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Preoperative Computed Tomography to Predict and Stratify the Risk of Severe Pancreatic Fistula After Pancreatoduodenectomy

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Abstract: The aim of this article is to assess whether measures of abdominal fat distribution, visceral density, and antropometric parameters obtained from computed tomography (CT) may predict postoperative pancreatic fistula (POPF) occurrence.

We analyzed 117 patients who underwent pancreatoduodenectomy (PD) and had a preoperative CT scan as staging in our center. CT images were processed to obtain measures of total fat volume (TFV), visceral fat volume (VfV), density of spleen, and pancreas, and diameter of pancreatic duct. The predictive ability of each parameter was investigated by receiver-operating characteristic (ROC) curves methodology and assessing optimal cutoff thresholds. A stepwise selection method was used to determine the best predictive model.

Clinically relevant (grades B and C) POPF occurred in 24 patients (20.5%). Areas under ROC-curves showed that none of the parameters was per se significantly predictive. The multivariate analysis revealed that a VfV >2334 cm³, TFV >4408 cm³, pancreas/spleen density ratio <0.707, and pancreatic duct diameter <5 mm were predictive of POPF. The risk of POPF progressively increased with the number of factors involved and age.

It is possible to deduce objective information on the risk of POPF from a simple and routine preoperative radiologic workup.

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Abbreviations: AIC = Akaike information criterion, AUC = area under the curve, CT = Computed tomography, HU = hounsfield units, IPMN = intraductal papillary mucinous neoplasm, PD = pancreatoduodenectomy, POPF = postoperative pancreatic fistula, ROC = receiver-operating characteristic, SFV = subcutaneous fat volume, TFV = total fat volume, VfV = visceral fat volume.

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INTRODUCTION

Postoperative pancreatic fistula (POPF) remains one of the most frequent and threatening complication after pancreatoduodenectomy (PD). The occurrence ranges from 10% to 30%,^{1,2} even in high-volume centers,^{3,4} and depending on its severity, it may be responsible for distant organ dysfunction and subsequent mortality, prolonged length of in-hospital stay, and increased health care costs.⁵ Both prevention and treatment of POPF are challenging. Among the potential strategies to reduce the incidence and the severity of POPF, different surgical techniques^{6–12} have been proposed along with the perioperative inhibition of exocrine pancreatic secretion.^{13–15}

An additional key factor to improve patient management may be to find reliable means of calculating and predicting the risk of POPF. The ability of anticipating the risk of POPF before surgery based on peculiar patient features might establish a more customized preoperative program for patients with high risk of fistula, potentially excluding subjects with elevated risk from surgical resection or to set up protocols for a strict and early detection of warning clinical scenario.

Previous studies and reviews described different variables correlated to the occurrence of POPF, in particular, patient characteristics such as American Society of Anesthesiology score, body mass index, age, malnutrition, muscle cachexia, medical history and morbidities,^{16–20} and intraoperative findings, that is, small Wirsung duct diameter, soft pancreatic texture, and estimated blood loss.²¹ Also baseline radiological findings, such as fat distribution, radiological characteristics of abdominal skeletal muscles, estimated pancreatic remnant volume, and pathway of the enhancement attenuation have been correlated with the risk of complication development and POPF, but with inconsistent results.^{22–29}

Despite the intrinsic gland characteristics appear to be universally recognized as useful parameters to predict POPF, these bear a subjective judgment and cannot be assessed preoperatively. Unbiased, exhaustive, and reliable predictors of POPF are warranted.

With the present study, we aimed to appraise the ability of preoperative fat body distribution and pancreatic features, assessed by preoperative computed tomography (CT) scan, to predict the occurrence of severe POPF and stratify the risk.

METHODS

Data for this retrospective study were extracted from a prospective database involving patients submitted to PD in our institution from January 2007 to March 2014.

The only inclusion criterion for the study was the availability of preoperative CT scan imaging in the electronic archives of our center.

CT Scan Analysis

All patients underwent a preoperative multiphase multi-detector CT scan before surgery, performed either with Brilliance iCT 256-slice or Brilliance 16-slice CT scanners (Philips Medical Systems, Eindhoven, Netherlands).

An unenhanced scan was followed by a postcontrast triphasic acquisition (arterial, portal venous, and equilibrium phase; 2-mm collimation), after the injection of 100 to 120 mL of nonionic iodinated contrast medium (Xenetix 350; Guerbet, Aulnay, France) into an antecubital vein, at a rate of 3.5 mL/s followed by the injection of 20 to 40 mL of saline solution.

