Table 3). This cost increase is explained further by greater itemized costs across all cost categories, but particularly for ICU, laboratory, radiology, pharmacy, and room outlays. Median costs for ICU use consisted of $3,050 for high risk patients, and $1,194 for all other patients (p = 0.011). Similarly, laboratory costs ($1,460 vs $572, p = 0.003), and radiology costs ($1,488 vs $150, p = 0.008) were significantly higher, reflecting the increased necessity for frequent diagnostic evaluations among high risk patients. Finally, there were increased room costs among high-risk patients ($15,983 vs $7,023), which is consistent with their 6-day increase in hospital stay.

The relevance of the Fistula Risk Score is further demonstrated by its positive and negative predictive values. For high risk patients, the positive predictive value was 87.5% and the negative predictive value was 89.7%. These findings imply that among patients who accrue at least 7 points, the risk of developing a CR-POPF is approximately 88%; those who register under 7 points have only a10% likelihood. In contrast, among low risk and negligible risk patients, the positive and negative

Table 4. Patterns of Fistula Based on the Fistula Risk Score for Patients with Postoperative Pancreatic Fistula (n = 93) among All 445 Pancreatoduodenectomies Performed Between 2002 and 2011

	Risk profile (model score)								
	Negligible risk (0 points)		Low risk (1–2 points)		Intermediate risk (3–6 points)		High risk (7–10 points)		
Variable	n	%	n	%	n	%	n	%	p Value
Patients with fistula, n (% of all fistula)	3	3	19	20	58	62	13	14	—
Risk factors									
Soft gland texture	—		3	16	51	88	13	100	<0.001
Ampullary, duodenal, cystic, islet cell	—		5	26	41	71	11	85	<0.001
Pancreatic duct diameter ≤3 mm	—		2	10	23	40	13	100	<0.001
Intraoperative blood loss >1,000 mL	—		—		4	7	4	31	<0.001
ISGPF classification, n (% of fistula)									<0.001
Grade A	3	100	13	68	17	29	2	15	
Grade B	—		6	32	37	64	7	54	
Grade C	—		—		4	7	4	31	
Clinically relevant fistulas, n (% of fistulas)	—		6	32	41	71	11	85	0.001
Latent fistula, n (%)	—		1	5	16	28	3	31	0.141
Percutaneous drainage for fistula, n (%)	—		1	5	9	16	1	8	0.540
Reoperation for fistula, n (%)	—		—		7	12	3	23	0.186
Hospital readmission for fistula, n (%)	—		1	5	12	22	4	40	0.110

ISGPF, International Study Group on Pancreatic Fistula.

predictive values were 23.6% and 96.2%, respectively. This indicates that patients with more than 2 points have only a 24% probability of developing a fistula; but those with 2 or fewer points have a scant (4%) possibility of developing a CR-POPF.

Last, the occurrence of a severe grade C fistula cannot be discriminated by Fistula Risk Score alone because this clinical scenario was distributed equally between intermediate and high risk rankings (Tables 3, 4). This is consistent with our previous findings in which no discreet predictive risk factors were identified that segregate between these 2 strata of CR-POPF.[13] Table 5 provides additional details regarding the clinical courses of these 8 patients.

DISCUSSION

Effective management of pancreatic fistula has proven to be a difficult challenge in pancreatic surgery. Despite advancements in operative techniques and improvements in postoperative patient care, more than 20% of patients still develop a POPF of some sort after pancreatic resection.[9] Faced with this adversity, there has been a paradigm shift among pancreatic surgeons in the management of pancreatic fistula, from a reactive "wait and see" approach that depends on treating fistulas when they become evident, to a proactive strategy that instead relies on early anticipation and timely prevention through attempted propylaxis.[14,20] However, this approach is predicated on the assumption that risk for fistula development can actually be predicted.

Although risk factors for POPF have historically been suggested in the literature, their relevence and applicability have been hampered by a plethora of baseline definitions for fistula.[21] Faced with such vagaries, the ISGPF produced a seminal paper that proposes a standardized definition of POPF, concentrating on those that have clinical impact on the patient.[9] With this now widely recognized framework in hand, specific risk factors for the development of clinically relevent POPF have been elicited.[13] Based on an extensive analysis of pre- and intraoperative variables, 4 distinct factors were discovered: Pancreatic duct size smaller than 3 mm; soft pancreatic parenchyma; ampullary, duodenal, cystic, or islet cell pathology; and excessive intraoperative blood loss. Furthermore, there appeared to be an additive clinical effect to the absolute number of risk factors accrued. This work seeks to extend this principle by developing a utilitarian risk score for gauging CR-POPF.

