Original Article

The establishment and validation of a clinical prediction model for postoperative biliary fistula after pancreaticoduodenectomy

Zhengrong Ou[1]^, An Yan[2], Weidong Zhu[1]

[1]Department of General Surgery, Ward Two, Yueyang Hospital Affiliated to Hunan Normal University, Yueyang, China; [2]Department of Hepatopancreatobiliary Surgery, The Third Xiangya Hospital, Central South University, Changsha, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: W Zhu; (III) Provision of study materials or patients: W Zhu, A Yan; (IV) Collection and assembly of data: A Yan; (V) Data analysis and interpretation: Z Ou; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Weidong Zhu, Master's Degree. Department of General Surgery, Ward Two, Yueyang Hospital Affiliated to Hunan Normal University, No. 263, Baling East Road, Yueyang Lou District, Yueyang 414000, China. Email: 1807161603@qq.com.

Background: At present, pancreaticoduodenectomy (PD) is a classic surgical treatment for benign and malignant tumors around ampulla. The operation is complicated and postoperative complications are frequent. Biliary fistula is the most common anastomotic fistula after pancreatic fistula. Our objective is to analyze the risk factors for biliary fistula after PD and to construct a nomogram to predict biliary fistula after PD.

Methods: The clinical data of a total of 196 patients who underwent PD from March 2014 to March 2024 in Yueyang Hospital Affiliated to Hunan Normal University and The Third Xiangya Hospital of Central South University were retrospectively analyzed. The number of included patients was divided in the ratio of 7:3 using the random split method, with 130 patients in the training set and 66 patients in the validation set. Predictors were screened and a nomogram prediction model was constructed by one-way logistic regression analysis, Lasso regression analysis and multifactorial logistic regression analysis. The discriminative ability, consistency and clinical effectiveness of the models were assessed by area under the curve (AUC) of the working characteristics of the subjects, calibration curve and decision curve analysis (DCA).

Results: The results of multifactorial logistic regression analysis showed that diabetes, low albumin, postoperative gastroparesis, abdominal bleeding, abdominal infection, and postoperative pancreatic fistula were the independent risk factors for biliary fistula after PD ($P<0.05$). The AUC of the column-line graph prediction model constructed from the above factors was 0.807 [95% confidence interval (CI): 0.652–0.962] in the training set and 0.782 (95% CI: 0.517–1.000) in the validation set, suggesting that the diagnostic efficacy of the model was better, and the calibration curves plotted in the training and validation sets were closer to the standard curves, suggesting that the model consistency was better. The plotted DCA curves also indicated a significant positive net gain.

Conclusions: The nomogram prediction model constructed by diabetes, albumin, postoperative gastroparesis, abdominal bleeding, abdominal infection, and postoperative pancreatic fistula can well identify high-risk patients with postoperative biliary fistula (POBF) in PD, which has a good clinical application value.

Keywords: Pancreaticoduodenectomy (PD); biliary fistula; risk factors; clinical prediction model; nomogram

Submitted May 17, 2024. Accepted for publication Sep 13, 2024. Published online Sep 27, 2024.
doi: 10.21037/gs-24-174
View this article at: https://dx.doi.org/10.21037/gs-24-174

^ ORCID: 0009-0002-3847-612X.

Introduction

Pancreaticoduodenectomy (PD) is the standard procedure for the treatment of benign and malignant tumors of the distal bile duct, head of the pancreas and jugular abdomen. Surgery for these tumors involves resection and reconstruction. It is considered one of the most complex procedures in general surgery due to its multi-organ involvement and complex gastrointestinal reconstruction (1,2). With the continuous update of surgeons' knowledge and advances in surgical techniques, the safety of surgery has been greatly improved and the mortality rate associated with surgery has gradually decreased, with a reported mortality rate of <5 percent (3-5). PD is often followed by complications such as pancreatic fistula, biliary fistula, gastrointestinal anastomotic fistula, bleeding, intra-abdominal abscess and delayed gastric emptying (DGE) (6,7). Serious postoperative complications may be the reason for reoperation, as well as for poor outcomes and reduced living conditions. The rate of postoperative complications in high-volume surgery centers is less than 15 percent, while in other surgery centers the rate can reach even 60 percent (8). The emergence of postoperative complications not only prolongs the patient's hospital stay and increases the patient's financial burden, but even endangers the patient's life.

A biliary fistula is a condition in which bile does not flow completely from the common bile duct or bilioenteric anastomosis into the intestinal cavity after surgery, and bile or bile-containing fluid continues to flow from the biliary tract breach into the abdominal cavity, retroperitoneum, or out of the body through a drain. Diagnostic criteria for biliary fistula were total bilirubin (TBil) in the abdominal drainage fluid >3 times the serum level in the same period at 3 days postoperatively, or the need for intervention or a second operation due to cholestatic peritonitis (9). The incidence of postoperative biliary fistula (POBF) after PD ranges from 4–12% (10). Biliary fistula is associated with sepsis, multi-organ failure, bleeding and death. Previous study has shown that males, low preoperative serum albumin levels and a history of preoperative cholangitis can be included as risk factors for the development of biliary fistula after PD (11). Although POBF is generally not life-threatening and most of them can be cured by conservative treatment, it causes discomfort and increases in-hospital treatment time and medical costs, which not only affects the normal work and life of patients after surgery, but also is likely to be re-hospitalized or even require a second operation within a short period of time, which brings about a heavy economic burden and even affects the long-term prognosis of patients. Therefore, the occurrence of biliary fistula after PD has attracted more and more scholars to study.

Although studies have identified risk factors for biliary fistula after PD, the results vary between studies, the risk factors for biliary fistula after PD have not been clarified, and there are no studies that have constructed predictive models for biliary fistula after PD. The aim of this study was to develop a valid and simple predictive tool that can directly reflect the predictive value of biliary fistula after PD, which can provide a reliable judgement of the occurrence of biliary fistula events after PD, and to a certain extent, provide a reliable tool for clinicians to judge whether or not biliary fistula prophylaxis and interventional treatment are needed. Meanwhile, this prediction tool can provide effective help to reduce adverse events such as biliary fistula after PD, thus improving the quality of life and prognosis of PD patients to some extent. We present this article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-24-174/rc).

Highlight box

Key findings

- Diabetes, preoperative low albumin, postoperative gastroparesis, postoperative abdominal bleeding, postoperative abdominal infection, and postoperative pancreatic fistula are risk factors for biliary fistula after pancreaticoduodenectomy.

What is known and what is new?

