International Journal of Surgery 68 (2019) 27–34

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.elsevier.com/locate/ijsu

Surgical management and outcome of grade-C pancreatic fistulas after pancreaticoduodenectomy: A retrospective multicenter cohort study

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ARTICLE INFO

Keywords:
Postoperative pancreatic fistula
Pancreaticoduodenectomy
Surgical strategy
Re-laparotomy
Outcome

ABSTRACT

Background: Management strategies for grade-C postoperative pancreatic fistula (POPF) following pancreaticoduodenectomy (PD) vary. The aim of this study was to evaluate surgical indications, approaches, and outcomes of grade-C POPF following PD.

Materials and methods: The clinical data of grade-C POPF patients from 9 high-volume institutions between January 1, 2012 and December 31, 2016 were retrospectively reviewed. The indications and outcomes of different surgical strategies were analyzed. Risk factors for unfavorable outcomes were evaluated by multivariate regression analysis.

Results: Out of 5115 patients that underwent PD, 68 were diagnosed as grade-C POPF, and 53 underwent re-laparotomy. Pancreas-preserving surgical strategies were mostly used in this cohort (96.2%). Postoperative hospital stay in the external wirsungostomy group tended to be shorter than the other two major surgical approaches (20 days *vs.* 38 days and 34.5 days). Mortality and morbidity were comparable among different surgical strategies. Prolonged high drain amylase level prior to the development of grade-C POPF was negatively associated with unfavorable outcomes after re-laparotomy (OR: 0.20, 95% CI: 0.05–0.82).

Conclusion: Pancreas-preserving approaches were preferred for grade-C POPF in this multicenter database, although the choice of definite procedure differed according to different clinical scenarios. Longstanding high amylase drainage may predict better outcomes after re-laparotomy.

1. Introduction

Postoperative pancreatic fistula (POPF) is associated with high morbidity and mortality rates after pancreaticoduodenectomy (PD) [1]. Despite the extensive experience with PD procedures and the decrease in overall complication rates, the rate of POPF remains mostly unchanged [2,3]. The international consensus on the grading of POPF was first introduced in 2005 by the International Study Group for Pancreatic Surgery (ISGPS) and was updated in 2016 [4,5]. Grade-B and grade-C POPF were defined as clinically relevant POPF (CR-POPF), which require intervention and even re-laparotomy.

Although the definition and grading of POPF are well-established, a

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https://doi.org/10.1016/j.ijsu.2019.05.019
Received 12 March 2019; Received in revised form 13 May 2019; Accepted 27 May 2019
Available online 10 June 2019
1743-9191/

consensus on the optimal treatment strategy for CR-POPF is still lacking [6–8]. A universal consensus on whether and when to perform re-laparotomy or provide conservative treatment for CR-POPF seems impossible, owing to the variation in surgeons' preferences, experience, and clinical situations. And it is also indisputable that the utility of surgical techniques for grade-C POPF may vary by the circumstances of the anastomosis and the patient's general condition. These unavoidable selection biases have resulted in heterogeneous and even conflicting reports about the management of CR-POPF [9–12]. However, guidelines are still needed in managing progressively deteriorating CR-POPF, such like POPF relevant organ failures, severe peritonitis, or dramatic bleeding. Moreover, if prompt surgery is selected, general guidance on choosing an appropriate surgical strategy is worthwhile, and may facilitate intraoperative decision-making and improve postoperative recovery. Completion pancreatectomy (CP) was once considered the standard procedure during re-laparotomy for severe CR-POPF [9,13]. However, the remarkably high rates of mortality and morbidity after CP make such an aggressive procedure suitable in only selected cases [13,14]. Some authors have even claimed that CP should no longer be considered a treatment for CR-POPF owing to the severe postoperative complications associated with this surgery [2]. In particular, new-onset diabetes after CP is difficult to control, and the risk of severe hypoglycemia and ketoacidosis may cause great harm and even death [6]. Therefore, pancreas-preserving approaches that maintain endocrine function or both endocrine and exocrine functions are increasingly preferred. Several reports have demonstrated the possible benefits of pancreas-preserving techniques over CP in terms of similar or better perioperative morbidity and mortality and preservation of pancreatic function [15–19]. However, these studies were mostly single-center investigations with relatively small sample sizes, reducing their power.

This study aims to review the clinical data of salvage re-laparotomy for grade-C POPF after PD in a large multicenter database. The indications and outcomes of different surgical approaches were evaluated in an attempt to provide a general guidance for the management of grade-C POPF after PD. In addition, the risk factors for unfavorable outcomes after re-laparotomy were assessed using multivariate analysis.

