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ORIGINAL ARTICLE

A comparative study of risk factors for pancreatic fistula after pancreatoduodenectomy or distal pancreatectomy

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Abstract

Background: Evidence associates various biometric and histological variables such as steatosis and absence of fibrosis as risk factors for post-operative pancreatic fistula (POPF) after pancreatoduodenectomy (PD). Following distal pancreatectomy (DP), the association between these factors and POPF is less clear. This study of patients, drawn from the same background population, undergoing PD or DP at a single centre is a comparative study of the risk factors for POPF after these two operations.

Methods: Associations between POPF and patient characteristics, pre-operative blood tests, data from pre-operative computed tomography (CT) imaging, assessment of histological steatosis and fibrosis were explored.

Results: 26/107 (24%) and 26/90 (29%) patients developed POPF after PD and DP respectively. Absence of fibrosis was associated with POPF ($p < 0.001$) after PD and its presence correlated with pancreatic duct width ($p < 0.001$). Steatosis was not associated with POPF ($p = 0.910$). Multivariable analysis showed pancreatic duct width ($p = 0.016$) and fibrosis ($p = 0.025$) to be independent predictors of POPF after PD. The only variable associated with POPF after DP was underlying pathology ($p = 0.005$).

Conclusion: Pancreatic duct width is the most important variable related to POPF after PD and is correlated with fibrosis. Steatosis was not related to POPF. In contrast, after DP POPF appears to be related to the underlying disease.

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Introduction

Following pancreatoduodenectomy (PD) and distal pancreatectomy (DP), peri-operative morbidity is considerable,[1–6] with post-operative pancreatic fistula (POPF) a major causal factor. POPF has benefited from a recent definition and grading of severity[7] and can be applied following either PD or DP. POPF affects up to 25%[1–4] and 40%[4,5] patients after PD and DP respectively.

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Risk factors for POPF following PD have been investigated in many studies. These include patient factors such as body mass index (BMI),[8–11] gender,[10–13] co-morbidity[14,15] and gland factors such as narrow pancreatic duct width,[11–15] pancreatic texture (firm/soft),[8] presence of steatosis[8,15,16] or absence of fibrosis.[8]

Pancreatic steatosis has attracted attention because of its association with adverse clinical outcomes after PD. A significant amount of pancreatic steatosis is present in over half of patients undergoing PD[8,9,11] and is associated with increasing BMI, visceral fat area and advanced age.[8,9,11] Notably also, it has been shown that pancreatic steatosis significantly increases a patient's risk of POPF after PD, with up to 60% of patients with steatosis suffering POPF after PD.[8,9,16–18]

However, risk factors for POPF following DP are less well understood. Reported associations are the surgical management of the pancreatic remnant, lack of use of somatostatin analogues, duct obstruction and BMI.[3,19] The role of pancreatic steatosis and absence of fibrosis in POPF following DP has not yet been investigated.

This is a study of patients, drawn from the same background population, undergoing PD or DP at a single institution, with the aim of reviewing and comparing risk factors for POPF. Specifically, histological assessment of the resected gland quantified both steatosis and fibrosis and these variables were correlated with other risk factors for POPF. Given that histological variables can only be assessed post operatively and, thus, of limited clinical value in terms of prediction of POPF, they were correlated with data from preoperative computed tomography (CT) images.

Methods

Importantly, in order to compare the relative importance of candidate risk factors for POPF after PD or DP, patients should be drawn from the same background population, operated upon over a similar time period and at the same institution. Consecutive patients undergoing DP between November 2003 and December 2011 or PD between August 2008 and December 2011 were identified from a prospectively maintained institutional database. The patient cohorts were derived in such a way to provide a similar number of patients with POPF so that any statistical tests had similar power to detect associations between variables and POPF after either operation.

Archived histological materials were retrieved and those sections adjacent to the surgical resection margin were selected. These were stained with haemotoxylin-eosin and assessed for both steatosis and fibrosis by a researcher blinded to the clinical outcome. Pancreatic fibrosis was quantified using a method previously described by Ammann *et al.*[20] Scores of perilobular and intralobular fibrosis were determined, and for both a score of 0 (no connective tissue), 1 (mild deposits) or 2 (moderate or severe amounts) was awarded. The perilobular and intralobular scores were added and scores ranging between 0 and 2 were considered non-fibrotic, and those between 3 and 4 as fibrotic.