- Some studies have identified risk factors for biliary fistula after pancreaticoduodenectomy, the results vary between studies, the risk factors for biliary fistula after pancreaticoduodenectomy have not been clarified.
- We add predictive models for biliary fistula after pancreaticoduodenectomy.

What is the implication, and what should change now?

- The predictors required for the model developed in this study are clinically available. Moreover, the previous complex regression equations were transformed into intuitive graphs, thus making the predictive model more readable for doctors to assess patients.
- The application of the model needs to be validated in future prospective studies.

Methods

Source of data and participants

Clinical data of a total of 196 patients who underwent PD

from March 2014 to March 2024 at Yueyang Hospital Affiliated to Hunan Normal University and Xiangya Third Hospital of Central South University were retrospectively analyzed. There were 119 males and 77 females. Average age 62.5 years; 31 patients had a history of smoking; drinking history of 20 cases; hypertension history: 41 cases; diabetes history 47 cases; history of coronary heart disease: 8 cases; there were 28 cases of hepatitis B. Biliary fistula occurred in 11 patients, including 8 patients with pancreatic fistula. Pancreatic fistula occurred in 42 patients. Gastrointestinal anastomotic fistula occurred in 4 cases. Chest infection occurred in 3 cases. Abdominal infection occurred in 25 cases. Pelvic infection occurred in 1 case. Abdominal hemorrhage occurred in 16 cases. DGE disorder was found in 17 cases. Pelvic effusion occurred in 8 cases. Abdominal effusion occurred in 16 cases. Pleural effusion occurred in 22 cases. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Committee of Yueyang Hospital Affiliated to Hunan Normal University (No. 2024012) and the Institutional Ethics Committee of The Third Xiangya Hospital of Central South University (No. S245), and all patients' informed consent was obtained.

Inclusion criteria and exclusion criteria

Inclusion criteria: (I) completion of standard PD (including portal vein and superior mesenteric vein reconstruction); (II) complete clinical data. Exclusion criteria: (I) intraoperative radical resection was not performed due to tumor metastasis; (II) emergency surgery; (III) incomplete clinical data.

Surgical method

Two grams (g) of piperacillin sodium were given at 0.5–1 h before surgery and during the operation to prevent infection. The head of the pancreas (including the uncinate process), distal stomach, duodenum, upper jejunum, gallbladder, and common bile duct were removed with standard PD surgery, and reconstructed using the Child method to ensure the integrity of the specimen. For pancreatojejunostomy (PJ), the PJ is characterized by a modified Kakita method (12), and improved Blumgart technology (13). A stent is placed in the pancreatic duct to drain pancreatic fluid to the jejunum, while avoiding anastomotic stenosis and reducing the risk of pancreatic fistula. Cholangiojejunostomy (CJ) was performed about 10–15 cm from the distal end of PJ, and full-layer continuous suture was used. End-to-mucosal mucosal double-layer gastrojejunostomy was performed 50 cm from the distal end of CJ. Preoperative vascular reconstruction was performed in patients with superior mesenteric vein and portal vein invasion or intravascular cancer embolus. Patients with lesions involving adjacent organs (including colon, liver, small intestine, spleen, and kidneys) underwent simultaneous excision of affected organs. The pancreaticojejunostomy was performed as a double-layer duct-to-mucosa approach. The outer layer was sutured with 3-0 Prolene running sutures, and the inner layer was sutured with 5-0 Prolene interrupted sutures. The hepaticojejunostomy was performed using a 4-0 polydioxanone in a running suture. Gastrojejunostomy was performed using 3-0 Stratafix (Suzhou, China). After the operation, 2 to 3 abdominal drainage tubes were placed according to the situation, one was extended from the pancreato-enteric anastomosis to the bilioenteric anastomosis (or one was placed at the pancreato-enteric anastomosis and one was placed at the bilioenteric anastomosis), and the other was placed at the Venturi foramina. The patient was transferred to the intensive care unit on the day after surgery, and transferred to the general ward the next day if his condition was stable.

Outcome

Predictors

Preoperative data were collected, including gender, age, smoking history, alcohol consumption history, diabetes, hypertension, coronary heart disease, haemoglobin, albumin, C-reactive protein, calcitonin, aspartate transaminase (AST), alanine transaminase (ALT), Bilirubin, amylase, hepatitis B, prothrombin time (PT), D-dimer, carcinoma embryonic antigen, cancer antigen 125 (CA125), CA199, alpha-fetoprotein. Intraoperative data, including surgical procedure, intraoperative bleeding, duration of surgery, and the presence of metastatic lesions during surgery. Postoperative data, including postoperative pancreatic fistula, gastrointestinal anastomotic fistula, biliary fistula, thoracic infection, abdominal infection, pelvic infection, abdominal bleeding, postoperative gastroparesis, abdominal effusion, pleural effusion, pelvic effusion. Postoperatively, antibiotics, proton pump inhibitors and maintenance of water and electrolyte balance and nutritional support were administered. Intravenous growth inhibitor analogues were administered for the first 7 days after surgery. The amylase concentration of

the abdominal drainage fluid was repeated on the days 1, 3, 5, 7 postoperative days (PODs). When a biliary fistula was suspected, the TBil level of the drainage fluid was measured. For patients with biliary fistula, magnetic resonance cholangiopancreatography was further improved for confirmation. In the absence of a clinically relevant postoperative anastomotic fistula, the drain is usually removed on days 5–7. After recovery of bowel function, the nasogastric tube (NGT) is removed and an oral liquid diet is started. The hospitalization period was observed for postoperative complications.

Diagnostic criteria for major postoperative complications

Pancreatic fistula: any amount of drainage fluid with an amylase level greater than three times the upper limit of normal serum amylase on or after the third POD that brings about a change in clinical decision-making such as drain flushing, laparotomy drainage, reoperation, etc. (14).

Biliary fistula: diagnostic criteria for biliary fistula were TBil in the abdominal drainage fluid >3 times the serum level in the same period at 3 days postoperatively, or the need for intervention or a second operation due to cholestatic peritonitis (9).

Gastrointestinal anastomotic fistula: it is a surgical incision that does not heal completely in the gastrointestinal tract, resulting in of gastrointestinal contents into the abdominal or thoracic cavity.

