ORIGINAL ARTICLE

Critical Appraisal of 232 Consecutive Distal Pancreatectomies With Emphasis on Risk Factors, Outcome, and Management of the Postoperative Pancreatic Fistula

A 21-Year Experience at a Single Institution

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Objective: To critically analyze a large single-institution experience with distal pancreatectomy (DP), with particular attention to the risk factors, outcome, and management of the postoperative pancreatic fistula (PF).

Design: Retrospective study.

Setting: Tertiary referral center.

Patients: A total of 232 consecutive patients with pancreatic or extrapancreatic disease necessitating DP over 21 years.

Interventions: Twenty-one patients underwent spleen-preserving DP, 117 underwent DP with splenectomy, and 94 underwent DP with multiorgan resection.

Main Outcome Measures: The perioperative and postoperative data of patients who underwent DP were analyzed. This included factors associated with postoperative morbidity with particular attention to the PF (defined by the International Study Group of Pancreatic Fistula) and changing trends in operative and perioperative data during the study period.

Results: The overall operative morbidity and mortality were 47% (107 patients) and 3% (7 patients), respectively. During the study period, the rates of resection increased from 3 cases to 23 per year, and increasingly these were performed for smaller and incidental lesions. The morbidity rate remained unchanged, but there was a decline in postoperative stay and the need for care in the intensive care unit. Pancreatic fistulas occurred in 72 patients (31%); 41 (18%) were grade A, 13 (6%) grade B, and 18 (8%) grade C. Increased weight, higher American Society of Anesthesiologists score, blood loss greater than 1 L, increased operation time, decreased albumin level, and sutured closure of the stump without main duct ligation were associated with a postoperative PF on univariate analysis. A DP with splenectomy was associated with a higher incidence of grade B or C PF and non–PF-related complications. Ninety-two percent of PFs were successfully managed nonoperatively. Clinical outcomes correlated well with PF grading, as evidenced by the progressive increase in outcome measures such as postoperative stay, readmissions, reoperations, radiologic interventions, and non–PF-related complications from grade A to C PFs.

Conclusions: Pancreatic fistula is the most common complication after DP and its incidence varies depending on the definition applied. Several risk factors for developing a PF were identified. Splenic preservation after DP is safe. The grade of a PF correlates well with clinical outcomes, and most PFs may be managed nonoperatively.

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In recent times, advances in operative technique and the perioperative care of patients have resulted in a low mortality rate for distal pancreatectomy (DP) as reported by several recent large series.[1-6] However, the morbidity rates have remained high, ranging from 22% to 47%.[4,6-9] The pancreatic fistula (PF) has consistently been reported as the most common complication after DP.[4-6] Although frequently of clinical inconsequence, it may result in numerous clinically significant and potentially life-threatening complications, such as intra-abdominal abscess, intra-abdominal hemorrhage, wound infection, and sepsis,[6] which often translate to a significant increase in hospitalization

costs.[7] The present report critically analyzes a large single-institution experience with DP, with particular attention to risk factors contributing to postoperative PF formation, its subsequent clinical sequelae, and its management.

METHODS

Between January 1, 1986, and December 31, 2006, 232 patients who underwent DP at Singapore General Hospital were identified from a prospectively maintained surgical database. All patient data were obtained retrospectively from the patients' clinical notes, operative records, anesthetic charts, and radiologic and pathological reports.

COMPLICATIONS AND DEFINITIONS

Only grade II and higher complications according to the guidelines proposed by Dindo et al[10] and DeOliveira et al[11] (Clavien classification) were routinely recorded. The only grade I complications recorded were grade A PFs and superficial wound infections. Other grade I complications, such as mild atelectasis treated via physiotherapy and transient confusion, were not reported. Delayed gastric emptying or postoperative ileus was defined as the inability to tolerate a regular diet or the need for a nasogastric tube more than 10 days postoperatively.[12] Mortality was defined as death within the same hospitalization or within 30 days of discharge. Postoperative stay was defined as the number of hospitalization days after surgery during the initial admission, as opposed to total postoperative hospitalization, which included the number of hospitalization days for readmissions. Intensive care unit (ICU) stay was applicable to patients who were admitted to the ICU immediately after surgery, as opposed to ICU transfer, which was defined as transfer of the patient from the high-dependency or general ward to the ICU for postoperative complications.

DEFINITION OF PF

Pancreatic fistula was defined and graded according to the system proposed by the International Study Group of Pancreatic Fistula (ISGPF).[13] Any drain output with an amylase content more than 3 times the upper limit of the normal serum amylase fluid level (>300 IU/L [to convert amylase to microkatals per liter, multiply by 0.0167)] at postoperative day 3 or later was considered a PF.[13,14] In addition, any complication of an intra-abdominal collection or abscess regardless of amylase content in the absence of an anastomotic leak was considered to be secondary to a PF.[9] Briefly, according to the ISGPF, grade A PFs are asymptomatic with only elevated drain amylase levels and no suspicious collections. Grade B fistulas are symptomatic; suspicious collections may be seen, but invasive treatment is not required. Grade C fistulas are clinically severe, where patients are frequently in critical condition, and this grade includes any PF requiring radiologic or surgical intervention.

