Risk factors for pancreatic fistula following distal pancreatectomy: a retrospective study of 211 consecutive patients

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Abstract

Background Postoperative pancreatic fistula (POPF) is a common complication following distal pancreatectomy (DP). Although the mortality from these procedures has decreased in the past decades, the rate of POPF remains high. The aim of this study was to identify risk factors associated with POPF after DP. Methods A retrospective review of a consecutive series of 211 patients who had undergone DP between January 2016 and October 2018 at a single institution was conducted. Patient demographic data, perioperative data and clinicopathological parameters were analysed to evaluate their correlation with the incidence of POPF using univariate and multivariate models. POPFs were defined by 2016 International Study Group criteria. Results Two hundred eleven consecutive patients were identified. The overall pancreatic fistula rate was 15.64%, and no 30-day or 90-day mortality was seen. Four predictors were independently associated with POPF: soft pancreatic texture (odds ratio (OR): 4.23, 95% confidence interval (CI): 1.71-10.45, P = 0.002), longer operating time (OR: 4.18, 95% CI: 1.67–10.46, P = 0.002), higher difference of albumin (OR: 6.41, 95% CI: 2.40–17.08, P <0.001), and history of cardiovascular disease(OR: 5.05, 95% CI: 1.97-13.01, P = 0.001). Conclusions Although DP can be performed with a low rate of mortality, POPF remains a common complication. Pancreatic texture, operating time, the difference of albumin and cardiovascular disease were risk factors for POPF after DP.

Background

Distal pancreatectomy (DP) is the main curative treatment performed for lesions in the body or tail of the pancreas. Although the perioperative mortality rate following pancreatic resections has decreased to less than 5%, morbidity rates remain high, even in high-volume centres [1, 2]. Postoperative pancreatic fistula (POPF) is one of the most severe complications after distal pancreatectomy (DP). The risk of POPF after DP is 20 to 30% [3-6]. While several studies have examined the preoperative, intraoperative and postoperative risk factors for this costly complication, few were focused on DP, and prediction of this complication remains an area of considerable interest. Our aim was to evaluate the risk factors of POPF following DP.

Methods

Patient cohort

A retrospective analysis of all consecutive DPs for both benign and malignant disease was conducted at our department from January 2016 and October 2018. This study included patients undergoing DP via open, laparoscopic and robotic approaches with or without spleen preservation.

Patients were excluded based on the following criteria: 1) history of pancreatectomy, 2) complicated with chronic renal insufficiency, 3) combined with pancreaticoduodenectomy or duodenum-preserving pancreatic head resection, 4) less than 18 years old.

Operative intervention

Conventional antibiotic prophylaxis was administered 30 minutes prior to the operation. Spleen-preserving DP was adopted in cases of benign diseases, such as chronic pancreatitis or benign tumours. Operative procedures were performed by experienced surgeons who specialise in pancreatic surgery. The surgical approach followed specific principles and guidelines, but the particular technique, such as simultaneous metastases intervention, pancreatic transection and remnant closure, was chosen according to the patient's needs, intraoperative situation and the surgeon's preference.

Postoperative care

Routine peritoneal drainage was placed at the stump of the pancreas to monitor POPF and avoid intra-abdominal fluid collection. Routine laboratory results, including albumin, blood platelet count(PLT), white blood cell (WBC) count, creatine kinase(CK), lactate dehydrogenase (LDH), and amylase concentration of drainage fluid, were collected on postoperative days (PODs) 1 and 3. Oral diet and walking were encouraged at an early stage. All patients underwent abdominal computed tomography (CT) or trans-abdominal ultrasound on POD 5 after surgery. Additional abdominal imaging was performed when there was a sign of possible intra-abdominal complication. Drains were removed based on iconography findings, amylase levels and characteristics of the drained fluid. If patients required additional drainage, removal of the drain was delayed.

