Severity of hyperechoic pancreas on preoperative ultrasonography: high potential as a clinically useful predictor of a postoperative pancreatic fistula

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Purpose: This study aimed to evaluate the effectiveness of using the severity of hyperechoic pancreas (HP) observed on preoperative ultrasonography (US) as a predictor of clinically relevant postoperative pancreatic fistula (CR-POPF).

Methods: A retrospective study was conducted with 94 patients who underwent pancreatectomy between April 2006 and March 2021. The severity of HP on US was classified into two categories (normal to mild vs. moderate to severe [obvious HP]). Multiple preoperative and intraoperative parameters were analyzed to predict CR-POPF.

Results: Out of the 94 patients, CR-POPF occurred in 21 (22%) patients, and obvious HP was observed in 30 (32%). Univariate analysis revealed that moderate to severe HP (obvious HP) was significantly associated with an increased incidence of CR-POPF ($P<0.001$). Factors such as the absence of pancreatitis, a small main pancreatic duct (<3 mm), intraoperative soft pancreas, increased body mass index, and lower pancreatic attenuation and attenuation index were also associated with CR-POPF (all $P<0.05$). Multivariate analysis showed that obvious HP and soft pancreatic texture were independent predictors of CR-POPF, with odds ratios of 11.53 ($P=0.001$) and 14.12 ($P=0.003$), respectively. The combination of obvious HP and soft pancreatic texture provided the most accurate prediction for CR-POPF.

Conclusion: The severity of HP, as observed on preoperative US, was significantly associated with CR-POPF. Severe HP may serve as a clinically useful predictor of POPF, especially when evaluated alongside the intraoperative pancreatic texture.

Keywords: Hyperechoic pancreas; Fatty pancreas; Postoperative pancreatic fistula; Ultrasonography

Key points: Obvious hyperechoic pancreas (HP) and soft pancreatic texture were independent predictors for clinically relevant postoperative pancreatic fistula (CR-POPF). The severity of HP on preoperative ultrasonography was significantly associated with CR-POPF. Obviously increased HP could be a clinically useful predictor of POPF.

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Introduction

Postoperative pancreatic fistula (POPF) is one of the most serious complications after pancreatectomy and is closely associated with postoperative mortality and morbidity. Its incidence rate ranges from 10% to 41% [1]. Therefore, predicting POPF in advance can help establish a surgical plan and assist in postoperative management; for this reason, several attempts to predict POPF have been made [1–9]. Well-established clinical predictors of POPF include high body mass index (BMI), small main pancreatic duct (MPD) size (<3 mm), and soft pancreatic texture [9–11].

Meanwhile, the global population of obese individuals is steadily increasing. Given the association between obesity and pancreatic steatosis, the incidence of pancreatic steatosis is also rising [12,13]. Several studies have attempted to predict POPF by assessing the presence and severity of pancreatic steatosis before surgery, as several reports have described an association between pancreatic steatosis and an increased rate of POPF [4,14]. Research has shown that measuring the degree of pancreatic attenuation on preoperative computed tomography (CT) scans can help predict POPF. Similarly, acquiring quantitative data on pancreatic steatosis and fibrosis from magnetic resonance imaging (MRI) scans has also been found to be useful in predicting POPF [2,4,7,9].

Ultrasonography (US) is a non-invasive and cost-effective diagnostic tool that is both safe and free of radiation, allowing for bedside examinations. However, only a few studies have attempted to predict POPF by measuring pancreatic elasticity or stiffness using US. Moreover, no studies have successfully predicted POPF by assessing pancreatic steatosis with US [15–18].

Therefore, the purpose of the current study was to evaluate the severity of hyperechoic pancreas (HP), which is indicative of pancreatic steatosis, through preoperative US, and assess its effectiveness as a predictor of POPF.

Materials and Methods

Compliance with Ethical Standards

This study received approval from the Institutional Review Board of the authors' affiliated institution (Chung-Ang University Hospital, No. 2403-016-19515), and the requirement for written informed consent was waived due to the retrospective nature of the study design.

Study Population

The subjects of this study comprised 352 patients who underwent pancreatic resection at the authors' affiliated hospital from April 2006 to March 2021. The exclusion criteria were as follows: (1) absence of a preoperative abdominal CT scan, including precontrast and portal venous phases (PVP); (2) lack of a preoperative transabdominal US; (3) severe atrophy of the upstream pancreas relative to the main pancreatic lesion on CT images; (4) non-visualization of the pancreas on US; (5) poor US image quality, rendering the pancreas unevaluable; (6) a previous history of pancreatectomy or chemotherapy for another malignancy; and (7) total pancreatectomy (Fig. 1).

Finally, 94 subjects were included in this study, consisting of 44 males (46.8%) and 50 females (53.2%). The final pathological diagnoses included pancreatic cancer (n=29), bile duct cancer (n=27), ampulla of Vater cancer (n=12), intraductal papillary mucinous neoplasm (n=10), benign pancreatic neoplasm (n=7), and miscellaneous diseases (n=9). The patients underwent various surgical procedures: pylorus-preserving pancreatoduodenectomy (n=45), pancreatoduodenectomy (n=20), distal pancreatectomy (n=26), subtotal pancreatectomy (n=1), and enucleation (n=2) (Table 1).