DGE (15) was subdivided into International Study Group on Pancreatic Surgery (ISGPF) grade A, B, and C in order of increasing severity. Grade A was defined as requiring a NGT within the POD 4–7, reinsertion of the NGT after removal on POD 3, or inability to tolerate a solid diet by POD 7. Grade B was defined as requiring NGT from POD 8–14, reinsertion of the NGT after POD 7, or inability to tolerate a solid diet by POD 14. Lastly, grade C was defined as the inability to discontinue the NGT, reinsertion of the NGT after POD 14, or inability to tolerate a solid diet by POD 21.

Abdominal bleeding: ISGPF (16) classified the severity of post-pancreatic bleeding into mild and severe. Mild bleeding: Small or moderate blood loss observed through a drainage tube, NGT, or ultrasound, reduced hemoglobin levels <3 g/dL, and transfusions of less than 3 units of red blood cells. Severe bleeding: hemoglobin level decreased >3 g/dL, clinical symptoms of hypovolemic shock, such as tachycardia, hypotension, oliguria, etc.

Statistical analysis

The number of selected patients was randomly divided in a ratio of 7:3, where 70% of the patients were used as a training set to build the prediction model and the remaining 30% of the patients were used as a validation set to verify the accuracy of the model. Data were statistically analyzed and plotted using SPSS 26.0 and R language software (4.3.1), and all analyses were two-tailed with a significance level of $P<0.05$. Continuous data were first tested for normality, and were expressed as mean ± standard deviation (SD) if they obeyed a normal distribution, and as median and quartiles [M (Q1, Q3)] otherwise. Categorical information is then expressed as frequency (percentage). For the comparison of differences between the training and validation sets, continuous data were first tested for normality, and *t*-tests were used if they were normally distributed, if both groups met the normal distribution and if the variance between the two groups was equal; otherwise, the nonparametric Wilcoxon rank-sum test was used. For categorical data, the χ^2 test or Fisher test was used for unordered outcomes.

Using the occurrence of biliary fistula after PD as the outcome variable in the training set data, a one-way logistic regression analysis was first performed, and then the factors that were statistically significant ($P<0.05$) in the one-way analysis were further screened for variables by means of Lasso regression (17). Based on this, the independent risk factors were further explored using multifactorial Logistic regression analysis and a nomogram prediction model was developed. The area under ROC curve (AUC), calibration curve, and decision curve analysis (DCA) were used to test the discrimination of the predictive model, the consistency of the model with the actual situation, and the clinical validity in the training and validation sets, respectively.

Results

Clinical characteristics of patients after PD

A total of 196 patients' clinical data were analyzed in this study; 130 PD patients were collected from the training group, of which 8 (6.2%) patients had biliary fistula, 79 (60.8%) were male, 71 (54.6%) were open surgery, 20 (15.4%) patients had a history of smoking, 14 (10.8%) patients had a history of alcohol consumption, 29 (22.3%) patients had a history of diabetes, 26 (20%) patients had a history of hypertension, 4 (3.1%) patients had a history of coronary artery disease, 23 (17.7%) patients had a history of

hepatitis B, 18 (13.8%) patients had intraoperative invasion of peripheral tissues, 26 (20%) patients had a pancreatic fistula postoperatively, 1 (0.8%) patient had a fistula of the gastrointestinal anastomosis, 2 (1.5%) patients had a chest infection, 15 (11.5%) patients had an abdominal cavity infection, 3 (2.3%) patients had postoperative pelvic infection, 11 (8.5%) patients had postoperative abdominal bleeding, 11 (8.5%) patients had postoperative gastroparesis, 12 (9.2%) patients had postoperative peritoneal effusion, 5 (3.8%) patients had postoperative pelvic effusion and 16 (12.3%) patients had postoperative pleural effusion. A total of 66 PD patients were collected in the validation group, of which 3 (4.5%) had biliary fistula, 40 (60.6%) were male, 29 (43.9%) were open, 11 (16.7%) patients had a history of smoking, 6 (9.1%) patients had a history of alcohol consumption, 18 (27.3%) patients had a history of diabetes, 15 (22.7%) patients had a history of hypertension, 4 (6.1%) patients had a history of coronary heart disease, 5 (7.6%) patients had a history of hepatitis B, 7 (10.6%) patients were found to have intraoperative invasion of peripheral tissues, 16 (24.2%) patients had postoperative pancreatic fistulae, 2 (3.0%) patients had postoperative gastrointestinal anastomotic fistulae, 1 (1.5%) patient had postoperative chest infection, 10 (15.2%) patients had postoperative abdominal infection, 2 (3.0%) patients had postoperative pelvic infection, 3 (4.5%) patients had postoperative abdominal bleeding, 6 (9.1%) patients had postoperative gastroparesis, 4 (6.1%) patients had postoperative peritoneal effusion, 4 (6.1%) patients had postoperative pelvic effusion and 6 (9.1%) patients had postoperative pleural effusion. The specific clinical characteristics of the two groups of patients are shown in *Table 1*, and the differences between the clinical characteristics and the incidence of POBFs were not statistically significant, except for CA125.

Analysis of risk factors in patients with biliary fistula after PD

Clinical information was included in a one-factor regression analysis using logistic regression analysis, and the results of the one-factor analysis indicated that possible risk factors including: diabetes, pancreatic fistula, abdominal infection, abdominal bleeding, gastroparesis, age, ALT, AST, albumin, PT. The results are shown in *Table 2*.

Indicators with statistically significant differences (P<0.05) in the univariate analysis were included in the Lasso regression analysis to further screen the variables, and a total of seven variables had non-zero coefficients in the Lasso regression model (*Figures 1*,*2*). These variables included diabetes, pancreatic fistula, abdominal infection, abdominal bleeding, gastroparesis, albumin, PT. These seven variables were then included in a multifactorial logistic regression analysis, and diabetes, pancreatic fistula, abdominal infection, abdominal bleeding, gastroparesis, and albumin were independent risk factors for biliary fistula after PD. The results are shown in *Table 3*.

Construction, validation and clinical application of predictive models

Based on the results of multifactorial logistic analysis of the patients' clinical data, the independent risk factors for biliary fistula after PD (diabetes, pancreatic fistula, abdominal infection, abdominal bleeding, gastroparesis, and albumin calculation scores) were summed up through the scores of each variable to calculate the total score, which was then projected onto a total scale to establish a nomogram of the probability of biliary fistula after PD (*Figure 3*). The ROC curves of the predictive model of this nomogram are plotted in the training and validation sets (*Figures 4*,*5*), respectively, and the results show that the predictive ability of this nomogram is high in both the training and validation sets {AUC: 0.807 [95% confidence interval (CI): 0.652–0.962] for the training set; AUC: 0.782 (95% CI: 0.517–1.000) for the validation set}. And the calibration curves of this model were plotted in the training set and validation set respectively (*Figures 6*,*7*), and the calibration curves showed that the predicted probability of biliary fistula infection after PD predicted by the nomogram was consistent with the actual situation. Finally, DCA analysis was performed on the nomogram in the training (red curve) and validation (blue curve) sets, and the results showed that the nomogram predictive model performed well and helped to make useful clinical decisions (*Figure 8*).

