



# Postoperative Pancreatic Fistula Following Pancreaticoduodenectomy—Stratification of Patient Risk

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## Abstract

**Background** Postoperative pancreatic fistula (POPF) remains a major cause of morbidity following pancreaticoduodenectomy (PD). We sought to develop and validate a risk score system that utilized preoperative computed tomography (CT) measurements, laboratory values, and intraoperative pancreatic texture to estimate risk of developing POPF after PD.

**Methods** Patients who underwent PD between 2014 and 2017 were identified. Pre- and intraoperative risk factors associated with POPF were identified. Three separate risk models were developed and assessed using multivariable analyses and receiver operating curves.

**Results** Among the 150 patients who underwent a PD, mean age was 64 years and the majority of the patients were male (59.3%,  $n = 89$ ). Overall, the incidence of BL/POPF following PD was 22%. On multivariable analysis, factors associated with POPF included preoperative total serum protein  $< 6$  g/dL (OR 3.35, 95% CI 1.04–10.34,  $p = 0.04$ ), radiologic pancreatic duct diameter (OR 0.72, 95% CI 0.53–0.97,  $p = 0.03$ ), intraoperative pancreatic gland texture estimated by surgeon (OR 0.17, 95% CI 0.05–0.62,  $p = 0.006$ ), as well as intraoperative pancreatic duct diameter measured by surgeon (OR 0.77, 95% CI 0.61–0.98,  $p = 0.030$ ). Each risk factor was assigned a weighted score (CT pancreatic duct diameter  $< 5$  mm: 8 points; soft pancreatic gland texture: 5 points; total serum protein  $< 6$  g/dL: 3 points; CT visceral abdominal fat  $\geq 230$  cm<sup>2</sup>: 2 points). Patients scoring 4–5 were at low risk of POPF, while patients with a score of 6–18 had a high risk for POPF. The Harrell's c-index for the scoring system was 0.71 (standard error [SD] 0.094) for the training set and 0.67 (SD 0.034) for the test set (with  $n = 1000$  bootstrapping resamples).

**Conclusion** A simple risk score for POPF that utilized preoperative radiologic and clinical variables combined with specific intraoperative factors was able to stratify patients relative to POPF risk with good discriminatory ability.

**Keywords** Pancreaticoduodenectomy · Pancreatic fistula · Morbidity

## Introduction

Pancreaticoduodenectomy (PD) is the operation of choice for both benign and malignant tumors of the head of the pancreas

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and periampullary region.<sup>1</sup> Over the past several decades, there has been a substantial reduction in mortality after PD to less than 5%, with specialized centers reporting rates as low as 1–2%.<sup>2</sup> Despite advances in surgical techniques and perioperative care, the decline in mortality has not been accompanied by a concomitant reduction in morbidity. In fact, the incidence of complications following PD remains in the range of 30–50%.<sup>3, 4</sup> In particular, postoperative pancreatic fistula (POPF) is widely recognized as the major cause of morbidity following pancreatic resection. POPF can result in catastrophic consequences for patients such as sepsis, hemorrhage, and death.<sup>5, 6</sup> Moreover, POPF can prolong the length of hospital stay, increase health care costs, delay initiation of adjuvant treatment, and potentially adversely affect oncologic outcomes.<sup>7</sup>