SURGERY

All 232 resections were performed via laparotomy. One patient had an attempted laparoscopic procedure that was converted because of intraoperative hemorrhage. The extent of surgery was classified as spleen-preserving DP, DP with splenectomy, or multiorgan resection with DP. Splenic vessels were preserved during spleen-preserving DP. A multiorgan resection was defined as any DP in which another intra-abdominal organ was resected concomitantly with the exception of cholecystectomies.

The choice of closure of the pancreatic stump was at the discretion of the surgeon, and this included hand-sutured closure, linear stapled closure, linear stapled closure with suture reinforcement, and pancreaticojejunostomy. In selected cases, the main pancreatic duct was identified and suture ligated. Occasionally, an omental patch was used to buttress the pancreatic stump. All patients had 1 or 2 closed drains placed in the peritoneal cavity close to the transected end of the pancreas. Perioperative somatostatin analogues were administered selectively.

POSTOPERATIVE MANAGEMENT

The postoperative treatment of all patients was directed by the surgeon. Patients were treated in the immediate postoperative period in either the surgical ICU or a high-dependency unit. The outputs of all drains were measured daily and drains were removed at the surgeon's discretion. In general, drains were maintained longer if the drain amylase level or total output was high. The drain amylase level was measured only selectively (this was not always on the third day), and not all patients had the drain fluid sent for amylase content determination (especially when the drain output was low, the contents were clear or serous, and the drain was removed early).

The management of a PF was also surgeon-based. In most instances, patients were started early and maintained on an oral diet for all grades of fistulas. In asymptomatic patients, the drains were usually removed within 7 days when the output was low, or patients were sent home with the drain. Clinically significant fistulas were managed with antibiotics and/or computed tomography (CT)–guided percutaneous or open surgical drainage. Parenteral nutrition and somatostatin analogues were used infrequently.

STATISTICS

All results are presented as median (range). Statistical analyses were performed with SPSS for Windows, version 10.0 (SPSS Inc, Chicago, Illinois). Univariate analyses were conducted with χ^2, Mann-Whitney, or Kruskal-Wallis tests as appropriate, and multivariate analyses were performed with multi–logistic regression analyses. All tests were 2 sided, and $P < .05$ was considered statistically significant.

RESULTS

One hundred two males and 130 females underwent DP. The median age was 55 years (range, 14-84 years), and the indications for surgery and patient operative data are summarized in **Table 1** and **Table 2**. Twelve patients had surgery performed for an emergency, including 3 for trauma. Of 94 patients who underwent multiorgan resection, 53 had 1, 30 had 2, 10 had 3, and 1 had 5 concomitant organs resected. These organs included the stomach (n=65), colon (n=32), small bowel (n=6), kidney (n=10), adrenal gland (n=12), and liver (n=6).

DP STRATIFIED BY EXTENT OF RESECTION

A DP with multiorgan resection was performed more frequently for larger and malignant tumors (Table 2). These resections were associated with increased blood loss, requirements for transfusion, operation time, morbidity and mortality, ICU admissions, and postoperative stay. These were also associated with an increase in grade B/C PFs and

Table 1. Indications for Surgery

Indication	No. of Patients			
	Overall (N = 232)	Spleen-Preserving DP (n = 21)	DP With Splenectomy (n = 117)	DP With Multiorgan Resection (n = 94)
Pancreatic disease	**164**	21	117	26
Ductal carcinoma	**30**	1	21	8
PEN	**22**	3	16	3
IPMN	**13**	0	10	3
MCN	**26**	5	18	3
SCN	**33**	5	25	3
SPPN	**14**	1	12	1
Pseudocyst	**6**	2	1	3
Other cysts	**10**	0	8	2
Chronic pancreatitis	**4**	1	3	0
Trauma	**3**	2	1	0
Metastases to pancreas	**1**	1	0	0
Others	**2**	0	2	0
Extrapancreatic disease	**68**	0	0	68
Gastric adenocarcinoma	**35**	0	0	35
GIST	**15**	0	0	15
Retroperitoneal sarcoma	**11**	0	0	11
Renal cell carcinoma	**2**	0	0	2
Colonic carcinoma	**3**	0	0	3
Others	**2**	0	0	2

Abbreviations: DP, distal pancreatectomy; GIST, gastrointestinal stromal tumor; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PEN, pancreatic endocrine neoplasm; SCN, serous cystic neoplasm; SPPN, solid pseudopapillary neoplasm.