2. Materials and Methods

2.1. Patients and definitions of clinical parameters

This is a multicenter, retrospective cohort study. The work has been reported in line with the STROCSS criteria [20]. After approval by the institutions' Medical Ethics Review Committee, clinical data were retrospectively accrued from January 2012 to December 2016 on grade-C POPF after PD from nine high-volume pancreatic centers. Each of these nine centers has an average PD volume of over 60 cases per year.

Grade-C POPF was defined according to the 2016 revised ISGPS criteria [5]: (1) an amylase concentration of drained fluid on post-operative day (POD) 3 or later exceeding 3 times the upper limit of the normal amylase level for each specific institution, and (2) severe clinical consequences requiring reoperation or accompanied with organ failure or death due to POPF. Patients who underwent salvage re-laparotomy for grade-C POPF were included in this study. The criteria for re-laparotomy include: (1) massive post-operative hemorrhage; (2) severe sepsis with/or organ failure; (3) general peritonitis; (4) inadequate interventional drainage of peritoneal collections. Information on demographics, pertinent medical history, PD techniques, pancreatic anastomosis, POPF manifestations, re-laparotomy procedure, and post-operative outcomes was collected for all enrolled patients using a predefined, standardized case-record form.

The amylase level of drained fluid was measured and recorded on POD 3 and also later if it was warranted on the basis of the clinical scenario. The fistula risk score (0–10 points) was calculated on the basis of the weighted influence of four risk factors according to the literature [21]. Severe sepsis was defined as the presence of systemic inflammatory response associated with organ dysfunction, hypotension, or hypoperfusion. General peritonitis was considered if the patient presented clinical symptoms such as abdominal pain, general peritoneal tenderness with guarding or rebound, and fever with body temperature over 38.5 °C, and was confirmed at re-laparotomy. Prolonged high drain amylase level was defined as the presence of high drain amylase level (exceeding 3 times the upper limit of the normal serum amylase level) for at least 24 h before its progression to grade-C POPF, according to the 2016 ISGPS criteria [5]. The degree of pancreaticojejunal anastomotic dehiscence observed during re-laparotomy was categorized as no dehiscence, mild dehiscence ($< 180^{\circ}$), and prominent dehiscence ($\geq 180^{\circ}$). Unplanned re-re-operation was defined as unplanned repeated re-operation either within 30 days after the re-laparotomy or during the hospital stay. Unfavorable outcomes after re-laparotomy were defined as acute severe complications (new-onset organ failure, severe sepsis, and bleeding), unplanned re-re-operation, and death within 90 days after re-laparotomy or during the same admission. Adjuvant therapy that was not initiated within 12 weeks after the operation for malignant tumors was considered a disruption.

2.2. Surgical strategies

The detailed surgical technique of PD was presented in Table 2. External wirsungostomy was defined as the external drainage of the main pancreatic duct through a polyethylene tube, either temporarily or permanently. Briefly, the open jejunum was closed by segmental resection using a stapler. The downstream hepatojejunal anastomosis is untouched. A 6 to 8 Fr polyethylene tube with lateral holes at one end is inserted into the main pancreatic duct. The drainage tube is then stitched to the pancreatic remnant and passes through the abdominal wall with further fixation onto the skin. Re-pancreaticojejunostomy (Re-PJ) involved the in situ repair of the original pancreatic anastomosis and repeated PJ after resection of the previous pancreatic anastomosis. Simple peritoneal drainage refers to thorough peritoneal lavage and drains placement, without manipulation of the pancreatic anastomosis. All the operations were done by highly experienced surgeons.

2.3. Statistical analysis

For univariate comparisons, the Mann–Whitney rank-sum test or Kruskal–Wallis test was used to evaluate continuous variables, and the Pearson χ^2 test or Fisher exact test was used for categorical variables. Variables that achieved statistical significance at a 0.1 level in the univariate analysis were included in the multivariate analysis. Odds ratio and its 95% confidence interval (CI) were presented. Unless otherwise specified, two-sided statistical tests were used, and a *P*-value of less than 0.05 was considered statistically significant. Data are presented as frequencies and percentages for categorical variables and as medians and interquartile ranges for continuous variables. Analyses were performed with SPSS v23.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Study population

From January 1, 2012 to December 31, 2016, a total of 5115 consecutive patients underwent PD in the participating hospitals. Of these, 68 patients (1.33%) were diagnosed with grade-C POPF according to the 2016 ISGPF criteria (Fig. 1). Fifteen patients (22.1%) did not undergo salvage re-laparotomy: one patient developed cardiac failure that was treated with inotropic agents for > 24 h; three patients developed respiratory failure and were intubated for > 24 h; and the remaining eleven patients died of POPF. Fifty-three patients (77.9%) underwent salvage re-laparotomy.