In 2005, the International Study Group of Pancreatic Fistula (ISGPF) established a universal definition for POPF, which has been validated and is currently the most used classification system<sup>8</sup>; this classification was recently updated in 2016.<sup>9</sup> The creation of a standardized classification of pancreatic fistula has enabled more accurate comparisons of the incidence of fistula among institutions, which has motivated efforts to understand and mitigate risk factors associated with POPF formation.<sup>5, 7, 10, 11</sup> Previous studies have described perioperative POPF risk factors, such as increased age, body mass index (BMI), intraabdominal fat thickness, pathological diagnosis, and smaller pancreatic duct width.<sup>11–15</sup> More recently, based on previously identified risk factors, scoring systems have been proposed as a means to estimate an individual patient's risk of developing POPF.<sup>16</sup> While some scoring systems have combined preoperative and intraoperative factors,<sup>16</sup> no study has defined POPF risk using preoperative radiologic and clinical variables along with specific intra-operative factors. Data to stratify patients relative to POPF risk may, however, be important in deciding the timing of drain removal, onset of oral feeding, hospital discharge planning, as well as the work-up for possible POPF following PD.<sup>6, 10</sup> Therefore, the objective of the current study was to develop and validate a risk score system that utilized preoperative computed tomography (CT) measurements with laboratory values and intraoperative pancreatic texture assessment to estimate the risk of developing POPF among patients undergoing PD.

## Methods

### Patient Selection and Perioperative Management

One hundred and fifty patients who underwent PD at The Ohio State University Wexner Medical Center between October 2014 and October 2017 were identified from a prospectively maintained database. Data on demographic, radiologic, pathologic, intraoperative, and postoperative parameters were recorded. The study was approved by the Institutional Review Board at The Ohio State University.

The 2016 ISGPS definition of POPF was utilized to classify fistula severity (Table 1). Postoperative complications were reported by type and graded according to the Clavien-Dindo classification. Patients who underwent either pylorus-preserving or classic PD were included. Prophylactic octreotide was not routinely used. Pancreatic consistency was determined by the surgeon at the time of operation and categorized as either soft or firm, while pancreatic duct diameter was measured intraoperatively with a sterile ruler before reconstruction. Abdominal drains were placed in all patients during surgery; amylase levels and cultures of the drainage fluid were evaluated on postoperative days 1, 3, and 5.

Drains were removed once patients tolerated a regular diet and maintained a normal drain output (< 100 mL/day).

### Radiological Measurements

Cross-sectional imaging with CT scan of the abdomen was performed in all patients within 90 days before the operation. All measurements were obtained using the Aquarius iNtuition edition (TeraRecon v4.4.12, Foster City, CA) imaging server platform. All CT scans were analyzed in the post contrast portal venous phase. Slice thickness varied between 1 and 5 mm. Pancreatic duct diameter, attenuation of pancreatic tissue, anteroposterior thickness of the pancreas, and the width of the pancreatic duct were obtained at the level of the confluence of the superior mesenteric and portal veins. The CT slice in which the superior mesenteric and splenic veins merged was chosen for measurement. The largest possible spherical region of interest (ROI) was defined to avoid the pancreatic duct and extrapancreatic structures. The ROIs were drawn three times in the same CT slice and the mean value was considered as the expressive value for attenuation of pancreas in Hounsfield units (HU).

The cross-sectional area of visceral fat area (VFA), subcutaneous fat area, and body circumference at the umbilicus (waist) and greater trochanter (hip) were measured at the level of the third lumbar vertebral body. A programmed algorithm that automatically selected all subcutaneous and visceral adipose tissue using attenuation limits of – 190 to – 30 HU was used, adjusted as necessary to reflect the anatomical borders. Fat cross-sectional areas were normalized by dividing values by the body surface area (BSA) calculated as the squared height of the patient. Waist-to-hip ratio (WHR) was calculated using circumference at the umbilicus (waist) and greater trochanter (hip). VFA ratio was calculated with the formula (visceral fat area / visceral fat area + subcutaneous fat area).

### Calculation of POPF Risk Score

For each patient, the POPF risk score was calculated by combining pre- and intra-operative risk factors associated with POPF formation. Three separate scoring models were developed based on regression coefficients obtained from the logistic regression models. The first (model I) assigned one point for each of the four risk factors and zero points for the absence of a risk factor. In model II, points were weighted based on the  $\beta$ -coefficients obtained from model I multiplied by 2 and rounded to the nearest digit. In model III, points were weighted by odds ratios (OR) obtained from model I.