Table 2. Operative Results in Patients and Comparison by Extent of Resection

	All DPs (N = 232)	Spleen-Preserving DP (n = 21)	DP With Splenectomy (n = 117)	DP With Multiorgan Resection (n = 94)	*P* Value[a]	*P* Value[b]
Tumor size, median (range), mm	55 (1-240)	20 (8-150)	40 (1-200)	75 (15-240)	.14	<.001
Indications, No. (%)					.15	<.001
Benign	59 (25)	10 (48)	40 (34)	9 (10)		
Premalignant	49 (21)	8 (38)	35 (30)	6 (6)		
Malignant	124 (53)	3 (14)	42 (36)	79 (84)		
Blood loss >1 L, No. (%)	39/194 (20)	1/20 (5)	9/98 (9)	29/76 (38)	.54	<.001
Perioperative transfusion, No. (%)	101/225 (45)	3/21 (14)	26/115 (23)	72/89 (81)	.39	<.001
Operation time, median (range), min	185 (55-710)	150 (85-350)	150 (55-325)	245 (105-710)	.67	<.001
Extent of resection right of SMV, No. (%)	36 (16)	2 (10)	19 (16)	15 (16)	.43	.73
Stump closure, No. (%)					.17	.30
Sutured	73/226 (32)	9/21 (43)	31/115 (27)	33/90 (37)		
Stapled	21/226 (9)	4/21 (19)	11/115 (10)	6/90 (7)		
Both	130/226 (58)	8/21 (38)	72/115 (63)	50/90 (56)		
Anastomosis	2/226 (1)	0	1/115 (1)	1/90 (1)		
Main duct ligated separately, No. (%)	42/226 (19)	4/21 (19)	15/115 (13)	23/90 (26)	.47	.07
Mortality, No. (%)	7 (3)	0	1 (1)	6 (6)	.67	.046
Morbidity, No. (%)	107/228 (47)	8/21 (38)	40/116 (35)	59/91 (65)	.75	<.001
PF, No. (%)	72/230 (31)	7/21 (33)	30/117 (26)	35/92 (38)	.46	.13
Grade B/C PF, No. (%)	32 (14)	0	14 (12)	18 (19)	.09	.05
Non–PF-related complications, No. (%)	69/229 (30)	1/21 (5)	24/117 (21)	44/91 (48)	.08	<.001
ICU admission, No. (%)	42 (18)	1 (5)	13 (11)	28 (30)	.38	.001
Reoperation within 30 d, No. (%)	11/231 (5)	0/21	4/117 (3)	7/93 (8)	.39	.21
Postoperative stay, median (range), d	8 (3-86)	7 (5-20)	7 (3-29)	11 (6-86)	.84	<.001
Readmission, No. (%)	26/231 (11)	0/21	12/117 (10)	14/93 (15)	.13	.13

Abbreviations: DP, distal pancreatectomy; ICU, intensive care unit; PF, pancreatic fistula; SMV, superior mesenteric vein.
[a] Comparison between spleen-preserving DP and DP with splenectomy.
[b] Comparison between all 3 groups.

non–PF-related complications. Subset analysis comparing DP with vs without splenectomy did not disclose any statistically significant difference between the 2 groups, although DP with splenectomy was associated with an increased risk of developing clinically significant PF and non–PF-related complications ($P=.09$ and $P=.08$).

Table 3. Trends in Operative and Perioperative Results Over Time

	1986-1992	1993-1999	2000-2006	*P* Value
No. of resections	19	50	163	
Resections per year, No.	3	7	23	
Age of patient, median (range), y	54 (14-77)	55 (16-81)	56 (17-84)	.11
ASA score, No. (%)				.01
1	8/17 (47)	23 (46)	36 (22)	
2	9/17 (53)	21 (42)	107 (66)	
3	0	6 (12)	18 (11)	
4	0	0	2 (1)	
Incidental lesions, No. (%)	2 (11)	7 (14)	66 (41)	<.001
Cystic lesions of the pancreas, No. (%)	7 (37)	21 (42)	74 (45)	.74
Size, median (range), mm	108 (10-240)	75 (10-210)	45 (1-240)	<.001
Emergency, No. (%)	1 (5)	3 (6)	8 (5)	.95
Indications, No. (%)				.29
Benign	5 (26)	7 (14)	47 (29)	
Premalignant	4 (21)	14 (28)	31 (19)	
Malignant	10 (53)	29 (58)	85 (52)	
Blood loss >1 L, No. (%)	4/11 (36)	10/43 (23)	25/140 (18)	.28
Perioperative transfusion, No. (%)	7/15 (47)	24/47 (51)	70/163 (43)	.61
Operative time, median (range), min	180 (85-305)	185 (80-650)	190 (55-710)	.81
Extent of resection, No. (%)				.22
Spleen-preserving DP	4 (21)	6 (12)	11 (7)	
DP and splenectomy	7 (37)	23 (46)	87 (53)	
Multiorgan resection	8 (42)	21 (42)	65 (40)	
Stump closure, No. (%)				<.001
Sutured	17/18 (94)	26/46 (57)	30/162 (19)	
Stapled	0	8/46 (17)	13/162 (8)	
Both	1/18 (6)	12/46 (26)	117/162 (72)	
Anastomosis	0	0	2/162 (1)	
Main duct ligated separately, No. (%)	7/18 (39)	14/46 (30)	21/162 (13)	.002
Mortality, No. (%)	1 (5)	3 (6)	3 (2)	.27
Morbidity, No. (%)	6/15 (40)	25/50 (50)	76/163 (47)	.79
PF, No. (%)	2/17 (12)	14/50 (28)	56/163 (34)	.14
Grade B/C PF, No. (%)	1 (5)	7 (14)	24 (15)	.53
Non–PF-related complications, No. (%)	4/16 (25)	21/50 (42)	44/119 (37)	.12
ICU admission, No. (%)	7 (37)	11 (22)	24 (15)	.04
Postoperative stay, median (range), d	8 (5-45)	11 (5-86)	8 (3-47)	.003
Reoperation within 30 d, No. (%)	2/18 (11)	3/50 (6)	6/163 (4)	.34
Readmission, No. (%)	2/18 (11)	8/50 (16)	16/163 (10)	.48

Abbreviations: ASA, American Society of Anesthesiologists; DP, distal pancreatectomy; ICU, intensive care unit; PF, pancreatic fistula.