Data collection and definitions

Data were collected on pre-, intra- and postoperative data. Preoperative data included patient demographics, past medical history, living habits and preoperative biochemical markers, such as serum albumin and Hemoglobin (Hb). The diameter of the main pancreatic duct (MPD) was assessed with a preoperative CT scan performed in the week before surgery. Intraoperative variables included operative approach, tumour location, tumour size, operative time, pancreatic transection and stump closure procedure (stapler or hand-sewn) and concomitant splenectomy or not. Gland texture was classified as soft or hard based on intraoperative inspection and palpation by the experienced surgeons. Postoperative clinical data included the result of laboratory tests and vitals on POD1 and clinicopathological parameters. To analyse the occurrence of pancreatic fistula and its classification, the amylase drainage and other complications were also collected.

The primary outcome of this study was POPF. According to the 2016 International Study Group of Pancreatic Surgery, POPF was defined as any drain fluid with a concentration of amylase more than 3 times the normal upper limit of serum amylase level on or after POD 3 and affiliated with a clinically relevant change in management [7]. Biochemical leaks that did not alter medical management were not included. The normal upper limit of serum amylase is 135 U/L in our institution. Amylase drainage fluid concentration more than 405 U/L was classified as POPF, if one of the following criteria was met: 1) persisting peripancreatic drainage more than 3 weeks; 2) changes in clinical management strategies due to POPF (such as usage of somatostatin analogues, blood transfusions or other medications; 3) need for reoperation; 4) requirement for percutaneous or endoscopic interventions; 5) signs of infection related to POPF; or 6) organ failure or death. All cases were followed up for up to 3 months.

In this article, the difference of albumin (DA) was defined as the level of preoperative albumin minus postoperative albumin on POD1.

Statistical analysis

To identify risk factors of pancreatic fistula for DPs, pre-, intra- and postoperative variables were compared with those of POPF and no POPF.

SPSS® Complex Samples v22.0 (IBM Corp, Armonk, NY) was used to analyse the data.

Continuous parameters were assessed by the Kolmogorov-Smirnov test to judge whether they were normally distributed. Normally and non-normally distributed continuous data were presented as means with standard deviations (SD) and medians with the interquartile range (IQR). Categorical variables were expressed as frequencies or percentages.

The Student's t-test was used to compare normally distributed data, while the Mann-Whitney U test was used to assess non-normally distributed data. Categorical variables were evaluated by the chi-squared or Fisher's exact test. For better clinical utility, all continuous parameters thought to be significant ($p < 0.10$) in the univariate analysis were evaluated for cut-off points by receiver operating characteristic (ROC) curves based on the maximal Youden index and divided into 2 groups.

Parameters that were considered significant in univariate analysis ($P < 0.10$) or expected to be important clinically were incorporated into the logistic regression analysis via a stepwise backward method to screen out independent risk factors, and results were expressed as adjusted odds ratios (ORs) with 95 percent confidence intervals (CI).

All data were evaluated by 2-tailed *P* values, and a *P* value of <0.05 was thought to be statistically significant. The statistical method of multiple imputation was used for handling the missing data [8]

Results

During this 34 months, a total of 226 consecutive cases that underwent DP at our department were screened out. Fifteen cases were excluded according to our exclusion criteria, including 5 patients who had a pancreatectomy history, 6 patients who had chronic renal insufficiency, 2 patients who were combined with pancreatic head resection and 2 patients younger than 18 years old. In the end, 211 patients who underwent DP were included in the study cohort. All included patients had complete clinical and pathological data in the study cohort (missing data less than 5%).

Patient characteristics

In total, 211 cases with a mean age of 52.07±13.81 years and a mean body mass index (BMI) of 22.97±3.67 were included in this study, 44.08% of whom were male patients. Cystic tumour and

pancreatic ductal adenocarcinoma accounted for approximately 39.34 and 37.44% of the diseases, respectively. The 3 most common concomitant diagnoses at the time of consultation were cardiovascular disease (29.38%), abdominal operation history (23.70%) and diabetes mellitus (15.17%). The characteristics of the patients are listed in Table 1. A detailed summary of preoperative data is shown in Table 2.