Ideally, fistula risk assessment begins in the preoperative setting. However, there are crucial inherent limitations of such an approach. First, today, although preoperative risk stratification systems are becoming more prevalant, they rarely actually disqualify patients from undergoing potentially curative resection for malignant, premalignant, and symptomatic periampullary conditions.[22-25] Even among patients with poor baseline physiology, reasonable surgical outcomes are within reach, particularly when a safe and sound technical operation is performed.[24] Furthermore, the majority of patients who are offered an operation with the intent of curative resection can expect to have some prolongation of survival, irrespective of the burden of comorbid conditions.[26] Second, preoperative risk assessment, in and of itself, seldom alters the postoperative course. This phenomenon was recently described, noting that, although escalating physiologic risk portends worse postoperative outcomes—increased morbidity, prolonged hospitalization, greater hospital costs—these effects can be attenuated by improved surgical performance.[26] Finally, although increasingly creeping into the conciousness of pancreatic surgeons, risk stratification is rarely actually used preoperatively—or even intraoperatively, for that matter. Complex scoring systems, such as those described by the Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM),[27] the Charlson Comorbidity Index,[28] and the National Surgical Quality Improvement Program (NSQIP),[29] are rigorous, difficult to implement, and not readily used in clinical management pathways. Other, more broadly used scoring systems—for example, the American Society of Anesthesiologists classification of physical status [30] and the Surgical Apgar Score [23]—are nonspecific and overly simplistic.

More relevant is the fact that, to date, there have been few, if any, preoperative predictors elucidated specifically for POPF development. One study assessing potential pre- and intraoperative factors described recent weight loss (defined as $\geq$3 kg over previous 6 months — a feature of most pancreatic resection patients) as the only factor predictive of POPF by multivariate analysis.[31] In addition, our original analysis of risk factors for CR-POPF in the ISGPF era (using 18 pre- and 24 intraoperative variables) failed to identify any preoperative drivers on multivariate analysis.[13]

Given these drawbacks, we sought to develop a simple risk prediction tool for pancreatic fistula, based on intraoperative assessment (where better recognized risk factors can be best evaluated), and describe clinical and economic correlations when applied in a high-volume pancreatic specialty center. The Fistula Risk Score developed in this study is based on 4 easily identifiable intraoperative parameters that emerged as most predictive of fistula after pancreatoduodenctomy. These 4 risk factors, enumerated above, merit some comment.

Table 5. Description of Eight Patients with Severe (Grade C) Fistulas among 445 Pancreatoduodenectomies (2002–2011)

Patient	Pathology	Texture	Duct size, mm	Blood loss, mL	FRS	Postoperative course
76-year-old man with chronic renal insufficiency, CAD	Ampullary adenocarcinoma (T1N0M0)	Soft	2	425	7	Initial drain amylase 3 IU/L on POD 6. Drain removed POD 7. Patient discharged home POD 7. Readmission POD 11. Reoperation/wide peripancreatic drainage. ICU admission and hospitalization for 52 days.
62-year-old man with diabetes, CAD	Mucinous cystadenoma	Soft	1	1,500	10	Initial drain amylase 37,600 IU/L on POD 6. Drain left in situ. Readmission POD 27. Antibiotics, TPN complicated by line sepsis. ICU admission.
69-year-old woman with diabetes	Metastatic renal cell carcinoma	Soft	4	200	4	Anastomotic dehiscence on POD 5 Reoperation and revision of anastomosis. ICU admission. Patient discharged to rehab POD 28.
70-year-old man with chronic renal insufficiency, CAD	Pancreatic pseudocyst	Soft	1	600	8	Sinister effluent on POD 6. Drain amylase level unmeasurable. Reoperation/wide peripancreatic drainage. ICU admission and hospitalization for 34 days.
81-year-old man with diabetes	Intraductal papillary mucinous neoplasm	Soft	4	500	5	Initial drain amylase 235 IU/L on POD 6. Drain removed POD 7. Readmission POD 16. Reoperation/wide peripancreatic drainage.
43-year-old man with obstructive jaundice requiring preoperative biliary stent	Duodenal adenocarcinoma	Soft	3	600	6	Initial drain amylase 1,351 IU/L on POD 6. Sepsis on POD 17. Antibiotics, TPN. Percutaneous drainage POD 17 ICU admission and hospitalization for 93 days.
67-year-old man with CAD, COPD	Duodenal adenocarcinoma	Soft	3	750	7	Initial drain amylase 87 IU/L on POD 6. Drain removed POD 7. Readmission on POD 11. Reoperation/wide peripancreatic drainage. ICU admission. Discharged home POD 20.
66-year-old man with no major comorbidities	Duodenal adenocarcinoma	Firm	5	1,100	4	Initial drain amylase 52 IU/L on POD 6. Drain removed POD 6. Readmission on POD 11 for UGI bleed, sepsis Death POD 11.

