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Risk Factors for Postoperative Pancreatic Fistula after Pancreatoduodenectomy: Role of Pancreatic Texture and Duct Diameter

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ABSTRACT

Background. Postoperative pancreatic fistula (POPF) remains the key driver of morbidity after pancreatoduodenectomy (PD). We evaluated anatomical and technical predictors of POPF with emphasis on pancreatic texture and main pancreatic duct (MPD) diameter.

Methods. Retrospective analysis of consecutive adults undergoing PD at a single HPB center (2016–Oct 2024). Patients were stratified by intraoperative pancreatic texture (soft vs hard) and MPD diameter (≤5 mm vs >5 mm). Outcomes were graded per ISGPS (2016). Multivariable logistic regression identified independent predictors of POPF.

Results. Among 293 patients, overall POPF occurred in 110 (37.5%), including clinically relevant POPF (CR-POPF; grades B/C) in 67 (22.9%). POPF was more frequent with soft than hard pancreas (54.4% vs 17.8%; p<0.001); grade C appeared only in soft glands. In soft pancreas, MPD ≤5 mm vs >5 mm was associated with higher POPF (53.8% vs 23.0%; p=0.013); a similar pattern was seen in hard glands (31.0% vs 9.1%; p=0.002). On multivariable analysis, higher drain amylase on postoperative day (POD) 1 independently predicted POPF (OR 1.011 per 1 IU/L; 95% CI 1.008–1.015; p<0.001), whereas larger MPD diameter reduced risk (OR 0.792 per mm; 95% CI 0.632–0.991; p=0.042). After adjustment, pancreatic texture showed no independent association (OR 1.177; p=0.748). In the soft-gland subgroup, invagination pancreatojejunostomy was linked to more grade C POPF (20.0% vs 6.0%), higher re-operation (20.0% vs 6.1%; p=0.036) and greater in-hospital mortality (24.0% vs 7.5%; p=0.023) compared with duct-to-mucosa anastomosis.

Conclusions. Small MPD diameter and soft texture identify patients at heightened risk of POPF after PD; early POD1 drain amylase is a strong independent predictor. When technically feasible—particularly in soft glands with narrow ducts—duct-to-mucosa pancreatojejunostomy is associated with fewer severe fistulas and lower mortality than invagination

Keywords: *pancreatoduodenectomy, postoperative pancreatic fistula, pancreatic texture, main pancreatic duct, pancreatojejunostomy,drain amylase*

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1. INTRODUCTION

Postoperative pancreatic fistula (POPF) remains one of the most serious complications following pancreatoduodenectomy (PD) [1, 2]. Despite advances in surgical technique and perioperative management, POPF continues to occur in 15–45% of patients and is associated with morbidity, prolonged hospital stay, and mortality of up to 9% [3]. According to the

International Study Group of Pancreatic Surgery [4], POPF is defined as the presence of drain fluid with amylase activity more than three times the upper normal serum level, and clinically relevant POPF is classified as grades B and C [5].

The development of POPF is multifactorial [6]. Patient-related (age, BMI, comorbidity), disease-related (tumor type), and intraoperative variables (blood loss, anastomotic technique) all contribute to risk. Among these, two anatomical factors—pancreatic texture and diameter of the main pancreatic duct (MPD)—are consistently recognized as the strongest predictors [7]. A soft gland with a narrow duct is technically challenging for anastomosis, prone to leakage, and remains the most vulnerable substrate for fistula formation [7].

Pancreatojejunostomy (PJA) is the standard reconstructive procedure after PD, but the optimal technique remains debated [8, 9]. Duct-to-mucosa and invagination methods are both widely used, with conflicting data regarding their comparative safety, particularly in patients with a soft gland and non-dilated duct [10].

Given these controversies, further evaluation of pancreatic texture, duct size, and anastomotic technique is needed to refine risk prediction and optimize surgical strategy [4].

