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ORIGINAL ARTICLE

Predictors and Outcomes of Pancreatic Fistula Following Pancreaticoduodenectomy: a Dual Center Experience

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Abstract

Fistula following leaked pancreatico-enteric anastomosis is a common, potentially lethal complication of pancreaticoduodenectomy (PD). Early assessment and prediction of its occurrence can improve postoperative outcomes. Various perioperative factors were analyzed for its contribution to clinically relevant postoperative pancreatic fistula (crPOPF). Also, the difference in clinical outcomes of patients with and without fistula was studied. Sixty-seven patients undergoing PD for malignancies were analyzed during 3-year period in a dual-institutional study. Various preoperative, intraoperative, and postoperative factors were assessed. The incidence and severity of POPF and its association with the development of other post-PD complications were observed. Patients with and without POPF were divided into groups and compared with univariate and multivariate analyses, to identify significant contributing factors. Clinically relevant POPF was present in 20.9% cases. crPOPF contributed to delayed gastric emptying, albeit insignificant ($p = 0.403$), but was significantly associated with increased incidence of post-pancreatectomy hemorrhagic ($p = 0.005$) and infectious complications ($p = 0.013$). Soft pancreas ($p = 0.024$), intraoperative blood loss ($p = 0.045$), blood transfusion ($p = 0.024$), and fistula risk score ($p = 0.001$) were significant predictors of crPOPF. First postoperative day (POD1) drain fluid amylase (DFA) values at cut-off of 1336 U/L (AUC = 0.871; $p < 0.001$) significantly predicted crPOPF with good sensitivity and specificity. POD1 DFA was only factor significant on multivariate analysis ($p = 0.014$). There was no significant difference in overall survival between groups. crPOPF results in significant post-pancreatectomy hemorrhagic and septic complications, along with increased mortality. It can be accurately predicted by several preoperative and intraoperative factors. POD1 DFA can independently predict crPOPF development.

Keywords Whipple's procedure · Complications · Clinically relevant POPF · Periampullary cancer

Introduction

Pancreaticoduodenectomy (PD) is the time-tested surgical treatment of choice for periampullary cancers. Ever since the first description in the early twentieth century, the operative mortality rate has significantly fallen from 18% in the 1970s [1] to less than 3% today in high-volume centers [2]. The postoperative morbidity, however, has reached a plateau at about 30–50% [3], with no significant reduction despite several technical modifications.

The most significant morbidity is the postoperative pancreatic fistula (POPF). The definition and grading of POPF was standardized by the International Study Group for Pancreatic Fistula (ISGPF) in 2005 [4], and later upgraded in 2016 to include two broad groups: clinically relevant POPF (crPOPF) and no POPF, including biochemical leaks (BL) [5]. A recent systematic review reported an incidence range of 6–60% for POPF, with an overall incidence of 18% for clinically relevant POPF [6].

Several factors have been identified to predict the development of POPF; namely, soft pancreatic texture, small main pancreatic duct (MPD) diameter, and operative blood loss [7]. Other factors, such as leucocyte count, serum C-reactive protein (CRP), serum procalcitonin, and neutrophil–lymphocyte ratio, have been studied selectively to predict

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the incidence and severity of pancreatic fistula [2, 8]. Early prediction may have the advantage of better postoperative preparedness, adequate drain care, and sounding the need for extended hospital stay, elevated treatment costs, and high-risk outcomes.

In this study, we aimed to assess clinical outcomes of crPOPF, and analyze the various factors that predict its development. We also estimated the utility of day one drain fluid amylase in the prediction of crPOPF.

Materials and Methods

Study Design and Patients

A retrospective review of prospectively maintained data was performed in the departments of surgical gastroenterology of two tertiary teaching institutions in northern India. The study included patients over a 3-year period, from January 2015 to December 2017, followed up till August 2019. The study obtained clearance from the institutional ethics committee of first author's institution, with reference no. IEC 38/17.

All patients who were scheduled to undergo pancreaticoduodenectomy for malignancy were included in the study. The patients were > 12 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance score not exceeding 2. Exclusion criteria included resection for benign conditions like chronic pancreatitis and borderline resectable cancers receiving neoadjuvant chemoradiotherapy. Informed consent was obtained from all included patients.

