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Role of Pancreatic Attenuation Index in Assessing Pancreatic Fat Content and Postpancreatectomy Outcomes

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Abstract

Background High fat content of pancreas can contribute to its soft texture, which is a strong predictor for postoperative pancreatic fistula (POPF). We propose to assess the relationship of pancreatic computed tomography (CT) attenuation index (PAI) with histopathological fat content of pancreas and postpancreatectomy outcomes.

Methodology Data was collected prospectively from patients who underwent pancreatic resections from February 2021 to January 2023. CT attenuation was measured in pancreas and spleen in three regions of interest each. The mean of the three values was taken as the mean pancreatic attenuation (P) and splenic attenuation (S). PAI was calculated (P-S and P/S) preoperatively. The fat content was calculated histologically in resected specimens. The pancreatic texture was also assessed intra-operatively by the operating surgeon to classify it as soft or firm. The relationship of PAI with fat content and postpancreatectomy outcomes such as delayed gastric emptying (DGE), postpancreatectomy hemorrhage (PPH) and POPF was assessed.

Results Seventy patients underwent pancreatic resections of which 59 were taken for analysis after satisfying the exclusion criteria. The PAI ranged from P-S (-23 to +19) and P/S (0.54–1.5). The histologic fat content of pancreas ranged from 0.4 to 42% (mean= 9.5076/standard deviation: 9.19520). Significant correlation was found between P-S and P/S (Spearman's rank correlation coefficient $\rho = -0.775$[95% confidence interval [CI]: −0.919 to −0.583], −0.743[95% CI: −0.896 to −0.467]) with pancreatic fat content. Postpancreatectomy outcomes noted were POPF(B/C):13, DGE:33, and PPH:3. Statistical significance was not seen between PAI and postpancreatectomy outcomes (POPF, $p = 0.067$ DGE; $p = 0.456$; PPH, $p = 0.891$).

Conclusion PAI may be used as a reliable tool in predicting pancreatic fat content. However, it did not show a statistically significant association in predicting postpancreatectomy outcomes.

Keywords
- pancreatic attenuation index
- postoperative pancreatic fistula
- pancreatic steatosis

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Introduction

Global prevalence of obesity is more than 650 million and coming to the Indian scenario it is 135 million.[1] The major health hazard associated with obesity is visceral fat deposition, which can lead to various metabolic complications.

Pancreatic steatosis is a by-product of visceral fat deposition. The clinical significance of pancreatic steatosis is the acquired proinflammatory status of the pancreas.[2]

In the early 1960s, the morbidity and mortality associated with pancreatic surgery were 60 and 25%, respectively. Presently, the mortality has reduced to 2 to 5%, but the morbidity remains almost the same.[3] Postoperative pancreatic fistula (POPF) is one among the dreaded complications associated with pancreatic surgeries. The texture of pancreas is a strong contributing risk factor. Clinically significant POPF (grade B/C) is seen in 11 to 37% of patients with soft pancreas and 1 to 6% patients with firm pancreas.[4–7] Fat deposition in pancreas (pancreatic steatosis) translates to a soft pancreas. The gold standard for the identification of pancreatic texture is intraoperative palpation by an experienced surgeon.[8]

Various imaging modalities can be used to predict pancreatic texture like ultrasonography (USG), magnetic resonance imaging (MRI), and computed tomography (CT). USG can assess the echogenicity as well as utilize the concept of elastography. MRI can detect the level of fibrosis in pancreas by various methods. Generally, pancreas is hyperintense in T1-weighted images and this can be lost in significant fibrosis. Diffusion-weighted images and MR elastography can also aid in the assessment.

Liver attenuation index has been widely used by radiologists to assess the fat content in the liver. Kim et al have shown the utilization of pancreatic attenuation index (PAI) to assess the fat content in pancreas.[9] A CT abdomen is a part of standard workup for pancreatic surgeries and it can aid us get a preoperative assessment of the fat content of the pancreas.

