Research Article

Pancreatic Fibrosis Assesed by Computed Axial Tomography as a Predictive Prognosis Factor of Pancreatic Fistula in Patients Submitted to Pancreatoduodenectomy

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Abstract

Introduction: Post-Operative Pancreatic Fistula (POPF) is an important cause of morbidity and mortality after pancreatic resection, occurring in 13 to 14% of patients. The early prediction of this potentially lethal complication could allow close monitoring in those patients at high risk of presenting it and thereby prevent severe post-operative complications. The present study evaluates the association between Computed Tomography (CT) density of the pancreas and an acinar score of the pancreatic resection margin as a predictive prognostic factor for POPF in patients undergoing the Whipple procedure at Centro Medico Nacional Siglo XXI.

Methods: Patients undergoing Pancreaticoduodenectomy (PD) at the Centro Médico Nacional Siglo XXI were included for analysis. CT densities of the pancreatic tail were measured in Non-Contrast (NCF) and Portal Venous (PVF) phases. Histologic slides of the pancreatic resection margins stained with hematoxylin-eosin were assessed under a light microscope to determine the content of acinar cells, collagen and fat.

Results: Thirty patients were included for analysis, POPF group (n = 16) and no POPF (n = 14). Non contrast density of the pancreatic tail was a good predictor of POPF (AUROC 0.754; 95% CI 0.577-0.932; p = 0.018). and a cut-off value of <35 HU predicted POPF with 70% sensitivity and 73.4% specificity. We found regular results for the AUROC analysis of pancreatic tail density in FPV (AUROC 0.625; 95% CI 0.422-0.828; p = 0.244) and poor results for the PVF / NCF index (AUROC 0.426; 95% CI 0.216-0.636; p = 0.493).

Conclusion: The ROC analysis of the tomographic determinations of the radiological densities of the parenchyma in the pancreatic tail reported good performance capacity for the values of the FNC but not for the density of the pancreas tail in FPV and FPV / FNC index. Non-contrast CT density of the pancreatic tail could predict the development of POPF after PD.

Introduction

Pancreatic Fistula (PF) is characterized by a leak of pancreatic fluid as a result of the interruption of the pancreatic ducts. Disruption of the pancreatic ducts can occur after acute or chronic pancreatitis, pancreatic resection or trauma. A PF is defined as an abnormal connection between the pancreas and adjacent or distant organs, structures, or spaces [1]. Pancreaticoduodenectomy (PD) is a complex, high-risk surgical procedure. The lowest operative mortality rates and the best long-term outcome have been demonstrated in high-volume centers [2]. The most common indication for resection of the head of the pancreas is the presence of a malignant or premalignant neoplasm of the pancreas or one of the other periampullary structures (bile duct, ampulla, or duodenum) [3-6]. According to the International Pancreatic Fistula Study Group (ISGPF), a postoperative pancreatic fistula (POPF)

is defined as an external fistula with a drainage outlet of any measurable volume after postoperative day 3 with an amylase level greater than three times the upper limit of the normal serum value. In 2016, the ISGPF updated the definition to additionally require a relevant clinical condition$_6$. To date several studies have aimed to identify predicting factors for the development of POPF like gland texture, pancreatic pathology, pancreatic duct diameter, and intra-operative blood loss which are now recognized as independent factors of POPF and incorporated into de Fistula Risk Score, however none of these factors are measurable pre-operatively [7].

There have been three previous studies searching the enhancement characteristics of the pancreas on pre-operative CT to predict the development of POPF [8-10]. Two of them focused on correlating pancreatic enhancement characteristics with histological fibrosis of the pancreas remnant without reference to acinar score, and one of them correlates the pancreatic enhancement characteristics with an acinar score which has previously been demonstrated that acinar cell density at the pancreatic resection margin is the histological component most predictive of POPF. The present study aims to evaluate the association between the density of the pancreatic tail on preoperative triple phase CT scan and the acinar score of the pancreatic resection margin, and development of POPF in our clinical center.