Study Protocol

Patients were evaluated with history, physical examination, and triple phase contrast-enhanced computed tomography (CECT) scans and/or magnetic resonance cholangiopancreatography (MRCP). Locoregional resectability was established and tumor dissemination ruled out and locoregional resectability was established. Routine hematological and biochemical work-up, including serum tumor markers, were noted. Upper gastrointestinal and side-viewing endoscopy were performed selectively if indicated.

Patients presenting with cholangitis, total bilirubin > 7 mg/dL, delayed surgery due to nutritional build-up or comorbid conditions underwent endoscopic biliary drainage. Surgery was usually deferred for 2–4 weeks in these patients. In case of stent blockage or difficult access, drainage was via percutaneous transhepatic biliary drainage (PTBD).

Standard antibiotic therapy included third-generation cephalosporin (cefoperazone-sulbactam) at induction, and continuing the same for 5 days postoperatively. In case of suspected septic complications, antibiotics were stepped-up empirically by an addition of aminoglycosides or carbapenems. Drugs were subsequently modified as per culture-sensitivity reports.

Surgery Performed

The procedure was performed under supervision of senior authors A.C., S.M., A.P., and S.C. The choice of surgery was per individual preference, either classical PD or pylorus-preserving pancreaticoduodenectomy (PPPD). Totally laparoscopic PD was attempted in selected patients. Staging laparoscopy was performed selectively, for large bulky tumors > 4 cm, elevated CA 19.9 levels > 1000, and gross lymph nodal disease or suspicious nodules on preoperative imaging.

The procedure was performed according to the standard description [9]. In patients with questionable resectability or aberrant arterial anatomy, artery-first approach was used. Venous resection was performed if needed to achieve R0. Reconstruction was performed according to surgeon preference. The pancreatico-enteric anastomosis was by either Cattel-Warren type duct-to-mucosa pancreaticojejunostomy (PJ), Blumgart PJ, dunking PJ, or binding pancreaticogastrostomy (PG). Hepaticojejunostomy was performed after a variable distance downstream by a standard modified Blumgart technique. This was followed by gastrojejunostomy or duodenojejunostomy. Procedure was always accompanied with a feeding jejunostomy (FJ). Closed drainage tube or flat drains were placed around the pancreatic anastomosis prior to closure.

Postoperative Care and Recovery

Postoperatively, drain fluid was routinely assayed for amylase on odd postoperative days (POD), namely, 1, 3, 5, and 7. POPF was defined with POD 3 drain amylase values [5]. The occurrence and severity of other complications such as delayed gastric emptying (DGE) and post-pancreatectomy hemorrhage (PPH) were noted and graded [10, 11]. Overall infectious and noninfectious complications were graded as per Clavien-Dindo system [12].

Postoperatively, drains were removed when fluid amylase content was normal, and output was negligible. Patients were discharged and followed up regularly.

Statistical Analysis

Data was analyzed using IBM SPSS Statistic v.16 for Windows (IBM, Armonk, NY). The various recorded factors were evaluated by univariate analysis for its association with crPOPF. Descriptive statistics was used to calculate the frequency and percentage of categorical data; mean, median, and interquartile range of quantitative data. For statistical analysis, the study population was divided into two groups—one with crPOPF and the other with no POPF (including BL).

Categorical variables were compared using the Chi-square test or Fisher exact test. Continuous variables were analyzed with *t* test or Mann-Whitney *U* test. The factors significant for crPOPF on univariate analysis were tested for independent association by multivariate logistical regression. Results were described as *p* value and odds ratio (OR), along with 95% confidence interval (CI).

The values of POD 1 DFA were plotted with ROC curve; diagnostic accuracy estimated by area under curve (AUC). Based on sensitivity and specificity levels, optimal cut-off value was determined. Overall survival was plotted with Kaplan-Meier curves, and differences were estimated with log rank test. Power of the study was considered 90% (Type II β error 10%) with an accepted α error of 5%. A two-tailed $p < 0.05$ was considered significant.