Methodology

This is a prospective observational study undertaken in our department from February 2021 to January 2023. The study was initiated after getting clearance from the institutional ethics committee and informed consent was taken from the study participants.

Inclusion criteria: Consecutive patients who underwent any type of pancreatic resections during the study period such as Whipple procedure, distal pancreatectomy (DP), median pancreatectomy, and Whipple + DP were included. Data of these patients were prospectively collected that included preoperative, intraoperative, and postoperative parameters. Patients with chronic calcific pancreatitis, diffuse pancreatic atrophy, severe ductal dilatation, and tumor infiltration that preclude histological or radiological assessment were excluded.

1. Radiology study tool
   The patients planned for resection underwent contrast-enhanced CT with pancreatic protocol. The CT was taken with a multidetector row CT unit (Gold seal Optima CT 660; GE Healthcare System, Boston, United States). Scans were triggered using the bolus tracking technique when the threshold of 150 Hounsfield unit was reached in the upper abdominal aorta. Contrast-enhanced scans included late arterial phase at 30 to 40 seconds from the start of contrast injection (12–15 seconds after bolus tracking), portal venous phase at 60 to 70 seconds (25–30 seconds delay after the arterial phase), and equilibrium phase at 3 minutes from contrast injection. The plain and contrast-enhanced images were reconstructed at 3 mm thickness. The CT images were viewed in revolution EVO image viewer (GE Healthcare System, Boston, United States) and were reviewed by a designated radiologist of more than 25 years experience. The plain CT and contrast images were viewed side by side. The PAI was measured in the prospective pancreatic specimen distal to (for DP) or proximal to (for Whipple procedure) the line of resection in plain CT images. CT attenuation values were measured in nontumorous pancreatic tissue at three sites average size of 10 to 30 mm^2 (►**Fig. 1**). The plain CT images were compared with the contrast-enhanced images in arterial, portal and equilibrium phases to avoid vascular structures and pancreatic duct, which may result in wrong interpretation. Mean of the three values were taken as the mean pancreatic attenuation. Three similar areas were selected in the spleen and mean splenic attenuation was calculated.
2. Pathology study tool
   The resected specimens were evaluated by a designated pathologist of more than 10 years experience. The pathologist was blinded to the intraoperative pancreatic texture and PAI. The specimen was grossed and nontumorous area adjacent to the line of resection was analyzed. Formalin fixed paraffin embedded sections were taken and stained with hematoxylin and eosin. The slides were examined using light microscope (Labomedlx 500, Labomed, Inc., Los Angeles, United States) in scanner view, low power and high power for intralobular and interlobar fat (►**Fig. 2**). The fat-laden areas were identified in low power and confirmed in high power (►**Fig. 3**). Three random areas were taken and the images were uploaded. The uploaded images were assessed with Adobe Photoshop[R] CS6 (Adobe Systems Inc., San Jose, California, United States). The quantitative measurement of the fat content was calculated using the measurement log tool (►**Fig. 4**). The area of fat in each image was calculated and the average was taken as the mean pancreatic fat content.
3. Perioperative assessment tools
   Preoperative demographic data including age, gender, body mass index (BMI), pancreatic duct diameter (measured radiologically), preoperative diabetic status, and American Society of Anaesthesiologists (ASA) grade were recorded. Intraoperatively, pancreatic texture was assessed by an operating surgeon of more than 25 years experience. Other details such as blood loss, duration of surgery, and the procedure done were also recorded. Pancreas-specific complications like POPF, delayed gastric emptying (DGE), and postpancreatectomy hemorrhage (PPH) were noted based on International Study Group