Methods

Patients and Clinical Data Collection

The study was approved by the institutional review board. Patients who underwent PD performed at two tertiary level institutions, Hospital de Especialidades and Hospital Oncología, between January of 2017 and January of 2019 were included for analysis. Patients without available pre-operative triple phase computed tomography, histologic slides of the pancreatic resection margin or an incomplete clinical record were excluded. Clinical data was collected from a prospectively maintained database. This included demographic data, pre-operative characteristics, histopathological diagnosis, post-operative complications and development of POPF. Fistula risk score was calculated for all patients.

Definitions

Post-Operative Pancreatic Fistula (POPF) was defined according to the International Study Group for Pancreatic Fistula (ISGPF) guidelines [11]. The ISGPS definition of Pancreatic Fistula (PF) provides three levels of severity. PF was classified as an asymptomatic, biochemical leak, previously grade A, or grade B or C, as clinically relevant as they require changes in the post-operative management and further diagnostic and therapeutic

interventions. For the purpose of this study, we combined grades A, B and C in the POPF group.

Histopathological data collection

Formalin-fixed paraffin hematoxylin and eosin stained slides of pancreatic resection margins were obtained for all patients. These were assessed under light microscopy for their acinar cell, collagen and fat content as a proportion of the total surface area on the examined slide (Figure 1) shows and example of the degrees of acinar, collagen and fat content in one of the slides. Slides were evaluated by one pathology specialist blinded to clinical outcomes.
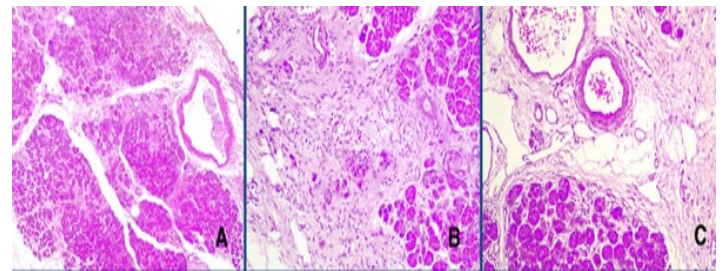

Figure 1: Example of histological section lamellae of the pancreatic resection margin. **A** Section stained with Hematoxylin and Eosin; magnification (10x) pancreatic neck margin due to ampula of Vater adenocarcinoma; acinar cells with minimal intra parenchymal collagen or fat. This was assigned an acinar score of 90%, collagen score 5%, fat score 5%. **B** Hematoxylin and Eosin; magnification (10x) pancreatic neck margin. The acinar cells have been replaced. This was assigned an acinar score of 50%, collagen score of 45%, and fat score of 5%. **C** Pancreatic neck margin due to a pancreatic ductal adenocarcinoma (20x); acinar cells are almost entirely replaced by collagen and fat. This slide was given an acinar score of 10%, collagen score of 70%, and fat score of 20%.

Radiological data collection

From the pre-operative triple phase CT scan enhancement values were measured by two authors. At the time of the assessment assessors were blinded to the clinical outcomes. The radiological density (Hounsfield units, HU) of the pancreatic parenchyma was measured by placing a Region of Interest (ROI) over the pancreatic tail. A ROI of 15 mm was placed, avoiding the pancreatic tumor, calcifications, ducts, blood vessels and non-pancreatic tissue at pancreatic tail Figure 2.

The following enhancement parameters were calculated at the pancreatic tail: contrast density (NCF); arterial phase density (AF); portal venous phase density (PVF); the ratio between Portal Venous And Non-Contrast Density (PVF/NCF).
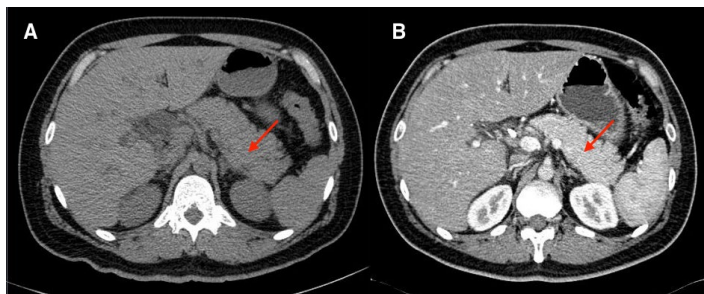
Figure 2: Representative pre-operative CT image of the pancreas in a patient with a high acinar score. The red arrows show the region of interest in the pancreatic tail. **A** Non-contrast (NCF) image with enhancement value of 44UH. **B** Image in portal venous phase (PVF) with enhancement value of 88UH.