TRENDS IN PERIOPERATIVE RESULTS OVER TIME

The annual rate of DPs increased progressively, and an increasing number of resections were performed for smaller, asymptomatic lesions in patients with higher American Society of Anesthesiologists (ASA) scores (**Table 3**). There was a change in the choice of stump closure adopted, from the predominant use of sutured closure to combined sutured and stapled closure, and a decline in the practice of main pancreatic duct ligation. The morbidity rate, including the incidence of PFs, remained relatively unchanged.

POSTOPERATIVE MORBIDITY

The overall morbidity and mortality rates were 47% and 3%, respectively (**Table 4**). The 7 deaths were due to pneumonia (n=3), acute myocardial infarction, pulmonary embolism, stroke, and anastomotic leak (n=1 each). Overall, 11 (5%) and 26 (11%) patients required a reoperation or were readmitted for postoperative complications. Univariate analyses demonstrated that increased age, higher ASA score, blood loss greater than 1 L, need for transfusion, splenectomy, increased operation time, multiorgan resection, decreased hemoglobin level, decreased albumin level, increased creatinine level, and a malignant lesion were significantly associated with a non–PF-related complication (**Table 5** and **Table 6**). None of these factors was an independent predictor of a non–PF-related complication (**Table 7**)

PANCREATIC FISTULA

Incidence

According to the ISGPF definition, PF occurred in 72 (31%) of patients. However, when the Johns Hopkins definition[12] of drainage of more than 50 mL of fluid per day with amylase content greater than 3 times the serum amylase level for more than 10 days postoperatively was applied, the incidence of PF was only 17% (38 patients).

Table 4. Postoperative Morbidity

Morbidity	No. (%)
Total Complications	**107/228** (47)
PF (Hopkins definition)	38/229 (17)
PF (ISGPF definition)	72/230 (31)
Grade A	41 (18)
Grade B	13 (6)
Grade C	18 (8)
Non–PF-related complications[a]	69/229 (30)
Cardiovascular	
Acute coronary syndrome/arrhythmia	11
Fluid overload	2
Stroke	1
Pulmonary	
Atelectasis	8
Pneumonia	14
Pleural effusion	17
Pulmonary embolism	1
Pneumothorax	1
Gastrointestinal tract	
Gastroparesis/ileus	8
Anastomosis leak or dehiscence	3
Genitourinary	
Acute renal failure	1
Urine infection	6
Acute retention of urine	2
Wound infection	17
Burst abdomen	1
Sepsis	1
Enterocutaneous fistula	1
Phlebitis	2
Deep vein thrombosis	2
Confusion	1
Others	4

Abbreviations: ISGPF, International Study Group of Pancreatic Fistula; PF, pancreatic fistula.

[a] Denominators and percentages are not given for individual complications because denominators vary and because some patients had more than 1 non–PF-related complication.

Risk Factors

On univariate analyses (Table 5 and Table 6), the rate of PF was significantly higher in patients with increased weight, higher ASA score, blood loss greater than 1 L, increased operation time, and decreased albumin level, and in patients who underwent sutured closure of the stump without main duct ligation. In addition to these 6 factors, performance of a splenectomy was predictive of a clinically significant PF. Decreased albumin level and increased operation time were independent risk factors for developing a PF and a grade B/C PF, respectively (Table 7)

Postoperative Outcome

Patients with a PF had increased length of postoperative stay, total postoperative hospitalization stay, readmission rates, reoperation rates, radiologic intervention rates, need for CT scan, intra-abdominal collections, and need for antibiotic therapy (**Table 8**). The intra-abdominal drains were maintained longer, and an increased proportion of patients were discharged with the drain in situ. Non–PF-related complications also occurred more frequently in patients with PFs. Six reoperations, 15 radiologic interventions, and 18 readmissions were directly related to a postoperative PF. Although 3 patients with PFs died, none of the deaths was directly attributed to a PF.

The outcomes of patients with grade A PF were similar to those of patients without PF. They differed only with regard to the need for postoperative CT ($P=.009$), antibiotic therapy ($P=.006$), and maintenance of the drain on discharge ($P=.009$). All patients with grade A fistulas were maintained on an oral diet, and no specific treatment was administered (antibiotic therapy in 8 of 41 patients [20%] with grade A PFs was indicated for other complications).

Twelve patients with grade B PFs underwent CT, and none demonstrated intra-abdominal collections. All of the patients with grade B PFs were treated with antibiotics. Two of 13 patients (15%) had drains on discharge, and readmission was required in 5 of 13 (38%). All 18 patients with grade C fistulas underwent CT, and 17 demonstrated intra-abdominal collections. Reoperation was required in 6 patients (33%), radiologic interventions in 15 (83%), and readmission in 13 (72%).