Images were saved as DICOM and transferred to an image workstation with dedicated volume assessment software (Philips Brilliance Workspace 2.0; Philips Medical Systems).

The unenhanced scan was used to generate a CT reconstruction of the upper abdomen (from the diaphragm to the kidneys) with a 5 mm thickness. Two different radiologists (D.F. and D.I.), blinded to patient information, measured total fat volume (TFV), visceral fat volume (VFV), and analyzed pixels with densities in the -190 Hounsfield units (HU) to -20 HU range, and subcutaneous fat volume (SFV) was obtained by subtracting VFV from TFV. The range density used allowed only fat to include in measurements, excluding all other intra-abdominal tissues having a different density cutoff value. The pancreas, spleen, and liver density were evaluated by manually drawing region of interests as big as possible on the parenchyma, carefully avoiding other structures (ie, vessels, pancreatic duct, and artifact zones); the obtained values were expressed in HU. Then the ratio between the density of the pancreas over the density of the spleen was calculated ($d_{\text{pancreas}}/d_{\text{spleen}}$). The spleen was chosen as reference of 1 as it does not contain fat tissue and its density is not influenced by amount of visceral or subcutaneous fat.

Bilateral retrorenal fat and main pancreatic duct diameter were also measured: retrorenal fat was calculated as the minimum distance between the posterior renal capsule and the junction of the abdominal wall and paraspinal musculature at the level of the renal veins.

The maximum diameter of the pancreatic duct was measured using the arterial phase in order to better identify the entire length of the duct.

Surgical Technique

Whipple or pylorus-preserving PD was performed by 3 different experienced pancreatic surgeons. A 2-layer duct-to-mucosa pancreatojejunostomy with either Child or Roux-en-Y technique was used for reconstruction. The main pancreatic duct was routinely managed with an internal catheter (Bracci type) secured to the jejunal mucosa. At the end of operation, 2 abdominal closed suction drains were placed: one next to the biliojejunal anastomosis and one closed to the pancreatojejunal anastomosis. Continuous intravenous infusion of octreotide (600 mcg/d) was given to all patients starting during surgery and ending at the resumption of oral feeding.

POPF Classification

POPF was defined as any output from abdominal drains with amylase-rich juice >3 times the serum value, measured from postoperative day 3 and stratified for severity into grade A, B, or C, according to the International Study Group for Pancreatic Fistula classification.¹ We grouped patients with no POPF or grade A POPF in a single cohort because of the quite similar impact on the clinical course. Patients with POPF B or C

were analyzed together for the significant and relevant effect on the outcome of these grades of fistula.

Statistical Analyses

The distribution of the candidate risk factors (BMI, TFV, VFV, retrorenal fat thickness, $d_{\text{pancreas}}/d_{\text{spleen}}$ ratio, Wirsung diameter, and age) according to POPF was summarized using mean (standard deviation) for normal variables or median (range) for skewed variables. The comparison between POPF groups was performed by the *t* test or the Mann–Whitney test.

The predictive ability of each single parameter (except for age) was investigated using the receiver-operating characteristic (ROC) curves methodology: we computed the area under the curve (AUC) index and evaluated the optimal cutpoint (as the one closest to the upperleft corner of the ROC plot),³⁰ together with other diagnostic measures (sensitivity, specificity, and positive and negative predictive values).

The variables dichotomized according to these thresholds were than used as predictors in a multivariate logistic regression model (adding also age and sex). Using an Akaike information criterion (AIC)-based stepwise selection method, we assessed the best predictive model. Finally, we computed the predicted probabilities of high-grade POPF according to each combination of the selected factors (Wirsung diameter, VFV, $d_{\text{pancreas}}/d_{\text{spleen}}$, and TFV) and for 3 different ages (60, 70, and 80 years). Then the probability of POPF for the considered combinations of risk factors was computed and graphically edited from the estimates of the logistic regression. All the analyses were performed with the R software version 3.0. A *P* value <0.05 was considered significant.

RESULTS

During the study period, we performed 179 PD, but we retrieved data of 117 (65.4%) patients because preoperative CT scan was performed and archived in our center. The patient and operative characteristics are summarized in Table 1. The overall rate of grade B/C POPF was 20.5% (24/117).

Patients with grade B/C POPF had a significantly higher TFV and VFV, a thicker retrorenal fat, and a smaller Wirsung duct diameter when compared with the no/grade A POPF group. In addition, patients of the first group were older in median of approximately 4 years and the ratio between the density of pancreas over the density of spleen was higher than the patients of the second group, although not statistically significant in a univariate analysis. The distribution of the body mass index was quite similar between the 2 groups (Table 2).