The aim of this study was to assess the incidence and risk factors of POPF after PD, focusing on pancreatic texture, MPD diameter, and the choice of PJA technique in patients with periampullary malignancies.

2. MATERIALS AND METHODS

Ethics

The study protocol was approved by the Institutional Review Board of the A.N. Syzganov National Scientific Center for Surgery (approval No. 9, dated 08.12.2015). The requirement for informed consent was waived due to the retrospective nature of the study.

Study design and setting

This was a single-center retrospective cohort study including consecutive patients who underwent PD at the Department of Hepatopancreatobiliary Surgery and Liver Transplantation, A.N. Syzganov National Scientific Center for Surgery (Almaty, Kazakhstan) between January 2016 and October 2024. The study was reported in accordance with the STROBE guidelines for observational studies [11].

Patient selection

Inclusion criteria: patients ≥18 years; PD (classic or pylorus-preserving) performed for periampullary malignancies (pancreatic head, ampulla of Vater, distal bile duct, or duodenum); complete perioperative records with drain amylase measurements available.

Exclusion criteria: total or completion pancreatectomy, palliative bypass without resection, benign or inflammatory pathology, multivisceral resections beyond standard venous resection, reoperations for complications after PD performed at outside institutions, and missing data necessary for ISGPS classification of POPF.

All eligible patients during the study period were included consecutively. No a priori sample size calculation was performed.

Surgical technique

Open PD was the standard approach; minimally invasive PD (laparoscopic or robot-assisted) was selectively performed and included in the analysis as a covariate. Reconstruction comprised PJA, hepaticojejunostomy, and gastro- or duodenojejunostomy. PJA was performed either by **duct-to-mucosa** or **invagination** technique, according to intraoperative findings and surgeon preference. Details of suture material, main pancreatic duct (MPD) stenting (internal or external), and its duration were recorded. At least one closed-suction drain was routinely placed adjacent to the anastomosis.

Variables and exposure assessment

Pancreatic texture (soft vs hard) was assessed intraoperatively by the lead surgeon (palpation and direct visualization) and documented in the operative report.

Main pancreatic duct (MPD) diameter was measured at the transection margin intraoperatively. For analysis, it was considered both as a continuous variable (per 1 mm) and dichotomized at **≤5 mm vs >5 mm**, a prespecified clinical threshold [4].

Patients were stratified by pancreatic texture (soft vs hard) and MPD diameter (≤5 mm vs >5 mm). A predefined subgroup analysis assessed the association of PJA technique with outcomes in patients with a soft pancreas.

Covariates

Demographics (age, sex, BMI), comorbidities, jaundice or cholangitis, prior abdominal surgery, tumor site and histology, CA 19-9 and serum albumin, preoperative biliary drainage, surgical approach (open vs minimally invasive), venous

resection, intraoperative blood loss (EBL), transfusion requirements, year of surgery, surgeon identifier, and MPD stenting.

Outcomes and definitions

The **primary endpoint** was *clinically relevant postoperative pancreatic fistula (CR-POPF)*, defined as ISGPS 2016 grade B or C [4]. **Secondary endpoints** included: overall POPF (grades A–C), grade C POPF, delayed gastric emptying (DGE) [12], postpancreatectomy hemorrhage (PPH) [13], bile leak [14], reoperation, length of hospital stay, and in-hospital, 30-day, and 90-day mortality.

Drain amylase (DFA): measured on postoperative days (POD) 1, 3, and 5 using the institutional laboratory assay. POPF was diagnosed per ISGPS 2016 definition as DFA >3× upper limit of normal (ULN) serum amylase on or after POD3, in combination with clinical criteria [4]. Biochemical leak was recorded separately and not considered CR-POPF.

Data sources and quality

Data were extracted from electronic medical records and operative reports by two trained reviewers, with discrepancies adjudicated by a senior investigator. Pancreatic texture and MPD diameter were taken directly from operative reports. Missing data were handled as described in the statistical analysis section.

