



UNIVERSITÀ
DEGLI STUDI
FIRENZE

FLORE

Repository istituzionale dell'Università degli Studi di Firenze

A preoperative predictive score of pancreatic fistula following pancreatoduodenectomy

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

A preoperative predictive score of pancreatic fistula following pancreatoduodenectomy / Roberts K.J.; Hodson J.; Mehrzad H.; Marudanayagam R.; Sutcliffe R.P.; Muiesan P.; Isaac J.; Bramhall S.R.; Mirza D.F.. - In: HPB. - ISSN 1365-182X. - ELETTRONICO. - 16:(2014), pp. 620-628. [10.1111/hpb.12186]

Availability:

The webpage <https://hdl.handle.net/2158/1200046> of the repository was last updated on 2020-07-07T09:50:36Z

Published version:

DOI: 10.1111/hpb.12186

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

Publisher copyright claim:

La data sopra indicata si riferisce all'ultimo aggiornamento della scheda del Repository FloRe - The above-mentioned date refers to the last update of the record in the Institutional Repository FloRe

(Article begins on next page)

ORIGINAL ARTICLE

A preoperative predictive score of pancreatic fistula following pancreatoduodenectomy

Keith J. Roberts¹, James Hodson², Homoyoon Mehrzad³, Ravi Marudanayagam¹, Robert P. Sutcliffe¹, Paolo Muiesan¹, John Isaac¹, Simon R. Bramhall¹ & Darius F. Mirza¹

¹Hepatobiliary and Pancreatic Surgery Unit, ²Department of Medical Statistics and ³Department of Radiology, University Hospitals Birmingham, Birmingham, UK

Abstract

Background: Various factors are related to the occurrence of postoperative pancreatic fistula (POPF) following pancreatoduodenectomy (PD). Some of the strongest are identified intra- or postoperatively, which limits their utility in predicting this complication. The preoperative prediction of POPF permits an individualized approach to patient consent and selection, and may influence postoperative management. This study sought to develop and test a score to predict POPF.

Methods: A post hoc analysis of a prospectively maintained database was conducted. Consecutive patients were randomly selected to modelling and validation sets at a ratio of 2 : 1, respectively. Patient data, preoperative blood tests and physical characteristics of the gland (assessed from preoperative computed tomography images) were subjected to univariate and multivariate analysis in the modelling set of patients. A score predictive of POPF was designed and tested in the validation set.

Results: Postoperative pancreatic fistula occurred in 77 of 325 (23.7%) patients. The occurrence of POPF was associated with 12 factors. On multivariate analysis, body mass index and pancreatic duct width were independently associated with POPF. A risk score to predict POPF was designed (area under the receiver operating characteristic curve: 0.832, 95% confidence interval 0.768–0.897; $P < 0.001$) and successfully tested upon the validation set.

Conclusions: Preoperative assessment of a patient's risk for POPF is possible using simple measurements. The present risk score is a valid tool with which to predict POPF in patients undergoing PD.

Received 16 May 2013; accepted 3 September 2013

Correspondence

Keith J. Roberts, 3rd Floor, Nuffield House, University Hospitals Birmingham, Mindelsohn Way, Edgbaston, Birmingham B15 2WB, UK. Tel: +44 7801 658505. Fax: +44 121 4141833. E-mail: j.k.roberts@bham.ac.uk

Introduction

The centralization of pancreatoduodenectomy (PD) procedures into high-volume centres has reduced perioperative mortality.^{1–4} Morbidity, however, remains high and affects 16–41% of patients, even in specialist units.^{3,5–7} The occurrence of a postoperative pancreatic fistula (POPF) is a major contributor to both morbidity and mortality. The importance of POPF has been recognized and, in order to facilitate the auditing of outcomes, comparisons

between centres performing PD and studies reviewing PD, the International Study Group for Pancreatic Fistula (ISGPF) has defined three grades of POPF.⁸ Various interventions (such as techniques of visceral reconstruction and abdominal drainage) and therapeutic drugs (such as somatostatin analogues) aimed at decreasing rates of POPF have been subject to review.^{9–13} These meta-analyses do not support a protective role against the development of clinically significant POPF.

In the absence of effective strategies to decrease the incidence of POPF, it is important to identify risk factors for its occurrence. Patient characteristics associated with POPF include increased body mass index (BMI), advanced age, male sex and comorbidity.^{14–18} Further factors that may predict POPF are the

This study was presented as an abstract at the 10th Congress of the European–African Hepato Pancreato Biliary Association, 29–31 May 2013, Belgrade.

findings of preoperative biochemical tests, but these have been less thoroughly investigated. A study of 2894 patients found elevated urea and low albumin to be predictive of postoperative complications.¹⁹ However, this study did not define these complications and predated the ISGPF definition of POPF. A more recent study identified high levels of both haemoglobin and sodium to be associated with POPF as defined by the ISGPF.²⁰ A further variable attracting increasing attention is pancreatic steatosis, a significant risk factor for POPF.^{14,17,18} However, this can only be identified at pathological assessment and thus has no role in preoperative risk analysis. Other factors that relate to POPF and can be identified at preoperative imaging include the pancreas gland width, duct width, and visceral and superficial fat thickness.^{16,20–23} Providing an individualized assessment of POPF risk *in the preoperative phase* would facilitate the provision of accurate patient counselling and obtaining of consent, and might alter aspects of clinical management such as patient selection for PD, the timing of drain removal and the instigation of early enteral feeding.

The aim of this study was to review patient factors that may relate to POPF in order to design a preoperative predictive risk score for POPF in patients undergoing PD.