Results

Demographics and Clinical Data

Overall

Seventy patients underwent pancreaticoduodenectomy during the study period, of which 67 were included in the study. The other 3 patients who underwent lateral pancreaticojejunostomy for coexisting chronic pancreatitis were excluded. The study group is comprised of about 56% males: ages ranging between 21 and 72 years. Nearly 85% of study population belonged to the 35–65 years age group. Jaundice was the commonest presenting symptom (Table 1); patients were symptomatic for 0.5–20 months prior to admission. Periampullary region was the commonest site of tumor. $N = 52$ patients underwent diagnostic or therapeutic endoscopy; the commonest finding being an ampullary mass.

Groupwise

There were no significant differences in the clinical, hematological, and biochemical parameters between crPOPF and no POPF groups. The imaging and endoscopic findings were comparable between groups. The two groups could be matched with regard to preoperative factors.

Surgical Details

Overall

Classical PD was the commonest performed procedure (Table 1). Two of these were performed totally laparoscopic, while one was converted to open in view of intraoperative bleeding. The median duration of surgery was 450 min (range, 270–950 min). There was median blood loss of 300 mL (range, 50–2000 mL), with 34 patients (50.7%) requiring intraoperative blood transfusions. The median transfusion requirement in these patients was 400 mL (range, 350–2000 mL). The median fistula risk score (FRS) for the entire cohort was 4 (range, 0–9); while that in patients who developed crPOPF was 6 (range, 1–9).

The pancreatic parenchymal consistency was soft in 30 patients. The median diameter of the main pancreatic duct encountered was 4 mm (range, 1–20 mm), while that of the bile duct was 15 mm (range, 8–35 mm). The commonest pancreatic anastomosis performed was the dunking pancreaticojejunostomy.

Groupwise

The type of surgery and reconstruction or duration of surgery were comparable between the groups. There was significantly higher intraoperative blood loss and transfusion requirement in the crPOPF group [Adjusted OR 1.001 (0.999–1.003); $p = 0.443$]. A subgroup analysis showed no significant difference in crPOPF between PG or PJ and invagination or duct-to mucosa PJ.

Soft pancreatic consistency significantly contributed to crPOPF development [adjusted OR 0.243 (0.005–12.211); $p = 0.479$]. Patients with smaller mean MPD diameter trended toward crPOPF development. Fistula risk score was significantly higher in crPOPF group [adjusted OR 2.075 (0.686–6.277); $p = 0.196$] Table 1.

Postoperative Complications

Overall

Clinically relevant POPF was present in 20.9% (n=14 patients). Among this, grade B fistula occurred in 9 patients and grade C in 5. No POPF occurred in $n = 32$ patients; biochemical leak in $n = 21$ patients.

A high incidence (70.1%) of delayed gastric emptying (DGE) was encountered in our study (Table 2). Most of them were grade A, with least effect on postoperative outcomes. Postoperative hemorrhage occurred in $n = 8$ patients (12.0%), with four patients having grade C. Other anastomotic leaks were found in 4.4%, with HJ leak being the commonest to manifest. However, most of these were self-limiting and required only prolonged drainage. Wound-related complications were present in 47.7% patients. About 62.5% of these patients had a prior history of biliary stenting as risk factor. Five patients required surgical re-exploration in the postoperative period; $n = 3$ were for grade C POPF-related hemorrhage.

Septic complications were seen in thirteen patients. These were those patients in whom source of infection could be documented with positive culture growth. However, there

