Drain management after distal pancreatectomy based on a predictive model, including drainage fluid amylase and biochemical inflammatory markers: a preliminary study

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Introduction

Postoperative pancreatic fistula (POPF) is the Achilles' heel of distal pancreatectomy. Surgeons use abdominal drains for early prediction, diagnosis, and timely management of POPF. The utility of drainage fluid in the prediction and diagnosis of POPF is a matter of debate.

Patients and methods

This is a retrospective cohort study of all patients who underwent distal pancreatectomy between January 2018 and January 2020. The present study aims to evaluate the association between drainage fluid amylase (DFA) and systemic inflammatory markers in the prediction of clinically relevant POPF.

Results

This study included 44 patients with a mean age of 40.3±16.3 years, and the female : male ratio was 2.7 : 1. POPF occurred in 11 (25%) patients. Of them, nine (20.5%) patients were managed by additional ultrasound-guided tube drainage. Higher drainage fluid amount and DFA-D1 were associated with a higher risk of POPF (P=0.036, and 0.009, respectively). The leukocytic count was significantly higher in POPF in the third postoperative day (POD) (P=0.032). POPF group had a significantly higher level of serum lactate dehydrogenase (LDH) on the fourth POD (P=0.001). Patients with high DFA-D1 (>330 IU/l), rising leukocytic count, and high serum LDH were significantly at higher risk of POPF (9/11 developed POPF, P=0.0001).

Conclusion

DFA-D1, rising leukocytic count, and high serum LDH level compromised a more robust predictive model for POPF. The cutoff value of DFA proposed by the ISGPF is applicable when combined with leukocytic count and serum LDH. Prospective large-scale studies are needed.

Keywords:
distal pancreatectomy, pancreatic carcinoma, pancreatic fistula

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Introduction

Distal pancreatectomy (DP) is the standard surgical technique for the management of benign and malignant lesions in the pancreatic tail and distal body [1]. Despite advancements in surgical techniques and perioperative care, the rate of postoperative morbidity after pancreatectomy is still high (20–60%) [2]. Postoperative pancreatic fistula (POPF) is the Achilles' heel of pancreatic surgery, and the prevalence of POPF after DP reaches up to 30% of cases [3,4]. The etiology, presentation, and management of POPF after DP are different from pancreaticoduodenectomy (PD), and special consideration is required [5].

Two recent randomized controlled trials challenged the value of abdominal drains after DP [6,7]. However, placement of surgical drains remains a very common surgical practice [5]. Surgeons using abdominal drains are aiming at prediction, timely management of POPF, and conversion of leakage into a controlled fistula [8,9]. POPF was defined by the International Study Group of Pancreatic Fistula (ISGPF) based on drainage fluid amylase (DFA) more than three times the upper normal level of serum amylase in the institution [10]. This definition was not considered applicable in clinical practice, and many studies were conducted for the determination of new cutoff values, risk scoring systems, and management algorithms [11].

Interpretation of DFA and drainage amount is targeted to predict the risk of POPF [12]. The utility of drainage fluid in the prediction and diagnosis of POPF is a matter of debate. The aim of the present study is to evaluate the association between DFA and systemic inflammatory markers in the detection of patients at risk for POPF.

Patients and methods

This is a retrospective cohort study of the diagnostic and predictive value of DFA and systemic inflammatory markers in the management of POPF after DP. This is a single-center experience conducted at an Academic University Hospital. The study population included all consecutive patients who had PD for the management of benign or malignant lesions. The study duration was between January 2018 and January 2020. Patients who had chronic pancreatitis, previous pancreatic surgery, completion pancreatectomy after complicated PD, and DP for traumatic causes were excluded from the study. The study was limited to patients with clinically relevant POPF mandating a change in the normal postoperative course in the form of longer drain placement, endoscopic or percutaneous drainage, or surgical reintervention [10].

The primary outcome in this study was the development of POPF and its relation to DFA and systematic inflammatory markers. Secondary outcomes were other postoperative complications, hospital stay, and early mortality. POPF was defined and graded according to the ISGPF by any amount of drainage fluid with DFA level more than three times the upper institutional limit of serum normal serum amylase [10]. The normal range of serum amylase in our institution was 40–110 IU/l. The cutoff value for the definition of POPF was DFA more than 330 IU/l. Dindo–Clavien classification was adopted for the grading of postoperative complications [13]. Early mortality was defined as mortality within 30 days after the index surgery.