Bias and study size

Selection bias was minimized by consecutive inclusion of all eligible cases during the study period. Indication bias regarding the choice of PJA technique was addressed in multivariable models and subgroup analysis. No sample size calculation was undertaken; study size was determined by the available cohort.

Statistical analysis

Continuous variables are reported as mean±SD or median (IQR) according to distribution; categorical variables as n (%). Group comparisons used χ^2 or Fisher's exact test for categorical data, and t test or Mann–Whitney U test for continuous data. Two-sided $p<0.05$ was considered significant. Multivariable logistic regression was performed to identify predictors of clinically relevant POPF (CR-POPF); covariates were selected a priori for clinical relevance. Model performance was evaluated using ROC analysis and calibration with bootstrap validation.

A predefined subgroup analysis examined the association of pancreatojejunostomy technique with outcomes in patients with a soft pancreas. Missing data were handled with multiple imputation when >5%; otherwise, complete-case analysis was applied. All analyses were conducted using IBM SPSS Statistics, version 27 (IBM Corp., Armonk, NY).

3. RESULTS

Baseline and intraoperative characteristics

A total of **293 patients** underwent PD, including 158 (54.0%) with a soft pancreas and 135 (46.0%) with a hard pancreas. Baseline characteristics are shown in **Table 1**.

Median age (61 vs. 60 years, p=0.243), sex distribution (p=0.110), and comorbidities (diabetes mellitus, cardiovascular disease) were similar between groups. The predominant tumor site was the pancreatic head (50.6% vs. 61.5%, p=0.264).

Patients with a soft pancreas had lower preoperative bilirubin levels (total: 34.7 vs. 46.7 mmol/L, p=0.014; direct: 28.0 vs. 42.9 mmol/L, p=0.009). Intraoperatively, MPD diameter ≤5 mm was more common in the soft group (75.3% vs. 43.0%, p<0.001). The duct-to-mucosa technique was applied more frequently in the hard pancreas group (91.9% vs. 84.2%, p=0.046), while MPD stenting was more often used in soft pancreas (79.1% vs. 63.4%, p=0.003).

Median DFA levels were significantly higher in the soft group on POD1, POD3, and POD5 (all p<0.001).

Table 1. Pre- and intraoperative characteristics by pancreatic texture

Variable	Soft (n=158)	Hard (n=135)	p-value
Age, years, median (IQR)	61 (55–66)	60 (49–66)	0.243
Male sex, n (%)	66 (41.8)	69 (51.1)	0.110
Diabetes mellitus, n (%)	27 (17.1)	31 (23.0)	0.197
Cardiovascular disease, n (%)	79 (50.0)	79 (58.5)	0.140
Tumor site: pancreatic head, n (%)	80 (50.6)	83 (61.5)	0.264
CA19-9, U/ml, median (IQR)	44.5 (11.3–213.3)	33.9 (9.3–142.5)	0.396

Variable	Soft (n=158)	Hard (n=135)	p-value
Total bilirubin, mmol/L, median (IQR)	34.7 (16.1–64.3)	46.7 (21.2–89.4)	0.014
Direct bilirubin, mmol/L, median (IQR)	28.0 (10.0–54.0)	42.9 (16.6–82.0)	0.009
MPD ≤5 mm, n (%)	119 (75.3)	58 (43.0)	<0.001
Duct-to-mucosa PJA, n (%)	133 (84.2)	124 (91.9)	0.046
MPD stenting, n (%)	125 (79.1)	85 (63.4)	0.003
DFA POD1, median (IQR), U/L	227.5 (28–872)	10.2 (1.7–116)	<0.001
DFA POD3, median (IQR), U/L	243.3 (29–1547)	21.0 (2.3–167)	<0.001
DFA POD5, median (IQR), U/L	281.5 (43–1140)	13.6 (1.9–141)	<0.001

Postoperative outcomes by pancreatic texture

Postoperative outcomes are presented in **Table 2**. Overall POPF occurred in **110 patients (37.5%),** including 67 (22.9%) CR-POPF (grades B/C). POPF was more frequent in the soft pancreas group (54.4% vs. 17.8%, p<0.001). Grade C POPF occurred only in patients with soft pancreas (8.2%). Mortality was higher in the soft group (10.1% vs. 2.3%, p=0.006).