Table 1 Preoperative and Intraoperative Factors assessed for crPOPF

Factor	Variable	Overall population *n* (%)	Group 1 (crPOPF) *n* (%)	Group 2 (No POPF) *n* (%)	*p* value
Preoperative factors: demographics and investigations					
Sex	Male	38 (56.7)	6 (42.9)	32 (60.4)	0.239
	Female	29 (43.3)	8 (57.1)	21 (39.6)	
Age	(in years)	48.2 ± 11.7	48.2 ± 12.1	48.2 ± 11.3	0.986
Duration of Symptoms	(in months)	3.7 ± 3.3	4.9 ± 5.2	3.4 ± 2.5	0.128
Hospital Stay	(in days)	20.1 ± 14.4	31.2 ± 26.2	17.2 ± 7.2	0.001*
Symptoms	Pain	43 (64.2)	8 (57.1)	35 (66.0)	0.537
	Jaundice	52 (77.6)	12 (85.7)	40 (75.5)	0.414
	Fever	33 (49.2)	10 (71.4)	23 (43.4)	0.062
Past History	Acute Pancreatitis	5 (7.4)	0 (0)	5 (9.4)	0.232
	Diabetes Mellitus	9 (13.4)	1 (7.1)	8 (15.1)	0.438
	Cholelithiasis	13 (19.4)	0 (0)	13 (14.5)	0.039*
Physical Examination	ECOG				
	Gr 0	9 (13.4)	1 (7.1)	8 (15.1)	0.692
	Gr 1	52 (77.6)	12 (85.7)	40 (75.5)	
	Gr 2	6 (9.0)	1 (7.1)	5 (9.4)	
	Body weight (in Kg)	53.9 ± 9.1	54.4 ± 10.2	53.8 ± 9.0	0.823
	BMI (in Kg/m^2)	21.7 ± 3.4	22.8 ± 3.7	21.4 ± 3.3	0.126
Tumor Site	Ampulla	41 (61.2)	9 (64.3)	32 (60.4)	0.364
	Distal CBD	12 (18.0)	4 (28.6)	8 (15.1)	
	Duodenum	7 (10.4)	1 (7.1)	6 (11.3)	
	Pancreatic head	7 (10.4)	0 (0)	7 (13.2)	
ERCP / Endoscopy	Stenting	34 (50.7)	7 (50.0)	27 (50.9)	0.950
	Ulcerative growth	17 (25.4)	4 (28.6)	13 (24.5)	0.580
	Mass lesion	21 (31.4)	3 (21.4)	18 (34.0)	
	Bulky ampulla	3 (4.4)	0 (0)	3 (5.7)	
PTBD		3 (4.4)	0 (0)	3 (5.7)	0.362
Intraoperative factors: surgical procedure and intraoperative findings					
Procedure	Classical/whipple PD	46 (68.7)	8 (57.1)	38 (71.7)	0.296
	PPPD	21 (31.3)	6 (42.9)	15 (28.3)	
Duration of Surgery	(in minutes)	465.4 ± 154.4	444 ± 165	471 ± 154	0.570
Blood Loss	(in mL)	420 ± 375	600 ± 530	371 ± 317	0.045*
Intra-op Transfusion	(in mL)	308 ± 424	532 ± 595	243 ± 356	0.024*
Pancreatic Anastomosis	Dunking PJ	25 (37.3)	6 (42.9)	19 (35.8)	0.904
	Duct to mucosa PJ	18 (26.8)	4 (28.6)	14 (26.4)	
	Blumgart type PJ	14 (20.9)	3 (21.4)	11 (20.8)	
	Binding PG	8 (12.0)	1 (7.1)	7 (13.2)	
	PJ stenting	2 (3.0)	5 (35.7)	13 (24.5)	0.401
Pancreatic Consistency	Soft	30 (44.8)	10 (71.4)	20 (37.7)	0.024*
	Firm/Hard	37 (55.2)	4 (28.6)	33 (62.3)	
Duct Diameters	MPD (in mm)	4.1 ± 2.9	3.5 ± 2.6	4.3 ± 2.9	0.366
	CBD/CHD (in mm)	16.5 ± 4.3	16.0 ± 3.5	16.6 ± 4.6	0.681
FRS[a]		3.7 ± 2.0	5.2 ± 2.2	3.3 ± 1.7	0.001*

*p value < 0.05 = significant

a Fistula risk score, as described by Callery et al. [7]