Surgical technique, peri and postoperative care

PD was performed by general surgeons as well as surgical oncologists according to the standardized described techniques, pylorus preserving or standard PD. Octreotide was administered in all patients pre operatively and post operatively until oral intake. The pancreatic anastomosis was performed as an end to side anastomosis, duct to mucosa in two layers using polypropylene 4-0 suture. An open drain was routinely placed adjacent to the pancreatic anastomosis. Intra operatively, the texture of the pancreatic gland was subjectively assessed by the surgeon using three grades as soft, firm or very firm. Patients went from the recovery room to the surgical floor unless continuous monitoring was needed. The nasogastric tube was removed until peristalsis present. A clear liquid diet was started once the nasogastric tube was removed and advanced to regular diet as tolerated. On the basis of the drain, quantity and characteristics, the amylase concentration of surgical drain fluid was determined and discontinued if the concentration was normal (< 3 x upper limit of normal serum amylase level) Operative drains were removed when the patient started with oral intake and the output of fluid was less than 200 ml per day.

Statistical Analyses

Continuous variables in two groups were compared using Whitney's Mann U analysis. The strength of correlation between continuous variables was analyzed using Pearson's R in a bidirectional way. The area under the ROC curve (AUROC) was calculated to assess the ability of radiological variables to predict the development of POPF. An AUROC> 0.6 with a p value of <0.05 denoted a study with good and significant predictive capacity. Youden's index was calculated for all ROC curves to determine an optimal cut-off value to distinguish between POPF and non-POPF patients. A value of p <0.05 was taken as statistically significant. All statistical analyzes were performed with SPSS version 24 in Spanish.

Results

Patient Population and Outcomes

During the period study of January 2017 to January 2019, 56 patients underwent PD at the institutions; of which 30 had available the histological slides of the pancreatic resection margin as well as CT images for analysis. The results of the population were classified based on the development of POPF, conforming two study groups: the POPF group (n=16) and the group without POPF (n=14). Regarding the distribution by POPF class, we found the following distribution: grade A (62.5%), grade B (18.8%) and grade C (18.8 %.), Table 1 describes the clinical characteristics of the study population. A predominance of the female gender was identified in the POPF group with 68.8% vs. 31.3%, similarly to the findings in the group without POPF, where a frequency of 71.4% female patients and 28.6%. A mean age of 57.81 ± 8.11 years and 57.86 ± 13.34 years was found, in the POPF group and in the group without POPF, respectively. Age, gender, ASA grade, diabetes and body mass index were not identified as factors associated with the development of POPF. Neither the surgical time duration nor the intra operatively bleeding were significantly associated. A soft pancreas texture measured intra-operatively and the FRS were significantly associated with POPF (p<0.046) and (p=0.001) respectively Table 2. Collagen score was significantly higher in patients without development of POPF (5.63 vs 16.43, p 0.048) and acinar score was higher in the POPF group (82.19 vs 73.57, p=0.293) however not significant Table 3. The pre-operatively radiological characteristics were recorded in both groups, which are shown in Table 4. The absence of a dilated pancreatic duct was associated with the development of POPF (p<0.001). The parameter in our population that demonstrated significant capacity to predict POPF was non contrast density in the pancreatic tail FNC (AUROC 0.754; IC 95% 0.577-0.932; p=0.018) Figure 3. Using Youden´s statistic, an optimal tail NCF cut off value of > 35HU was determined which predicts the development of POPF with 70% sensitivity and 73.4% specificity. Regular results were recorded for the ROC analysis of pancreatic tail density in PVF (AUROC 0.625; 95% CI 0.422-0.828; p = 0.244) and, the PVF/NCF index reported poor results after ROC analysis (AUROC 0.426; 95% CI 0.216-0.636; p = 0.493).