Materials and methods

Consecutive patients undergoing PD at a single centre [University Hospitals Birmingham National Health Service (NHS) Trust, Birmingham, UK] between February 2007 and February 2012 were identified from a prospectively maintained database. Patients for whom preoperative computed tomography (CT) imaging was unavailable were excluded from the study.

All patients underwent PD performed or supervised by a consultant hepatopancreatobiliary surgeon. Whether a pancreaticojejunostomy (PJ) or pancreaticogastrostomy (PG) was performed depended upon which surgeon performed the procedure. This decision was not made intraoperatively and reflects each surgeon's individual preferred technique of pancreatic anastomosis. Pancreatic duct stenting was not performed. A single tube drain was placed posterior to the hepaticojejunostomy and adjacent to the PJ or PG anastomosis via the right flank in each patient. Patients received 100 µg of a subcutaneous somatostatin analogue, octreotide, three times daily for the first 5 days postoperatively. A feeding nasojejunal tube was placed in each patient under a standard protocol to administer feed from the first postoperative day. Drain fluid amylase levels were assessed on postoperative day 5 and, if the patient was clinically well without biochemical evidence of POPF, the drain was removed and enteral feeding instigated.

Data gathered for each patient referred to patient variables including: gender; age; smoking history; comorbidity; BMI, and pathological diagnosis (pancreatic adenocarcinoma, cholangiocarcinoma, ampullary carcinoma, duodenal carcinoma, neuroendocrine tumour, intraductal papillary mucinous neoplasm, pancreatitis, other).

Data on preoperative biochemical results included: white cell count (WCC); haemoglobin; platelet count; international normalized ratio (INR); aspartate transaminase (AST); alanine transaminase (ALT); alkaline phosphatase (ALP); sodium; potassium; urea; creatinine; bilirubin; albumin, and neutrophil to lymphocyte ratio (NLR). Values immediately preceding the PD were recorded. The values were considered as continuous data.

Data on the surgical technique used included details of whether a pylorus-preserving PD or a classic Whipple procedure was conducted, and whether a PJ or a PG was performed.

Preoperative CT imaging was assessed. The sequence of slices 1 mm in thickness was selected for review. Data collected referred to the anteroposterior thickness of the pancreas gland and the width of the pancreatic duct (both obtained at the level of the confluence of the superior mesenteric and portal veins), and to the anteroposterior thickness of the superficial fat adjacent to the umbilicus and the anteroposterior thickness of the perirenal fat at the level of the left umbilical vein. Each measurement was recorded in triplicate and the values were averaged. Measurements were obtained by a single researcher (KJR) blinded to the patient's clinical outcome. A second researcher (a hepatobiliary radiologist, HM) reviewed the images for a random selection of 50 patients and recorded the same measurements. The comparison of the two sets of measurements provided an assessment of intraclass correlation.

Postoperative pancreatic fistula was defined and classified according to the ISGPF definition into Grades A, B and C.⁸

Statistical analysis

Initially, the patient group was randomly divided into two sets at a ratio of 2 : 1 by an independent statistician. The larger of the two sets, the 'modelling set', was used to produce a risk scoring model, which was then applied to the smaller 'validation set' in order to validate its predictive accuracy.

To produce the risk score, each of the potential predictors were first considered univariably for the data in the modelling set. For the categorical variables, Fisher's exact test was used to compare rates of pancreatic leak across the different levels of the factor. Receiver operating characteristic (ROC) curves were produced for the continuous variables to ascertain whether they were significant predictors of POPF. The factors found to be significant at this stage of the analysis were then entered simultaneously into a backwards stepwise binary logistic regression. The resulting model was then converted into a risk score.

The new risk score was then applied to the data in the validation set. An ROC curve was produced to test whether the score remained a significant predictor of POPF in this second set of data. The modelling and validation sets were then divided into deciles and quintiles, respectively, based on the risk score, and the actual rates of POPF in each category calculated. This allowed the relationship between the risk score and actual patient outcomes to be compared graphically.

Table 1 Characteristics of the whole group and patients in the modelling and validation sets. There was no significant difference in any characteristic between the modelling and validation sets

	Whole group (n = 325)	Modelling set (n = 217)	Validation set (n = 108)	P-value
Age, years, median (IQR)	67 (61–73)	67 (60–73)	68 (61–72)	0.955
Gender, male, n (%)	182 (56.3%)	120 (55.8%)	62 (57.4%)	0.812
BMI, kg/m ² , median (IQR)	24.9 (22.5–27.8)	25.0 (22.5–27.8)	24.6 (22.6–27.8)	0.952
Smoker, n (%)	53 (16.3%)	33 (15.2%)	20 (18.5%)	0.651
Preoperative diabetes, n (%)	46 (14.2%)	31 (14.3%)	15 (13.9%)	1.000
Diagnosis, n (%)				
Pancreatic adenocarcinoma	128 (39.4%)	88 (40.6%)	40 (37.0%)	0.169
Cholangiocarcinoma	47 (14.5%)	33 (15.2%)	14 (13.0%)	
Ampullary carcinoma	68 (20.9%)	40 (18.4%)	28 (25.9%)	
Duodenal carcinoma	20 (6.2%)	11 (5.1%)	9 (8.3%)	
Neuroendocrine tumour	15 (4.6%)	10 (4.6%)	5 (4.6%)	
Benign	22 (6.8%)	16 (7.4%)	6 (5.6%)	
Other	25 (7.7%)	19 (8.8%)	6 (5.6%)	
PPPD/Whipple procedure, n	294/31	193/24	101/7	0.231
PJ/PG, n	176/149	117/100	59/49	0.907
Pancreatic fistula, n (%) (ISGPF Grade A/B/C)	77 (23.7%) (29/28/20)	48 (22.1%) (21/19/8)	29 (26.9%) (8/9/12)	0.420

IQR, interquartile range; BMI, body mass index; PPPD, pylorus-preserving pancreaticoduodenectomy; PJ, pancreaticojejunostomy; PG, pancreaticogastrostomy; ISGPF, International Study Group on Pancreatic Fistula.