Clinical Parameters

The clinical data included both preoperative and intraoperative parameters. Preoperative characteristics consisted of the patient's age, sex, BMI, presence of diabetes mellitus, hypertension, and laboratory tests, which included serum amylase and lipase levels. Intraoperative parameters covered operative time, total blood loss, pancreatic texture, and the diameter of the MPD. All surgical procedures were performed by experienced surgical teams, each

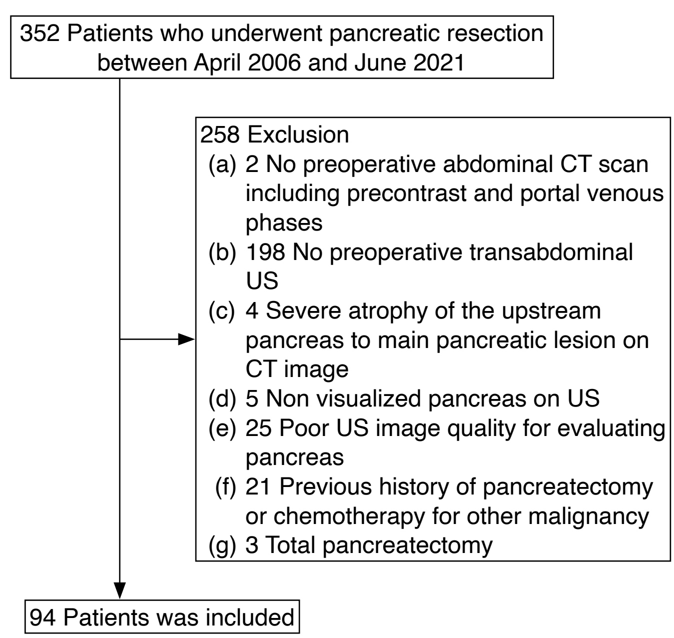

Fig. 1. **Flow diagram showing the patient selection criteria and study flow.** CT, computer tomography; US, ultrasonography.

Table 1. Clinical and imaging characteristics of the included patients

Variable	Value (n=94)
Age (year)	65 (57–72)
Sex (male/female)	44/50
BMI (kg/m^2)	23.4 (21.1–26.0)
Presence of diabetes mellitus (%)	27 (28.7)
Hypertension (%)	39 (41.5)
Preoperative amylase (U/L)	62.0 (44.0–85.0)
Preoperative lipase (U/L)	57.0 (25.5–103.0)
MPD diameter on CT (mm)	2.0 (0.0–4.0)
Acute pancreatitis on CT (%)	29 (30.9)
PAI	0.9 (0.8–1.0)
Pancreatic attenuation on CT (HU)	43.7 (36.8–49.3)
HP severity on US (normal/mild/moderate/severe)	19/45/20/10
Operation time (min)	360 (270–435)
Total blood loss (mL)	500 (300–700)
Pancreatic texture (soft/medium/hard)	20/62/12
MPD dilatation on operation (≥3 mm, %)	27 (28.7)
Diagnosis	
Pancreatic adenocarcinoma	29
Bile duct cancer	27
Ampulla of Vater cancer	12
IPMN	10
Benign neoplasm	7
Miscellaneous diseases	9
CR-POPF (%)	21 (22.3)

Values are presented as median (interquartile range) or number (%).
BMI, body mass index; MPD, main pancreatic duct; CT, computer tomography; PAI, pancreatic attenuation index; HU, Hounsfield units; HP, hyperechoic pancreas; US, ultrasound; IPMN, intraductal papillary mucinous neoplasm; CR-POPF, clinically relevant postoperative pancreatic fistula.

comprising two pancreatico-biliary surgeons with at least 15 years of experience. During the operations, the diameter of the pancreatic duct at the pancreatic resection margin was meticulously measured and documented. Additionally, the pancreatic texture—categorized as soft, medium, or hard—was evaluated through direct palpation by the surgeons [19,20].

Preoperative Imaging Analysis

Computed tomography

The most recent scan available from the operation was used. CT scans were conducted using three different MDCT systems: the LightSpeed VCT (64-channel, GE Healthcare, Milwaukee, WI, USA), the iCT 256 (256-channel, Philips Medical System, Best, Netherlands), and the IQon-Spectral CT (256-channel, Philips Medical System). Patients underwent scanning according to the local protocol, which included precontrast, arterial phase (AP), and PVP. The scans covered the area from the lung bases to the pelvic bone. The scans were acquired with a section thickness and reconstruction of 3 mm, a pitch of 0.915, a collimation of 0.625 mm, a rotation time of 0.4 seconds, a tube voltage of 100 kV, and a tube current ranging from 110 to 220 mAs. An intravenous contrast agent was administered at a rate of 3 mL/s, with the total volume ranging from 80 to 120 mL depending on the patient's weight. The precontrast image was first acquired, followed by the AP, which was obtained 15–17 seconds after the attenuation value reached 100 Hounsfield units in the abdominal aorta using the bolus tracking technique. The PVP was then obtained 30–33 seconds after the AP.

CT imaging analysis was conducted by a third-year radiology resident who was not aware of the histologic and clinical findings. The measurement methods were based on previous studies [5,21,22]. CT attenuation values were evaluated using precontrast images. Regions of interest (ROIs) were initially measured at three different locations in the body and tail of the pancreas, and the mean of these three ROIs was used to determine the extent of pancreatic parenchymal attenuation. In cases involving a pancreatic tumor, ROIs were positioned either upstream or downstream of the mass, depending on its location, to assess the remaining pancreas after surgery. Enhanced images in the PVP were reviewed concurrently to exclude the MPD, vessels, and pancreatic lesions, including neoplasms. Spleen attenuation was also measured, and the pancreatic attenuation index (PAI) was calculated as the ratio of pancreatic to spleen attenuation [7,8]. Furthermore, the presence or absence of imaging-based pancreatitis was evaluated by identifying signs indicative of acute pancreatitis, such as pancreatic swelling, peripancreatic fat infiltration, and peripancreatic fluid collection [23]. The MPD diameter was measured at its maximally dilated portion. The average time interval between the CT scan and subsequent pancreatectomy was 21.7 days (range, 1 to 34 days).

