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Pancreatic Configuration Index in Predicting Postoperative Pancreatic Fistula in a Tertiary Care Center in Nepal

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ABSTRACT

Background: Post-operative pancreatic fistula is the single most common and most significant cause of post-operative morbidity and perioperative mortality. Identification of at risk patient preoperatively help to take policy of extra vigilance to act on time. This study evaluated the predictive role and cut-off value of pancreatic configuration index to predict post-operative pancreatic fistula.

Methods: This was a prospective observational study in patients who had undergone pancreaticoduodenectomy from March 2017 to June 2018 at Tribhuvan University Teaching Hospital, Kathmandu, Nepal. The patients with age <16 years, those who underwent re-exploration or mortality before 3rd postoperative day, additional surgery besides pancreaticoduodenectomy were excluded from the study. Pancreatic configuration index was calculated as a ratio of pancreatic parenchymal thickness and pancreatic duct diameter. Predictive value of pancreatic configuration index in predicting post-operative pancreatic fistula was evaluated.

Results: Among 58 patients, 9 were excluded from study and 49 patients were included in the study. The mean age of the patients was 56.6 ± 13.9 years (21 to 79 years) and male to female ratio was 1.1:1 (26 vs 23). Post-operative pancreatic fistula developed in 13/49 (26.5%) patients. On both univariate and multivariate analysis, pancreatic texture (p = 0.022), main pancreatic duct diameter at neck (p = 0.002) and pancreatic configuration index (p = 0.001) were significantly associated with development of post-operative pancreatic fistula. The sensitivity and specificity of pancreatic configuration index to predict post-operative pancreatic fistula are 92.3% and 91.7% with positive predictive value of 80% and negative predictive value of 97.1%.

Conclusions: Pancreatic configuration index is a useful preoperative predictor of post-operative pancreatic fistula after pancreaticoduodenectomy.

Keywords: Pancreaticoduodenectomy; pancreatic configuration index; postoperative pancreatic fistula.

INTRODUCTION

Postoperative pancreatic fistula (POPF) is the single most significant cause of morbidity and mortality.[1] Post pancreaticoduodenectomy hemorrhage, delayed gastric emptying and intra-abdominal abscess are sequelae of POPF.[2-4] Thus, it is important to identify high risk patients.

Different studies have identified male gender, high BMI, soft pancreas, intraoperative bleeding > 1000 ml, pancreatic duct size, pancreatic texture, and drain fluid amylase >4000U/L on postoperative day 1 as predictor of POPF.[5-7] Yokoyama et al studied pancreatic configuration index (PCI), which was calculated by dividing axial thickness of pancreas by pancreatic duct diameter, and PCI ≥ 5 identified as an independent risk factor for POPF.[8]

Parameters used to calculate PCI are organ (pancreas) specific and can be measured preoperatively using computed tomography. Thus, we can predict POPF preoperatively in patients undergoing pancreaticoduodenectomy (PD). Preoperative prediction of POPF guide us for selective use of octreotide,

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taking extra measures (e.g. placement of stent in pancreaticojejunostomy, preoperative adequate nutritional supplementation, taking extra vigilance to act on time in high risk patients and ERAS protocol in low risk patient. We can also counsel patient and their relatives about risk of the procedure. Therefore, this study was aimed to analyse the preoperative predictive value of PCI for POPF after PD in Nepalese population at Tribhuvan University Teaching Hospital (TUTH).

METHODS

This was a prospective observational study conducted from March 2017 to June 2018 in the Department of GI and General Surgery, TUTH, Kathmandu, Nepal. Approval was taken prior to study from Institutional Review Board of the institute. All patients who underwent PD were included in the study. Patients with age <16 years, mortality or re-exploration before 3rd POD, and those who underwent additional surgeries along with PD were excluded from study. Age <16 years were excluded from the study because those patients were managed by pediatric surgeon. Clinical history, physical examination and investigations were recorded preoperatively in the preformed pro-forma.