Comparison Across PF Grades

Comparison across fistula grades demonstrated that higher-grade fistulas were significantly more likely to be associated with intra-abdominal collections, antibiotic therapy, somatostatin treatment, increased time for fistula closure, need for radiologic interventions, and reoperations as defined in the ISGPF classification scheme. However, other factors not included in the ISGPF classification, including need for CT, postoperative stay, readmissions, duration of drain, and the presence of non–PF-related complications, also increased progressively with fistula grade. Significant differences between grade B and C fistulas with respect to clinical factors distinct from the ISGPF scheme, including duration of drain and time for PF closure, were also observed. The readmission rate and total postoperative stay were also higher for grade C vs grade B fistulas, although these only approached statistical significance.

COMMENT

The number of DPs performed annually at our institution has been steadily increasing during the past 21 years. However, despite evidence from the literature suggesting that higher surgical volumes translate into improved outcomes,[1,5,15] the high morbidity rates, including postoperative PF rates associated with DP, remained unchanged. These high morbidity and PF rates (30% to 40%) after DP have also been reported by others[6] and could partly be explained by the increasing number of patients with higher ASA score and small lesions (with soft pancreas) undergoing resection. Nevertheless, we observed a steady decline in the need for immediate postoperative ICU care and postoperative hospitalization. There was also a trend toward decreasing mortality, although this was not statistically significant. These improving clinical outcomes may be the result of improved postoperative treatment of surgical patients and their complications, increasing case volume resulting in

Table 5. Univariate Analysis of Factors Associated With Postoperative Complications

Factor	Non–PF-Related Complications	*P* Value	PF	*P* Value	Grade B/C PF	*P* Value
Sex		.07		.10		.46
Male	36/99 (36)		37/100 (37)		16/102 (16)	
Female	33/130 (25)		35/130 (27)		16/130 (12)	
Diabetes		.74		.65		.83
Yes	15/53 (28)		18/53 (34)		7/54 (13)	
No	54/122 (44)		54/176 (31)		25/177 (14)	
ASA score		<.001		.01		.009
1	11/67 (16)		11/67 (16)		4/67 (6)	
2	43/136 (32)		49/136 (36)		20/137 (15)	
3	15/24 (63)		11/24 (46)		8/24 (33)	
4	0/2		1/2 (50)		0/2	
Indication		.12		.15		.25
Emergency	6/12 (50)		6/12 (50)		3/12 (25)	
Elective	63/217 (29)		66/218 (30)		29/220 (13)	
Site of transection		.46		.37		.98
Right of SMV	9/36 (25)		9/36 (25)		5/36 (14)	
Left of SMV	69/193 (36)		63/194 (33)		27/196 (14)	
Blood transfusion		<.001		.27		.16
Yes	47/100 (47)		36/100 (36)		18/101 (18)	
No	19/124 (15)		36/124 (29)		14/124 (11)	
Blood loss >1 L		<.001		.007		<.001
Yes	21/38 (55)		19/38 (50)		13/39 (33)	
No	33/155 (21)		42/155 (27)		14/155 (9)	
Splenectomy		.006		.96		.049
Yes	68/207 (33)		65/208 (31)		32/178 (15)	
No	1/22 (5)		7/22 (32)		0/22	
Multiorgan resection		<.001		.07		.051
Yes	44/91 (48)		35/92 (38)		18/94 (19)	
No	25/138 (18)		37/138 (27)		14/138 (10)	
Main duct ligated separately		.11		.14		.06
Yes	16/40 (40)		9/41 (22)		2/42 (5)	
No	50/183 (27)		62/183 (34)		29/184 (16)	
Stump closure		.12		.69		.77
Sutured	28/70 (40)		25/71 (35)		12/73 (16)	
Stapled	5/21 (24)		6/21 (29)		2/21 (10)	
Both	33/130 (25)		40/130 (31)		17/130 (13)	
Anastomosis	0/2		0/2		0/2	
Sutured closure without duct ligation		.18		.03		.01
Yes	14/36 (39)		17/36 (47)		10/37 (27)	
No	52/187 (28)		54/188 (29)		21/189 (11)	
Malignant potential		<.001		.50		.28
Benign	9/59 (15)		19/59 (32)		7/59 (12)	
Premalignant	9/49 (18)		12/49 (25)		4/49 (8)	
Malignant	51/121 (42)		41/122 (34)		21/124 (17)	
Octreotide		.16		.19		.49
Yes	21/58 (36)		23/58 (40)		10/58 (17)	
No	43/162 (27)		49/162 (30)		22/163 (14)	
Chronic pancreatitis		.17		.45		.56
Yes	11/45 (24)		12/45 (27)		5/45 (11)	
No	58/184 (32)		60/185 (32)		27/187 (14)	

Abbreviations: ASA, American Society of Anesthesiologists; PF, pancreatic fistula; SMV, superior mesenteric vein.

"streamlining" of patient care,[16] or increasing surgeon comfort and confidence in discharging patients early. These trends have also been attributed to the introduction of case management and clinical pathways.[4]

Although the PF is the main cause of post-DP morbidity, non–PF-related complications were also common, occurring in 30% of cases. In general, we found factors reflecting poorer premorbid status (greater age, higher ASA score, lower hemoglobin concentration, lower albumin levels, and increased creatinine levels) and factors associated with increased complexity of surgery (blood loss >1 L, need for perioperative transfusion, increased operation time, the presence of a malignant lesion, and DP with multiorgan resection) to be associated with increased non–PF-related complications. The impact of a splenectomy on non–PF-related complications is discussed later in this section.

