

Analysis of pancreatic fistula risk in patients with laparoscopic pancreatoduodenectomy: what matters

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Abstract

Objective: To analyse potential risk factors for postoperative pancreatic fistula (POPF).

Methods: A retrospective study on risk factors for POPF was conducted in patients undergoing laparoscopic pancreatoduodenectomy. Basic characteristics, and preoperative, intraoperative and postoperative patient data were collected and analysed.

Results: A total of 268 patients were enrolled in this study, including 54 patients with POPF following surgery (POPF incidence, 20.15%). Univariate analysis indicated that patient's age, body mass index (BMI), preoperative bilirubin level, pancreas texture, and drainage fluid amylase level on day 1 following surgery were associated with POPF. Multiple logistic regression analysis indicated that preoperative bilirubin level $\geq 170 \mu\text{mol/l}$, soft pancreas texture, BMI ≥ 25 , and age ≥ 65 years were independent risk factors associated with POPF.

Conclusions: For patients with preoperative bilirubin level $\geq 170 \mu\text{mol/l}$, soft pancreas texture, BMI ≥ 25 and age ≥ 65 years, clinically relevant measures should be taken as early as possible for the prophylaxis of POPF.

Keywords

Pancreatic fistula, laparoscopic, complications, risk factors

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Introduction

Pancreaticoduodenectomy is a classic surgical procedure for treating tumours around the ampulla of the pancreas and certain benign diseases, and it is also one of the most complicated operations because it involves the reconstruction of multiple organs.¹ With the continuous improvement of surgical techniques by clinicians and the application of high-tech products, laparoscopic pancreaticoduodenectomy has been gradually adopted in the clinical setting, and the mortality rate following pancreaticoduodenectomy has been greatly reduced.^{2,3} However, considering that the operation is very difficult, and patients are generally older, pancreaticoduodenectomy may be accompanied by many complications.⁴ The incidence of postoperative complications, such as pancreatic fistula, biliary fistula, haemorrhage, abdominal infection, and delayed gastric emptying can be as high as 20–70%.^{5–7} Thus, management of laparoscopic pancreaticoduodenectomy to reduce related complications is very essential to the satisfactory prognosis of patients.⁸

Postoperative pancreatic fistula (POPF) is one of the major complications of pancreaticoduodenectomy, and the mortality related to POPF is high. Occurrence of POPF may increase the chance of abdominal haemorrhage and infection, and lead to multiple organ function failure, and potentially threaten the patient's life.^{9,10} The incidence of POPF is reported to be between 10% and 30%, and the associated mortality rate is 20–40%.^{11–13} Therefore, it is of great research value and clinical significance to identify the risk factors of POPF, to aid clinicians in their constant efforts to prevent the occurrence of POPF. Discussions regarding risk factors related to POPF have been a clinical hotspot, with most scholars believing that the factors affecting POPF are diverse, involving various factors in the perioperative period.^{14–17} Sex, age,

body mass index (BMI), preoperative serum albumin, total bilirubin, haemoglobin levels, operative time, and intraoperative blood loss have all been reported as potentially related to the occurrence of POPF. However, the number of related reports remain limited, and sample sizes are generally small, so it is necessary to conduct further relevant research to help identify potential risk factors of POPF, in order to elucidate the management of laparoscopic pancreaticoduodenectomy.

The aim of the present study was to investigate potential risk factors for POPF, by retrospectively analysing data from patients undergoing laparoscopic pancreaticoduodenectomy.

Patients and methods

Study population

This retrospective study was conducted to analyse the potential risk factors of POPF. Sequential patients who had undergone laparoscopic pancreaticoduodenectomy between July 2017 and January 2019 in the Department of Hepatobiliary Surgery, The Third Affiliated Hospital of Soochow University, were selected for inclusion into the study. The inclusion criteria were as follows: (1) patients aged ≥ 18 years; (2) patients who had received the first laparoscopic pancreaticoduodenectomy at The Third Affiliated Hospital of Soochow University; and (3) patients with complete medical records.

The study was approved by the ethics committee of the Third affiliated hospital of Soochow university (20170118). Informed consent was not required from the study participants, as the study included anonymized data from patient records only.

Perioperative management

All patients underwent routine preoperative assessment to ensure that there were no

obvious surgical contraindications, and to ensure that the complex surgery could be tolerated. In patients with chronic diseases, such as diabetes and high blood pressure, doctors from relevant departments were invited to conduct consultations and actively treat the disease to maintain normal physiological ranges. Symptomatic treatment was provided to patients according to other related symptoms, such as correcting anaemia and electrolyte imbalance, and preventive use of antibiotics. Patients with pancreatitis symptoms were treated with somatostatin before surgery, and for patients with severe jaundice and coagulopathy, vitamin K1 was used to improve coagulation function. Two abdominal drainage tubes were routinely placed during surgery, one on the side of the anastomotic junction of the pancreas, and the other on the area of anastomosis of the biliary tract. Symptomatic treatments such as antibiotics, somatostatin and nutritional support were administered after surgery.