Abdominal US

All US images obtained at the authors' affiliated institution (n=75) were standardized and examined according to the Ultrasound Practice Guidelines published by the Korean Society of Radiology (KSR) and the Korean Society of Ultrasound in Medicine (KSUM) [24]. The remaining US studies acquired from an outside hospital (n=19) were suitable for evaluating the pancreatic parenchyma. The equipment used for the US exams included Philips IU22, HDI500, EPIQ 7, Canon Aplio 500/i900 (Canon Medical Systems, Otawara, Tochigi, Japan), and Samsung RS80A (Samsung Medison, Co. Ltd., Seoul, Korea). Two radiologists, with 3 and 15 years of experience in abdominal US respectively, and blinded to the clinical and

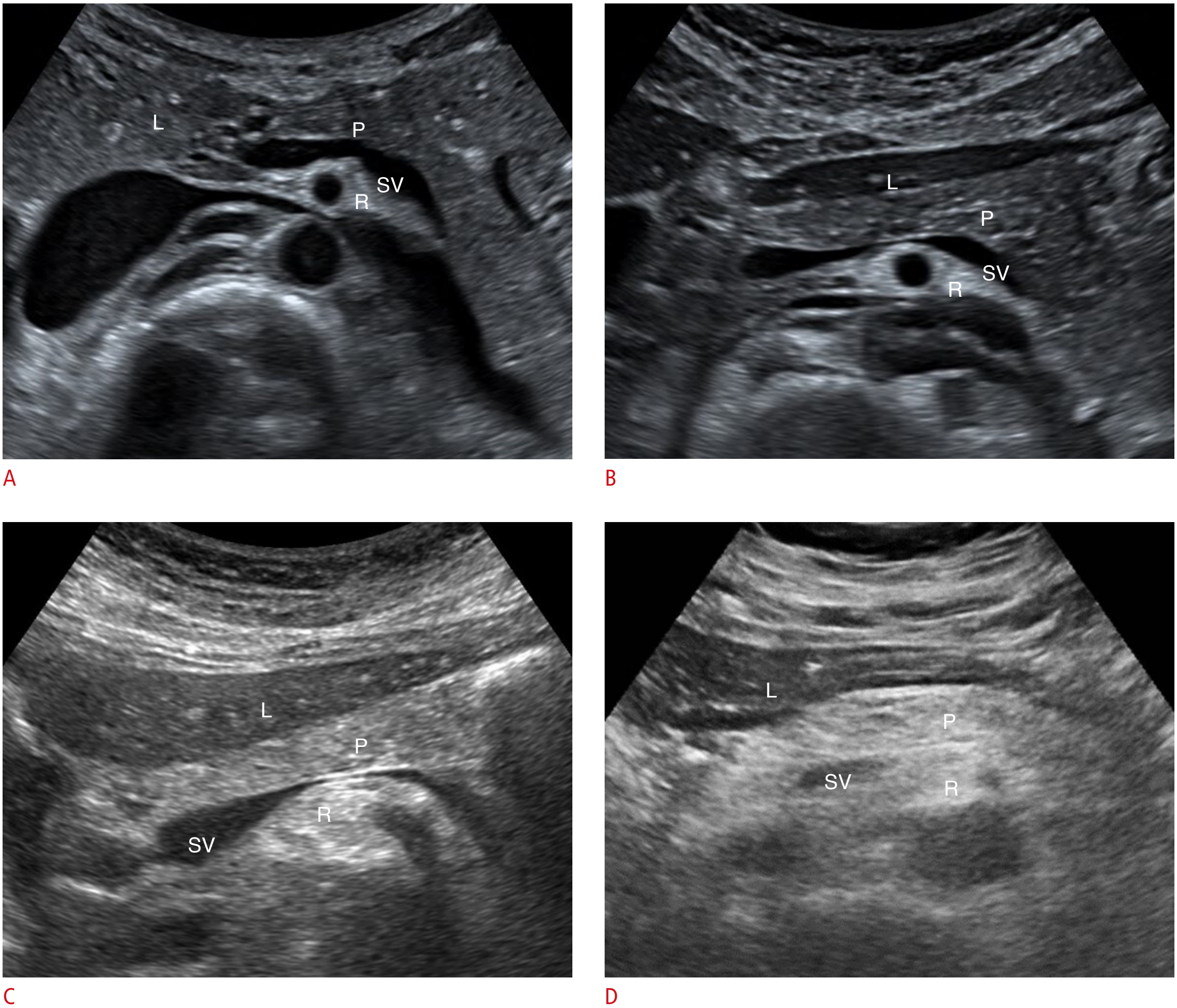

Fig. 2. Classification of hyperechoic pancreas (HP) on abdominal ultrasonography.
A. Normal pancreas shows similar echogenicity compared to the liver. B. Mild HP appears to be slightly hyperechoic compared to the liver. C. Moderate HP appears to be definitely hyperechoic compared to the liver, but hypoechoic compared to retroperitoneal fat. D. Severe HP appears to be similar or hyperechoic compared to retroperitoneal fat. P, pancreas; L, left hemiliver; R, retroperitoneal fat; SV, splenic vein.

laboratory data, independently reviewed the abdominal US images. They used the same commercial workstation with a 2,000×2,000 PACS monitor (Centricity, GE Healthcare) to grade HP. In cases of interobserver disagreement, they reached a consensus.