Receiver operating characteristic (ROC) analysis was performed to assess specificity, sensitivity, and AUC of models I–III. The model associated with the highest AUC was selected as the final POPF risk score model.

**Table 1** 2016 update of the ISGPF grading system for BL/POPF

Grade	Definition
Biochemical leak (formerly grade A POPF)	<ul style="list-style-type: none"> <li>• Increased amylase activity &gt; 3 times upper limit institutional normal serum value</li> </ul>
Grade B	<ul style="list-style-type: none"> <li>• Persisting pancreatic drainage &gt; 3 weeks</li> <li>• Clinically relevant change in management of POPF<sup>a</sup></li> <li>• POPF percutaneous or endoscopic specific interventions for collections</li> <li>• Angiographic procedures for POPF-related bleeding</li> <li>• Signs of infection related to POPF without organ failure</li> </ul>
Grade C	<ul style="list-style-type: none"> <li>• Reoperation for POPF</li> <li>• Signs of infection related to POPF with organ failure</li> <li>• POPF-related organ failure<sup>b</sup></li> <li>• POPF-related death</li> </ul>

<sup>a</sup> Prolongation of hospital or ICU stay, includes use of therapeutic agents specifically employed for fistula management or its consequences (of these: somatostatin analogs, TPN/TEN, blood product transfusion or other medications)

<sup>b</sup> Postoperative organ failure is defined as the need for re-intubation, hemodialysis, and/or inotropic agents > 24 h for respiratory, renal, or cardiac insufficiency, respectively

## Statistical Analysis

Descriptive statistics were presented as  $N$  (%) and mean  $\pm$  standard deviation for categorical and continuous factors, respectively. To assess bivariate associations between postoperative POPF formation and categorical and continuous factors, Chi-square test and Student's  $t$  test were used, respectively. Where appropriate, analyses for categorical factors were performed using Fisher's exact test, and for continuous factors, descriptive statistics were presented as median (IQR) and evaluated using Mann-Whitney  $U$  test. To assess the relationships between preoperative radiological measurements and postoperative POPF formation, logistic regression models were constructed to estimate odds ratios and the confidence intervals. Following bivariate analyses, to identify factors associated with fistula formation, multivariable logistic regression models were constructed using the Lemmishow and Hosmer model selection technique. All factors that were statistically significant in the aforementioned models were considered for risk score calculation. Bootstrapping was performed to obtain confidence intervals for AUC values. Statistical significance was assessed at  $\alpha = 0.05$ . All analyses were performed using SAS 9.4.

## Results

### Patient Characteristics

Among the 150 patients included in the study, mean age was 64 years and the majority of the patients were male (59.3%,  $n = 89$ ) (Table 2). Overall, the incidence of POPF following PD was 22%. There were largely no differences in demographic

characteristics among patients with and without POPF. However, patients who developed a POPF had a higher BMI ( $28.7 \pm 6.0$  kg/m<sup>2</sup> vs.  $26.7 \pm 5.98$  kg/m<sup>2</sup>,  $p = 0.016$ ) and a lower preoperative total serum protein (6.6 g/dL vs 7.0 g/dL,  $p = 0.03$ ) compared with patients without POPF. Bivariate analyses demonstrated that among the preoperative radiological measurements analyzed, lower CT pancreatic duct diameter (OR 0.66, 95% CI 0.49–0.88,  $p = 0.005$ ) and higher CT VFA (OR 0.99, 95% CI 0.98–0.99,  $p = 0.015$ ) were associated with higher odds of fistula formation (Table 3). Moreover, patients who developed a POPF were more likely to have a lower duct diameter as measured intraoperatively by the surgeon ( $3.5 \pm 2.2$  mm vs.  $4.8 \pm 2.7$  mm,  $p = 0.03$ ) (Fig. 1). Of note, preoperative radiological pancreatic duct measurements strongly correlated with intraoperative duct measurements (Supplemental Fig. 1). In addition to duct diameter, gland texture was associated with POPF, as patients with soft pancreatic gland had a higher incidence of POPF compared with patients with a firm gland (84.6%,  $n = 22$  vs. 50%,  $n = 44$ , respectively;  $p = 0.002$ ). Interestingly, pathological characteristics differed among patients with and without POPF. Specifically, patients who had POPF were more likely to have had a diagnosis of periampullary cancer (42.4%,  $n = 14$ ,  $p = 0.04$ ). Not surprisingly, mean length of stay was longer among patients who developed a POPF (12.5 days vs. 8.7 days,  $p = 0.01$ ).