Table 2 Postoperative factors: complications and histopathology

Factor	Variable	Overall population*n* (%)	Group 1 crPOPF *n* (%)	Group 2 No POPF *n* (%)	*p* value
Delayed gastric emptying	No	20 (29.8)	3 (21.4)	17 (32.1)	0.403
	Grade A	24 (35.8)	4 (28.6)	20 (37.7)	
	Grade B	13 (19.4)	3 (21.4)	10 (18.9)	
	Grade C	10 (15)	4 (28.6)	6 (11.3)	
Post pancreatectomy hemorrhage	No	59 (88)	11 (78.6)	49 (92.5)	0.005*
	Grade A	3 (4.5)	0 (0)	3 (5.7)	
	Grade B	1 (1.5)	0 (0)	1 (1.9)	
	Grade C	4 (6.0)	4 (21.4)	0 (0)	
Other anastomotic leaks	No	64 (95.5)	11 (61.1)	53 (100)	0.002*
	Hepaticojejunostomy	2 (3.0)	2 (11.1)	0 (0)	
	Gastrojejunostomy	1 (1.5)	1 (5.5)	0 (0)	
Other complications	Wound infection	32 (47.7)	9 (64.3)	23 (43.4)	0.164
	Sepsis	13 (19.4)	6 (42.9)	7 (13.2)	0.013*
	Re-exploration	5 (7.4)	3 (21.4)	2 (3.8)	0.025*
Clavien-Dindo complications	Grade I	29 (43.3)	1 (7.1)	28 (52.8)	< 0.001*
	Grade II	19 (28.3)	2 (14.3)	17 (32.1)	
	Grade III	12 (17.9)	7 (50.0)	5 (9.4)	
	Grade IV	3 (4.5)	1 (7.1)	2 (3.8)	
	Grade V	4 (6.0)	3 (21.4)	1 (1.9)	
Pathological tumor location	Ampulla	36 (53.7)	9 (64.3)	27 (50.9)	0.428
	Distal CBD	10 (15.0)	3 (21.4)	7 (13.2)	
	Pancreatic Head	15 (22.3)	1 (7.1)	14 (26.4)	
	Duodenum	6 (9.0)	1 (7.1)	5 (9.4)	
pT stage	T 1	2(3.0)	1 (7.1)	1 (2.0)	0.276
	T 2	36 (53.7)	10 (71.4)	26 (51.0)	
	T 3	23 (34.3)	3 (21.4)	20 (39.2)	
	T 4	4 (6.0)	0 (0)	4 (7.8)	
pN stage	N 0	37 (55.2)	9 (64.3)	28 (54.9)	0.687
	N 1	19 (28.3)	4 (28.6)	15 (29.4)	
	N 2	9 (13.4)	1 (7.1)	8 (15.7)	
	Lymph node ratio	0.11 ± 0.18	0.08 ± 0.1	0.1 ± 1.9	0.496
Tumor grading/differentiation	Well (Gr 1)	37 (55.2)	7 (50.0)	30 (50.8)	0.840
	Moderate (Gr 2)	24 (35.8)	6 (42.9)	18 (35.3)	
	Poor (Gr 3)	4 (6.0)	1 (7.1)	3 (5.9)	
Resection margins	Clear	60 (89.6)	11 (78.6)	49 (92.5)	0.131
	Positive (microscopic)	7 (10.4)	3 (21.4)	4 (7.5)	
Invasiveness	LVI	30 (44.7)	5 (35.7)	25 (47.2)	0.552
	PNI	12 (17.9)	1 (7.1)	11 (20.8)	0.435

*$p < 0.05$ = significant

was nearly 50% prevalence of postoperative systemic inflammatory response syndrome (SIRS) within the first 5 postoperative days.

Majority of patients in the study group were Clavien-Dindo (CD) grade I ($n = 29$ patients). Among the five patients who were re-explored, $n = 3$ recovered with CD grade IIIB, while the other two succumbed (CD grade V). There were four operative mortalities (within 30 days of surgery) in our study: three patients were due to grade C PPH and one due to severe sepsis, secondary to leaked pancreatic and biliary anastomosis.

Groupwise

There were no differences in incidence of DGE between the groups. Post-pancreatectomy hemorrhage (PPH) was

significantly higher with crPOPF, as were the development of other anastomotic leaks (Table 2). Likewise, sepsis and need for surgical re-exploration was significantly higher in the crPOPF group. There was no difference in wound-related complications. The Clavien-Dindo grade of complications was significantly different between the two groups, with serious complications (≥ grade III) greater in patients with crPOPF.