CAD, coronary artery disease; FRS, Fistula Risk Score; POD, postoperative day; TPN, total parenteral nutrition; UGI, upper gastrointestinal series.

Soft pancreatic parenchyma is the most widely recognized risk factor for pancreatic fistula.[32,33] There are several explanations for this association, particularly as it relates to reconstruction of the pancreatic-enteric anastomosis. First, a soft pancreas is more susceptible to ischemia and injury, either during operative dissection or in the event of its manipulation. This is particularly relevant when sutures are placed between the friable pancreatic parenchyma and the more resilient seromuscular layer of the jejunum or stomach. Sutures are more vulnerable to tearing through soft parenchyma as well as the fragile duct lining. Second, the soft pancreas is typically not associated with an obstructed pancreatic duct, and ductal dilatation seldom results. Finally, and probably most important, exocrine function is generally preserved in the soft pancreas, resulting in increased secretion of pancreatic juice, rich in proteolytic enzymes.[34,35] Naturally, the soft gland is more prone to leakage and activation of these caustic enzymes, and the attendant local and systemic consequences, including abscess, pancreatitis, pseudoaneurysm formation, shock, and sepsis. The other 3 risk factors bear some resemblance to the impact of a soft pancreas. The narrowed pancreatic duct diameter is not only more challenging to reconstruct, but also more likely to either occlude or dehisce. The smaller duct accommodates fewer sutures, and does not facilitate juxtaposition of the duct to bowel mucosa as easily. Pathologies other than pancreatic adenocarcinoma and chronic pancreatitis are more likely to result in soft parenchyma and usually do not result in normal or dilated ducts. Finally, the full impact of intraoperative blood loss is not well understood. However, it is our belief that volume loss, particularly when rapid, causes ischemia and poor healing of the pancreatic duct-to-mucosa anastomosis, which is compounded further by tissue edema from aggressive volume replacement in a "rebound" fashion. Resultant swelling of the anastomosis can result in duct occlusion or suture disruption.

Analysis of these 4 risk factors has revealed that although prevention, and ultimately management, of pancreatic fistula may begin during preoperative consultation,[31,36] comprehensive assessment of risk can occur only in the operating room, where these parameters are more precisely defined. The Fistula Risk Score proposed in this study relies on that precision in order to maintain its high predictability in patients who undergo pancreatoduodenectomy. Beyond that, the advantage of this risk assessment tool over other models is that it is simple, lends itself readily to surgical recall, and facilitates early recognition and prompt intervention specifically for pancreatic fistula. Points are assigned based on the presence and extent of the 4 risk factors, which can be described in the operative report. An aggregate of 0 to 10 points subsequently determines a patient's fistula risk profile. Patients with 0 points have a negligible risk of developing a CR-POPF, and rarely present with even biochemical fistulas. Those assigned 1 or 2 points alone have a low likelihood (14%) of developing any fistula, and less than one-third will be of the clinically relevant type. One-quarter of patients, who accumulate between 3 and 6 points, can be expected to develop pancreatic fistulas, but these are twice as likely to be clinically relevant. Finally, patients who acquire 7 or more points are considered high risk because the incidence of CR-POPF approaches 90%.

Clinical and economic outcomes beyond the incidence of pancreatic fistula alone also worsen in an escalating fashion. Patients require more invasive interventions, remain hospitalized longer, and incur greater hospital costs as points accumulate. This is particularly true among high risk patients. These patients, on average, remain hospitalized 6 days longer and accumulate $21,000 more in hospital costs. This is largely due to the development of more severe fistulas, more frequent diagnostic evaluations, increased use of parenteral nutrition, and a higher likelihood of invasive intervention for fistula management.

Although it is impossible to discuss all scenarios that arise when managing these clinically relevant fistulas, a few hypothetical cases illustrate further how the Fistula Risk Score can help drive fistula management with the aim of prevention or, at least, attenuation of effects.