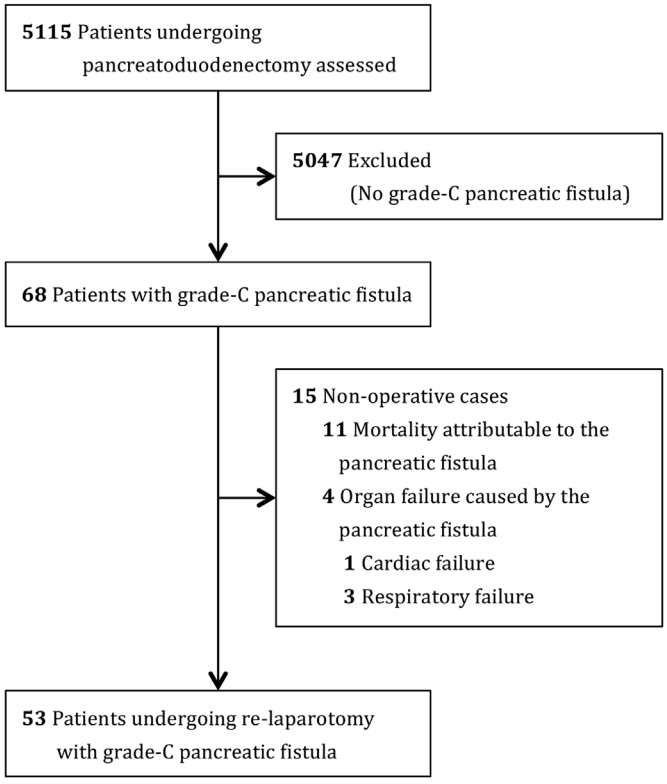

Fig. 1. Flow chart of patient selection.

3.2. Characteristics of the overall cohort

Of the 68 grade-C POPF patients, 43 (63.2%) were men. The overall 90-day mortality was 36.8%. The mortality of patients with organ failure who underwent re-laparotomy was significantly lower than those with organ failure who received conservative treatments (1/6 vs. 11/15, $P = 0.046$). Bleeding (n = 48, 70.6%), either peritoneal or gastrointestinal, was the most common co-complication and cause of re-laparotomy in patients with grade-C POPF. All the detailed information was presented in Table 1.

3.3. Characteristics and outcomes of re-laparotomy

The median time interval between PD and re-laparotomy was 9.5 days. The following re-laparotomy methods were used in the 53 study patients: external wirsungostomy (n = 20, 37.7%), re-PJ (n = 15, 28.3%), simple peritoneal drainage (n = 15, 28.3%), CP (n = 2, 3.77%), and pancreatogastrostomy (n = 1, 1.89%; Table 2). Of the 20 patients who underwent external wirsungostomy, 3 (15%) underwent planned repeat PJ at 6–9 months after the salvage re-laparotomy to restore pancreatic exocrine function. In another three patients (15%), the external pancreatic drainage tube was accidently pulled out. The remaining 14 patients either refused the repeat PJ or died before the scheduled re-operation was performed.

The three most frequently performed procedures (external wirsungostomy, re-PJ, and simple peritoneal drainage) were further analyzed. Bleeding was the most common indicator for re-laparotomy in all the three surgical procedures of this cohort, of which the rate was especially high in the group of simple peritoneal drainage (86.7%). And general peritonitis was more common in the external wirsungostomy group than in the other two groups (35% *vs.* 13.3% and 6.67%, Fig. 2). There are four patients that underwent external wirsungostomy (20%) had prominent dehiscence of pancreaticojejunal anastomosis. On the contrary, no patient in the groups of re-PJ and simple peritoneal drainage had prominent dehiscence (Fig. 3). The most frequent bleeding site observed during re-laparotomy was gastroduodenal artery stump (25.6%), followed by celiac axis (20.5%), portal/superior mesenteric/splenic vein (15.4%), pancreatic cut surface (12.8%), common/proper hepatic artery (7.69%), and splenic artery (2.56%) (Fig. 4).

Most of the outcomes of re-laparotomy were comparable among the three groups (Table 3). The length of postoperative hospital stay was

Table 1
Basic demographic and clinical characteristics of re-laparotomy (n = 53) and non-operative cases (n = 15).