Patients were initially evaluated through history taking, general examination, and local abdominal examination. Laboratory investigations included complete blood pictures, liver function tests, renal function tests, and pancreatic tumor markers. The diagnosis was established by triphasic pelviabdominal computerized tomography (CT) with thin cuts on the pancreas. CT angiography was performed to assess the relation of the pancreatic lesion to the surrounding vessels. Tissue biopsy was not a requirement for surgical intervention. Open or laparoscopic DP was performed by experienced pancreatic surgeons. The pancreatic division was performed with a minimum of 1 cm of grossly free margin. The procedure was coined as subtotal pancreatectomy when the resection entailed pancreatic body and tail resection (80% of pancreatic tissues) [14–16]. R0 resection was confirmed by the frozen histopathological examination of the cut margin. Pancreatic transection was performed using a scalpel, monopolar diathermy, energy-sealing device, or stapler. This was followed by oversewing of the cut margin by nonabsorbable sutures. A single abdominal drain was placed in the pancreatic bed near the cut end of the pancreas before abdominal closure.

Patients were transferred to the intensive care unit or the ward according to their condition. Routine antibiotic and selective octreotide prophylaxis were administered for five days, starting intraoperatively. Octreotide prophylaxis was given in case of small pancreatic duct diameter (<3 mm), thin pancreatic parenchyma, and soft pancreatic texture. The amount of drainage fluid was recorded daily. Complete blood count and DFA were assessed routinely on the first and third PODs. Assessment of serum lactate dehydrogenase (LDH) and abdominal sonography was routinely performed on the fourth POD. After discharge, patients were scheduled for follow-up after 2 weeks, 1 month, 6 months, 12 months, and then every 6 months.

The study was approved by the local ethical committee. Patient data were registered in a prospectively maintained sheet prepared for pancreatic surgery and employed since 2000. Patient data included demographic characteristics, clinical presentation, laboratory investigations, and findings on preoperative CT. Operative variables included liver status, pancreatic consistency, blood transfusion, and operative time. Postoperative variables included drainage fluid amount and amylase level on the first (DFA-D1) and third POD (DFA-D3). Leukocytic count and serum LDH were also recorded on the corresponding days. The normal upper level for serum LDH was 280 IU/l. Other postoperative data included postoperative complications and early mortality.

Statistical analyses were performed using SPSS version 17 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were mentioned as percentages for categorical variables and means with standard deviations for continuous variables. Continuous data were compared for independent samples using the t-test or Mann–Whitney test, and categorical data were compared using the χ^2 test. The strength of the association between variables was further assessed by the Spearman correlation coefficient. For assessment of the diagnostic utility of DFA, patients were classified into high or low DFA based on a cutoff value of more than 330 IU/l. The highest DFA level on first or third PODs was considered for classification. The statistical significance level was set at less than 0.05.

Results

A total of 48 patients underwent DP in the duration between January 2018 and January 2020. However, 4 patients with chronic pancreatitis were excluded. The present study included 44 patients, with a mean age of 40.3±16.3 years and a mean BMI of 28.9±4.9 kg/m^2. The female : male ratio was 2.7 : 1. Patients' demographic and preoperative data are summarized in Table 1. Laparoscopic DP was performed in 10 (22.7%) patients. Overall, 18 (40.9%) patients required one unit of blood transfusion, and one (2.3%) patient required more than one unit. Operative data are summarized in Table 2.

The mean postoperative hospital stay was 8.3±6.5 days. The hospital stay was significantly higher in patients with POPF (7.2±6.1 vs 11.8±7 days, *P*=0.039). Data regarding the pancreatic pathology, incidence, and grading of postoperative complications are summarized in Table 3. POPF occurred in 11 (25%) patients. Of them, nine (20.5%) patients were managed by additional ultrasound-guided tube drainage. There were no cases of early mortality.

