

ORIGINAL RESEARCH ARTICLE

Risk factors of pancreatic fistula after resection of pancreatic body and tail duct adenocarcinoma

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ABSTRACT

Objective: To investigate the risk factors of pancreatic fistula after resection of pancreatic body and tail duct adenocarcinoma. **Methods** all cases of pancreatic body and tail resection for pancreatic body and tail duct adenocarcinoma in Union Hospital Affiliated to Tongji Medical College of Huazhong University of science and technology from January 2016 to December 2018 were analyzed retrospectively in a single center. The preoperative, intraoperative and postoperative data were collected and analyzed by spssv22.0. The definition and grouping of pancreatic fistula were implemented according to the standards formulated by the international pancreatic fistula research group in 2016. All cases were followed up for at least 3 months. **Results:** A total of 91 cases were included in the study. The overall pancreatic fistula rate was 25.27% (23/91). No death occurred within 90 days after operation. Three risk factors for pancreatic fistula were identified: Pancreatic texture (soft) [odds ratio =8.965,95% confidence interval (2.400,33.490), p=0.001], combined with cardiovascular disease [odds ratio =9.148,95% confidence interval (1.936,43.225), p=0.05], albumin <26.50g/l [odds ratio =6.100,95% confidence interval (1.846,20.157), p=0.003]. **Conclusion** soft pancreas, complicated with cardiovascular disease and low albumin level on the first day after operation are independent risk factors for pancreatic fistula after operation of pancreatic duct adenocarcinoma. Due to the limitations of the study, the results need to be further verified.

Keywords: pancreatic ductal adenocarcinoma; resection of body and tail of pancreas; pancreatic fistula; risk factors

1. Introduction

Pancreatic ductal adenocarcinoma of the body and tail (PDA) is an occult and aggressive malignant tumor. Distal pancreatectomy (DP) is a conventional surgical method for the treatment of pancreatic body and tail lesions, but the overall incidence of

postoperative complications is still high (35%~65%) [1-2]. Postoperative pancreatic fistula is one of the important complications after DP, with an incidence of 20%~30% [3-6]. Postoperative pancreatic fistula is closely related to abdominal bleeding, infection and other complications [2,7]. The incidence of pancreatic body and tail cancer is significantly lower than that

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of pancreatic head, and the resection rate is lower than 30% [8]. Some studies have pointed out that the incidence of pancreatic fistula after DP is higher than that after pancreaticoduodenectomy, but the research on it lags behind the research on pancreatic fistula after pancreaticoduodenectomy [9]. With the increase of the discovery rate of pancreatic malignant tumors and the promotion of transformation treatment, the number of PDA operations has gradually increased [10], and the pathological type is one of the important factors affecting the occurrence of pancreatic fistula after pancreatic surgery [11]. The purpose of this study was to explore the risk factors of pancreatic fistula after PDA in order to provide theoretical basis for clinical management.

2. Data and methods

2.1. Basic data

Retrospectively collected the case data of DP surgery for PDA in Union Hospital Affiliated to Tongji Medical College of Huazhong University of science and technology from January 2016 to December 2018. Exclusion criteria: a. History of pancreatic surgery; b. Combined with chronic organ dysfunction; c. Simultaneous pancreatectomy or total pancreatectomy; d. Pathology confirmed non PDA.

A total of 91 patients were included in the study. The median age was 60 years old. The body mass index (BMI) was (22.53 ± 3.89) kg/m². There were 52 male patients (57.14%). There were 22 cases (24.18%) with diabetes and 12 cases (13.19%) with cardiovascular diseases (**Table 1**), including 5 cases of coronary heart disease, 2 cases of atrial fibrillation, 2 cases of frequent ventricular premature beats, 1 case of grade II atrioventricular block, 1 case of severe aortic insufficiency, and 1 case of hypertrophic cardiomyopathy.