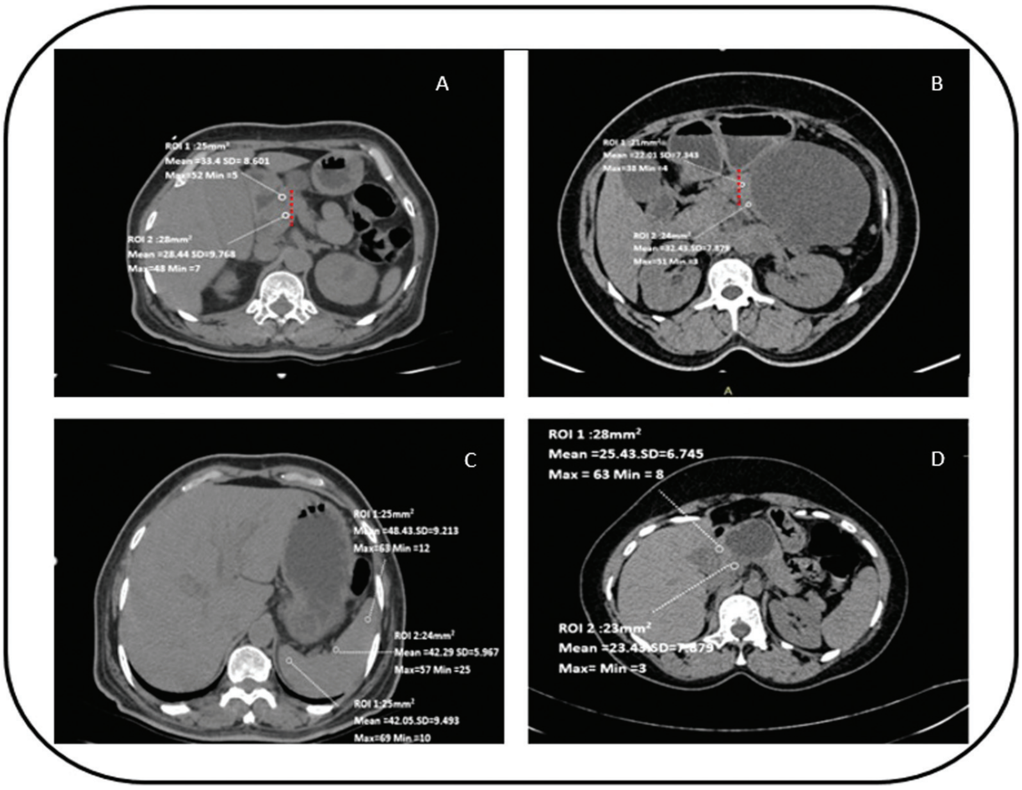

Fig. 1 The calculation of CT attenuation index. (**A, B,** and **D**) Hounsfield unit (HU) of pancreas in plain phase. (**C**) HU of spleen in plain phase. *Red line denoted the line of transection (PAI) was calculated by utilizing the same technique of Kim et al.[9] CT, computed tomography; P, mean pancreatic attenuation; PAI, pancreatic attenuation index; S, mean splenic attenuation. P-S and P/S are the pancreatic CT attenuation indices.

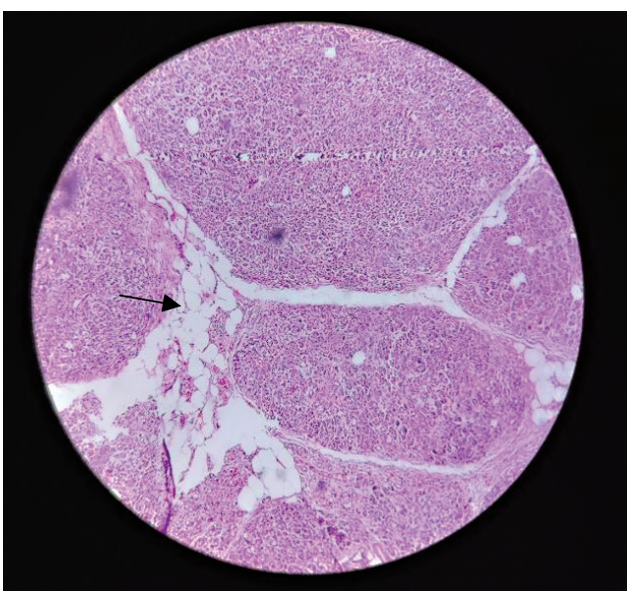

Fig. 2 Fat lobules in low power.