Histopathology, Adjuvant Therapy, and Outcomes

Overall

The final histology was adenocarcinoma in all except 3 patients. The other pathologies identified were pancreatic neuroendocrine tumor and solid pseudopapillary neoplasm. Histopathology corroborated ampulla as the commonest site of tumor origin ($n = 36$) (Table 2). Microscopic margin positivity in final resected specimen was found in $n = 7$ patients. Four patients had posterior surface involved, two had retroperitoneal uncinate margin involved, and one patient had both these margins positive. There was no R2 resection in our study group.

Forty-two patients received adjuvant gemcitabine-based chemotherapy, including one concurrent chemoradiotherapy.

Nine patients were lost to follow-up. Fifty-four patients were followed up for a median duration of 15.5 months postsurgery (range, 3–47). $N = 15$ patients died during their follow-up period; 39 patients are alive. The mean overall survival (OS) was 33.4 ± 3.5 months (95% CI, 26.5–40.2 months). Disease recurrence and distant metastasis were found in 11 patients on surveillance; none of these patients survived.

Groupwise

Histopathological tumor characteristics, namely, location, T-status, N-status, were comparable between both groups. Although R1 resection was higher in crPOPF group, this was not statistically significant. The mean overall survival (OS) was not significantly different between the groups (18.6 ± 2.9 months, 95% CI 12.8–24.4; v/s 38.5 ± 3.3 months, 95% CI 31.8–45.1; $p = 0.368$) (Fig. 1).

Drain fluid amylase values were significantly elevated on postoperative days 1, 3, and 5 in the crPOPF group. (Table 3) On ROC analysis, POD 1 drain fluid amylase showed good accuracy (AUC = 0.871) in predicting crPOPF. The best cut-off value was 1336 U/L, with sensitivity of 78.6% and specificity of 8.9% (Fig. 2).

The day one DFA value was the only factor found significant on multivariate analysis [adjusted OR 1.008 (1.001–1.012); $p = 0.014$].

Discussion

Despite technical advancements, newer anastomotic modalities, and usage of adjuncts, no modality has been universally accepted to reduce anastomotic leak rates [13]. The FRS, which includes several pre- and post-operative factors, has predicted POPF with good accuracy [7], and was validated in our study as a significant predictor. Individual components like soft pancreatic consistency, higher intraoperative blood loss, and transfusion were significant contributors to crPOPF. Other factors, namely, MPD diameter and site of primary tumor, were contributory but not statistically significant. Nearly one-third of the patients with MPD size ≤ 3 mm developed crPOPF, while only 11.7% of > 3 mm ducts

