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ORIGINAL ARTICLE

Natural History of Intra-abdominal Fluid Collections Following Pancreatic Surgery

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Abstract
Background Little data are available for non-abscess abdominal fluid collections (AFCs) after pancreatic surgery and their clinical implications. We sought to analyze the natural history of such collections in a population of patients subject to routine postoperative imaging.
Methods From 1995 to 2011, 709 patients underwent pancreatic resections and routine postoperative monitoring with abdominal ultrasound according to a unit protocol. AFCs were classified as asymptomatic (no interventional treatment), symptomatic (need for percutaneous drainage of sterile, amylase-poor fluid), and pancreatic fistula (drainage of amylase-rich fluid).
Results Ninety-seven of 149 AFCs (65 %) were asymptomatic and resolved spontaneously after a median follow-up of 22 days (interquartile range, 9–52 days). Among 52 (35 %) AFCs requiring percutaneous drainage, there were 20 pancreatic fistulas and 32 symptomatic collections. A stepwise logistic regression model identified three factors associated with the need for interventional treatment, i.e., body mass index ≥25 (odds ratio, 3.23; 95 % confidence interval (CI), 1.32 to 7.91), pancreatic fistula (odds ratio, 2.93; 95 % CI, 1.20 to 7.17), and biliary fistula (odds ratio, 3.92; 95 % CI, 1.35 to 11.31).
Conclusions One fourth of patients develop various types of non-abscess AFCs after pancreatic surgery. Around half of them are asymptomatic and resolve spontaneously.

Keywords Pancreaticoduodenectomy · Pancreatectomy · Distal pancreatectomy · Complications · Abdominal fluid collections

Introduction

The marked decrease in postoperative mortality reported over recent decades for pancreatic resections is not paralleled by significant changes in morbidity rates.[1,2] Various types of fluid collections within the abdomen remain among the most common complications of pancreatic surgery as no effective prophylaxis is available despite many technical and pharmacological attempts.

In more recent series, the incidence of intra-abdominal abscesses following pancreatic resections ranges from 6 to 11 %.[3–6] However, little is known about non-abscess abdominal fluid collections (AFCs). Such findings, as generally believed, are relatively common in the early postoperative course of patients subject to pancreatic surgery and often resolve spontaneously.[7,8] Nevertheless, there is little evidence to support such claims as AFCs are rarely reported even in randomized clinical trials focused on the technical aspects of pancreatectomy.[2,9–11] This is partly related to the retrospective design of most studies on complications associated with pancreatic surgery and lack of routine postoperative abdominal imaging in asymptomatic patients. Consequently, many aspects related to the natural history of AFCs remain to be clarified to provide information useful for clinical decision making in the early postoperative period.[12–16]

Since 1990, data of all patients undergoing pancreatic surgery at our academic tertiary surgical center have been

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documented prospectively in a computerized database. Moreover, all patients are subject to routine abdominal ultrasound (US) before drain removal and at follow-up visits. Such a unit protocol allows for early identification and monitoring of potential abdominal complications in otherwise asymptomatic patients. Given the paucity of published data on non-abscess abdominal collections after pancreatic surgery, the aim of this study was to analyze the natural history of AFCs and identify risk factors predicting the need for interventional treatment of such collections.

Methods

Patients and Perioperative Care

An electronic database of all patients undergoing pancreatic resections between 1990 and 2011 at our academic tertiary surgical center was reviewed. All relevant data, including demographics, clinical findings, details of surgical procedures, and histopathological parameters, were collected prospectively using a standardized form. The present study was limited to the period of 1995 through 2011 when results of routine imaging tests were incorporated in the database. The study was approved by the Bioethics Committee of Jagiellonian University.