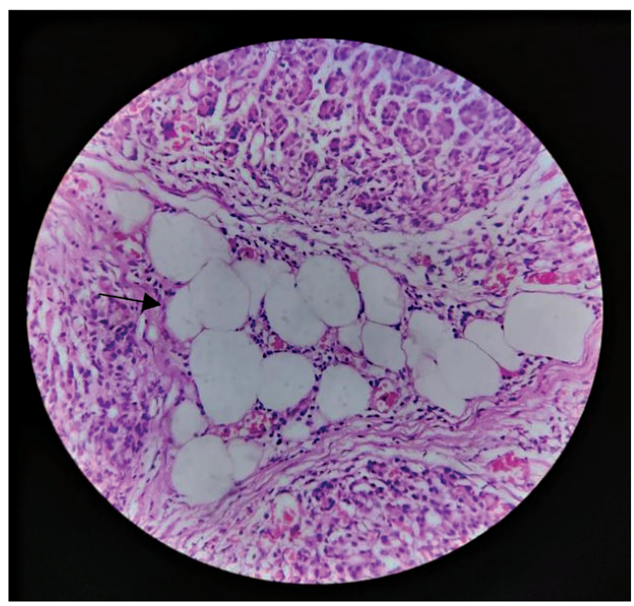

Fig. 3 Confirmation of the fat in high power.

of Pancreatic Surgery (ISGPS) definitions and guidelines.[10–12] The morbidity grading was done according to Clavien Dindo grading.[13]

Statistical Analysis

Data was entered into Microsoft Excel (Microsoft Inc. Redmond, United States) and analyzed using SPSS 27(IBM Inc. Endicott, New York, United States). Quantitative variables were summarized as mean and standard deviation. Qualitative variables were summarized as proportions. The normality of continuous data was assessed by the Kolmogorov–Smirnov test. Spearman correlation coefficient(ρ) was used to assess the correlation between PAI with POPF as well as pancreatic texture and 95% confidence intervals were