Data collection

The following patient data were reviewed and extracted from patients' medical records, including surgical records and pathology reports: (1) Preoperative data regarding patient sex, age, hypertension, diabetes history, and post-admission preoperative bilirubin, albumin and haemoglobin values; (2) Intraoperative data regarding reduction of preoperative jaundice, intraoperative blood loss, pancreatic texture, pancreatic duct diameter, and pancreatic duct drainage; and (3) Postoperative data regarding the pathological type of disease and serum albumin value, and routine postoperative blood and biochemical test results obtained on the second postoperative day. In addition, data were extracted regarding patients' postoperative albumin levels.

Diagnostic criteria for pancreatic fistula

Pancreatic fistula was diagnosed according to the International Study Group for Pancreatic Fistula (ISGPF) criteria,¹⁸ using the following definitions: The drainage volume of the anastomotic stoma or pancreatic stump on the 3rd day or later after surgery was >10 ml/day, the drainage fluid amylase concentration was 3 times higher than the upper limit of the normal plasma amylase value, and it occurred more than 3 days in succession; Or the patient had clinical symptoms (such as fever), ultrasound or computed tomography imaging found that the fluid around the anastomosis accumulates, and puncture confirmed that the amylase concentration in the liquid was more than three times the upper limit of the normal plasma amylase value. In particular, it should be noted that grade B postoperative pancreatic fistula requires a change in the postoperative management; drains are either left in place >3 weeks or repositioned through endoscopic or percutaneous procedures. Grade C postoperative pancreatic fistula refers to those postoperative pancreatic fistulae that require reoperation or lead to single or multiple organ failure and/or mortality attributable to the pancreatic fistula.

Statistical analyses

Data are presented as *n* and % prevalence, or mean \pm SD, and were analysed using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA). The risk factors for postoperative pancreatic fistula were firstly analysed by single-factor χ^2 -test or Fisher's exact probability method, and statistical significance was set at $P < 0.05$. Statistically significant variables were further applied to a logistic regression model for multivariate analysis. A P value < 0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 268 patients were enrolled in the study, 54 of whom had POPF following surgery, giving a POPF incidence rate of 20.15% for the present study population. Among the 268 enrolled patients, 162 were male and 106 were female, and the mean age was 61.4 ± 8.9 years. All patients were diagnosed by postoperative pathology. Among the 54 patients with POPF, there were 20 cases of pancreatic head cancer, 14 cases of ampullary carcinoma, 8 cases of duodenal papillary carcinoma, 7 cases of pancreatic squamous cell carcinoma, 3 cases of pancreatic cystadenoma, 2 cases of duodenal papilloma (Figure 1).

Univariate analysis of risk factors of POPF

Univariate analyses of risk factor for POPF revealed that patient's age, BMI, preoperative bilirubin level, pancreas texture, and amylase level in drainage fluid on the first day following surgery were associated with POPF (all $P < 0.05$; Table 1). Sex, history of

upper abdominal surgery, hypertension, diabetes, preoperative albumin level, preoperative jaundice reduction, preoperative use of somatostatin, intraoperative blood loss, and the duration of operation were not related to POPF (all $P > 0.05$).

Multivariate regression analysis of risk factors of POPF

An unconditional multiple logistic regression analysis was further performed on the five variables with significant differences in the univariate analysis. The multiple logistic regression analysis indicated that preoperative bilirubin level $\geq 170 \mu\text{mol/l}$, soft pancreas texture, BMI ≥ 25 , and age ≥ 65 years were independent risk factors associated with POPF (Table 2).

Discussion

Pancreaticoduodenectomy is an effective treatment for chronic pancreatitis, duodenal obstruction, pancreatic head lumps, lower common bile duct obstruction and pancreatic cancer, but the incidence of POPF remains relatively high.¹⁹ With continuous improvements of medical technology and the progress and development of various suture techniques, the incidence of pancreatic fistula has been largely reduced, but the incidence of POPF remains as high as 10–30%, which poses a serious threat to the prognosis of patients.^{20,21} In the present study, the incidence of postoperative pancreatic fistula was 20.15%, which is at the middle of the reported range for POPF incidence. The incidence rate of POPF in the present study may be related to the following: pancreaticoduodenectomy has been introduced in The Third Affiliated Hospital of Soochow University during the previous 5 years, and the doctor's endoscopic surgery skills are relatively mature and experienced. However, the study only included patient data obtained between July 2017