All procedures were carried out by four senior consultant surgeons experienced in pancreatobiliary surgery and using a similar technique of dissection. Technical variations of pancreatic resections, e.g., pylorus preservation, types of pancreatic anastomosis, extent of lymphadenectomy, were performed according to the surgeons' preferences and classified as defined by the recent guidelines.[17] Abdominal drains were routinely used and typically removed on postoperative day (POD) 4 to 5 if daily drainage was <50 ml of unsuspected effluent with low amylase content. Patients received perioperative antibiotic prophylaxis, most commonly first-generation and second-generation cephalosporins, and low-molecular-weight heparin was used to minimize the risk of thromboembolic events. Postoperative analgesia was provided by epidural infusion of bupivacaine and fentanyl combined with intravenous morphine chloride and nonsteroidal anti-inflammatory drugs as required. Prophylactic octreotide was used under surgeon's discretion in a dose of 100 μg s.c. starting before surgery and followed up every 8 h for 5 days. As a unit protocol, abdominal US was carried out in all patients prior to drain removal (POD 4 to 5) and immediately before discharge. US and/or computed tomography (CT) were also performed in any patient with laboratory abnormalities (raised total white blood cell [WBC] count and increased C-reactive protein or procalcitonin levels), fever, or abdominal discomfort. Follow-up examinations were carried out as clinically required and included routine US in all patients 1 to 2 weeks after discharge.

Postoperative Complications

All deviations from the normal postoperative course were recorded and prospectively verified by a pancreatic research fellow (M.S.). Major surgical complications were classified according to the current definitions, i.e., postoperative pancreatic fistula (POPF: drain output of any measurable volume of fluid on or after POD 3 with an amylase content greater than three times the serum amylase activity),[18] delayed gastric emptying (inability to return to a standard diet by the end of the first postoperative week with prolonged nasogastric intubation),[19] postpancreatectomy hemorrhage (evidence of blood loss from drains, nasogastric tube, or on ultrasonography associated with a decrease in hemoglobin concentration).[20] Bile leak was defined as bilious abdominal drainage confirmed by a contrast study through an abdominal drain or cholangiography.[21] Abdominal abscess was defined as collection of fluid diagnosed with US/CT and positive cultures obtained by percutaneous drainage or at reoperation, regardless of amylase content.[22] Non-abscess AFC was defined as a collection of fluid measuring ≥3 cm in diameter demonstrated by transabdominal US or CT scan.[9] Asymptomatic AFCs were followed up with US/CT until spontaneous resolution. AFCs associated with clinical (abdominal discomfort and fever) or laboratory abnormalities (high WBC count and increased C-reactive protein or procalcitonin levels) were drained under US guidance, and aspirated fluid was sent for culture and amylase assay. Sterile collections of amylase-rich fluid were classified as POPFs and those with low amylase content were reported as symptomatic AFCs. Other surgical and medical complications were defined as previously described.[23] Operative mortality was defined as any in-hospital death or death occurring within 30 days from surgery.

Statistical Analysis

The differences in proportions between groups were evaluated using the chi-square test, and the Mann–Whitney *U* test was used to detect differences in quantitative variables. Potential risk factors for AFCs requiring interventional treatment were evaluated by univariate analysis using cross-tabulations and a stepwise logistic regression model. The following factors were analyzed: sex, age (≤65 vs >65 years), American Society of Anesthesiology (ASA) physical status (1–2 vs 3–4), diagnosis (benign vs malignant), preexisting diseases (no vs yes), body mass index (BMI <25 vs ≥25), preoperative body weight loss (<10 vs ≥10 %), preoperative albumin level (<35 vs ≥35 g/dl), preoperative bilirubin level (<30 vs ≥30 μmol/L), preoperative biliary drainage (no vs yes), type of resection (pancreaticoduodenectomy, distal pancreatectomy, total pancreatectomy, and other), lymph node

dissection (standard vs extended), operative time (≤300 vs >300 min), use of somatostatin analogs (no vs yes), need for autologous blood transfusion (no vs yes), pancreatic gland texture (hard vs soft), pancreatic fistula (no vs yes), biliary fistula (no vs yes), and enteric fistula (no vs yes). Significance level (P) <0.05 was considered statistically significant in a two-tailed analysis. Statistical analysis was performed using the IBM SPSS v.20 (SPSS Inc., Chicago, IL, USA) software package.