Discussion

Globally, pancreatic cancer has become the third leading cause of cancer-related deaths, with an increasing incidence in recent years (18). Despite significant improvements in the multidisciplinary treatment of pancreatic cancer, the prognosis of the disease remains poor, with a 5-year overall survival rate of about 10 percent (19). For pancreatic cancer patients, surgical resection remains the only effective way to achieve curative potential and long-term survival (20). The types of standard resection procedures for pancreatic

Table 1 Patients' specific clinical characteristics

Clinical characteristics	Training (n=130)	Validation (n=66)	t/χ^2	P
Gender, n (%)			0.000	>0.99
Male	79 (60.8)	40 (60.6)		
Female	51 (39.2)	26 (39.4)		
Surgical procedures, n (%)			1.997	0.18
Open laparotomy	71 (54.6)	29 (43.9)		
Laparoscopic surgery	59 (45.4)	37 (56.1)		
Smoking, n (%)			0.054	0.84
Yes	20 (15.4)	11 (16.7)		
No	110 (84.6)	55 (83.3)		
Drinking, n (%)			0.135	0.80
Yes	14 (10.8)	6 (9.1)		
No	116 (89.2)	60 (90.9)		
Diabetes, n (%)			0.592	0.48
Yes	29 (22.3)	18 (27.3)		
No	101 (77.7)	48 (72.7)		
Hypertension, n (%)			0.197	0.71
Yes	26 (20.0)	15 (22.7)		
No	104 (80.0)	51 (77.3)		
Coronary heart disease, n (%)			0.995	0.45
Yes	4 (3.1)	4 (6.1)		
No	126 (96.9)	62 (93.9)		
Hepatitis B, n (%)			3.659	0.08
Yes	23 (17.7)	5 (7.6)		
No	107 (82.3)	61 (92.4)		
Metastasis, n (%)			0.413	0.65
Yes	18 (13.8)	7 (10.6)		
No	112 (86.2)	59 (89.4)		
Biliary fistula, n (%)			0.214	0.75
Yes	8 (6.2)	3 (4.5)		
No	122 (93.8)	63 (95.5)		
Pancreatic fistula, n (%)			0.468	0.58
Yes	26 (20.0)	16 (24.2)		
No	104 (80.0)	50 (75.8)		
Gastrointestinal anastomosis fistula, n (%)			1.485	0.26
Yes	1 (0.8)	2 (3.0)		
No	129 (99.2)	64 (97.0)		
Chest infection, n (%)			0.000	>0.99
Yes	2 (1.5)	1 (1.5)		
No	128 (98.5)	65 (98.5)		

Table 1 (*continued*)

Table 1 (*continued*)

Clinical characteristics	Training (n=130)	Validation (n=66)	t/χ^2	P
Abdominal infection, n (%)			0.514	0.50
Yes	15 (11.5)	10 (15.2)		
No	115 (88.5)	56 (84.8)		
Pelvic infection, n (%)			0.092	0.76
Yes	3 (2.3)	2 (3.0)		
No	127 (97.7)	64 (97.0)		
Abdominal bleeding, n (%)			1.012	0.39
Yes	11 (8.5)	3 (4.5)		
No	119 (91.5)	63 (95.5)		
Gastroparesis, n (%)			0.022	>0.99
Yes	11 (8.5)	6 (9.1)		
No	119 (91.5)	60 (90.9)		
Seroperitoneum, n (%)			0.587	0.59
Yes	12 (9.2)	4 (6.1)		
No	118 (90.8)	62 (93.9)		
Pelvic effusion, n (%)			0.085	0.77
Yes	5 (3.8)	4 (6.1)		
No	125 (96.2)	62 (93.9)		
Pleural effusion, n (%)			0.455	0.63
Yes	16 (12.3)	6 (9.1)		
No	114 (87.7)	60 (90.9)		
Age (year, $\bar{x}\pm s$)	61.82±11.040	63.74±10.365	–1.179	0.24
Hb (g/L, $\bar{x}\pm s$)	121.043±19.733	121.126±22.809	–0.026	0.98
C-reactive protein (mg/dL, $\bar{x}\pm s$)	27.078±49.493	17.011±29.091	1.523	0.13
Procalcitonin (ng/mL, $\bar{x}\pm s$)	0.309±0.797	1.400±8.918	–1.388	0.17
Alanine transaminase (U/L, $\bar{x}\pm s$)	126.540±152.662	98.833±141.670	1.230	0.22
Aspartate transaminase (U/L, $\bar{x}\pm s$)	105.348±145.051	76.223±84.589	1.505	0.13
Albumin (g/L, $\bar{x}\pm s$)	38.158±5.591	38.241±5.655	–0.098	0.92
Total bilirubin (μmol/L, $\bar{x}\pm s$)	81.087±85.909	63.473±84.868	1.362	0.18
Indirect bilirubin (μmol/L, $\bar{x}\pm s$)	24.591±25.858	19.439±23.770	1.354	0.17
Amylase (g/dL, $\bar{x}\pm s$)	97.948±94.840	144.955±261.427	–1.830	0.07
Prothrombin time (s, $\bar{x}\pm s$)	14.625±16.129	14.339±16.409	0.116	0.91
D-dimer (μg/mL, $\bar{x}\pm s$)	0.953±1.999	1.056±1.939	–0.344	0.73
Carcinoma embryonic antigen (ng/mL, $\bar{x}\pm s$)	15.075±112.397	3.742±4.322	0.818	0.41
CA125 (ng/mL, $\bar{x}\pm s$)	18.575±17.817	39.906±102.971	–2.301	0.02
CA199 (ng/mL, $\bar{x}\pm s$)	497.294±1,904.648	308.552±643.169	0.782	0.44
Alpha-fetoprotein (ng/mL, $\bar{x}\pm s$)	4.760±11.362	3.381±2.134	0.976	0.33
Time of operation (minutes, $\bar{x}\pm s$)	420.82±90.228	438.92±90.743	–1.325	0.19
Amount of bleeding (mL, $\bar{x}\pm s$)	440.62±449.314	481.06±431.078	–0.604	0.55

Hb, hemoglobin; CA, cancer antigen.