Table 2. Postoperative complications by pancreatic texture

Variable	Soft (n=158)	Hard (n=135)	p-value
POPF overall, n (%)	86 (54.4)	24 (17.8)	<0.001
- Grade A	29 (18.4)	14 (10.4)	
- Grade B	44 (27.8)	10 (7.4)	
- Grade C	13 (8.2)	0	
Biliary fistula, n (%)	4 (2.5)	0	–
Delayed gastric emptying, n (%)	6 (3.8)	8 (5.9)	0.395
Reoperation, n (%)	13 (8.2)	4 (3.0)	0.053
Wound infection, n (%)	13 (8.2)	4 (3.0)	0.055
Mortality, n (%)	16 (10.1)	3 (2.3)	0.006

Outcomes by MPD diameter

When stratified by MPD diameter (≤5 vs. >5 mm), CR-POPF was significantly more common in the ≤5 mm subgroup for both soft and hard pancreas (Table 3). In the soft pancreas group, mortality tended to be higher in patients with MPD ≤5 mm (12.6% vs. 2.6%, p=0.057).

Table 3. Postoperative complications by MPD diameter and pancreatic texture

Complication, n (%)	Soft, ≤5 mm (n=119)	Soft, >5 mm (n=39)	p-value	Hard, ≤5 mm (n=58)	Hard, >5 mm (n=77)	p-value
CR-POPF (B/C)	50 (42.0)	7 (17.9)	0.013	8 (13.8)	2 (2.6)	0.002
Grade C POPF	12 (10.1)	1 (2.6)		0	0	

Complication, n (%)	Soft, ≤5 mm (n=119)	Soft, >5 mm (n=39)	p-value	Hard, ≤5 mm (n=58)	Hard, >5 mm (n=77)	p-value
Mortality	15 (12.6)	1 (2.6)	0.057	2 (3.4)	1 (1.3)	0.394

Outcomes by PJA technique in soft pancreas

In patients with soft pancreas, POPF tended to occur more frequently after invagination than duct-to-mucosa PJA, with higher rates of grade C POPF, reoperation, and mortality (**Table 4**).

Table 4. Postoperative complications by PJA technique in soft pancreas

Complication	Duct-to-mucosa (n=133)	Invagination (n=25)	p-value
CR-POPF (B/C), n (%)	47 (35.3)	10 (40.0)	0.196
Grade C POPF, n (%)	8 (6.0)	5 (20.0)	
Reoperation, n (%)	8 (6.1)	5 (20.0)	0.036
Mortality, n (%)	10 (7.5)	6 (24.0)	0.023

Association of PJA technique with pancreatic texture

The distribution of pancreatic texture by PJA method is shown in **Table 5**. Soft pancreas predominated in patients who underwent invagination.

Table 5. Association between pancreatic texture and PJA technique

Pancreatic texture	Duct-to-mucosa (n=257)	Invagination (n=36)	p-value
Soft, n (%)	133 (51.8)	25 (69.4)	0.033
Hard, n (%)	124 (48.2)	11 (30.6)	

Drain amylase trends

Median DFA values were consistently higher in patients with soft pancreas across POD1, POD3, and POD5 for both duct-to-mucosa and invagination PJA (Figures 1 and 2).

Figure 1. DFA levels by pancreatic texture in duct-to-mucosa PJA.