Results

Postoperative Complications

A total of 718 patients who underwent pancreatic resections were identified in the database between 1995 and 2011. Details of routine US imaging were available in 709 cases, and this group constituted the final study population (Table 1). There were 373 males and 336 females, with a median age of 59 years (range, 21 to 83 years). No neoadjuvant therapy was used for patients with preoperatively verified malignancy. The overall morbidity rate was 46 % (326 of 709 patients), with surgical and nonsurgical complications diagnosed in 31 and 27 % of patients, respectively (Table 2). Reoperation was required in 57 (8 %) cases, including abdominal abscess (n=24), abdominal bleeding (n=22), wound dehiscence (n=6), and other (n=5). The median postoperative hospital stay was 22 days (interquartile range (IQR), 14–34 days) and was significantly (P<0.001) longer in patients who developed complications (median, 28 days; IQR, 18–40 days) than for uneventful recovery (median, 12 days; IQR, 10–15 days). Thirty-one (4 %) patients died postoperatively.

Table 1 Patient demographics and clinicopathological parameters

Age, years, median (IQR)	59 (48–66)
Female/male, *n* (%)	336 (47)/373 (53)
Diagnosis, *n* (%)	
Pancreatic cancer	300 (42)
Ampullary cancer	150 (21)
Chronic pancreatitis	93 (13)
Endocrine tumors	55 (8)
Cystic tumor	36 (5)
Miscellaneous	75 (11)
Comorbidities, *n* (%)	
Circulatory[a]	173 (24)
Pulmonary[b]	28 (4)
Diabetes mellitus	97 (14)
ASA physical status (1–2/3–4)	489/220
BMI, median (IQR)	23.5 (21.2–26.5)
Serum albumin, g/dl, median (IQR)	40 (37–44)
Serum bilirubin, μmol/L, median (IQR)	15 (8–41)
Preoperative biliary drainage, *n* (%)	101 (14)
Procedure, *n* (%)	
Pancreaticoduodenectomy (PD)	253 (36)
Pylorus-preserving PD	153 (22)
Distal pancreatectomy	188 (27)
Total pancreatectomy	85 (12)
Segmental resection	11 (2)
Enucleation	19 (3)

Values in parentheses are percentages (unless indicated)

IQR interquartile range

[a] Ischemic heart disease, arrhythmia, previous myocardial infarction, and coronary artery disease

[b] Asthma and chronic obstructive pulmonary disease

Abdominal Fluid Collections

There were 149 (21 %) non-abscess AFCs, including 135 adjacent to the pancreatic remnant or in the bed of the resected pancreas and 14 distant collections. The median time from surgery to the diagnosis of AFCs was 7 days (IQR, 5–11 days; Fig. 1), and their median diameter was 6 cm (IQR, 4.5–7.0 cm).

Table 2 Morbidity and mortality rates in 709 patients

Complications	No. (percent) of patients
Any complication	326 (46)
Surgical complications	219 (31)
Abdominal fluid collection	149 (21)
Pancreatic fistula	140 (20)
Delayed gastric emptying	60 (8)
Wound infection	54 (8)
Intra-abdominal abscess	43 (6)
Abdominal bleeding	31 (4)
Enteric fistula	21 (3)
Biliary fistula	17 (2)
Gastrointestinal bleeding	12 (2)
Acute pancreatitis	14 (2)
Wound dehiscence	6 (1)
Ileus	3 (1)
Nonsurgical complications	188 (27)
Pneumonia	148 (21)
Sepsis	47 (7)
Pulmonary embolism	35 (5)
Cardiocirculatory failure	32 (5)
Renal failure	28 (4)
Urinary infection	23 (3)
Liver failure	18 (3)
Thrombophlebitis	7 (1)
Death	31 (4)
Reoperation	57 (8)