Pancreatic steatosis was scored in two ways. The first, a method similar to the fibrosis scoring system and previously described by Gaujoux *et al.*[8] involved scoring the amount of perilobular and intralobular fat. The scoring criteria used for perilobular fatty infiltration were: 0 (no fatty infiltration), 1 (some adipocytes) and 2 (numerous adipocytes separating the lobules) and similarly for intralobular fibrosis: 0 (no or rare adipocytes in some lobules), 1 (scattered adipocytes among most of the lobules) and 2 (numerous adipocytes among most of the adipocytes forming clusters of more than 10 cells). Once added together, if the intralobular and perilobular fat scores were between 0 and 2 the sample was considered as free of fatty infiltration whereas those that came to 3 or 4 were deemed a high steatosis score and thus fatty.

A percentage of fatty infiltration was also recorded according to the method previously described by Rosso *et al.*[9] This was a ratio of fat cells (both intralobular and perilobular) to the overall tissue surface.

Patient demographic variables and preoperative blood tests were recorded. Pre-operative assessment of the pancreatic duct width was assessed at the pancreatic neck, to the left of the junction between the superior mesenteric and portal veins. Pre-operative CT images were also used to measure abdominal wall thickness and peri-renal fat thickness. The former was measured as the antero-posterior thickness of the superficial fascia adjacent to the umbilicus and the latter was measured from the posterior margin of the left kidney to the anterior border of the posterior abdominal wall at the level of the left renal vein.

POPF was defined using the International Study Group of Pancreatic Fistula (ISGPF) definition.[7] PD were all performed through an open incision. The pancreaticoenteric reconstruction was performed at the discretion of the operating surgeon (the relationship between this and POPF is reported in the results). All patients received post operative somatostatin analogue for five post operative days or until resolution of a POPF. DP were performed using an open technique in patients with documented or suspected pancreatic cancer in order to facilitate regional lymphadenectomy. The pancreatic transection line was sutured at open DP and stapled at laparoscopic DP.

At PD a single tube drain was placed behind the pancreatic anastomosis in all patients. Prior to 2012 drain fluid was assessed for amylase on post operative day 5 and removed if drain fluid amylase levels were low. During 2012 we began testing drain fluid amylase on post operative day 1 (which stratified patients into enhanced recovery or standard protocols) and then day 3 at which point it was removed if the drain fluid amylase was low. For patients with a distal pancreatectomy a single tube drain was placed adjacent to the cut surface of the pancreas with drain fluid being checked on post operative day 5.

All patients received intravenous antibiotics at induction of anaesthesia, continued for three post operative doses. In the presence of a biliary stent intravenous fluconazole was added and prophylaxis continued for three post operative days.

Institutional approval for the study was obtained.

Statistical analysis

Initially, comparisons were made between the two surgical groups (PD vs. DP). Normally distributed variables were reported as mean ± standard deviation (SD) and compared between groups using t-tests, with median (interquartile range) and Mann–Whitney tests used for non-parametric variables. Nominal variables were compared between groups using Fisher's exact tests, with Kendall's tau used for ordinal variables.

The two surgical cohorts were then split, and associations between a range of factors and POPF assessed within each group separately. Multivariable analyses were then performed, to identify independent predictors of POPF, using a binary logistic regression model with a forwards stepwise entry method. Due to the amount of missing data for the radiological pancreas densities, these factors were initially considered for inclusion in the analysis, then excluded if they were not part of the final model, in order to maximise the available sample size.

Further assessment of variables was then performed, using Spearman's correlation coefficients (Rho) to measure association between factors. For the fibrosis and steatosis scores, receiver operating characteristic (ROC) curves were used to quantify their ability to predict POPF, and Jonckheere–Terpstra tests to assess their relationship with pancreatic duct width. Inter-rater consistency of these scores was also assessed, using quadratic weighted Kappa statistics for categorical variables. For continuous variables, intra-class correlation coefficients (ICCs) were used. A two-way random effects model with absolute agreement was employed, with the quoted coefficients relating to consistency for single measures.

All analyses were performed using IBM SPSS Statistics 22 (IBM Corp. Armonk, NY), with $p < 0.05$ deemed to be indicative of statistical significance. A medical statistician provided advice on study design and performed data analysis (JH).