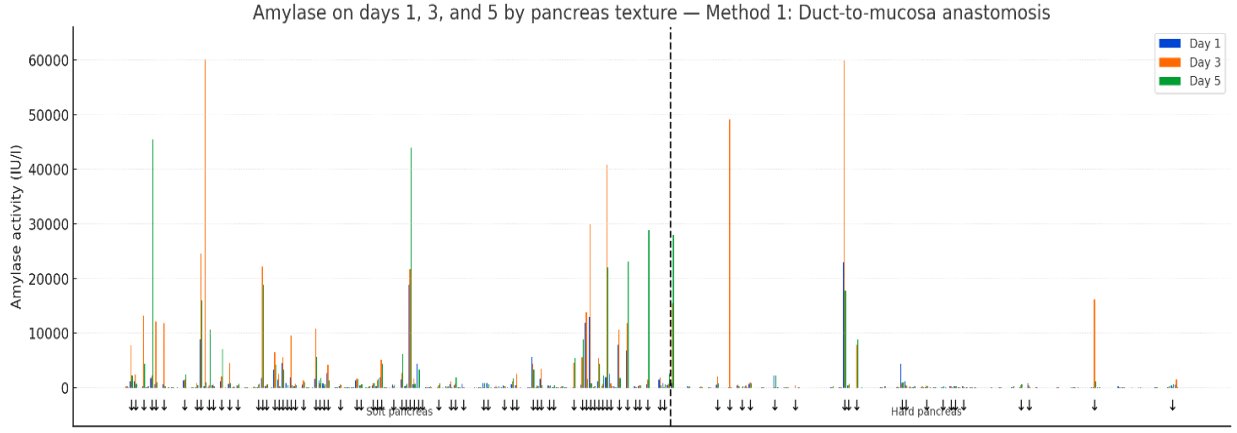
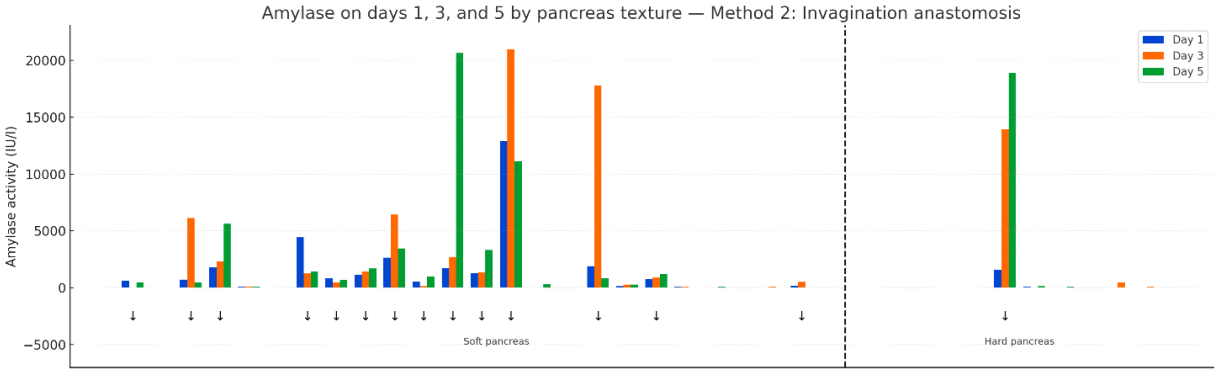


Figure 2. DFA levels by pancreatic texture in invagination PJA.



Multivariable analysis

Multivariable logistic regression identified **DFA on POD1** as the strongest independent predictor of POPF (OR 1.011; 95% CI 1.008–1.015; p<0.001). Larger MPD diameter was associated with lower risk (OR 0.792; 95% CI 0.632–0.991; p=0.042). Tumor localization at the Vater's papilla was also associated with increased risk compared to pancreatic head tumors (OR 2.77; 95% CI 1.08–7.13; p=0.035). Pancreatic texture was not independently significant after adjustment (Table 6).