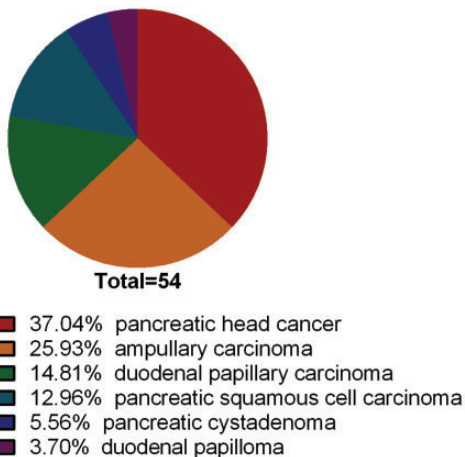


Figure 1. Pie chart showing the proportions of different pathological types of disease in 54 patients with postoperative pancreatic fistula.

Table 1. Univariate analysis of risk factors for postoperative pancreatic fistula in 268 adult patients who had undergone laparoscopic pancreatoduodenectomy.

| Factor | Total cases | Cases of pancreatic leakage | χ^2 | Statistical significance |
|---|-------------|-----------------------------|----------|--------------------------|
| Sex | | | 0.592 | NS |
| Female | 162 | 38 | | |
| Male | 106 | 16 | | |
| Age, years | | | 0.195 | $P = 0.008$ |
| ≥ 65 | 85 | 32 | | |
| < 65 | 183 | 22 | | |
| Body mass index | | | 1.407 | $P = 0.015$ |
| ≥ 25 | 115 | 30 | | |
| < 25 | 153 | 24 | | |
| Upper abdominal surgery history | | | 0.106 | NS |
| Yes | 59 | 12 | | |
| No | 209 | 42 | | |
| Hypertension | | | 1.004 | NS |
| Yes | 98 | 23 | | |
| No | 170 | 31 | | |
| Diabetes | | | 0.947 | NS |
| Yes | 65 | 14 | | |
| No | 203 | 40 | | |
| Preoperative bilirubin level | | | 1.108 | $P = 0.007$ |
| $\geq 170 \mu\text{mol/l}$ | 55 | 28 | | |
| $< 170 \mu\text{mol/l}$ | 213 | 26 | | |
| Preoperative albumin level | | | 0.995 | NS |
| $\geq 30 \text{ g/l}$ | 199 | 40 | | |
| $< 30 \text{ g/l}$ | 69 | 14 | | |
| Preoperative jaundice reduction | | | 1.335 | NS |
| Yes | 68 | 15 | | |
| No | 200 | 39 | | |
| Preoperative use of somatostatin | | | 0.452 | NS |
| Yes | 209 | 41 | | |
| No | 59 | 13 | | |
| Pancreas texture | | | 1.493 | $P = 0.027$ |
| Soft | 104 | 33 | | |
| Hard | 164 | 21 | | |
| Intraoperative blood loss | | | 0.922 | NS |
| $\geq 300 \text{ ml}$ | 58 | 10 | | |
| $< 300 \text{ ml}$ | 210 | 44 | | |
| Duration of operation | | | 1.508 | NS |
| $\geq 6 \text{ h}$ | 117 | 22 | | |
| $< 6 \text{ h}$ | 151 | 32 | | |
| Drainage fluid amylase level on day 1 following surgery | | | 1.812 | $P = 0.015$ |
| $\geq 5000 \text{ U/l}$ | 180 | 35 | | |
| $< 5000 \text{ U/l}$ | 88 | 19 | | |

Data presented as n prevalence.

NS, no statistically significant association ($P > 0.05$).

Table 2. Logistic regression analysis of risk factors for postoperative pancreatic fistula in adult patients who had undergone laparoscopic pancreaticoduodenectomy.

| Factor | β | $\bar{S}x$ | OR | 95% CI | Statistical significance | Rank |
|---|---------|------------|------|-------------|--------------------------|------|
| Preoperative bilirubin level $\geq 170 \mu\text{mol/l}$ | 0.89 | 0.29 | 4.38 | 1.15, 9.53 | $P=0.048$ | 1 |
| Soft pancreas texture | 0.92 | 0.31 | 5.31 | 1.23, 10.75 | $P=0.031$ | 2 |
| Age ≥ 65 years | 1.03 | 0.45 | 4.97 | 1.37, 9.86 | $P=0.042$ | 3 |
| BMI ≥ 25 | 0.99 | 0.39 | 5.67 | 2.24, 13.42 | $P=0.019$ | 4 |

BMI, body mass index; OR, odds ratio; CI confidence interval.

and January 2019 (most recent 2 years), and the incidence of POPF may have been higher during the first three years that pancreaticoduodenectomy was introduced. The present authors attempted to identify potential risk factors related to POPF, and found that preoperative bilirubin level $\geq 170 \mu\text{mol/l}$, soft pancreas texture, BMI ≥ 25 , and age ≥ 65 years were independent risk factors associated with POPF. These results suggest that patients with such clinical risk factors should be alerted to health care providers in order to prevent the occurrence of POPF.