In general, normal pancreatic echogenicity is considered to be similar to that of the normal liver or kidney. If the pancreas exhibits higher echogenicity than the liver (especially the left lobe) under the same US window, HP can be diagnosed [25,26]. When the left lobe of the liver is not visible in the same window as the pancreas or displays increased echogenicity, the pancreas's echogenicity is instead compared to that of the right kidney and spleen [12,27]. Pancreatic echogenicity was assessed using a four-level grading system based on previous studies [25,26,28,29]: (1) normal, similar echogenicity to the liver; (2) mild, slightly increased echogenicity compared with the liver; (3) moderate, definitely hyperechoic compared to the liver, but hypoechoic compared to retroperitoneal fat; (4) severe, similar or hyperechoic compared to retroperitoneal fat (Fig. 2). Measurements of pancreatic echogenicity were primarily conducted in the pancreatic body, located anterior to the splenic vein and the mid-line of the vertebral body. Additionally, in the presence of focal pancreatic lesions in this region, the echogenicity of the downstream pancreatic parenchyma was assessed, with consideration of the remaining pancreas after surgery. The mean time interval between the ultrasound examination and subsequent pancreatectomy was 13.7 days (range, 0 to 36.3 days).

POPF Diagnosis

The diagnosis of a pancreatic fistula is made based on the criteria established by the International Study Group of Pancreatic Fistula (ISGPF). This includes an amylase level that exceeds three times the upper normal serum level, measured from the third postoperative day onwards, either from a surgically or percutaneously placed drain. The severity of the pancreatic fistula is assessed using the ISGPF grading system [3,7,30]:

(1) POPF grade A: A transient fistula without clinical implications. The patient is asymptomatic and only elevated amylase levels are noted on drainage. A CT scan shows no significant postoperative complications.

(2) POPF grade B: A symptomatic and clinically suspected fistula requiring a change of management or therapeutic intervention. A CT scan may show peripancreatic fluid collection(s) that require drain repositioning.

(3) POPF grade C: A severe, clinically significant fistula causing a critical condition such as sepsis or organ dysfunction. In such cases, a major change in management or aggressive therapeutic intervention is required. A CT scan may reveal worrisome or large peripancreatic fluid collections that necessitate immediate supplemental percutaneous drainage.

In accordance with previous research, grades B and C POPF are categorized as clinically relevant POPF (CR-POPF) [30].

Statistical Analysis

The statistical analysis was conducted using SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA). Continuous variables were presented as medians with interquartile ranges. The Mann-Whitney U test was utilized to compare continuous variables, and the chi-square test was used for categorical variables. The interobserver agreements regarding the severity of HP on US between two radiologists were analyzed using the κ statistic, with the following interpretations: poor (<0.20), fair (0.20–0.39), moderate (0.40–0.59), substantial (0.60–0.79), and almost perfect (≥0.80). The severity of HP on US was divided into two categories based on the previously mentioned four-scale grading system: normal and mild HP versus moderate to severe HP (obvious HP). All subsequent analyses were performed using these categories. Pancreatic texture was analyzed by comparing two groups: soft versus medium to hard. The cut-off values were set at 3 mm for the diameter of the MPD and 400 mL for total blood loss during the operation [3,31]. BMI was divided into two groups with a cut-off value of 25.0 kg/m^2 [32,33]. Statistical significance was established at P<0.05. Multivariate analysis was conducted using variables that achieved a P-value of <0.05 in the univariate analysis to identify independent risk factors for CR-POPF.

Results

Of the 94 subjects, 51 (54.3%) developed POPF. According to the ISGPS definition [30], CR-POPF was observed in 21 patients (22.3%), with grade B in 12 (12.8%) and grade C in nine (9.6%).

Risk Factors of CR-POPF

Table 2 summarizes the results of univariate and multivariate analyses for predicting CR-POPF. In the univariate analysis, seven variables were significantly associated with CR-POPF: BMI over 25 kg/m^2 (P<0.001), small MPD (<3 mm) (P=0.002), absence of pancreatitis on CT (P=0.003), lower PAI (P=0.036), decreased pancreatic attenuation (P<0.001), obvious HP (P<0.001), and soft pancreas (P<0.001). However, the multivariate analysis revealed that only a soft pancreas and obvious HP were independent risk factors for the development of CR-POPF, with odds ratios of 14.12 (P=0.003) and 11.53 (P=0.001), respectively.

Associations among HP, Pancreatic Texture, and CR-POPF

In total, 79.8% (75/94) of patients had HP on US, with mild, moderate, and severe degrees of severity in 45 (47.9%), 20 (21.3%), and 10 (10.6%), respectively. Therefore, 30 (31.9%) patients had obvious HP. The interobserver agreement for the severity of HP on US was substantial (κ=0.74).

Table 3 and Fig. 3 illustrate the association between HP and CR-POPF. CR-POPF occurred in 17 out of 30 patients (56.7%) in the obvious HP group, whereas only four out of 64 patients (6.3%) experienced it in the non-obvious HP group. The incidence of CR-POPF was significantly higher in the obvious HP group compared to the non-obvious HP group (P<0.001). The sensitivity, specificity, and accuracy were 0.57, 0.94, and 0.82, respectively.