Table 2 Univariate logistic regression analysis

Clinical characteristics	B	SE	OR	95% CI	P
Gender	−0.656	0.624	0.519	0.153–1.764	0.29
Smoking	0.178	0.807	1.195	0.246–5.819	0.83
Drinking	0.724	0.820	2.062	0.413–10.288	0.38
Diabetes	2.175	0.699	8.806	2.238–34.657	0.002
Hypertension	−1.015	1.064	0.363	0.045–2.917	0.34
Coronary heart disease	−0.560	1.098	0.571	0.066–4.916	0.61
Hepatitis B	0.875	0.710	2.400	0.596–9.657	0.22
Metastasis	0.448	0.813	1.565	0.318–7.700	0.58
Minimally invasive surgery	−0.549	0.644	0.578	0.164–2.040	0.39
Pancreatic fistula	3.867	1.067	47.812	5.910–386.806	<0.001
Gastrointestinal anastomosis fistula	1.803	1.200	6.067	0.578–63.676	0.13
Chest infection	2.214	1.267	9.150	0.764–109.636	0.08
Abdominal infection	2.350	0.652	10.484	2.920–37.641	<0.001
Pelvic infection	1.510	1.164	4.525	0.462–44.325	0.20
Abdominal bleeding	2.579	0.681	13.182	3.472–50.046	<0.001
Gastroparesis	2.943	0.681	18.982	5.000–72.066	<0.001
Seroperitoneum	0.125	1.083	1.133	0.136–9.464	0.91
Pelvic effusion	0.794	1.109	2.212	0.252–19.461	0.47
Pleural effusion	−0.247	1.074	0.781	0.095–6.411	0.78
Age	0.088	0.037	1.092	1.015–1.175	0.02
Hb	−0.01	0.015	0.990	0.961–1.020	0.53
C-reactive protein	−0.012	0.015	0.988	0.959–1.017	0.99
Procalcitonin	−0.193	0.587	0.824	0.261–2.606	0.74
Alanine transaminase	0.003	0.001	1.003	1.000–1.006	0.03
Aspartate transaminase	0.004	0.002	1.004	1.000–1.007	0.03
Albumin	−0.318	0.081	0.728	0.621–0.853	<0.001
Total bilirubin	0.001	0.004	1.001	0.994–1.008	0.88
Indirect bilirubin	0.009	0.010	1.009	0.989–1.029	0.38
Amylase	−0.008	0.007	0.992	0.980–1.005	0.23
Prothrombin time	0.025	0.010	1.025	1.005–1.045	0.01
D-dimer	0.121	0.093	1.128	0.941–1.353	0.19
Carcinoma embryonic antigen	0.000	0.004	1.000	0.991–1.008	0.92
CA125	−0.015	0.022	0.985	0.943–1.029	0.49
CA199	0.000	0.000	1.000	1.000–1.000	0.55
Alpha-fetoprotein	−0.028	0.090	0.972	0.815–1.160	0.76
Time of operation	−0.003	0.004	0.997	0.990–1.005	0.49
Amount of bleeding	0.000	0.001	1.000	0.999–1.002	0.41

SE, standard error; OR, odds ratio; CI, confidence interval; CA, cancer antigen.

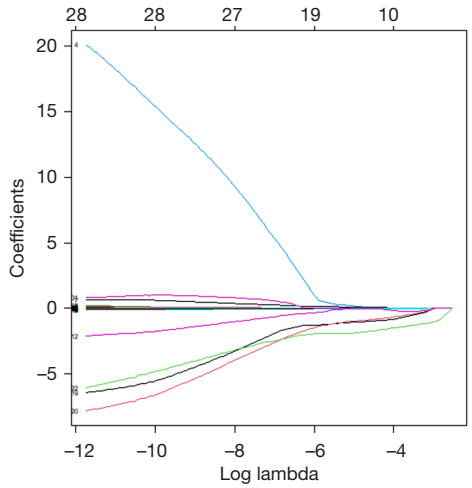

Figure 1 Coefficient curves for 10 clinical features.

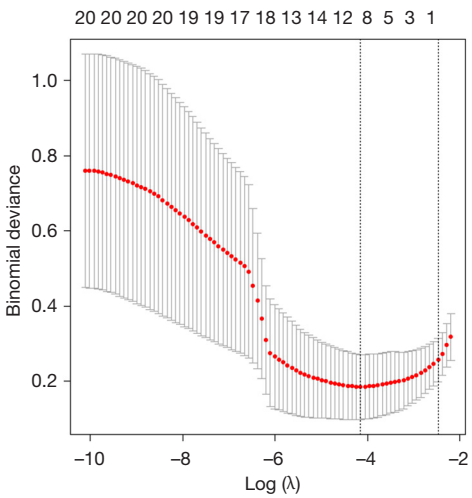

Figure 2 Lasso regression 10-fold cross-validation to select the most appropriate clinical features.

cancer include PD, with or without vascular resection, distal pancreatectomy, and total pancreatectomy, with PD being the most widely used. PD is considered one of the most technically difficult procedures because it involves resection of many organs and haemodialysis, and it also brings many complications such as pancreatic fistula, abdominal infection, bleeding, biliary fistula, and DGE, which can have a serious impact on the patient's prognosis. Among them, the potential clinical impact of biliary fistula should not be underestimated, which often leads to prolonged hospital stay, delayed removal of abdominal drainage tubes and the need for additional invasive operations, which increases the patient's mental burden and hospitalization costs, and, in severe cases, can lead to water-electrolyte disorders, and even life-threatening. Andrianello *et al.* suggested that when a biliary fistula coexists with a pancreatic fistula it may be aggravating or even life threatening (21). The aim of this study was to explore the independent influencing factors of biliary fistula after PD and to develop a predictive model based on common clinical data, which would help clinicians to consider the possibility of biliary fistula after PD at an early stage, and then to improve the relevant investigations and to guide the treatment to improve the clinical prognosis of these patients.