The value of DFA, serum LDH, and leukocytic count comparing patients who had POPF with patients without POPF is summarized in Table 4. The abdominal drain was removed after 5.3±1.4 days in the case of no POPF compared with 8.7±3.8 days in the case of POPF (*P*=0.000). Higher drainage fluid amount and DFA-D1 was associated with a higher risk of POPF (*P*=0.036 and 0.009, respectively). The leukocytic count was significantly higher in POPF in

Table 1 Demographic and preoperative data

	n (%)
Age (years)	40.3±16.3
Female sex	32 (72.7)
BMI (kg/m^2)	28.9±4.9
Clinical presentation	
Abdominal pain	35 (79.5)
Accidentally discovered	6 (13.6)
Hypoglycemic attacks	5 (11.5)
Weight loss	8(18.2)
Diabetic patient	4 (9.1)
Preoperative leukocytic count	7.4±4.5
Preoperative CT findings	
Origin	
Pancreatic tail	19 (43.2)
Pancreatic body	12 (27.3)
Pancreatic body and tail	9 (20.5)
Pancreatic body and neck	3 (6.8)
Infiltration from nearby organs	1 (2.3)
Size (cm)	8.2±3.2
LN enlargement	14 (31.8)
Abutting surrounding vessels	
Superior mesenteric artery	
Superior mesenteric vein	5 (11.4)
Celiac axis	2 (4.5)

CT, computerized tomography; LN, lymph node.

Table 2 Operative data

	n (%)
Liver status	
Normal	33 (75)
Fatty	4 (9.1)
Cirrhotic	7 (15.9)
The extent of resection	
Distal pancreatectomy	34 (77.3)
Subtotal pancreatectomy	10 (22.7)
Pancreatic consistency	
Soft	26 (59.1)
Firm	18 (40.9)
Tumor size (cm)	8.4±4
Pancreatic duct diameter (mm)	1.7±0.8
Operative time (h)	3.7±0.8

Table 3 Postoperative data

	n (%)
Pancreatic pathology	
Benign diseases	6 (13.6)
Neuroendocrine tumors	4 (6)
Solid pseudopapillary tumor	10 (22.7)
Lymphoma	2 (4.5)
Pancreatic adenocarcinoma	22 (50)
Postoperative complications	18 (40.9)
Dindo–Clavien classification	
I	4 (9.1)
II	4 (9.1)
IIIa	10 (22.7)
Wound infection	6 (13.7)
Abdominal collection	6 (13.7)
Internal hemorrhage	1 (2.3)
POPF	11 (25)
Grade of POPF	
A	2 (4.5)
B	9 (20.5)

POPF, postoperative pancreatic fistula.

Table 4 Relation of biochemical tests to the postoperative pancreatic fistula

	No POPF (mean±SD)	POPF (mean±SD)	*P* value
First POD drain amount (cc)	184.9±156.2	79.1±67.4	0.036
First POD drain amylase (U/l)	722±644	1966±1627	0.046
First POD WBCs (×1000/ml)	16.6±4.5	21.2±12.1	0.07
First POD LDH (U/l)	409.7±220	521.5±282.4	0.4
Third POD drain amount (ml)	92.9±233	37.3±30.4	0.44
Third POD drain amylase (U/l)	269.6±293.5	2789±4141	0.069
Third POD WBCs (×1000/ml)	14.6±5	19±7.4	0.032
Third POD LDH (U/l)	458.6±129	448±75.7	0.9
Fifth POD drain amount (ml)	54.1±97	40±63	0.69
Fifth POD drain amylase (U/l)	32.5±7.3	1626±1639	0.44
Fifth POD WBCs (×1000/ml)	11.4±4.4	17.4±4.6	0.003
Fifth POD LDH (U/l)	482.5±83.4	684±342	0.001
Drain removal (days)	5.3±1.4	8.7±3.8	0.000
Hospital stay (days)	7.2±6.1	11.8±7	0.039

LDH, lactate dehydrogenase; POD, postoperative day; POPF, postoperative pancreatic fistula; WBCs, white blood cells.

the third POD (*P*=0.032). POPF group has a significantly higher level of serum LDH on the fourth POD (*P*=0.001).

Patients with high DFA-D1 (330 IU/l) were significantly at higher risk for POPF (*P*=0.002). However, of the 15 patients with high DFA-D1, eight patients only (53.3%) had POPF. Further analysis was performed combining the high-risk criteria of high DFA, rising leukocytic count on the third POD, and high serum LDH. The rising leukocytic count was assessed comparing the levels on third POD with first POD. Those high-risk group (11 patients) based on laboratory investigations were significantly at higher risk of POPF (9/11 developed POPF, *P*=0.0001).