In the intraoperative assessment of pancreatic texture, specimens were classified as follows: 20 (21.3%) as soft, 62 (66.0%) as medium, and 12 (12.8%) as hard. Table 4 presents a comparison of CR-POPF between the soft pancreas group and the combined medium to hard pancreas group. The results indicate that CR-POPF developed in 14 out of 20 patients (70.0%) with a soft pancreas, compared to only seven out of 74 patients (9.5%) with a medium to hard pancreas. The incidence of CR-POPF was significantly higher in patients with a soft pancreas than in those with a medium

Table 2. Univariate and multivariate analyses for predicting CR-POPF

Variable	CR-POPF development		Univariate P-value	Multivariate	
	(+) (n=21)	(–) (n=73)		OR	P-value
Age (year)	67 (53–74)	63 (58–70)	0.621		
Sex			0.160		
Male	7 (33.3)	37 (50.7)			
Female	14 (66.7)	36 (49.3)			
BMI (kg/m^2)			<0.001	2.26	0.305
<25.0	7 (33.3)	58 (79.5)			
≥25.0	14 (66.7)	15 (20.5)			
Diabetes mellitus	6 (28.6)	21 (28.8)	0.986		
Hypertension	10 (47.6)	29 (39.7)	0.518		
Preoperative amylase (U/L)	58.0 (49.0–79.5)	63.0 (42.3–84.3)	0.154		
Preoperative lipase (U/L)	67.0 (33.0–151.25)	49.0 (23.0–98.0)	0.247		
Diameter of the MPD on CT (mm)			0.002	2.01	0.530
<3.0	18 (85.7)	35 (47.9)			
≥3.0	3 (14.3)	38 (52.1)			
Acute pancreatitis on CT			0.003	2.56	0.534
Present	1 (4.8)	28 (38.4)			
Absent	20 (95.2)	45 (61.6)			
PAI	0.9 (0.7–0.9)	0.9 (0.8–1.0)	0.036	2.71	0.675
Pancreatic attenuation on CT (HU)	43.7 (36.6–49.1)	43.7 (36.3–49.3)	<0.001	0.99	0.540
HP			<0.001	11.53	0.001
Obvious HP	17 (81.0)	13 (17.8)			
Non-obvious HP	4 (19.0)	60 (82.2)			
Operation time (min)	390 (315–425)	360 (265–440)	0.567		
Total blood loss (mL)			0.893		
≤400	8 (38.1)	29 (39.7)			
>400	13 (61.9)	44 (60.3)			
Pancreatic texture			<0.001	14.12	0.003
Soft	14 (66.7)	6 (8.2)			
Medium/Hard	7 (33.3)	55 (75.3)/12 (16.4)			
Surgical method			0.794		
PPPD	10 (47.6)	35 (47.9)			
PD	6 (28.6)	14 (19.2)			
DP	5 (23.8)	21 (28.8)			
SP	0	1 (1.4)			
Enucleation	0	2 (2.7)			

Values are presented as median (interquartile range) or number (%).

CR-POPF, clinically relevant postoperative pancreatic fistula; OR, odds ratio; BMI, body mass index; MPD, main pancreatic duct; CT, computer tomography; PAI, pancreatic attenuation index; HU, Hounsfield units; HP, hyperechoic pancreas; PPPD, pylorus-preserving pancreatoduodenectomy; PD, pancreatoduodenectomy; DP, distal pancreatectomy; SP, subtotal pancreatectomy.

to hard pancreas (P<0.001, sensitivity=0.70, specificity=0.91, accuracy=0.86).

Table 5 presents the development of CR-POPF based on the combination of HP severity and pancreatic texture. Initially, the relationships between HP severity and CR-POPF, as well as pancreatic texture and CR-POPF, were assessed separately. Subsequently, the

Table 3. CR-POPF development according to HP severity

HP	CR-POPF development	Absence of CR-POPF	Statistics
Obvious HP (moderate, severe HP)	17/30 (56.7)	13/30 (43.3)	Sensitivity: 0.57 Specificity: 0.94
Non-obvious HP (normal, mild HP)	4/64 (6.3)	60/64 (93.8)	PPV: 0.81 NPV: 0.82 Accuracy: 0.82

Values are presented as number (%).
CR-POPF, clinically relevant postoperative pancreatic fistula; HP, hyperechoic pancreas; PPV, positive predictive value; NPV, negative predictive value.

Table 4. CR-POPF development according to pancreatic texture

Pancreatic texture	CR-POPF development	Absence of CR-POPF	Statistics
Soft	14/20 (70.0)	6/20 (30.0)	Sensitivity: 0.70 Specificity: 0.91
Medium or hard	7/74 (9.5)	67/74 (90.5)	PPV: 0.67 NPV: 0.92 Accuracy: 0.86

Values are presented as number (%).
CR-POPF, clinically relevant postoperative pancreatic fistula; PPV, positive predictive value; NPV, negative predictive value.