Data describing the cohorts were expressed as the median (interquartile range). The Mann–Whitney *U*-test and chi-squared test were used to explore cohort characteristics.

Statistical tests were two-tailed. A *P*-value of <0.05 was accepted as indicative of statistical significance. All analyses were performed using IBM SPSS Version 19.0 (IBM Corp., Armonk, NY, USA). A medical statistician (JH) provided advice during the study design, and performed the analyses and modelling.

Results

A total of 325 patients were included in the study; 217 patients were randomly selected into the modelling set and the remaining 108 were selected into the validation set. Table 1 describes the whole cohort and provides a comparison between the validation and test sets. There was no significant difference in any characteristic between the two sets.

Risk factors for POPF

The results of the univariable analysis on the modelling set are reproduced in Tables 2 and 3 and the results of the multivariable analysis in Table 4. The resulting model contained BMI (*P* = 0.011) and pancreatic duct width (*P* < 0.001). A risk score derived from this model to predict the likelihood of POPF is calculated thus:

$$\frac{\exp(-3.206 + 0.107[BMI] - 0.404[\text{pancreatic duct width mm}])}{1 + \{\exp(-3.206 + 0.107[BMI] - 0.404[\text{pancreatic duct width mm}])\}}$$

Confidence intervals (95% CIs) can be calculated as follows: lower CI = (risk score*0.814) – 2, and upper CI = (risk score*1.110) + 5.7. An ROC curve was produced to test the accuracy of this risk score in predicting POPF (Fig. 1). The area under the ROC curve was found to be 0.832 (95% CI 0.768–0.897; *P* < 0.001).

In order to validate the risk score, it was applied to the validation set. The area under the ROC curve for the validation set was found to be 0.751 (95% CI 0.649–0.852), which did not differ significantly from the area under the ROC curve for the modelling set (*P* = 0.241).

Figure 2 further evaluates the performance of the risk score. Patients in the modelling set were divided into deciles based on their risk scores. Patients in the validation set were then divided into quintiles because there were fewer patients in this set. The observed rate of pancreatic leaks was then calculated for each of the percentiles and plotted at the mean value within each interval. A reference line was added to indicate where the points would lie if the risk score had performed perfectly. As Fig. 2 shows, the plotted points are close to this line, a further indication of the accuracy of the risk score. Figure 3 demonstrates graphically the risk for POPF relative to BMI and pancreatic duct width as predicted by the score. Thus, obese patients (BMI: 30–35 kg/m²) with a narrow duct (< 3 mm in diameter) have a 30–55% risk for developing POPF, whereas patients with a pancreatic duct diameter of >10 mm, regardless of BMI, have a risk of <5%.

A web-based calculator for this risk score is available at <http://www.uhb.nhs.uk/preoperative-prediction-of-pancreatic-fistula-calculator.htm>.

Table 2 Univariate analysis of continuous factors in the modelling set ($n = 217$)

Factor	n	Pancreatic fistula		AUROC (SE)	a	P-value
		No	Yes			
Patient factor						
Age, years, median (IQR)	217	66.7 (59.8–73.4)	66.9 (60.7–73.3)	0.502 (0.047)	+	0.961
BMI, kg/m ² , median (IQR)	211	24.7 (22.0–27.0)	26.8 (24.0–32.4)	0.677 (0.045)	+	< 0.001
Biochemical result, median (IQR)						
White cell count, ×10 ⁹ /l	216	7.70 (6.60–9.80)	7.90 (6.63–9.48)	0.508 (0.046)	–	0.865
Platelet count, ×10 ⁹ /l	216	306 (244–395)	297 (237–342)	0.552 (0.046)	–	0.271
Haemoglobin, g/dl	216	12.6 (11.7–13.5)	12.6 (11.0–13.7)	0.506 (0.051)	–	0.901
International normalized ratio	212	1.00 (1.00–1.10)	1.00 (0.90–1.10)	0.516 (0.049)	–	0.743
Aspartate transaminase, IU/l	209	52.0 (28.0–84.5)	32.0 (21.3–69.5)	0.598 (0.048)	–	0.039
Alanine transaminase, IU/l	48	50.0 (30.3–140.3)	40.0 (15.8–118.8)	0.559 (0.115)	–	0.568
Alkaline phosphatase, IU/l	216	558 (280–955)	293 (193–672)	0.630 (0.047)	–	0.006
Sodium, mmol/l	216	139 (136–142)	140 (138–142)	0.548 (0.045)	+	0.308
Potassium, mmol/l	213	4.30 (3.90–4.60)	4.20 (3.90–4.47)	0.529 (0.046)	–	0.534
Urea, mmol/l	216	5.20 (4.30–6.68)	5.70 (4.63–7.10)	0.558 (0.047)	+	0.220
Creatinine, μmol/l	216	75.0 (64.0–92.8)	78.5 (66.8–98.5)	0.567 (0.048)	+	0.157
Bilirubin, μmol/l	216	39.5 (14.0–130.0)	14.0 (6.0–50.0)	0.659 (0.047)	–	0.001
Albumin, g/l	216	41.0 (38.0–44.0)	41.0 (38.0–43.0)	0.502 (0.046)	–	0.969
Neutrophil count, ×10 ⁹ /l	216	5.00 (3.80–6.60)	5.30 (4.25–6.35)	0.523 (0.045)	+	0.632
Lymphocyte count, ×10 ⁹ /l	216	1.90 (1.40–2.40)	1.85 (1.30–2.45)	0.519 (0.047)	–	0.687
Neutrophil : lymphocyte ratio	216	2.74 (1.91–4.00)	3.29 (1.66–4.85)	0.518 (0.049)	+	0.711
Data from CT imaging, median (IQR)						
Pancreas width, mm	217	14.9 (12.7–17.8)	17.2 (14.3–20.0)	0.644 (0.044)	+	0.002
Pancreas duct diameter, mm	217	4.90 (1.75–7.15)	0.00 (0.00–1.47)	0.801 (0.033)	–	< 0.001
Renal fat thickness, mm	217	10.0 (4.5–16.1)	11.5 (6.3–18.8)	0.581 (0.046)	+	0.086
Superficial fat thickness, mm	217	13.0 (9.0–19.3)	14.2 (9.2–24.0)	0.552 (0.048)	+	0.276