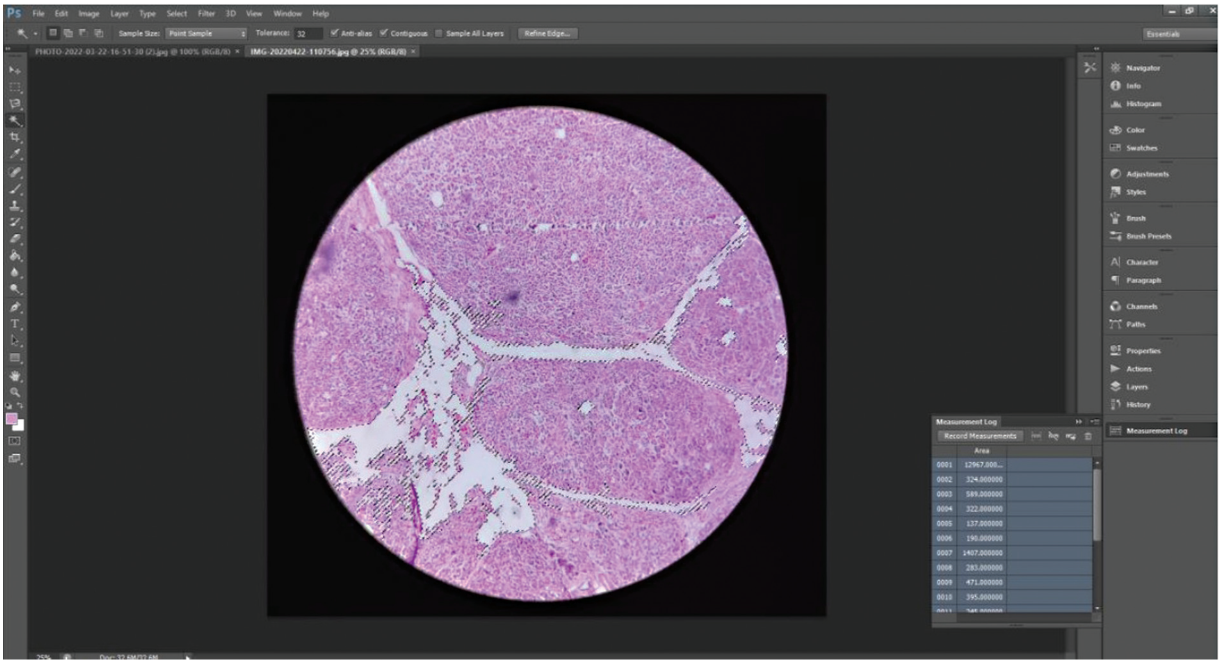

Fig. 4 Calculation of fat-filled area using Adobe photoshop CS.[6]

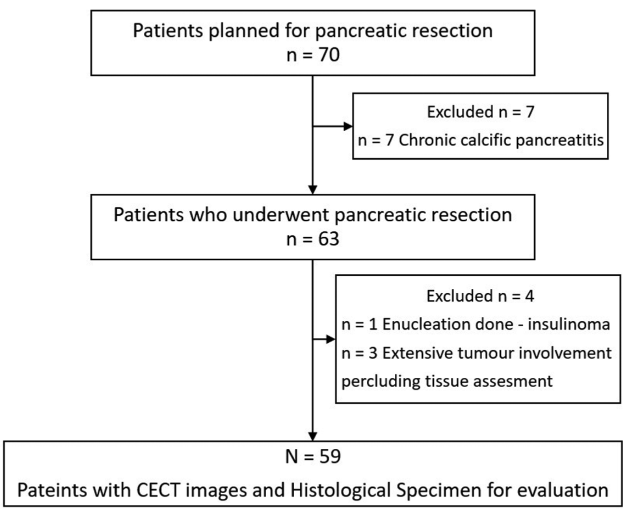

Fig. 5 Inclusion flowchart.

calculated. Receiver operating characteristic (ROC) curve was plotted for PAI with pancreatic texture and POPF. ROC curves were plotted for pancreatic fat content with pancreatic texture and POPF. Cutoff values were calculated on the basis of the maximum values of the Youden index, calculated by [sensitivity + specificity – 1]. Chi-squared test was used to study the association between categorical values. *p*-Value less than 0.05 was considered significant.

Results

Seventy patients underwent pancreatic resections during the study period, out of which 11 were excluded (Chronic Calcific Pancreatitis, CCP: 7, enucleation: 1, and inadequate normal pancreas in specimen: 3). The age group ranged from 19 to 77 years with a mean age of 49.4. The demographic details are detailed in ►**Table 1**.

The P-S ranged from −23 to19 (mean: −6.72/standard deviation [SD]: 7.856) and P/S ranged 0.54 to 1.5 (mean: 0.8473/SD: 0.157). Pancreatic fat content ranged from 0.4 to 42% (mean: 9.5076 /SD: 9.19520). PAI and fat percentage showed a non-normal distribution pattern. Intraoperative palpation revealed soft pancreas in 35 and firm pancreas in 24 patients.

The Spearman correlation study showed a significant correlation of PAI (P-S and P/S) with pancreatic fat, ρ: −0.743 (95% CI: 0.919 to 0.583) (p=0.02) for P-S and 0.775 (95% CI: 0.896 to 0.467 (p=0.001) for P/S (►**Fig. 7**). This was in similar to that of the pilot study by Kim et al9 that had ρ-Value of 0.622 for P-S and 0.616 for P/S.

PAI and POPF did not show a statistically significant relationship on assessment by Mann–Whitney U test. A statistically significant association was not seen with DGE and PPH. Preoperative factors like diabetic status, BMI, or the pathology of the tumor did not show any statistical significance with POPF in our study. A multivariate logistic regression analysis was done for identifying factors contributing to POPF. However, no statistically significant association could be demonstrated.