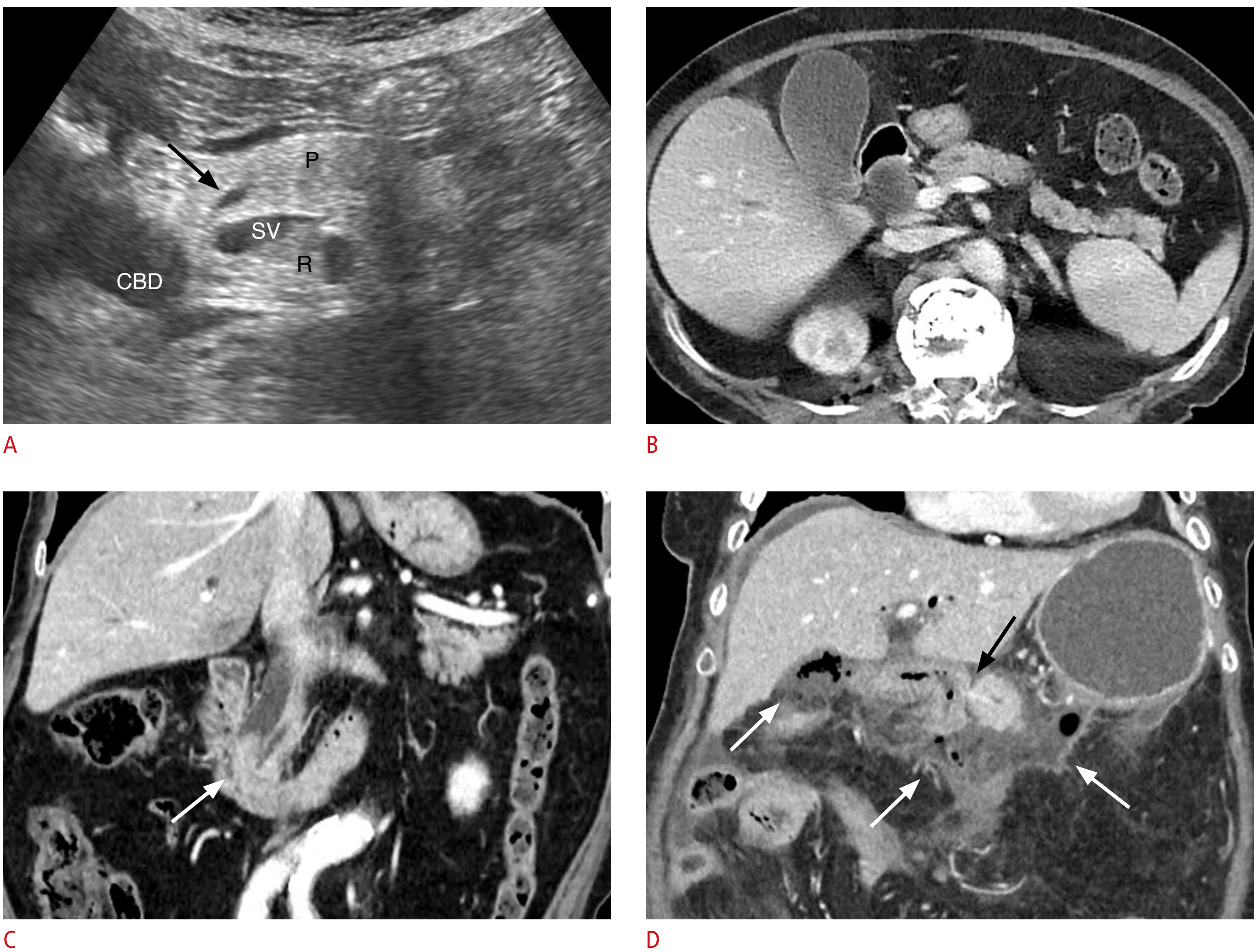

Fig. 3. A 79-year-old woman with ampulla of Vater (AoV) cancer who developed a clinically relevant postoperative pancreatic fistula. A. Preoperative ultrasonography shows the pancreas (P) exhibiting hyperechogenicity similar to retroperitoneal fat (R), indicating severe hyperechoic pancreas. Borderline dilation of main pancreatic duct (arrow) and marked dilation of bile duct (CBD) are also identified. SV, splenic vein. B, C. Enhanced axial, and coronal computed tomography images confirm these findings, with a visible mass at the AoV (arrow). The patient underwent pylorus-preserving pancreaticoduodenectomy, where a soft pancreatic texture was noted intraoperatively. D. On postoperative day (POD) 4, due to elevated pancreatic enzyme levels in the percutaneous drain tube and the onset of fever, a coronal computed tomography scan was performed, revealing air-containing fluid collections (white arrows) around the pancreaticojejunostomy site (black arrow). Immediate supplemental percutaneous drainage was initiated; however, on POD 8, the patient required emergency embolization to control active bleeding from a pseudoaneurysm in the operative bed (not shown).

Table 5. CR-POPF development according to the combination of HP severity and pancreatic texture

HP+Pancreatic texture		CR-POPF development	Absence of CR-POPF	Statistics
Obvious HP	+Soft	14/14 (100)	0/14 (0)	Sensitivity: 1.00
Obvious HP	+Medium or hard	3/16 (18.8)	13/16 (81.3)	Specificity: 0.91
Non-obvious HP	+Soft	0/6 (0)	6/6 (100)	PPV: 0.67
				NPV: 1.00
Non-obvious HP	+Medium or hard	4/58 (6.9)	54/58 (93.1)	Accuracy: 0.93

Values are presented as number (%).
CR-POPF, clinically relevant postoperative pancreatic fistula; HP, hyperechoic pancreas; PPV, positive predictive value; NPV, negative predictive value.

Table 6. Comparison of clinical parameters according to HP severity

Variable	HP on US		P-value
	Obvious HP (n=30)	Non-obvious HP (n=64)	
Age (year)	71 (63–77)	61 (57–69)	0.006
Male sex	8 (26.7)	36 (56.3)	0.007
BMI (kg/m^2)	25.7 (24.0–27.6)	22.5 (20.6–24.0)	<0.001
Diabetes mellitus	10 (33.3)	17 (26.6)	0.499
Hypertension	17 (56.7)	22 (34.4)	0.041
Preoperative amylase (U/L)	62.0 (51.0–90.5)	61.5 (42.0–79.5)	0.403
Preoperative lipase (U/L)	67.0 (28.3–123.3)	49.0 (23.0–101.0)	0.461
MPD diameter on CT (mm)	1.0 (0.0–2.8)	3.0 (1.0–4.0)	0.023
Acute pancreatitis on CT	5 (16.7)	24 (37.5)	0.041
PAI	0.7 (0.6–0.9)	1.0 (0.9–1.1)	<0.001
Pancreatic attenuation on CT (HU)	38.5 (30.1–46.3)	44.8 (37.6–49.5)	0.007
Operation time (min)	370 (289–418)	360 (264–441)	0.868
Total blood loss (mL)	500 (263–600)	600 (300–725)	0.589
Soft pancreatic texture	14 (46.7)	6 (9.4)	<0.001
MPD dilatation during operation	8 (26.7)	19 (29.7)	0.763
CR-POPF development	17 (56.7)	4 (6.3)	<0.001