The diagnostic performance measures of each parameter, according to the ROC-curve methodology, are reported in Table 3. The AUC was quite low for all variables suggesting that none of the risk factors taken singularly can accurately predict the occurrence of severe POPF. This motivated the search for a predictive model based on the combination of several factors, using multivariate analysis. The effect of the parameters (considered as dichotomous variables based on the previously evaluated optimal cutoffs) and age on the risk of severe POPF, according to the final model, are reported in Table 4. Patients with high VFV ($>2334 \text{ cm}^3$), high TFV ($>4408 \text{ cm}^3$), and high pancreas/spleen density ratio (>0.707) had an odds of developing grade B or C POPF equal to 4.9, 4.5, and 4.7 times the odds for patients with low values of these parameters, respectively. Moreover, a wide Wirsung diameter ($>5 \text{ mm}$) reduced the odds of severe POPF of about 5 times. Finally, age had an increasing effect of severe POPF.

TABLE 1. Patient and Operative Characteristics

	Overall, n = 117	POPF (No or Grade A), n = 93	POPF (Grade B or C), n = 24
Male/Female	56/61	45/48	11/13
Pathology			
IPMN	14 (11.9)	11 (11.8)	3 (12.5)
Neuroendocrine tumor	7 (6.0)	7 (7.5)	—
Pancreatitis	7 (6.0)	7 (7.5)	—
Bile duct carcinoma	9 (7.6)	7 (7.5)	2 (8.3)
Periampullary carcinoma	78 (66.7)	58 (62.4)	20 (83.3)
Pancreatic head	57	42	15
Duodenum	7	7	2
Ampulla of Vater	14	9	3
Ampullary adenoma	2 (1.8)	2 (2.1)	—
ASA score			
≤2		57 (61.3)	14 (51.4)
>2		36 (38.7)	10 (41.6)
Operation time, h	5.35 (4.02–6.17)	5.27 (3.45–6.08)	5.50 (5.12–6.41)
Blood loss, mL	500 (375–1000)	500 (300–1000)	650 (500–1225)
Length of stay, d	17.0 (12.0–27.0)	14.5 (10.0–21.0)	28.5 (22.2–56.7)
Mortality	6 (5.1%)	2 (2.2%)	4 (16.6%)
Cause of death			
Abdominal hemorrhage	2	1	1
Septic shock	4	1	3

IPMN = intraductal papillary mucinous neoplasm, POPF = postoperative pancreatic fistula. Data are numbers (%) or median (interquartile range).

Using this statistical model, we sought to evaluate the potential combinations of factors increasing the likelihood of developing severe POPF in patients with given characteristics. Figure 1 depicts the probability of severe POPF for all the combinations of the risk factor in the final model in an ideal patient aged 60. A higher risk (48%) than what observed in the present series was detected only when all 4 risk factors occurred. The probability of severe POPF showed a clear cluster distribution with an estimated risk ranging from 17% to 15% with 3 factors present, from 4.1% to 3.5% with 2 adverse parameters, and <1% with only 1 or no factors present.

A similar cluster distribution of severe POPF was observed in the analysis of an ideal patient aged 70 years. In this case, the risk of severe POPF with all 4 adverse parameters present was close to 66%. The risk dropped approximately to 30% with the occurrence of 3 variables, in a range of 8.5% to 7.2% with 2

factors, and ≤2% with 1 or no variables (Figure 2). As shown in Figure 3, the probability of severe POPF in the age of 80 was >80% when all 4 variables present, and remained quite high (from 48.2% to 45.1%) with 3 variables. The risk was similar to the overall rate with 1 factor present (16.8%–14.4%) and close to ≤4% when 1 or no adverse parameters were present.

DISCUSSION

The results of the present study suggest that the risk of occurrence of clinically relevant POPF may be predicted with relative accuracy and simplicity by combining specific information obtained by preoperative CT such as TFV and VFV, pancreas density, pancreatic duct diameter, in combination with patient age. Even if it has been already suggested that obesity

TABLE 2. Distribution of the Risk Factors in the 2 Outcome Groups

Factors	POPF (No or Grade A), n = 93	POPF (Grade B or C), n = 24	P Value
Age, y	70.24 (61.69; 76.71)	74.03 (68.70; 77.05)	0.061
Body mass index*	24.79 (3.43)	25.95 (3.66)	0.148
VFV, cm ³	1800 (1225; 2504)	2702 (2348; 3665)	0.001
TFV, cm ³	4100 (3381; 5312)	5432 (4534; 7176)	0.001
Retrorenal fat, mm	10 (6; 15)	16.5 (10; 25)	0.006
Pancreas/spleen density ratio*	0.83 (0.231)	0.88 (0.211)	0.332
Wirsung diameter, mm	4 (2; 7)	2 (2; 4)	0.015

POPF = postoperative pancreatic fistula, SD = standard deviation, TFV = total fat volume, VFV = visceral fat volume. Data as median (interquartile range).