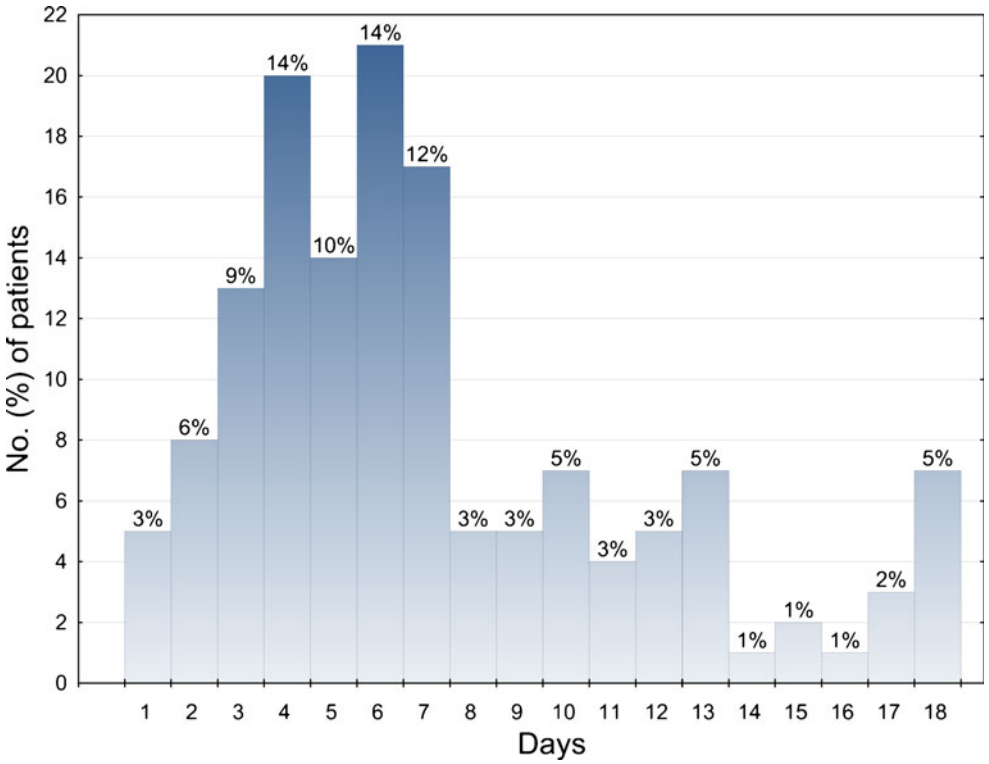

Fig. 1 Time elapsed from surgery to the diagnosis of AFC

The proportion of patients diagnosed with early (≤POD 7) and late (after POD 7) AFCs was similar for symptomatic (50 vs 50 %) and asymptomatic (55 vs 45 %) collections (Fig. 2). Collections defined as POPF were more common in the early postoperative period (70 vs 30 %), but the difference was statistically insignificant (P=0.163). The median time to drain removal was 8 days (IQR, 5–12 days) and was significantly (P=0.010) longer for patients with AFCs (14 days; IQR, 10–24 days) than