Results

Cohort characteristics

Amongst 107 patients who underwent PD 26 (24%) developed POPF as did 26 of 90 (29%) patients undergoing DP ($p = 1.000$) (Table 1). The ISGPF grade (A, B, C) was 11, 7, 8 and 16, 10 and 0 for the PD and DP groups respectively with severity worse amongst the PD group ($p = 0.013$).

Characteristics of the two patient cohorts are presented in Table 1. Gender, age, rates of pre-operative diabetes, pathology, amount of pancreatic steatosis, fibrosis, duct width, abdominal wall thickness and perirenal fat thickness all differed significantly between the two cohorts.

Inter-rater assessment of histological and radiological variables

Analyses of the inter-rater assessment of histological variables showed good agreement between observers (RMB and JHS) with weighted Kappa statistics of 0.825 and 0.898 for the fibrosis score and steatosis scores respectively.

Associations with POPF after pancreatectomy

Following PD, POPF was associated with significantly higher BMI and narrower pancreatic ducts. Patients developing POPF also had significantly lower levels of fibrosis, although there was no significant association with steatosis (Table 2).

Following DP the only associations with POPF was the underlying pathology, with the highest rates of POPF in NET and benign tumours ($p = 0.005$). None of the histological or radiological variables were found to be significantly associated with POPF after DP (Table 2).

Data from preoperative blood tests are also analysed, but are not presented, given that none were associated with POPF after either DP or PD.

Association between histological variables and POPF after pancreatoduodenectomy

Increasing pancreatic fibrosis was associated with increasing pancreatic duct width (AUROC 0.74, $p < 0.001$) but not pancreatic steatosis (AUROC 0.51, $p = 0.910$, Figs. 1 and 2).

Multivariable analysis

Multivariable analysis was then performed, in order to identify independent associations with POPF following PD. All factors in Table 2 were considered for inclusion. The resulting model found POPF to be significantly less likely in patients with high fibrosis score and with larger pancreatic duct widths (Table 3).

Correlation between pancreatic fibrosis and preoperative variables

Increasing pancreatic duct width as measured on CT was significantly positively correlated with pancreatic fibrosis ($p < 0.001$) and negatively correlated with BMI ($p = 0.001$).

Correlation between pancreatic steatosis and preoperative variables

There was a clear relationship between 'fatty' variables amongst the PD cohort. BMI was positively associated with abdominal wall thickness ($p < 0.001$) and both the steatosis score ($p = 0.008$) and % steatosis ($p = 0.030$) values. There was no evidence of a significant correlation of pancreatic duct width with steatosis ($p = 0.654$).

Discussion

This was a study of risk factors for POPF with specific comparison between patients undergoing PD or DP. Risk factors for POPF after PD are well described and thus the comparison with a similar number of patients undergoing DP permitted insight into which factors, if any, are common to POPF after either procedure. Given recent interest in pancreatic fibrosis and steatosis as protective and causal factors for POPF respectively the secondary aim of this study was to correlate post-operative histological findings to pre-operative radiological observations. The main finding was a strong relationship between pancreatic fibrosis and duct width, which in turn were negatively related to POPF risk amongst patients undergoing PD. Two other notable observations were made: firstly, steatosis appeared to play no significant role in POPF development following PD and secondly the risk factors for POPF after DP largely remain unclear.

Table 1 Comparison of the two surgical cohorts. Continuous variables are expressed as medians and interquartile ranges, with p-values from Mann–Whitney tests. Fisher's exact test is used for categorical variables, unless stated otherwise

	Valid N	Type of resection		
		PD n=107	*DP n=90*	*p-Value*
Demographic information				
Gender (male)	197	59 (55%)	29 (32%)	**0.002**
Age at operation (years)	197	67.5 (60.9–74.3)	58.4 (43.3–67.0)	**<0.001**
BMI (kg/m^2)	195	25.5 (22.7–30.0)	26.1 (22.9–30.0)	0.627
Pre-operative diabetes	197	3 (3%)	19 (21%)	**<0.001**
Current Smoker	196	35 (33%)	34 (38%)	0.455
POPF*	197			0.707
None		81 (76%)	64 (71%)	
Grade A		11 (10%)	16 (18%)	
Grade B		7 (7%)	10 (11%)	
Grade C		8 (7%)	0 (0%)	
Pathology	197			**<0.001**
ADC		45 (42%)	12 (12%)	
Other malignancy		48 (45%)	13 (14%)	
NET		5 (5%)	21 (23%)	
Benign		9 (8%)	45 (50%)	
Histological variables				
Steatosis score	165	2 (1–3)	1 (1–2)	0.186
High steatosis score	165	28 (29%)	16 (23%)	0.377
Steatosis (%)	161	10 (5–23)	8 (3–13)	**0.044**
Fibrosis score	165	2 (1–4)	1 (0–2)	**<0.001**
High fibrosis score	165	41 (43%)	10 (14%)	**<0.001**
Radiological variables				
Pancreas duct width (mm)	168	5 (0–7)	1 (1–1)	**<0.001**
Abdominal wall thickness (mm)	162	14.2 (9.0–23.3)	19.0 (13.0–25.0)	**0.010**
Perirenal fat thickness (mm)	162	10 (5–17)	6 (4–11)	**0.005**