*Data as mean (SD), *t* test.

TABLE 3. Diagnostic Performance of the Risk Factors in the Identification of Grade B or C Fistula

Factors	AUC	Optimal Cutpoint	Sensitivity	Specificity	PPV	NPV
Body mass index	0.614	26.4	0.542	0.742	0.138	0.649
VFV, cm ³	0.711	2334	0.750	0.731	0.081	0.581
TFV, cm ³	0.712	4408	0.792	0.645	0.077	0.635
Retrorenal fat, mm	0.674	16.5	0.542	0.785	0.131	0.606
Pancreas/spleen density ratio	0.554	0.707	0.875	0.275	0.107	0.759
Wirsung diameter, mm	0.657	5	0.409	0.875	0.724	0.073

AUC = area under the curve, NPV = negative predictive value, PPV = positive predictive value, TFV = total fat volume, VFV = visceral fat volume.

might be a handy predictor of complications after PD,³¹ differently from Hashimoto et al,²⁴ we found that body mass index per se did not predict POPF, suggesting that the distribution of fat is more important than obesity and that probably the amount and specific organ deposition of visceral fat plays a central role in this process.

Predicting the risk of POPF before surgery with a routine and widely available diagnostic tool such as CT scan may be noteworthy to optimize perioperative care and to provide individualized strategies for patients at high risk but also to offer adequate information to patients for alternatives to operation.

There are accepted and recognized predictive factors of POPF, such as surgeon definition of the texture of the parenchyma, diameter of the main pancreatic duct, intraoperative blood loss, and histopathologic subtypes directly related with the degree of parenchymal fibrosis. Some of them suffer partial objectiveness such as the firmness of the gland texture or can be evaluated only intraoperatively or postoperatively.^{18,21} Furthermore, the measurement of the pancreatic duct during operation may be not completely reliable if considered the tissue edema and distortion produced by surgical maneuvers.

Despite our study suggests that the occurrence of severe POPF was significantly associated with TFV, VFV, thickness of retrorenal fat, and diameter of main pancreatic duct, the accuracy and absolute predictive ability, as shown by the ROC curves, and the analysis of sensitivity, specificity and predictive values was low. Therefore, the present results did not allow us to select an ideal and single parameter to predict the occurrence of POPF. Accordingly, we further analyzed the categorical parameters together, using logistic regression and AIC-based model selection to evaluate the optimal combination of risk factors. By doing so, we observed that a TFV >4408 cm³, a VFV >2335 cm³, a ratio between pancreas and spleen density >0.7, and a diameter of the main pancreatic duct <5 mm (together with older age) were significantly related to clinically relevant POPF by increasing the risk of this outcome of almost 5-fold.

An association between increased adipose abdominal composition and postoperative complications after pancreatic surgery has been widely reported.^{22,23,32} Mathur et al³³ observed a relationship between pancreatic steatosis and pancreatic fistula and measurement of soft pancreas by magnetic resonance was found predictive of POPF.³⁴

The role of adipose tissue in promoting POPF onset might be partially explained by the arising idea to consider visceral fat as an endocrine organ, able to modulate inflammatory pathways. In fact, fatty tissue is not merely a storage of adipocytes and preadipocytes, but it is also composed from macrophages, endothelial cells, fibroblasts, and leukocytes.^{35,36} It has been observed that adipose tissue can produce hormone-like adipokines involved in regulation of metabolism and immune system^{37–39} and can secrete various cytokines that directly modulate the inflammatory response.⁴⁰ Particularly visceral fat produces interleukin-8, inducing protein-10, and monocyte chemoattractant protein-1, promoting local inflammation.³⁵ This condition may be particularly dangerous because persisting inflammation at a local site sustained by an anastomotic dehiscence may play a significant role in the alteration of the immune response against cancer. Chronic tissue irritation stimulates a persisting attempt of the host to generate wounding. Tumor development at inflammatory sites has now been repeatedly observed in a variety of tissues⁴¹ including pancreatic one suggesting that a chronic wound microenvironment may stimulate cancer cell growth and recurrence.⁴² Also, it has been proven that neoplastic cells may acquire metastatic potential and preferential growth in wound site with persisting inflammation.^{43,44} Furthermore, the effects of locally activated pancreatic enzymes, for their intense lytic activity in a fatty tissue, may be devastating such as the erosion of vessels, necrosis of vital organs, and predisposition to overinfection of dead tissue. Indeed, we observed a substantial increase of mortality in patients with grade B/C fistula due to septic shock and hemorrhage. The systemic spillover of such mediators may also account for the well-known generalized consequences of a