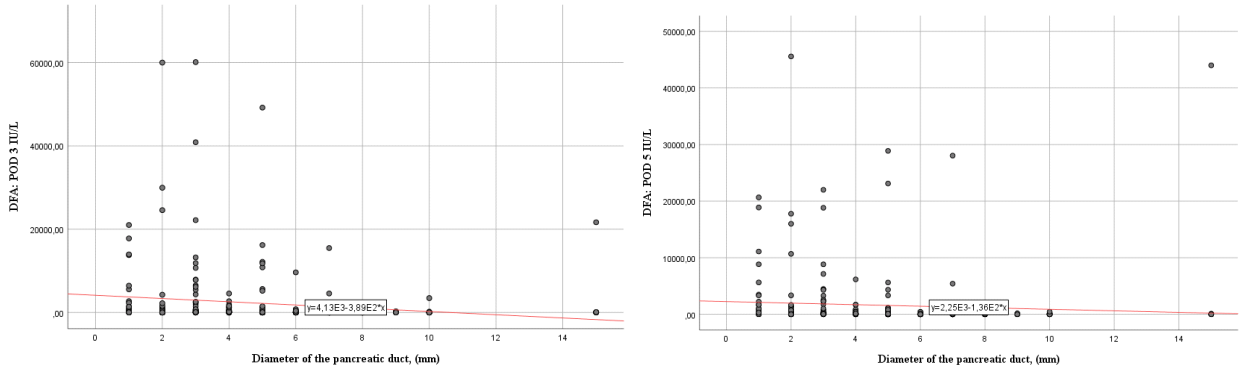
Table 6. Multivariable logistic regression for predictors of POPF

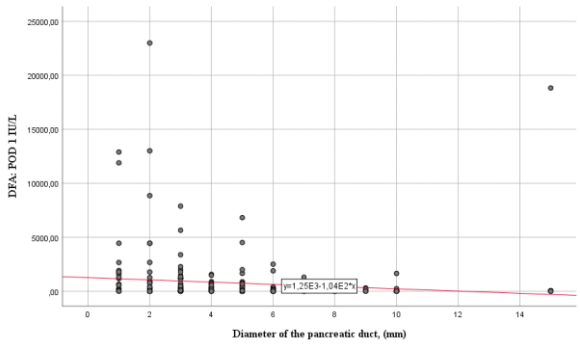
Variable	OR	95% CI	p-value
DFA POD1 (per 1000 U/L)	1.011	1.008–1.015	<0.001
MPD diameter (per mm)	0.792	0.632–0.991	0.042
Tumor localization – Vater's	2.770	1.076–7.132	0.035
Tumor localization – bile duct	2.677	0.383–18.704	0.321
Tumor localization – duodenum	1.753	0.153–20.131	0.652
Pancreatic texture (soft vs hard)	1.177	0.416–3.176	0.748

Correlation analysis

Spearman's rank correlation showed an inverse association between MPD diameter and DFA levels on POD1 (ρ= –0.35), POD3 (ρ= –0.31), and POD5 (ρ= –0.35), all p<0.001 (Figure 3).

Figure 3. Correlation between MPD diameter and DFA levels on POD1, POD3, and POD5.





4. DISCUSSION

In this large single-center series of 293 pancreatoduodenectomies, we found that both pancreatic texture and main pancreatic duct (MPD) diameter were strongly associated with POPF. Soft parenchyma and a duct diameter ≤5 mm were linked to significantly higher rates of POPF, while duct-to-mucosa pancreatojejunostomy was associated with lower rates of severe fistulas and mortality compared to invagination, particularly in patients with a soft gland. Importantly, early postoperative day (POD) 1 drain amylase emerged as an independent predictor of clinically relevant POPF (CR-POPF).

Our findings are consistent with prior reports identifying soft pancreatic parenchyma and non-dilated MPD as the two dominant anatomical risk factors for POPF [15]. Rates of POPF in soft glands in our cohort (54%) mirror those reported in international series, where incidences range from 40% to 60% [16]. Conversely, hard or fibrotic glands were relatively protected, with fistula rates below 20%. This aligns with the pathophysiological concept that fibrosis and ductal obstruction decrease exocrine output and improve anastomotic stability [15].