Thirty-five patients had soft pancreas and 24 had firm pancreas. A statistically significant association was seen between P-S and P/S with pancreatic texture. A ROC was plotted for PAI with pancreatic texture (►**Fig. 6A**). The area under the curve (AUC) are 0.775 (*p*-value =0.023) and 0.786 (*p*-value =0.012), respectively. The cut-off value obtained for P-S for predicting pancreatic texture was 4.65; it was having 74% sensitivity and 80% specificity in predicting the texture of pancreas. Likewise, a P/S value of 0.89 has a sensitivity of 80% and specificity 60%.

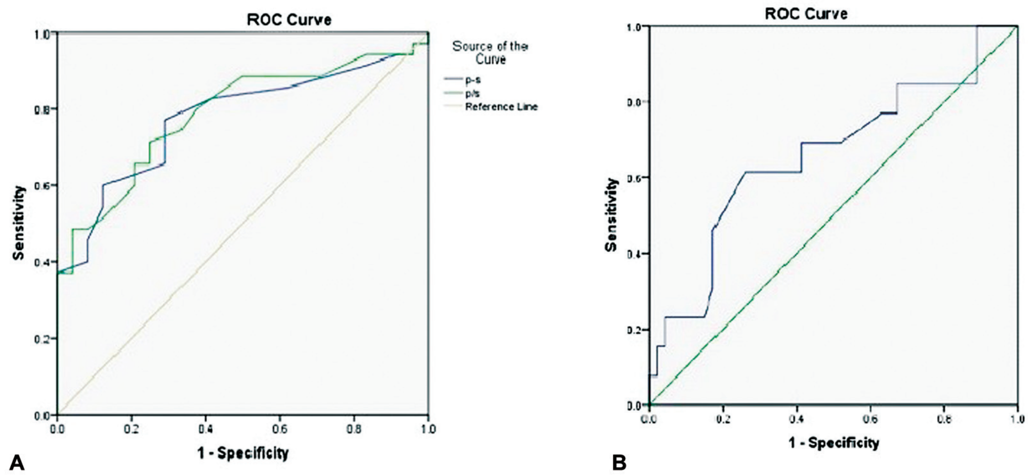

Fig. 6 (**A**) Receiver operating characteristic (ROC) curve plotted for pancreatic attenuation index (PAI) and pancreatic texture. (**B**) ROC curve plotted for pancreatic fat and postoperative pancreatic fistula. P, mean pancreatic attenuation; S, mean splenic attenuation.

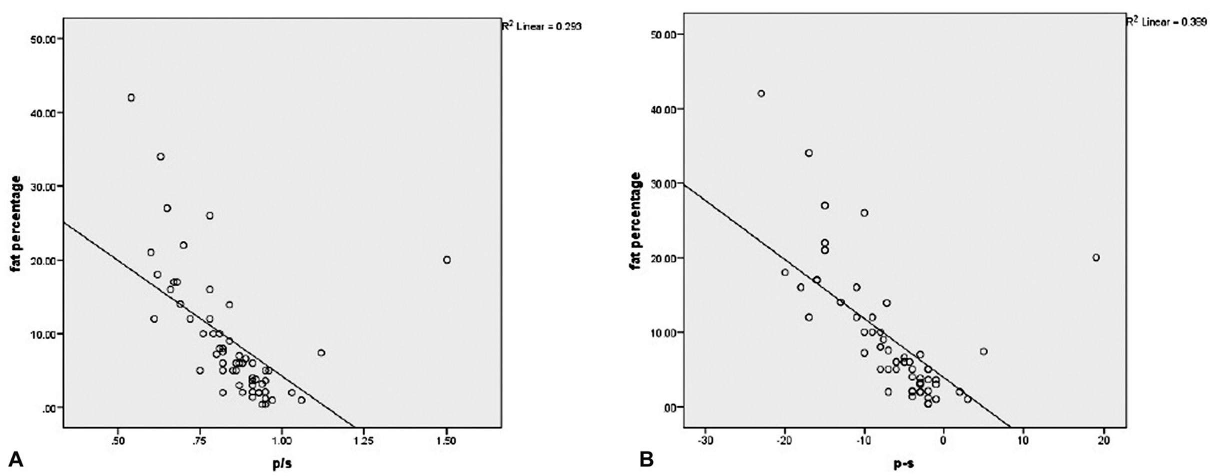

Fig. 7 Scatterplots and regression lines showing correlations between pancreatic fat fraction and PAI. (**A**) P-S = –0.743. (**B**) P/S = –0.775. P, mean pancreatic attenuation; PAI, pancreatic attenuation index; S, mean splenic attenuation.