Preoperative pancreatic protocol CECT abdomen was studied and maximum thickness of pancreatic parenchyma and pancreatic duct diameter at pancreatic neck (transection line in pancreaticoduodenectomy in front of portal vein) in axial section was measured in millimeters as stated in the study done by Yokoyama et al.[8] PCI was calculated by dividing maximum thickness of pancreatic parenchyma by main pancreatic duct diameter at pancreatic neck (Figure 1) and it was recorded.

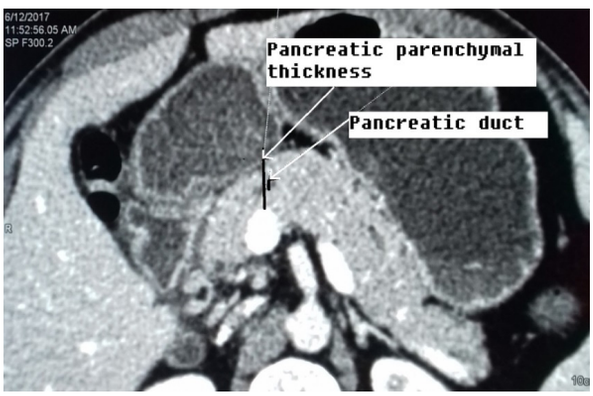

Figure 1. Axial CT scan in portal venous phase measuring pancreatic parenchymal thickness and pancreatic duct diameter at the neck of the pancreas.

Patients were admitted at least 2 days prior to surgery. Preoperative assessment and study variables were recorded. All pancreaticoduodenectomies were performed in four GI surgery units by four trained gastrointestinal surgeons at TUTH. Pancreaticojejunostomy were performed by end to end dunking method. Braun's jejunojejunostomy was performed in all cases after loop gastrojejunostomy. The left abdominal drain was placed close to the pancreaticojejunostomy and right drain near the hepaticojejunostomy in Morrison's pouch. Octreotide (100 µg subcutaneous) was given in all cases starting before pancreatic transection and continued 8 hourly for at least 5 days postoperatively. Drain amylase was checked in 3rd POD to determine whether POPF developed or not. Nasogastric tube was removed and sips started on either 2nd or 3rd POD. Right drain was removed on 3rd to 5th POD and left drain on 5th to 7th POD after the exclusion of POPF, PPH, biliary or intestinal fistula.

Death within the same hospital admission or within postoperative day 30 was considered as perioperative mortality. Postoperative complications were reported according to Clavién Dindo classification adopted for pancreatic surgery and ≥ 3 were considered severe postoperative complication.[9] According to International Study Group for Pancreatic Surgery (ISGPS) (2016), postoperative pancreatic fistula was defined as a drain output of any measurable volume of fluid with amylase level greater than 3 times the upper institutional normal serum amylase level, associated with a clinically relevant development/condition related directly to the POPF. Grade A POPF was regarded as biochemical leak and only Grade B and C were defined as clinically relevant POPF.[10] Biliary leakage was defined as bilirubin concentration in the drain fluid at least 3 times the serum bilirubin concentration on or after POD 3.[11] DGE and PPH were defined according to ISGPS definitions.[12, 13]

The results were expressed in either mean ± SD or median (range) for the quantitative data and differences between 2 groups were compared using student *t*-Test as parametric test and Mann-Whitney U-Test as nonparametric test. The categorical data were expressed in number (percentage) and compared between two groups using x^2 test (parametric test) or Fisher's exact test (nonparametric test). The predictive value of the PCI for predicting POPF was assessed using a receiver operating characteristic (ROC) curve analysis. The area under the ROC curve (AUC) and the cut-off value of PCI evaluated using ROC curve analysis. Variables which have a significant association with POPF in univariate analysis were analysed in multivariate logistic regression analysis to examine the relationship between the POPF and individual variable independently. The *P* value < 0.05 was taken as statistically significant. All data were analysed using SPSS (version 23.0).