Diabetes is a metabolic disease that leads to poor physical tolerance of the patient. High blood sugar acts as a source of energy, leading to the continuous growth and multiplication of cancer cells (22). The results of the present study likewise suggest that diabetes is a risk factor for biliary fistula after PD. A hyperglycaemic state affects blood circulation around the wound, leading to slower wound healing, which increases the risk and likelihood of a biliary fistula. Jester *et al.* showed that diabetes is a risk factor for biliary fistula

Table 3 multiple logistic regression analysis

Clinical characteristics	B	SE	OR	95% CI	P
Prothrombin time	0.082	0.107	1.010	0.864–1.022	0.45
Albumin	–0.214	0.084	0.746	0.634–0.862	0.01
Pancreatic fistula	2.493	0.905	12.099	2.053–71.300	0.01
Diabetes	1.727	0.870	5.624	1.021–30.965	0.047
Abdominal infection	1.738	0.880	2.432	1.528–9.250	0.048
Abdominal bleeding	2.082	1.046	8.019	1.032–62.342	0.047
Gastroparesis	2.876	1.031	12.892	2.920–72.084	0.01

SE, standard error; OR, odds ratio; CI, confidence interval.

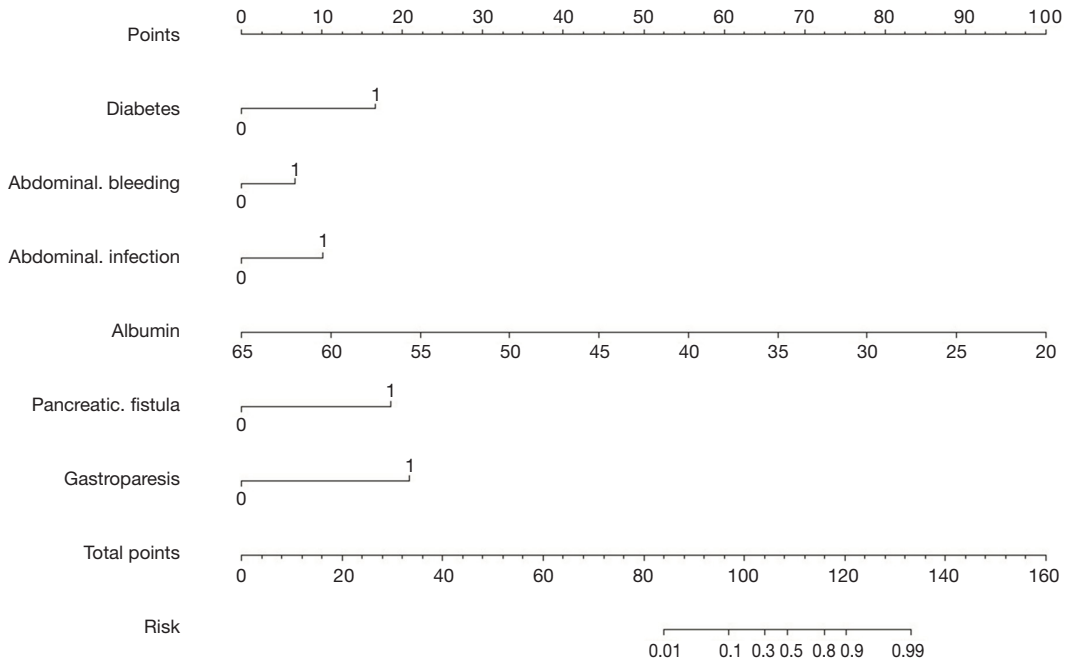

Figure 3 Predictive nomogram of biliary fistula after pancreaticoduodenectomy.

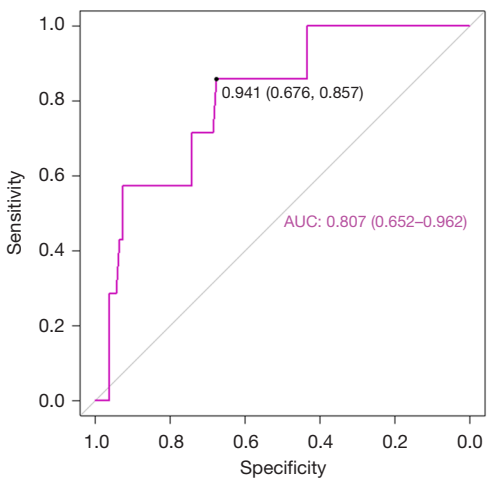

Figure 4 The ROC curve of the nomogram prediction model is plotted in the training set. AUC, area under the curve; ROC, receiver operating characteristic.

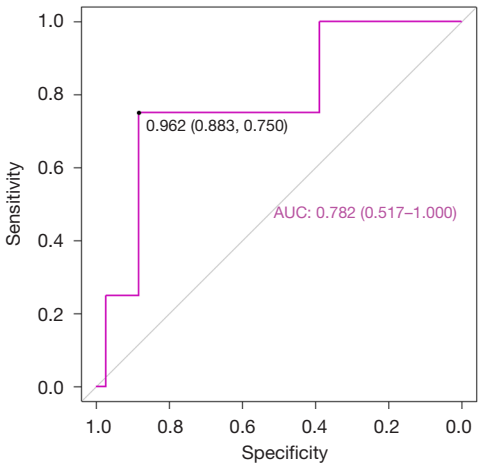

Figure 5 The ROC curve of the nomogram prediction model was plotted in the validation set. AUC, area under the curve; ROC, receiver operating characteristic.

after PD (23).

Hypoalbuminaemia is a reduced level of blood albumin, which can be caused by insufficient production by the liver, increased loss from the kidneys and gastrointestinal tract, or irregular distribution in the body. During any surgical procedure, reduced albumin levels can affect the quality of the anastomosis formed (24). Due to the invasive nature of PD, an exacerbated systemic immune response occurs postoperatively. Consequently, immunonutritional dysregulation leads to a decrease in albumin concentration,

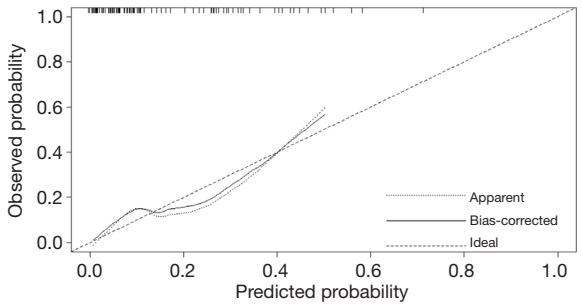

Figure 6 Calibration curve of the nomogram of the training set.

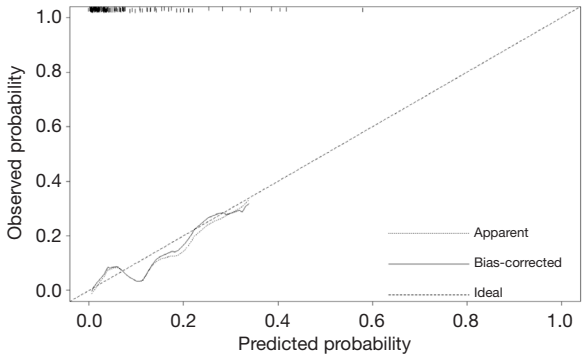

Figure 7 Calibration curve of the nomogram of the validation set.