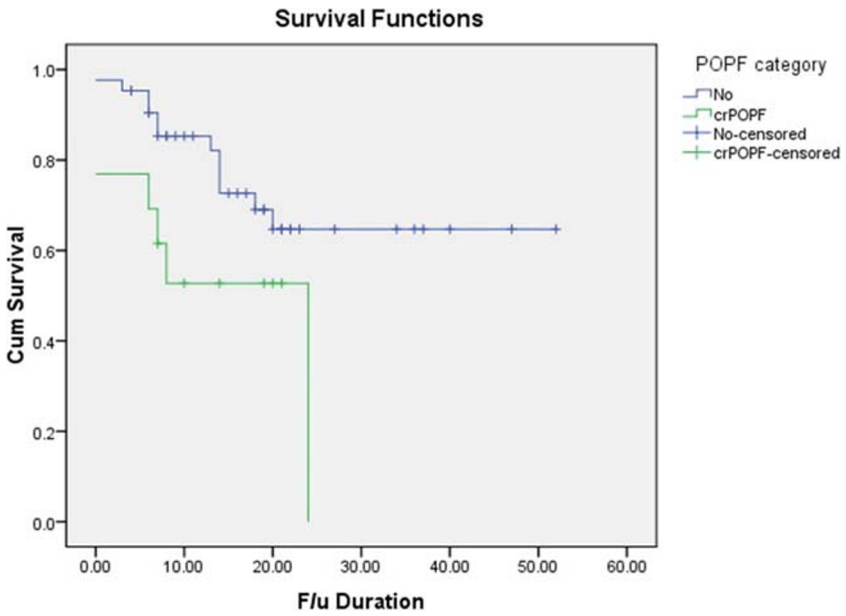

Fig. 1 Kaplan-Meier curve for overall survival: crPOPF vs no POPF

Table 3 Analysis of postoperative markers

Post-op day	Investigation	crPOPF (mean ± SD/median)	No POPF (mean ± SD/median)	*p* value	95% CI
POD 1	Drain fluid amylase (U/L)	9687 ± 11,290 / 3555	1263 ± 3174 / 409	< 0.001*	4947–11,900
POD 3	Drain fluid amylase (U/L)	6234 ± 9963 / 1593.5	429 ± 732 / 130	< 0.001*	3102–8507
POD 5	Drain fluid amylase (U/L)	3352 ± 5264 / 511	135 ± 324 / 37	< 0.001*	1793–4641

*p value < 0.05 = significant

developed fistula. Among patients with crPOPF, 71.4% had MPD size ≤ 3 mm, similar to the previously published studies [7, 14].

No patient with subclinical chronic pancreatitis, diagnosed on histopathology, developed crPOPF. This could be explained by progressive parenchymal fibrosis and pancreatic ductal dilatation. Tumors arising from pancreatic head and distal bile ducts were associated with POPF in nearly one-third cases. These were similar to findings described by Callery et al. and Pratt et al. [7, 14], explained by relatively normal parenchyma with undilated MPD. Preoperative biliary stenting significantly contributed to wound-related infectious complications, but there was no relation to POPF.

The type of surgery and reconstruction were non-contributory to development of crPOPF. Binding PG trended to lower leak rate compared with PJ (12.5% vs 22.8%, p = 0.506). These findings corroborated with previous RCT and meta-analysis [13, 15, 16]; however, statistical significance shown by Lyu et al. [17] could not be replicated. Likewise, there was no difference in POPF rate between the duct-to-mucosa versus invagination type PJ (22.2% vs 24.0%, p = 0.892), similar to previous studies [18, 19].

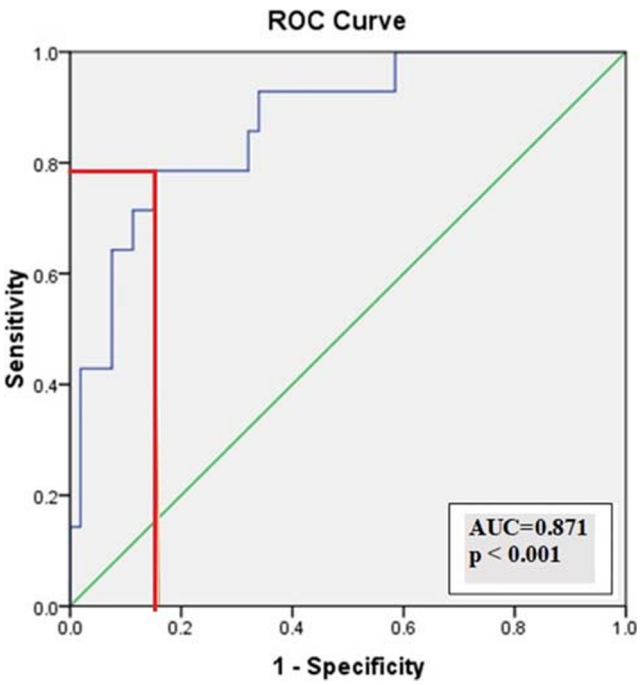

Fig. 2 Receiver operator characteristic curve: postoperative day 1 drain fluid amylase

While nearly 70% of all crPOPF occurred in the soft pancreas, only one-third of patients with soft parenchyma developed crPOPF. In contrast, the firm-to-hard glands had a 10.8% fistula rate. This significant contribution of pancreatic texture is well known [7, 20, 21]. The three times higher rate of POPF in soft pancreas can be explained by higher exocrine activity, smaller mean MPD diameter (≤ 3 mm), and presence of numerous side branches divided during parenchymal transection [22].