RESULTS

During study period of 15 months, 58 pancreaticoduodenectomy were performed. Among 58 PD, 9 were excluded and 49 PD were included in the study. There were 26 (53.1%) males and 23 (46.9%) females among 49 included cases. The demographic and clinical characteristics of the patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients

Characteristics	Values
Age (years)	56.59 ± 13.93
Gender	
Male	26 (53.1%)
Female	23 (46.9%)
BMI	21.79 ± 3.93
Jaundice	39 (79.6%)
Hypoalbuminemia	21 (42.9%)
Pathology	
Malignant	45 (91.8%)
Non-malignant	4 (8.2%)
Disease origin	
Pancreatic origin	19 (38.8%)
Non-pancreatic origin	30 (61.2%)

The most common indication of PD was ampullary adenocarcinoma which was seen in 19 (38.8%) patients (Figure 2).

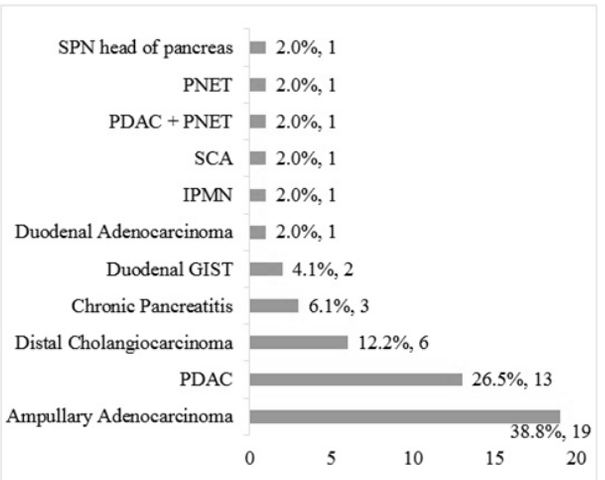

Figure 2. Different pathologies as an indication of pancreaticoduodenectomy.

Clinically relevant Postoperative pancreatic fistula (POPF) developed in 13 (26.5%) patients (grade B in 10 and grade C in 3 patients). PPH developed in 7 (14.2%) patients, DGE in 13 (26.5%), and severe post-operative complications (Clavién Dindo classification ≥ 3) in 11 (22.4%) patients. Among all grade B POPF (10 patients), DGE was present in 9 patients, PPH in 5 patients, intra-abdominal collection in one patient who required percutaneous drainage, and burst abdomen in 1 patient. Among grade C POPF (3 patients), 2 patients underwent re-exploration for PPH and one patient died because of sepsis. There were 5 (10.2%) mortalities, however, 2 cases were POPF related mortality, one mortality due to cardiac arrhythmia, and 2 mortalities due to hospital acquired pneumonia.

On univariate analysis of the different variables, pancreatic parenchymal thickness was not significantly associated with development of POPF, however, ratio of pancreatic parenchymal thickness and pancreatic duct diameter (PCI) was significantly associated with development of POPF. Other than PCI, pancreatic duct diameter, and pancreatic texture were significantly associated with development of POPF (Table 2).

Table 2. Association of different variables with development of POPF.

Variables	POPF		p-value
	No	Yes	
Age (years)	57.4 ± 12.6	54.3 ± 17.5	0.77
Gender			**0.21**
Female	15 (65.2%)	8 (34.8%)	
Male	21 (80.8%)	5 (19.2%)	
BMI	21.5 ± 4.2	22.5 ± 3.1	0.34
Jaundice			**0.06**
Absent	5 (50%)	5 (50%)	
Present	31 (79.5%)	8 (20.5%)	
Albumin (mg/dl)	33.8 ± 9.7	37.1 ± 6.3	0.22
Pan Thick (mm)	15.8 ± 5.1	17.4 ± 4.7	0.22
PD (mm)	5.3 ± 2.4	3 ± 0.9	0.002
PTx			**0.022**
Soft	11 (55%)	9 (45%)	
Firm/Hard	25 (86.2%)	4 (13.8%)	
PCI	3.4 ± 1.3	6 ± 1.5	0.001
OpTime (min)	411.2 ± 69.1	360.8 ± 77.1	0.06
Blood loss (ml)	350 (200-900)	400 (200-1000)	0.44
Pathology			**0.74**
Pancreatic	15 (78.9%)	4 (21.1%)	
Non-pancreatic	21 (70%)	9 (30%)	