Attention should be paid to the pathology of POPF. It has been reported that pancreatic fistula may be related to following aspects:²²⁻²⁴ (1) When tissue and tissue are anastomosed, the needle passes through the pancreatic tissue and may break through the expanded small pancreatic duct, which may also cause pinhole infiltration, thereby causing leakage of pancreatic juice; (2) When the pancreas and intestine are anastomosed, there must be a gap between the needles, which causes pancreatic juice to leak out from the gap; (3) There is high pressure in the jejunal intestine tube. At the end of surgery, if the intestines cannot work normally and peristalsis is weak, and there is a long jejunal bridge after co-operating with the pancreas, this can easily cause pancreatic juice and bile retention in the intestine. Therefore, in the state of high tension in which the pancreatic

jejunal anastomosis is present, if the tension is too large, the anastomosis is easily broken, resulting in leakage of pancreatic secretion; (4) During surgery involving digestive tract reconstruction plus gastrointestinal dysfunction, it is easy to make biliary fluid flow back to the pancreatic anastomosis area, so that trypsin is activated, and then trypsin can digest the anastomosis and nearby tissues, finally leading to pancreatic fistula; and (5) Some clinicians have insufficient surgical experience, the anatomy cannot be clearly identified and the operation is inadequate, the distance between the two needles during anastomosis may be inaccurate, and repeated knotting may lead to rupture of the pancreatic tissue and ischemia, and finally lead to POPF.

Obstructive jaundice is a common condition in patients prior to laparoscopic pancreaticoduodenectomy.^{25,26} Severe jaundice may cause damage to liver function and lead to decreased liver synthesis and detoxification, and as the bile cannot enter the intestine, the ability of bile acid salt to inhibit intestinal bacteria is reduced.²⁷ The present study showed that preoperative severe jaundice (preoperative bilirubin $\geq 170 \mu\text{mol/l}$) was an independent risk factor for POPF, which is consistent with the findings of previous reports. It remains controversial whether patients should be treated to reduce jaundice prior to surgery.^{28,29} In the present study, no difference was observed regarding the incidence of

POPF between patients with and without preoperative jaundice reduction measures. Therefore, future research should include a standard prospective study to further understand whether preoperative jaundice-reducing measures can reduce the incidence of POPF in patients with severe jaundice.

Patient age is shown to be an important risk factor for postoperative mortality and complication rates. A retrospective study by Rosso et al.³⁰ found that patients' age was positively correlated with pancreatic fat infiltration, and pancreatic fat infiltration was positively correlated with clinical risk prediction scores of POPF. Currently, it is believed that the degree of pancreatic fat infiltration increases with age, making the pancreatic anastomosis more difficult, which may lead to an increase in the incidence of POPF.^{31–33} Furthermore, the degree of pancreatic fat infiltration and degree of fibrosis can affect the texture of the pancreas.^{10,34} However, previous studies on the effects of pancreatic texture on POPF have reported different conclusions.^{35,36} It is worth-noting that the judgment of pancreas texture in each study is essentially based on the operator's hand, and there is no uniform objective evaluation standard. Furthermore, the different anastomosis methods may have important influence on the occurrence of POPF. Therefore, the development of objective and quantifiable criteria for assessing the texture of the pancreas are warranted to further reveal the relationship between pancreas texture and POPF.

Several potential limitations must be considered in the present study. First, it should be acknowledged that, due to the limitations of clinical data, the study only included data obtained over the most recent two out of five years of pancreaticoduodenectomy introduced at The Third Affiliated Hospital of Soochow University, thus the results may be biased since data from the earlier three years were not included.

Secondly, this was a single-centre study with a relatively limited number of cases. The relatively small study population may not have provided enough power to detect the potential risk factors for POPF. Future studies with a larger sample and broader areas are needed to identify the risks of POPF. Despite these shortcomings, the results of this study, being one of the very few analyses of risk factors for POPF, may still provide some inspiration for clinical health workers.

In conclusion, preoperative bilirubin level $\geq 170 \mu\text{mol/l}$, soft pancreas texture, BMI ≥ 25 , and age ≥ 65 years were independent risk factors associated with POPF. From a clinical perspective, medical staff should pay attention to preoperative jaundice and standardized judgment of pancreatic texture, which may be helpful for the early prevention and recognition of POPF. Considering the limited sample size of this study, further investigations with larger samples are needed to validate the present results and identify potential risk factors for POPF.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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