Values are presented as median (interquartile range) or number (%).
HP, hyperechoic pancreas; US, ultrasonography; BMI, body mass index; MPD, main pancreatic duct; CT, computer tomography; PAI, pancreatic attenuation index; HU, Hounsfield units; CR-POPF, clinically relevant postoperative pancreatic fistula.

occurrence of CR-POPF was evaluated by simultaneously considering these two parameters. In cases where patients exhibited obvious HP and had a soft pancreas, CR-POPF occurred in all instances (14/14, 100%). Conversely, only 6.9% (4/58) of patients with non-obvious HP and a medium to hard pancreas developed CR-POPF. The sensitivity, specificity, and accuracy of predicting CR-POPF using the combination of HP severity and pancreatic texture were 1.00, 0.91, and 0.93, respectively.

Comparison of Clinical Features According to HP Severity

Table 6 shows a comparison of clinical parameters between the obvious HP and non-obvious HP groups. The obvious HP group had significantly higher values for age, proportion of female patients, BMI, and incidence of hypertension than the non-obvious HP group (P=0.006, P=0.007, P<0.001, and P=0.041, respectively). Additionally, this group exhibited a smaller MPD diameter and a lower rate of pancreatitis than the non-obvious HP group (P=0.023 and P=0.041, respectively). Pancreatic attenuation and PAI on preoperative CT scans were also notably lower in the obvious HP group compared to the non-obvious HP group (38.5 vs. 44.8, P=0.007; 0.7 vs. 1.0, P<0.001, respectively). Furthermore, the obvious HP group had a higher prevalence of soft pancreas (46.7% [14/30] vs. 9.4% [6/64], P<0.001) and a higher incidence rate of CR-POPF (56.7% [17/30] vs. 6.3% [4/64], P<0.001) than the non-obvious HP group. No significant differences were observed in other variables between the two groups.

Discussion

This study investigated predictors of CR-POPF. The results revealed that a soft pancreatic texture during surgery and moderate to severe HP (obvious HP) were significant predictors of CR-POPF on multivariate analysis. Furthermore, when these two factors were combined into a single variable and assessed for their predictive value, they demonstrated excellent diagnostic accuracy. These findings suggest that both soft pancreatic texture and the severity of HP are clinically useful predictors of CR-POPF.

POPF remains a significant and frequent complication following pancreatectomy, contributing substantially to morbidity and mortality. It is also linked to several other adverse outcomes, including extended hospital stays, readmissions, increased healthcare expenses, and delays in the administration of adjuvant therapies [3,34,35]. Efforts to mitigate the risk of POPF in individuals prone to fistula formation have included various strategies such as employing different anastomotic techniques, inserting pancreatic duct stents, using somatostatin analogues, and placing drains [1]. Therefore, for patients at high risk of developing POPF, predicting the likelihood of fistula formation before surgery enables the implementation of advanced treatments or management strategies and allows for more intensive and frequent monitoring. By doing so, many of the secondary complications associated with POPF can be minimized, leading to improved outcomes. The meta-analysis by Kamarajah et al., published in 2021 [36], which examined studies reporting risk factors for POPF following pancreatoduodenectomy, reported a pooled incidence of CR-POPF at 19% (95% confidence interval [CI], 17% to 22%). In the present study, the incidence of CR-POPF was 22%, which falls within the reported 95% CI and aligns with findings from previous research.

Reported strong risk factors for POPF include soft pancreatic texture, high BMI, and small MPD [1,9–11]. Among these, soft pancreatic texture is particularly noteworthy. Despite its subjective assessment, it has been shown to be a reliable predictor of POPF in several studies [14,37]. Consistent with prior findings, soft pancreatic texture emerged as the most significant risk factor for developing CR-POPF in this study, with an odds ratio of 14.12 (P=0.003). Several factors may explain the link between soft pancreatic texture and clinically relevant POPF, especially during intraoperative anastomotic repair. Firstly, a soft pancreas usually does not exhibit pancreatic duct dilatation, which complicates the anastomosis procedure. Secondly, the soft pancreas is more susceptible to direct injury or ischemic changes during surgery, particularly when sutures are placed between the pancreatic parenchyma and the seromuscular layer of the jejunum or stomach. Lastly, a soft pancreas often retains robust exocrine function, leading to the secretion of pancreatic juice rich in proteolytic enzymes. This can lead to the proteolytic degradation of the anastomosis [3,4,14].