Characteristic	Re-laparotomy n = 53 (%)	Non-operative cases n = 15 (%)
Age, median (IQR), yrs	64 (56–71)	64 (62–73)
Sex, male	34 (64.2)	9 (60)
BMI, mean ± SD, Kg/m^2	22.9 ± 3.32	23.0 ± 2.75
ASA class		
I-II	41 (77.3)	12 (80)
III-IV	12 (22.6)	3 (20)
Co-morbidities		
Chronic pancreatitis	1 (1.87)	0
Diabetes Mellitus	9 (17.0)	2 (13.3)
Cardiovascular disease	17 (32.1)	3 (20)
Chronic obstructive pulmonary disease	2 (3.77)	0
History of upper abdominal surgery	4 (7.55)	0
Preoperative total bilirubin, median (IQR), umol/L	18.6 (9.9–101.2)	59 (19.8–161.8)
Preoperative albumin, median (IQR), umol/L	38 (35–41.9)	36.9 (32.7–40.7)
Operative data		
Details on pancreaticoduodenectomy (PD)		
Operative time, median (IQR), min	270 (180–375)	260 (205.5–492.5)
Operative approach, open	49 (92.5)	13 (86.7)
Pylorus-preserving pancreatoduodenectomy	14 (26.4)	2 (13.3)
Reconstruction method, pancreaticojejunostomy	51 (96.2)	14 (93.3)
Additional organ resection	3 (5.66)	2 (13.3)
Vascular resection/repair	11 (20.8)	1 (6.67)
Estimated blood loss, median (IQR), mL	400 (200–600)	400 (150–500)
Texture of the pancreas, soft	39 (73.6)	9 (60)
Diameter of the pancreatic duct, median (IQR), mm	3 (2.5–4)	2.5 (1–3)
Invaginating anastomosis	25 (47.2)	5 (33.3)
Duct to mucosa anastomosis	28 (52.8)	10 (66.7)
Trans-anastomotic stent	34 (64.2)	13 (86.7)
Peritoneal drain placement	53 (100)	15 (100)
Pathology		
Pancreatic adenocarcinoma	17 (32.1)	5 (33.3)
Pancreatic cystic neoplasm	1 (1.89)	0
Neuroendocrine tumor	2 (3.77)	1 (6.67)
Pancreatitis	1 (1.89)	0
Duodenal papillary/Ampullary/ Distal bile duct tumor	29 (53.7)	9 (60)
Characteristics of the grade-C POPF		
Sentinel bleeding	19 (35.8)	3 (20)
Prolonged high drain amylase levels	39 (73.6)	9 (60)
Fistula Risk Score, median (IQR)	5 (3–6)	5 (1–7)
Co-complications		
Peritoneal bleeding	33 (62.3)	3 (20)
Gastrointestinal bleeding	10 (18.9)	2 (13.3)
Severe sepsis	17 (32.1)	10 (66.7)
General peritonitis	12 (22.6)	2 (13.3)
Single organ failure	5 (11.3)	4 (26.7)
Multiple organ failure	1 (1.89)	11 (73.3)
Readmission	7 (13.2)	0
90-day mortality	14 (26.4)	11 (73.3)
90-day mortality of organ failure patients	1 (16.7)	11 (73.3)
Time interval between PD and re-laparotomy, median (IQR), days	9.5 (7.25–13.0)	–

ASA indicates American society of anesthesiologists; BMI, body mass index; PD, pancreaticoduodenectomy; POPF, postoperative pancreatic fistula; IQR, interquartile range; SD, standard deviation.

Table 2
POPF-related interventions or events of this cohort (n = 68).

Type	Number (%)
Re-laparotomy	53 (77.9)
Completion pancreatectomy	2 (3.77)
Simple peritoneal drainage	15 (28.3)
External wirsungostomy	20 (37.7)
Re-pancreaticojejunostomy	15 (28.3)
Pancreaticogastrostomy	1 (1.89)
Non-operative cases	15 (22.1)
Cardiac failure	1 (1.47)
Respiratory failure	3 (4.41)
Mortality attributable to POPF	11 (16.2)

significantly lower in the external wirsungostomy group than in the simple peritoneal drainage group (20 days *vs.* 38 days, $P = 0.03$), and tended to be lower, but not significantly lower, than that in the re-PJ group (20 days *vs.* 34.5 days, $P = 0.068$). Adjuvant therapy might have benefited 90.6% (n = 48) of grade-C POPF patients in the whole cohort, yet it was delayed in 12.5% (n = 6) and never delivered in 66.7% (n = 32) of these patients. In particular, 81.8% (n = 9) patients who underwent simple peritoneal drainage did not receive adjuvant therapy, and none of the patients in this group received adjuvant therapy on time. In contrast, 26.3% (n = 5) of patients who underwent external wirsungostomy and 26.7% (n = 4) of those who underwent re-PJ received adjuvant therapy on time. However, these differences were not significant ($P = 0.062$, $P = 0.063$, respectively).

3.4. Factors influencing re-laparotomy outcomes

In the univariate analysis, we evaluated variables that were possibly associated with unfavorable re-laparotomy outcomes (e.g., age, sex, ASA class, comorbidities, invaginating anastomosis, and additional organ resection during PD). Three parameters, namely, additional organ resection during PD (OR: 7.37, 95% CI: 0.80–68.16), prolonged high drain amylase level (OR: 0.22, 95% CI: 0.06–0.85), and high fever (≥39 °C) before re-laparotomy (OR: 2.74, 95% CI: 0.82–9.19), were identified as possible risk factors for unfavorable re-laparotomy outcomes. These factors were included in a multivariate regression model, and only prolonged high drain amylase level (OR: 0.20, 95% CI: 0.05–0.82) was found to be independently and negatively associated with unfavorable re-laparotomy outcomes (Table 4).