2.2. Method

1. Operation process and postoperative management. All PDA cases were treated with pancreaticotomy and splenectomy. Antibiotics were

given 30 minutes before operation. The operation was performed by surgeons with rich experience in pancreatic surgery. The operation process follows the relevant principles of resection of pancreatic body and tail cancer. During the operation, personalized treatment methods can be selected according to the actual situation. For example, the transverse non absorbable line of the pancreas is sutured "8" at the main pancreatic duct first, and then the discontinuous vertical mattress varus suture at the anterior and posterior edges of the pancreas about 1cm away from the broken end. Abdominal drainage tube was routinely placed at the severed end of pancreas after operation. Somatostatin and its analogues are not used routinely. Routine blood routine, biochemical and amylase concentration detection in drainage fluid shall be completed on the first day after operation. All cases advocated early eating, early getting out of bed and early pulling out of abdominal drainage tube. If the patient only has biochemical fistula and the overall condition recovers well, he can take the tube home and follow up closely.

2. Observation indicators. a. Occurrence and grading of pancreatic fistula; b. The risk factors influencing the occurrence of pancreatic fistula after PDA: Including the medical records before, during and on the first day after operation; c. Recovery within 90 days after operation.

3. Evaluation criteria. The diameter of pancreatic duct refers to the diameter of the main pancreatic duct from the tumor to the head of the pancreas, which is measured by abdominal CT images within one week before operation. Smoking: Smoking for more than 3 months and ≥ 5 cigarettes /d, or quitting smoking for less than 3 months. Drinking: More than 3 months accumulatively at the time of seeing a doctor, and the alcohol intake >25 g/d, or less than 3 months after abstinence. The definition of cardiovascular disease is based on the definition and classification of cardiovascular disease in the summary of China cardiovascular disease report 2018 [12]. The judgment standard of pancreatic fistula is that the amylase concentration in drainage fluid exceeds 3 times of the upper limit of

serum amylase 3 days after operation and is related to clinical prognosis [13]. The upper limit of normal serum amylase in this institution is 135u/l. When the amylase concentration in drainage fluid is greater than 405u/l at least 3 days after operation, and one of the following conditions occurs, it is determined as postoperative pancreatic fistula: a. The abdominal drainage tube is placed for more than 3 weeks; b. Clinical treatment was changed due to pancreatic fistula; c. Percutaneous or endoscopic puncture intervention; d. Vascular intervention for abdominal hemorrhage; E. Reoperation; f. Organ failure or death occurs. If one of the first four articles is satisfied, it will be classified as grade B pancreatic fistula, and if one of the last two articles is satisfied, it will be classified as grade C pancreatic fistula.

4. Follow up. After discharge, the patients were followed up by outpatient, Internet or telephone for at least 90 days to understand the recovery of the patients, such as abdominal symptoms and signs, whether there was pancreatic fistula and related complications, the drainage of the drainage tube of the patients who took the tube home and the time to pull it out.

2.3. Statistical analysis

SPSS (version 22.0) statistical software was used for analysis. The continuity data are $\bar{x} \pm s$ expressed by or median and interquartile spacing [M and (P₂₅, P₇₅)], and T or Mann Whitney U are used to test the selection of fracture and cross-sectional suture methods. The hardness and softness of pancreatic texture are analyzed by two factors. For classified data analysis χ^2 or Fisher exact test. More than one experienced surgeon makes judgment by touching the pancreas during operation. The standard scope of lymph node dissection includes No.10, No.11 and No.18 lymph nodes. When the tumor is limited to the pancreatic body, it includes No.9 lymph nodes. Those beyond the above scope of dissection are defined as expanded lymph nodes. The linear cutting and suturing devices used in the operation are all Johnson & Johnson series products, and the nail bin is selected according to the thickness of the pancreas; During manual suture, the continuous data of $p < 0.10$ in single strand factor analysis will be used to find the best cut-off point through the receiver operating characteristic (ROC) curve based on the maximum Jordan index [14].

In univariate analysis, variables with $p < 0.10$ or considered clinically significant will be included in multivariate logistic regression analysis, and the results are expressed by odds ratio (or) and 95% confidence interval (CI).