### Multivariable Analysis: Risk Model for POPF

Pre-operative and intraoperative factors associated with development of POPF were analyzed separately. In multivariable analysis of pre-operative risk factors (model A), preoperative total serum protein < 6 g/dL (OR 3.35, 95% CI 1.04–10.34,  $p = 0.04$ ) and radiologic pancreatic duct diameter (OR 0.72, 95%

**Table 2** Patient characteristics and clinical findings

	Total patients	No BL/POPF ( <i>n</i> = 117)	BL/POPF ( <i>n</i> = 33)	<i>p</i> value
Age	63.8 ± 12.4	64.0 ± 12.3	62.6 ± 12.6	0.54
Gender—male	89 (59.3%)	67 (57.3%)	22 (66.7%)	0.12
Body mass index (kg/m <sup>2</sup> )	27.1 ± 6.0	26.7 ± 6.0	28.7 ± 6.0	<i>0.01</i>
Smoking	93 (62.0%)	71 (60.7%)	22 (66.7%)	0.53
Diabetes mellitus	52 (34.7%)	41 (35.0%)	11 (33.3%)	0.86
Coronary artery disease	26 (17.3%)	18 (15.4%)	8 (24.3%)	0.15
Hyperlipidemia	56 (37.3%)	44 (37.6%)	12 (36.4%)	0.75
Modified Frailty Index Score				0.82
0	38 (25.3%)	28 (23.9%)	10 (30.3%)	
1	49 (32.7%)	38 (32.5%)	11 (33.3%)	
2	36 (24.0%)	29 (24.8%)	7 (21.2%)	
3	20 (13.3%)	16 (13.7%)	4 (12.1%)	
≥ 4	7 (4.7%)	6 (5.1%)	1 (3.0%)	
Preop. total bilirubin (mg/dL)	2.7 ± 3.8	2.9 ± 4.1	1.8 ± 2.5	0.16
Preop. total serum protein (g/dL)	6.8 ± 1.0	7.1 ± 0.8	6.7 ± 1.0	<i>0.03</i>
Neoadjuvant chemotherapy	30 (20.0%)	27 (23.1%)	3 (9.1%)	0.08
Duration of surgery (h)	5.5 ± 1.5	5.5 ± 1.4	5.4 ± 1.4	0.63
Pancreatic texture—by surgeon				<i>0.002</i>
Soft	66 (57.9%)	44 (50.0%)	22 (84.6%)	
Firm	48 (42.1%)	44 (50.0%)	4 (15.4%)	
Duct diameter—by surgeon (mm)	4.5 ± 2.6	4.8 ± 2.7	3.5 ± 2.2	<i>0.03</i>
Major vascular invasion	18 (12.0%)	17 (14.5%)	1 (3.0%)	0.07
Intraop. octreotide administration	8 (5.3%)	5 (4.3%)	3 (9.0%)	0.17
Estimated blood loss (mL)	371.4 ± 305.8	384.2 ± 322.7	326.5 ± 252.4	0.34
Pathological characteristics				<i>0.04</i>
Pancreatic adenocarcinoma	75 (50%)	60 (51.2%)	15 (45.5%)	
Neuroendocrine cancer	14 (9.3%)	12 (10.2%)	2 (6.0%)	
Periapillary cancer	10 (6.7%)	10 (8.8%)	0 (0.0%)	
Benign/premalign lesions	9 (6.0%)	6 (5.1%)	3 (9.1%)	
Other	42 (28.0%)	29 (24.7%)	13 (39.4%)	
Length of hospital stay (days)	9.5 ± 7.0	8.7 ± 5.4	12.5 ± 10.7	<i>0.01</i>
Morbidity	75 (50.0)	51 (43.5)	24 (72.7)	<i>0.003</i>
Mortality	3 (2.0)	1 (0.9)	2 (6.1)	0.12