The most common and clinically relevant complication after DP is a PF,[17] which is associated with complications such as pancreatic fluid collection, intra-abdominal abscess, wound infection, and sepsis.[18] These have been thought by some to occur more frequently with

Table 6. Univariate Analysis of Factors (Continuous Variables) Associated With Postoperative Complications[a]

	Complication				
	Present		Absent		
Factor	No.	Median (Range)	No.	Median (Range)	*P* Value
Non–PF-Related Complications					
Age, y	69	64 (32-84)	160	54 (14-84)	<.001
Weight, kg	53	57 (34-90)	126	55 (35-113)	.43
Hb, g/dL	65	12.6 (8.0-15.0)	158	13.0 (8.0-18.0)	.01
Albumin, g/dL	52	3.6 (1.5-5.0)	136	3.9 (1.8-4.9)	<.001
Creatinine, mg/dL	64	0.9 (0.4-16.1)	157	0.8 (0.5-4.5)	.05
Operation time, min	69	225 (80-710)	159	170 (55-670)	<.001
PF					
Age, y	72	58 (36-90)	158	55 (14-84)	.07
Weight, kg	58	58 (36-90)	121	55 (34-113)	.046
Hb, g/dL	71	12.9 (8.0-16.0)	152	12.8 (8.0-18.0)	.73
Albumin, g/dL	59	3.6 (1.5-4.7)	129	3.9 (1.7-5.0)	.001
Operation time, min	72	205 (80-710)	157	180 (55-650)	.009
Grade B/C PF					
Age, y	32	57 (18-84)	200	55 (14-84)	.63
Weight, kg	25	62 (43-90)	155	55 (34-113)	.007
Hb, g/dL	31	13.0 (9.0-15.0)	192	12.8 (8.0-18.0)	.44
Albumin, g/dL	25	3.6 (1.5-4.4)	163	3.8 (1.7-5.0)	.01
Operation time, min	32	245 (80-710)	199	185 (55-650)	.006

Abbreviations: Hb, hemoglobin; PF, pancreatic fistula.
SI conversion factors: To convert Hb and albumin to grams per liter, multiply by 10; creatinine to micromoles per liter, multiply by 88.4.
[a] Other factors, including presence of ischemic heart disease, hypertension, chronic obstructive lung disease, renal impairment, previous abdominal surgery, platelet count, serum alkaline phosphatase level, serum bilirubin level, and tumor size, were not significant in predicting a PF.

DP than with pancreaticoduodenectomy,[2,4] although a recent study demonstrated that the incidence of PF for these 2 procedures is similar.[19] The incidence of postoperative PF is highly variable, ranging from 0% to 64% in the literature,[9] and this has been partly attributed to the variability of definitions used.[13] A recent review showed that more than 25 definitions of PF have been used that vary with respect to the amount of daily output from the drain, duration of drainage, and amylase concentration of the fluid.[20] However, the recent ISGPF consensus statement has resulted in an internationally accepted definition that will allow more meaningful comparisons between the PF rates of various institutions in the future.[13] This classification system has been recently validated for PDs,[14] and it has been shown to correlate well with clinical and economic outcome.

Our present findings confirm the important impact of the definition of a PF on its incidence; we found the incidence of PF to be 31% with the ISGPF definition[13] vs 17% with the Johns Hopkins definition.[12] Of these, 18% were grade A fistulas, 6% were grade B, and 8% were grade C. These rates were comparable to the 20% to 33% rates reported in several recent series.[9,19,21,22] In the largest series of DP to date, Kleef et al[6] reported a PF rate of only 11.6%. However, the authors adopted a stringent definition resulting in only grade B and C PFs being reported.

The occurrence of a PF has a significant effect on health care cost and is a huge drain on health care resources. A recent study demonstrated that occurrence of a PF doubles the cost and dramatically increases health care utilization.[9] The economic burden of a PF was further shown by Pratt et al[14] for PDs, where the authors also demonstrated that costs increased in tandem with the severity grade of a PF. Although cost was not specifically analyzed in this study, we demonstrated that the occurrence of a PF was associated with worse clinical outcomes and increased use of various clinical resources, which would logically translate to increased costs.

Thus far, only one study has addressed the effect on clinical outcomes of increasing grades of PFs after DP.[19] In that study, although the authors supposedly applied the grading proposed by the ISGPF, they classified PFs requiring percutaneous drainage as grade B fistulas. This is contrary to the original ISGPF report,[13] which classifies all PFs requiring percutaneous or surgical drainage as grade C. The present analysis reaffirms the findings of Pratt et al[14] that clinical outcomes worsened with the grade of PF after PD. However, in their subsequent study, they reported that the clinical impact of grade C PFs was no more severe than that of grade B after DP as opposed to PFs after PD.[19] In our study, we successfully demonstrated (albeit with some difficulty) that the clinical outcome of a grade C PF was worse than that of a grade B PF (Table 8). Hence, this is the first study, to our knowledge, to successfully validate the ISGPF classification scheme for PF after DP. A grade C fistula was significantly associated with increased reoperation, need for percutaneous drainage, duration of drain placement, and time for fistula closure compared with a grade B fistula. It was also associated with an increase in readmission and total postoperative hospitalization ($P=.06$ and $P=.07$). This difference is likely owing to the small sample size of 8

patients with a clinically relevant fistula in the previous study as opposed to our present analysis, resulting in a type II error.