The pancreatic fat content showed an association with POPF ($p = 0.038$). An ROC was plotted with pancreatic fat content in X axis and POPF in Y axis (►**Fig. 6B**). The AUC was 0.657. A cutoff value of 6.2% for pancreatic fat content showed 69% sensitivity and 59% specificity identifying clinically significant POPF. The pancreatic fat content also showed a statistically significant association with texture of pancreas ($p = 0.004$).

Discussion

This study showed a strong correlation between PAI with pancreatic fat content. The ρ-value obtained in our study for PAI (P-S and P/S were –0.743 and –0.775, respectively) shows a better correlation compared with the study by Kim et al that had ρ-value of –0.622 for P-S and –0.616 for P/S(9). Gnanasekaran et al used PAI and pancreatic enhancement ratio (PER) in predicting POPF. PER is a marker of pancreatic fibrosis. In their study, PAI did not show any association with pancreatic fat or POPF, while PER was found to be helpful in predicting POPF.[14] Kusafuka et al used pancreatic–visceral CT attenuation ratio and a value of more than 0.40 was significant risk factor of POPF. Both studies quoted before assumed that lower pancreatic CT attenuation denotes a fatty pancreas. In contrast, the study by Ohgi et al found that higher pancreatic attenuation was seen in cases of POPF.[15] The precision of CT-guided risk calculation of pancreas may be improved by using other imaging modalities like ultrasound shear wave elastography (USWE) and MRI. Sushma et al noted that USWE values are lower in patients who had POPF and may help in predicting soft pancreas.[16] Many studies have shown the value of MRI in the assessment of pancreatic fibrosis that indirectly indicates a firm pancreas.[17] Our study observed a significant association for PAI and fat content with pancreatic texture and we were able to derive cutoff values for the prediction of the same. In our study, pancreatic fat content showed association with POPF (p-value = 0.038). A meta-analysis by Zhou et al also showed that high pancreatic fat content can lead to POPF.[18] Hence, a preoperative identification of a fatty pancreas may act as a surrogate marker of a soft pancreas that is a strong risk factor for POPF.

Table 1 Demographic characteristics

	$n = 59$
Age	19–77 (mean: 49.44)
Gender: M/F	30/ 29
Diagnosis	
Ampullary CA	15 (25%)
CA duodenum	12 (20%)
Cystic neoplasm	13 (22%)
Neuroendocrine tumor	9 (15%)
PDAC	7 (11.9%)
Others[a]	3 (5%)
Preoperative diabetes mellitus (yes/no)	30 / 29
BMI (kg/m2)	18.1–31 (23.97)
PAI P-S	−23 to 19 (mean: −6.72/SD: 7.856)
PAI P/S	0.54–1.5 (mean: 0.8473/SD: 0.157)
Pancreatic fat percentage	0.4–42 (mean: 9.5076/SD: 9.19520)
Procedure: PPPD/PD/DP/MVR/DPS +PPPD	26/12/17/2/2
Pancreatic texture judged (firm/soft)	34 (soft)/25 (firm)
Duration of surgery	364–580(mean: 421/SD: 101.3)
Intraoperative blood loss (mL)	50–550 mL (191 mL)

Abbreviations: CA, carcinoma; MVR, multivisceral resection; P, mean pancreatic attenuation; PAI, pancreatic attenuation index; PDAC, pancreatic ductal adenocarcinoma; PPPD, pylorus preserving pancreaticoduodenectomy; S, mean splenic attenuation; SD, standard deviation.
[a]Others account for diagnosis like benign etiology and low-grade or high-grade dysplasia.
Note: The details of postoperative morbidity are listed in ►**Table 2**.