Intraoperative parameters

Laparotomy was performed in 65.88% of patients. The majority of the patients in these 2 groups underwent DP combined with splenectomy (Group POPF *VS* Group no-POPF: 93.94% *VS* 91.01%). The median operative time was 241.00 (IQR, 192.00-326.00) minutes (Group POPF *VS* Group no-POPF: 317 (IQR, 250-370) min *VS* 227 (IQR, 186-311) min). The pancreatic stump was closed by stapler technique more frequently than hand suture (stapler *VS* suture, 64.93% *VS* 35.07%), and no additional coverage was used. Seven cases□3.32%□underwent radical DP with resection of the celiac axis. Eighty-six cases were judged to have soft pancreatic texture. The median size of the tumour was 3.50 (IQR, 2.30-5.00) cm (Table 3).

Postoperative course

The following surgical complications were identified: 33 (15.64%) patients developed POPF, among which, 28 patients were classified as Grade B pancreatic fistula, and 5 patients were classified as Grade C pancreatic fistula; 14.69% of cases had abdominal infection, 3.79% of patients required minimally invasive therapy, 1.90% of cases had abdominal bleeding, 1.42% of patients underwent a second operation, 0.95% of cases had organ failure and no patients died due to POPF. The median length of hospital stay was 14 (11-16) d (Group POPF *VS* Group no-POPF: 25 (15-30) d *VS* 13 (11-15) d, $P < 0.0001$). A detailed summary of all postoperative data is shown in Table 4. No patients died during hospitalization, and no 30-day or 90-day mortality was seen.

Univariate analysis

As is shown in the table, no significant differences were found between the 2 groups with regard to age, body mass index, history of alcohol consumption, smoking and abdominal surgery, diabetes and multiple biochemical markers (i.e., preoperative serum albumin, platelet count, haemoglobin level). The MPD and diameters of the tumour measured between the 2 groups of patients were also equivalent. The closure technique (stapler versus scalpel), tumour location and splenectomy also showed no significant differences.

Conversely, a significant correlation was observed between POPF and the following factors: pancreatic texture (soft VS hard: 40.76% VS 59.24%, $P < 0.001$), operative time (Group POPF VS Group no-POPF: 317.00 min VS 227.00, $P < 0.001$), history of cardiovascular disease (yes *VS* no: 29.38% *VS* 70.62%, $P = 0.006$) and DA (Group POPF *VS* Group no-POPF: 13.92g/L *VS* 10.12g/L, $P < 0.001$).

ROC curve revealed that the optimal cut-off value for operative time and DA was 280.00 min (≤ 280.00 min *VS* > 280.00 min: 57.82% *VS* 42.18%, *P* < 0.001) and 12.50 g/L (≤12.50 g/L *VS* >12.50 g/L: 58.77% *VS* 41.23%, *P* < 0.001).

The risk factors for the development of pancreatic fistula are presented in Tables 1-4.

Multivariate logistic regression analysis

The suspect risk factors that were demonstrated in the univariate analysis (sex, history of cardiovascular disease, operation time, DA, surgical procedure and pancreatic texture) were entered into the binary logistic regression analysis via a stepwise backward method to identify the independent risk factors for POPF. The results showed that higher DA (OR=6.41, 95% CI: 2.40-17.08, *P* <0.001), soft pancreas (OR=4.23, 95% CI: 1.71-10.45, *P* = 0.002), history of cardiovascular disease (OR=4.23, 95% CI: 1.97-13.01, *P* = 0.001), and longer operation time (OR=4.18, 95% CI: 1.67-10.46, *P* = 0.002) were independent risk factors for pancreatic fistula after DP (Table 5).

However, sex and surgical procedure failed to have a statistically significant influence on the development of pancreatic fistula.