The identification of patients at high risk of developing a PF is important because it has the potential of incurring cost savings. It allows surgeons to identify and administer costly prophylactic treatment to selected patients who will benefit the most from any "PF-reducing" therapy. However, risk factors for developing a PF after DP remain unclear.[7] Various technical and demographic factors have been implicated in the development of PF, including method of stump closure,[6,7,22] concomitant splenectomy, indication for resection (malignant vs benign or elective vs emergent),[7] concomitant organ resections,[6] longer operation time,[6] body mass index,[23] and use of somatostatin analogues.[24]

The controversy regarding the impact of stump closure on the PF rate is far from resolved because there are many conflicting data in the literature. Several studies have demonstrated that sutured closure is superior to stapled closure,[6,25] whereas others have demonstrated the contrary.[7,26] To further complicate matters, some studies have shown no difference between the 2 methods.[8,21,22] A recent meta-analysis failed to draw firm conclusions on the optimal method for stump closure, although there was a trend toward favoring stapled closure.[18] Kleef et al[6] demonstrated that the pancreatic anastomosis had the lowest leak rate (0%) followed by the seromuscular patch (8.3%), suture (9.3%), and stapler (15.9%). However, the authors warned against performing a routine pancreatic anastomosis because of the potentially devastating complication of leakage of bowel contents. More innovative techniques, such as sandwich fibrin glue[27,28] and ultrasonic dissection,[17,29] have also been proposed to reduce pancreatic stump leak.

Two recent studies demonstrated that specific ligation of the pancreatic duct is an important factor in reducing the incidence of PF.[21,22] Furthermore, careful analysis of the results of the study by Kleef et al[6] seemed to indirectly support the practice of main duct ligation; all of their patients who underwent sutured closure had ligation of the main duct, whereas patients who underwent stapled closure did not. In the present analysis, we observed a trend toward a lower rate of PF formation after main duct ligation ($P=.14$ for any fistula and $P=.06$ for clinically significant fistulas). However, subset analysis demonstrated that main duct ligation is especially important after sutured closure of the pancreatic stump. We were unable to assess the influence of main duct ligation in stapled-alone or in combined stapled and sutured closure; the sample size of patients was too small. Sutured closure without ligation of the main pancreatic duct was a significant risk factor in developing a PF on univariate analysis, and this approached statistical significance on multivariate analysis ($P=.06$). There was no difference between the various techniques of parenchymal closure, although, notably, we also observed a low leak rate (0%) after a pancreaticoenteric anastomosis (n=4).

In addition to sutured closure without ligation of the main duct, factors reflecting a patient's poor premorbid status (increased ASA score, decreased albumin levels, and increased body weight) and factors indicating a more complex surgery (longer operation time and blood loss >1 L) were significantly associated with a PF, including clinically relevant fistulas. The identification of increased ASA score and decreased albumin level as risk factors for a PF has not been reported previously. However, it is easy to understand why these are risk factors because they reflect a patient's premorbid status. It is also well known that low albumin levels indicate poor nutritional status and are associated with increased risk of anastomotic leak after bowel resection.

The role of splenic preservation after DP remains debatable. Although splenectomy has consistently been shown to be associated with increased infectious complications after resection of other intra-abdominal organs, there is presently little evidence demonstrating improved outcome after DP with splenic preservation.[30] The experience of Shoup et al[30] with 46 DPs with splenic preservation demonstrated a reduction in perioperative infectious complications, severe complications, and length of hospital stay compared with 79 DPs with splenectomy.[30] However, others have not reported this benefit.[31,32] We found splenectomy to be a significant risk factor in developing non–PF-related complications and grade B/C fistulas on univariate analysis. Although a major confounding factor is that splenectomy was frequently performed in patients who underwent DP with multiorgan

Table 7. Multivariate Analyses of Factors Associated With Postoperative Complications

Factor	Hazard Ratio (95% CI)	*P* Value
Non–PF-Related Complications		
ASA score	NA	.31
Blood transfusion	2.21 (0.65-7.57)	.20
Blood loss >1 L	2.44 (0.77-7.68)	.13
Splenectomy	2.86 (0.31-26.09)	.35
Multiorgan resection	0.68 (0.20-2.30)	.53
Malignant potential	NA	.49
Age	1.03 (1.00-1.07)	.09
Albumin	0.99 (0.90-1.08)	.77
Hemoglobin	0.88 (0.67-1.15)	.35
Creatinine	1.00 (1.00-1.01)	.22
Operation time	1.00 (1.00-1.01)	.54
PF		
ASA score	NA	.46
Blood loss >1 L	0.97 (0.30-3.16)	.95
Sutured closure without duct ligation	3.40 (0.96-12.07)	.06
Albumin level	0.92 (0.85-0.99)	.02
Operation time	1.00 (1.00-1.01)	.26
Weight	1.02 (0.99-1.05)	.30
Grade B/C PF		
ASA score	NA	.17
Blood loss >1 L	1.20 (0.28-5.11)	.81
Splenectomy	1.80 (NA)	>.99
Sutured closure without duct ligation	3.84 (0.71-20.79)	.12
Albumin level	0.97 (0.87-1.08)	.61
Operation time	1.01 (1.00-1.01)	.04
Weight	1.04 (1.00-1.08)	.09

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; NA, not applicable; PF, pancreatic fistula.