*p-Value from Kendall's tau to account for the ordinal nature of the factor. Bold p-values are significant at $p < 0.05$. BMI = body mass index; POPF = post-operative pancreatic fistula; ADC = adenocarcinoma; NET = neuroendocrine tumour; PD = pancreatoduodenectomy; DP = distal pancreatectomy.

Like other recent studies,[8,15] pancreatic duct width was found to be an important variable in POPF development after PD. Furthermore, increasing pancreatic fibrosis was shown to be strongly related to increasing pancreatic duct width; patients with these features had the lowest risk of POPF. Associations between variables related to POPF were explored. It was interesting to note that increasing duct width was associated with decreasing patient BMI in the PD cohort. It is likely that patients with a dilated pancreatic duct will have an element of pancreas exocrine insufficiency, which may explain this relationship. Other associations with POPF were expected such as physical associations with obesity – BMI and abdominal fat thickness. However, despite recent interest in its role in POPF development after PD,[8,9] pancreatic steatosis was not shown to be significant significantly predictive after either DP or PD. In the present study, steatosis was assessed according to two previously published methods[8,9] both of which were found to be easily reproducible though neither were associated with POPF. It was reassuring, in terms of validating the accuracy of these methods used, that pancreatic steatosis was associated with other 'fatty' variables (such as BMI) and thus it seems likely that histological steatosis was assessed correctly in the present study and the results are reliable. Furthermore, correlation between the two researchers (one of which is a specialist pancreatic histopathologist) who independently assessed histological steatosis was strong.

By including a cohort of patients undergoing DP, this study aimed to review risk factors for POPF based upon assumptions that they would be similar for those responsible for POPF after PD. This assumption was incorrect; only underlying pathology was significantly related to POPF after DP and, as stated above, unlike after PD histological and radiological features of the gland

Table 2 Relationship of tested variables with the occurrence of post-operative pancreatic fistula (POPF) after either distal pancreatectomy or pancreaticoduodenectomy. Continuous variables are expressed as medians and interquartile ranges, with p-values from Mann–Whitney tests. Fisher's exact test is used for categorical variables, unless stated otherwise

	Valid N	PD			DP		
		POPF –ve (n=81)	*POPF +ve (n=26)*	*p-Value*	*POPF –ve (n=64)*	*POPF +ve (n=26)*	*p-Value*
Demographic information							
Gender (male)	197	45	14	1.000	21	8	1.000
Age at operation (years)	197	68.4 (61.1–74.3)	66.4 (57.4–73.3)	0.506	58.8 (44.1–69.1)	56.1 (41.6–65.6)	0.408
BMI (kg/m^2)	195	24.3 (22.4–27.2)	29.1 (25.1–34.7)	**0.002**	25.6 (23.0–28.3)	28.1 (22.3–32.5)	0.319
Pre-operative diabetes	197	2	1	0.570	12	7	0.404
Current Smoker	196	24	11	0.240	27	7	0.237
PG/PJ	107	33/48	12/14	0.920	–	–	–
Laparoscopic procedure	197	0	0	1.000	3	3	0.350
Sutured/stapled remnant	92	–	–	–	61/3	23/3	0.350
Splenectomy	197	0	0	1.000	56	23	1.000
Pathology	197			0.062			**0.005**
ADC		37	8		10	1	
Other malignancy		32	16		13	0	
NET		3	2		11	10	
Benign		9	0		30	15	
Histological variables							
Steatosis score	165	2 (1–3)	2 (1–3)	0.906	1 (1–3)	2 (1–2)	0.507
High steatosis score	165	22	6	0.796	13	3	0.529
Steatosis (%)	161	10 (5–22)	11 (4–26)	0.872	9 (4–15)	5 (2–10)	0.112
Fibrosis score	165	3 (1–4)	1 (1–2)	**<0.001**	1 (0–2)	1 (0–1)	0.267
High fibrosis score	165	39	2	**<0.001**	8	2	0.713
Radiological variables							
Pancreas duct width (mm)	168	5 (3–7)	0 (0–3)	**<0.001**	1 (1–1)	1 (1–1)	0.779
Abdominal wall thickness (mm)	162	12.1 (8.6–20.2)	19.8 (11.0–30.0)	**0.014**	16.5 (13.0–26.0)	20.0 (15.0–24.0)	0.527
Perirenal fat thickness (mm)	162	10 (4–16)	12 (8–19)	0.101	6 (2–11)	5 (4–13)	0.498