Pan Thick= pancreatic parenchymal thickness, PD = Pancreatic duct diameter, PCI = Pancreatic configuration index, PTx = Pancreatic texture, OpTime = Operative time. Categorical data expressed in number (%) and continuous data in mean ± SD or median (range). $p < 0.05$ is statistically significant

PCI, pancreatic duct diameter, and pancreatic texture were also significantly associated with development of POPF on multivariate analysis (Table 3).

Table 3. Multivariate analysis of PCI, pancreatic duct and pancreatic texture.

Characteristics	Odds ratio (95% CI)	p-value
PCI	4.853 (1.346-17.499)	0.001
Pancreatic duct	0.866 (0.319-2.349)	0.002
Pancreatic texture	5.759 (0.799-41.525)	0.015

p< 0.05 is statistically significant

The ROC curve analysis of PCI to predict POPF showed the AUC of 0.956 (p = 0.001, 95% CI = 0.900-1.000) (Figure 3). Considering cut-off point of PCI 4.95, this test showed sensitivity of 92.3%, specificity of 91.7%, positive predictive value of 80%, and negative predictive value of 97.1%.

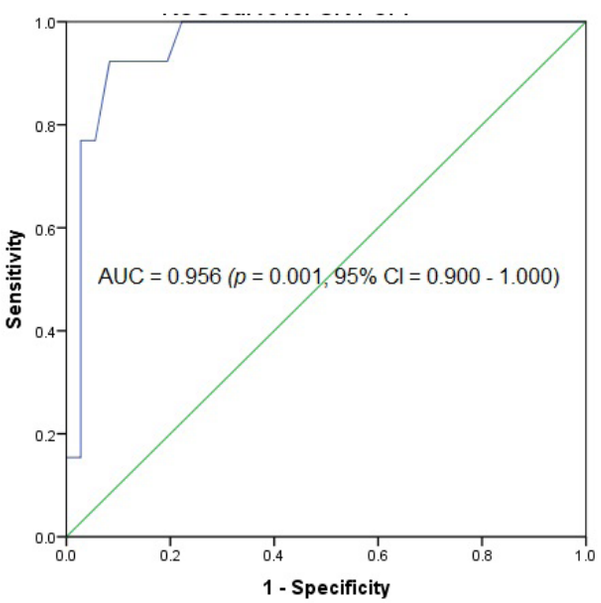

Figure 3. The ROC Curve of pancreatic configuration index to predict postoperative pancreatic fistula.

All the patients were grouped into low risk (PCI < 5) and high risk (PCI ≥ 5) groups and different variables were analysed between these two groups. Other than POPF, small pancreatic duct diameter (≤ 5 mm), PPH and severe postoperative complication were significantly common in high risk group. However, there were no differences in texture of the pancreas, and mortality between high risk and low risk group (Table 4).

Table 4. Association of PCI with different variables.

Variables	PCI		p-value
	< 5 (n = 34)	≥ 5 (n = 15)	
POPF			0.001
Present	1 (7.7%)	12 (92.3%)	
Absent	33 (91.7%)	3 (8.3%)	
Pancreatic duct (mm)			0.02
≤ 5	20 (57.1%)	15 (42.9%)	
> 5	14 (100%)	0 (0%)	
Pancreatic Texture			0.24
Soft	12 (60 %)	8 (40%)	
Firm/hard	22 (75.9%)	7 (24.1%)	
PPH			0.002
Present	1 (14.3%)	6 (85.7%)	
Absent	33 (78.6%)	9 (21.4%)	
Severe postoperative complication			0.01
Present	3 (27.3%)	8 (72.7%)	
Absent	31 (81.6%)	7 (18.4%)	
Mortality			0.635
Present	3 (60 %)	2 (40%)	
Absent	31 (70.5%)	13 (29.5%)	