^a+ or – indicates a positive or negative association with pancreatic fistula, respectively.

AUROC, area under the receiver operating characteristic curve; SE, standard error; IQR, interquartile range; BMI, body mass index; CT, computed tomography.

Associations between severity of POPF and independent variables

The associations between ISGPF grade, pancreatic duct width and BMI were explored in the whole cohort. There was no significant difference in pancreatic duct width or BMI between patients with POPF of ISGPF Grade A and those with Grade B or C POPF (Table 5).

Interobserver variation in data derived from CT measurements

There was generally strong correlation between reviewers' observations of preoperative CT imaging. Assessments of pancreatic duct width by the surgeon and hepatobiliary radiologist produced an intraclass correlation of 0.831 and a mean ± [2 × standard errors of the mean (SEM)] difference of 0.48 ± 0.51 mm.

Discussion

This study reviewed various factors associated with the occurrence of POPF following PD with the aim of developing a preoperative

score predictive of POPF. Variables identified intra- or postoperatively were purposefully excluded from analysis. The main findings were that BMI and pancreatic duct width independently correlated (positively and negatively, respectively) with POPF. These results were used to construct a statistical model to predict risk for POPF. The utility of this score was validated successfully in a separate cohort of patients.

This is not the first study to develop a predictive score for POPF. Gaujoux *et al.* identified that BMI, pancreatic steatosis and an absence of pancreatic fibrosis were independently associated with POPF.¹⁴ The index derived in that study was based upon the presence or absence of these categorical variables and gave a score of 0–3. Callery *et al.* reported a well-conducted study that used four variables to construct a score with four categorical risks for POPF.²⁴ The variables were an assessment of pancreatic texture (firm or soft), pancreatic duct width, pathology and intraoperative blood loss. Yamamoto *et al.* developed a risk score based upon preoperative variables and included five factors yielding a score of 0–7.²⁵ This latter score and the present score share a clear

advantage as they can be applied in the preoperative phase, but only the present study uses continuous data and presents a patient's risk as a continuous value. Considering the pancreatic duct width as a binary outcome greatly limits the ability of this variable to predict POPF risk. Furthermore, recording a patient's BMI and pancreatic duct width is easy and reproducible. The score reported by Yamamoto *et al.*²⁵ requires four measurements from CT imaging. The strong correlation between the interpreta-

tion of data obtained from CT imaging by the surgeon and hepatobiliary radiologist in the present study demonstrates that this risk assessment can be carried out by the surgeon in the outpatient setting.

A preoperative score predictive of POPF clearly cannot include characteristics of the gland that are identified intra- or postoperatively, some of which are strongly associated with POPF. These include the histological assessment of pancreatic steatosis^{14,17,18} and fibrosis,^{14,18} a soft or hard gland at palpation^{16,24,26–28} and pancreatic duct width.^{22–24} Increasing evidence, however, indicates that an indirect assessment of the gland is possible. Fatty pancreas, first described in 1933,²⁹ is associated with obesity^{14,17} and a local inflammatory state, so-called non-alcoholic pancreatic disease.³⁰ The association between obesity and pancreatic disease has only recently been appreciated and an increased BMI associated with POPF following PD^{14,31} and distal pancreatectomy.³² Hepatic steatosis, related to increased BMI, is reliably assessed by measuring hepatic density in non-contrast CT imaging.^{33,34} A recent study assessed the utility of CT imaging to indirectly assess pancreatic density as a surrogate for steatosis and the relationship with POPF; a significant association was identified.²⁰ In the present study, preoperative CT scans for over 75% of patients did not include a non-contrast CT sequence. It was therefore not possible

Table 3 Univariate analysis of categorical factors in the modelling set ($n = 217$)

Factor	<i>n</i>	Rate of leaks	<i>P</i> -value ^a
Sex			1
Male	120	21.7%	
Female	95	22.1%	
Pathological diagnosis ^b			< 0.001
Pancreatic carcinoma/ cholangiocarcinoma/ampullary carcinoma	167	17.4%	
Duodenal carcinoma	16	62.5%	
Benign disease/neuroendocrine tumour/other disease	34	26.5%	
Operation			0.434
Pylorus-preserving pancreaticoduodenectomy	193	21.2%	
Whipple procedure	24	29.2%	
Pancreatic reconstruction			0.140
Pancreaticojejunostomy	117	17.9%	
Pancreaticogastrostomy	100	27.0%	
Smoker			0.042
Non-smoker	108	24.1%	
Ex-smoker	66	25.8%	
Current smoker	33	6.1%	
Preoperative diabetes			0.842
No	180	21.7%	
Type 1	5	20.0%	
Type 2	26	26.9%	

^aFisher's exact test.