Discussion

Although the mortality of DP has decreased markedly over the past decades, the POPF incidence of this operation mode is still the major issue. The leaked pancreatic juice destroys the surrounding tissues, which remains the main cause of secondary complications, such as abdominal haemorrhage, pancreatic pseudocyst, sepsis, organ dysfunction and even death [1, 3, 4, 9, 10]. Our work also demonstrates that POPF clearly affects the short-term prognosis of the patients (Table 4). However, the strides in both risk prediction and prevention measures of POFP for DP have fallen behind when compared to that of fistula following pancreaticoduodenectomy [11]. The primary reason for this is that surgical complications associated with a pancreatic fistula in a DP are less complicated due to the absence of a biliary and enteric anastomosis, which did not attract enough attention from the physician, and the fact that pancreatic body and tail lesions occur less frequently than pancreatic head lesions also played a role in it [10, 12].

The increased pressure in the main pancreatic duct [13] and the necrosis of the pancreatic stump [6, 14] were thought of as two factors for pancreatic fistula formation after DP. Several studies have emphasized the management of the pancreatic remnant after DP, such as the closure techniques, including pancreatico-intestinal anastomosis [5, 6], stapler and suture [4, 14-17], main pancreatic duct ligation [4, 14, 18, 19], biologic glues [20, 21], mesh reinforcement [3, 22] and pancreatic duct stent [23-25]. However, the optimal management of the pancreatic stump following DP has still not been established [4, 6, 14-16, 18, 26]. In our work, the closure techniques also did not affect the rate of POPF. Somatostatin analogues, a type of drug widely used in pancreatic surgery, have also been shown to be ineffective in reducing the POPF in some studies [4, 21, 27-30]. In this study, the much-discussed treatment of pancreatic stump

(stapler *VS* suture) was not found to be related to the occurrence of pancreatic fistula. Although no prospective randomised clinical trials have pointed out that mesh coverage of the pancreatic remnant may be a potential approach to reduce the occurrence of POPF in patients undergone DP [3, 22], we seldom use this mesh because of the expenses associated with it. As consensus for optimising the management strategy of the pancreatic stump remains to be reached [4], it has clinical value for screening out patients with a high risk of pancreatic fistula.

Although management of the pancreatic remnant following DP remains a popular topic, studies evaluating the risk factors for DP are lacking, and the risk factors for POPF following pancreatoduodenctomy remain to be proven for POFP after DP [3, 4, 9, 11]. To our knowledge, surgical techniques and perioperative management are essential to the outcome of surgical patients. Since various techniques for management of the pancreatic remnant have proven to be invalid for decreasing the fistula rate, particular attention should be paid to the perioperative management, which include the risk factors [9, 31].

The incidence of POPF and the length of hospital stay in this study are comparable to previous reports [17, 24]. No 30-day or 90-day mortality was seen. Several POPF risk factors of DP were identified: soft pancreatic texture, history of cardiovascular disease, DA and operative time.

The soft pancreas has been regarded as a key risk factor for POPF, especially for a pancreatoduodenctomy [32, 33]. In this cohort study, 86 cases, 23 of which developed a POPF, were classified as having soft pancreas. Statistical analysis indicated that soft pancreatic texture was an important risk factor for POPF following DP (OR: 4.23, 95% CI: 1.71-10.45, $P = 0.002$). Hashimoto et al. reviewed 205 consecutive cases of DPs and showed that soft pancreatic parenchyma is an independent risk factor of POPF (OR: 4.89, 95% CI: 1.42–16.77, $P = 0.012$) [13]. On the contrary, a polycentric, retrospective study of 2,026 cases involving 52 doctors showed that patients with soft pancreas have a higher risk of developing a POPF in univariate analysis, but not independently associated with POPF after DP [11]. This may be because they did not analyse the linear relationship of possible risk factors and study the correlations between researchers, as practices varied between the surgeons. A soft pancreas that usually contains abundant pancreatic ducts and acini is fragile and can easily be injured during the operation. The regeneration of pancreatic acini and fibrotic gland leads to a hard pancreas with impaired exocrine function. The fibrotic pancreatic tissue is believed to be less prone to pancreatic leakage. This may partly explain why patients with hard pancreas have a lower incidence of POPF after DP.