Suppose a 68-year-old woman is referred for resection of a 2.0-cm, biopsy-proven adenocarcinoma in the head of the pancreas. Intraoperatively, palpation of the gland reveals firm pancreatic parenchyma behind the mass, and inspection of the transection surface of the neck demonstrates a 3-mm duct. At the completion of the case a drain is placed in the vicinity of the pancreaticojejunostomy; intraoperative blood loss is estimated to be 250 mL. The patient has an uneventful recovery, but on postoperative day 6, the amylase level from the drain effluent measures 1,012 IU/L. How should her drain be managed? This scenario represents a common management dilemma pancreatic surgeons face after pancreatoduodenectomy. In this case, the patient has only a single risk factor for pancreatic fistula (small pancreatic duct diameter), yet presents with a moderately elevated drain amylase level. According to the Fistula Risk Score, her total score is 2 points, which classifies her risk as low risk, with only an 8% likelihood of developing a fistula of any severity. More specifically, she has only a 1 in 3 chance of that fistula being of the clinically relevant type, which translates to a 3% overall risk of developing a CR-POPF. Given this estimate, the drain can then be

safely removed and the surgeon might better anticipate an uncomplicated postoperative course.

Now, take the example of another patient who is found to harbor a 2.0-cm adenocarcinoma in the uncinate process. In contrast to the first scenario, the gland is felt to be soft, and the pancreatic duct measures just 2 mm at the transection margin. Because of the tumor's involvement of the superior mesenteric vein, the intraoperative blood loss is increased to 1,200 mL. How, then, should her drain be managed, when the drain amylase level returns a concentration of 809 IU/L? In this case, the Fistula Risk Score is 8 points—0 points for the pancreatic adenocarcinoma; 2 points for the soft gland; 3 points for the 2-mm pancreatic duct; and 3 points for blood loss greater than 1,000 mL. This classifies her as high risk, with an 80% chance of developing a fistula of any severity. Even worse, the likelihood of that fistula being a CR-POPF is 6 to 1, which equates to a 69% overall risk of developing a CR-POPF. Intraoperatively, given immediate recognition of this risk factor profile, the surgeon could consider fistula management adjuncts perhaps not routinely used for all cases, such as placing an externalized transanastomotic stent,[37,38] or applying prophylactic octreotide.[39] Alternatively, with this knowledge, in the postoperative recovery period, one might elect to keep the drain in situ for an extended period of time, or conceivably study further with axial imaging in order to delineate the presence or extent of a POPF. Perhaps an anticipated early discharge from the hospital would be delayed. A more aggressive therapeutic approach might be triggered (eg, the patient could be made nil per os and placed on parenteral nutrition until the volume of drain effluent and/or concentration of amylase decreased considerably).

Finally, consider this situation: a 72-year-old woman with a side-branch intraductal papillary mucinous neoplasm in the head of the pancreas loses 1,400 mL of blood during pancreatoduodenectomy and requires pressor support and aggressive fluid resuscitation and transfusion. As anticipated, the gland at the neck transection is soft and the pancreatic duct is narrowed to 2 mm. How might the anastomosis be managed differently given these facts? This presents a difficult decision for the operating surgeon, particularly in light of how tenuous her condition is given the extensive blood loss. The calculated Fistula Risk Score is 9 points—1 point for the cystic neoplasm; 2 points for the soft gland; 3 points for the 2 mm pancreatic duct; and 3 points for blood loss greater than 1,000 mL. She is also deemed high risk, but has a 100% chance of developing any type of pancreatic fistula. Furthermore, because the likelihood of that fistula being a CR-POPF is 6 to 1, her overall risk of developing a CR-POPF is 85%. Given this situation, heavy consideration would be given to an alternative to a delicate duct-to-mucosa reconstruction. Options include an alternative pancreatico-jejunostomy technique (ie, "dunking" or "binding" approaches), premeditated occlusion of the distal remnant with no enteric reconstruction, or at the very least, additional wide drainage. Even completion pancreatectomy of the distal gland may be a plausible initial maneuver.