Variables presented as *N* (%) or mean ± SD

Statistically significant *p*-values are presented in italics

CI 0.53–0.97, *p* = 0.03) were associated with increased odds of POPF. When intra-operative risk factors (model B) were assessed, intraoperative pancreatic gland texture (OR 0.17, 95% CI 0.05–0.62, *p* = 0.006), as well as intraoperative pancreatic duct diameter measured by surgeon (OR 0.77, 95% CI 0.61–0.98, *p* = 0.030) were strongly correlated with POPF formation (Table 4). Of note, results were similar when pancreatic duct diameter measured by CT was included in the multivariable analysis as a categorical variable (Supplemental Table 1).

Three risk score calculation models to predict POPF were developed and weights were assigned to the variables; mean scores with 95% CI AUC from a bootstrapping analysis were assessed (Table 5). Whereas model I and II had comparable results, model III performed better (Fig. 2). In model III, each risk

factor was assigned a weighted score (CT pancreatic duct diameter < 5 mm: 8 points; soft pancreatic gland texture: 5 points; total serum protein < 6 g/dL: 3 points; CT visceral abdominal fat ≥ 230 cm<sup>2</sup>: 2 points). The risk of POPF was then categorized relative to the total score. Patients scoring 4–5 were at low risk of POPF, while patients with a score of 6–18 had a high risk for POPF. The Harrell's c-index for the scoring system was 0.71 (standard error [SD] 0.094) for the training set and 0.67 (SD 0.034) for the test set (with *n* = 1000 bootstrapping re-samples).

Among the 26 patients in the current study who develop a POPF, 76.9% (*n* = 20) were categorized as high risk, whereas 6 (23.1%) patients were categorized as low risk. In addition, among the 105 patients who did not develop a POPF, 64 (60.9%) were at high risk for POPF, while 41 (39.1%) were at low risk for POPF.

**Table 3** Bivariate analysis of preoperative radiological measurements on abdominal CT

	Total	no BL/POPF	BL/POPF	OR	OR CI	p
Pancreatic thickness (mm)	13.9 ± 3.2	13.8 ± 3.2	14.1 ± 3.5	1.03	0.92–1.16	0.65
Pancreatic width (mm)	26.6 ± 5.8	26.3 ± 5.7	28.0 ± 6.0	1.05	0.99–1.12	0.12
Pancreatic duct diameter (mm)	4.4 ± 2.7	4.7 ± 2.7	3.5 ± 2.2	0.66	0.49–0.88	<i>0.005</i>
Pancreatic density (HU)	155.0 ± 40.6	157.1 ± 40.5	149.6 ± 41.1	0.99	0.99–1.01	0.35
Waist/hip ratio (mm)	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	6.67	0.04–100	0.46
Visceral fat area (cm <sup>2</sup> )	184.0 ± 118.7	171.5 ± 105.3	230.0 ± 150.3	0.99	0.98–0.99	<i>0.01</i>
Subcutaneous fat area (cm <sup>2</sup> )	211.7 ± 122.4	208.0 ± 123.5	224.8 ± 119.1	1.00	1.00–1.01	0.49
VFA/VFA + SFA ratio (cm <sup>2</sup> )	1.0 ± 0.7	1.0 ± 0.7	1.2 ± 0.9	1.01	0.99–1.04	0.34