On the other hand, we sought to determine the biserial correlation coefficient between the presence of postoperative pancreatic fistula and the histopathological scores, finding a low correlation coefficient in the negative sense and statistically not significant for the acinar cell score (Pearson's R = -. 287, p = 0.124); for the collagen score a low correlation coefficient in the positive sense, statistically not significant (Pearson's R = .351, p = 0.057) and for the fat score a very low correlation coefficient in the negative sense and statistically not significant (Pearson = -0.113, p = 0.551) Table 5.

	POPF (n=16)			No POPF (n=14)			
	Medium Frequency	Percentage	Desv. Est.	Medium Frequency	Percentage	Desv. Est.	p-value
Gender							
Female	11	68.8%		10	71.4%		0.918
Male	5	31.3%		4	28.6%		
Age (years)	57.81		8.11	57.86		13.34	0.759
Diabetic	4	25.0%		2	14.3%		0.637
IMC (kg/m²)	26.39		5.29	24.23		3.64	0.355
ASA							
2	7	43.8%		5	35.7%		0.728
3	9	56.3%		9	64.3%		

ASA: American Society of Anesthesiologists; POPF: Postoperative pancreatic fistula; *Mann-Whitney U test for independent samples; Significance p value <0.05; Fountain; Collection instrument.

Table 1: Clinical characteristics of patients submitted to PD.

	POPF (n=16)			No POPF (n=14)			
	Medium Frequency	Percentage	Desv. Est.	Medium Frequency	percentage	Desv. Est.	p-value
Duration of surgery (minutes)							
	397.50		88.79	436.93		87.58	0.294
Blood loss (ml.)							
	903.13		829.35	683.57		367.85	0.580
Tumor size (mm)							
	23.09		12.42	27.21		15.94	0.637
Fístula Risk Score							
	5.31		1.20	2.71		1.33	**<0.001**
Soft pancreas							
	10	62.5%		3	21.4%		**0.046**
Firm pancreas							
	6	37.5%		10	71.4%		0.120
Very firm pancreas							
	0	0.0%		1	7.1%		0.759
Mortality	1	6.3%		2	14.3%		0.728

Length of stay (days)						
	27.25		22.71	10.14		5.31	**<0.001**

POPF: Postoperative pancreatic fistula; *Mann-Whitney U test for independent samples; Significance p value <0.05; Fountain; Collection instrument

Table 2: Operative data of patients submitted to PD.

	POPF (n=16)			No POPF (n=14)			
	Medium Frequency	percentage	Desv. Est.	Medium Frequency	percentage	Desv. Est.	p-value
Acinar score							
	82.19		10.95	73.57		18.34	0.294
Collagen score							
	5.63		9.81	16.43		19.16	0.070
Fat Score							
	12.19		8.36	10.00		11.44	0.120
Histopathological diagnosis							
Ampulla of Vater	9	56.3%		8	57.1%		
Adenocarcinoma Ductal pancreatic adenocarcinoma	3	18.8%		3	21.4%		
Pancreatobiliar adenocarcinoma	1	6.3%		1	7.1%		
Pancreatic Cistoadenoma	1	6.3%		1	7.1%		
Duodenal Coristoma	1	6.3%		1	7.1%		
Pancreatic head quist	1	6.3%					

NC: Non-Contracted Phase; POPF: Postoperative Pancreatic Fistula; PV: Venous Portal Phase; TC: Computed Axial Tomography; *Mann-Whitney U Test for independent samples; Significance p value <0.05; Fountain; Collection instrument

Table 3: Acinar, collagen and fat scores and histopathological diagnosis of patients submitted to PD.