4. Discussion

The optimal management strategy for CR-POPF remains controversial [6,7]. Re-laparotomy was once the only effective treatment for severe CR-POPF, but it was associated with considerable morbidity and mortality. In a recent published large retrospective study, the authors suggested aggressive clinical management for grade-C POPFs did not improve or worsen 90-day mortality [8]. With the development of medical technology, conservative strategies, including various non-surgical interventions, have been widely used in the management of CR-POPF with favorable outcomes. A recent paper even recommended primary interventional catheter drainage as the first choice of treatment for CR-POPF, using a so-called “step-up approach” to optimize treatment performance [12]. Nevertheless, surgery remains an undeniably valuable and occasionally the best choice in patients with severe complications such as general peritonitis, severe sepsis, and massive bleeding, and also when interventional drainage is not possible or not effective.

For decades, CP was considered the standard procedure in re-laparotomy for grade-C POPF. However, CP was gradually abandoned by pancreatic surgeons because of its remarkably high mortality and morbidity [13,14]. CP is an aggressive procedure and may be difficult to perform in the setting of severe inflammation. Spleen-preserving CP is a better choice than CP combined with splenectomy, owing to the risk of ischemia of the remnant stomach and the gastrojejunal anastomosis when splenectomy is performed. However, it might be extremely difficult to preserve the spleen during re-laparotomy. Currently, surgeons tend to follow a strategy of “damage control,” by selecting a quicker and less-invasive procedure. This trend is well reflected in the current study, as there were only two cases (3.77%) of CP, and the remaining 51 operations involved a roughly pancreas-preserving approach. Pancreas-preserving strategies have been gaining popularity owing to their ability to maintain the endocrine and exocrine functions of the pancreas. In addition, these operations are easier to perform, lead to less blood loss, and have a shorter operative time. Recently, a systematic review that included 140 patients who underwent various types of pancreas-preserving surgical strategies for grade-C POPF after PD

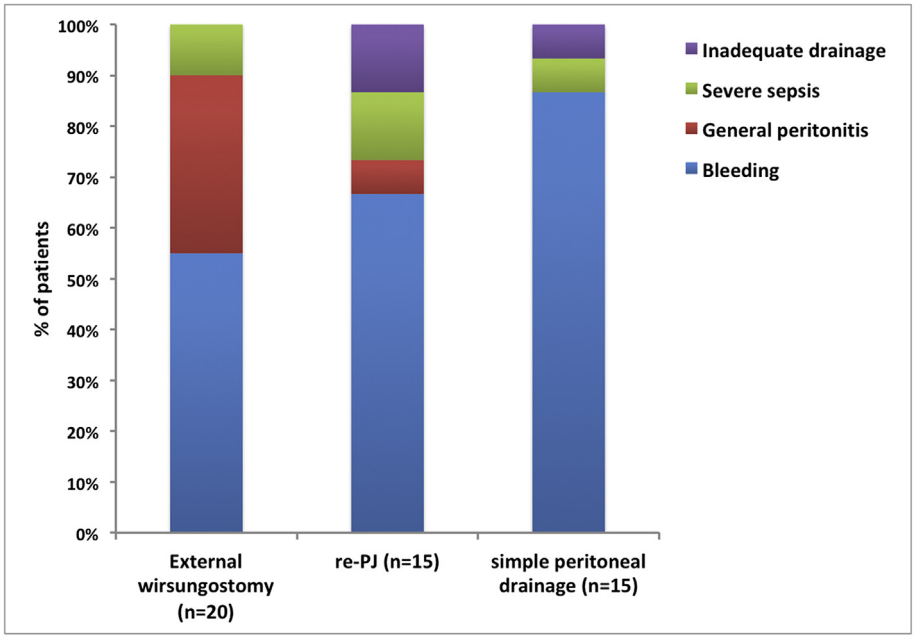

Fig. 2. Indicators of re-laparotomy using the three most frequently used surgical strategies in this cohort.