Variables are presented as mean ± SD

HU Hounsfield unit

Statistically significant *p*-values are presented in italics

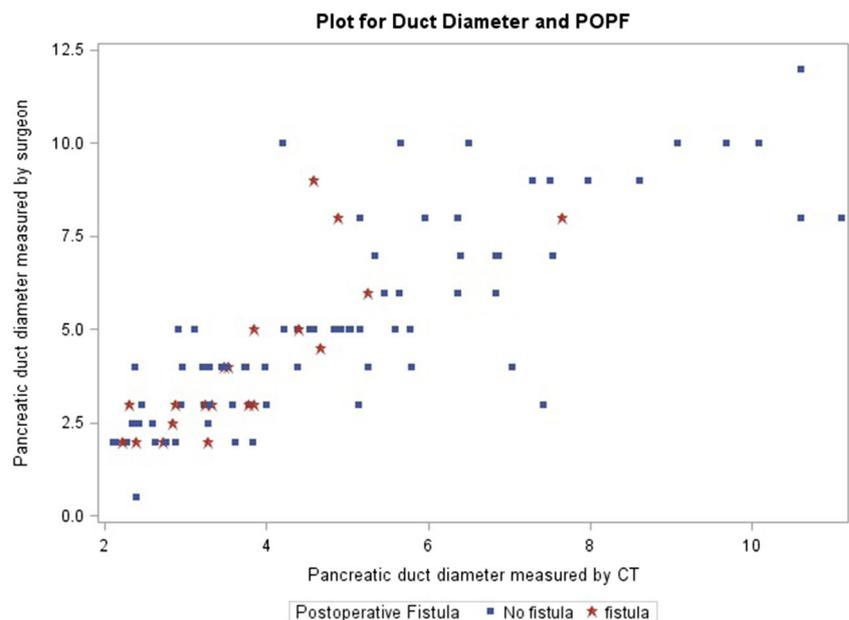
### Discussion

Despite a decrease in mortality associated with PD over the last several decades, the burden of postoperative morbidity associated with the development of POPF has remained largely unchanged.<sup>17</sup> Given the importance of POPF relative to patient outcomes, several investigators have sought to identify factors associated with POPF risk.<sup>11–15</sup> Previous studies mostly focused, however, only on gland consistency or duct diameter.<sup>11–15</sup> The current study was important because we examined risk of POPF from a broader perspective. Specifically, the current study examined preoperative factors (e.g., laboratory values, patient morphometric data, CT imaging parameters), as well as intraoperative factors (e.g., pancreatic duct size, gland consistency) to define a scoring system to stratify patients with regard to POPF risk. Of note, lower preoperative total protein, an increased visceral fat

area (VFA) on CT, a soft pancreatic gland, as well as small pancreatic duct diameter—assessed by either CT or intraoperative measurement—were each associated with an increased risk of POPF. In addition, combining these factors into a single scoring system was able to stratify patients with good discriminatory ability on both the testing (AUC 0.71) and bootstrapping validation (AUC 0.67) datasets. The identification of high-risk patients may aid surgeons in decision-making regarding perioperative management, as well as inform a surgeon’s clinical suspicion concerning the likelihood of a pancreatic leak.

Several risk factors related to patient characteristics, pancreatic gland features, and operative events have been associated with POPF risk.<sup>12–14, 17, 18</sup> One of the most widely recognized risk factors for pancreatic fistula is a soft pancreatic parenchyma.<sup>7, 19</sup> In the current study, we similarly noted that soft pancreatic gland texture was associated with an increased