The predictive value of POD1 drain amylase has also been well documented [17], and our data reinforce its role as an early biomarker. While biochemical leaks (formerly grade A) are not clinically significant, elevated POD1 DFA allows early risk stratification and may guide selective drain management or intensified monitoring [4].

The debate between duct-to-mucosa and invagination pancreatojejunostomy remains unresolved internationally. Randomized controlled trials and meta-analyses have reported heterogeneous results, with some showing no difference and others favoring duct-to-mucosa for soft glands [18, 19]. In our subgroup, invagination was associated with a threefold higher risk of grade C POPF, more reoperations, and higher in-hospital mortality. These findings support the hypothesis that invagination may predispose to stump ischemia and necrosis in fragile soft parenchyma, while duct-to-mucosa ensures more precise alignment of ductal and jejunal mucosa [18].

The link between small MPD diameter and POPF likely reflects both technical and physiological challenges. Anastomosis of a narrow duct increases the risk of suture cut-through, poor drainage, and leakage of pancreatic juice. Soft parenchyma adds vulnerability due to high enzymatic activity and poor suture-holding capacity. Together, these anatomical features create a “high-risk pancreas” where anastomotic failure is most likely. Elevated drain amylase on POD1 provides an early surrogate of this failure cascade, reflecting subclinical leakage before clinical manifestations [20].

Strengths and limitations

The main strengths of our study are the relatively large single-center cohort, standardized definitions [5], and comprehensive analysis incorporating both anatomical and technical variables. Consecutive inclusion minimized selection bias, and subgroup analyses added granularity.

However, several limitations must be acknowledged. First, the retrospective design is inherently prone to bias. Second, surgeon experience and technical preference (especially for PJA technique) may have influenced outcomes, introducing confounding by indication. Although multivariable adjustment was applied, residual confounding cannot be excluded. Third, this is a single-center study, and findings may not be generalizable to centers with different patient populations or surgical practices. Finally, no external validation was performed, and predictive modeling was internally validated only.

Clinical implications and future research

Our results underscore the need for individualized risk stratification in PD. Patients with soft pancreas and MPD ≤5 mm should be considered high risk, with early postoperative DFA serving as a reliable adjunct for clinical decision-making. Surgeons should favor duct-to-mucosa anastomosis whenever technically feasible in this subgroup, given its association with reduced severe POPF and mortality.

Future research should focus on multicenter prospective validation of these findings, the role of selective drain management guided by POD1 amylase, and the development of tailored perioperative strategies (e.g., somatostatin analogs, novel

anastomotic techniques) for high-risk patients.

5. CONCLUSION

In summary, pancreatic texture, MPD diameter, and POD1 drain amylase are key predictors of POPF after pancreatoduodenectomy. Soft glands with small ducts represent the highest-risk group. When feasible, duct-to-mucosa anastomosis should be preferred over invagination to reduce severe fistulas and mortality. These data support the integration of anatomical and early biochemical markers into routine risk assessment and management after PD.

Authors' Contribution S.T

S. Tileuov: study conception and design, surgeries, revising the discussion section of the manuscript. A.T. Dzhumabekov: study design, data analysis and interpretation, revising the discussion section of the manuscript. M. Doskhanov: data acquisition, analysis, and interpretation; surgeries, revising the results section of the manuscript. B. Baimakhanov: data collection, surgeries, drafting and revising the results section, final approval of the manuscript. R. Emiroglu: data collection, surgeries, drafting and revising the results section, final approval of the manuscript. G. Ismailova: study conception and design, overall responsibility for the study, data analysis and interpretation, final approval of the manuscript. Sh. Kaniyev: data collection, medical diagnoses, surgical pathologic evaluations. Zh. Ospan: data collection, medical diagnoses, surgical pathologic evaluations. I. Fakhradiyev: overall coordination, statistical oversight, writing and editing of introduction, methods, and discussion, final approval of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest statement

The authors declare no conflict of interest.

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