These important findings have prompted us to propose and adopt several systematic measures to improve our Clinical Carepath for Pancreatic Resection.[19] Specifically, we now favor a selective approach to the use of operative drains, and infrequently use them in patients with low Fistula Risk Scores (fewer than 2 points). Second, among patients with scores greater than 7 points, we consider adjunctive techniques for the management of the pancreatic remnant, including reconstruction of the pancreatico-jejunstomy via "dunking" or "binding" techniques, reconstruction using a pancreaticogastrostomy, or even delaying completion of the pancreatic-enteric anastomosis during the initial operation—particularly in situations in which the patient's hemodynamic parameters are suboptimal for a viable anastomosis. Furthermore, among patients who accrue 9 or 10 points, we frequently elect to widely drain the peripancreatic space, with 2 or even 3 operative drains. Third, the Fistula Risk Score is often most helpful when making decisions on whether to remove the operative drain, especially in those patients with marginal or borderline-high amylase concentrations. For example, a patient with an amylase content of 450 IU/L on postoperative day 6, and a Fistula Risk Score of 6 or 7 points, might benefit from continued in situ drainage, in order to help seal the pancreatico-enteric anastomosis. On the other hand, a similar patient, with the same amylase concentration and a Fistula Risk Score of 3 or 4 points, likely does not require any additional drainage. Fourth, although not yet substantiated in a randomized fashion, it is our impression that prophylactic octreotide may be beneficial in at-risk scenarios, specifically in intermediate and high risk cases. Finally, we consider prophylactic placement of feeding jejunostomy tubes in elderly patients (greater than 75 years of age) with Fistula Risk Scores greater than 7 points. These patients increasingly rely on total parenteral nutrition (50%) for resolution of POPF, and are at an increased risk for bloodstream infections and venous thromboembolism. These complications can perhaps be avoided with prophylactic distal enteric feeding tubes.

There are several limitations of this study that merit further comment. First, gland texture was measured at the discretion of the operating surgeon, and was

classified as either firm or soft, rather than on a gradient as some others have described. Nor do we have any formal histopathologic correlate for this assessment. In an attempt to quantitatively assess gland texture, Lee and colleagues[35] characterized pancreatic fat content, as measured by MRI, and correlated it to gland texture and the likelihood of developing pancreatic fistula. This was not the objective of our study and was not possible because very few patients underwent preoperative MRI in our series. Additionally, Hashimoto and associates[36] have recently described the ability to preoperatively predict parenchymal texture by enhancement features on triple phase CT. Good correlation was seen with histologic evidence of fibrosis as well as CR-POPF development.[36] Second, the association between blood loss and fistula development is poorly understood and was not explained by this analysis. We hypothesize that excessive blood loss causes hypoperfusion (if not ischemia), and therefore compromises healing of the pancreatic duct-to-mucosa anastomosis. However, it is also possible that aggressive fluid resuscitation and blood replacement may also promote tissue edema and further challenge the integrity of the pancreatic-enteric anastomosis. Third, an inherent drawback of this study is that prospective evaluation of the Fistula Risk Score was performed within a single pancreatic surgical specialty practice, with homogeneity among the operating surgeons with respect to technical approaches and postoperative management. It is unclear whether similar results could be obtained in other surgical centers with heterogeneity of perioperative management strategies (including different anastomotic reconstruction techniques or when the drain amylase is evaluated).[20] For example, although closed-suction drains were routinely placed in the vicinity of the pancreatic remnant, we understand that this practice is neither universally used nor widely accepted. Similar results may not be observed in centers where operative drains are not placed. One potential advantage of the Fistula Risk Score, however, is that it could potentially enable the operating surgeon to distinguish those patients who may not require or even benefit from in situ drainage. Although this study does not randomize patients to receive operative drains, our data suggest that their use may not be warranted in patients with negligible risk, or even low risk. Finally, because the surgeons were consciously aware of the core elements of the Fistula Risk Score throughout the second cohort, it is difficult to determine whether the knowledge of the score biased management approaches. It is possible that this bias may have altered these results because we observed an 8% decrease in the incidence of pancreatic fistula between cohorts 1 and 2. Obviously, it would be difficult to create a randomized, controlled trial of using the Fistula Risk Score or not, once it is understood, but external validation remains a possibility.

CONCLUSIONS

Despite these limitations, we have derived a simple 10-point Fistula Risk Score, accrued from ISGPF risk factors, which accurately predicts, with excellent discrimination, the development of clinically relevant postoperative pancreatic fistula after pancreatoduodenectomy. The strength of this study lies in the ability to validate this scoring system in a large population of patients in a pancreatic surgery specialty practice. This system, which can be easily incorporated into the surgeon's operative note, has the potential to act as an objective description of risk for comparative studies of pancreatic fistula prevention and management in the future. This Fistula Risk Score can be readily learned, and can help surgeons anticipate, identify, and control pancreatic fistula proactively, with the aim of achieving better outcomes from this daunting postoperative complication.

Author Contributions

Study conception and design: Callery, Pratt, Vollmer
Acquisition of data: Pratt, Kent, Vollmer
Analysis and interpretation of data: Callery, Pratt, Kent, Vollmer
Drafting of manuscript: Callery, Pratt, Vollmer
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