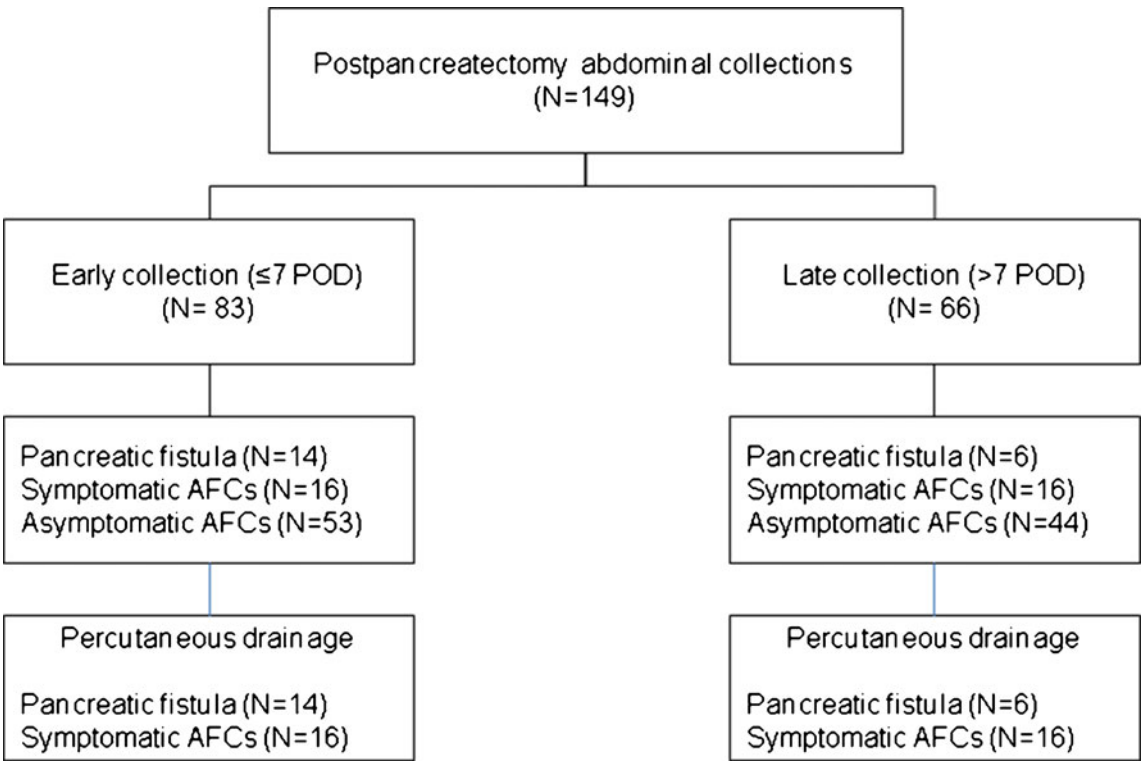

Fig. 2 Types of AFCs in relation to time. *POD* postoperative day

without collections (5 days; IQR, 4–8 days). The proportion of patients who develop AFCs after drain removal was higher for collections defined as symptomatic (53 %) and POPF (75 %). However, asymptomatic collections were diagnosed more commonly before drain removal (59 %). Ninety-seven of 149 AFCs (65 %) were asymptomatic and resolved spontaneously after a median follow-up of 22 days (IQR, 9–52 days). Fifty-two (35 %) AFCs required percutaneous drainage after a median time from diagnosis of 8 days (IQR, 4–19 days). The median time from drainage to resolution of AFCs was 25 days (IQR, 6–78 days). Four patients required additional percutaneous interventions for new or recurrent fluid collections, and five were reoperated on due to persistent symptomatic AFCs. There were no drainage-related complications. Hospital readmission related to collection was required in 27 patients (4 %) (Table 3).

Risk Factors for Fluid Collections Requiring Interventional Treatment

Univariate analysis of potential risk factors associated with the need for percutaneous drainage of AFCs is summarized in Table 4. Subsequent regression analysis (Table 5) of those variables that significantly affected the rate of interventional treatment in the univariate analysis identified three factors increasing the risk for drainage, i.e., BMI ≥25 (odds ratio, 3.23; 95 % confidence interval (CI), 1.32 to 7.91), pancreatic fistula (odds ratio, 2.93; 95 % CI, 1.20 to 7.17), and biliary fistula (odds ratio, 3.92; 95 % CI, 1.35 to 11.31).

Discussion

Surgical complications associated with pancreatic surgery have gained much attention over the recent years. Various aspects of POPF, delayed gastric emptying, abdominal bleeding, and abscesses were extensively analyzed, including recommendations for appropriate diagnosis and severity assessment.[18–20] In contrast, little data are available for asymptomatic non-abscess AFCs and their clinical implications. Therefore, we sought to analyze the natural history of such collections in a population of patients subject to routine postoperative imaging. This study demonstrated that about 14 % of patients after pancreatic resections developed transient AFCs that eventually resolved spontaneously without any intervention and a further 8 % required percutaneous drainage for symptomatic collections. The need for percutaneous drainage was significantly increased among patients with high BMI and by coexisting pancreatic or biliary fistula.

Previous reports suggested that the incidence of AFCs varies from 4 to 30 %.[13,24–28] However, such numbers derived from retrospective studies are inherently biased by the fact that imaging tests are carried out only in patients with symptoms suggestive of intra-abdominal complications. Only a few studies provided some limited data from prospective observations. In the study of Bassi et al. using routine US imaging, 17 of 114 (15 %) patients were diagnosed with fluid collections <5 cm in diameter on POD 3 after pancreaticoduodenectomy or distal pancreatectomy.[9] In another report, 30 of 50 (60 %) patients subject to pancreaticoduodenectomy with a soft pancreas had AFCs on POD 7 diagnosed with routine CT scans.[29] Nevertheless, neither of these reports provided information on the actual nature of such collections or their natural history. In the present study, 97 of 709 (14 %) patients monitored with routine postoperative US developed asymptomatic AFCs that regressed spontaneously after a median follow-up of 22 days. Another 52 (8 %) patients had fluid collections requiring percutaneous drainage, and the need for interventional treatment was significantly associated with high BMI, pancreatic fistula, and biliary fistula with odds ratios of about 3.