Table 1. Basic characteristics of cases

Clinical factors	All cases (91 Cases)	Postoperative pancreatic fistula (3 Cases)	Non postoperative pancreatic fistula (8 Cases)	t/Z/ χ^2 Value	P value
Age [M(P ₂₅ , P ₇₅), years]	60(3,66)	63(50,66)	59(33,66)	-0.027	0.978
Body mass index ($\bar{x} \pm s$, kg/m ²)	22.53±3.89	22.87±4.34	22.40±3.74	-0.479	0.633
Sex [cases (%)]				0.005	0.944
Female		39(42.86)	10(10.99)	29(31.87)	
Male		52(7.14)	13(14.28)	39(42.86)	
Smoking history [cases (%)]					1.1780.278
Have		28(30.77)	5(5.50)	23(25.27)	
Nothing		63(69.23)	18(19.78)	45(49.46)	
Drinking history [cases (%)]					0.3780.539

Have	20(21.98)	4(4.40)	16(17.58)
Nothing	71(78.02)	19(20.88)	52(57.14)
History of abdominal surgery [cases (%)]			0.2270.634
Have	19(20.88)	4(4.40)	15(16.48)
Nothing	72(79.12)	19(20.88)	53(58.24)
Diabetes [cases (%)]			0.7730.379
Have	22(24.18)	4(4.40)	18(19.78)
Nothing	69(75.82)	19(20.88)	50(54.94)
Combined with cardiovascular disease [cases (%)]			7.9990.010
Yes	12(13.19)	7(7.69)	5(5.50)
No	79(86.81)	16(17.58)	63(69.23)

3. Results

3.1. Postoperative conditions

Postoperative pancreatic fistula occurred in 23 patients. The overall pancreatic fistula rate was 25.27% (23/91), of which 4 cases (4.40%) developed into grade C pancreatic fistula. The average hospital stay

was 14 days (12~18 days). 13 cases (14.29%) developed abdominal infection, 6 cases (6.59%) needed abdominal puncture, 3 cases (3.30%) underwent interventional surgery due to abdominal hemorrhage, 3 cases (3.30%) underwent reoperation, and 1 case (1.10%) developed acute renal insufficiency. Six patients (6.59%) were readmitted due to postoperative complications within 90 days after operation, and no death occurred.

Table 2. Preoperative examination data

Index	Postoperative pancreatic fistula (23 Cases)	Non postoperative pancreatic fistula (68 Cases)	t(Z) value	P value
Serum albumin ($\bar{x} \pm s$, g/l)	40.00±5.84	4038±4.74	0.305	0.761
Total serum protein ($\bar{x} \pm s$, g/l)	66.34±4.54	65.84±6.46	-0.344	0.732
CA19-9[M(P ₂₅ ,P ₇₅),U/ml]		446.75(99.78,1200.00)	389.70(50.80,1200.00)	0.427 0.669
CA125[M(P ₂₅ ,P ₇₅),U/ml]		32.85(24.70,61.65)	20.95(14.90,55.15)	1.513 0.130
Hemoglobin ($\bar{x} \pm s$, g/l)		126.00±16.58	126.90±17.08	0.219 0.827
Lactate dehydrogenase ($\bar{x} \pm s$, u/l)		185.35±127.67	164.63±31.56	- 0.237 1.192
Platelet count ($\bar{x} \pm s$, x10 ⁹ /l)		196.17±62.65	174.12±70.35	- 0.186 1.334
Alanine aminotransferase [m (P ₂₅ , P ₇₅), u/l]		19.00(10.00,24.00)	16.00(11.00,29.00)	- 0.952 0.060
Aspartate aminotransferase [m (P ₂₅ , P ₇₅), u/l]		17.00(15.00,19.00)	20.00(15.00,24.00)	-1400 0.162
Leukocyte count ($\bar{x} \pm s$, × 10 ⁹ /L)		5.43±1.25	5.52±1.92	0.212 0.833

3.2. Single factor analysis of pancreatic fistula after PDA

Through analysis, the following factors may be related to the occurrence of postoperative pancreatic fistula: Pancreatic texture ($p<0.001$), operation time ($p=0.018$), cardiovascular disease ($p=0.010$), extended lymph node dissection ($p=0.008$), and postoperative serum albumin ($p=0.005$). However, there was no significant difference in other preoperative, intraoperative, and postoperative data (**Table 1 to table 4**).

Through ROC curve analysis, it was found that the optimal cut-off points of operation time and postoperative serum albumin were 280min and 26.50g/l respectively, and the data of the two groups were divided into groups. Single factor analysis again still had statistical significance ($p=0.016$ and $p=0.001$), as shown in **Table 3** and **Table 4**.