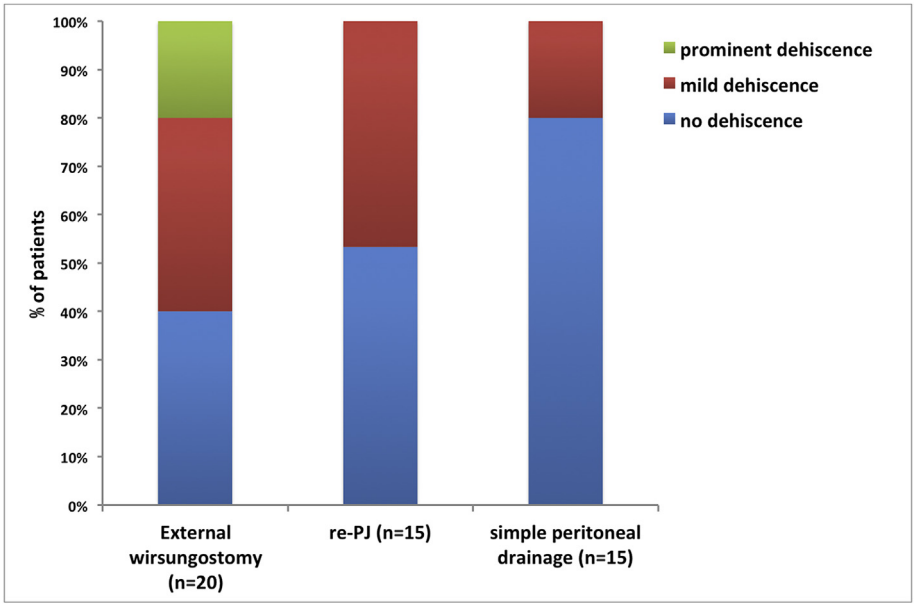

Fig. 3. Degree of pancreaticojejunal anastomotic dehiscence observed during re-laparotomy using the three most frequently used surgical strategies in this cohort.

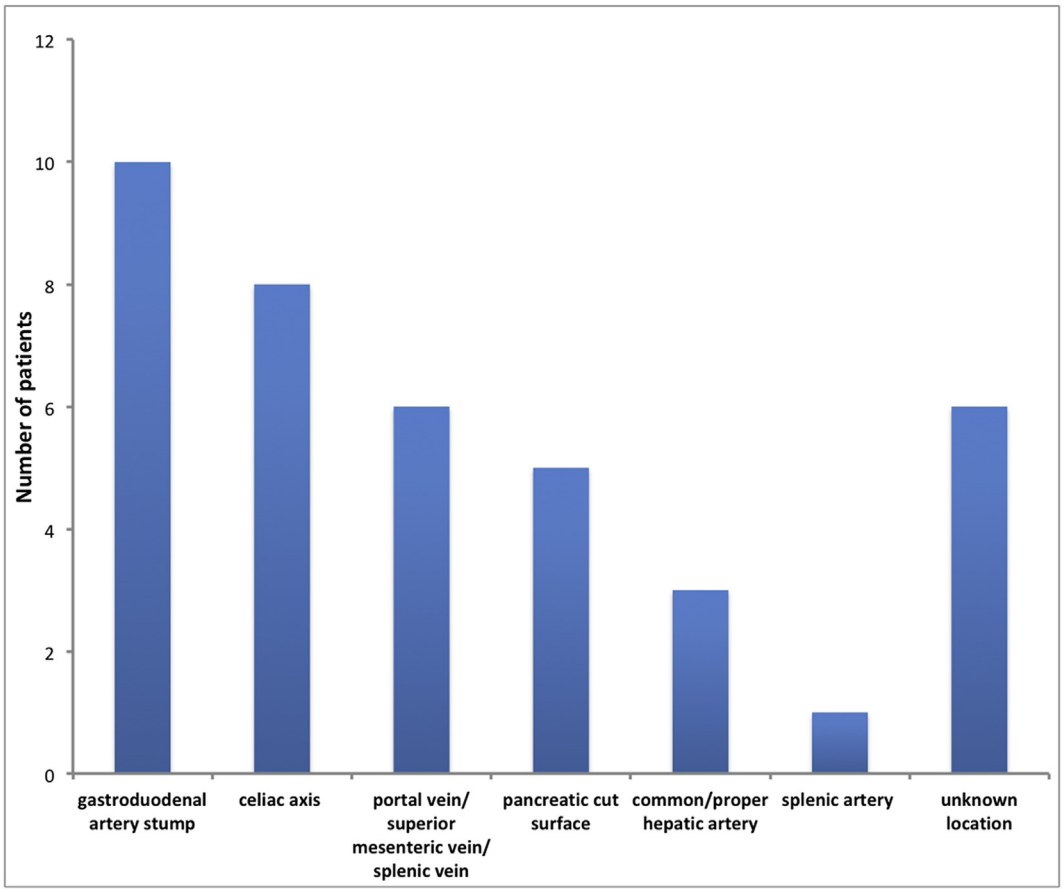

Fig. 4. Bleeding sites observed during re-laparotomy.

demonstrated that the success rate of pancreas-preserving procedures was nearly 94%, and the rate for further re-intervention was 25% [22]. Since each medical center manages surgical procedures differently, and each surgeon has their own preference, any effort to standardize the surgical approach for grade-C POPF in the setting of distinct intraoperative conditions seems impractical. However, some universal guidance for surgical approaches for grade-C POPF is still of interest.