*Normally distributed variables reported as mean ± SD, with p-values from t-tests. Bold p-values are significant at $p < 0.05$. BMI-body mass index; INR-international normalised ratio; NLR-neutrophil to lymphocyte ratio; Hu-Hounsfield units. BMI = body mass index; POPF = post-operative pancreatic fistula; ADC = adenocarcinoma; NET = neuroendocrine tumour; PD = pancreatoduodenectomy; DP = distal pancreatectomy; PG = pancreatogastrostomy; PJ = pancreatojejunostomy.

were not related to POPF. A comparison of the PD and DP cohorts perhaps helps explain these observations further (Table 2). The area of the gland where the resection is performed during DP is typically not affected by downstream obstruction as opposed to PD. Evidence for this is provided by the lower rate of fibrosis and narrower duct width amongst the DP cohort. This fails to be the full explanation, however, as a small number of patients undergoing DP did have fibrotic glands and/or a dilated pancreatic duct and yet these variables were not significantly different amongst DP patients who did or did not develop POPF. A type 2 error may be responsible for this. Had the DP cohort been presented on their own questions regarding the validity of the data could be raised. In a large cohort of patients (n = 452) Ferrone *et al*. observed increasing BMI, male gender and the need for additional organ resection as risk factors for POPF after DP.[21] In a larger cohort (n = 704) Nathan *et al*. observed that a DP for trauma had a higher incidence of POPF and that a combination of stapled and sutured closure were associated with a lower rate of POPF than sutured stump closure.[22] A low albumin level has also been associated with POPF after DP[19] as well as a stapled closure, advanced age and prolonged operation time.[3] All of these studies reported variables found to be related to POPF after DP using multivariable analysis, though it is noted that the variables related to POPF are not consistently reported. Furthermore, these studies contained more patients than the present study supporting the notion that a type 2 error may be responsible for the lack of significance in the present study. However, the DP and PD cohorts were of a similar size and with a

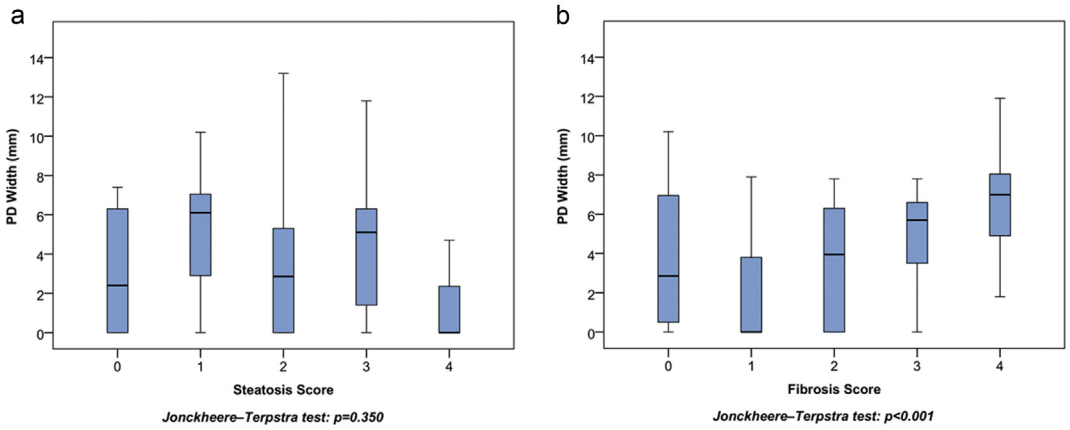

Figure 1 Boxplots showing the relationship between histological variables, pancreatic steatosis (a) and pancreatic fibrosis (b), and pancreatic duct width. PD = pancreatic duct width