Discussion

POPF is the most dreaded complication after DP. It can lead to local abdominal sepsis and secondary hemorrhage and may lead to multiorgan failure owing to sepsis [17,18]. Most of the available studies are concerned with POPF after PD, and results are usually extrapolated to DP. However, POPF, after DP, is a different entity with a higher prevalence [19]. Moreover, the risk factors for POPF after DP are different. A recent study including 9366 patients concluded that soft pancreas and smaller main pancreatic duct diameter were independent risk factors for POPF after PD and were not significantly associated with higher POPF after DP (*P* value for both factors was <0.001 in PD and ≥0.169 in DP, respectively) [20]. The diagnosis of POPF after DP should be studied as a separate entity to reach the most efficient management strategy.

POPF does not necessitate surgical or radiological intervention if properly drained. The timing of removal of surgical drains is controversial as premature removal can lead to a worse outcome if late POPF occurred, and delayed removal can lead to ascending infection through the drain [8–11]. This was the rationale for drain management based on the prediction of the risk of POPF. Many studies proposed the prediction of POPF based on DFA at different PODs with variable cutoff values [2,3,5,11,12,21]. This study provides a new predictive model for proper drain management based on a combination of DFA and inflammatory biochemical markers.

Multiple studies targeted the detection of risk factors and predictors of POPF after pancreatectomy in general; however, few studies exclusively reported a predictive value for DFA for POPF after DP. The most recent and powerful study was a multicenter study by Maggino and colleagues that included 338 patients who underwent DP, and DFA-D1 was significantly associated with a higher risk of POPF. A cutoff value of DFA-D1 more than 2000 U/l was identified for prediction of POPF with a specificity and sensitivity of 62.1 and 74.3%, respectively. This was tested on a validation cohort of 166 patients. The cutoff value of DFAs on the first POD (>2000 IU/l) had the advantages of simplicity, high predictive availability, and frequent use for patient follow-up after pancreatic surgery [3].The following study by Daniel and colleagues was conducted to test the validity of the cutoff value of DFA-D1 proposed by Maggino and colleagues. It was tested on 1007 patients included in the National Surgery Quality Improvement Program Database. The cutoff value of 2000 IU/l was found to have the highest sensitivity and specificity of 67.98 and 63.81%, respectively. However, 11% of patients who had DFA-D1 less than 2000 U/l developed POPF, whereas 32.2% of patients with DFA-D1 more than 2000 IU/l did not develop POPF [5].

We propose a comprehensive and cost-effective predictive model for POPF. DFA-D1 may be a variant owing to individual patient variation in response to surgical trauma. The addition of two frequently used inflammatory markers to DFA-D1 increased the diagnostic utility of DFA-D1 from 53.3 to 81.8% (P=0.002 vs 0.0001, respectively). Rising leukocytic count LDH after elevated DFA-D1 was a strong predictor of an ongoing, rather than resolving, inflammatory process. On the day planned for patient discharge in an uneventful course, a third component of the predictive model, which is serum LDH, is assessed. This combination warrants high risk for POPF. In high-risk patients, drain removal should be delayed, and scheduling for earlier outpatient follow-up visits should be performed. Pelviabdominal ultrasound, or CT in highly suspicious cases, should be performed before drain removal to confirm the absence of indolent collections.

There are a number of limitations to this study. The first limitation is its retrospective nature. However, data were extracted from a prospectively maintained pancreatic sheet. Another limitation is the small sample size. Moreover, the variation in the indications of DP and inclusion of benign and malignant lesions may add a cofounding bias. Lastly, inclusion of subtotal pancreatectomy in the DP may lead to confounding bias and less homogeneity of the index surgery. A prospective study on a large-scale of patients is planned to lead to a higher level of evidence.

Conclusion

In conclusion, POPF is the most frequent complication after DP. DFA-D1, rising leukocytic count, and high serum LDH level compromised a more powerful predictive model for POPF. The cutoff value of DFA proposed by the ISGPF is applicable when combined with leukocytic count and serum LDH. There is a need for further prospective large-scale studies to confirm the findings of the present study.

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Conflicts of interest

There are no conflicts of interest.

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