**Fig. 1** Distribution of POPF according to pancreatic duct diameter



**Table 4** Multivariable analysis of risk factors for BL/POPF

Model A—Evaluation of pre-operative risk factors			
Preoperative risk factors	Odds ratio	95% CI	<i>p</i> value
Preop. total serum protein < 6 g/dL	3.35	1.04–10.37	<i>0.04</i>
Neoadjuvant chemotherapy	0.19	0.02–1.66	0.13
CT pancreatic duct diameter (mm) <sup>a</sup>	0.72	0.53–0.97	<i>0.03</i>
CT pancreatic thickness (mm) <sup>a</sup>	0.82	0.66–1.01	0.07
CT pancreatic density (HU) <sup>a</sup>	0.99	0.98–1.00	0.18
Model B—Evaluation of intra-operative risk factors			
Intraoperative risk factors	Odds ratio	95% CI	<i>p</i> value
Estimated blood loss (mL)	1.00	0.99–1.00	0.29
Pancreatic duct diameter measured by surgeon	0.77	0.61–0.98	<i>0.03</i>
Pancreatic gland texture estimated by surgeon	0.17	0.05–0.62	<i>0.006</i>

Adjusted for gender, body mass index, and smoking status

CT computerized tomography, BMI body mass index, HU Hounsfield unit

Statistically significant *p*-values are presented in italics

<sup>a</sup> Expressed as continuous variables

risk of developing POPF. In fact, only pancreatic duct diameter was weighted more heavily than pancreatic gland consistency in the POPF risk model (CT pancreatic duct diameter < 5 mm: 8 points; soft pancreatic gland texture: 5 points). The reasons why a soft gland may be associated with an increased risk of POPF are undoubtedly multifactorial. A soft pancreas may be more prone to ischemia and injury during the surgical dissection, as well as less likely to hold sutures between the friable pancreatic parenchyma and the seromuscular layer of the jejunum or stomach.<sup>14</sup> In addition, unlike an atrophic hard pancreas, the soft pancreas generally has preserved exocrine function, which may result in increased pancreatic secretions rich in proteolytic enzymes.<sup>20, 21</sup> Conversely, the lower rates of pancreatic fistula after PD in the setting of a firm pancreas may be associated with both lower pancreatic exocrine secretion due to prolonged pancreatic duct obstruction and pancreatic fibrosis, as well as the greater technical ease of sewing to a hard gland.<sup>22</sup>

In addition to pancreatic gland texture, pancreatic duct diameter was associated with risk of POPF. Indeed, a small pancreatic duct can present surgeons with a technical challenge during the reconstruction of the pancreaticojejunostomy. Several studies have suggested that a pancreatic duct diameter < 5 mm was

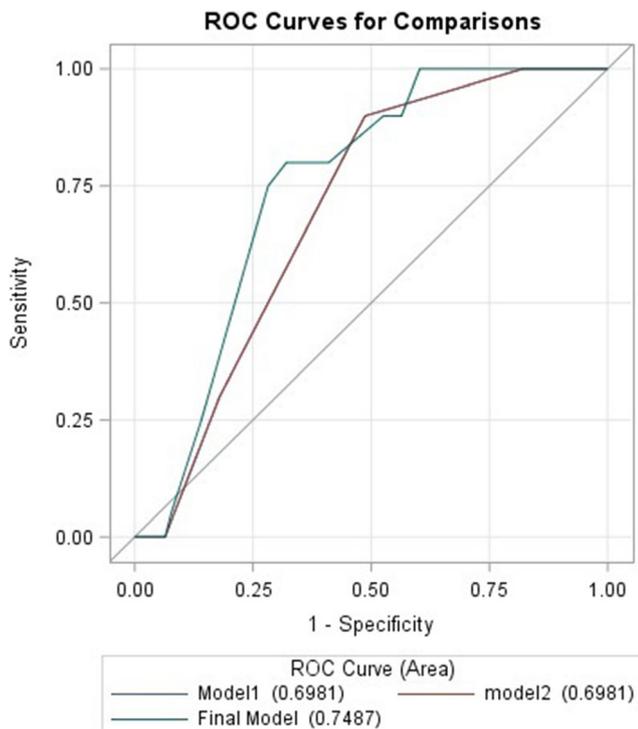
generally associated with a higher risk of POPF development.<sup>1, 14, 15, 18, 23</sup> In the current study, each 1-mm increase in diameter of the pancreatic duct was associated with a 28% decrease in the odds of POPF (Table 4). The measurement of the pancreatic duct diameter can typically be performed using preoperative CT imaging or, alternatively, by intraoperative manual assessment by the surgeon with the use of a sterile ruler.<sup>12, 14, 24</sup> Importantly, we noted that there was a strong correlation between the radiologist assessment of duct size on preoperative CT scan versus the surgical intraoperative measurement (Fig. 1). Given the strong correlation, we chose to utilize the radiological pancreatic duct measurement in the predictive scoring scheme given the benefits of having such information available prior to surgery.