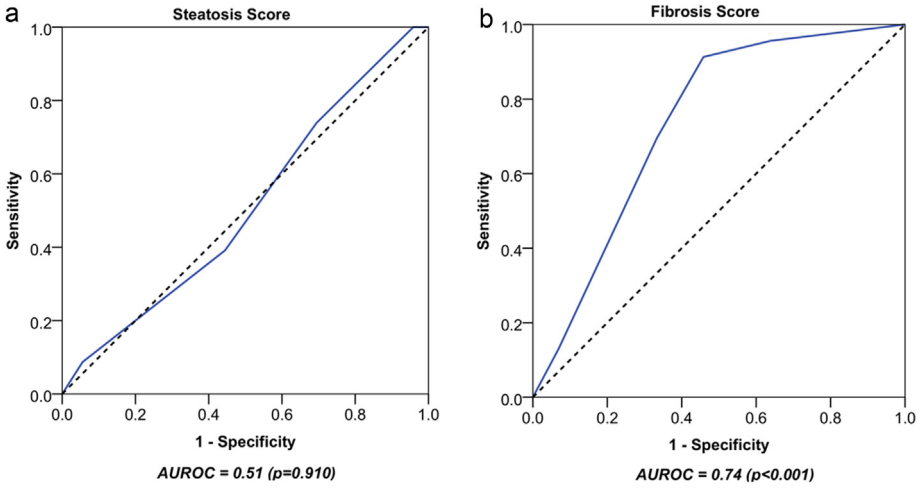

Figure 2 ROC curves showing the ability of histological variables, pancreatic steatosis (a) and pancreatic fibrosis (b), to predict POPF after PD

similar number of affected patients with POPF; the identification of several risk factors following PD in this study suggests the study is adequately powered to observe POPF in that setting and therefore it seems reasonable to question the relative impact of risk factors upon POPF occurrence after DP reported elsewhere.

Table 3 Multivariable analysis of the predictors of post operative pancreatic fistula following pancreatoduodenectomy (PD). Results are from a binary logistic regression model, using a forwards stepwise entry method. All factors applicable to PD from Table 2 were initially considered for inclusion. The final model was based on N = 95. Bold p-values are significant at $p < 0.05$

	Odds Ratio (95% CI)	p-Value
Fibrosis Score (High)	0.16 (0.03–0.79)	**0.025**
Pancreas duct width (per mm)	0.78 (0.63–0.96)	**0.016**

Furthermore, randomised trials which have studied techniques of managing the stump at DP have demonstrated conflicting results with the majority showing no significant effect of the tested interventions.[23–27]

Though this is a retrospective observational study the fact that risk factors were clearly identified amongst the PD (largely concordant with other data series) but not DP groups suggest that characteristics of the gland are not responsible for understanding which patients develop POPF after DP whilst others do not. A further untested variable, which may become important protective factor against POPF,[28,29] is the role of neoadjuvant chemotherapy or chemoradiotherapy. Among recent series of pancreatic resection in this setting rates of POPF are very low. Whether this relates to the disease (lower rate of POPF among patients with pancreatic cancer), increased duration of pancreatic duct obstruction or a direct consequence of the neoadjuvant treatment is unclear.

The clinical value of understanding risk factors for POPF can be questioned. An understanding of risk permits individualised patient consent and it is conceivable that the knowledge of a patients POPF risk prior to surgery may influence both surgeons and patients' treatment choice if that patient is deemed at high risk of surgery. More fundamentally an understanding of risk factors is essential to design appropriate clinical trials or interventions. In the case of POPF it may be that these variables cannot be meaningfully modified prior to surgery but risk stratification could at least be used to both design and present data from clinical trials. For example to ensure equal distribution of patients based upon POPF risk between two trial groups.

In summary, an absence of fibrosis and not presence of steatosis appears to be the most important histological feature of the pancreas gland related to POPF development after PD. Fibrosis was correlated with duct width, and these were the only factors associated with POPF after multivariable analysis. However, characteristics of the gland that relate to POPF after DP remain unclear.

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None.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2017.04.013.