Table 2 Postoperative complications

Postoperative complications	Incidence $n = 59$
DGE	33
POPF (B/C)	13
PPH	3
GJ/DJ leak	0
Bile leak	2
Intra-abdominal collection requiring drainage	6
SSI	12
Relaparotomy	2
Portal vein thrombosis	0
Renal failure	1
Hepatic dysfunction	1
Autonomic dysfunction	1
Myocardial infarction	1
Postoperative pancreatitis	3
Clostridium difficile colitis	1
90-day mortality	2

Abbreviations: CI, confidence interval; DGE, delayed gastric emptying; DJ, duodenojejunostomy; GJ, gastrojejunostomy; P, mean pancreatic attenuation; PAI, pancreatic attenuation index; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy hemorrhage; S, mean splenic attenuation; SSI, surgical site infection.

POPF has multiple risk factors, either modifiable or nonmodifiable. Fistula risk score put forward small duct diameter, soft pancreas, high-risk pathology (ampullary, duodenal, and islet cell neoplasms), and excessive blood loss as high-risk factors.[19] Postoperative pancreatitis can also lead to POPF. We had three patients with postoperative pancreatitis in the immediate postoperative period and all three developed a grade B/C POPF. High pancreatic fat content is a strong risk factor for acute pancreatitis. Surgical procedures have always shown a relationship with POPF. The chance of POPF in literature was 13% in pancreaticoduodenectomy (PD), 29% in DP, and 41% in central pancreatectomy.[20,21] In our study, we had 18% in PD, 35% in DP, and 100% in combined PD with distal pancreaticosplenectomy (DPS).

High pancreatic fat content can lead to higher insulin resistance and may lead to new onset DM or worsening of DM following resection. Kanwat et al noted that patients with POPF had more incidence of endocrine insufficiency after Whipple procedure.[22] Kim et al also showed that low PAI is associated with impaired glucose metabolism. In our study, we could not get any statistically significant relationship of preoperative diabetic status with PAI or POPF. Lifestyle modifications and weight reduction may improve pancreatic steatosis thereby improving the risk profile; hence, there may be an option for delaying surgeries in relatively benign pancreatic pathologies if the PAI is not favorable.

Early detection of high-risk cases will help in planning which patients could be taken up for an enhanced recovery after surgery (ERAS) protocol[23] or an intensive follow-up in postoperative period. POPF can be an inciting event for PPH. During the event of a pancreatic fistula, the leaked pancreatic enzymes can result in pseudoaneurysm formation due to its proteolytic activity on the arteries in the surgical bed like GDA, splenic artery ,hepatic artery etc and result in PPH.[24]

There is some evidence to show that somatostatin analogues and steroid may be useful in reduction of POPF. Our unit routinely gives 100 µg of octreotide subcutaneously prior to pancreatic transection in high-risk cases that is then continued for the next 5 days and tapered based on the drain fluid amylase value. Many randomized controlled trial have identified that there is a role for steroid administration in the reduction of POPF.[25] Preoperatively identified high-risk cases can thus undergo pharmacological prophylaxis thereby reducing the chances of POPF.

Limitation

The risk factors for postpancreatectomy outcomes are multifactorial, and for the assessment of individual factors a larger sample size is required. We were not able to validate PAI as a preoperative risk predictor because of the same. We could not assess the interobserver variation in assessment of the CT images due to the lack of resources during the coronavirus disease 2019 pandemic. Even with all the resource constraints ,we were able to shed some light in identifying a preoperative tool in the prediction of POPF and pancreatic fat content.

Conclusion

PAI seems to be useful tool in predicting the pancreatic fat content. This may help the surgeon in identifying a high-risk pancreas preoperatively, and in turn help modify the perioperative treatment protocols.

Conflict of Interest
None declared.

Acknowledgment
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