TABLE 4. Estimated Effects of the Dichotomous Parameters on the Risk of Grade B or C Fistula in the Logistic Regression Model

Factors	Odd Ratio	95% Confidential Interval	P Value
Age, y	1.080	1.003–1.162	0.040
VFV, cm ³ (>2334)	4.872	1.408–16.860	0.012
TFV, cm ³ (>4408)	4.453	1.139–17.408	0.032
Pancreas/spleen density ratio (>0.707)	4.733	1.024–21.873	0.047
Wirsung diameter, mm (>5)	0.194	0.051–0.737	0.016

TFV = total fat volume, VFV = visceral fat volume.

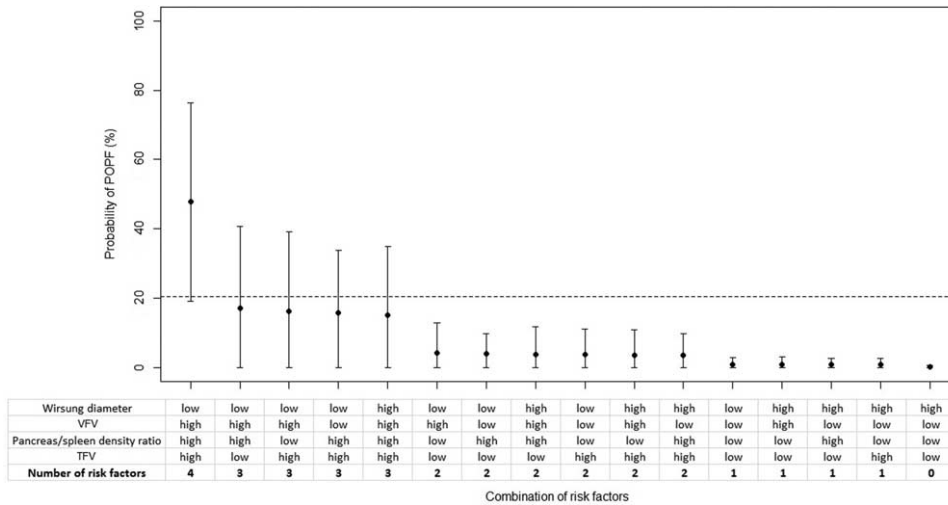


FIGURE 1. Predicted probability of grade B or C fistula for an ideal patient aged 60 and for each combination of the risk factors included in the final model.

severe POPF such as systemic inflammatory response syndrome and subsequent organ dysfunction.

Therefore, performing PD in patients with elevated TFV, VFV, fatty gland, and small pancreatic duct may be demanding and worrisome.

Based on the results of our logistic analysis, we constructed a statistical model to scale the risk of POPF according to different combinations of the above variables. The originality of our study and analysis stands mainly in the findings suggesting an increased hazard linked to the sum up of the risk factors related to age. If one considers, in general, the overall postoperative complication rate in the elderly linked to surgery per se and the associated medical comorbidities that considerably challenge the postoperative course, the counseling of PD is even more difficult. A meta-analysis⁴⁵ on 11 trials comparing outcomes after PD between subjects with age <75–80 or >75–80 years demonstrated that the rate of POPF did not significantly differ but morbidity and mortality rates were

higher in the elderly. These results match the common clinical sense, as it is everyday experience that the same type of surgical complication may have profound and different outcomes according to patient frailty.

Yet, our results suggest a correlation between age and POPF occurrence. Even more relevant, the number of the risk factors analyzed deeply affected the probability of POPF. We observed a clear distribution of risk in 4 well-defined clusters according to the number of parameters. The combination of the type of risk seemed less important. When the predicted risk was evaluated per age group, these clusters were even more evident. In particular, for patients around 60 years old, the probability of developing severe POPF was over the average (20.5%) only when all 4 risk factors were present, whereas within an ideal population of subjects of 70 years, the risk was approximately 66% and increased to 81% in octogenarian patients. In these 2 subgroups, the risk of POPF remained quite high also with 3 risk factors and lowered below the average only when