Pancreas-preserving strategies mainly include external wirsungostomy, drainage of the dehiscent anastomosis, occlusion of the pancreatic stump, internal wirsungostomy, subtotal pancreatectomy, and repair or redo of the pancreatic anastomosis [23]. In this study, external wirsungostomy was the most frequently used surgical strategy, followed by re-PJ and simple peritoneal drainage. Although there were no significant differences in mortality, morbidity, and disruption of

Table 3
Outcomes of the grade-C POPF after salvage re-laparotomy (n = 53).

Outcome	Overall n = 53 (%)	External wirsungostomy n = 20 (%)	Re- pancreaticojejunostomy n = 15 (%)	Simple peritoneal drainage n = 15 (%)	P^a	P^b
Acute major complications						
Severe sepsis	19 (35.8)	6 (30)	7 (46.7)	5 (33.3)	0.486	0.918
Bleeding	5 (9.43)	2 (10)	0	3 (20)	0.207	0.403
New-onset organ failure	14 (26.4)	4 (20)	6 (40)	4 (26.7)	0.195	0.642
Unplanned re-re-operation	5 (9.43)	1 (5)	2 (13.3)	2 (13.3)	0.383	0.383
90-day mortality	14 (26.4)	5 (25)	5 (33.3)	4 (26.7)	0.589	0.911
Length of post-operative hospital stay, median (IQR), days	32 (17.3–41)	20 (10.5–37.5)	34.5 (18.8–49.3)	38 (29.3–55.8)	0.068	**0.030**
Long-term complications (n = 39)						
New-onset diabetes	10 (25.6)	3 (20)	2 (20)	2 (18.2)	0.870	0.884
New-onset exocrine pancreatic insufficiency	26 (66.7)	12 (80)	6 (60)	5 (45.5)	0.355	0.114
Disruption of adjuvant therapy						
No	10 (20.8)	5 (26.3)	4 (26.7)	0	0.982	0.062
Delayed	6 (12.5)	2 (10.5)	2 (13.3)	2 (18.2)	0.801	0.552
Never delivered	32 (66.7)	12 (63.2)	9 (60)	9 (81.8)	0.851	0.282
Not Applicable	5 (9.43)	1	0	4	–	–

IQR indicates interquartile range.
[a] Comparison between External wirsungostomy with Re-pancreaticojejunostomy.
[b] Comparison between External wirsungostomy with Simple peritoneal drainage.

Table 4
Multivariate analysis of predictors of unfavorable outcomes after re-laparotomy (n = 53).

Characteristic	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Additional organ resection during PD				
No	Ref	0.047	Ref	0.438
Yes	7.37 (0.80–68.16)		4.66 (0.36–59.72)	
Prolonged high drain amylase level				
No	Ref	0.022	Ref	0.025
Yes	0.22 (0.06–0.85)		0.20 (0.05–0.82)	
High fever (≥39 °C) before re-laparotomy				
No	Ref	0.098	Ref	0.376
Yes	2.74 (0.82–9.19)		1.96 (0.44–8.69)	

CI indicated confidential interval; OR, odds ratio; PD, pancreaticoduodenectomy; POPF, postoperative pancreatic fistula.

adjuvant therapy among the different types of surgical strategies, external wirsungostomy seems to be superior to the other two strategies with regard to the length of postoperative hospital stay. It has been widely accepted that apart from an open pancreas remnant, intestinal leakage and subsequent peritonitis are the main causes of clinical deterioration of patients' condition. So, it is rational to close the intestinal stump and perform external drainage of the pancreatic duct. Recently, several reports have demonstrated that external wirsungostomy is a better alternative to CP with comparable mortality and morbidity and less chance of developing exocrine and endocrine dysfunction [15–18]. Several randomized controlled trials have demonstrated that external stents reduce the rate of CR-POPF after PD in high-risk patients, such as those with soft pancreatic texture and small pancreatic duct [23,24]. In contrast to other pancreas-preserving procedures, external wirsungostomy drains away dangerous pancreatic fluid from the surgical site, an effect similar to CP or pancreatic duct closure. However, unlike CP, it preserves the pancreatic endocrine function and even exocrine function after the pancreatic anastomosis is surgically restored. Of course, external wirsungostomy has several drawbacks, such as the potential need for another operation to restore the pancreatic anastomosis, the risk of accidental pullout of the external drainage tube, and possible tube occlusion and rupture. An alternative pancreas-preserving technique using a bridging internal or external stent was reported recently [25]. This technique avoids a second operation to restore the pancreatic anastomosis. It's a promising strategy that needs to be verified in larger studies.