Few authors stated that preoperative hypoalbuminaemia seems to be one of the risk factors for POPF following DP [11, 26, 34]. Lower levels of albumin are believed to be more likely to result in pancreatic leakage. In contrast, there was no significant difference in the level of the preoperative albumin between the two groups in our work, nor was it in the work of Kawabata [35]. We found that patients with higher DA are more prone to develop a POPF, and statistical analysis of the DA showed a difference between these 2 groups. The result (OR: 6.41, 95% CI: 2.40-17.08, $P < 0.001$) indicated that DA is an independent risk factor of POPF. Albumin, usually marked as a biomarker of nutritional status of patients, performs a

number of important functions including transport drugs, contributing to the maintenance of plasma pH, plasma osmotic pressure and blood volume [36, 37]. It is also known that albumin can provide nutrition and energy to the fast-growing tissues, reduce the inflammatory response and stimulate repair or remodelling, such as wound healing [37, 38]. It remains to be proven whether exogenous albumin can reduce the risk of POPF for high-risk patients.

In this study, operation time (> 280.00 min) was independently associated with increased in the risk of POPF (OR: 4.18, 95% CI: 1.67-10.46, P = 0.002). In accordance with our result, a retrospective study showed that an operative time longer than 480.00 minutes was associated with a 4.21-fold increase in pancreatic fistula risk [1]. An analysis of 120 cases identified longer operative time was a risk factor for POPF, although not clinically significant POPF [39]. In another two studies, operative time was judged as the only notable predictor of POPF [26, 35]. Operative time is usually associated with extended resection, blood loss, inflammatory status, intraoperative hypothermia and pancreatic malignancies.

Aside from soft pancreatic texture, operating time and DA, cardiovascular disease also has an important effect on POPF. To our knowledge, this is the first study which identifies the cardiovascular disease as independent predictors for POPF after DP. In this study, 62 cases had a history of cardiovascular disease, 29.03% of which developed into a POPF, and multivariate analysis showed that it was associated with pancreatic fistula risk (OR:5.05, 95% CI: 1.97-13.01, P = 0.002). Cardiovascular disease, manifesting as atherosclerosis and ischaemia, is not conducive to neoangiogenesis and wound-healing [40].

The diameter of main pancreatic duct has been considered to be a key risk factor for POPF after pancreaticoduodenectomy [32, 33]. However, it has not been proven to be a risk factor for POPF after DP in our work. In practice, it is extremely rare to see a dilated downstream segment of the pancreatic duct.

In this single-centre retrospective analysis, we demonstrated that DP can be performed safely with extremely low postoperative mortality. Perioperative data, including pre-, intra- and post-operative variables were considered in this analysis, which makes it more convincing. Our findings indicated that soft pancreatic texture, longer operation time, higher DA and history of cardiovascular disease are risk factors. To reduce the rate of POPF, we can shorten surgery time by a faster operation and screening the patients with high risk.

Our study has its own limitations. First, it is a retrospective study performed at a single institution; hence, we were unable to eliminate some bias, such as selection bias. Second, our sample size remains limited, which weakens the credibility of this study. In the future, a multi-centre prospective study should be carried out, and those risk factors of POPF should be externally validated.

Abbreviations

POPF: Postoperative pancreatic fistula; DP: Distal pancreatectomy; DA: Difference of albumin; OR: Odds ratio; CI: Confidence interval; SD: standard deviations; IQR: Interquartile range; WBC: White blood cell; CK: Creatine kinase; LDH: Lactate dehydrogenase; postoperative days: POD; Hb: Hemoglobin.

Declarations

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Authors' contributions

HW: study concept and suggestions; RW and JS: collection of clinical data and methodology; YZ, RW, and JH: statistical analysis and interpretation; JS and JH: preparation of the first draft of the manuscript; HW and YZ: revision of the manuscript. All authors have approved the final version of the manuscript.

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Availability of data and materials

The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics statement

Written informed consent from patients was performed before participation, and the study was approved by the Human Subjects Protection Committee of the Huazhong University of Science and Technology.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Tables

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Supplementary Files

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