	POPF (n=16)			No POPF (n=14)			
	Medium Frequency	Percentage	Desv. Est.	Medium Frequency	Percentage	Desv. Est.	p-value*
Pancreatic duct (mm)							
	2.94		0.93	5.36		2.10	**<0.001**
Pancreatic tail density NC							
	41.72		11.17	31.80		8.75	**0.017**
Pancreatic tail density PV							
	87.80		17.17	75.47		26.81	0.257
Pancreatic tail Índex PV/NC							
	2.18		0.72	2.32		0.93	0.498

Pancreatic duct dilatation (>3mm)							
Positive	3	18.8%		13	92.9%		**<0.001**

NC: Non-contracted phase; POPF: Postoperative pancreatic fistula; PV: Venous portal phase; TC: Computed axial tomography; *Mann-Whitney U test for independent samples; Significance p value <0.05; Fountain; Collection instrument.

Table 4: Radiological data of pre-operative TC of patients submitted to PD.

	Acinar score		Collagen score		Fat score	
	R de Pearson	p-value	R de Pearson	p-value	R de Pearson	p-value
NC pancreatic tail						
	0.168	0.376	-0.307	0.098	0.230	0.222
PV pancreatic tail						
	0.378	0.040	-0.488	0.006	0.192	0.309
Índex PV/NC						
	0.263	0.160	-0.252	0.180	-0.008	0.968

NC: Non-contracted phase; PV: Venous portal phase; TC: Computed axial tomography; Significance p value <0.05; Fountain; Collection instrument

Table 5: Correlation between CT pancreatic tail enhancement characteristics and histopathological scores of patients submitted to PD.
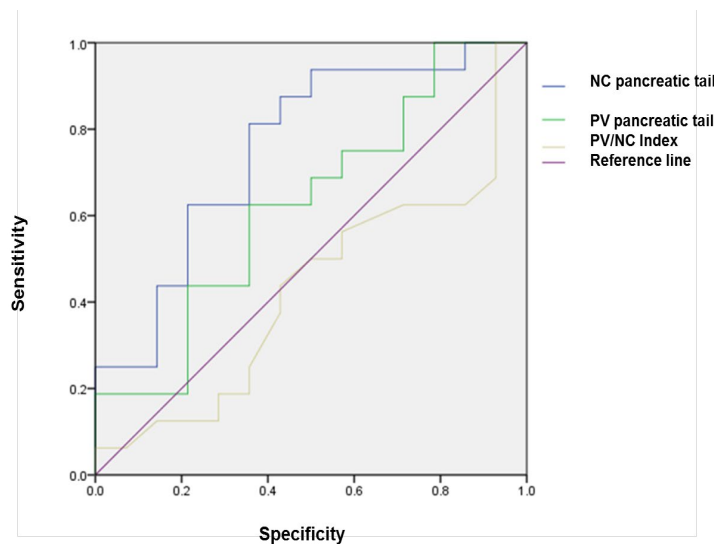

Figure 3: Receptor operating characteristic curve (ROC) of the radiographic density of the parenchyma in the tail of the pancreas. NC pancreatic tail density (AUROC 0.754; 95% CI 0.577-0.932; p = 0.018); pancreatic tail density in PV (AUROC 0.625; 95% CI 0.422-0.828; p = 0.244); PV / NC index (AUROC 0.426; 95% CI 0.216-0.636; p = 0.493).

Discussion

To this day, POPF remains a challenge in postoperative management in the PD surgery. It increases patient distress, prolongs hospitalization, and increases the cost of medical care. In high-volume centers, as the ones in this study, PD associated mortality has decreased to less than 5%, however, rates of POPF are still high and is a major determinant factor causing morbidity and mortality. A clinically relevant PF still occurs in 5 to 30% of cases despite all known efforts and remains the major cause of post-operative morbidity. Until know there are three studies that describe the enhancement characteristics on pre-operative CT as a method to estimate the risk of developing a POPF, Hashimoto Y. et al in 2011 showed that dual phase CT scan can be used as a tool