The incidence rate of intra-abdominal collections associated with POPF ranges from 20 to 81 % and is markedly higher in patients with fistula grades B and C.[30–33] In this study, the proportion of asymptomatic collections was similar in patients with and without pancreatic fistula (14 vs 13 %, P=0.816), and the median time to their resolution was

Table 3 Type of abdominal collections by surgical procedure

	Pancreaticoduodenectomy (n=406)	Distal pancreatectomy (n=188)	Total pancreatectomy (n=85)	Segmental resection or enucleation (n=30)	Total (n=709)	P value[a]
Abscess	24 (6)	9 (5)	7 (8)	3 (10)	43 (6)	0.552
Pancreatic fistula (POPF)	15 (4)	3 (2)	0 (0)	2 (7)	20 (3)	0.031
Symptomatic AFCs	16 (4)	11 (6)	3 (4)	2 (7)	32 (5)	0.820
Asymptomatic AFCs	50 (12)	34 (18)	10 (12)	3 (10)	97 (14)	0.366

Values in parentheses are percentages

POPF postoperative pancreatic fistula, *AFCs* abdominal fluid collections

[a] Chi-square test

Table 4 Univariate analysis of risk factors for non-abscess abdominal collections requiring percutaneous drainage (chi-square test)

Factor	Abdominal fluid collections requiring drainage		
	Yes (n=52)	No (n=97)	P value
Age (years)			0.944
≤65	41 (79)	76 (78)	
>65	11 (21)	21 (22)	
Gender			0.496
Female	25 (48)	41 (42)	
Male	27 (52)	56 (58)	
Diagnosis			0.716
Benign	12 (23)	25 (26)	
Malignant	40 (77)	72 (74)	
Comorbidities			0.350
No	23 (44)	41 (42)	
Yes	29 (56)	56 (58)	
ASA physical status			0.791
1 or 2	37 (71)	67 (69)	
3 or 4	15 (29)	30 (31)	
BMI			0.047
<25	31 (60)	73 (75)	
≥25	21 (40)	24 (25)	
Body weight loss >10 %			0.107
No	37 (71)	56 (58)	
Yes	15 (29)	41 (42)	
Albumin, g/dl			0.409
≤35	9 (17)	12 (12)	
>35	43 (83)	85 (88)	
Bilirubin, μmol/L			0.357
≤30	44 (85)	76 (78)	
>30	8 (15)	21 (22)	
Preoperative biliary drainage			0.917
No	39 (75)	72 (74)	
Yes	13 (25)	25 (26)	
Procedure			0.279
Pancreaticoduodenectomy	31 (60)	50 (52)	
Distal pancreatectomy	14 (27)	34 (35)	
Total pancreatectomy	3 (6)	10 (10)	
Other	4 (7)	3 (3)	
Operative time (min)			0.275
≤300	29 (56)	45 (46)	
>300	23 (44)	52 (54)	
Lymph node dissection			0.362
Standard	34 (65)	56 (58)	
Extended	18 (35)	41 (42)	
Pancreatic gland texture			0.219
Hard	11 (21)	13 (13)	
Soft	41 (79)	84 (87)	
Somatostatin use			0.105
No	17 (33)	45 (46)	
Yes	35 (67)	52 (54)	
Need for blood transfusion			0.079
No	19 (37)	50 (52)	
Yes	33 (63)	47 (48)	
Pancreatic fistula			0.005
No	30 (58)	77 (79)	
Yes	22 (42)	20 (21)	
Biliary fistula			0.006
No	44 (85)	94 (97)	
Yes	8 (15)	3 (3)	
Enteric fistula			0.477
No	51 (98)	93 (96)	
Yes	1 (2)	4 (4)	

comparable (17 vs 23 days, P=0.668). However, the proportion of patients with symptomatic collections requiring drainage was significantly higher (14 vs 6 %, P<0.001), and all of them were verified as POPF due to high amylase content. This suggests that asymptomatic AFCs do not always require interventional treatment in a patient with POPF. Such an opinion is supported by observations made by Pratt et al. who reported percutaneous drainage only in 14 of 34 patients with POPF grades B and C and fluid collections after various pancreatic resections.[33]