3.3. Multi factor analysis of pancreatic fistula after PDA

Suspicious variables found in univariate analysis: Pancreatic texture, operation time, cardiovascular disease, extended lymph node dissection, and serum albumin on the first day after operation were included in the multivariate logistic regression model analysis. The results showed that pancreatic texture (soft), cardiovascular history, and

serum albumin on the first day after operation ($<26.50\text{g/l}$) were independent risk factors for postoperative pancreatic fistula after DP ($p<0.05$), while operation time and extended lymph node dissection did not become independent risk factors (**Table 5**).

4. Discussion

A total of 91 cases were included in this study. No death occurred during the perioperative period. The incidence of pancreatic fistula after operation was 25.27% (23/91), which was equivalent to 20%~30% reported in the literature [3-6]. Pancreatic fistula has a great impact on the short-term prognosis of patients, which is a major challenge that pancreatic surgeons need to face. The measures that can effectively reduce the incidence of pancreatic fistula are still controversial. Therefore, screening high-risk patients has important clinical significance: Actively take preventive measures for patients with high risk of pancreatic fistula to reduce the incidence of pancreatic fistula, and continue to take rapid rehabilitation strategies for patients with low risk of pancreatic fistula. This study included the data before, during and on the first day after the operation longitudinally, hoping to help clinicians screen out high-risk groups of pancreatic fistula on the first day after the operation. Three risk factors of pancreatic fistula after PDA were found by analysis.

Table 3. Intraoperative data

Clinical factors	Postoperative	Non postoperative		Z/ χ^2/t P value value
	pancreatic fistula (23 Cases)	pancreatic fistula (8 Cases)		
Operation time [M(P ₂₅ , P ₇₅), min]	323.00(269.00,390.00)	26800(205.00,330.00)	2.357	0.018
Intraoperative blood loss [m (P ₂₅ , P ₇₅),37000(290.00,800.00) ml]		30000(270.00,400.00)	-1.599	0.110
Operation method [cases (%)]		0.607	0.819	
Minimal invasive		7(7.69)	20(21.98)	
Transfer	3(3.29)	6(6.60)		
Open	13(14.29)	42(46.15)		
Stump closure mode [cases (%)]			0.180	0.810
Manual suture	12(13.19)	32(35.16)		
Closer closed	11(12.09)	36(39.56)		

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Pancreatic texture [cases (%)]			1.2767	<0.001
Soft	18(19.78)	24(26.37)		
Hard	5(5.50)	44(48.35)		
Tumor diameter [M(P ₂₅ , P ₇₅), cm]	400(300,900)	3.90(3.00,5.25)	0.352	0.725
Tumor location [cases (%)]			0.002	>0.999
Pancreatic body	16(17.58)	47(51.65)		
Tail of pancreas	7(7.69)	21(23.08)		
Diameter of pancreatic duct (mm)	2.31±0.59	2.56±0.88	0.642	0.523
Lymphadenectomy [cases (%)]			7.382	0.008
Yes	5(5.50)	37(40.66)		
No	18(19.78)	31(34.07)		
Modified Appleby procedure [cases (%)]			2.079	0.149
Yes	3(3.29)	3(3.30)		
No	20(21.98)	65(71.43)		
Perigastric varices [cases (%)]			1.911	0.167
Yes	10(10.99)	19(20.88)		
No	13(14.28)	49(53.85)		
Operation time [cases (%)]			6.110	0.016
<280 Min	6(659)	38(4176)		
>280 Min	17(1868)	30(32.97)		

Soft pancreas is a risk factor for postoperative pancreatic fistula. In this study, the incidence of postoperative pancreatic fistula in the soft pancreas group was 42.86%. Statistical analysis showed that it was an independent risk factor for postoperative pancreatic fistula [or=8.965,95%ci (2.400,33.490), p=0.001], which was consistent with other research results: A retrospective study also pointed out that soft pancreas was a risk factor for postoperative pancreatic fistula [or=4.89,95%ci (1.42,16.77), p=0.012][15], Meta analysis also showed that soft pancreatic texture was a risk factor for postoperative pancreatic fistula [16]. It is generally believed that the soft or hard texture of the pancreas is related to the ductal system and the number of acini in the parenchyma. The more developed the ductal system in the parenchyma, the more the number of acini, the softer the texture of the pancreas; On the contrary, due to inflammation, the number of acini decreases, ductal system shrinks, and pancreatic parenchyma fibrosis, and its texture will gradually harden [17]. The pancreatic secretion function of soft texture is often better than that of hard texture, and it is more vulnerable to injury during operation.