in the noninvasive assessment of pancreatic fibrosis similar to that achieved by immunohistochemically staining of histopathology specimens. They used the pancreatic enhancement ratio (L/E ratio), and ≤ 1.0 correlated with a soft pancreas, a small pancreatic duct, and an increased risk of developing a POPF [8]. Kang J. et al in 2017 evaluate the pre-operative CT and fecal elastase 1 levels to predict the development of PF after PD and concluded that the mean value of enhancement ratio on equilibrium phase was significantly higher in the patients without PF than patients with PF and was a predictor for the development of PF (odds ratio=0.243, p=0.002) and the mean pre-operative elastase 1 levels were higher in the PF patients ut no significant difference in ROC curve analysis [9]. Nahm C. et al in 2018 study the association between the density of the pancreas on pre-operative triple phase CT scan and the acinar score of the pancreatic margin and concluded that the parameters that demonstrated significant capacity to predict POPF were NC density in the pancreatic tail and the ratio of pancreatic tail densities between PV and NC phases. The PV/NC demonstrated in their study the greatest capacity to predict POPF (AUROC 0.712, p=0.030) with a cut-off value of <2.29, they also demonstrated that all CT parameters predictive of POPF significantly correlated with acinar, collagen and fat scores of the pancreatic margin and both tail NC and tail PV/NC correlated most strongly with the acinar score [10]. The present study took into consideration the result of Nahm C. et al to verify in our population the use of pre-operative CT as a tool to assess the pancreatic fibrosis to predict the development of POPF. In our study the CT parameter with the greatest capacity was NC in the pancreatic tail (AUROC 0.754; 95% CI 0.577-0.932; p = 0.018) with a cut off value of > 35HU, nevertheless neither of the CT parameters correlated with the histopathological scores probably related to the number of cases. It demonstrated that pre-operative pancreatic CT can be used to predict the development of POPF after PD and that simple non-contrast assessment of the density of the pancreatic tail can predict de development of POPF, although in our study it did not correlated with the acinar score and do not validate the significant association between the acinar score and the development of POPF as Nahm C. et al argues in his work nevertheless more patient must be included to verify this data

Contrast enhancement characteristics of the pancreas are reflective of the acinar cell density of the remnant because acinar cell rich pancreas are more vascular and rich in arterial venous shunts [12], taking up a greater volume of intravenous contrast in arterial phase, and subsequently demonstrating washout in portal venous phase [8]. Non-contrast CT radio density has also been demonstrated to be significantly higher in normal healthy acinar rich pancreas compared with the fibrotic acinar poor pancreas associated with chronic pancreatitis [13]. Therefore, an acinar rich remnant pancreas at high risk of POPF is likely to demonstrate greater radio density on non-contrast images as compared with a collagen rich fibrotic remnant pancreas al low risk of POPF.

In our study PV phase and NC/PV ratio was not shown to be predictive of POPF. This may be explained by the difference in the number of patients as well as the inter hospital and patient to patient variability in the timing and quality of post contrast image acquisition which affects the reproducibility of this parameters. All this favors the pancreatic tail NC parameter which does not require contrast enhancement.

One of the advantages observed in this study is that this method is of clinical relevance due to its simplicity, non-invasive characteristics, and availability in pre-operative evaluation. Since the use of an abdominal CT with contrast is a routine component in the preoperative evaluation of patients prior to pancreatic resection, this method of predicting POPF can be carried out in most patients without the need for additional studies. This method is also a highly valuable tool in patient counseling. Although the high-risk prediction of POPF may by itself affect the surgeon's recommendation for resection, it allows the patient to be advised and managed their expectations despite the risk of complications after pancreatic resection. The type of patients subjected to this procedure has a high post-operative morbidity that can be greatly impacted on the quality of life and limited prognosis inherent in the underlying disease. In addition, pre-operative quantitative assessment of pancreatic fibrosis may be helpful in stratifying patients for inclusion in clinical trials evaluating yet-to-be-determined techniques to decrease the risk of POPF. Our study has limitations. Clinical records were incomplete or not available for analysis neither all the cases had triple phase CT scan, limiting the sample size of the present study. There is need to validate these findings in a greater population, particularly owing the fact that there were a low number of patients who developed POPF.

Conclusion

This study showed that non- contrast pancreatic tail enhancement characteristics are predictive of the development of POPF after pancreatoduodenectomy in our study population. CT enhancement characteristics of the pancreatic tail specifically may be useful in pre-operative risk stratification, patient counseling, and to help direct the pre and post-operative patient care.

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