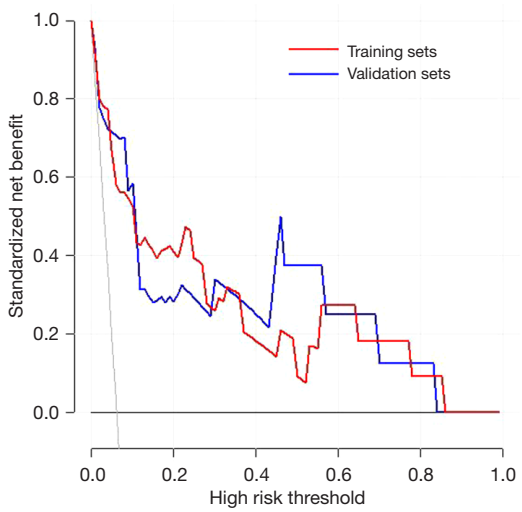

Figure 8 Analysis of the decision curve of nomogram for predicting biliary fistula after pancreaticoduodenectomy.

total lymphocyte counts (including helper T cells, interleukins 2 and 3, and T cells). An impaired immunonutritional status is therefore an important factor contributing to increased postoperative complications, including biliary fistulae after PD. Hypoalbuminaemia is an independent risk factor for biliary fistula after PD, as shown by Aydin *et al.* (11).

Pancreatic fistula is the most serious complication of PD (25). Postoperative pancreatic fistula remains one of the refractory complications despite the fact that a number of strategies have been applied to reduce its occurrence. According to the definition of the International Study Group on Pancreatic Fistula (14), patients were categorized as having a grade A, B or C fistula. Briefly, pancreatic fistulas after PD are classified into three grades—grade A: asymptomatic fistulas defined as the discharge of transient pancreatic amylase-containing output from a surgically localized drain on or after the third POD, with a pancreatic amylase level greater than three times the upper serum reference value; grade B: symptomatic fistulas requiring therapeutic management and prolonged hospitalization; and grade C: leaks that require active diagnostic management and therapeutic intervention and are associated with a prolonged hospital stay. Andrianello and Burkhart *et al.* showed that pancreatic fistula was significantly associated with biliary fistula after PD (21,26). The presence of a pancreatic fistula causes irritation and damage to the surrounding tissues, and the collection of pancreatic fluid in the abdominal cavity provides an environment for bacterial growth, increasing the risk of infection, making healing of the biliary-intestinal anastomosis difficult, and increasing the likelihood of a biliary fistula. The occurrence of pancreatic fistula and biliary fistula are closely related and causally related.

Postoperative DGE, also known clinically as gastroparesis, occurs in 19–57% of cases after PD (27,28). Although DGE is not life-threatening, it is a common and annoying complication. It usually subsides spontaneously with or without prokinetic medication and takes weeks or more to treat conservatively with drainage through a NGT (29). The pathogenesis of DGE is multifactorial and poorly understood. It has been speculated that pyloric denervation, loss of the pyloric pump, gastric arrhythmia, duodenal sinus ischaemia, lack of gastric motility in duodenal resection, reduced activity of the gastric motility receptor and inflammation may contribute to DGE (30). When gastric emptying is impaired after PD, abnormal secretion of gastric acid and other digestive juices may affect the secretion and excretion of bile, thus increasing the risk of biliary fistula. Furthermore, the elevated intra-abdominal pressure caused by the retention of gastric contents may exert pressure on the biliary system, affecting the flow of bile and thus increasing the risk of biliary fistula. Elevated intra-abdominal pressure may also aggravate an existing

biliary fistula, making it more difficult to heal.

Abdominal infections cause oedema, inflammation and necrosis of the tissues in the operated area, which may lead to poor healing of the bile ducts, thus increasing the risk of biliary fistula. In addition, abdominal infection may affect the treatment and prognosis of biliary fistula. The presence of infection may make healing of the fistula more difficult, requiring longer and more costly treatment.

Abdominal bleeding is a serious complication after PD, and this bleeding may affect biliary fistulae in several ways. Firstly, bleeding may lead to inadequate blood supply to the tissues in the operated area, which may affect the healing process and thus increase the incidence of biliary fistula. In addition, bleeding may cause local inflammation and infection, further affecting bile duct healing. Secondly, abdominal bleeding may exacerbate the severity of biliary fistula. If bile flows into the abdominal cavity through the fistula and mixes with blood, cholestatic peritonitis may develop. Previous study has shown that small, thin-walled bile ducts (<5 mm), biliary infections and impaired blood supply may lead to biliary fistulas (31). Andrianello *et al.* considered bile duct diameter as the only risk factor affecting biliary fistula after PD (21). However, Zhou *et al.* considered severe atherosclerotic celiac shaft stenosis as a new risk factor for biliary fistula after PD (32). Inconsistent with the results of our study, the reason for this discrepancy may be related to factors such as differences in sample selection, incomplete consistency in the risk factors included, and variability in study methods. Therefore, a rigorous study design with a larger sample size and more included variables is still needed to further confirm and expand our findings in the future.

Limitations

Our current study has several limitations. First, our study was retrospective and could not eliminate bias in the data, second, our data came from only two institutions, and the data obtained were not representative of all post-PD patients. Third, data collection was incomplete, and risk factor analyses did not include all potential factors affecting biliary fistulae after PD, such as analyses that did not address bile duct diameter. We took this indicator into account when collecting patient information. However, when we collected patient information, we found that some patients lacked clinical data of bile duct diameter due to the improved image data in other hospitals, so we did not include this indicator. Finally, although we assessed several variables, the impact of unidentified confounders cannot be ignored. To overcome these limitations, external validation and prospective multicenter studies with large numbers of patients are needed.

Conclusions

In summary, diabetes, preoperative low albumin, postoperative gastroparesis, postoperative abdominal bleeding, postoperative abdominal infection, and postoperative pancreatic fistula are risk factors for biliary fistula after PD. The predictors required for the model developed in this study are clinically available. Moreover, the previous complex regression equations were transformed into intuitive graphs, thus making the predictive model more readable for doctors to assess patients. The application of the model needs to be validated in future prospective studies.