Table 8. Outcomes of Patients With and Without PF and Comparisons Between Fistula Grades[a]

	No PF (n = 158)	PF (n = 72)	*P* Value[b]	Grade A (n = 41)	Grade B (n = 13)	Grade C (n = 18)	*P* Value[c]	*P* Value[d]
CT performed	6 (4)	36 (50)	<.001	6 (15)	12 (92)	18 (100)	<.001	.23
Intra-abdominal collection	2 (1)	29 (40)	<.002	0	12 (92)	17 (94)	<.001	.81
Postoperative stay, median (range), d	8 (3-86)	11 (4-47)	<.001	9 (4-34)	15 (5-25)	19 (8-47)	.02	.47
Readmissions	7/157 (5)	19/72 (26)	<.001	1/41 (2)	5/13 (38)	13/18 (72)	<.001	.06
Total postoperative hospitalization, median (range), d	8 (7-86)	13 (4-80)	<.001	9 (4-34)	21 (10-37)	29 (11-80)	<.001	.07
Radiologic intervention	1/157 (1)	16/72 (22)	<.001	0/41	1/13 (8)	15/18 (83)	<.001	<.001
Reoperation	3/157 (2)	8/72 (11)	.003	2/41 (5)	0/13	6/18 (33)	.002	.02
Intervention or reoperation	4/157 (3)	20/72 (28)	<.001	2/41 (5)	1/13 (8)	17/18 (94)	<.001	<.002
ICU transfer	7 (4)	5 (7)	.43	2 (5)	2 (15)	1 (6)	.42	.36
Antibiotic therapy	9/154 (6)	39/72 (54)	<.001	8/41 (20)	13/13 (100)	18/18 (100)	<.001	NA
Required TPN	6 (4)	3 (4)	.89	1 (2)	1 (8)	1 (6)	.67	.81
Somatostatin analogue therapy	1/155 (1)	4/72 (6)	.02	0/41	1/13 (8)	3/18 (17)	.03	.43
Discharged with drain	4/154 (3)	11/72 (15)	<.001	5/41 (12)	2/13 (15)	4/18 (22)	.62	.64
Duration of drain, median (range), d	5 (2-19)	10 (4-220)	<.001	8 (4-50)	20 (7-45)	40 (8-220)	<.001	<.001
Median time to PF closure after surgery, median (range), d	NA	NA	NA	8 (4-50)	20 (7-45)	37 (17-365)	<.001	.01
Non–PF-related complications	35/157 (22)	34/72 (47)	<.001	10/41 (24)	11/13 (85)	13/18 (72)	<.001	.42
Mortality	4 (3)	3 (4)	.50	1 (2)	2 (15)	0	.08	.09

Abbreviations: CT, computed tomography; ICU, intensive care unit; NA, not applicable; PF, pancreatic fistula; TPN, total parenteral nutrition.

[a] The clinical outcomes and types of treatment administered to patients (CT scan, antibiotic therapy, reoperation, etc) were for any complication and not limited to those performed specifically for fistula management. Values are number (percentage) unless otherwise stated.

[b] Comparison between patients with and without PF.

[c] Comparison between grades A, B, and C PF.

[d] Comparison between grades B and C PF.

resection, subset analysis comparing only spleen-preserving DP vs DP with splenectomy also demonstrated a trend toward a decrease in non–PF-related complications and grade B/C fistulas. It is also interesting that splenectomy was the only factor not associated with an increased risk of developing a PF but was associated with an increased risk of a clinically significant PF in this study. This suggests that splenic preservation does not decrease the occurrence of PF but may protect against its progression to infectious complications. These observations are consistent with the findings of Shoup et al[30] and seem to support the hypothesis that alterations in the immune system after splenectomy give rise to increased postoperative infectious complications.

Currently, the management of a PF after DP is not standardized.[22] Most studies report that PFs can be managed conservatively[8,22] with antibiotics, supplemental nutrition, somatostatin analogues, and adequate drainage. In our experience, 92% of PFs and 81% of clinically relevant PFs were successfully managed nonoperatively. Most patients were maintained on an oral diet (96%), and somatostatin analogues (6%) were infrequently used. Overall, patients with PFs had their drains removed early, at a median duration of 10 days, and only 15% of patients were discharged with the drain. Patients with PFs were frequently discharged early (median postoperative stay, 11 days), with a readmission rate of 26%. Applying this management policy, we achieved a low clinically significant PF rate of 13%. This practice was, however, contrary to the management policy advocated by other investigators, some of whom have proposed the use of parenteral nutrition[22] and/or somatostatin analogues[6,22] in the treatment of PFs and others who have proposed the prolonged maintenance of the intra-abdominal drain.[8]

In summary, PF is the most common complication after DP, and its incidence varies depending on the definition applied. Increased weight, higher ASA score, blood loss greater than 1 L, increased operation time, decreased albumin level, and sutured closure of the stump without main duct ligation are risk factors for developing a PF. Splenic preservation after DP is safe and may result in a decrease in clinically significant PF and non–PF-related complications. This study also demonstrates that the ISGPF grading of PF correlates well with clinical outcomes.

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