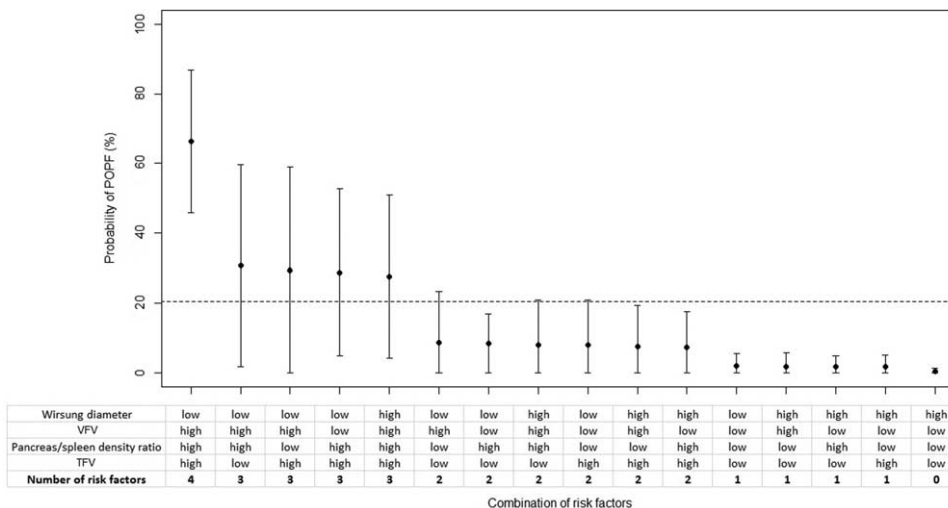


FIGURE 2. Predicted probability of grade B or C fistula for an ideal patient aged 70 and for each combination of the risk factors included in the final model.

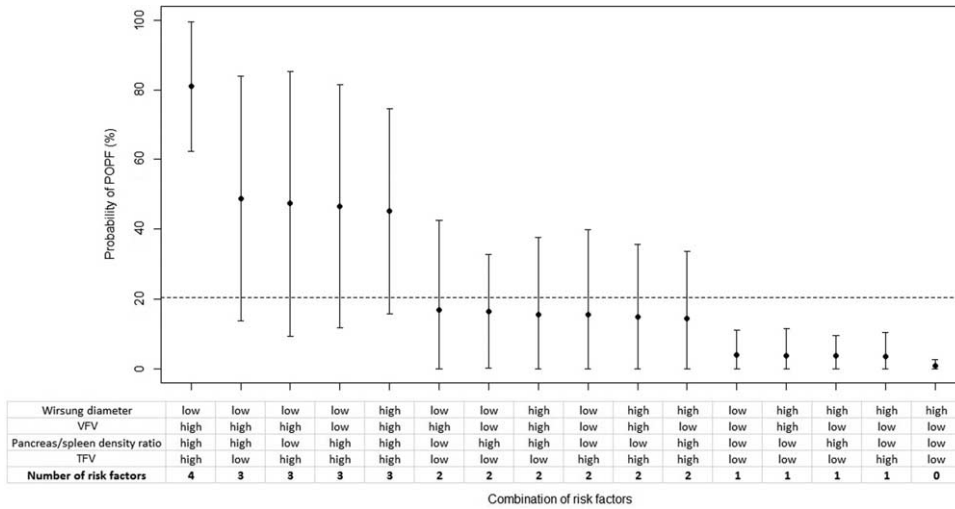


FIGURE 3. Predicted probability of grade B or C fistula for an ideal patient aged 80 and for each combination of the risk factors included in the final model.

≤2 parameters were present. It may be proposed that in patients >70 years, PD should be proposed with caution and according to number of risk factors and severity of associated diseases, and ideally, a frailty score should be coupled with these findings.

These remarks lead to some final considerations. First, we can deduce useful and objective information on the risk of POPF from a simple and routine preoperative radiologic workup matching anthropometric measurements of pancreatic structure and fat volume calculation with patient age. Second, given the calculated probability of POPF, surgeons will be able to not only give an accurate informed consent, but also select specific and tailored perioperative procedures, strategies, and pathways. Despite there are no sufficient evidences to suggest substantial changes in clinical practice, it may be taken into consideration that peculiar surgical techniques,^{6–10} such as pancreatogastroanastomosis^{11,12} or duct-to-mucosa with stent in main pancreatic duct,⁴⁶ routine use of new and potent inhibitor of the exocrine secretion,¹⁵ maximization and optimization of pancreatic anastomosis drainage, and planned postoperative radiological investigations even in absence of specific suspicious symptoms or laboratory findings, might decrease severe POPF rate or its consequences.

The present study has several limitations: we performed a retrospective analysis of the data. Therefore, a prospective validation of the results is lacking and the risk of POPF was stratified by estimates derived from a logistic analysis. Moreover, as any retrospective study, there is a large potential of selection bias in our patient population.