^bBecause of the number of different pathological diagnoses, some were grouped together. Patients with pancreatic adenocarcinoma, ampullary carcinoma and cholangiocarcinoma had similar rates of pancreatic fistula (PF) as did those with other diseases, neuroendocrine tumours and benign disease.

Table 4 Multivariate backwards stepwise logistic regression model on the data in the modelling set ($n = 217$)

Factor	Coefficient	Odds ratio (95% CI)	<i>P</i> -value
Constant	-3.026	0.049	0.01
Body mass index	0.107	1.113 (1.025–1.209)	0.011
Pancreatic duct width	-0.404	0.668 (0.568–0.786)	<0.001

95% CI, 95% confidence interval.

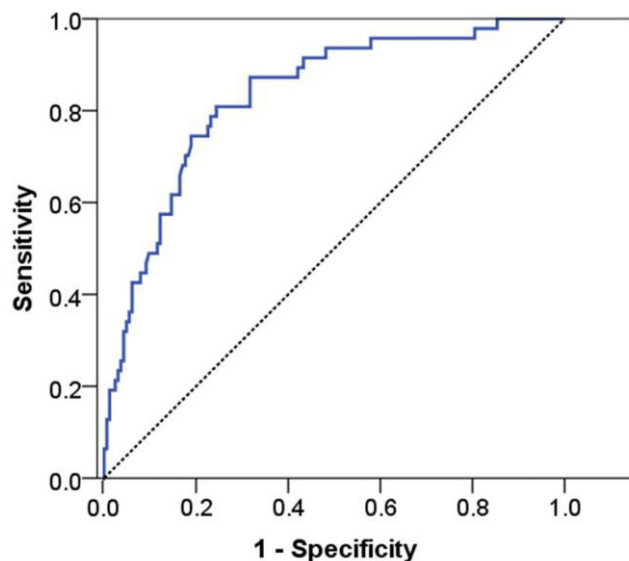


Figure 1 Receiver operating characteristic curve of risk score in the modelling set

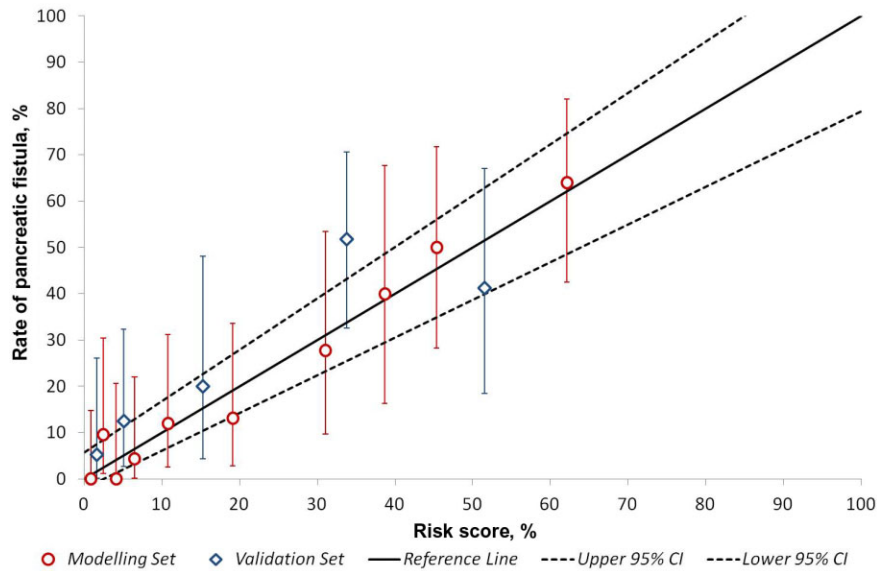


Figure 2 Comparison between the scoring system and observed rates of postoperative pancreatic fistula (POPF). The performance of the risk score in both the modelling and validation cohorts is demonstrated with the actual observed rate of POPF; bars represent 95% confidence intervals (CIs). There were twice as many patients within the modelling group (divided into deciles) as the validation group (divided into quintiles). The solid line indicates the perfect performance of the score; the dashed lines indicate the 95% CI

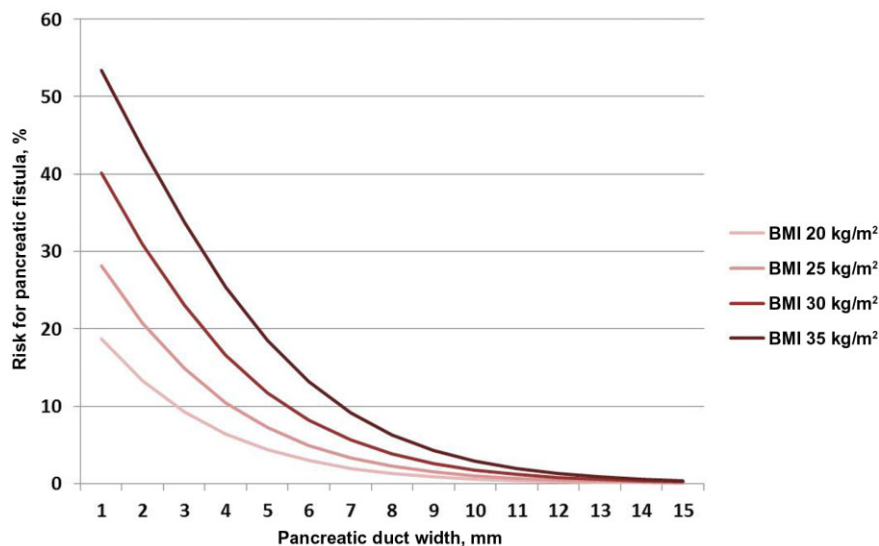


Figure 3 Graphical representation of risk for postoperative pancreatic fistula (POPF) as predicted by the risk score. Pancreatic duct width was measured from preoperative computed tomography imaging. BMI, body mass index

to assess pancreatic density as determined by CT analysis in this study.