p < 0.05 is statistically significant

DISCUSSION

Pancreatic thickness and main pancreatic duct diameter at neck of pancreas are independent risk factors for the development of POPF.[14] Though pancreatic duct diameter is associated with development of POPF, pancreatic thickness is not associated with POPF in our study. Therefore, combination of more than one indexes to predict POPF is more powerful. Yokoyama et al combined these 2 indexes (the axial thickness and main pancreatic duct diameter at neck on CT scan) to calculate pancreatic configuration index (PCI) by dividing pancreatic thickness with main pancreatic duct diameter in millimeters. The PCI level may represent the pancreatic exocrine function, and the patients with higher pancreatic exocrine function may have a higher risk of developing POPF after PD.[8]

Yokoyama et al studied PCI value of 5.3 as a cut-off

point in ROC curve analysis which has sensitivity of 79%, specificity 64.5%, positive predictive value of 45%, negative predictive value of 89% with area under the ROC curve = 0.749. His study showed PCI of ≥ 5 as an independent risk factor in multivariate analysis.[8] In our study, the ROC curve analysis showed AUC for PCI to predict POPF was 0.956 (p= 0.001, 95% CI = 0.900-1.000). Considering cut-off value of PCI = 4.95 in the ROC curve analysis to predict POPF, this test has sensitivity of 92.3%, specificity 91.7%, positive predictive value = 80%, negative predictive value = 97.1%. Compared to the study by Yokoyama et al, our study showed higher sensitivity and specificity of PCI to predict POPF. His study was retrospective in nature and there is heterogeneity in the management, for example, use of pancreatic duct stent in selected cases, inclusion of patients who underwent portal vein resection, performance of different types of PD (pylorus preserving PD, subtotal stomach preserving PD, classic PD) and pancreaticojejunostomy (duct to mucosa and invagination).[8] This could be the reason that PCI is a better predictor in our study. Our study also showed high risk patients (PCI ≥ 5) had higher severe postoperative complications after PD.

The benefit of PCI is that it can be calculated by using preoperative variables instead of intra/postoperative variable and it is objective assessment unlike parenchymal texture which is subjective assessment and vary surgeon to surgeon.[15] However, measurement of pancreatic parenchymal thickness and pancreatic duct diameter is more accurate in console of CT room rather than measuring in the CT film. Thus, the drawback of PCI is that, either CT scan should be done in the same hospital or recorded file should be available. This is single centered study and needs multicentered prospective study to generalise results.

The POPF rate has been reported from 12% to 32.7% in the studies.[16-19] In our study, POPF rate was 26.5% which is similar to the study done by Kajiwara T et al (2010) in Japan.[17] DGE has been reported from 19% to 57% in the literature.[12, 20] In our study, DGE were observed in 13(26.5%) patients which is similar to other study.[17] PPH is an uncommon complication after PD but this is one of the major cause of peri-operative mortality.[21] The incidence of PPH and perioperative mortality have been reported from 4% to 16% and 11% to 54% respectively.[21-23] In our study, PPH developed in 7 (14.2%) and mortalities in 5 (10.2%) patients.

Soft texture of the pancreas is associated with fatty infiltration which has decreased mechanical resistance at the anastomosis site and increased lipolytic effect with pancreatic enzymes. Thus, soft pancreatic texture is a high risk of developing POPF.[24] Besides soft pancreas, small main pancreatic duct, thickened pancreatic parenchyma, blood loss, and pathology of non-pancreatic origin (compared with pancreatic origin pathology) were studied as risk factor for the development of POPF.[5-8,16] In our study, soft pancreatic texture (p = *0.022)*, small pancreatic duct (p = 0.002) were significantly associated with development of POPF. The duration of surgery, intra-operative blood loss, and pathology of origin (pancreatic vs non-pancreatic) were not associated with development of POPF in our study.

CONCLUSIONS

Pancreatic configuration index is an excellent preoperative test to predict POPF in patients undergoing pancreaticoduodenectomy. High pancreatic configuration index is associated with increased risk of development of POPF.

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