Among other complications, delayed gastric emptying had an overall unexpectedly high incidence, but was not significantly different between the two groups. Nonetheless, the incidences of higher grades of DGE, grade B (21.4% vs 18.9%) and grade C (28.6% vs 11.3%), were more with crPOPF. This can be explained by a locoregional pro-inflammatory milieu surrounding the stomach, resulting in secondary gastroparesis. Postoperative hemorrhagic complications were significantly higher with crPOPF. Grade C PPH was seen exclusively in patients with coexisting pancreatic fistula [11, 23].

Infectious complications of post-PD, namely, surgical site infections (SSI) and systemic sepsis, were commoner in the crPOPF group. Likewise, the need for surgical re-exploration of patients was nearly 6 times higher in the crPOPF group. These indicate the higher morbidity and prolonged hospital stay in these patients, much in line with the ISGPF criteria [4, 5].

The patients in the crPOPF group had significantly higher incidence of severe complications (beyond Clavien-Dindo grade III) (78.5% vs 15.1%). Patients with crPOPF required surgical intervention nearly 5 times more than those without. There was a twofold increased risk of organ failure with crPOPF, with nearly 11 times increased mortality rate.

POD 1 drain fluid amylase was the only independent predictor of crPOPF on multivariate analysis. The median values of first postoperative day DFA was significantly higher in the crPOPF group compared with no POPF (3555 U/L; range, 273–38,760 U/L vs 409 U/L; range, 4–21,835 U/L). Nearly 80% of patients with crPOPF had values greater than 1000 U/L, while about 42% patients had values exceeding 10,000 U/L. Only one patient had DFA value less than 10 times upper normal limit. In contrast, with no POPF, 41.5% had values

less than three times normal limit of amylase in drain fluid. Thirty percent of the patients had values greater than 1000 U/L, while 68% had amylase values less than 10 times the upper limit (800 U/L). The best-chosen cut-off for POD 1 DFA in our study was 1336 U/L, which showed good sensitivity and specificity in predicting crPOPF.

Our results are similar to the findings of Ansorge et al. and Dugalic et al. [24, 25], with good sensitivity and specificity values at similar cut-off values. Similar studies have also suggested the inclusion of POD 1 DFA as a predictor of crPOPF [26–28]. The meta-analysis by Giglio et al. [29] showed 89% accuracy, 91% pooled sensitivity, and 84% pooled specificity for POD 1 DFA in the prediction of crPOPF. Liu et al. [30] also demonstrated similar sensitivity but poorer specificity values.

Our study is limited by the heterogeneity and lack of standardization in surgical procedures adopted by each of the senior authors in the study. The cut-off values obtained for POD 1 DFA need to be prospectively validated internally and externally before their inclusion as decision-making criteria in routine postoperative care. Moreover, the decision for drain removal should be prospectively be based on these pararmeters, a project which is currently underway.

Conclusion

Clinically relevant POPF results in significant morbidity following pancreaticoduodenectomy including increased incidence of hemorrhagic and infectious complications, leading to prolonged hospital stay. Soft pancreas, intraoperative blood loss and transfusion, and fistula risk score contribute to its development. First postoperative day drain fluid amylase can predict crPOPF with high accuracy, sensitivity, and specificity. We recommend its inclusion in the routine postoperative care of patients undergoing pancreatic head resections.

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Authors' Contributions All authors contributed to the study conception and design, but was headed by Shakeel Masood and Abhijit Chandra. Material preparation, data collection, and analysis were performed by Suneed Kumar, Shibumon M. Madhavan, and Dinesh Kumar. The first draft of the manuscript was written by Suneed Kumar, and all authors commented on previous versions of the manuscript. The manuscript was critically revised and edited by Anshuman Pandey, Smita Chauhan, and Abhijit Chandra. All authors read and approved the final manuscript. Overall supervision of the study was by Shakeel Masood.

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Data Availability Masterchart/excel spreadsheet of study subjects will be available on request.

Compliance with Ethical Standards The study obtained clearance for Institutional Ethics Committee with ref. # IEC 38/17. Informed written consent for treatment, use of clinical details and publication of data was obtained from all the subjects of the study.

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval The study obtained clearance for Institutional Ethics Committee with ref. # IEC 38/17.

Informed Consent Informed written consent for treatment, use of clinical details and publication of data was obtained from all the subjects of the study.

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