Pancreatic steatosis can be assessed using other radiological modalities, including magnetic resonance imaging (MRI),^{35–37} magnetic resonance spectroscopy^{38,39} and endoscopic ultrasound.⁴⁰ The clinical application of these techniques is limited by their infrequent use; for example, fewer than 10% of patients undergoing PD are assessed by MRI.⁴¹

Quantifying a patient's risk for POPF prior to PD is essential if the clinician is to provide individualized care to a patient considered for PD because POPF is responsible for the majority of morbidity and mortality following this procedure. The data presented in this study demonstrate that an individual's risk for POPF can vary from <1% to >50% based upon considerations of BMI and pancreatic duct width alone. Elucidating a patient's risk for POPF has several advantages. Preoperative consent and counselling can

Table 5 Associations of International Study Group on Pancreatic Fistula grades of postoperative pancreatic fistula (POPF), pancreatic duct width and body mass index, showing the lack of significant difference between associations with POPF of Grade A, and POPF of Grades B and C

	Postoperative pancreatic fistula			P-value
	None (n = 246)	Grade A (n = 28)	Grades B + C (n = 48)	
Pancreatic duct width	5 (1.7–7.2)	0 (0–0)	0 (0–2.7)	0.097
Body mass index	24.5 (22.1–27.0)	26.4 (24.0–30.6)	26.3 (23.7–30.3)	0.936

be tailored to each patient. The selection of patients and operative technique can be optimized as it is in patients with borderline fitness and those with lesions of uncertain pathological behaviour. For example, the decision to undertake partial or total pancreatic resection in a patient with an intraductal papillary mucinous neoplasm may be influenced by the risk for POPF, and a patient with a cystic lesion of the head of the pancreas that is deemed to be benign but is associated with a risk for malignant transformation in the future is likely to be influenced into pursuing conservative or surgical treatment depending upon his or her risk for POPF. Patients with proven malignant disease are unlikely to decline PD if they are deemed to be at high risk for POPF, but their clinical management may vary. Patients at low risk for POPF may benefit from the early removal of abdominal drains and/or the instigation of enteral feeding. Those at high risk may benefit from the placement of a feeding jejunostomy at the time of PD as the incidence of infective complications is lower than with parenteral nutrition, and complications with tube obstruction or dislodgement are lower than with nasojejunal feeding.⁴² Finally, trials of operative or therapeutic interventions aimed at decreasing rates of POPF have largely failed to demonstrate clinical benefit. Studies may now be designed to target those patients with the highest degree of risk for POPF.

It can be argued that ISGPF Grade A fistulae are not clinically relevant and therefore should not be considered as representing an important complication. There was no significant difference in either pancreatic duct width or BMI between patients with Grade A POPF and those with Grade B or C POPF. Both of these factors independently predispose to POPF as defined by an amylase-rich drain effluent, but whether other unidentified factors influence which patients will develop clinically relevant POPF is unclear and warrants further investigation. All factors analysed in this study were used to discriminate between patients who developed Grade A POPF and those who developed Grade B or C POPF; however, no significant factor was identified (data not shown). There are theoretical advantages to measuring visceral fat rather than BMI. Visceral fat can be regarded as a metabolic organ in its own right, in comparison with superficial fat, and is associated with metabolic syndrome,⁴³ which, in turn, has been associated with fatty pancreas.^{38,44,45} Tranchart *et al.* reviewed the potential role of the visceral fat area (VFA) in predicting POPF.⁴⁶ In non-contrast CT images, the VFA emerged as an independent predictor of Grade B and C POPF in comparison with no POPF and Grade A POPF.⁴⁶

However, Tranchart *et al.* observed that the BMI of patients with Grade B or C POPF was significantly different from that of patients without POPF or with Grade A POPF, presumably in keeping with the VFA findings.⁴⁶ This lack of correlation between BMI and the occurrence of Grade A POPF differs from the findings of the present study; furthermore, assessing the VFA is more complex than the technique used in the present study and requires additional software and training.⁴⁶ In addition, the area under the ROC curve generated from the predictive score in the present study (0.832) is higher than that obtained by Tranchart *et al.*⁴⁶ using VFA alone (0.77), which indicates the former's greater sensitivity and specificity in the prediction of POPF. In another study, retro-renal fat thickness was associated with POPF,²¹ but this was not observed in the present cohort or by Tranchart *et al.*⁴⁶ Although there is some conflict among the data regarding which assessment of body fat is most useful in predicting POPF, there is overwhelming evidence for the association of obesity with POPF. Whether obesity and its relation to risk for POPF are most optimally assessed by physical characteristics such as BMI, radiological characteristics such as VFA or possibly pancreatic density or the pathological assessment of the resected gland remains to be elucidated. The advantage of using BMI is that it is the easiest characteristic to measure and is available in the preoperative period.