In the present study, obvious HP emerged as a second significant predictor for developing CR-POPF (odds ratio, 11.53; P=0.001). As in the study of Al-Haddad et al. [27], it was hypothesized that HP indicates pancreatic fat infiltration. This assumption is supported by the relatively clear descriptions of fatty liver infiltration observed on ultrasound. Consequently, pancreatic steatosis may lead to similar outcomes as those proposed for nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH). The initial process by which NAFLD or NASH develops involves increased tissue resistance to insulin in obese patients, leading to hyperinsulinemia. This condition impairs mitochondrial β-oxidation of free fatty acids, resulting in the accumulation of fat in zone 3 hepatocytes [27,38]. Despite the assumption that the pathophysiology of pancreatic and hepatic steatosis is similar, notable histological differences exist between the two. Hepatic steatosis is characterized solely by the accumulation of fat within hepatocytes, whereas pancreatic steatosis involves fat accumulation not only within islet or acinar cells but also in adipocytes outside these cells [39]. When comparing clinical parameters according to HP severity in Table 6, the group with obvious HP had significantly lower pancreatic attenuation and PAI on preoperative CT scans compared to the non-obvious HP group (38.5 vs. 44.8, P=0.007; 0.7 vs. 1.0, P<0.001, respectively). This finding suggests that HP severity can serve as an indicator of pancreatic steatosis, although it does not imply that pancreatic steatosis is completely analogous to hepatic steatosis. To date, no study has assessed pancreatic steatosis using ultrasound to elucidate its association with CR-POPF as in the present study. However, Mathur et al. [14] demonstrated through surgical pathology specimens from patients undergoing pancreatoduodenectomy that the risk of fistula increases with the number of intralobular, interlobular, and total pancreatic fat components. Lee et al. [4] also demonstrated that increased pancreatic fat is a significant risk factor for POPF, not only through histological examinations but also by quantifying pancreatic fat using T1-weighted gradient-echo in-phase and opposed-phase sequences on MRI. The consistency of the pancreatic gland is primarily influenced by the extent of fatty infiltration and the degree of parenchymal fibrosis [1]. Therefore, it can be inferred that an increase in pancreatic fat leads to a softer gland consistency, which significantly increases the likelihood of POPF. This is due to mechanisms similar to those previously described for the occurrence of POPF in soft pancreas.

Although both HP severity and pancreatic texture are excellent predictors of CR-POPF, combining these factors further increases sensitivity, specificity, and accuracy in predicting CR-POPF, with sensitivity reaching 1, specificity at 0.91, and accuracy at 0.93

(Table 5). In cases where patients exhibit pronounced HP and have a soft pancreatic texture, CR-POPF occurs in up to 100% of instances. Therefore, evaluating these two factors both before and during surgery, and considering them collectively, can help predict and reduce the incidence of POPF, ultimately improving patient outcomes.

Meanwhile, upon examining the correlation between various parameters measured by CT and the severity of HP, the obvious HP group demonstrated significantly smaller MPD diameters, fewer instances of acute pancreatitis, and lower PAI and pancreatic attenuation on CT compared to the non-obvious HP group (Table 6). Given that fatty infiltration or less acute inflammation are primary determinants of a soft pancreas, the absence of pancreatic duct dilatation, typically observed in soft pancreas, can be extrapolated to pancreatic steatosis, which includes the obvious HP group [10,40]. The low incidence of acute pancreatitis in the obvious HP group can be attributed to the presence of interstitial edema, commonly seen in acute pancreatitis, which results in hypoechoic or heterogeneous echogenicity along with enlargement [24]. CT attenuation and PAI are indices that reflect the consistency of the pancreatic gland, indicating the degree of fatty infiltration and fibrosis within the pancreas. Therefore, it can be inferred that these values were low in the obvious HP group [5,8].

In this study, several factors were associated with CR-POPF in the univariate analysis. These included moderate to severe hyperplasia (obvious HP) ($P<0.001$), absence of pancreatitis ($P=0.003$), a small MPD (<3 mm) ($P=0.002$), intraoperative soft pancreatic texture ($P<0.001$), a BMI over 25 kg/m^2 ($P<0.001$), lower pancreatic attenuation ($P<0.001$), and lower PAI ($P=0.036$). However, these associations were not observed in the multivariate analyses. Among these factors, only soft pancreatic texture and obvious HP were identified as independent risk factors for CR-POPF in this study. Previous research has suggested that all seven factors identified in the univariate analysis may directly or indirectly reflect pancreatic consistency, including the degree of pancreatic fibrosis and fatty infiltration, and are associated with the occurrence of CR-POPF [3,5,8,19]. However, the conclusion that only soft pancreatic texture and obvious HP are significant predictors in the multivariate analysis may be due to confounding effects. Additionally, it could be argued that the severity of HP is a more powerful predictor of CR-POPF than other known factors. The discrepancies between the results of this study and those of previous studies may be attributed to differences in various study settings, such as the characteristics of the populations (e.g., different ethnicities) and the CT settings used. To achieve a better understanding of POPF, additional research, such as multicenter studies with larger populations, is warranted.

The present study has several limitations. First, it is a retrospective single-center study, which may introduce selection bias in the included patients. Second, the relatively small number of patients undergoing pancreatic resection were included, which could affect the generalizability of the findings. Third, the evaluation of pancreatic texture was subjectively performed by the surgeon and classified using an ambiguous grading system, leading to potential inter- or intra-observer variability. Similarly, the severity of HP was also classified using a simple four-level grading system, which may introduce ambiguity. Therefore, the study results suggest that future research could benefit from a more quantitative assessment of HP severity. Fourth, pancreas evaluation via US may present limitations. The assessment of US severity involved examining part of the pancreas shown with the surrounding structures in one window. It would be difficult to say that this represents heterogeneous pancreatic echogenicity resulting from situations such as pancreatic duct obstruction. Since this study sought to predict POPF by examining pancreatic steatosis, a condition prevalent in the obese population, excluding patients with challenges in pancreas detection on US may have introduced selection bias. Fifth, the histological findings of pancreatic tissue were not confirmed. In this study, it was assumed that HP indicates pancreatic fat replacement [27], but it remains uncertain if HP accurately reflects true pancreatic steatosis. Some studies have questioned the value of pancreatic steatosis in predicting POPF [2,19], and fibrosis might accompany steatosis, leading to fibro-fatty changes [9]. Further histological examinations are required to clarify the association between HP severity and the extent of steatosis or fibrosis.

In conclusion, the severity of HP observed on preoperative US was significantly associated with CR-POPF following pancreatectomy. Notably, obvious HP was identified as an independent risk factor for CR-POPF and could serve as a clinically useful predictor. Particularly when evaluated in conjunction with intraoperative pancreatic texture, the clinical relevance of HP severity on US is further emphasized.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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