In the analysis of indicators for re-laparotomy, we found bleeding was the most common indicator in patients who underwent simple peritoneal drainage, while general peritonitis was more common in patients undergoing external wirsungostomy. Moreover, the degree of pancreaticojejunal anastomotic dehiscence appeared to be more severe in patients who underwent external wirsungostomy than those undergoing simple peritoneal drainage or re-PJ. Taken together, these findings indicated a more severe anastomosis disruption and local inflammatory response in the cases of external wirsungostomy that makes preserving or re-doing the pancreaticojejunal anastomosis unpractical.

Interestingly, in the multivariate analysis, we found that patients who had a less-severe pancreatic fistula for at least 24 h before developing a grade-C POPF tended to have better outcomes than those who had a rapidly progressive course to grade-C POPF. In other words, patients who initially presented with a rapidly deteriorating POPF that required urgent operation tended to have a higher risk of unfavorable events after re-laparotomy such as acute major complications, mortality, and unplanned re-re-laparotomy. This phenomenon may be partially explained by the greater inflammatory response and more pernicious clinical course in patients with a straightforward grade-C POPF, reflecting the fulminant nature of disease. Further studies are warranted to validate this finding and to elucidate the exact underlying mechanism.

There are several limitations to the current study. First, its retrospective nature introduced confounding and selection bias, as no randomization was undertaken. Second, this study was a clustered analysis of heterogeneous practices, since each medical center manages surgical procedures differently, and each surgeon has his/her own preferences. The bias resulting from these factors limits the statistical reliability of these data. In addition, despite the fact that all nine hospitals were high-volume centers, only 68 cases out of 5115 PDs were eligible for analysis because of the extreme rarity of grade-C POPF. It is difficult to make reliable comparisons among such a small number of cases. This mandates further verification of these results in a larger sample and the identification of other possible factors that were too infrequent to show a significant difference in the current study.

5. Conclusion

Pancreas-preserving approaches were mostly preferred in this cohort. External wirsungostomy was the most common used surgical

procedure for grade-C POPF, and was associated with a relatively short length of hospital stay. However, external wirsungostomy has several drawbacks, such as the potential need for re-anastomosis and risks of accidental pullout, occlusion, and rupture of the external drainage tube. A tailored approach is recommended as surgeons take into consideration the condition of the surgical site, comorbidities, and the prognosis of the primary disease. Moreover, any benefit of aggressive surgery must be weighed against the risk of postoperative morbidity and mortality.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declarations of interest

None.

Availability of data

The authors confirm that the data supporting the findings of this study are available within the article.

Ethical approval

This study was approved by the Medical Ethics Review Committee of the First Affiliated Hospital of Zhejiang University School of Medicine.

Sources of funding

This work was supported by National High Technology Research and Development Program of China (No. S2015AA020405), Training Program of the Key Program of the National Natural Science Foundation of China (No. 91442115), National Natural Science Foundation of China (No. 81672337), Key Program of the National Natural Science Foundation of China (No. 81530079), Key research and development Project of Zhejiang Province (No.2015C03044), Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents, Zhejiang Provincial Key Innovation Team of Pancreatic Cancer Diagnosis & Treatment (No. 2013TD06).

Author contribution

Conception/design (TM, XB, TL); data acquisition (WC, ML, GJ, KZ, DF, FY, RQ, XL, WL, LZ, KJ, PW, CS, AL, YY, YM, HW); data interpretation (all authors); manuscript drafting (TM, TL); critical revisions (all authors); final approval (all authors).

Conflicts of interest

There are no conflicts of interest amongst any of the authors.

Research registration number

NCT03129607.

Guarantor

Tingbo Liang.

CRediT authorship contribution statement

Tao Ma: Conceptualization, Methodology, Writing - original draft. **Xueli Bai:** Conceptualization, Methodology, Data curation. **Wen Chen:** Investigation, Data curation, Software. **Mengyi Lao:** Investigation, Data curation. **Gang Jin:** Investigation, Resources. **Kailian Zheng:** Investigation, Resources. **Deliang Fu:** Investigation, Resources. **Feng Yang:** Investigation, Resources. **Renyi Qin:** Investigation, Resources. **Xu Li:** Investigation, Resources. **Wenhui Lou:** Investigation, Resources. **Lei Zhang:** Investigation, Resources. **Kuirong Jiang:** Investigation, Resources. **Pengfei Wu:** Investigation, Resources. **Chenghao Shao:** Investigation, Resources. **Anan Liu:** Investigation, Resources. **Yinmo Yang:** Investigation, Resources. **Yongsu Ma:** Investigation, Resources. **Heshui Wu:** Investigation, Resources. **Tingbo Liang:** Conceptualization, Project administration, Writing - review & editing, Supervision.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.05.019.

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