The other component of the predictive score is pancreatic duct width. Its negative association with POPF has been observed previously.^{16,22,23} Others have considered pancreatic duct width as a binary variable and refer to it as either normal or wide. Considering duct width as a continuous variable makes it possible to identify risk for POPF with much greater predictive accuracy.

In conclusion, this study has developed a score predictive of POPF based solely upon preoperative information, which is simple and quick to use and has been validated within a separate cohort of patients. An individualized assessment of risk for POPF enhances preoperative counselling and patient selection for PD. Furthermore, the stratification of risk may permit a change to established clinical practice and facilitate research into risk factors for and strategies to decrease POPF amongst those patients at highest risk.

Acknowledgements

The authors would like to acknowledge Chris Coldham, who is responsible for prospective data collection within the Hepatobiliary and Pancreatic Surgery Unit, University Hospitals Birmingham, and Professor J. A. C. Buckels and Mr

D. Mayer, consultant surgeons within the same unit. Thanks to Gordon McKenzie (medical student, University of Birmingham) for help with data collection.

Conflicts of interest

None declared.

References

- Balzano G, Zerbi A, Capretti G, Rocchetti S, Capitanio V, Di Carlo V. (2008) Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. *Br J Surg* 95:357–362.
- de Wilde RF, Besselink MG, van der Tweel I, de Hingh IH, van Eijck CH, Dejong CH *et al.* (2012) Impact of nationwide centralization of pancreaticoduodenectomy on hospital mortality. *Br J Surg* 99:404–410.
- Schmidt CM, Turrini O, Parikh P, House MG, Zyromski NJ, Nakeeb A *et al.* (2010) Effect of hospital volume, surgeon experience, and surgeon volume on patient outcomes after pancreaticoduodenectomy: a single-institution experience. *Arch Surg* 145:634–640.
- van Heek NT, Kuhlmann KF, Scholten RJ, de Castro SM, Busch OR, van Gulik TM *et al.* (2005) Hospital volume and mortality after pancreatic resection: a systematic review and an evaluation of intervention in the Netherlands. *Ann Surg* 242:781–788.
- Aroori S, Puneet P, Bramhall SR, Muiesan P, Mayer AD, Mirza DF *et al.* (2011) Outcomes comparing a pancreaticogastrostomy (PG) and a pancreaticojejunostomy (PJ) after a pancreaticoduodenectomy (PD). *HPB* 13:723–731.
- McPhee JT, Hill JS, Whalen GF, Zayaruzny M, Litwin DE, Sullivan ME *et al.* (2007) Perioperative mortality for pancreatotomy: a national perspective. *Ann Surg* 246:246–253.
- Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J *et al.* (2006) 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg* 10:1199–1210.
- Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J *et al.* (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138:8–13.
- Connor S, Alexakis N, Garden OJ, Leandros E, Bramis J, Wigmore SJ. (2005) Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. *Br J Surg* 92:1059–1067.
- Diener MK, Fitzmaurice C, Schwarzer G, Seiler CM, Antes G, Knaebel HP *et al.* (2011) Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database Syst Rev* (5)CD006053.
- Diener MK, Tadjalli-Mehr K, Wente MN, Kieser M, Buchler MW, Seiler CM. (2011) Risk–benefit assessment of closed intra-abdominal drains after pancreatic surgery: a systematic review and meta-analysis assessing the current state of evidence. *Langenbecks Arch Surg* 396:41–52.
- Koti RS, Gurusamy KS, Fusai G, Davidson BR. (2010) Meta-analysis of randomized controlled trials on the effectiveness of somatostatin analogues for pancreatic surgery: a Cochrane review. *HPB* 12:155–165.
- Wente MN, Shrikhande SV, Muller MW, Diener MK, Seiler CM, Friess H *et al.* (2007) Pancreaticojejunostomy versus pancreaticogastrostomy: systematic review and meta-analysis. *Am J Surg* 193:171–183.
- Gaujoux S, Cortes A, Couvelard A, Noullet S, Clavel L, Rebours V *et al.* (2010) Fatty pancreas and increased body mass index are risk factors of pancreatic fistula after pancreaticoduodenectomy. *Surgery* 148:15–23.
- Lermite E, Pessaux P, Brehant O, Teyssedou C, Pelletier I, Etienne S *et al.* (2007) Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. *J Am Coll Surg* 204:588–596.
- Lin JW, Cameron JL, Yeo CJ, Riall TS, Lillemoe KD. (2004) Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *J Gastrointest Surg* 8:951–959.
- Mathur A, Pitt HA, Marine M, Saxena R, Schmidt CM, Howard TJ *et al.* (2007) Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg* 246:1058–1064.
- Rosso E, Casnedi S, Pessaux P, Oussoultzoglou E, Panaro F, Mahfud M *et al.* (2009) The role of ‘fatty pancreas’ and of BMI in the occurrence of pancreatic fistula after pancreaticoduodenectomy. *J Gastrointest Surg* 13:1845–1851.
- Winter JM, Cameron JL, Yeo CJ, Alao B, Lillemoe KD, Campbell KA *et al.* (2007) Biochemical markers predict morbidity and mortality after pancreaticoduodenectomy. *J Am Coll Surg* 204:1029–1036.
- Roberts KJ, Storey R, Hodson J, Morris-Stiff G, Smith AM. (2013) Can pancreatic fistula following resection be predicted by the use of preoperative CT imaging? *Pancreatol* 13:423–428.
- House MG, Fong Y, Arnaoutakis DJ, Sharma R, Winston CB, Protic M *et al.* (2008) Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. *J Gastrointest Surg* 12:270–278.
- Pratt WB, Callery MP, Vollmer CM Jr. (2008) Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. *World J Surg* 32:419–428.
- Yang YM, Tian XD, Zhuang Y, Wang WM, Wan YL, Huang YT. (2005) Risk factors of pancreatic leakage after pancreaticoduodenectomy. *World J Gastroenterol* 11:2456–2461.
- Callery MP, Pratt WB, Kent TS, Chaikof EL, Vollmer CM Jr. (2013) A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg* 216:1–14.
- Yamamoto Y, Sakamoto Y, Nara S, Esaki M, Shimada K, Kosuge T. (2011) A preoperative predictive scoring system for postoperative pancreatic fistula after pancreaticoduodenectomy. *World J Surg* 35:2747–2755.
- DeOliveira ML, Winter JM, Schafer M, Cunningham SC, Cameron JL, Yeo CJ *et al.* (2006) Assessment of complications after pancreatic surgery: a novel grading system applied to 633 patients undergoing pancreaticoduodenectomy. *Ann Surg* 244:931–937.
- Fuks D, Piessen G, Huet E, Tavernier M, Zerbib P, Michot F *et al.* (2009) Life-threatening postoperative pancreatic fistula (grade C) after pancreaticoduodenectomy: incidence, prognosis, and risk factors. *Am J Surg* 197:702–709.
- Kim WS, Choi DW, Choi SH, Heo JS, Kim MJ, Song SC *et al.* (2011) Clinical validation of the ISGPF classification and the risk factors of pancreatic fistula formation following duct-to-mucosa pancreaticojejunostomy by one surgeon at a single centre. *J Gastrointest Surg* 15:2187–2192.
- Ogilvie R. (1933) The islands of the Langerhans in 19 cases of obesity. *J Pathol* 37:473–481.
- Mathur A, Marine M, Lu D, Swartz-Basile DA, Saxena R, Zyromski NJ *et al.* (2007) Non-alcoholic fatty pancreas disease. *HPB* 9:312–318.
- Shimoda M, Katoh M, Yukihiro I, Kita J, Sawada T, Kubota K. (2012) Body mass index is a risk factor of pancreatic fistula after pancreaticoduodenectomy. *Am Surg* 78:190–194.