REFERENCES

1. Bassi C, Dervenis C, Butturini G, et al. International Study Group on Pancreatic Fistula Definition Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery*. 2005;138:8–13.
2. Büchler MW, Wagner M, Schmied BM, et al. Changes in morbidity after pancreatic resection: toward the end of completion pancreatectomy. *Arch Surg*. 2003;138:1310–1314.
3. Lau K, Salami A, Barden G, et al. The effect of a regional hepatopancreaticobiliary surgical program on clinical volume, quality

of cancer care, and outcomes in the Veterans Affairs system. *JAMA Surg*. 2014;149:1153–1161.

4. Schmidt CM, Turrini O, Parikh P, et al. Effect of hospital volume, surgeon experience, and surgeon volume on patient outcomes after pancreaticoduodenectomy: a single-institution experience. *Arch Surg*. 2010;145:634–640.
5. Enestvedt CK, Diggs BS, Cassera MA, et al. Complications nearly double the cost of care after pancreaticoduodenectomy. *Am J Surg*. 2012;204:332–338.
6. Diener MK, Fitzmaurice C, Schwarzer G, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. *Cochrane Database Syst Rev*. (5):2011:CD006053.
7. Diener MK, Tadjalli-Mehr K, Wente MN, et al. 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*. 2011;396:41–52.
8. Peng S, Mou Y, Cai X, et al. Binding pancreaticojejunostomy is a new technique to minimize leakage. *Am J Surg*. 2002;183:283–285.
9. Heeger K, Fendrich V, Waldmann J, et al. Reduced complication rate after modified binding purse-string-mattress sutures pancreaticogastrostomy versus duct-to-mucosa pancreaticojejunostomy. *Surgeon*. 2013;11:246–252.
10. Neychev VK, Sladinger PF. Minimizing shear and compressive stress during pancreaticojejunostomy: rationale of a new technical modification. *JAMA Surg*. 2014;149:203–207.
11. Chen Z, Song X, Yang D, et al. Pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy: A meta-analysis of randomised control trials. *Eur J Surg Oncol*. 2014;40:1177–1185.
12. Xiong JJ, Tan CL, Szatmary P, et al. Meta-analysis of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. *Br J Surg*. 2014;101:1196–1208.
13. Koti RS, Gurusamy KS, Fusai G, et al. Meta-analysis of randomized controlled trials on the effectiveness of somatostatin analogues for pancreatic surgery: a Cochrane review. *HPB (Oxford)*. 2010;12:155–165.