Acknowledgments

Funding: This work was supported by the Science and Health Joint Project of the Hunan Provincial Natural Science Foundation of China (No. 2021JJ70051).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-24-174/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-174/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-24-174/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-24-174/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the

Institutional Ethics Committee of Yueyang Hospital Affiliated to Hunan Normal University (No. 2024012) and the Institutional Ethics Committee of The Third Xiangya Hospital of Central South University (No. S245), and all patients' informed consent was obtained.

References

1. McMillan MT, Malleo G, Bassi C, et al. Defining the practice of pancreatoduodenectomy around the world. HPB (Oxford) 2015;17:1145-54.
2. Xiang Y, Wu J, Lin C, et al. Pancreatic reconstruction techniques after pancreaticoduodenectomy: a review of the literature. Expert Rev Gastroenterol Hepatol 2019;13:797-806.
3. Cameron JL, Riall TS, Coleman J, et al. One thousand consecutive pancreaticoduodenectomies. Ann Surg 2006;244:10-5.
4. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg 2004;8:935-49; discussion 949-50.
5. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg 2002;236:355-66; discussion 366-8.
6. Jiang YL, Zhang RC, Zhou YC. Comparison of overall survival and perioperative outcomes of laparoscopic pancreaticoduodenectomy and open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. BMC Cancer 2019;19:781.
7. Karim SAM, Abdulla KS, Abdulkarim QH, et al. The outcomes and complications of pancreaticoduodenectomy (Whipple procedure): Cross sectional study. Int J Surg 2018;52:383-7.
8. Scaife CL, Hewitt KC, Mone MC, et al. Comparison of intraoperative versus delayed enteral feeding tube placement in patients undergoing a Whipple procedure. HPB (Oxford) 2014;16:62-9.
9. Koch M, Garden OJ, Padbury R, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149:680-8.
10. Antolovic D, Koch M, Galindo L, et al. Hepaticojejunostomy--analysis of risk factors for postoperative bile leaks and surgical complications. J Gastrointest Surg 2007;11:555-61.
11. Aydin HO, Soy EHA, Kirnap M, et al. Predisposing risk factors for isolated bile leakage after pancreaticoduodenectomy. Ann Ital Chir 2023;94:587-93.
12. Kakita A, Takahashi T, Yoshida M, et al. A simpler and more reliable technique of pancreatojejunal anastomosis. Surg Today 1996;26:532-5.
13. Grobmyer SR, Kooby D, Blumgart LH, et al. Novel pancreaticojejunostomy with a low rate of anastomotic failure-related complications. J Am Coll Surg 2010;210:54-9.
14. Bassi C, Marchegiani G, Dervenis C, et al. The 2016 update of the International Study Group (ISGPS) definition and grading of postoperative pancreatic fistula: 11 Years After. Surgery 2017;161:584-91.
15. Wente MN, Bassi C, Dervenis C, et al. Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 2007;142:761-8.
16. Wente MN, Veit JA, Bassi C, et al. Postpancreatectomy hemorrhage (PPH): an International Study Group of Pancreatic Surgery (ISGPS) definition. Surgery 2007;142:20-5.
17. Kidd AC, McGettrick M, Tsim S, et al. Survival prediction in mesothelioma using a scalable Lasso regression model: instructions for use and initial performance using clinical predictors. BMJ Open Respir Res 2018;5:e000240.
18. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12-49.
19. Grossberg AJ, Chu LC, Deig CR, et al. Multidisciplinary standards of care and recent progress in pancreatic ductal adenocarcinoma. CA Cancer J Clin 2020;70:375-403.
20. Hu JX, Zhao CF, Chen WB, et al. Pancreatic cancer: A review of epidemiology, trend, and risk factors. World J Gastroenterol 2021;27:4298-321.
21. Andrianello S, Marchegiani G, Malleo G, et al. Biliary

fistula after pancreaticoduodenectomy: data from 1618 consecutive pancreaticoduodenectomies. HPB (Oxford) 2017;19:264-9.
22. Arase Y, Kobayashi M, Suzuki F, et al. Effect of type 2 diabetes on risk for malignancies includes hepatocellular carcinoma in chronic hepatitis C. Hepatology 2013;57:964-73.
23. Jester AL, Chung CW, Becerra DC, et al. The Impact of Hepaticojejunostomy Leaks After Pancreatoduodenectomy: a Devastating Source of Morbidity and Mortality. J Gastrointest Surg 2017;21:1017-24.
24. Jakhmola CK, Kumar A. Whipple's pancreaticoduodenectomy: Outcomes at a tertiary care hospital. Med J Armed Forces India 2014;70:321-6.
25. Farges O, Bendersky N, Truant S, et al. The Theory and Practice of Pancreatic Surgery in France. Ann Surg 2017;266:797-804.
26. Burkhart RA, Relles D, Pineda DM, et al. Defining treatment and outcomes of hepaticojejunostomy failure following pancreaticoduodenectomy. J Gastrointest Surg 2013;17:451-60.
27. Healy JM, Kunstman JW, Salem RR. Proposal and critical appraisal of exclusion criteria to the international study group for pancreatic surgery definition of delayed gastric emptying. J Am Coll Surg 2015;220:1036-1043.e1.
28. Welsch T, Borm M, Degrate L, et al. Evaluation of the International Study Group of Pancreatic Surgery definition of delayed gastric emptying after pancreatoduodenectomy in a high-volume centre. Br J Surg 2010;97:1043-50.
29. Miyazaki Y, Oda T, Shimomura O, et al. Retrocolic Gastrojejunostomy After Pancreaticoduodenectomy: A Satisfactory Delayed Gastric-Emptying Rate. Pancreas 2019;48:579-84.
30. Mao SH, Shyr BS, Chen SC, et al. Risk factors for delayed gastric emptying in pancreaticoduodenectomy. Sci Rep 2022;12:22270.
31. El Nakeeb A, El Sorogy M, Hamed H, et al. Biliary leakage following pancreaticoduodenectomy: Prevalence, risk factors and management. Hepatobiliary Pancreat Dis Int 2019;18:67-72.
32. Zhou Y, Wang W, Shi Y, et al. Substantial atherosclerotic celiac axis stenosis is a new risk factor for biliary fistula after pancreaticoduodenectomy. Int J Surg 2018;49:62-7.

Cite this article as: Ou Z, Yan A, Zhu W. The establishment and validation of a clinical prediction model for postoperative biliary fistula after pancreaticoduodenectomy. Gland Surg 2024;13(9):1605-1618. doi: 10.21037/gs-24-174