Data for the impact of biliary fistulas on abdominal complications after pancreatic surgery are scarce. The largest study, of Burkhart et al., reported hepaticojejunostomy leaks after pancreaticoduodenectomy in 16 of 715 patients (2.2 %).[21] Leaks were significantly associated with pancreatic fistula (50 vs 12 %, P<0.001), wound infection (38 vs 8 %, P=0.003), delayed gastric emptying (31 vs 10 %, P=0.036), and sepsis (31 vs 3 %, P<0.001). However, the authors provided no information about abdominal collections. Another retrospective analysis of 149 patients subject to pancreatoduodenectomy revealed that early (≤7 days postoperatively) collections were associated with either

Table 5 Multivariable logistic regression analysis of risk factors for non-abscess abdominal collections requiring percutaneous drainage

Factor	Odds ratio (95 % CI)	P value
BMI		
<25	Reference	0.010
≥25	3.23 (1.32–7.91)	
Pancreatic fistula		
No	Reference	0.018
Yes	2.93 (1.20–7.17)	
Biliary fistula		
No	Reference	0.012
Yes	3.92 (1.35–11.31)	

pancreatic anastomotic or biliary leaks.[13] Nevertheless, any formal analysis of such an association for biliary fistula was not possible due to very small sample size, i.e., only three patients with biliary leaks.

The only preoperative factor significantly associated in this study with the need for interventional treatment of AFCs was BMI ≥25. A supplementary analysis failed to confirm such a relationship with other abdominal complications, including asymptomatic AFCs and POPF (data not shown). This correlation is somehow controversial not only for pancreatic surgery but also for other types of abdominal surgery.[34] A recent meta-analysis of 17 studies and a total of 4,045 patients showed no definitive detrimental effects of overweight/obesity on postoperative outcomes, with only four studies reporting higher rates of POPF (odds ratio range, 1.6–4.2).[35] In fact, even those studies suggesting increased morbidity rates among patients with high BMI provided no detailed data necessary to establish a potential association between overweight and various types of abdominal collections.

The present analysis has some inherent limitations. First, we used abdominal US for screening of asymptomatic patients, and this could underestimate rates of fluid collections compared to CT. The operator-dependent characteristics of such imaging must be taken into account, though; all examinations were carried out by surgeons acquainted with US assessment of patients following abdominal surgery and a caseload of about 1,000 per year. Second, asymptomatic collections were not verified by percutaneous aspiration, and this may raise the question about their actual nature. However, such collections were evenly distributed among patients with pancreatic, biliary, and enteric fistulas, and time to their resolution was not affected by these complications. This provides some evidence that asymptomatic collections were most probably unrelated to other abdominal complications. Third, we could not examine the correlation between drain removal and fluid collections as drains were routinely removed on POD 4 to 5 after US excluded potential abdominal complications. Therefore, prolonged drainage in our case was a consequence of abnormal recovery based on US or clinical findings. Some previous studies suggested that early drain removal (POD 3 or 4) is superior to prolonged drainage (POD 5 or 8) in terms of reduced rates of abdominal complications.[9,11] Similar benefits were demonstrated by a retrospective cohort study in patients without routine abdominal drainage.[36] However, the latter group published earlier the only existing randomized clinical trial on routine intraperitoneal drainage after pancreatic resections and failed to demonstrate significant differences in the incidence of abdominal collections (6.8 vs 2.2 % in drained and not drained group, respectively) or abscesses (6.8 vs 6.6 %).[10] Therefore, the question of whether routine drainage increases the risk of abdominal collections in pancreatic surgery remains unanswered.

Conclusion

In conclusion, this study demonstrated that approximately one fourth of patients develop various types of AFCs after pancreatic surgery. About half of them are asymptomatic and resolve spontaneously. However, collections associated with pancreatic and biliary fistulas, as well as those in patients with high BMI, are likely to require interventional treatment.

Conflict of Interest None.

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