Another radiological variable of clinical importance relative to POPF risk was visceral abdominal fat as assessed on preoperative CT scan.<sup>6</sup> Other investigators had suggested an association between increased BMI and POPF risk; however, the distribution of excessive abdominal fat, rather than a simple calculation of BMI, has not been well examined.<sup>25–29</sup> Data from the current study suggest that VFA—and not simply BMI—may be a risk factor for POPF. Recently, visceral fat has been increasingly recognized as an endocrine organ with

**Table 5** Point values used in risk score calculation for post-operative fistula formation

Point values for risk score calculation			
	Model I	Model II	Model III
Pancreatic duct diameter < 5 mm	1 vs 0	2 vs 1	8 vs 1
Soft pancreatic gland	1 vs 0	2 vs 1	5 vs 1
Total serum protein < 6 g/dL	1 vs 0	1 vs 0	3 vs 1
Visceral abdominal fat ≥ 230 cm <sup>2</sup>	1 vs 0	1 vs 0	2 vs 1
Mean (95% CI) for AUC			
AUC (95% CI)	0.67 (0.60–0.74)	0.67 (0.60–0.74)	0.71 (0.64–0.78)

All expressed as binary variables



**Fig. 2** Receiver operating characteristics (ROC) curves showing the sensitivity and specificity of the models for predicting BL/POPF

the ability to regulate inflammatory pathways.<sup>30</sup> As such, the presence of excessive intraabdominal fat may mediate pro-inflammatory responses that may impact healing following surgery.<sup>31</sup> In addition to increased VFA, preoperative nutritional status may be another factor associated with the risk of post-operative complications in general and POPF in particular.<sup>32</sup> Specifically, low levels of total serum protein may reflect overall poor nutritional status and identify patients at higher risk of anastomotic leak after a range of surgical procedures.<sup>32–34</sup> To this point, we noted that lower preoperative serum total protein levels were independently associated with risk of POPF. Of note, patients with a total serum protein level < 6 mg/dL had over a 3-fold increased risk of POPF formation.

There are several limitations that should be considered when interpreting the results of the current study. As with all retrospective studies, selection bias was a possibility; patients who were deemed a very high risk may not have been offered an operation. In addition, due to the small sample size of patients with clinically relevant POPF (grades B and C), we were unable to stratify scores according to POPF grade. Moreover, surgical technique was not standardized; therefore, there was the possibility of confounding due to differences in technical aspects of the case. In addition, evaluation of pancreatic texture was performed manually by the surgeon and was somewhat subjective, thereby potentially limiting the reproducibility of the score. Nevertheless, intraoperative assessment remains the gold standard for the estimation of pancreatic texture.<sup>35</sup>

In conclusion, a simple risk score for POPF that utilized preoperative radiologic and clinical variables combined with specific intra-operative factors was able to stratify patients relative to POPF risk with good discriminatory ability. Given that POPF remains one of the most relevant complications after PD, a score to stratify patient risk for POPF may help orient and tailor clinical decisions regarding postoperative management.

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### Compliance with Ethical Standards

The study was approved by the Institutional Review Board at The Ohio State University.

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