32. Sledzianowski JF, Duffas JP, Muscari F, Suc B, Fourtanier F. (2005) Risk factors for mortality and intra-abdominal morbidity after distal pancreatectomy. *Surgery* 137:180–185.
33. Kodama Y, Ng CS, Wu TT, Ayers GD, Curley SA, Abdalla EK *et al.* (2007) Comparison of CT methods for determining the fat content of the liver. *AJR Am J Roentgenol* 188:1307–1312.
34. Speliotes EK, Massaro JM, Hoffmann U, Foster MC, Sahani DV, Hirschhorn JN *et al.* (2008) Liver fat is reproducibly measured using computed tomography in the Framingham Heart Study. *J Gastroenterol Hepatol* 23:894–899.
35. Hu HH, Kim HW, Nayak KS, Goran MI. (2010) Comparison of fat–water MRI and single-voxel MRS in the assessment of hepatic and pancreatic fat fractions in humans. *Obesity (Silver Spring)* 18:841–847.
36. Kim Z, Kim MJ, Kim JH, Jin SY, Kim YB, Seo D *et al.* (2009) Prediction of postoperative pancreatic fistula in pancreaticoduodenectomy patients using preoperative MRI: a pilot study. *HPB* 11:215–221.
37. Lee SE, Jang JY, Lim CS, Kang MJ, Kim SH, Kim MA *et al.* (2010) Measurement of pancreatic fat by magnetic resonance imaging: predicting the occurrence of pancreatic fistula after pancreatoduodenectomy. *Ann Surg* 251:932–936.
38. Lingvay I, Esser V, Legendre JL, Price AL, Wertz KM, Adams-Huet B *et al.* (2009) Non-invasive quantification of pancreatic fat in humans. *J Clin Endocrinol Metab* 94:4070–4076.
39. Zyromski NJ, Mathur A, Gowda GA, Murphy C, Swartz-Basile DA, Wade TE *et al.* (2009) Nuclear magnetic resonance spectroscopy-based metabolomics of the fatty pancreas: implicating fat in pancreatic pathology. *Pancreatology* 9:410–419.
40. Al-Haddad M, Khashab M, Zyromski N, Pungpapong S, Wallace MB, Scolapio J *et al.* (2009) Risk factors for hyperechogenic pancreas on endoscopic ultrasound: a case–control study. *Pancreas* 38:672–675.
41. Cameron JL, Riall TS, Coleman J, Belcher KA. (2006) One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 244:10–15.
42. Gerritsen A, Besselink MG, Cieslak KP, Vriens MR, Steenhagen E, van Hillegersberg R *et al.* (2012) Efficacy and complications of nasojejunal, jejunostomy and parenteral feeding after pancreaticoduodenectomy. *J Gastrointest Surg* 16:1144–1151.
43. Wajchenberg BL. (2000) Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev* 21:697–738.
44. Lee JS, Kim SH, Jun DW, Han JH, Jang EC, Park JY *et al.* (2009) Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome. *World J Gastroenterol* 15:1869–1875.
45. Smits MM, van Geenen EJ. (2011) The clinical significance of pancreatic steatosis. *Nat Rev Gastroenterol Hepatol* 8:169–177.
46. Tranchart H, Gaujoux S, Rebours V, Vullierme MP, Dokmak S, Levy P *et al.* (2012) Preoperative CT scan helps to predict the occurrence of severe pancreatic fistula after pancreaticoduodenectomy. *Ann Surg* 256:139–145.