14. Connor S, Alexakis N, Garden OJ, et al. Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. *Br J Surg*. 2005;92:1059–1067.
15. Allen PJ, Gönen M, Brennan MF, et al. Pasireotide for postoperative pancreatic fistula. *N Engl J Med*. 2014;370:2014–2022.
16. Lermite E, Pessaux P, Brehant O, et al. Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. *J Am Coll Surg*. 2007;204:588–596.
17. Lin JW, Cameron JL, Yeo CJ, et al. Risk factors and outcomes in postpancreaticoduodenectomy pancreaticocutaneous fistula. *J Gastrointest Surg*. 2004;8:951–959.
18. Braga M, Capretti G, Pecorelli N, et al. A prognostic score to predict major complications after pancreaticoduodenectomy. *Ann Surg*. 2011;254:702–707.
19. Wellner UF, Kayser G, Lapshyn H, et al. A simple scoring system based on clinical factors related to pancreatic texture predicts postoperative pancreatic fistula preoperatively. *HPB (Oxford)*. 2010;12:696–702.
20. Sierzega M, Niekowal B, Kulig J, et al. Nutritional status affects the rate of pancreatic fistula after distal pancreatectomy: a multivariate analysis of 132 patients. *J Am Coll Surg*. 2007;205:52–59.
21. Callery MP, Pratt WB, Kent TS, et al. A prospectively validated clinical risk score accurately predicts pancreatic fistula after pancreatoduodenectomy. *J Am Coll Surg*. 2013;216:1–14.
22. Kirihara Y, Takahashi N, Hashimoto Y, et al. Prediction of pancreatic anastomotic failure after pancreatoduodenectomy: the use of preoperative, quantitative computed tomography to measure remnant pancreatic volume and body composition. *Ann Surg*. 2013;257:512–519.
23. McAuliffe JC, Parks K, Kumar P, et al. Computed tomography attenuation and patient characteristics as predictors of complications after pancreaticoduodenectomy. *HPB (Oxford)*. 2013;15:709–715.
24. Hashimoto Y, Sclabas GM, Takahashi N, et al. Dual-phase computed tomography for assessment of pancreatic fibrosis and anastomotic failure risk following pancreatoduodenectomy. *J Gastrointest Surg*. 2011;15:2193–2204.
25. Kanda M, Fujii T, Suenaga M, et al. Estimated pancreatic parenchymal remnant volume accurately predicts clinically relevant pancreatic fistula after pancreatoduodenectomy. *Surgery*. 2014;156:601–610.
26. Frozanpor F, Loizou L, Ansoorge C, et al. Preoperative pancreas CT/MRI characteristics predict fistula rate after pancreaticoduodenectomy. *World J Surg*. 2012;36:1858–1865.
27. Roberts KJ, Storey R, Hodson J, et al. Pre-operative prediction of pancreatic fistula: is it possible? *Pancreatol*. 2013;13:423–428.
28. Shimizu A, Tani M, Kawai M, et al. Influence of visceral obesity for postoperative pulmonary complications after pancreaticoduodenectomy. *J Gastrointest Surg*. 2011;15:1401–1410.
29. Tranchart H, Gaujoux S, Rebours V, et al. Preoperative CT scan helps to predict the occurrence of severe pancreatic fistula after pancreaticoduodenectomy. *Ann Surg*. 2012;256:139–145.
30. Rota M, Antolini L. Finding the optimal cut-point for Gaussian and gamma distributed biomarkers. *Computat Statist Data Analysis*. 2014;69:1–14.
31. Pratt WB, Callery MP, Vollmer CM Jr. Risk prediction for development of pancreatic fistula using the ISGPF classification scheme. *World J Surg*. 2008;32:419–428.
32. House MG, Fong Y, Arnaoutakis DJ, et al. Preoperative predictors for complications after pancreaticoduodenectomy: impact of BMI and body fat distribution. *J Gastrointest Surg*. 2008;12:270–278.
33. Mathur A, Pitt HA, Marine M, et al. Fatty pancreas: a factor in postoperative pancreatic fistula. *Ann Surg*. 2007;246:1058–1064.
34. Dinter DJ, Aramin N, Weiss C, et al. Prediction of anastomotic leakage after pancreatic head resections by dynamic magnetic resonance imaging (dMRI). *J Gastrointest Surg*. 2009;13:735–744.
35. Juge-Aubry CE, Henrichot E, Meier CA. Adipose tissue a regulator of inflammation. *Best Pract Res Clin Endocrinol Metab*. 2005;19:547–566.
36. Wozniak SE, Gee LL, Wachtel MS, et al. Adipose tissue: the new endocrine organ? A review article. *Dig Dis Sci*. 2009;54:1847–1856.
37. Jia S, Li Y, Parodo J, et al. Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. *J Clin Invest*. 2004;113:1318–1327.
38. Bokarewa M, Nagaev I, Dahlberg L, et al. Resistin, an adipokine with potent proinflammatory properties. *J Immunol*. 2005;174:5789–5795.
39. Bekri S, Gual P, Anty R, et al. Increased adipose tissue expression of hepcidin in severe obesity is independent from diabetes and NASH. *Gastroenterology*. 2006;131:788–796.
40. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol*. 2006;6:772–783.
41. Hofer SOP, Molema G, Hermens RAEC, et al. The effect of surgical wounding on tumour development. *Eur J Surg Oncol*. 1999;25:231–243.
42. Nagai S, Fujii T, Kodera Y, et al. Recurrence pattern and prognosis of pancreatic cancer after pancreatic fistula. *Ann Surg Oncol*. 2011;18:2329–2337.
43. Hofer SOP, Shrajer D, Reichner JS, et al. Wound-induced tumor progression. A possible role in tumor recurrence after tumor resection. *Arch Surg*. 1998;133:383–389.
44. Mathur A, Hernandez J, Shaheen F, et al. Preoperative computed tomography measurements of pancreatic steatosis and visceral fat: prognostic markers for dissemination and lethality of pancreatic adenocarcinoma. *HPB (Oxford)*. 2011;13:404–410.
45. Sukharamwala P, Szuchmacher M, Smith J, et al. Advanced age is a risk factor for post-operative complications and mortality after a pancreaticoduodenectomy: a meta-analysis and systematic review. *HPB (Oxford)*. 2012;14:649–657.
46. Motoi F, Egawa S, Rikiyama T, et al. Randomized clinical trial of external stent drainage of the pancreatic duct to reduce postoperative pancreatic fistula after pancreaticojejunostomy. *Br J Surg*. 2012;99:524–531.