Some studies have pointed out that preoperative hypoproteinemia is a risk factor for pancreatic fistula. In this study, the overall protein level of all cases is within the normal range, and there is no significant correlation between preoperative protein level and pancreatic fistula (p>0.05). Through analysis, we found that serum albumin <26.50g/l on the first day after operation was an independent risk factor for pancreatic fistula [or=6.100,95%ci (1.846,20.157), p=0.003]. Serum albumin level can reflect the changes of body metabolism, liver and kidney function [18], and also plays an important role in drug transport, maintaining plasma osmotic pressure and blood volume, and maintaining the stability of human circulation [19]. In addition, serum albumin can supply the repaired tissue as an energy material, reduce the inflammatory reaction of the damaged tissue and promote its repair and reconstruction [19-20]. In addition, the decrease of protein content can aggravate tissue edema, so a lower protein content is not conducive to the recovery of patients.

Cardiovascular disease is also an important factor for postoperative pancreatic fistula. In this study, 58.33%

(7/12) of the 12 cases with cardiovascular disease had postoperative pancreatic fistula. Multivariate analysis showed that cardiovascular disease was an independent risk factor for postoperative pancreatic fistula [OR=9.148, 95%CI (1.936, 43.225), $p=0.05$]. A study involving 381 cases pointed out that the incidence of postoperative complications in patients with cardiovascular disease was higher than that in patients without cardiovascular disease [21]. Some data show that cardiovascular disease is usually characterized by atherosclerosis and tissue ischemia. Meanwhile, the sclerotic artery will affect the formation of normal neovascularization and is not conducive to wound healing [22]. The delayed repair of wound surface may be one of the main factors of pancreatic fistula after cardiovascular surgery.

The diameter of pancreatic duct is considered as one of the important risk factors for postoperative pancreatic fistula [11]. In this study, it was found that there was no statistical significance between the diameter of pancreatic duct and the occurrence of pancreatic fistula, and the pancreatic duct of most patients was not dilated, which was also in line with the actual clinical situation: In the case of pancreatic head disease, the downstream pancreatic duct was often narrowed due to compression or invasion, thus making the upstream pancreatic duct passively dilated, while in the case of pancreatic body and tail disease, the downstream pancreatic duct was often not affected. Manual suture and obturator closure are relatively hot topics in DP, but no consensus has been reached on which method can more effectively reduce pancreatic fistula. This study also found that there is no statistical difference between the two in reducing pancreatic fistula ($p=0.810$). Somatostatin and its analogues can effectively reduce the secretion of pancreatic juice, which is considered to be beneficial to reduce the occurrence of pancreatic fistula. In this study, they did not show an advantage ($p=0.201$). In addition, it was considered as a risk factor for pancreatic fistula in other studies, such as amylase and BMI in drainage fluid on the first day after operation, which also failed to become an independent risk factor for pancreatic fistula.

This study also has many shortcomings: As a retrospective study, there will inevitably be some biases; The sample size of the study is too small; Some potentially

important data were not included in the study; The results have not been further verified. These can affect the reliability of the results. Therefore, prospective and multi-center research still needs to be carried out.

In conclusion, this single center and retrospective study confirmed that the operation for pancreatic body and tail cancer is relatively safe, but the incidence of pancreatic fistula is high. This study found that soft pancreas, history of cardiovascular disease and serum albumin ($<26.50\text{g/l}$) on the first day after operation are independent risk factors for pancreatic fistula. The comprehensive utilization of these risk factors will help to screen patients with high risk of pancreatic fistula. However, due to the limitations of this paper, the results still need to be further confirmed.

Conflict of interest

The authors declare no conflict of interest.

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